ORIGINAL ARTICLE

Prolonged Cardiac Monitoring to Detect Atrial Fibrillation after Cryptogenic Stroke or Transient Ischemic Attack: A Meta-Analysis of Randomized Controlled Trials

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Background: The cause of ischemic stroke or transient ischemic attack (TIA) remains unclear after initial cardiac monitoring in approximately one-third of patients. Randomized controlled trials (RCTs) showed that the prolonged cardiac monitoring of patients with cryptogenic stroke or TIA increased detection of atrial fibrillation (AF). We aimed to perform a meta-analysis of all RCTs that evaluated the prolonged monitoring ≥7 days in patients with cryptogenic stroke or TIA.

Methods: We searched PubMed, EMBASE, Cochrane CENTRAL, and relevant references for RCTs without language restriction (inception through December 2014) and performed meta-analysis using random effects model. Detection of AF, use of anticoagulation at follow-up, recurrent stroke or TIA, and mortality were major outcomes.

Results: Four RCTs with 1149 total patients were included in the meta-analysis. Prolonged cardiac monitoring ≥7 days compared to shorter cardiac monitoring of ≤48 hours duration increased the detection of AF (≥30 seconds duration) in patients after cryptogenic stroke or TIA (13.8% vs. 2.5%; odds ratio [OR], 6.4; 95% confidence interval [CI], 3.50–11.73; $P < 0.00001$; I^2, 0%]. It also increased the odds of AF detection of any duration (22.6% vs. 5.2%; 5.68[3.3–9.77]; $P < 0.00001$; I^2, 0%). The patients who underwent prolonged monitoring were more likely to be on anticoagulation at follow-up (2.21[1.52–3.21]; $P < 0.0001$; I^2, 0%). No differences in recurrent stroke or TIA (0.78[0.40–1.55]; $P = 0.48$; I^2, 0%) and mortality (1.33[0.29–6.00]; $P = 0.71$; I^2, 0%] were observed between two strategies.

Conclusion: Prolonged cardiac monitoring improves detection of atrial fibrillation and anticoagulation use after cryptogenic stroke or TIA and therefore should be considered instead of shorter duration of cardiac monitoring.

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cardiac monitor; atrial fibrillation; stroke; TIA; meta-analysis

Stroke leads to significant death and disability.[1] Atrial fibrillation (AF) is a common cause of ischemic stroke and results in more recurrence and higher mortality after a stroke.[2] It has been suggested that one third of the strokes and transient ischemic attack (TIA) are cryptogenic in origin and, therefore, require additional investigation and intervention.[3] In patients with stroke or TIA,

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monitoring during hospital admission usually results in approximately 10% detection of atrial fibrillation[4] while additional 11% can be detected with prolonged monitoring.[5] Patients with a diagnosis of atrial fibrillation after a stroke or TIA are managed with anticoagulation to prevent future stroke. In absence of documented AF diagnosis, they are managed with antiplatelet agents that are inferior in preventing stroke but result in increased risks of bleeding compared to anticoagulants.[6–8]

The American Heart Association/American Stroke Association guidelines for stroke prevention recommend up to 1 month of cardiac monitoring in patients with cryptogenic stroke or TIA to investigate AF on the basis of observational studies.[9] Two previous meta-analyses with mostly heterogeneous observational studies found that the detection of atrial fibrillation increased significantly by longer monitoring.[10,11] However, no meta-analysis has been published with the data from RCTs only. Therefore, to evaluate the efficacy of prolonged cardiac monitoring of ≥7 days in detecting AF in patients with cryptogenic stroke or TIA, and investigate its effects on anticoagulation use and mortality, we performed a meta-analysis of all RCTs.

METHODS

Data Sources and Search Strategy

The meta-analysis was performed in accordance with PRISMA statement.[12] We searched MEDLINE, EMBASE, and Cochrane CENTRAL register of clinical trials for RCTs without language restriction from inception through December 2014. The search terms were "cardiac monitor" or "loop monitor" or "implantable cardiac monitor" and "cryptogenic stroke" or "stroke" or "cerebrovascular accident" or "CVA" or "transient ischemic attack" or "TIA" with restriction to randomized designs. Two investigators (K.D. and B.C.) independently performed the database search and agreed on final study selection. We also searched ClinicalTrials.gov for past or ongoing trials of interest and performed manual search for all relevant references including reviews and meta-analyses.

Study Inclusion and Exclusion Criteria

Randomized controlled trials comparing prolonged (≥7 days) versus shorter (≤48 Hours) cardiac monitoring in patients with cryptogenic stroke or TIA were included. Studies reporting any one of our major outcomes were included. We excluded the studies that were nonrandomized.

Data Extraction

Data were extracted by two investigators (K.D. and B.C.) in duplicate using standardized data-extraction tables. We obtained data on study and patient characteristics, type and duration of cardiac monitoring, and outcomes of interest including adverse events.

Outcomes

The detection of atrial fibrillation was the primary outcome. The use of anticoagulant at follow-up, recurrent stroke or TIA, and mortality were the secondary outcomes.

Statistical Analysis

Odds ratio (OR) with 95% confidence interval (CI) was used to pool the binary outcomes. Crude events from each study were used to compute OR with 95% CI. In addition, we calculated AF detection rates. We used DerSimonian-Laird random effects model for meta-analysis and considered $P < 0.05$ (two-tailed) to be statistically significant for computed effects. Begg's funnel plot was used to visually examine publication bias at outcome level. We used Jadad scale[13] to assess the quality of studies on the basis of randomization, blinding, and attrition of participants. For studies reporting different durations of follow-up, we used the data with the longest follow-up period. Study heterogeneity was evaluated with Cochran's Q and I^2 statistics with $I^2 > 60\%$ being significant heterogeneity, in which case sensitivity analyses were planned, although they were not performed as we did not observe significant heterogeneity in all outcomes of interest. We used Review Manager (RevMan 5.3, Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark) for meta-analysis.

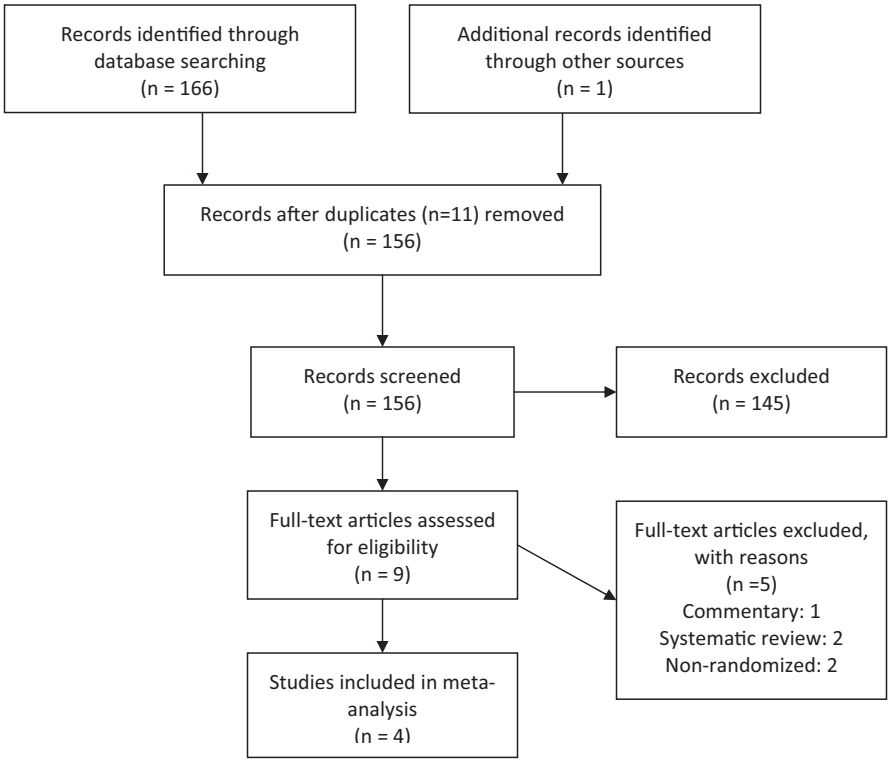

Figure 1. Flow diagram for study selection.

RESULTS

Description of Included Studies

The flow diagram for study selection is shown in Figure 1. Initial electronic databases and manual search resulted in 167 citations with 11 duplicates. We reviewed 156 studies for eligibility and extracted nine studies for full-text review. A total of four RCTs[14–17] with 1149 patients (577 in longer monitoring and 572 in shorter monitoring) were included in the meta-analysis.

The individual study and patient characteristics are presented in Table 1. The duration of follow up was 14 days to 12 months. The patients were mostly Caucasian males and had stroke as index event.

Primary Outcome: Detection of Atrial Fibrillation

Prolonged cardiac monitoring (≥7 days) increased the detection rate of ≥ 30 seconds atrial fibrillation in patients after cryptogenic stroke or TIA compared with shorter cardiac monitoring of ≤48 Hour duration (13.8% vs. 2.5%; OR, 6.4; 95% CI, 3.50-11.73; $P < 0.00001$; I^2, 0%) as shown in Figure 2. Kamel et al.'s study did not detect any atrial fibrillation at follow-up in both intervention and control arms.[17] Prolonged cardiac monitoring also increased the detection of any duration of atrial fibrillation (22.6% vs. 5.2%; 5.68 [3.3–9.77]; $P < 0.00001$; I^2, 0%) compared to shorter monitoring.

SECONDARY OUTCOMES

Anticoagulation Use at Follow-Up

The use of anticoagulation at follow-up (Figure 3) was significantly higher in patients who underwent prolonged monitoring (2.21 [1.52–3.21]; $P < 0.0001$; I^2, 0%] compared to shorter cardiac monitoring awing to increased AF detection. No patients received anticoagulation at follow-up in the study by Kamel et al., as there was no detection of atrial fibrillation.

Recurrent Stroke or TIA and Mortality

At follow-up (Figure 3), prolonged monitoring compared to shorter monitoring did not show

Table 1. Baseline Study and Patient Characteristics

				Patients Characteristics at Baseline							
Study (Ref. No.)	**Total Patients, n**	**Device Type**	**Follow-Up Duration**	**Age (Years) (mean ± SD)**	**Female (%)**	**White (%)**	**Diabetes (%)**	**HTN (%)**	**Ischemic Stroke (%)**	**TIA (%)**	**Antiplatelet Agents Use (%)**
Gladstone, 2014[16]	I:286	30-day noninvasive ambulatory ECG monitor	3 months	I:72.5 ± 8.5	I:46.2	I:89.9	I:19.2	I:71.3	I:65.7	I:34.3	na
	C:285			C:73.2 ± 8.8	C:43.9	C:91.2	C:19.3	C:67.0	C:60.4	C:39.6	
Higgins, 2013[14]	I:50	7-day noninvasive cardiac event monitor	14 days and 3 months	I:67.1 ± 11.1	I:52	na	I:8	I:56	I:70	I:30	I:72
	C:50			C:64.6 ± 13.3	C:36		C:22	C:60	C:66	C:34	C:78
Kamel, 2013[17]	I:20	21-day mobile cardiac	3 and 12 months	I:65 ± 12	I:40	Na	I:20	I:75	I:60	I:40	I:na
	C:20	Outpatient telemetry		C:69 ± 9	C:45		C:30	C:70	C:75	C:25	C:na
Sanna, 2014[15]	I:221	Insertable cardiac monitor	6 and 12 months	I:61.6 ± 11.4	I:35.7	I:87.8	I:15.4	I:65.2	I:90.5	I:9.5	I:95.9
	C:220			C:61.4 ± 11.3	C:37.3	C:86.8	C:17.3	C:57.7	C:91.4	C:8.6	C:96.4

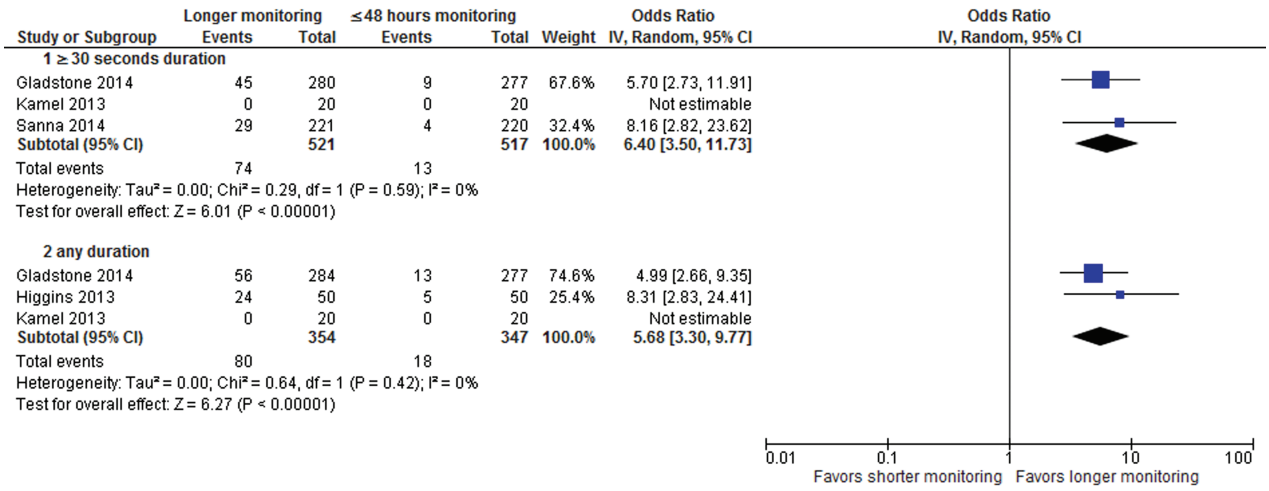

Figure 2. Forest plot for detection of atrial fibrillation.

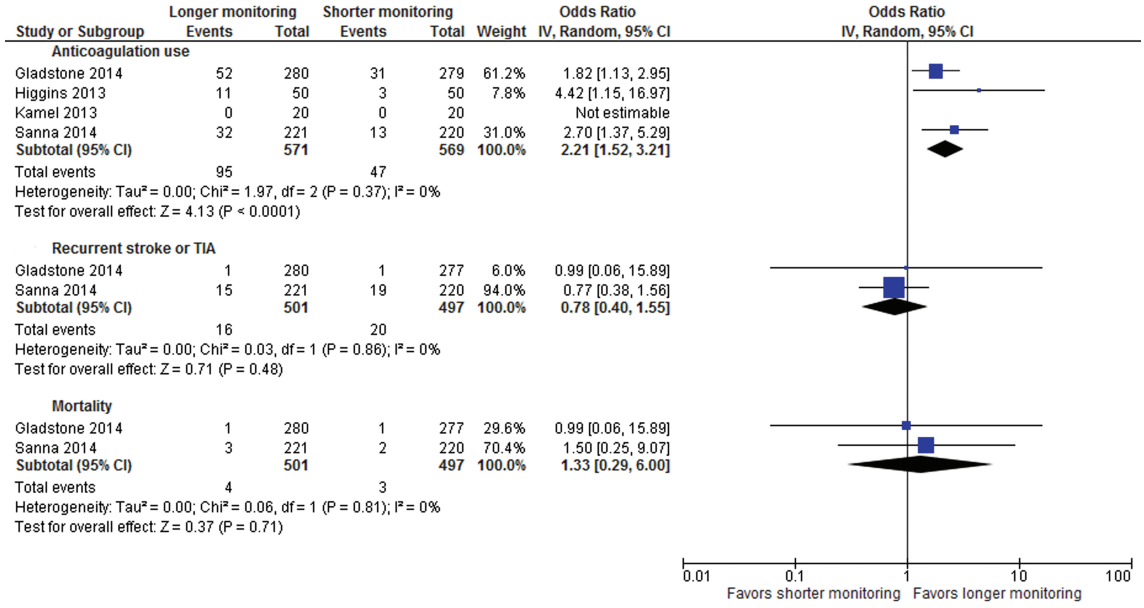

Figure 3. Forest plot for anticoagulation use, recurrent stroke or TIA and mortality.

any difference in recurrent stroke or TIA (0.78 [0.40–1.55]; P = 0.48; I^2, 0%) and mortality (1.33 [0.29–6.00]; P = 0.71; I^2, 0%). None of the studies were powered to detect a difference in mortality. Only two studies reported on these outcomes.[15,16] In Higgins et al.'s study, there were a total of four events of stroke, TIA, MI, or death in each arm.

Study Quality and Publication Bias

Jadad score was three for all studies. Funnel plots were symmetrical for all outcomes indicating that there was no publication bias that was confirmed by Egger's regression intercept and Begg's rank correlation. No heterogeneity was observed for all outcomes as indicated by I^2 statistics.

DISCUSSION

The major findings of the current meta-analysis were in patients with cryptogenic stroke or TIA, prolonged cardiac monitoring (≥7 days) compared to shorter monitoring (≤48 hours) increased the detection of atrial fibrillation and the use of

anticoagulation at follow-up. It, however, resulted in no differences in recurrent stroke or TIA and mortality.

A prior meta-analysis that included mostly single-arm observational studies and only one RCT showed that atrial fibrillation detection rate was 11.5% with longer cardiac monitoring.[10] The meta-analysis, however, was limited by small sample sizes and significant heterogeneity observed as noted by the authors. Current AHA/American Stroke Association guidelines recommend prolonged cardiac monitoring up to 30 days in patients with cryptogenic stroke or TIA on the basis of observational studies.[5,9] The strength of current meta-analysis lies on the fact that it includes all available RCTs on this topic of great interest and we performed analyses on the use of anticoagulation at follow-up, recurrent stroke or TIA, and mortality.

A higher detection rate of atrial fibrillation has important clinical implications as it increases the rate of being initiated on anticoagulation as evidenced in the current meta-analysis. These patients otherwise would just be getting antiplatelet agents which are inferior to antithrombotic agents in stroke prevention in atrial fibrillation. In addition, device-detected atrial fibrillation significantly increases the risks of future stroke.[18,19] Although the study did not find any advantage on recurrent stroke or TIA and mortality outcomes, it should be noted that the studies were not designed to detect difference in such outcomes.

Study Limitations

The current meta-analysis has several limitations including lack of patient-level data, different duration of follow-up among studies, and variations in type of device. It was not possible to ascertain which device and follow-up duration worked better compared to the others. It must be noted that there were not enough studies to define the exact duration of monitoring required although longer the duration of monitoring, higher the detection rate was. Since the shortest device monitoring was for 1 week duration, it may be suggested that a minimum of one week monitoring is beneficial but depending on patients' interests and choices, a longer duration of monitoring should be recommended. Despite all these limitations, the current meta-analysis is strengthened by inclusion of randomized trials and absence of detectable heterogeneity in all outcomes.

CONCLUSIONS

The current meta-analysis of randomized trials shows that prolonged cardiac monitoring improves detection of atrial fibrillation and anticoagulation use after cryptogenic stroke or TIA and therefore supports the updated AHA/American Stroke Association guidelines 2014. Further randomized trials should be designed to define the optimum duration of follow-up and the effects on the risks of recurrent stroke or mortality.

Authors' Contributions: *Drs. K. Dahal and B. Chapagain had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: K. Dahal. Acquisition, analysis, or interpretation of data: K. Dahal, B. Chapagain, R. Maharjan, H.H. Farah, A. Nazeer, R.J. Lootens, A. Rosenfeld. Drafting of the manuscript: K. Dahal, B. Chapagain. Critical revision of the manuscript for important intellectual content: R. Maharjan, H.H. Farah, A. Nazeer, R.J. Lootens, A. Rosenfeld. Statistical analysis: K. Dahal. Study supervision: B. Chapagain, R. Maharjan, H.H. Farah, A. Nazeer, R.J. Lootens, A. Rosenfeld.*

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