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## Refining Prediction of Atrial Fibrillation-Related Stroke Using the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc Score: the Atherosclerosis Risk in Communities (ARIC) study and Multi-Ethnic Study of Atherosclerosis (MESA)

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### Abstract

**Background:** In people with atrial fibrillation (AF), periods of sinus rhythm present an opportunity to detect pro-thrombotic atrial remodeling through measurement of P-wave indices (PWIs)—prolonged P-wave duration, abnormal P-wave axis, advanced inter-atrial block, and abnormal P-wave terminal force in lead VI. We hypothesized that addition of PWIs to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score would improve its ability to predict AF-related ischemic stroke.

**Methods:** We included 2229 Atherosclerosis Risk in Communities (ARIC) study and 700 Multi-Ethnic Study of Atherosclerosis (MESA) participants with incident AF who were not on anticoagulants within 1 year of AF diagnosis. PWIs were obtained from study visit ECGs before development of AF. AF was ascertained using study visit ECGs and hospital records. Ischemic stroke cases were based on physician adjudication of hospital records. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) of PWIs for ischemic stroke. Improvement in 1-year stroke prediction was assessed by C-statistic,

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categorical net reclassification improvement (NRI), and relative integrated discrimination improvement (IDI).

**Results:** Abnormal P-wave axis was the only PWI associated with increased ischemic stroke risk (HR, 1.84; 95% CI, 1.33-2.55) independent of CHA<sub>2</sub>DS<sub>2</sub>-VASc variables and that resulted in meaningful improvement in stroke prediction. The beta estimate was approximately twice that of the CHA<sub>2</sub>DS<sub>2</sub>-VASc variables, thus abnormal P-wave axis was assigned 2 points to create the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score. This improved the C-statistic (95% CI) from 0.60 (0.51-0.69) to 0.67 (0.60-0.75) in ARIC and 0.68 (0.52-0.84) to 0.75 (0.60-0.91) in MESA (validation cohort). In ARIC and MESA, the categorical NRI (95% CI) were 0.25 (0.13-0.39) and 0.51 (0.18-0.86), respectively, and the relative IDI (95% CI) were 1.19 (0.96-1.44) and 0.82 (0.36-1.39), respectively.

**Conclusions:** Abnormal P-wave axis—an ECG correlate of left atrial abnormality—improves ischemic stroke prediction in AF. Compared with CHA<sub>2</sub>DS<sub>2</sub>-VASc, the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc is a better prediction tool for AF-related ischemic stroke.

### Keywords

Atrial Fibrillation; Stroke; CHA<sub>2</sub>DS<sub>2</sub>-VASc score

## Introduction

Atrial fibrillation (AF) is associated with a 5-fold increased risk of stroke.<sup>1</sup> Current practice guidelines recommend risk stratification with the CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, sex) score to identify appropriate candidates for systemic anticoagulation to prevent stroke.<sup>2,3</sup> Unfortunately, emerging clinical evidence has highlighted limitations in the predictive value of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>4-9</sup> Use of markers that more directly reflect the underlying mechanisms of AF-related thromboembolism may help improve the current risk stratification paradigm.

There has been increasing recognition of the contribution of pro-thrombotic remodeling of the atrial architecture to thromboembolism risk.<sup>6,10</sup> Abnormal atrial conduction measured through analysis of P-wave morphology—P-wave indices (PWIs)—has been associated with atrial remodeling<sup>11-14</sup> and stroke.<sup>15-21</sup> In people with AF, periods of sinus rhythm present an opportunity to detect underlying atrial remodeling through measurement of PWIs. We hypothesized that addition of PWIs to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score would augment stroke risk prediction in individuals with AF. We tested this hypothesis in the Atherosclerosis Risk in Communities (ARIC) study and validated our findings in the Multi-Ethnic Study of Atherosclerosis (MESA), two large prospective community-based cohort studies in the United States.

## Methods

### Data Availability

Some access restrictions apply to the data underlying the findings. The consent signed by study participants does not allow the public release of their data. Data from the ARIC study

can be accessed by contacting the ARIC Coordinating Center (aricpub@unc.edu). Data from the MESA study can be accessed by contacting the MESA data coordinating center (chscweb@u.washington.edu).

### Study Population

The ARIC study was designed to evaluate risk factors, etiology, and clinical manifestations of atherosclerotic coronary heart disease in the general population. Between the years of 1987 and 1989, 15792 men and women aged 45-64 years were recruited and enrolled from four United States communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and suburban Minneapolis, MN). After the baseline examination, participants have completed 5 follow-up study visits, the most recent in 2016-17. In between study visits, participants (or proxy) have been contacted annually by telephone (semi-annually since 2012) to ascertain information on hospitalizations and deaths. Active community-wide surveillance of local hospitals has been performed to identify additional hospitalizations and cardiovascular events. Further details regarding outcome ascertainment procedures, study design, and population statistics have been previously described.<sup>22</sup> Approval for the study was obtained from the institutional review board on human research at each participating institution and all participants provided informed consent.

The present analysis utilized data obtained from the baseline study visit in 1987-89 through 2013. We excluded participants with missing ECG data (n=242), missing P-wave indices at baseline (n=45), prevalent AF (n=37), and those who were not white or black from all study sites and nonwhite from Minneapolis and Washington County (due to small sample size; n=103) resulting in a baseline cohort of 15365 participants. We then identified 2625 cases of incident AF after the baseline study visit. Due to the potential bias introduced by anticoagulant use when studying stroke risk, participants with anticoagulant use within 1 year of AF diagnosis (n=172) were excluded. We also excluded those without follow-up beyond AF date (n=224) resulting in a final cohort of 2229 participants with incident AF.

Two-dimensional (2D) and three-dimensional (3D) echocardiograms were performed during visit 5 (2011-2013). 2D echocardiograms were performed on 6,538 participants during visit 5. As previously done, exclusions were made for race (n=42) resulting in 6,496 participants. Of these, 6,008 had interpretable ECGs with PWV values. Of these, 5,830 had interpretable 2D echocardiogram data. 3D echocardiograms were performed on 3,035 participants during visit 5. Exclusions were made for race (n=16), poor image quality (n=1779), severe valvular heart disease or history of valve surgery (n=64), and missing body mass index or body surface area data (n=34) resulting in a final analysis cohort of 1,142 participants with 3D echocardiograms.

The MESA study was designed to investigate the prevalence, natural history, and correlates of subclinical cardiovascular disease. Between the years of 2000 and 2002, 6814 men and women aged 45-85 without prevalent cardiovascular disease were recruited and enrolled from six United States communities (Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St. Paul, MN). After the initial baseline study visit, there have been five additional follow-up visits, the most recent ongoing in 2016-18. Participants are contacted on an annual basis to identify new

hospitalizations and medical diagnoses. Death certificates and medical records are then reviewed for purposes of outcome ascertainment. Further details on study protocol and procedures have been previously described.<sup>23</sup> Approval for the study was obtained from the institutional review board on human research at each participating institution and all participants provided informed consent.

The present analysis utilized data obtained during the baseline visit in 2000-02 through 2014. We excluded participants with prevalent AF (n=66) or missing ECG or P-wave indices at baseline (n=49), and identified 876 cases of incident AF. We then excluded those without follow-up beyond the date of AF diagnosis (n=117), oral anticoagulant use within 1 year of AF diagnosis (n=54), and those with invalid P-wave axis measurements (n=5) resulting in a final cohort of 700 participants with incident AF.

### Measurement of P-Wave Indices

Measurement of PWIs in ARIC<sup>17</sup> and MESA<sup>23</sup> was done in a consistent manner and has been described. We evaluated P-wave axis, P-wave duration, advanced inter-atrial block (aIAB), and P-wave terminal force in lead V1 using a standard 12-lead ECG (Figure 1). P-wave axis is a measure of the net direction of atrial depolarization. It is determined by measuring net positive or negative P-wave deflections on all six limb leads and calculating the net direction of electrical activity using the hexaxial reference system (Figure 1). It is a standard, computer-generated ECG index that was reported on all ECGs in ARIC and MESA. Abnormal P-wave axis (aPWA) was defined as any value outside 0-75°. P-wave duration is a reflection of the time required for right and left atrial depolarization. It was measured from the conclusion of the T-P segment (P wave onset) to return to baseline (PR interval). For biphasic P-waves, P-wave duration encompassed both positive and negative deflections from baseline. Prolonged P-wave duration (PPWD) was present if the maximum P-wave duration in any lead was >120 ms on a standard 12-lead ECG. aIAB is an indicator of inter-atrial conduction block in Bachman's bundle such that the left atrium is activated superiorly. It was defined as PPWD + biphasic P-wave morphology in leads III and aVF with biphasic morphology or notched morphology in lead II. P-wave terminal force in lead V1 is a measure of left atrial activation. It is determined by multiplying the duration (ms) and the depth ( $\mu\text{V}$ ) of the downward deflection (terminal portion) of the P-wave in lead V1. Abnormal P-wave terminal force in lead V1 (aPTFV1) was defined as  $-4000 \mu\text{V}\cdot\text{ms}$ . All P-wave indices were computed from the closest sinus rhythm ECG prior to AF diagnosis.

### Stroke Classification

Details on stroke identification and specific classification criteria for ischemic stroke in the ARIC<sup>24</sup> and MESA<sup>25</sup> cohorts have been described. In ARIC, potential cases of stroke were identified from review of hospital records and death certificates. Classification of stroke was then adjudicated by physicians with assistance of a computerized algorithm utilizing validated criteria from the National Survey of Stroke by the National Institute of Neurological Disorders. Strokes were classified as definite or probable thrombotic stroke, definite or probable cardioembolic stroke, definite or probable subarachnoid hemorrhage, definite or probable brain hemorrhage, and possible stroke of undetermined type. The

primary endpoint in our study was ischemic stroke, which included all thrombotic and cardioembolic strokes (definite and probable).

In MESA, potential cases of stroke were identified from review of medical records and death certificates. Stroke was defined as a focal neurologic deficit lasting 24 hours or until death or if the deficit lasted <24 hours and there was a clinically relevant lesion on brain imaging. Cases with focal neurological deficits secondary to brain trauma, tumor, infections, or other nonvascular cause were excluded. Cases were physician adjudicated by members of the MESA study events committee. Strokes were sub-classified as subarachnoid hemorrhage, intra-parenchymal hemorrhage, other hemorrhage, brain infarction or other stroke. We included all non-hemorrhagic strokes in our analysis. Due to the relatively low number of stroke events, we elected to use a composite primary endpoint of stroke and transient ischemic attack (TIA) for the MESA analysis. In MESA, TIA was defined as one or more documented episodes of focal neurologic deficit lasting 30 seconds to 24 hours without brain imaging documenting stroke.

### Assessment of Covariates

The covariates included in our analysis—age, sex, heart failure<sup>26,27</sup>, hypertension<sup>28,29</sup>, diabetes<sup>29,30</sup>, myocardial infarction<sup>27,31</sup>, stroke, TIA<sup>32</sup>, and peripheral arterial disease<sup>27,33</sup>—were derived from data obtained during participant interviews, clinical examinations, and review of medical records as previously described. Prevalent (at baseline visit) and incident (during follow-up) variables were included. Precise definitions were comparable in ARIC and MESA. All covariates in ARIC and MESA were ascertained at the time of AF diagnosis or at the most recent study visit exam prior to AF diagnosis.

### AF Ascertainment

AF cases were ascertained by review of ECGs during study visits and hospital discharge records. AF associated with cardiothoracic surgery was not considered. Further details on specific ascertainment procedures in ARIC<sup>34</sup> and MESA<sup>35</sup> have been previously described.

### Anticoagulation Status

Use of anticoagulants was captured through participant interviews during each study visit in MESA and ARIC and annually in ARIC after 2006. During the time period of our analysis in both ARIC and MESA, Coumadin was the only anticoagulant captured during participant interviews.

### Echocardiography

2D and 3D echocardiography analysis protocols have been previously described.<sup>36,37</sup> Briefly, two-dimensional echocardiograms were performed using dedicated Philips iE33 Ultrasound systems with Vision 2011. Three-dimensional echocardiograms were performed using a dedicated Philips X3-1 transducer. Echocardiograms were analyzed at the Echocardiography Reading Center (ERC; Brigham and Women's Hospital, Boston, MA) in accordance with American Society of Echocardiography recommendations.

## N Terminal Pro B-Type Natriuretic Peptide (NT-proBNP) Levels

NT-ProBNP levels were measured from participant plasma samples obtained during ARIC visit 5 using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics).

## Statistical Analysis

We used the ARIC sample to derive a novel risk score for AF-related ischemic stroke prediction by incorporating PWIs with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score variables. We used the MESA sample to validate our risk score.

In the ARIC sample, we used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) of abnormal PWIs for ischemic stroke. Person-years at risk were calculated from the date of AF ascertainment until the date of ischemic stroke, death not due to stroke, loss to follow-up, or end of follow-up, whichever occurred first.

We constructed 2 models for the association of each PVI and CHA<sub>2</sub>DS<sub>2</sub>-VASc variable with incident ischemic stroke in ARIC. Model 1 was an unadjusted model. Model 2 was adjusted for remaining CHA<sub>2</sub>DS<sub>2</sub>-VASc variables: age, sex, heart failure, hypertension, diabetes, previous stroke/TIA, previous myocardial infarction, and peripheral arterial disease.

To estimate the predictive value of PWIs for stroke, we constructed 6 models for 1-year stroke risk which were used in our cohort of participants with incident AF. Model A was constructed with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score variables. Models B to E were constructed by adding aPWA, PPWD, aPTFV1, and aIAB to Model A, respectively. Model F was constructed by adding all 4 PWIs to Model A. We evaluated model performance by calculating the C-statistic, categorical net reclassification improvement (NRI), and relative integrated discrimination improvement (IDI) using Model A as the benchmark for comparison. Reclassification categories were defined as <1%, 1–2%, and >2% 1-year risk of stroke. We used the Hosmer-Lemeshow chi-squared statistic to evaluate model calibration and also compared observed to predicted stroke rates for score categories

To create our risk score for 1-year stroke prediction, we screened our results for PWIs that resulted in meaningful improvement in risk reclassification and model discrimination. To assign a point value for the candidate PVI, we compared the coefficient of the PVI with the coefficient of CHA<sub>2</sub>DS<sub>2</sub>-VASc variables in the same Cox proportional hazards model for ischemic stroke. We validated the new score in MESA.

To estimate the odds of structural heart disease for abnormal PWIs, we conducted a cross-sectional analysis in participants from visit 5 who underwent 2D and 3D echocardiograms. We utilized logistic regression models to calculate odds ratios. Model a was unadjusted. Model b was additionally adjusted for age, sex, and race. Data are presented as odds ratios (95% CI) for categorical variables and difference (95% CI) for continuous variables.

Finally, we calculated the C-statistic of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score for 5-year ischemic stroke in participants without AF with abnormal PWIs and participants with AF. For

participants without AF, we used our baseline cohort (15,365 participants at visit 1). Baseline ECGs were used to evaluate PWIs. For participants with AF, we utilized our cohort of participants with incident AF (2229 participants with incident AF). Participants were followed until their first ischemic stroke, death, or censorship.

The proportional hazards assumption was assessed with scaled Schoenfeld residuals for both graphical and numerical tests, time interaction terms, and inspection of log negative log survival curves. Model assumptions were not violated in any model. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and STATA 13.0, College Station, TX: StataCorp LP. To evaluate whether differences between baseline characteristics were statistically significant, a Student's t-test was used for continuous variables and a chi-squared test was used for categorical variables. All *P* values reported were 2-sided, and statistical significance threshold was chosen as 0.05.

## Results

In the ARIC sample, we identified 163 ischemic strokes over a mean follow-up time of 5.4 years after AF diagnosis. There were 47 ischemic strokes within the first year after AF diagnosis. In the MESA sample, we identified 31 cases of stroke/TIA over a mean follow-up time of 3.3 years after AF diagnosis. There were 10 or fewer cases of stroke/TIA within the first year after AF diagnosis. Due to the Centers for Medicare and Medicaid Services sparse cell suppression policy which stipulates that no cell (e.g. admittances, discharges, patients, services) 10 or less may be displayed, we are unable to report the exact number of events in the first year after AF diagnosis. The mean (SD) time period from ECG detection of aPWA to AF diagnosis in ARIC and MESA was 8.0 (5.3) and 4.4 (3.0) years, respectively.

The baseline characteristics of participants at the time of AF diagnosis in each study sample are listed in Table 1. In the ARIC sample, participants who developed stroke were more likely to be women and to have prevalent heart failure, hypertension, myocardial infarction, stroke/TIA, peripheral arterial disease, aPWA, PPWD, aPTFV1, and aIAB. There were no statistically significant differences in the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores between participants who did and did not develop stroke. In the MESA sample, participants who developed stroke were on average older, more likely to be women, and more likely to have prevalent hypertension, heart failure, stroke/TIA, and aPWA than MESA participants who did not develop stroke. Participants who developed stroke or TIA in MESA had higher CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores compared to those who did not.

Table 2 lists the results of our Cox proportional hazards models that were used to estimate the association between abnormal PWIs and ischemic stroke in the ARIC cohort. aPWA and aIAB were associated with increased risk of ischemic stroke in the unadjusted model (model 1). These associations remained significant after adjustment for the individual CHA<sub>2</sub>DS<sub>2</sub>-VASc variables (model 2). PPWD and aPTFV1 were not associated with increased risk of ischemic stroke in either model.

Table 3 lists our analysis of stroke risk prediction model discrimination, risk reclassification, and calibration. Model A, which was constructed with the CHA<sub>2</sub>DS<sub>2</sub>-VASc variables, served

as our benchmark for stroke prediction. aPWA was the only PWI which resulted in meaningful improvement in discrimination and risk reclassification. For 1-year stroke risk, the addition of aPWA (model B) to model A improved the C-statistic (95% CI) from 0.659 (0.574-0.743) to 0.738 (0.663-0.814) corresponding to categorical NRI (95% CI) of 0.266 (0.084-0.442) and relative IDI (95%) of 0.773 (0.474-1.131). The addition of all PWIs to model A (model F) improved the C-statistic (95% CI) from 0.659 (0.574-0.743) to 0.749 (0.678-0.820) corresponding to categorical NRI (95% CI) of 0.374 (0.215-0.521) and relative IDI (95%) of 1.04 (0.652-1.52). All models were well calibrated for 1-year stroke risk.

Based on our findings that aPWA was the only PWI that significantly improved prediction of ischemic stroke, we constructed a new risk score by incorporating aPWA into the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. In model B, the beta estimates of aPWA and CHA<sub>2</sub>DS<sub>2</sub>-VASc score, modeled as a continuous variable, for 1-year stroke risk were 0.582 and 0.262, respectively. Thus, aPWA was assigned a value of 2 points to create the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score— aPWA (2 points), age (1 point for 65-74, 2 points for ≥75), sex (1 point for female), heart failure (1 point), hypertension (1 point), diabetes (1 point), previous myocardial infarction/peripheral artery disease (1 point), prevalent stroke/TIA (2 points).

In the ARIC sample, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score had modest discrimination for 1-year stroke risk when assessed by C-statistic (0.60, 95% CI 0.51-0.69). The P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc demonstrated superior model discrimination assessed by C-statistic (0.67, 95% CI 0.60-0.75) and IDI (1.19, 95% CI 0.96-1.44). This corresponded to a substantial categorical NRI (0.25, 95% CI 0.13-0.39) (Table 4). Compared to its performance in ARIC, in the MESA sample, the CHA<sub>2</sub>DS<sub>2</sub>-VASc had better discrimination assessed by C-statistic (0.68, 95% CI 0.52-0.84). The P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc again demonstrated superior discrimination properties assessed by C-statistic (0.75, 95% CI 0.60-0.91) and relative IDI (0.82, 95% CI 0.36-1.39). This corresponded to a substantial categorical NRI (0.51, 95% CI 0.18-0.86) (Table 4).

Table 5 lists our analysis of 1-year stroke risk reclassification using the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score compared to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. In ARIC participants who developed stroke within 1 year of AF diagnosis, 14% were correctly reclassified to higher risk categories while 6% were incorrectly classified to lower risk categories. In those who did not develop stroke, 20.9% were correctly reclassified to lower risk categories while 5.3% were incorrectly reclassified to higher risk categories. In MESA participants who developed stroke within 1 year of AF diagnosis, 33.3% were correctly reclassified to higher risk categories and no participants were incorrectly reclassified to lower risk categories. In those who did not develop stroke, 8.5% were incorrectly reclassified to higher risk categories while 26.3% were correctly reclassified to lower risk categories.

Figure 2 depicts the observed and predicted 1-year stroke risk for P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score categories in ARIC and MESA. The score was well calibrated in ARIC. Given the low number of events in MESA, some variation between observed and predicted risk is to be expected. A 2% annual stroke risk, which is the threshold for anticoagulation according to the 2014 AHA/ACC/HRS<sup>2</sup> practice guidelines, corresponded to a score of 4-5.



The association of PWIs with structural heart disease is displayed in Table 6. After adjustment for age, sex, and race, all abnormal PWIs were independently associated with left atrial enlargement, greater LV mass, greater LV end diastolic dimension. PPWD, aPWA, and aIAB were associated with higher N-terminal pro b-type natriuretic peptide levels. PPWD, aPTFV1, and aPWA were associated with lower LV ejection fraction. aPWA and PPWD were associated with lower left atrial emptying fraction. aPWA was associated with lower left atrial global longitudinal strain.

The predictive value of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score for 5-year ischemic stroke risk is listed in supplemental table 1. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score had a C-statistic of 0.682 (0.617-0.748) and 0.636 (0.577-0.695) in participants without AF with any abnormal PWi and participants with AF, respectively.

## Discussion

In this study, we demonstrated that aPWA and aIAB were independently associated with AF-related ischemic stroke. We found that use of aPWA improved ischemic stroke prediction over and above the CHA<sub>2</sub>DS<sub>2</sub>-VASc score variables. We derived and validated the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score—aPWA (2 points), age (1 point for 65-74, 2 points for ≥75), sex (1 point for female), heart failure (1 point), hypertension (1 point), diabetes (1 point), previous myocardial infarction/peripheral artery disease (1 point), prevalent stroke/TIA (2 points)—for prediction of AF-related stroke using data from 2 large community-based prospective cohort studies. We found that this scoring system had superior discrimination compared to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and resulted in significant improvement in ischemic stroke-risk reclassification. Of note, while aIAB was independently associated with AF-related stroke, it did not improve risk prediction in our models. This was likely due to its low prevalence in our population.

Fibrotic atrial remodeling and enlargement are critical components of the proarrhythmic and prothrombotic substrate underlying development of AF and AF-related stroke.<sup>10</sup> Measurement of PWIs forms the basis for ECG-based detection of this substrate.<sup>11–14</sup> Our analysis supports an association between abnormal PWIs and adverse cardiac remodeling including left atrial enlargement, an independent risk factor for development of AF and cardioembolic/cryptogenic stroke.<sup>38,39</sup> Abnormal PWIs—PPWD<sup>40,41</sup>, aIAB<sup>16,42,43</sup>, aPTFV1<sup>17,18,40</sup>, and aPWA<sup>15,44</sup>—have been found to be independently associated with AF and stroke in the general population, even after adjustment for AF. However, the clinical utility of PWIs has not been well established.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is recommended for AF-related stroke prediction despite emerging evidence that has highlighted limitations in its discriminatory capacity. In a meta-analysis of 8 clinical studies, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score demonstrated only modest discrimination (C-statistic 0.675, 95% CI 0.656-0.694) in non-anticoagulated AF patients.<sup>9</sup> Furthermore, individuals with low risk scores of 0-1 have been found to still have clinically significant stroke risk. A study of 73,242 low-risk AF patients from the National Health Insurance Research Database in Taiwan reported that the annual stroke rates of patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of 0 and 1 were 1.09% and 1.72%, respectively.<sup>5</sup> Analysis of

186,750 AF patients from the same database indicated that males with a score of 1 had annual stroke rates ranging from 1.96% (95% CI, 1.56-2.42) to as high as 3.5% (95% CI, 3.27-3.74%).<sup>4</sup> Limitations in the predictive value of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score may arise from the fact that it only measures atherosclerotic risk factors and does not completely or directly reflect mechanisms of AF-related thromboembolism. Our study is the first to incorporate ECG-based markers of atrial remodeling (PWIs) into a clinically applicable risk score that outperformed the CHA<sub>2</sub>DS<sub>2</sub>-VASc score for prediction of AF-related stroke.

A large component of the improvement in stroke risk reclassification achieved by the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score was derived from correctly identifying low risk individuals. There is disagreement between the 2012 ESC<sup>3</sup> and the 2014 AHA/ACC/HRS<sup>2</sup> practice guidelines on the precise definition of low risk. Specifically, the 2012 ESC guidelines recommend anticoagulation for CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 whereas the ACC/AHA/HRS guidelines recommend anticoagulation for a score of 2 and equivocate at a score of 1. Use of the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score may address this clinical equipoise and aid in scenarios where the perceived risk/benefit ratio of anticoagulation therapy for prevention of AF-related stroke is unclear.

Considering PWA in stroke prediction has a practical advantage: it is automatically reported on the 12-lead ECG printout. Commercially available ECG recorders do not routinely report the other PWIs—PPWD, aIAB, aPTFV1. Calculation of these indices requires ECG digitalization and specialized analytic software to allow for precise measurements making them impractical for everyday clinical use, particularly in the primary care setting. In contrast, P-wave axis is a routine, automated index that is reported on the 12-lead ECG printout by most commercially available ECG recorders. Thus, the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score is a feasible score for use in the primary care setting.

PWA is also reproducible. Data on the short-term reliability and stability of P-wave indices are available from a subset of 63 ARIC participants. In this study, two 12-lead ECGs were obtained from participants during two study visits spaced two weeks apart. The absolute within-visit and between-visit difference of P-wave axis was 5.1 +/- 5.8 and 6.6+/-7.2 degrees, respectively. The reported intraclass correlation coefficient (ICC) was 0.78. P wave duration and P-wave terminal force were not as reliable with reported ICCs of 0.58 and 0.46, respectively.<sup>45</sup>

Notably, we found that stroke prediction by the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in people without AF but with abnormal PWA was comparable to people with AF. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been shown to have predictive value in the absence of detected AF.<sup>46</sup> It is unclear if individuals without AF will benefit from anticoagulation guided by CHA<sub>2</sub>DS<sub>2</sub>-VASc score given the relatively lower proportion of cardioembolism compared to people with AF. However, people without AF who have underlying prothrombotic atrial remodeling may benefit from anticoagulation as stroke in this population may be cardioembolic.<sup>15</sup> Thus, PWIs may have a role in stroke risk prediction and guiding anticoagulation therapy in people without AF in addition to enhancing stroke risk prediction in people with AF. If our findings are validated in other studies, further research should be conducted to determine whether

anticoagulation can reduce stroke risk in people without AF but with abnormal PWIs and other markers of atrial remodeling.

The principal strengths of our study include the use of 2 large community-based, racially diverse, prospective cohorts with long follow-up duration, extensive measurement of covariates, and rigorous physician-adjudication of stroke. Some limitations should be noted. First, AF was identified primarily from hospital discharge records. Thus, we were unable to account for subclinical AF or AF managed exclusively in ambulatory clinics. However, AF incidence in the ARIC study is consistent with other population-based studies and utilizing hospital discharge records for the purposes of AF detection has been previously validated.<sup>34,47-49</sup> Second, due to low number of stroke events in the MESA study, we used a composite endpoint of stroke/TIA for purposes of score validation. Third, anticoagulant use was not captured annually in MESA or ARIC (until 2006). Therefore, we likely were unable to exclude all participants on anticoagulants within 1 year of AF diagnosis. However, the use of anticoagulants for AF-related stroke prevention in the United States did not become widespread until after 2006, when risk stratification using the CHADS<sub>2</sub> score was recommended by practice guidelines.<sup>50</sup> Thus, we do not suspect that this will have significantly biased our results. Fourth, anticoagulants other than Coumadin were not captured in ARIC. However, novel oral anticoagulants were not introduced in United States markets until 2010, which is towards the end of our analysis period. Thus, aside from enoxaparin, Coumadin was likely the primary ambulatory anticoagulant used in the United States during our analysis period. Fifth, our analysis was based on PWIs obtained prior to AF diagnosis. Thus, the clinical utility of the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score is limited in patients with persistent or permanent AF who have no available sinus ECGs and unclear in patients with AF whose only available sinus rhythm ECGs were obtained after AF diagnosis. Finally, as inherent in all observational studies, although we adjusted for potential confounders in our analyses, we could not exclude residual confounding by imperfectly measured and unmeasured factors.

## Conclusion

In summary, aPWA was associated with an increased risk of AF-related ischemic stroke. When included with CHA<sub>2</sub>DS<sub>2</sub>-VASc score variables to create the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score, aPWA helped to improve prediction of AF-related ischemic stroke in 2 large prospective community-based cohorts. Further research is needed to clarify the biological correlates of aPWA as well its accuracy and precision in detecting a pro-thrombotic atrial substrate.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Clinical Perspective

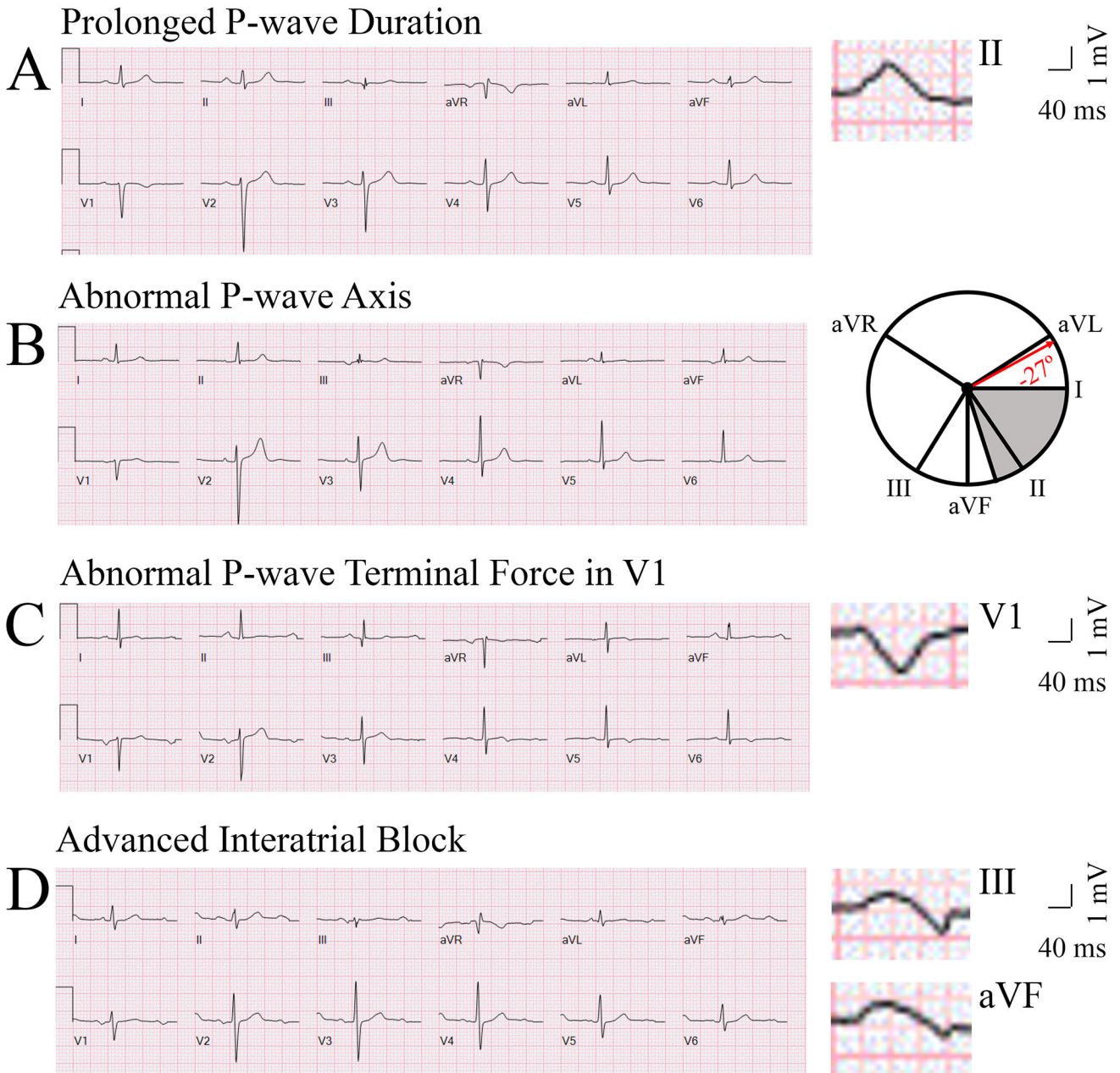
#### What Is New?

- Recent studies have highlighted limitations in the predictive value of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score
- We found that in people with atrial fibrillation, abnormal P-wave indices during sinus rhythm are associated with stroke independent of CHA<sub>2</sub>DS<sub>2</sub>-VASc variables
- We derived the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score—abnormal P-wave axis (2 points), age (1 point for 65-74, 2 points for 75), sex (1 point for female), heart failure (1 point), hypertension (1 point), diabetes (1 point), previous myocardial infarction/peripheral artery disease (1 point), prevalent stroke/transient ischemic attack (2 points)—for prediction of atrial fibrillation-related stroke using data from 2 large community-based prospective cohort studies.

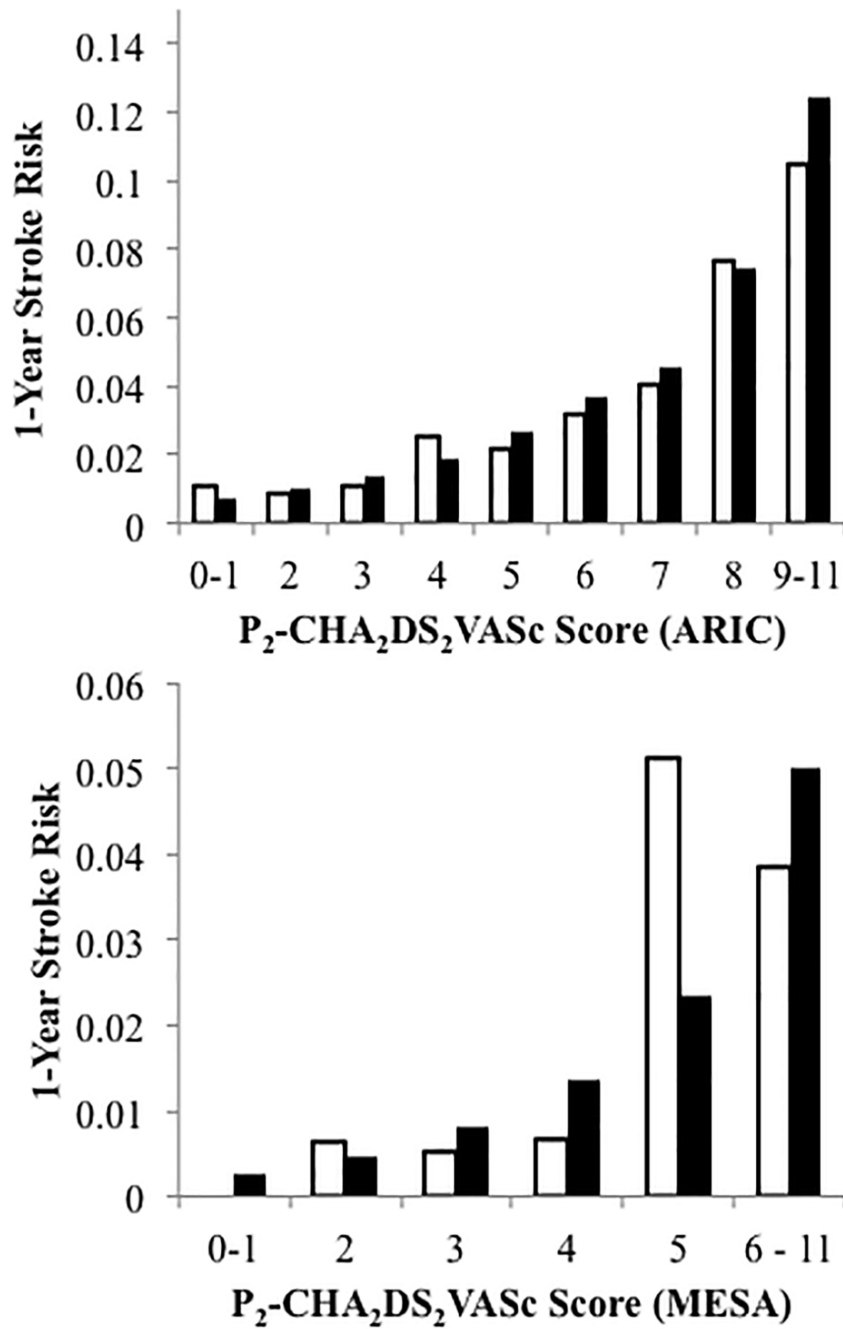
#### What Are the Clinical Implications?

- Use of markers reflecting left atrial remodeling, such as P-wave indices, are important for stroke risk prediction in people with atrial fibrillation
- If our findings are validated in other independent cohorts, use of the P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score may help improve atrial fibrillation-related stroke-risk assessment in the general population





**Figure 1.** Representative electrocardiogram tracings of abnormal P-wave indices—Prolonged P-wave duration (A), Abnormal P-wave axis (B), Abnormal P-wave terminal force in V1 (C), and Advanced Interatrial block (D). The maximal P-wave duration on panel A is seen in lead II (136 ms). The P-wave axis on panel B is  $-27^\circ$ . The grey area on the hexaxial reference system (lead I  $0^\circ$ , lead II  $60^\circ$ , aVF  $90^\circ$ , aVR  $-150^\circ$ , aVL  $-30^\circ$ ) in panel B represents normal P-wave axis ( $0$ - $75^\circ$ ). The P-wave terminal force on panel C is  $-9632 \mu\text{V}\cdot\text{ms}$  (amplitude  $-112 \mu\text{V}$ , duration 86 ms). The maximal P-wave duration on panel D is seen in lead III (136 ms). Biphasic P-waves can be seen in III and aVF.



**Figure 2.** Observed (white bars) and predicted (black bars) 1-year stroke risk for P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc score categories in the Atherosclerosis Risk in Communities (ARIC) Study and the Multi-Ethnic Study of Atherosclerosis (MESA).

**Table 1:**

Clinical Characteristics at time of Atrial Fibrillation diagnosis, Atherosclerosis Risk in Communities (ARIC) Study and Multi-Ethnic Study of Atherosclerosis (MESA)

Characteristic	ARIC			MESA		
	All N=2229	No Stroke N=2066	Stroke N=163	All N=700	No Stroke/TIA N=669	Stroke/TIA N=31
Age (Years)	73 +/- 8	73 +/- 8	69 +/- 8 <sup>‡</sup>	76 +/- 8	76 +/- 8	79 +/- 6 <sup>‡</sup>
Female Sex	1039 (47)	955 (46)	84 (52)	315 (45)	299 (45)	16 (52)
Diabetes	679 (30)	622 (30)	57 (35)	129 (18)	//	//
Hypertension	1661 (75)	1533 (74)	128 (79)	476 (68)	452 (68)	24 (77)
Previous MI	524 (24)	485 (23)	39 (24)	40 (6)	40 (6)	//
Heart Failure	840 (38)	774 (37)	66 (41)	55 (8)	//	//
PAD	205 (9.0)	181 (9)	24 (15) <sup>‡</sup>	15 (2)	15 (2)	//
Past Stroke/TIA	326 (15)	297 (14)	29 (18)	45 (6)	//	//
CHADS <sub>2</sub>	2.1 +/- 1.3	2.0 +/- 1.3	2.1 +/- 1.4	1.6 +/- 1.0	1.6 +/- 1.0	2.1 +/- 1.2 <sup>‡</sup>
CHA <sub>2</sub> DS <sub>2</sub> VASc	3.6 +/- 1.7	3.6 +/- 1.7	3.7 +/- 1.9	3.0 +/- 1.3	3.0 +/- 1.3	3.6 +/- 1.4 <sup>‡</sup>
Race						
Black	414 (19)	375 (18)	39 (24)	142 (20)	//	//
White	1815 (81)	1691 (82)	124 (76)	342 (49)	323 (48)	19 (61)
Chinese	§	§	§	94 (13)	92 (14)	//
Hispanic	§	§	§	122 (17)	115 (17)	//
aPWA	529 (24)	472 (23)	57 (35) <sup>‡</sup>	82 (12)	74 (11)	//
PWA (degrees)	51 +/- 26	51 +/- 26	49 +/- 30	50 +/- 29	50 +/- 28	40 +/- 47
PPWD	921 (41)	851 (41)	70 (43)	157 (22)	//	//
PWD (ms)	113 +/- 18	112 +/- 18	115 +/- 21	110 +/- 22	110 +/- 20	99 +/- 41
aPTFV <sub>1</sub>	670 (30)	617 (30)	53 (33)	160 (23)	//	//
PTFV <sub>1</sub> (µV * ms)	2492 +/- 2240	2471 +/- 2218	2762 +/- 2491	2675 +/- 2205	2704 +/- 2222	2059 +/- 1707
aIAB	99 (4.4)	81 (3.9)	18 (11) <sup>‡</sup>	§	§	§
Current Smoker	465 (21)	434 (21)	31(19)	53 (7)	//	//
COPD	248 (11)	224 (11)	24 (15)	34 (5)	//	//

\* Data are presented as n(%) or mean +/- standard deviation.

<sup>‡</sup>P-value <0.05 from  $\chi^2$  tests or *t* tests for comparisons of those who did or did not experience an incident or recurrent stroke or TIA (MESA) during follow-up

<sup>‡‡</sup>P-value <0.01 from  $\chi^2$  tests or *t* tests for comparisons of those who did or did not experience an incident or recurrent stroke or TIA (MESA) during follow-up

§ indicates variable unavailable in ARIC/MESA database

// indicates suppressed due to small cell size in accordance with the Centers for Medicare & Medicaid sparse cell suppression policy.

Abbreviations: Myocardial Infarction (MI), Peripheral Arterial Disease (PAD), Transient Ischemic Attack (TIA), Abnormal P-wave Axis (aPWA), Prolonged P-wave Duration (PPWD), Abnormal P-wave Terminal Force in V1 (aPTFV1), Advanced Interatrial Block (aIAB)

**Table 2.**

Association of P-wave Indices with Ischemic Stroke in Participants with Atrial Fibrillation, Atherosclerosis Risk in Communities (ARIC) Study

Variable	Model 1*		Model 2*	
	HR (95% CI)	P	HR (95% CI)	P
Abnormal P-wave Axis	1.92 (1.40-2.66)	<0.0001	1.88 (1.36-2.61)	0.0001
Prolonged P-wave Duration	1.04 (0.76-1.42)	0.82	0.97 (0.71-1.33)	0.83
Abnormal P-wave Terminal Force in V1	1.27 (0.91-1.76)	0.15	1.08 (0.77-1.51)	0.67
Advanced Interatrial Block	3.22 (1.98-5.27)	<0.0001	2.93 (1.78-4.81)	<0.0001
Age	1.01 (0.98-1.03)	0.67	0.99 (0.97-1.02)	0.59
Male sex	0.79 (0.58-1.07)	0.13	0.90 (0.65-1.23)	0.49
Stroke/Transient Ischemic Attack	1.57 (1.05-2.35)	0.03	1.40 (0.93-2.10)	0.10
Heart Failure	1.66 (1.21-2.28)	0.002	1.48 (1.07-2.05)	0.02
Hypertension	2.00 (1.37-2.92)	0.0003	1.80 (1.22-2.66)	0.003
Diabetes	1.72 (1.24-2.38)	0.001	1.49 (1.07-2.08)	0.02
Myocardial Infarction	1.20 (0.84-1.72)	0.32	1.01 (0.69-1.46)	0.97
Peripheral Arterial Disease	1.94 (1.26-2.99)	0.003	1.89 (1.22-2.93)	0.004

\* Model 1: Unadjusted Cox proportional hazards model. Model 2: Cox proportional hazards model adjusted for remaining CHA<sub>2</sub>DS<sub>2</sub>VASc variables of age, sex, stroke/transient ischemic attack, heart failure, hypertension, diabetes, myocardial infarction and peripheral artery disease

Abbreviations: Confidence Interval (CI), Hazard Ratio (HR)

**Table 3.**

Performance of Predictive Models for 1-Year Ischemic Stroke Risk in Participants with Atrial Fibrillation, Atherosclerosis Risk in Communities (ARIC) Study

Model <sup>‡</sup>	C-statistic (95% CI)	$\chi^2$ (P-value) <sup>*</sup>	NRI (95% CI) <sup>‡</sup>	Relative IDI (95% CI)
A	0.659 (0.574, 0.743)	4.7 (0.86)		
B	0.738 (0.663, 0.814)	10.4 (0.32)	0.266 (0.084, 0.442)	0.773 (0.474, 1.131)
C	0.659 (0.575, 0.743)	4.7 (0.86)	0.001 (−0.001, 0.002)	0.001 (−0.001, 0.002)
D	0.668 (0.586, 0.750)	3.1 (0.96)	−0.052 (−0.151, 0.026)	0.067 (−0.010, 0.138)
E	0.666 (0.581, 0.751)	8.5 (0.48)	0.072 (−0.040, 0.184)	0.239 (0.050, 0.498)
F	0.749 (0.678, 0.820)	5.1 (0.82)	0.374 (0.215, 0.521)	1.04 (0.652, 1.52)

\* Hosmer-Lemeshow chi-squared statistic

<sup>‡</sup> For categorical NRI, we used the following categories for 1-year stroke risk: <1%, 1-<2%, and ≥2%. (Based on 47 cases)

<sup>‡</sup> Model A: age, sex, stroke/transient ischemic attack, heart failure, hypertension, diabetes, myocardial infarction and peripheral artery disease

Model B: Model A + abnormal P-wave axis

Model C: Model A + prolonged P-wave duration

Model D: Model A + abnormal P-wave terminal force in V1

Model E: Model A + advanced inter-atrial block

Model F: Model A + abnormal P-wave axis, prolonged P-wave duration, abnormal P-wave terminal force in V1, and advanced inter-atrial block

Abbreviations: Category-based Net Reclassification Index (NRI), Integrative Discrimination Improvement (IDI)

**Table 4.**

Performance of P<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>VASc score for 1-Year Ischemic Stroke Risk in Participants with Atrial Fibrillation, Atherosclerosis Risk in Communities (ARIC) Study and Multi-Ethnic Study of Atherosclerosis (MESA)

		C-statistic (95% CI)	NRI (95% CI)*	Relative IDI (95% CI)
ARIC	CHA <sub>2</sub> DS <sub>2</sub> VASc <sup>†</sup>	0.60 (0.51-0.69)		
	P <sub>2</sub> -CHA <sub>2</sub> DS <sub>2</sub> VASc <sup>‡</sup>	0.67 (0.60-0.75)	0.25 (0.13, 0.39)	1.19 (0.96, 1.44)
MESA	CHA <sub>2</sub> DS <sub>2</sub> VASc <sup>†</sup>	0.68 (0.52-0.84)		
	P <sub>2</sub> -CHA <sub>2</sub> DS <sub>2</sub> VASc <sup>‡</sup>	0.75 (0.60-0.91)	0.51 (0.18, 0.86)	0.82 (0.36, 1.39)

\* For categorical NRI, we used the following categories for stroke risk: <1%, 1-<2%, and ≥2%

<sup>†</sup> age (1 point for >65, 2 points for >75), sex (1 point for female), Heart Failure (1 point), hypertension (1 point), diabetes (1 point), previous myocardial infarction/peripheral artery disease (1 point), prevalent stroke/transient ischemic attack (2 points)

<sup>‡</sup>CHA<sub>2</sub>DS<sub>2</sub>VASc + abnormal P-wave axis (2 points)

Abbreviations: Category-based Net Reclassification Improvement (NRI), Integrated Discrimination Improvement (IDI)

**Table 5.**

Improvement in Reclassification of 1-Year Stroke Risk in the Atherosclerosis Risk in Communities (ARIC) study.

		P <sub>2</sub> -CHA <sub>2</sub> DS <sub>2</sub> VASc <sup>§</sup>				P <sub>2</sub> -CHA <sub>2</sub> DS <sub>2</sub> VASc <sup>§</sup>				
		<1%	1-2%	>2%	Total	<1%	1-2%	>2%	Total	
CHA <sub>2</sub> DS <sub>2</sub> VASc <sup>‡</sup>	<1%	19	3*	0*	22	<1%	290	22 <sup>‡</sup>	0 <sup>‡</sup>	312
	1-2%	3 <sup>‡</sup>	9	4*	16	1-2%	167*	686	94 <sup>‡</sup>	947
	>2%	0 <sup>‡</sup>	0 <sup>‡</sup>	9	9	>2%	0*	290*	633	923
	Total	22	12	13	47	Total	457	998	727	2182
Participants with stroke in 1 year					Participants without stroke in 1 year					

\* Favorable reclassification

<sup>‡</sup> Unfavorable reclassification

<sup>‡</sup> age (1 point for >65, 2 points for >75), sex (1 point for female), Heart Failure (1 point), hypertension (1 point), diabetes (1 point), previous myocardial infarction/peripheral artery disease (1 point), prevalent stroke/transient ischemic attack (2 points)

<sup>§</sup>CHA<sub>2</sub>DS<sub>2</sub>VASc + abnormal P-wave axis (2 points)

Abbreviations: Category-based Net Reclassification Index (NRI), Relative Integrative Discrimination Improvement (IDI), TIA (transient ischemic attack)

**Table 6:**

**Association Between Structural Heart Disease and Abnormal P-wave Indices**

Structural Heart Disease Variable*	Model <sup>†</sup>	aPWA	PPWD	aPTFVI	aIAB
Left atrial volume index >34 ml/m <sup>2</sup>	Model a	1.74 (1.50-2.01) <sup>§</sup>	2.16 (1.86-2.50) <sup>§</sup>	1.57 (1.36-1.82) <sup>§</sup>	2.18 (1.61-2.97) <sup>§</sup>
	Model b	1.69 (1.46-1.96) <sup>§</sup>	1.93 (1.66-2.24) <sup>§</sup>	1.49 (1.29-1.74) <sup>§</sup>	1.79 (1.31-2.44) <sup>§</sup>
Left ventricular mass index >115 g/m <sup>2</sup> for men, >95 g/m <sup>2</sup> for women	Model a	1.20 (1.01-1.41) <sup>‡</sup>	1.94 (1.65-2.29) <sup>§</sup>	1.69 (1.43-1.99) <sup>§</sup>	2.35 (1.70-3.26) <sup>§</sup>
	Model b	1.19 (1.01-1.41) <sup>‡</sup>	2.06 (1.74-2.43) <sup>§</sup>	1.67 (1.42-1.98) <sup>§</sup>	2.39 (1.71-3.33) <sup>§</sup>
Left ventricular end diastolic diameter >5.8 cm for men, >5.2 cm for women	Model a	1.43 (1.03-1.98) <sup>‡</sup>	2.45 (1.75-3.42) <sup>§</sup>	1.72 (1.24-2.38) <sup>§</sup>	2.26 (1.23-4.14) <sup>§</sup>
	Model b	1.43 (1.03-1.99) <sup>‡</sup>	2.75 (1.96-3.87) <sup>§</sup>	1.75 (1.26-2.43) <sup>§</sup>	2.71 (1.46-5.01) <sup>§</sup>
Left ventricular ejection fraction < 52% for men, <54% for female	Model a	1.28 (1.05-1.57) <sup>‡</sup>	1.34 (1.10-1.64) <sup>§</sup>	1.46 (1.19-1.79) <sup>§</sup>	1.21 (0.75-1.96) <sup>§</sup>
	Model b	1.20 (0.98-1.48)	1.20 (0.98-1.48)	1.33 (1.08-1.63) <sup>§</sup>	1.08 (0.66-1.76) <sup>§</sup>
NT-Pro BNP pg/ml, difference (95% CI)	Model a	203.6 (156.1 to 251.2) <sup>§</sup>	92.2 (45.6 to 138.9) <sup>§</sup>	52.0 (3.51 to 100.5) <sup>‡</sup>	279 (160 to 399) <sup>§</sup>
	Model b	197.1 (149.7 to 244.5) <sup>§</sup>	67.8 (20.6 to 115.0) <sup>§</sup>	38.9 (-9.68 to 87.5) <sup>§</sup>	230 (111 to 350) <sup>§</sup>
LAGLS %, difference (95% CI)	Model a	-1.65 (0.87, 2.43) <sup>§</sup>	-1.10 (0.33, 1.86) <sup>§</sup>	0.15 (-0.94, 0.63) <sup>§</sup>	-1.28 (-0.84, 3.41) <sup>§</sup>
	Model b	-1.40 (0.63, 2.16) <sup>§</sup>	-0.53 (-0.25, 1.30) <sup>§</sup>	0.46 (-1.23, 0.31) <sup>§</sup>	-0.38 (-1.73, 2.49) <sup>§</sup>
LAEF %, difference (95% CI)	Model a	-3.23 (-4.69, -1.78) <sup>§</sup>	-2.29 (-3.72, -0.85) <sup>§</sup>	-0.49 (-1.95, 0.97) <sup>§</sup>	-3.18 (-7.15, 0.80) <sup>§</sup>
	Model b	-2.85 (-4.29, -1.40) <sup>§</sup>	-1.57 (-3.03, -0.10) <sup>‡</sup>	-0.03 (-1.48, 1.42) <sup>§</sup>	-1.97 (-5.95, 2.00) <sup>§</sup>

\* Data displayed as odds ratio (95% CI) unless otherwise stated. Difference is the difference in number of units (pg/ml for NT-Pro BNP and % for LAGLS and LAEF) between participants with an abnormal PWI and participants with a normal PWI. For example, compared to participants with normal PWA, those with abnormal PWA have higher NT-pro BNP, and lower LAGLS and LVEF

<sup>†</sup> Logistic regression models. Model a is unadjusted. Model b is adjusted for age, sex, and race.

<sup>‡</sup> P-value < 0.05

<sup>§</sup> P-value < 0.01

Abbreviations: Abnormal P-wave axis (aPWA), Prolonged P-wave duration (PPWD), Abnormal P-wave terminal force in VI (aPTFVI), Advanced interatrial block (aIAB), N-terminal pro b-type natriuretic peptide (NT-Pro BNP), Left atrial global longitudinal strain (L-AGLS), Left atrial emptying fraction (L-AEF)