# Subclinical atrial fibrillation – what is the risk of stroke?

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Atrial fibrillation is the most common arrhythmia and as such, it has become a significant public health issue due to its impact on patient morbidity and mortality. The prevalence of atrial fibrillation (AF) almost doubled in the last decade, being currently 2% in unselected patient populations. Its occurrence varies with age (present in almost 20% of octogenarians) and concomitant diseases. The most prevalent concomitant diseases are hypertension, diabetes, heart failure, renal failure, and cognitive decline. Cognitive decline or stroke may be actually the first manifestation of undiagnosed atrial fibrillation. In the majority of cases, atrial fibrillation is more of a syndrome than a disease in itself, with a multitude of etiologic factors and mechanisms. The risk of cardioembolic stroke increases with the number of comorbidities and age. The overall age-adjusted risk of stroke in patients with atrial fibrillation is 5 times higher than in the general population. Nowadays, the detection of asymptomatic episodes of atrial fibrillation by cardiac electronic implantable devices (CIED), referred to as device detected or subclinical atrial fibrillation, has opened new frontiers in AF management. The risk of stroke and subsequent need for anticoagulation treatment in this group of patients with device detected AF is however not clear. Here, we will review the literature to determine the association of subclinical atrial fibrillation with the risk of stroke.

**Key words:** arrhythmia, subclinical atrial fibrilation

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## INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia globally, and due to its impact on morbidity, mortality and quality of life, it has become a significant public health problem. The prevalence of AF is about 2% in unselected populations, significantly varying with age and sex[1]. During brief episodes of atrial fibrillation, patients may remain asymptomatic, which renders this arrhythmia challenging to capture. Such subclinical episodes may however represent warning signs for developing detectable forms of AF and even subclinical/asymptomatic atrial fibrillation (SCAF) may portend significant thromboembolic risk. SCAF is often discovered only after an ischaemic stroke or heart failure or remain silent even after stroke, which leads to inadequate antiaggregant treatment. Current guidelines address none of these issues related to anticoagulation treatment in patients with SCAF (ref.[2]). The risk of stroke and subsequent need for anticoagulation treatment is not clear in the SCAF population, either. There is, however, an expert consensus statement[3] and a few trials which we will review to question the need for anticoagulation treatment in SCAF, and the threshold for starting the treatment.

## SCAF EPIDEMIOLOGY

The prevalence of AF had increased dramatically over the last three decades, in part due to our greater ability to treat both acute and chronic heart disease and non-cardiac disease, thus improving life expectancy. The population is aging; moreover, with the use of external loop recorders and implantable devices ever increasing, AF is nowadays more likely to be diagnosed than in the past. The prevalence of AF is 2.3% in patients older than 40 years and 6% in patients older than 65 years[4]. The incidence ranges between 0.21 and 0.41 per 1,000 person/years[1]. 50% of cases have permanent AF, paroxysmal and persistent are found in 25% each[1]. The highest prevalence rate, up to 3.2%, was found in developed countries while the lowest in the Asia-Pacific region[5]. In one third of all AF occurrences, some secondary trigger can be observed, such as myocardial infarction, infection or surgery[6]. This should be taken into account, particularly so while interpreting SCAF episodes and their significance. In the TRENDS trial, which included only patients without prior anticoagulation treatment or antiarrhythmic drug use and no history of AF, the incidence of SCAF was 30% (ref.[7]). Newly detected AF was defined as a device detected atrial high rate episode lasting more than 5 minutes. In another landmark trial (ASSERT) (ref.[8]), SCAF was defined as an atrial high rate episode of ≥ 190 bpm lasting more than 6 min. Subclinical atrial fibrillations detected by implantable devices occurred in 10.1% of cases in the ASSERT trial[8].

Clinically silent AF is often revealed after pacemaker implantation. AF occurs more often in patients with a sick sinus syndrome (68%) than with an AV blockade (37%) (ref.[9]). The median time to the first occurrence was 21.2

days after pacemaker implantion[9]. In the MOST trial, the pacemakers were programmed to log on an episode as an atrial high-rate episode (AHRE) when the atrial rate was ≥ 220/min and lasting for ten consecutive beats, however only AHREs lasting more than 5 min were included in the final analysis[10]. In 51.3% patients, at least one AHRE episode was observed during the follow-up (median duration follow up 27 months), although at least 60% of patients had a history of unspecified supraventricular tachycardia[10]. In the BEATS trial, the atrial tachycardia detection was programmed to 8 atrial cycles at 170/min. Based on pacemaker counter data, atrial tachycardias (AT) were recorded during follow-up at least once in 85% of patients with sinus node disease and in 83% patients with other pacing indications, mostly AV blockades[11]. Of the patients with sinus node disease and device-detected AT (DDAT), the episodes were confirmed by 12 lead ECG/Holter recordings in 18% of patients; in patients with other pacing indications, it was only 10% of patients. The total number of SCAF observed in the BEATS trial was 67% in sinus node disease patients and 73% in the other pacing indications group[11]. In the BEATS trial, the use of anticoagulation or antiarrhythmic drugs was not an exclusion criterion. In another monocentric retrospective analysis (445 patients), AF was detected in 55.3% of patients including patients both with (65.8%) and without (51.8%) the history of clinical arrhythmia[12].

### SCAF terminology

At present, there are generally two European heart rhythm association (EHRA) consensus documents[3,13] dealing with subclinical forms of atrial fibrillation. We find it useful to delineate all types of AF/AT episodes. Although EHRA issued both documents, there are differences in definitions of AHRE rate (180 vs. 190/min), length of subclinical AF (5 vs. 6 min) and excessive supraventricular ectopic activity (ESVEA), which is defined only in the document by Gorenek et al.[3], see Table 1 for details.

### HOW TO DETECT SCAF

The detection rate of subclinical AF depends heavily on the length of ECG monitoring and amount of classical risk factors for AF. There were two principal landmarks in the search for subclinical forms of atrial fibrillation. The first was the development and then refining of device detection algorithms. The second was the need for detection of AF in patients with cryptogenic stroke (or, as it is termed now, embolic stroke of undetermined source, ESUS) and causal connection of these diseases[14]. In 2014, two important trials comparing standard 24-h ECG Holter with extended ECG monitoring in the cryptogenic stroke patients were published[15,16]. The EMBRACE trial compared a 24-h ECG Holter monitoring vs. a 30-day external loop recorder (ELR) in 572 cryptogenic stroke patients of 55 years and older less than six months after stroke. The result was stunning, AF was detected in 16.1% of ELR patients while only in 3.2% patients in the standard arm[15]. The CRYSTAL-AF trial compared the standard 24-h ECG Holter monitoring against 6-month implantable loop recorder (ILR) in 441 patients over 40 years of age, less than three months after a cryptogenic stroke. Not surprisingly, AF was detected in 12.4% in the active arm (ILR) and only 2% in the standard arm[16]. Lower detection rate comparing ILR vs. ELR might be explained by lower risk patients (younger) in the CRYSTAL-AF trial, which also explains the lower AF capture in the standard arm (2% vs. 3% in the EMBRACE trial) (ref.[15,16]). These results led to the recommendation in stroke guidelines for 30 days ECG monitoring after stroke or transient ischaemic attack with no apparent cause[17]. The development of the focus aimed at subclinical atrial fibrillation is also traceable by Pubmed search, from which the effect of fundamental SCAF publications (such as AIDA (ref.[18]), MOST (ref.[10]), ASSERT (ref.[8]) or TRENDS (ref.[7]) trials) on the number of papers devoted to SCAF are apparent, see Fig. 1. In patients with cardiac implantable devices, the average SCAF detection rate is 30%; the peaks of 60% rates were reported in the early trials where the inclusion

**Table 1.** EHRA consensus documents, subclinical atrial fibrillation terminology[2,3].

| Definition | EHRA consensus document: Screening for atrial fibrillation[2] | EHRA consensus document: Device detected subclinical atrial tachycardias[3] |
|---|---|---|
| SCAF (Subclinical atrial fibrillation) | Episodes of AF/AT with duration between 5 min to 24 h detected in patients without clinical history or symptoms of AF | AHREs (> 6 min and <24 h) with lack of symptoms in patients with CIEDs;detected with continous ECG monitoring (intracardiac) and without prior diagnosis of AF (ECG or holter monitoring) |
| Asymptomatic or clinically silent AF | Episodes of at least of 30 s ECG documented absolutely irregular RR intervals with no discernable distinct P waves in the absence of symptoms typically associated with AF | Documented AF in the absence of any symptoms or prior diagnosis Often presenting with a complication related to AF |
| AHRE (Atrial high-rate episodes) | Episodes of at least 5 min and of AT/AF with atrial rate >180/min detected by continous monitoring by CIEDs | Atrial tachyarrhythmia episodes of with rate >190/min detected by CIEDs |
| ESVEA (Excesive supraventricular ectopic activity) | – | 30PSC/h (729/24h) or episode of PSC runs ≥ 20 beats |

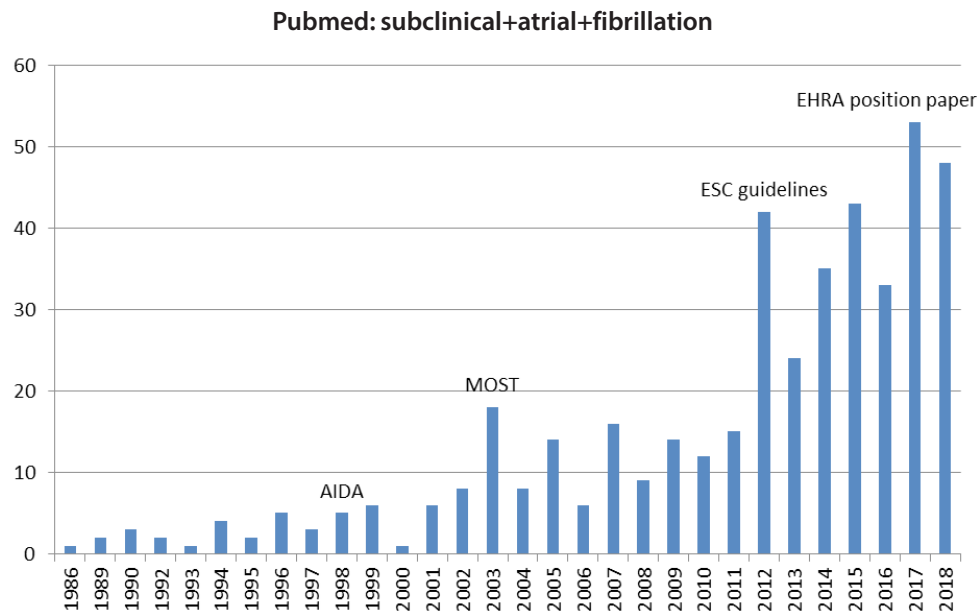**Pubmed: subclinical+atrial+fibrillation**



**Fig. 1.** Evolution of the number of publications related to SCAF, with indication of the milestone studies of subclinical atrial fibrillation as documented by Medline database; best match search – keywords in the title.
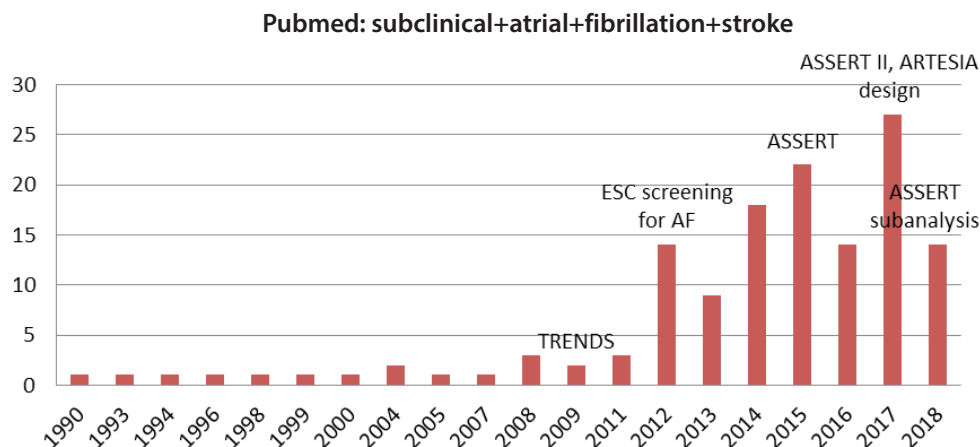
**Pubmed: subclinical+atrial+fibrillation+stroke**



**Fig. 2.** Evolution of the number of publications with indication of the milestone studies of subclinical atrial fibrillation and its association with stroke as documented by Medline database; best match search – keywords in the title.

criteria according to AF history were not so strict[3]. With the exception of the ASSERT trial[8], data on the percentage of previous paroxysmal AF were not provided.

**Detection algorithms reliability/remote monitoring**

Cardiac implantable devices (CIEDs) provide various rhythm monitoring features depending on the type and year of issue. The early ones were able only to detect predefined AHREs, while nowadays, most devices can record full disclosure ECG of each episode, AF burden, and ventricular rate. With the number of CIEDs recipients growing exponentially, we have to find effective ways to make use of their extensive diagnostic power. A unique opportunity for SCAF detection is remote monitoring of CIEDs. At least two non-randomized trials evaluated the

effectiveness and accuracy of AF detection in home monitoring systems[19,20]. Both studies reported optimization of medical treatment associated with earlier detection of SCAF. No data loss was observed in either of the studies. Three more randomized trials (TRUST, CONNECT, IN-TIME) (ref.[21-23]) confirmed the efficacy, safety and reduction of time to the clinical decision in remotely monitored patients; in these trials, however, AF detection was not the primary end-point.

The AF detection algorithms are in most cases correct, there are however several limitations. One of the issues is associated with oversensing of far-field R waves on the atrial channel, which may occur both during ventricular sensing or ventricular pacing. This false positive AF detection may occur in 2-20% depending on the tip to

ring electrode spacing and position of the atrial lead[24,25]. The other issue of CIEDs is atrial undersensing causing underdetection of AF and erroneous logging of long-lasting episodes as multiple short episodes. The positive predictive value for SCAF detection has been shown to be 91% for Biotronik devices[26] and 95.3% for Medtronic devices[27]. For St. Jude Medical devices, more specific data are available: for AF episodes lasting >6 h, the positive predictive value has been shown to be 96.7% while for AF episodes lasting between 6 min and 6 hours, the positive predictive value has been shown to be only 82.7% (ref.[28]).

## Controversies

A growing number of CIEDs and thus detected SCAF spurred interest in the effective management of this patient group, first of all regarding the initiation of anticoagulation treatment. We have to ask the right questions, however. What is the key parameter for starting the anticoagulation treatment? The length of the AHRE episode? The frequency of the particular AHRE? Clustering of the episodes? How reliable is the detection algorithm of each device and do we have to wait for another ECG confirmation of SCAF episode? Are thus device-detected episodes somehow different from AF episodes detected by ECG Holter or loop recorder? What are those episodes themselves – are they indicators of risk or mere risk factors? Given the results of TRENDS and ASSERT trials, are we still convinced that the temporal relationship between AF and stroke even exists?

## What is the stroke risk?

From the Framingham study, we know that the AF-related thromboembolic risk rises linearly from the 6th to 9th decade from 1.5 to 24%, respectively[29]. Approximately 17% of strokes are attributable to documented AF. Moreover, AF-related strokes are associated with a higher mortality rate[29]. We however do not know whether it holds true also for subclinical atrial fibrillation. Major trials assessing the risk of thromboembolic events are summarized in Table 2. We may state that in all of these trials, the risk of a thromboembolic event is increased when AHRE is detected. An episode of at least 5 min of device-detected AF was associated with an increased risk of thromboembolic event, the risk was further increasing with the duration of the AHRE (ref.[3,7,8,10,26]). The threshold is not clear as the cut-off values for minimal AF burden were either chosen arbitrarily or represented by median values. We have insufficient data to confirm that the frequency during AHRE plays any role in the stroke risk[3,7,8,10,26]. Mahajan et al. reported in a meta-analysis of 7 trials (15,353 patients) a 2.4-fold increase of the stroke risk in SCAF patients (95% CI 1.8–3.3, $P$<0.001, I2=0%, $P$=0.69 for heterogeneity) irrespective of AHRE duration[30]. The absolute annual stroke risk in SCAF patients was 1.89 (95% CI 1.02–3.52), and 0.93 (95% CI 0.58–1.49) in patients without SCAF; including only patients with a median $CHADS_2$ score of 2.1, the absolute risk increased to 2.76 (95% CI 1.46–5.23) (ref.[30]). In five studies including altogether 8551 patients, 181 strokes were observed, of which only 98 strokes occurred in patients who had an AF episode during follow-up[30]. In the TRENDS and ASSERT trials, AF episodes were detected in a period of 30 days before stroke only in 55% and 22% of patients[7,8]. A TRENDS substudy on the temporal proximity of AF episodes to thromboembolic events however demonstrated a higher AF burden in patients with AHRE < 30 days before stroke[31].

Similarly, the ASSERT trial showed in patients with detected SCAF within 30 days of stroke longer AHRE episodes; besides, SCAF longer than 24 h was associated with significantly increased risk of stroke, see Table 3 (ref.[32]). While the risk of stroke is increased even in shorter AHREs, the guidelines[2] recommend starting anticoagulation in case of AHREs lasting 5-6 min with >180/min in

Table 2. SCAF trials characteristics according to AHRE frequency, follow-up and thromboembolic risk.

| STUDY | YEAR | n | Follow-up | Rate/bpm | Duration | HR for TE event |
|---|---|---|---|---|---|---|
| MOST | 2003 | 312 | 27 m | >220 | 5 min | 6.7 |
| AT 500 registry | 2005 | 725 | 22 m | >274 | 24 h | 3.1 |
| TRENDS | 2009 | 2486 | 1.4 yr | >175 | 5.5 h | 2.2 |
| Home monitoring/CRT | 2012 | 560 | 370 days | >180 | 3.8 h | 9.4 |
| ASSERT | 2012 | 2580 | 2.5 yr | >190 | >6 min | 2.5 |
| SOS-AF | 2014 | 10,016 | 2 yr | >175 | 1h | 2.11 |
| RATE | 2016 | 5379 | 22.9 m | - | Short AHRE – 1 EGM Long AHRE – blond 1 EGM | 1.75/long AHRE |
| ASSERT FU | 2017 | 2455 | 2.5 yr | >190 | > 6 min | 3.24 for AHRE >24 h |

Table 3. Risk of stroke in ASSERT trial according to AHRE duration[32].

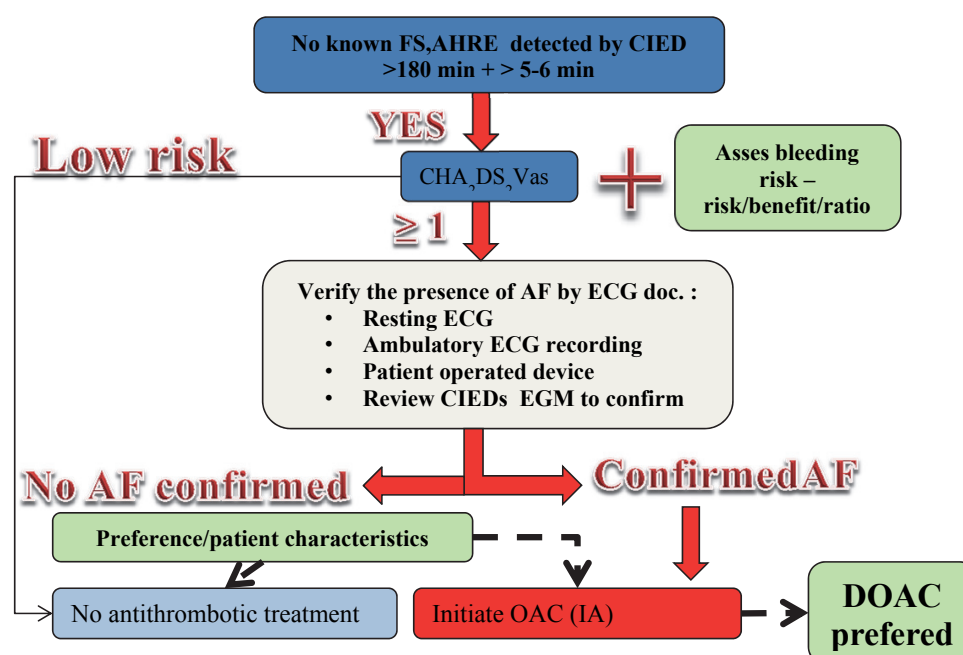| AHRE | Event rate %/year | aHR (1 year) | 95%CI | $P$ |
|---|---|---|---|---|
| no SCAF (< 6 min) | 0.54 | 1 | - | - |
| > 6  min – 6 h | 1.14 | 1.75 | 0.69-4.44 | 0.24 |
| > 6-24 h | 0.95 | 1.85 | 0.43-8.01 | 0.41 |
| > 24 h | 3.08 | 5.37 | 2.08-13.87 | 0.001 |

**Fig. 3.** Algorithm for anticoagulation initiation in patients with AHRE as a surrogate for AF detection. Modified from Kirchhof P. et al. Eur J Cardiothorac Surg 2016;50(5):e1-e88.

$CHA_2DS_2Vasc$ score $\geq 1$ – for more details, see the algorithm in the Fig. 3. The EHRA position paper[3] defines the threshold as follows: for patients with $CHA_2DS_2Vasc \geq 2$ in males and $\geq 3$ in females, oral anticoagulation (OAC) is recommended for AF burden > 5.5 h/day. The lower duration may merit OAC if multiple risk factors are present[3]. There were also attempts to administer the OAC treatment only during device-detected arrhythmia. The IMPACT trial was prematurely stopped for futility, the strategy of early initiation and interruption of anticoagulation based on remotely detected AT did neither prevent thromboembolism events nor bleeding[33]. The TACTIC trial[34] tested intermittent anticoagulation in patients with continuous AF burden monitoring in low to moderate risk patients with rare episodes of AF. Pacemaker (PM)/Implantable cardioverter-defibrillator (ICD)-guided DOAC administration has been shown to be feasible and reduced the use of anticoagulation therapy by 75%. The trial however did not have sufficient statistical power to show a significant difference in bleeding and thromboembolic episodes. Intermittent AF burden-related anticoagulation might be promising in low to moderate risk patients but in high-risk patient AF might be only one of the causes of TE risk. Atrial cardiomyopathy might be an isolated risk factor for thromboembolic events irrespective of atrial fibrillation[35]. Two other randomized controlled trials (ARTESIA, NCT 01938248; NOAH-AFNET 6, NCT 02618577) are testing the potential of AHRE-guided anticoagulation therapy. In ARTESIA trial[36], inclusion criterion is at least one episode of AHRE > 6 min with an atrial rate > 175/min while a single episode lasting >24 h is an exclusion criterion; the primary end-point is stroke and systemic embolism and the patients are randomized to groups administered either apixaban (5 mg bi-daily) or aspirin 81 mg/d.

The NOAH AFNET 6 trial tests whether oral anticoagulation with edoxaban is superior in prevention of stroke or cardiovascular death compared with aspirin or no antithrombotic therapy based on evidence-based indications[37].

## CONCLUSION

Subclinical atrial fibrillation is quite common, especially in patients with cardiac implantable devices where it occurs in 30% of patients. SCAF duration $\geq 24$ h is associated with significant risk of thromboembolic events. The minimum threshold to start anticoagulation is unknown and the recommendations of ESC/EHRA are contradictory. There is no good clinical evidence that anticoagulation treatment in AHRE/SCAF is effective. Two trials are ongoing. At present, an individual approach accounting for thromboembolic risk factors and AHRE duration has to be adopted.

### Search strategy and selection criteria
Our research strategy was aimed at evaluating studies on the link between subclinical atrial fibrillation and the risk of stroke. Scientific articles from 1986 to 2018 were searched using the PubMed and Web of Science databases. All searches were up to date as of October 2018. The search terms used included "subclinical atrial fibrillation," "stroke risk," "device detected atrial fibrillation," "SCAF," "AHRE." Only English language papers were reviewed.

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