Very short AF

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Very short paroxysms account for more than half of the cases of atrial fibrillation detected after stroke and TIA: a systematic review and meta-analysis

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**Background** Guidelines suggest that only poststroke atrial fibrillation episodes lasting 30 s or longer should be considered for anticoagulation. However, little evidence supports this recommendation.

**Aims** We performed a systematic review and meta-analysis to investigate the frequency of poststroke atrial fibrillation lasting less than 30 s in stroke and transient ischemic attack patients.

**Methods** We searched PubMed, Embase, and Scopus from 1980 to June 30, 2014 for studies reporting the detection of poststroke atrial fibrillation of less than 30 s and of 30 s or longer. The primary endpoint was the proportion of screened patients diagnosed with poststroke atrial fibrillation lasting less than 30 s. The secondary endpoint was the proportion of patients diagnosed with poststroke atrial fibrillation shorter than 30 s among the overall number of patients in whom a poststroke atrial fibrillation was detected after stroke or transient ischemic attack.

**Results** From 28 290 titles, we included nine studies in the random-effects meta-analysis. Among stroke and transient ischemic attack patients without a history of atrial fibrillation, 9·0% (95% confidence interval: 4·9–14·3) experienced episodes of poststroke atrial fibrillation shorter than 30 s. An additional 6·5% (95% confidence interval: 3·2–10·9) experienced episodes of poststroke atrial fibrillation longer than 30 s. Among all patients with poststroke atrial fibrillation, 56·3% (95% confidence interval: 37·7–74·0) had poststroke atrial fibrillation episodes shorter than 30 s. Among stroke and transient ischemic attack patients, 56·3% (95% confidence interval: 37·7–74·0) had poststroke atrial fibrillation episodes shorter than 30 s during diagnostic evaluation.

**Conclusions** The clinical and prognostic significance of poststroke atrial fibrillation episodes shorter than 30 s is unknown. The high frequency of poststroke atrial fibrillation episodes shorter than 30 s justify further investigation into the risk of stroke recurrence and the risk–benefit profile of anticoagulation for this patient population.

Key words: atrial fibrillation, cardiac embolism, cardio-aortic embolism, meta-analysis, transient ischemic attack, screening

**Background**

Current guidelines recommend that only atrial fibrillation (AF) episodes lasting 30 s or longer should be considered for anticoagulation (1,2). However, there are contrasting expert opinions regarding the duration of AF which warrants anticoagulation (3). Patients with short AF episodes may experience more frequent episodes than patients who have longer episodes (4), and many short episodes could result in the same AF burden and increased risk of stroke as a single long-standing episode (5). Furthermore, short episodes are a predictive precursor to longer episodes, stroke, and death (6).

Chronic and paroxysmal AFs are associated with a similar stroke risk (7). Recent evidence in patients with implanted pacemakers and implantable cardioverter defibrillators indicates that the presence of subclinical atrial tachyarrhythmias lasting more than six-minutes, without clinical AF, increases the risk of stroke by a factor of 2·5 (8). However, we are not aware of any prospective studies assessing whether the risk of AF paroxysms shorter than 30 s has a lower risk of stroke than those lasting 30 s or longer.

Stroke and transient ischemic attack (TIA) patients are at increased risk of AF (9). A better understanding of the frequency of poststroke AF (PSAF) shorter than 30 s would help establish the potential impact on the incident risk of stroke or systemic embolism and the risk–benefit profile of anticoagulation. In the present study, we performed a systematic review and meta-analysis of studies reporting atrial fibrillation after stroke. We calculated the proportion of stroke and TIA patients with AF episodes lasting less than 30 s and greater than 30 s detected by continuous electrocardiographic monitoring.

**Methods**

We conducted this systematic review by searching PubMed, Embase, and Scopus from 1980 to June 30, 2014. We used a predetermined protocol and search form. To be included in the meta-analysis, articles had to be written in English. Studies had to include patients with ischemic stroke or TIA and had to provide the number of patients without previously known AF undergoing invasive or noninvasive PSAF screening and the number of patients diagnosed with AF after stroke or TIA, whether this was the primary endpoint or not. Duplicated publications and those not published as full manuscripts (e.g. only presented at scientific meetings) were excluded. Fifty studies fulfilled these initial selection criteria. Among them, we finally selected only those reporting
the duration of AF episodes. We assessed the quality of studies according to the Cochrane Handbook (10). More details about this systematic review can be found elsewhere (11).

**Analysis**

The primary endpoint was the proportion of patients identified with a PSAF episode lasting less than 30 s, and was calculated for each cohort by dividing the number of patients newly diagnosed with PSAF episodes shorter than 30 s by the number of screened patients without a previous diagnosis of AF. The secondary endpoint was the fraction of PSAF patients identified with PSAF episodes shorter than 30 s, which was calculated for each cohort as the number of patients diagnosed with PSAF episodes shorter than 30 s divided by the overall number of patients in whom a PSAF was detected.

We used inverse variance weights to produce summary estimates directly using the proportion of patients diagnosed with PSAF and an arcsine transformed proportion of patients diagnosed with PSAF. We chose the arcsine transformation because it produces stable variances in cases of small numbers of observations, including zeros. For cohorts with no or all patients diagnosed with AF, we calculated the variance of the proportion by increasing or decreasing the number of observed diagnoses by 0.5 so that the studies could be included in summary statistics. For the variance of the arcsine transformed values, we followed the analytical method described by Rücker et al (12). We combined studies using random effects analyses for untransformed and transformed measures because of the heterogeneity in study populations, diagnostic technology, and timing of the diagnostic investigation. Summary statistics calculated using the arcsine-transformed proportions and variances did not differ from those calculated on the proportions directly; we report the results of the analysis in which we used the arcsine transform. We assessed between-study heterogeneity with the Q statistic (considered statistically significant if \( P < 0.1 \)) and \( I^2 \), which is not influenced by the number of studies. For random effects models, we estimated interstudy variance using the iterative method of Paule and Mandel (13).

We used funnel plots and Egger regression tests for investigating publication bias (14). A \( P \) value <0.1 was deemed significant for publication bias in the Egger regression tests. We performed the meta-analyses with Microsoft Excel (Microsoft Excel 2011 for Macintosh, Redmond, WA, USA). The analytic variance of the arcsine-transformed proportion and the Paule and Mandel interstudy variance were computed using \( R^2 \) 2.15.0 (R, Vienna, Austria).

**Results**

We identified a total of 28 290 articles, and we initially selected 50 from which we could extract data regarding the overall number of stroke or TIA patients without a history of AF undergoing PSAF screening and the number finally diagnosed with PSAF. Nine of these initial 50 studies reported results for PSAF lasting less than 30 s and were therefore used for the present analyses (Fig. 1). The meta-analysis comprised 1558 patients undergoing continuous cardiac monitoring during a total of 33 158 patient-days. The mean age was 66 ± 6 years and 56.4% (95% CI 54.3–58.4) were males.

![Fig. 1 PRISMA flow diagram.](image-url)
Studies included in the meta-analysis are described in Table 1. One study used continuous inpatient cardiac telemetry, one study used 24-h Holter monitoring, three studies used mobile cardiac outpatient telemetry, three studies used external loop recorders, and the remaining one used implantable loop recorders. The mean time from stroke or TIA to initiation of monitoring was 35 ± 31 days (median 29, range 1–90 days). The average duration of monitoring across studies was 64 ± 139 days (median 21, range 1–435 days). Every patient was screened with at least one method before entering each study (e.g. admission electrocardiogram), and 56·6% of the studies used at least admission electrocardiogram and 24-h Holter monitoring as pre-entry screening methods (Table 1).

The random effects summary proportion indicates 16·9% (10·9–24·0%) of stroke and TIA patients were diagnosed with a PSAF. Among stroke and TIA patients without a history of AF undergoing one PSAF cardiac monitoring method, 9·0% (95% CI 3·2–10·9) had PSAF episodes lasting less than 30 s and 6·5% (95% CI 4·2–11·8%) had PSAF episodes lasting 30 s or longer (Fig. 2). Overall, 56·3% (95% CI 34·9–76·5%) of patients with a newly detected AF had PSAF episodes lasting less than 30 s (Fig. 3).

We performed a sensitivity analysis by excluding a potential outlier study which reported higher rates of PSAF [Higgins et al. (21)] In the sensitivity analysis, we found an overall proportion of PSAF of 14·7% (95% CI 11·0–18·7). While the proportion of stroke and TIA patients with PSAF episodes of less than 30 s was 7·6% (95% CI 4·2–11·8%), the proportion with PSAF lasting 30 s or longer was 5·7% (95% CI 2·8–9·6%). The results remain unchanged for the proportion of newly detected AF lasting <30 s (56·3%; 95% CI 34·9–76·5%).

The Egger regression tests were only significant for the analysis of the proportion of overall PSAFs of less than 30 s; however, all funnel plots showed asymmetry (Fig. 4). Figure 5 illustrates the main sources of bias.

Discussion

Short lasting PSAF episodes may not be as benign as currently perceived and may expose patients at a high risk of stroke recurrence. Furthermore, the detection of very brief episodes of AF after stroke or TIA could probably provide a clue towards the elucidation of the causative mechanism.

In our systematic review and meta-analysis of nine studies reporting the detection of poststroke AF in 1558 participants after over 33 000 patient-days of monitoring, a PSAF was detected among 16·9% of the patients. Since most cohorts in this meta-analysis were screened with mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording, the observed proportion of PSAF detection is consistent with our prior meta-analysis showing a combined proportion of PSAF for mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording of 14·7% (95% CI 13·0–21·2) based on 19 studies (11). Of note, this number should not be regarded as the optimal PSAF detection yield as we have found that by subsequently combining different screening methods, PSAF can be
detected in up to one-fourth of ischemic stroke and TIA patients without prior history of AF (11).

Importantly, our study identified that PSAF episodes shorter than 30 s were detected in 8·9% of patients screened and represented over 55% of all the diagnosed PSAFs. This is higher than observed in one prior study which identified less than 30% of AF patients had exclusively episodes shorter than five-minutes based on analysis of implanted pacemakers (23).

About 90% of AFs are triggered by focal ectopic firing in pulmonary vein and nonpulmonary vein foci generated by imbalances of autonomic function, mainly within the ganglionated plexi of the cardiac intrinsic autonomic nervous system, regard-
less of the presence of cardiac structural damage (e.g. left atrial enlargement) (9). AF recurrence and perpetuation generally occur as a consequence of acute and chronic AF-related microstructural changes in the atrial endothelium and myocardium (24). Myocarditis was identified in 66% of biopsies of patients with paroxysmal lone AF, meaning that structural myocardial changes secondary to AF are frequent even in the presence of short-lasting episodes of AF without associated risk factors of prior cardiac damage (25). Moreover, poststroke inflammation could further potentiate AF recurrence (9,26). In a recent study, 40% of patients with AF episodes shorter than 20 s at 14 days poststroke had AF at 90 days compared with only 28% of patients without any PSAF episodes at 14 days (27). This finding supports the conception that very brief PSAF episodes could be markers of recurrent longer PSAF paroxysms if patients are monitored during longer periods (e.g. 2 years with implantable loop recorders). However, these findings need further confirmation. The recurrence rate of short-lasting PSAF paroxysms and their prognostic significance is still unclear. Because of the lack of knowledge about the clinical significance of AF episodes shorter than 30 s, whether patients with short-lasting AF paroxysms require oral anticoagulation or not is controversial (2).

The higher relative frequency of short-lasting PSAF in our study compared with prior studies may be related to differences in the populations undergoing cardiac monitoring: highly selected populations of patients with recent ischemic stroke or TIA compared with cohorts of patients with implanted pacemakers and cardiac conduction abnormalities, regardless of their history of cerebrovascular disease. Within the first few weeks after stroke or TIA, patients are more prone to be diagnosed with PSAF. Potential explanations include (1): an increase incident risk of atrial tachyarrhythmia/AF in the few days prior to stroke which may be first detected during poststroke monitoring (28,29), and (b)
neurogenic mechanisms triggered by the stroke or TIA through autonomic and inflammatory pathways inducing transient PSAF episodes during the first weeks after the event (9).

This study has some limitations. We combined patient cohorts which varied in the time since stroke onset, the number of previous AF evaluations, the type of stroke, and who were evaluated by different diagnostic methods which may result in heterogeneity. However, a sensitivity analysis after removing a potential outlier study revealed similar results (21). Second, the overall number of studies in our analysis is small compared with the total number of studies evaluating the frequency of PSAF. Nevertheless, not all technologies used to evaluate PSAF are able to detect short episodes, and few studies report the duration of AF episodes or stratify PSAFs on this basis. Third, having limited our systematic search to articles to full publications in English may have resulted in publication bias, as shown by the Egger tests and funnel plots. Despite this, there is some evidence showing that trials published in languages other than English have generally little effect on summary treatment effect estimates (30). The decision to include only full publications and to exclude studies published as abstracts was based on prioritizing quality as full publications usually undergo a more thorough review process. Despite the aforementioned limitations and to the best of our knowledge, the present study is the first to show the high frequency of short-lasting paroxysms of AF after ischemic stroke and TIA.

Our study shows that very brief paroxysms of AF make up more than half of newly detected cases of AF after ischemic stroke and TIA. The risk of stroke recurrence and the potential benefits of routine anticoagulation in this patient population are unknown. However, observing a brief episode of AF may be the only evidence on which to decide about mechanistic-guided secondary preventive treatments in stroke and TIA patients. In view of the high risk of stroke recurrence in patients with AF (31) and the current pathophysiological knowledge of PSAF (9), until the aforementioned limitations and to the best of our knowledge, the present study is the first to show the high frequency of short-lasting paroxysms of AF after ischemic stroke and TIA.

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References


