2015

Very short AF

Gustavo Saposnik

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

Luciano A. Sposato[1]*, Lauren E. Cipriano[2], Patricia M. Riccio[1], Vladimir Hachinski[1], and Gustavo Saposnik[3,4]

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 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.**

Correspondence: Luciano A. Sposato*, Room ALL-130 UH, 339 Windermere Road, London, ON N6A 5A5, Canada.
E-mail: lucianosposato@gmail.com and lsposato@uwo.ca
Twitter: @SposatoL
[1]Department of Clinical Neurological Sciences, London Health Sciences Centre. Western University, London, ON, Canada
[2]Ivey Business School, Western University, London, ON, Canada
[3]Stroke Outcomes Research Center, Division of Neurology, Department of Medicine, St. Michael's Hospital and Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Institute for Clinical Evaluative Sciences, Toronto, ON, Canada.
[4]Li Ka Shing Knowledge Institute, Toronto, ON, Canada

Received: 22 May 2015; Accepted: 24 March 2015

Conflict of interest: Luciano Sposato has received speaker honoraria from Boehringer Ingelheim.

Funding: Dr. Saposnik is supported by the Distinguished Clinician Scientist Award from the Heart and Stroke Foundation of Canada (HSFC). Lauren Cipriano is supported by a grant from the Natural Science and Engineering Research Council of Canada (NSERC).

DOI: 10.1111/ijs.12555

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 $P < 0{\cdot}1$) 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 2.15.0 (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.

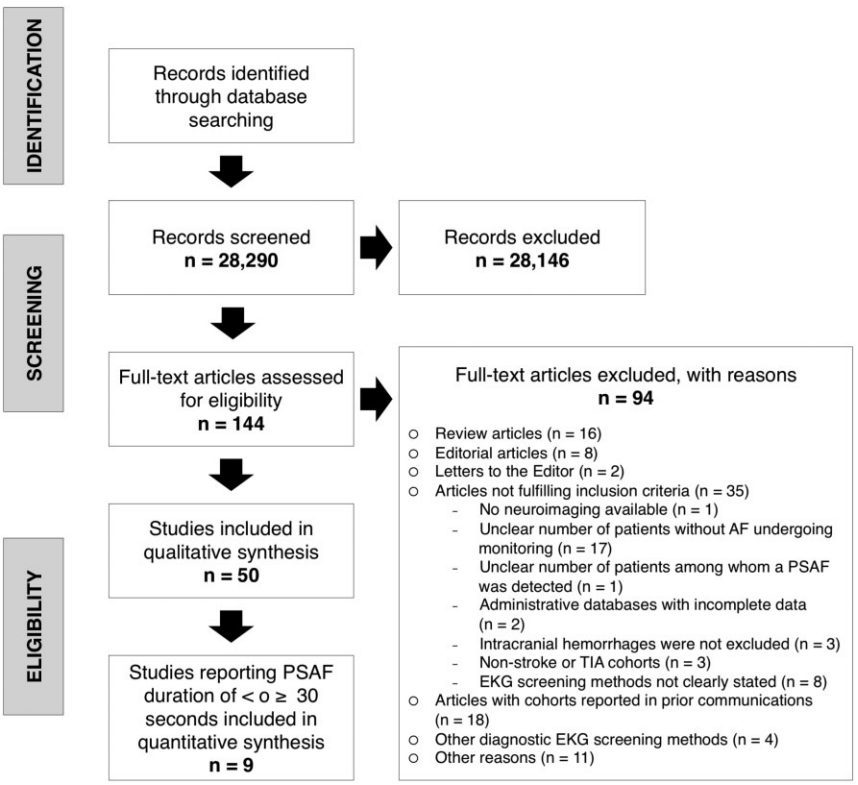

Fig. 1 PRISMA flow diagram.

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 55·6% 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 4·9–14·3) had PSAF episodes lasting less than 30 s and 6·5% (95% CI 3·2–10·9) had at least one PSAF episode lasting 30 s or longer (Fig. 2). Overall, 56·3% (95% CI 37·7–74·0) 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.

Table 1 Description of study cohorts

Main author	Age (years)	Male gender	HTN	DM	Smoking	Hyperlipidemia	Prior stroke	CAD	HF	Design	Qualifying event	Type of event	Screening method	Monitoring initiation	Monitoring duration	Prior screening
González Toledo (15)	69·3	67·3	84·4	23·2	48·3	53·1	21·8	20·4	11·4	Prospective	IS + TIA	Unselected	CICT	1 Day	12·2 Days	aEKG
Alhadramy (16)	65·0	49·8	62·6	15·2	12·1	NA	6·8	15·2	1·8	Retrospective	IS + TIA	Unselected	Holter	NA	1 Day	aEKG
Miller (17)	68·5	50·0	87·0	42·0	21·0	63·0	23·0	24·0	8·0	Retrospective	IS + TIA	Cryptogenic	MCOT	33 Days	21 Days	NA
Rabinstein (18)	66·0	64·0	73·4	15·6	46·1	82·0	NA	NA	NA	Prospective	IS	Cryptogenic + Unselected	MCOT	28 Days	21 Days	aEKG + Holter
Tayal (4)	66·0	51·8	76·8	16·1	35·7	75·0	NA	14·3	1·8	Retrospective	IS + TIA	Cryptogenic	MCOT	20 Days	21 Days	aEKG + CICT + Holter
Flint (19)	64·6	61·5	66·0	14·7	NA	90·8	18·8	NA	4·6	Prospective	IS	Cryptogenic	ELR	29 Days	24·5 Days	NA
Gladstone (20)	72·5	53·8	71·3	19·2	55·9	66·8	15·7	NA	1·7	Prospective	IS + TIA	Cryptogenic	ELR	75 Days	30 Days	aEKG + CICT + Holter
Higgins (21)	67·1	48·0	58·0	15·0	32·0	NA	NA	16·0	NA	Prospective	IS + TIA	Unselected	ELR	7 Days	14 Days	aEKG + sEKG + Holter
Dion (22)	48·8	62·5	29·2	0·0	41·7	33·3	NA	NA	NA	Prospective	IS + TIA	Cryptogenic	ILR	90 Days	435 Days	aEKG + Holter

Results are expressed as proportions (%) unless specified. HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; IS, ischemic stroke; TIA, transient ischemic attack; CICT, continuous inpatient cardiac telemetry; MCOT, mobile cardiac outpatient telemetry; ELR, external loop recording; ILR, implantable loop recording; aEKG, admission electrocardiogram; sEKG, serial electrocardiogram; NA, not available.

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 16·9% (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

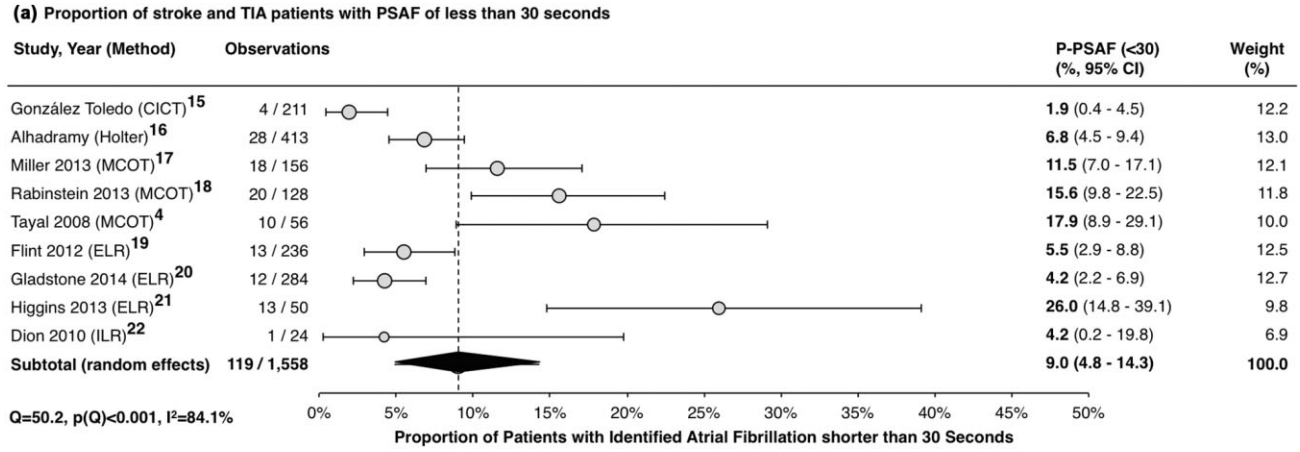

Fig. 2 Panel a shows the summary measure for the overall proportion of patients with PSAF of less than 30 s. Panel b shows the overall proportion of patients with PSAF of 30 s or longer.
CICT, continuous inpatient cardiac telemetry; ELR, external loop recording; ILR, implantable loop recording; MCOT, mobile cardiac outpatient telemetry.

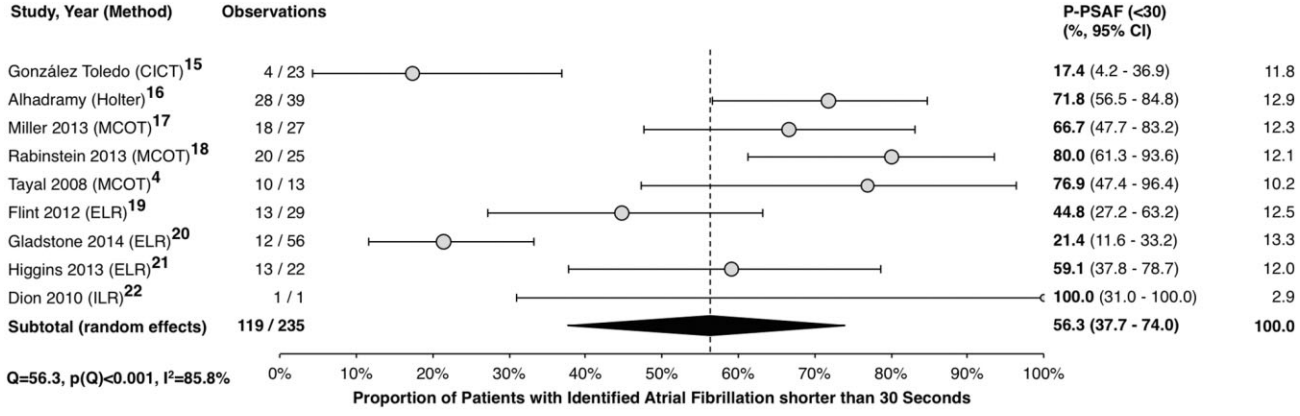

Fig. 3 Proportion of overall PSAF lasting less than 30 s.
CICT, continuous inpatient cardiac telemetry; ELR, external loop recording; ILR, implantable loop recording; MCOT, mobile cardiac outpatient telemetry.

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-

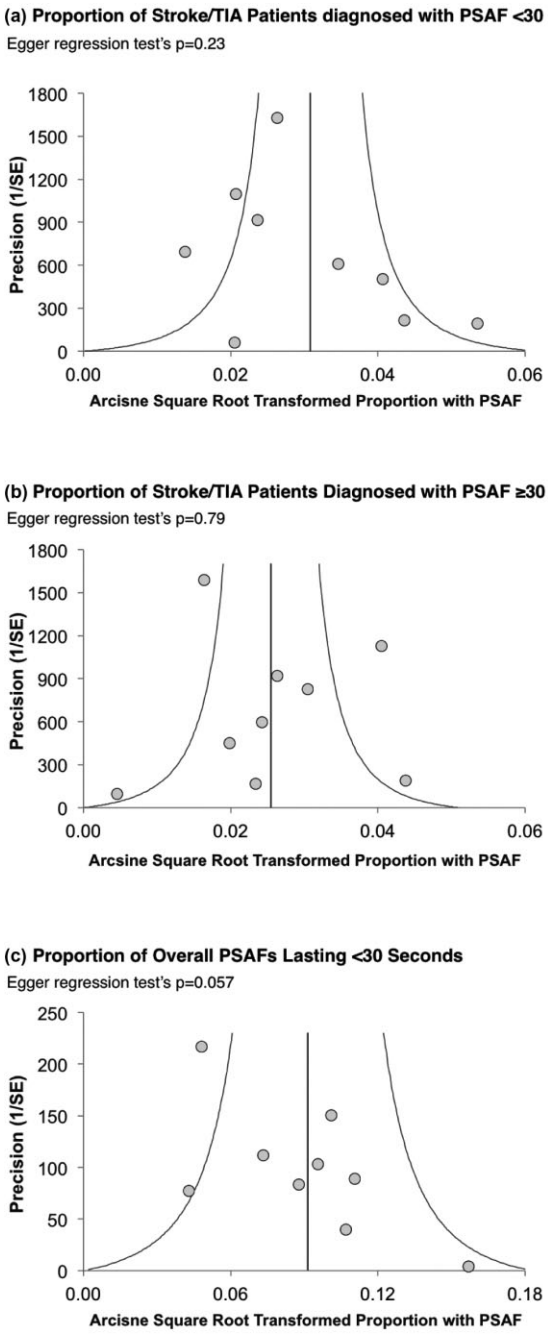

Fig. 4 Funnel plots for patients with PSAF of less than (a) 30 s, (b) 30 s or more, and (c) for the proportion with PSAF of less than 30 s among all the PSAF cases, respectively.
SE, standard error.

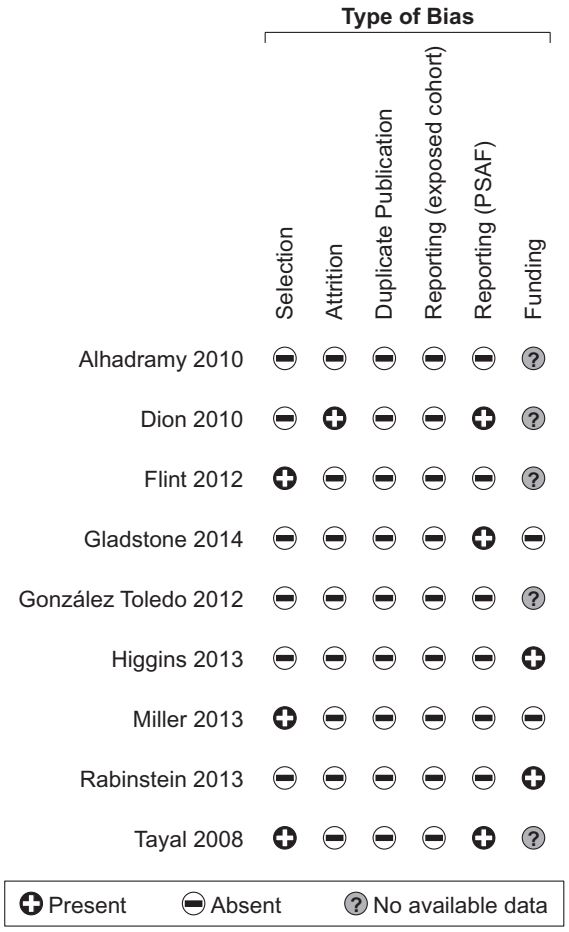

Fig. 5 Sources of bias.

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 specific prognostic implications of very brief PSAF episodes are better characterized, rather than neglecting them, physicians should base anticoagulation decisions on currently available risk stratification schemes as done with other types of AF (32). Occurring in nearly 10% of all ischemic stroke and TIA patients, the high frequency of AF episodes lasting less than 30 s justifies further investigation to determine their clinical significance.

References

1 European Heart Rhythm Association, European Association for Cardio–Thoracic Surgery, Camm AJ *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; **31:**2369–429.

2 Rankin AJ, Tran R, Abdul-Rahim AH, Rankin AC, Lees KR. Clinically Important Atrial Arrhythmia and Stroke Risk: A UK Wide Online Survey among Stroke Physicians and Cardiologists. *QJM* 2014; **107:**895–902.

3 Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J* 2010; **31:**967–75.

4 Tayal AH, Tian M, Kelly KM *et al.* Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology* 2008; **71:**1696–701.

5 Kirchhof P, Lip GY, Van Gelder IC *et al.* Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options–a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. *Europace* 2012; **14:**8–27.

6 Glotzer TV, Hellkamp AS, Zimmerman J *et al.* Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). *Circulation* 2003; **107:**1614–9.

7 Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000; **35:**183–7.

8 Healey JS, Connolly SJ, Gold MR *et al.* Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012; **366:**120–9.

9 Sposato LA, Riccio PM, Hachinski V. Poststroke atrial fibrillation: cause or consequence? Critical review of current views. *Neurology* 2014; **82:**1180–6.

10 Higgins JPT, Altman DG. Assessing risk of bias in included studies; in Higgins JPT, Green S (eds): Cochrane Handbook for Systematic Reviews of Interventions Version 501. Chichester, UK, Wiley, 2008**:**1–53.

11 Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after Stroke and transient ischemic attack: a systematic review and meta-analysis to guide clinical decision making. *Lancet Neurol* 2015; **14:**377–87.

12 Rücker G, Schwarzer G, Carpenter J, Olkin I. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta–analysis with zero cells. *Stat Med* 2009; **28:**721–38.

13 Paule RC, Mandel J. Consensus values and weighting factors. *J Res Natl Bur Stand* 1982; **87:**377–85.

14 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta–analysis detected by a simple, graphical test. *BMJ* 1997; **315:**629–34.

15 González Toledo ME, Klein FR, Riccio PM *et al.* Atrial fibrillation detected after acute ischemic stroke: evidence supporting the neurogenic hypothesis. *J Stroke Cerebrovasc Dis* 2013; **22:**e486–91.

16 Alhadramy O, Jeerakathil TJ, Majumdar SR, Najjar E, Choy J, Saqqur M. Prevalence and predictors of paroxysmal atrial fibrillation on Holter monitor in patients with stroke or transient ischemic attack. *Stroke* 2010; **41:**2596–600.

17 Miller DJ, Khan MA, Schultz LR, Simpson JR, Katramados AM, Russman AN. Outpatient cardiac telemetry detects a high rate of atrial fibrillation in cryptogenic stroke. *J Neurol Sci* 2013; **324:**57–61.

18 Rabinstein AA, Fugate JE, Mandrekar J *et al.* Paroxysmal atrial fibrillation in cryptogenic stroke: case–control study. *J Stroke Cerebrovasc Dis* 2013; **22:**1405–11.

19 Flint AC, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxysmal atrial fibrillation by 30–day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke* 2012; **43:**2788–90.

20 Gladstone DJ, Spring M, Dorian P *et al.* Atrial fibrillation in patients with cryptogenic stroke. *New Eng J Med* 2014; **370:**2467–77.

21 Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees KR. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: randomized, controlled trial. *Stroke* 2013; **44:**2525–31.

22 Dion F, Saudeau D, Bonnaud I *et al.* Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: prospective study. *J Interv Card Electrophysiol* 2010; **28:**101–7.

23 Botto GL, Padeletti L, Santini M *et al.* Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. *J Cardiovasc Electrophysiol* 2009; **20:**241–8.

24 Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle: evidence for electrical uncoupling of side-to-side fiber connections with increasing age. *Circ Res* 1986; **58:**356–71.

25 Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997; **96:**1180–4.
26 Isaac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation. A systematic review of the published data. *J Am Coll Cardiol* 2007; **50:**2021–8.
27 Higgins P, Dawson J, MacFarlane PW, McArthur K, Langhorne P, Lees KR. Predictive value of newly detected atrial fibrillation paroxysms in patients with acute ischemic stroke, for atrial fibrillation after 90 days. *Stroke* 2014; **45:**2134–6.
28 Daoud EG, Glotzer TV, Wyse DG *et al*. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm* 2011; **8:**1416–23.
29 Turakhia MP, Ziegler PD, Bucksa A, Xu X, Than C, Singer D Atrial arrhythmia burden increases just proximal to stroke: insights from remote monitoring in a national health care system. 2014. Presented at Heart Rhythm Society Scientific Sessions; May 8, 2014; San Francisco, California. Available at http://ondemand.hrsonline.org/common/presentation-detail.aspx/15/35/1169/8418 (accessed February 23, 2015).
30 Jüni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *Int J Epidemiol* 2002; **31:**115–23.
31 Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007; **69:**546–54.
32 Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010; **137:**263–72.