Electrocardiographic Monitoring for Detecting Atrial Fibrillation after Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis

Running title: Dussault et al.; Electrocardiographic monitoring after stroke

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Journal Subject Codes: [33] Other diagnostic testing, [53] Embolic stroke
Abstract:

**Background** - Atrial fibrillation (AF) is a major cause of stroke. While standard investigations following an event include electrocardiographic (ECG) monitoring, the optimal duration to detect AF is unclear. We performed a systematic review and meta-analysis to determine whether the duration of ECG-monitoring following an ischemic event is related to the detection of AF.

**Methods and Results** - Prospective studies that reported the proportion of new AF diagnosed using ECG-monitoring for greater than 12 hours in patients with recent stroke or TIA were analyzed. Studies were excluded if the stroke was hemorrhagic or AF was previously diagnosed. A total of 31 articles met inclusion criteria. Longer duration of monitoring was associated with an increased detection of AF when examining monitoring time as a continuous variable (p<0.001 for meta-regression analysis). When dichotomizing studies based on monitoring duration, studies with monitoring lasting ≤ 72 hours detected AF in 5.1% whereas monitoring lasting ≥ 7 days detected AF in 15%. The proportion of new diagnosis increased to 29.15% with extended monitoring for 3 months. Significant heterogeneity within studies was detected for both groups (≤72 hours: \( I^2 = 91.3\% \); ≥7 days: \( I^2 = 75.8\) ). When assessing the odds of AF detection in the 3 randomized controlled trial, there was a 7.26 increased odds of AF with long-term monitoring (95% CI [3.99-12.83]; p-value <0.001).

**Conclusions** - Longer duration of electrocardiographic monitoring after cryptogenic stroke is associated with a greater detection of AF. Future investigation is needed to determine the optimal duration of long-term monitoring.

**Key words:** atrial fibrillation, meta-analysis, electrocardiography, stroke
Introduction

Stroke is a leading cause of disability and is the second most common cause of death worldwide. Cardio-embolism from atrial fibrillation (AF) is a major source of ischemic stroke, second only to cerebrovascular atherosclerotic disease. While significant attention has focused on the treatment and prevention of AF, determining whether paroxysmal AF is the cause of a cryptogenic ischemic stroke or transient ischemic attack (TIA) remains a challenge. The diagnosis of new AF after stroke or TIA occurs in 10% of people, while an additional 11% of new AF can be detected with 30 days of continuous electrocardiographic (ECG) monitoring. However, detecting paroxysmal AF by ECG monitoring can be difficult since patients may be asymptomatic or have long periods between episodes. Although the American Heart and Stroke Associations have recently updated their recommendations to support the use of prolonged AF monitoring for 30 days after cryptogenic stroke (Class IIa; level of evidence C), further evidence is needed to support this recommendation.

Therefore, based on the PRISMA reporting guidelines, this systematic review and meta-analysis was conducted to evaluate the relationship between the duration of ECG monitoring after cryptogenic stroke or TIA and the detection of new AF.

Methods

Eligibility Criteria

Randomized control trials (RCT) and prospective observational studies in English up until August 4, 2014 were considered. Any study published prior to August 4, 2014 was eligible for inclusion and the earliest identified study was published in November 1985. Inclusion criteria were patients with newly diagnosed ischemic stroke and/or TIA who underwent ECG monitoring for a minimum of 12 hours. Studies with patients having a prior history of AF or diagnosis of
hemorrhagic stroke were excluded from the analysis. Additionally, abstracts and retrospective studies were excluded.

**Information Sources, Search Strategy, and Data Extraction**

Our strategy (Appendix Table 1) involved a detailed search of PubMED/MEDLINE, Embase, Cochrane library, clinical trials registry, relevant bibliographies, and Google Scholar. There were a total of 20,479 potential articles identified on initial review that were screened for relevance using titles (performed by C.D., E.S., M.N., H.T., and J.W.). A total of 89 studies remained after the initial screen (Figure 1). These studies underwent full abstract and article review by 4 authors (performed by C.D., E.S., M.N., and H.T.) and resulted in the exclusion of 58 additional studies (Supplemental table 2). The final cohort of articles used in this meta-analysis included 31 studies: 3 RCTs7-9 and 28 prospective observational studies.10-36 All 31 studies underwent primary data extraction. For studies which examined more than one modality for detecting AF in the same patient population, patient data were included for each; thus, the final number of study specific AF proportions exceeded 31 (figure 1). Discrepancies related to article eligibility or data extraction were resolved between all 5 authors (C.D., E.S., M.N., H.T., and J.W).

**Data Items and Outcome Measures**

Three approaches were used to address the aim of the study. First, a meta-analysis of all included studies was conducted using the proportion of newly diagnosed AF after ischemic stroke as the metameter of interest. Meta-regression was then used to evaluate the relationship between duration of monitoring and proportion of newly diagnosed AF. Secondly, separate meta-analyses for short-term (<72 hours) and long-term (>7 days) ECG monitoring were performed to compare the difference in proportions of newly diagnosed AF between these two strategies. Potential sources of heterogeneity for each of these sub-groups were explored based on pre-specified
variables as described below. Lastly, a meta-analysis of the 3 RCTs was conducted to determine
the odds of detecting AF with long-term versus short-term ECG monitoring.

Pre-specified variables for sub-group analyses were extracted at the time of study review
and placed into a standardized data extraction form. These variables are presented in the
evidence table (Supplemental table 3) and included: screening for AF prior to the study period
(defined as any continuous ECG monitoring prior to study commencement); pre-specified
criteria for diagnosing AF on ECG monitoring (AF > 30s vs no definition specified) and time
from incident stroke or TIA to commencement of monitoring (categorized as < 72hrs, 72hr-
30days, or >30days).

Statistical Methods
In total, four separate meta-analyses were performed (proportion of newly diagnosed AF in all
studies, in short-term monitoring studies, in long-term monitoring studies, and in RCTs).
Proportion of detected AF was the metamer of interest for all analyses except for that of the
RCTs, in which the metamer was the odds ratio of detecting AF by long-term versus short-term
monitoring. All analyses used the random effects model. Measures of heterogeneity were
assessed using the Q statistic and $I^2$. Higher values of each of these measures suggest significant
heterogeneity between the studies included in the meta-analysis and should prompt further
subgroup analyses to better determine the causes of heterogeneity. Individual stratified random-
effects meta-analysis models on pre-determined variables were performed in our sub-group
analyses of short- and long-term monitoring groups. The random-effects model was chosen for
most analyses as a high degree of variability was expected among the prospective studies
included in the meta-analysis. However, for the sub-group analysis specific for the 3 RCTs, a
fixed-effect model was used as a very low degree of variability was anticipated. Finally, a meta-
regression using the unrestricted maximum likelihood model for duration of monitoring was performed including all studies in the model. As the duration of monitoring in days was not normally distributed, this was log-transformed to allow for the model to meet the assumptions of normality and equal variance. Statistical analysis and figure generation was performed using the Comprehensive Meta-Analysis software (Biostat Inc., Englewood, NJ).

Results

Meta-Analysis of All Studies

A total of 8715 patients were included from 31 studies. The overall proportion of new AF detected by ECG monitoring following ischemic stroke or TIA was 7.4% (95% CI: 5.6%, 9.7%) (Figure 2A). Significant heterogeneity was observed based on a high Q statistic of 435.2 (p < 0.0001) and I² of 90.12% (Figure 2A).

Meta-regression using the unrestricted maximal likelihood model to determine the relationship between duration of monitoring and AF detection rate demonstrated a statistically significant positive relationship between AF detection rate and duration of monitoring (p<0.001 for slope and intercept, R²: 62.1%) (Figure 3). Extending the ECG monitoring duration from 24 hours to 30 days increased the proportion of patients diagnosed with AF from 4.38% to 15.2%, continuing monitoring out to 180 days resulted in the detection of AF in 29.15%.

Meta-Analyses of Studies with either Short- or Long-Term ECG Monitoring

Separate meta-analyses were performed on studies with either short-term (≤ 72 hours) or long-term (≥ 7days) ECG monitoring (Figure 2). Of the 31 studies, 15 were categorized as short-term and 16 as long-term. The proportion of newly diagnosed AF with short-term ECG monitoring was 5.1% (95% CI: 3.4%, 7.5%). Significant heterogeneity was observed, with a Q statistic of 285.8 (p < 0.0001) and an I² of 91.3% (Figure 2B). The proportion of newly diagnosed AF with
long-term ECG monitoring was 15% (95% CI: 11%, 19%). The amount of heterogeneity was statistically significant with a Q statistic of 66.03 (p < 0.0001) and an I² of 75.77% (Table 1).

When assessing for causes of heterogeneity through the use of sub-group analyses, only the variable of pre-specified AF definition within long-term monitoring studies was found to be a significant source of heterogeneity (p=.006) (Table 1).

**Long-term versus short-term monitoring in Randomized Controlled Trials**

A total of 3 RCTs with 1,113 patients directly compared long-term versus short-term monitoring for the detection of new onset AF, with sample sizes ranging from 100 to 572 participants. Overall, long-term monitoring was associated with a 7.26 odds of detecting AF compared with traditional short-term monitoring (fixed effect model OR 7.26; 95% CI: 4.04 to 13.04, p <0.001). No heterogeneity was observed across the studies (I² =0%, p =0.394) (Figure 4).

**Discussion**

Atrial fibrillation is an important cause of cryptogenic stroke, responsible for between 20% and 58% of all cerebrovascular ischemic events \(^{37,38}\); however, the detection of AF can be elusive and the exact duration of monitoring following cryptogenic stroke is currently unknown. As such, the primary aim of the current study was to determine whether increasing the duration of ECG monitoring is associated with a larger proportion of newly diagnosed AF. We found that increasing the duration of monitoring from 24 hours to 30 days tripled the detection of AF and extending the duration of monitoring to 180 days further increased the proportion diagnosed with AF to nearly 30%. This finding was supported by 2 separate analyses which examined the effect of time as both a continuous and dichotomous variable. Additionally, a meta-analysis of RCTs demonstrated that long-term monitoring was associated with 7-fold odds of diagnosing AF versus short term monitoring, further strengthening our results that long-term monitoring
increases the proportion diagnosed with AF after ischemic stroke or TIA. These results support the recent guideline changes recommending at least 30 days of ECG monitoring after cryptogenic stroke.3.

Despite these findings, the optimal duration of ECG monitoring after ischemic stroke or TIA remains undefined. Our study results suggest that if we extend ECG monitoring indefinitely, we will continue to diagnose an increasing proportion with new AF. However, we cannot clearly conclude that AF episodes remote from the cerebral ischemic event are actually causative. If we were to assume that a causal relationship exists without clear evidence, we could potentially subject a large number of patients to high-risk interventions such as initiation of anticoagulants without a clear benefit. As such, further investigation is needed to determine whether the detection and treatment of AF with long-term monitoring actually improves outcomes.

Although we cannot determine from this study the optimal duration of monitoring, we have demonstrated that at 30 days, nearly one-fifth of patients with cryptogenic stroke will be diagnosed with AF. This is an important finding for clinicians managing these patients, as patients with cryptogenic ischemic strokes who have risk factors for atrial fibrillation and multiple predictors for recurrent embolic events may benefit from empiric anticoagulation during electrocardiographic monitoring.

These study results must be interpreted in the context of the study design. Significant heterogeneity was observed between studies in this meta-analysis. Identifying the sources of this heterogeneity could potentially help further identify the subgroup of patients in which long-term monitoring is more likely to increase atrial fibrillation detection. Despite our attempt to identify these potential sources of heterogeneity a priori, sub-group analyses using these pre-specified variables failed to fully explain this. In fact, the only source of heterogeneity we identified was
whether studies had a pre-specified criterion for diagnosing AF on ECG monitoring. A possible explanation for our inability to detect sources of heterogeneity is that most included studies were small, which limited our power to detect within study differences. However, there may be additional sources of heterogeneity that we were unable to account for including: patient compliance with ambulatory ECG monitoring; varying quality of the studies; geographic location; and unreported patient characteristics. Another limitation of this study is that we were unable to directly assess the frequency and duration of recorded AF episodes within included studies. Although longer and more frequent episodes of atrial fibrillation would more firmly support a causative relationship with cryptogenic stroke, this may not be of clinical relevance as any duration or frequency of detected AF is likely enough to consider anticoagulation in these high-risk patients. In addition, our meta-analyses of short-term and long-term monitoring, which detected a nearly 10% difference in the proportion diagnosed with AF, is similar to the proportional difference found in the current body of literature and reinforces the validity of these results.

**Conclusion**

We conclude from the current study that longer duration of ECG monitoring after ischemic stroke or TIA increases the proportion diagnosed with AF. Future studies are needed to determine the optimal duration of long-term monitoring which corresponds with the greatest reduction in outcomes, primarily that of recurrent stroke and death.

**Acknowledgment:** We thank Dr. Michel Stoto and Ellie Caniglia in providing assistance and guidance in performing these analyses.

**Conflict of Interest Disclosures:** None
References:


**Table 1:** Sub-group analyses of short-term and long-term ECG monitoring

<table>
<thead>
<tr>
<th>Variable</th>
<th>Short-term Monitoring</th>
<th>p-value</th>
<th>Long-term Monitoring</th>
<th>p-value</th>
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<td>Yes</td>
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<td>Inpatient/&lt; 72 h</td>
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AF: Atrial Fibrillation

**Figure Legends:**

**Figure 1:** Flow Diagram for choosing studies for inclusion

RCT: Randomized controlled trials

**Figure 2:** Forrest plot with proportion of AF detected for: (A) All; (B), short-term ECG monitoring (≤72 hours); and (C) long-term ECG monitoring (≥7 days)

**Figure 3:** Meta-regression analysis assessing the relationship between duration of AF monitoring and AF event rate. Y axis: Logarithm of the event rate. X axis: Logarithm of the
number of hours of monitoring. Each circle represents a study. The circle size varies by the number of subjects included in each study, with the studies with larger number of subjects having larger circles.

**Figure 4:** Forrest plot of RCTs comparing long-term versus short-term monitoring.
Records identified through database searching (n=20,479)

Duplicate articles (n=254)

Records screened (n=20,225)

Full-text articles assessed for eligibility (n=89)

Excluded Studies: Based on abstract information-only (n=20,136)

Full-text Articles Excluded (n=58)
- Retrospective Studies (n=21)
- Different Monitoring (n=5)
- Abstract Only (n=6)
- Meta-Analysis / Review / Editorial (n=6)
- Other (n=20)

Studies included for Objective 1 (n=31)

Studies included for Objective 2 (RCTs-only) (n=3)
### Odds Ratio and 95% CI

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### Effect Size and 95% Interval

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