

Subclinical atrial fibrillation: when to give NAO?

Giuseppe Patti^{1,2*} and Alessandro Sticchi²

¹*Dipartimento di Medicina Clinica, Sanità Pubblica, Scienze della Vita e dell'Ambiente, Università dell'Aquila, Italy; and*

²*Policlinico Campus Bio-Medico di Roma, Italy*

KEYWORDS

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Atrial fibrillation is defined as subclinical (SAF) when occurs without symptoms and is discovered only during the interrogation of permanent or temporary cardiac implantable devices. The significant interest in this condition derives from the fact that could easily be otherwise undiagnosed, portending to a potential serious neurological and cardiovascular consequences. The diagnosis of SAF is important for both the primary form and for patients after a stroke, and an appropriate management of antithrombotic treatment becomes a central instrument of prevention. Atrial fibrillation carries a five times increase in the thromboembolic risk. The subclinical asymptomatic forms of atrial tachyarrhythmias and fibrillation, diagnosed by interrogation of implantable cardiac devices, foretell a non-irrelevant risk of stroke, significantly higher than the one for patients without rhythm disturbances. Regardless the cause, the long-lasting asymptomatic arrhythmias, in patients with a significant risk profile, predict more important consequences and can justify anticoagulant treatment, also in primary prevention settings.

Introduction

Atrial fibrillation is the most common of the cardiac rhythm changes with pathological significance.¹ The incidence of atrial fibrillation is constantly increasing due to the increase in risk factors and the age of the population.² However, the prevalence observed in the literature of about 3% of the population, with even higher values in the elderly group (around 24% in men and 16% in women), does not include patients suffering from subclinical or silent atrial fibrillation (SAF), whose number is also constantly increasing, mainly due to the expanding use of implanted cardiac devices.^{1,2} The term SAF means, in fact, the finding of asymptomatic forms highlighted in the continuous recordings of temporary or permanent implantable cardiac devices for the diagnosis and control of short and long duration of cardiac rhythm.³ Various studies have shown that symptomatology alone does not allow to accurately determine the presence of atrial fibrillation, given the poor correlation between symptoms and episodes of paroxysmal

atrial fibrillation, not always felt by the patient.³ Subsequently, with the spread of implantable devices, for monitoring only or by stimulation, it emerged that more than 90% of atrial arrhythmias are asymptomatic and, conversely, the patient's symptoms correspond in 20% of cases to arrhythmic episodes, legitimizing the definition of FAS as an asymptomatic form found by devices.⁴

Subclinical atrial fibrillation is detected in at least one-third of patients in the first years after implantation of a cardiac device and its finding entails a risk of approximately six times to develop clinically relevant atrial fibrillation later.⁵ The presence of atrial fibrillation leads to an increased risk of thromboembolism and stroke, but further studies are currently needed to clarify this role for SAF.⁵ Clinically relevant atrial fibrillation is associated on average with an increase in the risk of stroke of about five times compared to the population not affected by this arrhythmia, and the stroke from atrial fibrillation is correlated with a greater severity, a higher risk of recurrence and a higher mortality than stroke of other origin.^{6,7}

In asymptomatic patients, atrial fibrillation may be discovered for first time following a thromboembolic ischaemic event; in the absence of clinically evident stroke, SAF

*Corresponding author. Email: g.patti@unicampus.it

Take home message

- The incidence of atrial fibrillation is continuously increasing in both clinical and subclinical forms.
- Subclinical atrial fibrillation and forms of atrial tachyarrhythmias are found in 30–50% of patients carrying cardiac devices.
- Subclinical atrial fibrillation is a predictor of future clinical atrial fibrillation.
- Subclinical atrial fibrillation and forms of atrial tachyarrhythmias lasting >5 min appear to configure a higher risk of stroke than the control population without such arrhythmias.
- The patient's arrhythmic load correlates with the increased risk of thromboembolism.
- In the event of subclinical atrial fibrillation and atrial tachyarrhythmias, the initiation of anticoagulant therapy in primary prophylaxis must be evaluated through an assessment of the risk of thromboembolism using the CHA₂DS₂-VASc score, correlating this stratification of risk with duration and the arrhythmic load of the event recorded during the monitoring.

can be associated with recurrence of asymptomatic cerebral ischaemic events resulting in memory and cognitive deficits.⁸ As for clinically evident atrial fibrillation, it is therefore crucial to determine more accurately the correlation between SAF and brain deficits, to delineate adequate antithrombotic strategies for primary and secondary prophylaxis of thromboembolic events and their long-term consequences, even in the brain.

Thromboembolic risk in subclinical atrial fibrillation

Atrial fibrillation is related to the onset of thromboembolic ischaemic events, to prevent which the role of oral anticoagulant therapy is well recognized. Considering the possible evolution of SAF towards a form with clinical contents, we could, already in the asymptomatic phase, use anticoagulant therapy in primary prophylaxis.⁹ The literature on this topic is composed of numerous studies that have highlighted the efficacy of anticoagulant therapy (both with vitamin K antagonists and with direct oral anticoagulants) for the prevention of stroke in different clinical-pathological variants of non-valvular atrial fibrillation, including the paroxysmal forms.^{10,11} However, the percentage of patients in the real world taking anticoagulant therapy is very low in those who have SAF with no history of a previous stroke (<25%).¹²

The studies present in the literature on the subject are heterogeneous in terms of patient characteristics, types of implanted devices, and definitions of the endpoints, and this makes comparison analyses difficult. What these studies have in common is a low incidence of thromboembolic events in the group of patients without SAF (<1.2% per

year), and a high prevalence of atrial fibrillation already known in the group of patients with SAF (between 20% and 60% in the various studies), and therefore exposed to the resulting risk of thromboembolism.¹³

Various evidences have confirmed the association between atrial tachyarrhythmias and risk of thromboembolic events, even in patients without previous history of atrial fibrillation, with a higher incidence in the group with evidence of repeated paroxysmal forms.¹⁴ Specifically, in over 15 000 patients enrolled in seven studies, the significant association between SAF and stroke risk was demonstrated, albeit with a different SAF duration time limit in each study.¹⁵ The risk of stroke in patients with SAF was 2.4 times higher than in the control group without SAF, with a percentage of 1.89 per 100 people/year vs. 0.93 per 100 people/year in patients without SAF. In a meta-analysis of three studies, the population with SAF had a CHADS₂ score of 2.1 ± 1 had an annual incidence of stroke of 2.76% compared to 1.08% in patients without SAF.¹⁵ The risk of stroke in patients without a history of previous stroke and with SAF finding is however lower than both the risk of patients with a history of stroke and evidence of asymptomatic episodes of paroxysmal atrial fibrillation and of patients with clinically evident fibrillation, probably for the 'arrhythmic burden less than the subclinical form compared to the clinically relevant one'.¹⁵ Other factors that could contribute to a lower thromboembolic risk in the SAF compared to the clinically evident form are a lower thromboembolic risk profile (as evidenced by a lower CHADS₂ score), the concomitant intake of anticoagulant therapy and a particular attention to the control of concomitant risk factors.¹⁵

Duration and timing of thromboembolic events in subclinical atrial fibrillation

The threshold of duration of arrhythmic episodes for stroke prediction in SAF varies considerably in the literature, passing from the 5 min of the MOST study, which showed an increase of about four times the risk of thromboembolism, to 6 min of the ASSERT study, to 1 h of the SOS-AF and at >5.5 h of total arrhythmic load during the day of the TRENDS study.¹⁵ Other studies have instead correlated the risk of stroke at longer intervals, such as episodes lasting >24 h, or >12 h in patients with heart failure enrolled in the Finnish CardioVersion Trial.¹⁵⁻¹⁷ Despite the aforementioned great variability of temporal thresholds, the overlapping of these thresholds in some studies has led to the validation of three main reference ranges: a range with SAF duration <5 min, an intermediate range with duration between 5 min and 24 h, and one with a duration >24 h. The two extreme intervals were related to a thromboembolic risk <1.68% for SAF <5 min and >4% for SAF duration >24 h, with an intermediate risk in the case of duration between 5 and 24 h.⁹ An inverse relationship was demonstrated between the time intervals of asymptomatic arrhythmic episodes related to thromboembolic events and the basal risk profile assessed with the CHADS₂ score.¹⁸ Recent evidence also supports that for very short episodes of SAF, between 15 and 20 s, there is a very low risk of

stroke, such as not to require prophylaxis with anticoagulant therapy.¹⁵⁻¹⁷

However, a *post hoc* analysis of the TRENDS and ASSERT studies showed that only 29% of cerebral ischaemic events were related to the presence of SAF within 30 days prior to the event or directly associated with the presence of SAF at the time of the event.^{19,20} However, in these studies an accurate distinction between cardioembolic or non-cardioembolic nature of stroke was not performed and there was no specific evaluation based on the concomitant anticoagulant therapy, as the use of the latter in patients with history of previous fibrillation, it may have selected patients with a higher relative risk of atherothrombotic stroke instead of cardioembolic stroke.

Causality of thromboembolic events in the subclinical atrial fibrillation

The formation of the thrombus that causes the stroke in atrial fibrillation has been classically related to the blood stasis in the left atrium and in particular of the left auricle due to the lack of an effective contraction. Cardiovascular risk factors such as advanced age, high blood pressure, and diabetes are predisposing because they cause an 'atrial myopathy' with alterations of atrial tissue that can lead to the development of atrial arrhythmias and consequent thromboembolism due to contractile dysfunction and stasis of blood in the cardiac chamber.²¹ However, regarding the timing of connection between these events, the data are controversial. It has been suggested that for an arrhythmic load of at least 5.5 h the risk of stroke is higher after 5-10 days from the arrhythmia and loses significance after 30 days.²² However, as already pointed out, in the TRENDS study 73% of patients with cerebral ischaemic events had not recorded arrhythmic events in the 30 days preceding the stroke and in the ASSERT study, where only 8% of patients who had had a stroke had recorded at least 6 min of fibrillation in the 30 days before the event.^{19,20} Thrombus formation mechanisms in atrial fibrillation are therefore multiple and complex, as they are also influenced by concomitant risk factors.

Subclinical atrial fibrillation and anticoagulation

As for patients with evidence of SAF the management of anticoagulant therapy remains controversial at present, because, as indicated above, the data on time discrimination or the length of the arrhythmic episode are not conclusive. In the absence of specific data, most of these patients currently do not receive anticoagulant therapy,²³ although it is known that the risk of stroke is independent of the presence of symptoms related to atrial fibrillation. Furthermore, implantation and monitoring through implantable devices in many cases favours an observation and waiting strategy as a clinical-therapeutic choice. The introduction of oral anticoagulant therapy in primary prevention must however be evaluated with careful balance between thromboembolic risk and bleeding risk.

The randomized, open-label study, IMPACT, aimed to evaluate the net composite endpoint of thromboembolic events and bleedings in patients randomized to ICD/CRT-D with 'active home monitoring' and systematic initiation of anticoagulant therapy in case of detection of atrial fibrillation with pre-specified criteria vs. ICD/CRT-D with routine monitoring and conventional therapy in case of detection of atrial fibrillation. The trial was stopped early after a 75% analysis of the data due to the event overlap between the two treatment arms.²⁴ We are currently awaiting the results of three studies that should lead to specific answers regarding the benefits of anticoagulant therapy in terms of protection against ischaemic events, compared to the risk of bleeding, in patients with long-term arrhythmia monitoring, also to further define the very role of this rhythm recording information. The LOOP trial is enrolling 6000 patients at risk of atrial fibrillation, of which 1500 randomized to loop recorders and 4500 randomized to a standard approach, in order to evaluate whether the remote monitoring of cardiac rhythm by the device and subsequent antithrombotic strategies in the case of atrial fibrillation diagnosis they prevent cerebral ischaemic events. The prospective ARTESiA study is randomized in double-blind patients with evidence of SAF, detected by interrogation of implanted cardiac devices, to anticoagulant therapy with apixaban or aspirin (81 mg daily) and will consider the thromboembolic and haemorrhagic ischaemic events as endpoints; in particular, the ischaemic endpoint of cerebral ischaemic events will be evaluated by magnetic resonance using the DWI technique for the search of infarct areas. Finally, the NOAH-AFNET 6 is also a multicentre randomized trial that aims to evaluate the superiority of edoxaban vs. aspirin therapy in SAF patients.

Current scientific evidence needs further results that can shed light on this issue and, pending further data, it seems reasonable that the use of anticoagulant therapy is personalized and to be preferred in the case of at least a moderate risk profile. In an attempt to give greater clarity on the subject, the consensus document of the European Heart Rhythm Association has been prepared, which indicates to stratify the risk of patients with evidence of SAF through the CHA₂DS₂-VASc score, the sex and the duration of the arrhythmic event, recommending a possible therapeutic approach with vitamin K antagonists or new oral anticoagulants depending on the risk profile reached by the patient²⁵ (Table 1).

Future prospects

The incidence of atrial fibrillation in the coming years is expected to increase, both in the clinically evident and, probably even more, in the subclinical forms. In fact, the increasingly widespread cardiac rhythm monitoring systems, considering also those of a playful-sporting type, are expected to highlight an increasing number of asymptomatic atrial arrhythmic forms that will pose the demand for a possible prophylaxis treatment for thromboembolism. Furthermore, the further development of the technologies will allow electrocardiographic monitoring with live data transmission from implanted cardiac devices. All this can

Table 1 Current vision of International Societies

EHRA/HRS/APHRS/SOLEACE 2017 Patients with sub-clinical atrial fibrillation	
Duration	>5.5 h/day
Thrombo-embolic risk evaluation	CHA ₂ DS ₂ -VASC score: stratify by values
Oral anticoagulant treatment	<ul style="list-style-type: none"> • Indicated if arrhythmia duration >5.5 h a day and CHA₂DS₂-VASC score ≥2 (men) or ≥3 (women) (the duration of the arrhythmia can be reduced if multiple thromboembolic risk factors are present) • To be considered, based on the bleeding risk, if arrhythmia duration >5.5 h a day and CHA₂DS₂-VASC score ≥1 (men) or ≥2 (women) • Not indicated, regardless of duration, if CHA₂DS₂-VASC score 0 (men) or 1 (women)

lead to an increasingly early diagnosis in high-risk patients and to a possible improvement in primary stroke prevention related to atrial fibrillation. In addition, the trials currently underway should answer important questions, especially regarding the use of the new oral anticoagulants in these subclinical arrhythmic forms, assessing their benefit against the risk of bleeding. It is probably more necessary in these patients to seek a more accurate stratification of thromboembolic and haemorrhagic risk than the current CHA₂DS₂-VASC and HAS-BLED scores.

Conclusions

The presence of atrial fibrillation is associated with a five-fold increase in the risk of thromboembolism. The subclinical and asymptomatic forms of atrial fibrillation and atrial tachyarrhythmias, detected by interrogation of implanted cardiac devices, correlate with a non-negligible and superior incidence of stroke compared to patients without such rhythm alterations. Regardless of the cause, long-term asymptomatic arrhythmic forms, in subjects with a significant risk profile, are associated with more serious outcomes and may justify anticoagulation even in primary prophylaxis.

Conflict of interest: none declared.

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