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REVIEW

Global Neurology

Subclinical atrial fibrillation and risk of stroke: An update

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Abstract

Stroke is one of the major causes of death and disability. Atrial fibrillation causes 15% of strokes, 60% is caused by cerebrovascular disease, whereas 25% of cases have no known cause. The technological advancement of cardiac implanted electronic devices has enabled the identification of subclinical atrial fibrillation (SCAF). The literature shows that SCAF is very frequent in the elderly population and that it represents a risk factors for the onset of stroke or systemic embolic disease, regardless of other cardiovascular risk factors. While for clinical atrial fibrillation (AF) the advantages of anticoagulant therapy based on the CHA_2DS_2-VASC score have been well established, much has been said about the usefulness of anticoagulant therapy in the case of SCAF. The role of AF and CHA_2DS_2-VASC score is much debated. A study has recently clearly shown how the SCAF burden together with CHA_2DS_2-VASC score play an important role in determining the risk of progression to persistent AF. Based on these data, the ongoing ARTESIA and AFNET-NOAH studies will provide us with data to evaluate the efficacy of anticoagulant therapy in SCAF.

Keywords: *atrial fibrillation, atrial fibrillation burden, Implantable devices, stroke*

Introduction

Atrial fibrillation (AF) is a major cause of stroke, which is a significant cause of disability and death. Cases of AF are increasing due to the ageing of the population [1]. Stroke is caused by AF in 15% of cases, in 60% of cases it's caused by other documented cerebrovascular disease, while in 25% of cases the cause is unknown [2]. Almost 30 years have passed since the publication of the Framingham study data, which showed that the presence of AF is associated with a 5-fold increased risk of stroke [3]. However, while in the past it was necessary a high burden of AF, since the diagnosis could be made by means of 12-channel electrocardiographic recording, we now have at our disposal a series of data derived from cardiac implanted electronic devices (CIED). These devices allow us to identify, record and review numerous episodes of tachyarrhythmia, even of short duration, which before we were not able to recognize, that has greatly increased the number and the proportion of patients with these silent atrial tachyarrhythmias. The atrial arrhythmias detected by implanted devices have been termed silent AF, subclinical atrial fibrillation (SCAF), atrial high rate episodes (AHRE), or CIED-detected AHRE; these terms have come to be used interchangeably.

Clinical role of SCAF

In recent years, we have had difficulty understanding the clinical significance of SCAF. In particular, there are still a number of questions relating to the thromboembolic risk of SCAF, depending on their duration, the temporal relationship between them and acute cerebrovascular events and, consequently, the type of therapy to be established and whether we should consider SCAF as a direct cause of stroke or, more trivially, as a marker of higher risk, similar to diabetes or hypertension.

The MOST (Mode Selection Trial) study, published in 2003, was the first to establish a link between these short phases of silent atrial tachyarrhythmia and stroke risk. This study showed that patients with a single AHRE lasting longer than 5 min, detected by their pacemaker, had an increased risk of stroke, death, permanent AF, and an increase in the combined endpoint of death and non-fatal stroke. SCAF episodes can trigger chronic changes in the atria, promoting clot formation. In fact, there is scientific evidence that AF can induce changes in atrial structure and endothelial function, also promoting a state of hypercoagulability and chronic inflammation [4-7]. In subsequent years, many other studies have confirmed this association between AHRE and stroke risk. As shown in Table 1, each study evaluated a single pre-defined cutpoint of AF burden or a combination of AF burden and clinical risk factors. All studies showed at least a doubling of stroke risk when AHREs are detected [8-14]. The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) is a study conducted on 2,580 hypertensive aged >65 years and without previous history of AF, who were implanted with a pacemaker (2451) or a cardioverter-defibrillator (129) in the preceding 8 weeks [9]. Among these patients 10.1% had one SCAF lasting more than 6 minutes in the first 3 months of the study. In 2.5 years of follow-up, regardless of any further detection of atrial arrhythmia, these patients had a 2.49-fold higher stroke risk than the group without AHRE detected. In addition, one third of patients had at least one episode of SCAF detected over the 2.5-year mean follow-up period. SCAF lasting more than 6 minutes, compared to no episodes, has been associated with an increased risk of ischemic stroke or systemic embolism (Hazard Ratio, 1.77; 95% CI, from 1.01 to 3.10; P = 0.047). The risk increased progressively depending on the burden of AF; in fact,

Summary of Studies on AF Detected by CIEDs and TE Risk							
Year	**Study (Ref.#)**	**Patients (n)**	**Duration of Follow-up (median)**	**Atrial rate cut off. Beats/min**	**AF Burden Cutpoint**	**HR for TE Event**	**TE Event Rate;**
2003	Ancillary MOST [8]	312	27 months	>220	5 min	6.7; p=0.020	3.2% overall
2005	Italian AT500 Registry [10]	725	22 months	>174	24 h	3.1; p=0.044	1.2% annual rate
2009	Botto et al. [11]	568	1 yr	>174	CHADS2+AF burden	N/A	2.5% overall
2009	TRENDS [12]	2486	1.4 yrs	>175	5.5 h	2.2; p=0.060	1.2% overall
2012	Home Monitor CRT [13]	560	370 days	>180	3.8 h	9.4; p=0.006	2.0% overall
2012	ASSERT [9]	2580	2.5 yrs	>190	6 min	2.5; p=0.007	1.7% overall
2014	SOS [14]	10016	2 yrs		1 h	2.11; p=0.008	
2017	ASSERT-II [15]	256	16.3 months	>190	5 min		

AF = atrial fibrillation; ASSERT = Asymptomatic atrial fibrillation and stroke evaluation in pacemaker patients and the atrial fibrillation reduction atrial pacing trial; CHADS2 = Congestive heart failure, hypertension, Age >75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism; CIED = cardiac implanted electronic device; CRT = cardiac resynchronization therapy; HR = hazard ratio; MOST = Mode selection trial; N/A = not available; SOS = Stroke prevention strategies; TE = thromboembolic.

Table 1. Modified from Taya V. The Cacophony of Silent Atrial Fibrillation. J Am Coll Cardiol. 2018;12;71[22]:2612-2615. [24].

compared to patients without SCAF, if it lasted more than 6 hours we noticed an increase in the risk of adverse events with a HR 2.99 (P = 0.001) which became equal to 4.96 (P < 0.001) when the SCAF lasted more than 24 hours [9]. The risk of ischemic stroke or systemic embolism associated with SCAF before 3 months was 13%, which is analogous to the risk of stroke associated with atrial fibrillation reported by Framingham researchers [9]. SCAF is a common entity, not only in patients with implanted pacemakers and defibrillators, but also in 30%-35% of older individuals with cardiovascular disease.

In the ASSERT-II trial: Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor Jeff S. Healey et al. recruited patients ≥65 years old with a CHA_2DS_2-VASc score of ≥2, with a clinical diagnosis of obstructive sleep apnea, or a BMI >30 kg/m2 and diagnosis of left atrial enlargement (volume ≥58 mL9 or diameter ≥4.4 cm) or an elevated N-terminal pro–B-type natriuretic peptide (NT-pro BNP) ≥290 pg/mL [15]. The main purpose of the study was to detect SCAF lasting ≥5 minutes in line with the methodology of the ASSERT and TRENDS studies [9,12] which demonstrated the association between SCAF and stroke. Patients presenting with symptoms attributable to arrhythmias such as palpitations, with history of atrial fibrillation or flutter, with indication for oral anticoagulation or with PMK or ICD implanted have been ruled out. 256 patients were enrolled and implanted with an Implantable Cardiac Monitor (ICM) SJM CONFIRM-AF (DM2100). The average age of the patients was 74 years, their average CHA_2DS_2-VASC score was 4, and 48% had a history of stroke, systemic embolism or transient ischemic attack. The mean follow-up was 16.3 months. SCAF ≥5 minutes was detected in 90 patients in the follow-up period: in 34% of cases it was detected in the first 30 days, in 64% in the first 6 months and in 87% in the first year. SCAF ≥5 minutes occurred with an incidence rate of 34.4% per person per year (95% CI, 27.7-42.3). Patients with SCAF were older, had a larger left atrial diameter, lower systolic blood pressure and a prevalence of heart failure and diabetes mellitus. Increased age, greater left atrial diameter and lower systolic blood pressure were identified as independent predictors for SCAF. The frequency of SCAF was not significantly different among patients with a history of stroke, systemic embolism, or transient ischemic attack than among those without such a history. The main result of this study is that long-term cardiac monitoring with an ICM was frequently able to detect SCAF lasting ≥5 minutes, especially in older patients and those with cardiovascular risk factors.

CHA_2DS_2-Vasc Score, Burden of SCAF and Risk of Stroke

Both the TRENDS (The Relationship Between Daily Atrial Tachyarrhythmia Burden from Implantable Device Diagnostics and Stroke Risk) and ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) studies have shown that SCAF is associated with an increased risk of stroke [9,12]. However, unlike clinical AF in which stroke risk is increased 4–5 times, for SCAF the risk is only 2–2.5 times increased, and the absolute risk of stroke observed in these studies was much lower than expected based on the subjects' CHADS-2 score [9,12,16]. In addition to the clinical stroke risk factors quantified using the CHA2DS2-VASc score, the duration of SCAF appears to influence the risk of thromboembolic events in patients [12, 17]. In the TRENDS study, patients with SCAF burden below the median value of 5.5 hours did not show any increase in thromboembolic risk, while those with higher burden had a modest increase in risk, with a hazard ratio of 2.20 [12]. More recently, an analysis of ASSERT suggests a substantial increase in the absolute risk of stroke or systemic embolism when patients developed an episode of SCAF lasting at least 24 hours continuously [9]. Their absolute risk was about 15% in 3 years, a rate very similar to that of patients with clinical AF. However, among patients with shorter episodes, the ASSERT analysis did not show any increased risk [9]. Thromboembolic risk increases even with short-term SCAF, but chiefly with increased burden of AF, especially when a progression from paroxysmal to permanent clinical AF has developed [18]. Among patients with SCAF, only 24% of individuals progress to episodes of more than 23 hours in 2.4 years [19]. These individuals are at highest risk of adverse outcomes, primarily stroke, but also incident heart failure [20]. In patients with clinical AF, the "progression" from paroxysmal to persistent AF has been linked to worse clinical outcomes [21]. Recently, Boriani et al. [19] took an important step forward by pooling patient level data from 6580 patients from 3 studies to determine the prevalence of SCAF and the rate of progression to long-term episodes. On an average follow-up of 2.4 years, the duration of SCAF >5 minutes developed in 34% of patients. During this period, half of the patients with SCAF progressed to longer episodes (1, 6, 12 or 23 hours), and a quarter developed episodes lasting >23 hours [19]. The Authors determined that the presence of longer initial episodes and a CHADS-2 >2 score were associated with a faster progression to AF episodes lasting >23 hours. This study suggests the possibility of identifying patients with SCAF with a higher risk of developing long-term episodes and strokes. The use of oral anticoagulants for the treatment of patients with SCAF is controversial and is the subject of 2 ongoing clinical studies: ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) [22] and NOAH-AFNET (non-vitamin K anticoagulant oral antagonist in patients with Atrial High rate episodes) [23].

Conclusion

Over the years, for the progressive diffusion of implantable devices, capable of recognizing SCAF, the role of this type of arrhythmia in favoring the appearance of acute cerebrovascular syndromes has been highlighted. The question of whether and when to start anticoagulant therapy in patients with SCAF is legitimate, given the increased risk of hemorrhagic side effects of this therapy, which discourages its use on a broad basis in these patients. The main determinants of thrombotic risk are represented by AF burden and CHA_2DS_2-VASC score values, but literature data are still not satisfactory in indicating threshold values to be used. Ongoing studies will help us determine the criteria for initiating appropriate anticoagulation in patients with SCAF.

References

1. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J.* 2013;34: 2746–2751.
2. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. *Neurology.* 1978;28: 973-7.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22: 983–8.
4. Freestone B, Lip GY. The endothelium and atrial fibrillation: the prothrombotic state revisited. *Hamostaseologie.* 2008;28: 207–212.
5. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J *Am Coll Cardiol*. 2012;60: 2263–2270.
6. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet.* 2009;373: 155–166.
7. Inoue H, Nozawa T, Okumura K, Jong-Dae L, Shimizu A, et al. Prothrombotic activity is increased in patients with nonvalvular atrialfibrillation and risk factors for embolism. *Chest.* 2004;126: 687–692.
8. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, 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.
9. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366: 120–9.
10. Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, et al. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. *J Am Coll Cardiol.* 2005;46: 1913–20.
11. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia 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.
12. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009;2: 474–80.
13. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, et al. Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. *Europace.* 2012;14: 230–7.
14. Boriani G, Glotzer TV, Santini M, West TM, De Melis M,et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J.* 2014;35: 508–16.
15. Healey JS, Alings M, Ha A, Leong-Sit P, Birnie DH, et al. Subclinical Atrial Fibrillation in Older Patients. *Circulation.* 2017;136: 1276-1283.
16. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285: 2864–2870.
17. Van Gelder IC, Healey JS, Crijns HJ, Wang J, Hohnloser SH, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J*. 2017;38: 1339–1344.

18. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J.* 2015;36: 281–287a.
19. Boriani G, Glotzer T, Ziegler P, De Melis M, di S. Stefano L, et al. Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to higher device-detected atrial fibrillation burden. *Heart Rhythm.* 2018;15: 376–383.
20. Wong JA, Conen D, McIntyre WF, Wang J, Van Gelder IC, et al. Progression of subclinical atrial fibrillation and heart failure outcomes: an ASSERT sub-study. *Heart Rhythm.* 2017;14: S164.
21. De Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, et al. Progression from paroxysmal to persistent atrial fibrillation: clinical correlates and prognosis. *J Am Coll Cardiol.* 2010;55: 725–731.
22. Lopes RD, Alings M, Connolly SJ, Beresh H, Granger CB, et al. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Sub- Clinical Atrial Fibrillation (ARTESiA) trial. *Am Heart J.* 2017;189: 137–145.
23. Kirchhof P, Blank B, Calvert M, Camm AJ, Chlouverakis G, et al. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH-AFNET 6) trial. *Am Heart J.* 2017;190: 12–18.
24. Glotzer TV. The Cacophony of Silent Atrial Fibrillation. *J Am Coll Cardiol.* 2018;71: 2612-2615.

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