
Despite thorough diagnostic evaluations to determine stroke cause, ≈1 in 3 strokes remain cryptogenic. Atrial fibrillation (AF) has long been established as a risk factor for stroke; however, recent evidence suggests that other atrial derangements may also play a role. In this study, Kamel et al conducted a longitudinal, population-based study of participants aged 45 to 64 years without clinically apparent AF at baseline (n=14,542) enrolled in the Atherosclerosis Risk in Communities Study in 1987 to 1989, and followed up every 3 years thereafter, to evaluate whether ECG-defined atrial abnormality (abnormally increased P-wave terminal force in lead V\textsubscript{1} [PTFV\textsubscript{1}] >4000 uV x ms) was associated with increased risk of nonlacunar stroke. They found that atrial abnormality was an independent risk factor for nonlacunar strokes, suggesting that it is a cardiogenic source.

Over a median follow-up of 22 years (interquartile range, 19–23 years), 904 participants (6.2%) experienced a definite or probable ischemic stroke. Stroke incidence was higher among those with left atrial abnormality (incidence rate per 1000 person-years, 6.3; 95% confidence interval [CI], 5.4–7.4) than those without (2.9; 95% CI, 2.7–3.1; P<0.001). Left atrial abnormality was associated with incident ischemic stroke (hazard ratio, 1.33; 95% CI, 1.11–1.59), after adjusting for potential confounders and incident AF. This association was observed among those with nonlacunar strokes (hazard ratio, 1.49; 95% CI, 1.07–2.07), but was not observed in those with lacunar strokes (hazard ratio, 0.89; 95% CI, 0.57–1.40). No interactions were observed across age, sex, or race.

Although the authors have previously described the association between ECG-defined atrial abnormality and incident stroke, this was the first study to show that the association is only present in nonlacunar strokes. The study’s strengths include the large sample size, long-term rigorous follow-up, with ECG and review of hospital discharge records, systematic classification of stroke subtypes using data abstraction, a software program, and independent physician adjudication, and robust validation of the automated PTFV\textsubscript{1} measurements in a subset of participants. The study’s main limitation is the lack of continuous cardiac monitoring to rule out subclinical AF as a mediator in the relationship between left atrial abnormality and stroke. Nevertheless, this study suggests that ECG, a noninvasive, widely available, automated, and cheap tool, can be helpful in identifying an underlying cardioembolic source of strokes among individuals who would have heretofore been considered cryptogenic. Further research is needed to determine the optimal management of individuals with left atrial abnormalities in the absence of AF.

Previously, the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) trial showed that the rate of AF detection among individuals with cryptogenic stroke or transient ischemic attack is 30% within 3 years after the index event. Failure to diagnose AF as the underlying cause of stroke or transient ischemic attack may result in suboptimal antithrombotic therapy. This study suggested a post hoc analysis of the CRYSTAL AF trial to identify potential predictors of AF in individuals with cryptogenic stroke/transient ischemic attack, to determine who may benefit from long-term monitoring with an insertable cardiac monitor. CRYSTAL AF was a prospective, parallel, randomized trial comparing time with AF detection through continuous monitoring with an insertable cardiac monitor versus routine follow-up. In this study, they analyzed individuals assigned to the intervention arm (n=221). The authors performed cox regression models to determine potential predictors of AF. Covariates included age, sex, race, body mass index, type and severity of index ischemic event, congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke or transient ischemic accident (CHADS\textsubscript{2} score, diabetes mellitus, hypertension, congestive heart failure, PR interval, patent foramen ovale, and premature atrial contractions.

Among 221 individuals, AF was detected in 29 patients within 12 months and 42 patients at 36 months. The rate of AF detection was higher in participants who were older, had diabetes mellitus, had longer PR intervals, and had a greater number of premature atrial contractions on the screening Holter or telemetry test. After multivariate analysis, age (hazard ratio per decade 1.9 [1.3–2.8]; P=0.0009) and PR interval (hazard ratio, 1.3 [1.2–1.4]; P=0.0001) remained significant, with moderate predictive ability to determine
which cryptogenic stroke/transient ischemic attack patients subsequently developed AF (receiver operating characteristic curve of 0.78). Significant interaction was found between baseline use of PR interval-prolonging medications and PR interval on the likelihood of AF detection ($P=0.009$).

This study helps target the population that would have a higher yield for long-term monitoring for AF; however, the predictive model proposed was limited by suboptimal discriminative capacity and lack of inclusion of potential biomarker risk factors. The study is further limited by the small sample size and homogenous racial composition (88% white), limiting generalizability. Nevertheless, the study highlights the need for future studies to better select those who may benefit from long-term cardiac monitoring to guide therapy for subclinical AF.
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