Delayed Detection of Atrial Fibrillation after Ischemic Stroke

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Background: Detection of atrial fibrillation (AF) after ischemic stroke is important because anticoagulation is indicated to reduce the risk of recurrent stroke. However, no consensus exists about the optimum method for detecting underlying paroxysmal AF not apparent on presentation with stroke. The aim of this study was to characterize the rate, timing, and predictors of delayed detection of AF after stroke. *Methods:* The Virtual International Stroke Trials Archive provided data from 3464 patients in the placebo arms of 4 clinical trials of therapies for acute ischemic stroke. Patients who had AF by history or on the baseline electrocardiogram were excluded. Electrocardiograms were obtained routinely and as clinically indicated. The time to detection of AF was evaluated using Kaplan-Meier survival statistics. Cox proportional hazards analysis was used to evaluate risk factors for AF. *Results:* Among 2504 qualifying patients, AF was detected in 174 (6.9%; 95% confidence interval [CI] 6.0%-8.0%). In 68% of patients, AF was detected more than 48 hours after presentation. Detection of AF was associated with increasing age (hazard ratio [HR] 1.6/decade; 95% CI 1.4-1.9; $P < .005$), female sex (HR 1.7; CI 1.2-2.4; $P < .005$), congestive heart failure (HR 1.9; CI 1.1-3.4; $P = .02$), and the absence of hypertension (HR 1.6; CI 1.1-2.2; $P = .01$). *Conclusions:* Delayed detection of AF was common in this large cohort of patients carefully monitored after ischemic stroke. Current methods of screening may fail to detect underlying paroxysmal AF in a substantial proportion of patients. **Key Words:** Stroke prevention—atrial fibrillation—diagnostic methods—cardiac embolism—electrocardiography.

The cause of ischemic stroke remains unknown in approximately one third of patients.[1,2] In one series, two thirds of cryptogenic strokes appeared embolic, but extensive investigation failed to reveal a clear source.[3] Some proportion of these cryptogenic strokes may be caused by undetected atrial fibrillation (AF), because asymptomatic and paroxysmal AF is common[4] and increases the risk of stroke as much as chronic AF.[5-7] As a result, clinical guidelines recommend at least 24 hours of cardiac monitoring after stroke as an opportunity to make a delayed diagnosis of paroxysmal AF[6] and, in practice, patients are commonly admitted to telemetry beds for 24 to 48 hours of continuous electrocardiography (ECG).[8] However, there is no agreement on the optimum type and duration of monitoring.[6] Despite this uncertainty, detection of AF is important, because treatment with anticoagulation decreases the annual risk of recurrent stroke by two thirds.[9]

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Several studies have used 24 to 72 hours of Holter monitoring to look for previously undiagnosed AF in patients with ischemic stroke.[10-16] A recent systematic review of these studies indicated that the yield of Holter monitoring is 4.6%.[17] Three studies have examined the yield of longer periods of monitoring with cardiac event monitors; these studies detected AF in 5.3% to 7.7% of patients who had negative findings on Holter studies.[11-13]

These 3 studies suggest that prolonging the duration of monitoring beyond the standard 24 or 48 hours detects more cases of paroxysmal AF, but such prolonged monitoring is not widely accepted, perhaps because of the small size of these studies. The largest involved 88 patients[11] and, therefore, the results of these studies may be subject to the play of chance. It would be ideal to replicate their findings in a large prospective cohort study involving several weeks of monitoring for AF in patients with stroke. Unfortunately, no such data exist. However, randomized trials of therapies for acute stroke enroll and closely follow up large numbers of patients for several months, and reliably record adverse events such as the development of new AF. Although limited by the lack of uniform cardiac monitoring, such trials can provide a minimum estimate of the rate of AF in this population and validation of the prospective studies described above. Therefore, we examined the delayed detection of AF up to 3 months after ischemic stroke in a large cohort of patients followed up closely in 4 randomized trials.

Methods

Design

We retrospectively studied the rate, timing, and predictors of delayed detection of AF in a cohort of patients with ischemic stroke. To take advantage of the close monitoring and follow-up required in randomized clinical trials, we examined data from patients in the placebo arms of 4 trials: Clomethiazole Acute Stroke Study in Ischemic Stroke (CLASS-I), NXY-059 for Acute Ischemic Stroke (SAINT-I), NXY-059 for the Treatment of Acute Ischemic Stroke (SAINT-II), and Effects of Repinotan in Patients with Acute Ischemic Stroke (mRECT). Data from these trials were obtained from the Virtual International Stroke Trials Archive. Details of CLASS-I, SAINT-I, SAINT-II, and Virtual International Stroke Trials Archive have been published elsewhere.[18-21] The design and results of mRECT were presented in abstract form at the XIV European Stroke Conference.[22] Briefly, all 4 studies were randomized, double-blinded, placebo-controlled trials of neuroprotective agents in acute ischemic stroke. All trials were approved by the institutional review boards at the participating institutions. Our analysis was certified as exempt from review by our institutional review board because the data had been collected for other purposes and lacked patient identifying information.

Patients

All 4 trials enrolled adult patients with ischemic stroke within 12 hours of the onset of symptoms. CLASS-I excluded patients with severe systemic illness. mRECT excluded patients with very large hemispheric strokes, lacunar strokes, or significant cardiac disease. We excluded patients with a known history of AF or AF on their baseline ECG from our analysis.

Measurements

Predictor variables in our analysis were the patients' demographic characteristics; the specific trial they were enrolled in; their systolic and diastolic blood pressure readings at baseline, 24 hours, and 7 days; and the presence of hypertension, coronary artery disease, congestive heart failure, diabetes mellitus, and a history of myocardial infarction. The primary outcome was a diagnosis of AF, which was ascertained by ECG and recorded as an adverse event or as an indication for therapy specific to AF. Patients were followed up for 90 days in all 4 trials. In all trials, ECGs were obtained as clinically indicated, and continuous ECG was used at the discretion of the treating physician. ECGs were mandated in SAINT-I and SAINT-II at baseline, 24 hours, and 72 hours; in mRECT at baseline, 24 hours, and 48 hours; and in CLASS-I at baseline.

Statistical Analysis

Descriptive statistics and exact binomial confidence interval (CI) were used to calculate the percentage of patients in whom AF was detected. The rate of detection of AF was calculated per 1000 person-years. The time to detection of AF was evaluated using Kaplan-Meier survival statistics in unadjusted analyses. Follow-up was censored at the end of the study period (90 days) or at the time of death. Cox proportional hazards analysis was used to identify independent predictors of detection of AF, beginning with all covariates and eliminating in a stepwise fashion variables that were not significant ($P > .10$). The proportionality assumption was checked by plotting log-minus-log plots of each covariate included in the final model. Multivariable analyses were performed with and without imputing missing values. All analyses were performed with software (Stata, Version 10, Statacorp, College Station, TX). The first author (H.K.) vouches for the integrity of the data and the accuracy of the data analysis.

Results

Data were obtained from 3464 patients; 960 had a history of AF or AF on their baseline ECG and were excluded. The 2504 patients who qualified for our analysis had a high prevalence of cardiovascular risk factors (Table 1). AF was detected in 174 (6.9% [95% CI 6.0%-8.0%]) patients. The rate of detection of AF was 301 per 1000 person-years (95% CI 260-349/1000 person-years). Overall, 2286