Prognostications of Fibrillations

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Post-hospital evaluation for the cause of ischemic stroke has gained increased attention in the last decade, particularly the search for paroxysmal atrial fibrillation. Initial studies of Holter monitoring documented rates of atrial fibrillation of ≈5% or 1 in 20 patients.[1] Further, prolonged monitoring for as long as 1 week appeared to increase detection rates, with a range of 5.7% to 7.7%.[1] When devices became available to increase monitoring ≤21 days, detection rates over 20% were documented.[2] A 2014 systematic review of detection of atrial fibrillation after stroke found an overall rate of detection of 11.5%; however, detection rates varied based on patient selection, device selected, timing of device placement, duration of monitoring, and diagnostic criteria for paroxysmal atrial fibrillation.[3] Two randomized trials of prolonged monitoring after ischemic stroke, both published after the 2014 systematic review, found higher rates of atrial fibrillation with longer duration of monitoring. The 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) trial found a 90-day rate of 16.1% in patients undergoing 30 consecutive days of monitoring versus 3.2% of patients undergoing 24 hours of monitoring.[4] In the Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial, the 6-month rate was 8.9% in patients who had an implanted cardiac monitor versus 1.4% in patients who had routine evaluation. The lower rates of detection in CRYSTAL-AF compared with EMBRACE may have been attributable to a younger cohort of patients being evaluated; the mean age was 61.5 years in CRYSTAL-AF and 72.9 years in EMBRACE. In both trials, there was incremental detection of atrial fibrillation episodes over time, that is, new atrial fibrillation was identified continuously over time in both studies.[5] EMBRACE followed a small number of patients out to 3 years; the rate of atrial fibrillation was 30% in those with the implanted cardiac monitor and 3% in those who had routine monitoring.

In most studies, the minimum duration of atrial fibrillation that is considered clinically important is 30 seconds and a criterion for meeting an end point. According to the American Heart Association and American College of Cardiology guidelines, the definition of paroxysmal atrial fibrillation is an episode lasting <7 days;[6] however, the minimum duration that is clinically important has not been absolutely defined. By convention, a continuous rhythm of 30 seconds has been considered clinically important though AHA guidelines from 2006 acknowledged that "episodes of atrial fibrillation briefer than 30 seconds may be important in certain clinical situations involving symptomatic patients, preexcitation or in assessing the effectiveness of therapeutic interventions."[7] The 2014 guidelines do not describe a minimum duration.[6] Future research will be required to determine whether episodes <30 seconds are associated with a greater stroke risk in affected individuals.

Concomitant with the interest in monitoring for atrial fibrillation poststroke, there has also been interest in predicting which patients are most likely to have atrial fibrillation during outpatient evaluation. A potential goal of this work would be to identify those at highest risk and target monitoring and treatment strategies. Risk scores have been proposed to identify these patients; however, these scoring systems have not been widely adopted because of relatively low sensitivities and specificities.[8–10] In this issue of Stroke, Favilla and colleagues sought to determine clinical and paraclinical features that best predicted the risk of future detection of atrial fibrillation, defined, in contrast to EMBRACE and CRSYTAL-AF, as episodes of any duration.[11] The overall detection rate was 14%; of these patients, 42% had episodes lasting <30 seconds. The mean age in this cohort was 62.9 years. In the multivariable analysis, age >60 years and prior cortical or cerebellar infarction were predictors of detecting atrial fibrillation. When both features were present, 33% of these patients were later identified as having atrial fibrillation. When neither feature was present, 4% were later identified as having atrial fibrillation. Notably, factors that had previously been associated with atrial fibrillation in other studies, such as atrial size, were not significantly associated with atrial fibrillation in this study. Though these findings require validation in an independent cohort, they are nonetheless intriguing and may represent a tool in settings with limited resources. A 2010 United States–based cost-effectiveness study of outpatient cardiac monitoring in patients with cryptogenic stroke suggested that even with detection rates as low as 4%, the cost-utility ratio was $13 000 per quality-adjusted life-year gained.[12] Interventions with cost-utility ratios <$50 000 per quality-adjusted life-year gained are generally considered worthwhile and argue in favor of universal application of outpatient cardiac monitoring in patients with cryptogenic stroke. Therefore, in settings which are not as resource-constrained, a prognostication tool may not be as valuable.

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Whether atrial fibrillation detected after ischemic stroke is the cause or result of the event or simply an event that occurred independently requires further study. Some reports suggest that infarctions in certain brain locations, such as the insula, increase the chance of finding atrial fibrillation;[13,14] however, that was not the case in the current study by Favilla and colleagues nor in the EMBRACE trial.[15] Further analysis of the CRYSTAL-AF data is ongoing.[16] Having data on the rate of atrial fibrillation in age and sex-matched controls without any history of stroke, those with intracerebral hemorrhage, and those with other nonstroke brain injury might shed light on whether atrial fibrillation detected after ischemic stroke truly occurs at an increased rate.

An important question is the therapeutic consequence once occult paroxysmal atrial fibrillation has been detected in patients with stroke. Certainly, other potential causes of stroke should be carefully evaluated in the absence of a direct cause–effect relationship. Moreover, oral anticoagulation with either vitamin K antagonists or non-vitamin K oral anticoagulants is recommended to prevent thromboembolism among patients with clinically apparent nonvalvular atrial fibrillation and a CHA_2DS_2-VASc (combined stroke risk score: congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke/transient ischemic attack, vascular disease, sex) score of >1.[17] However, it remains to be shown whether long-term oral anticoagulation provides a reasonable balance of safety and efficacy among patients with cryptogenic stroke and occult paroxysmal atrial fibrillation, particularly among young patients (<60 years of age) with structurally normal hearts. In this context, ongoing trials, such as RESPECT-ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source)[18] and NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source),[19] are randomizing patients with cryptogenic stroke to aspirin or one of the newer oral anticoagulants. If indeed 10% to 20% of these patients have underlying paroxysmal atrial fibrillation as the cause of their stroke and there is a statistically significant advantage to anticoagulation over antiplatelet therapy in this group of patients, prediction models and long-term cardiac monitoring may become a moot point. Nevertheless, patients with cryptogenic stroke who continue to have strokes despite anticoagulation may be those who are targeted for long-term monitoring. If paroxysmal atrial fibrillation is identified in patients refractory to anticoagulation, other methods of treating atrial fibrillation, such as atrial appendage occlusion, atrial appendage ligation, and pulmonary artery ablation, may be considered.

In summary, atrial fibrillation is increasingly being identified in patients with cryptogenic stroke. Longer duration of cardiac monitoring results in higher detection rates. Whether all the episodes detected, particularly brief ones, are clinically relevant requires further study. Further, whether episodes of atrial fibrillation detected after stroke is a result rather than the cause of stroke also merits additional investigation. Clinical prognostication tools may be beneficial, especially in settings where resources, such as cardiac outpatient monitors, are limited. Ongoing trials of non-vitamin K oral anticoagulants in the setting of cryptogenic stroke are of particular interest; if positive, that might limit the need for outpatient cardiac monitoring or prognostication tools.

Disclosures

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