SUPPLEMENTAL MATERIAL

P-Wave Morphology and the Risk of Incident Ischemic Stroke in the Multi-Ethnic Study of Atherosclerosis

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Supplemental Appendix

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Supplemental Methods

Covariate Definitions

Left ventricular hypertrophy was defined using a standard validated threshold for the Cornell voltage-duration product.[1] Hypertension was defined using Joint National Commission VI guidelines.[2] Diabetes status was based on the American Diabetes Association's 2003 fasting criteria.[3] A glomerular filtration rate <60 ml/min/1.73 m^2 was considered chronic kidney disease.[4] Body mass index was categorized into four categories using thresholds of 25, 30, and 40 kg/m^2.

Ascertainment of Atrial Fibrillation

First, we ascertained AF using the 12-lead ECG done at the final study visit. Second, we recorded all diagnoses of AF identified during the course of endpoint investigation and adjudication. All hospitalizations during study follow-up were investigated, and medical records were reviewed for a predefined list of *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) codes, including codes 427.3x for AF, which was documented in study records even if a study endpoint had not occurred. Similarly, all outpatient events representing possible primary study endpoints were investigated using medical record review and physician questionnaires, and diagnoses of AF associated with these events were recorded. Third, among participants enrolled in Medicare, we searched linked administrative data to identify any inpatient or outpatient claims for AF (*ICD-9-CM* codes 427.3x). In a sensitivity analysis, we also included self-reports of AF to maximize our sensitivity for this important covariate.

Statistical Analyses

After visually inspecting their distributions, we used means with standard deviations (SD) and t-tests to compare P-wave predictor variables in participants with and without stroke. Among the 4,236 participants with available follow-up ECG data, we compared P-wave measurements at baseline and 5-year follow-up.

All models controlled for AF as a time-varying covariate. Additionally, we included age, sex, race, and any of the above baseline covariates that were significantly associated with incident stroke in univariate analyses at a threshold of P <0.20; sensitivity analyses that forced all baseline covariates into the models did not appreciably change our results. We verified the proportional hazards assumption by checking an interaction term between P-wave predictor variables and time.

In post hoc analyses, we additionally included systolic blood pressure, antihypertensive medication use, and the PR interval on ECG, as these variables are part of the Framingham risk score for AF;[5] prevalent heart failure was not included because MESA participants were free of vascular disease at baseline, and the presence of a heart murmur was not included because this information was not available. Furthermore, to assess whether P-wave measurements have incremental value for stroke prediction in addition to established risk scores, we calculated the

Framingham stroke risk score[6] and determined changes in the c-statistic and the net reclassification improvement (using standard risk categories of 5%, 10%, and 20%[7]) after including $PTFV_1$ in 1-SD increments.

Sensitivity Analyses

We performed the Sobel-Goodman mediation test to determine the degree to which AF mediated any associations between P-wave morphology and stroke. This statistical test uses multivariable methods to isolate the pathways between a predictor, a potential mediator, and an outcome; it is considered the gold standard when formally testing the significance of a proposed mediation pathway.[8] We further assessed the independence of any associations between P-wave morphology and stroke by performing subgroup analyses limited to participants without any AF diagnoses throughout the study period. Since clinically apparent AF often manifests after a prolonged period of subclinical AF,[9] we performed sensitivity analyses in which AF diagnoses at any time during the entire study period was assumed to have been present from baseline. To ensure that we did not miss cases of AF, we repeated these sensitivity analyses in participants ≥65 years of age at baseline and enrolled in Medicare throughout the study period, which ensured AF ascertainment via linked Medicare claims data during the entire duration of follow-up. Lastly, to ensure further that subclinical AF would have had time to manifest, we repeated these Medicare-only subset analyses excluding participants who had a stroke during the 2 years before final follow-up.

To ensure further that associations between our P-wave predictors and stroke were not mediated by non-atrial vascular disease, we performed post hoc sensitivity analyses controlling for carotid intima media thickness and degree of carotid stenosis on ultrasound.

Lastly, we also used our baseline models to examine the associations between P-wave predictor variables and the risk of myocardial infarction (MI) and all-cause mortality. Since we hypothesized that P-wave morphology specifically reflects an atrial cardiomyopathy that causes cardiac embolism, rather than simply reflecting general cardiovascular risk, we expected to find a stronger association with stroke than with MI or death.

Supplemental Results

Among participants with ECG data at 5-year follow-up, $PTFV_1$ increased by a mean 13.9%, and remained stable or increased in 3,093 participants (67.7%) while regressing in 1,475 participants (32.3%).

The Sobel-Goodman test indicated that AF mediated only 11% of the association between $PTFV_1$ and stroke. We found the same association between $PTFV_1$ and stroke in participants free of any AF diagnoses throughout the study (HR per 1-SD, 1.25; 95% CI, 1.02-1.52). In models adjusting for incident AF, our findings were unchanged when we modeled incident AF as having been present from baseline (HR per 1-SD, 1.20; 95% CI, 1.02-1.43), even when including self-reports of AF (HR per 1-SD, 1.21; 95% CI, 1.02-1.43). We found a significant association when limiting this analysis to participants ≥65 years of age at baseline and enrolled in Medicare throughout the study period (HR per 1-SD, 1.31; 95% CI, 1.04-1.66), even for stroke occurring at least 2 years before final follow-up (HR per 1-SD, 1.45; 95% CI, 1.09-1.91).

We found no significant association between baseline $PTFV_1$ and subsequent MI (HR per 1-SD, 1.06; 95% CI, 0.93-1.20) or death (HR per 1-SD, 1.05; 95% CI, 0.96-1.14). The associations between $PTFV_1$ and stroke were not materially changed in sensitivity analyses controlling for ultrasound measurements of carotid plaque (HR per 1-SD, 1.20; 95% CI, 1.01-1.43).

The inclusion of additional covariates from the Framingham AF risk score did not change the association between $PTFV_1$ and stroke (HR per 1-SD, 1.22; 95% CI, 1.03-1.45).

The c-statistic of the Framingham stroke risk score (0.76; 95% CI, 0.72-0.79) did not appreciably change after adding $PTFV_1$ (0.76; 95% CI, 0.72-0.80), but the addition of $PTFV_1$ led to a significant net reclassification improvement (0.113, $P < 0.001$).

Supplemental Table I. Baseline P-Wave Measurements, Stratified by the Occurrence of Incident Ischemic Stroke

Characteristic	Stroke (N = 121)	No Stroke (N = 6,620)	*P* value
P-wave terminal force in lead V_1 ($PTFV_1$):			
Mean (SD), μV*ms	2,860 (1,996)	2,171 (1,786)	<.001
≥95th percentile, N (%)	14 (11.6)	324 (4.9)	.001
P-wave mean area:			
Mean (SD), μV*ms	3,702 (1,020)	3,554 (953)	.09
≥95th percentile, N (%)	11 (9.1)	325 (4.9)	.04
P-wave maximum area:			
Mean (SD), μV*ms	6,689 (2,507)	6,364 (2,100)	.09
≥95th percentile, N (%)	8 (6.6)	330 (5.0)	.42
P-wave mean duration:			
Mean (SD), ms	107.0 (13.0)	103.4 (13.1)	.003
≥95th percentile, N (%)	13 (10.7)	390 (5.9)	.03
P-wave maximum duration:			
Mean (SD), ms	109.8 (13.3)	106.0 (12.7)	.001
≥95th percentile, N (%)	15 (12.4)	411 (6.2)	.006

Abbreviations: SD, standard deviation.

Supplemental References

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