When to set anticoagulant therapy in asymptomatic AF? looking for a cut-off duration

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The incidence of atrial fibrillation (AF) is progressively increasing, in line with the aging of the population and with the increase in chronic diseases. The care burden of the disease and above all to its consequences (i.e. ischaemic stroke and heart failure) significantly impacts the various health systems with forecasts of exponential increase in the near future. Clinical forms of AF, i.e. those diagnosed with electrocardiogram, have a clear correlation with systemic embolic events and also with a reduction in survival. Thromboembolic prophylaxis in these patients, with anticoagulant drugs, has in fact been shown to greatly reduce the incidence of ischaemic stroke and improve survival. In recent decades, the widespread use of therapeutic intra-cardiac devices, which allow constant and continuous monitoring of myocardial electrical activity, is bringing to light a large number of atrial high rate episodes (AHREs), which are not associated with clinical manifestation. The incidence of these findings grows linearly with the duration of the observation. More independent studies have shown that AHREs are associated with a risk of stroke that is higher (about double) than controls but significantly lower than in patients with manifest AF. However, taking into consideration patients with ischaemic stroke and wearers of implantable devices, no temporal correlation emerged between the incidence of the ischaemic episode and arrhythmia. The presence of AHRE is associated with an approximately six-fold increase in the incidence of clinical AF but only a minority of these patients meet the criteria for prescribing anticoagulation. Pending the publication of the studies still in progress, the European Society of Cardiology guidelines for the treatment of AF recommend considering the initiation of anticoagulant therapy in patients with long-lasting AHRE (> 24 h) associated with a high embolic risk. In patients with episodes of shorter duration (1-24 h), especially if with high burden, anticoagulant therapy can be considered in case of very high embolic risk (e.g. secondary prevention, CHADVASc ≥ 3).

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Patients with implantable intra-cardiac devices (ICDs) represent a unique population characterized by frequent comorbidities that predispose to the development of atrial arrhythmias. These devices, which are often equipped with an atrial lead, allow to continuously record the electrical activity of the heart and detect a large number of arrhythmias regardless of the presence of symptoms. In fact, their increasingly widespread use is bringing to light a large number of high atrial rate episodes (defined as AHREs: atrial high rate episodes), asymptomatic and therefore would never have come to medical attention.

Although they can be confused, AHREs differ from AF in the mode of diagnosis, the absence of symptoms, and, as we will see later, for a different embolic risk. The response of an AHRE generates, for the cardiologist who approaches it, the problem regarding its interpretation and its eventual treatment.

Atrial high rate episode: definition and incidence

The term AHRE defines the episodes of atrial tachycardia automatically recognized by implantable cardiac devices, based on certain criteria established by the manufacturer; the events should be viewed by a physician to rule out false positives, mainly represented by artefacts (external interference or malfunctions) or other specific forms of supraventricular arrhythmia (e.g., episodes of atrial flutter, SVPT supraventricular paroxysmal tachycardia or PMT pacemaker-mediated tachycardia).

To date, there is no universally accepted definition and the various manufacturers of cardiac devices use different cut-offs (both for frequency and duration) for the recognition of these episodes. Different definitions have also been adopted in the various studies in the literature and this makes a global interpretation of the results much more complex. For example, in the ASSERT study (Subclinical Atrial Fibrillation and the Risk of Stroke—N Engl J Med 2012; 366:120–129), one of the main works published on the subject, significant episodes of atrial tachycardia with a frequency greater than 190 bpm and lasting at least 6 min were considered, whereas in the TRENDS study (The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostic and stroke risk—Circ Arrhythm Electrophysiol. 2009 Oct; 2(5):474-80) episodes were analyzed with a duration of more than 20 s and a frequency of at least 175 bpm. In a recent EHRA consensus, AHREs were defined as episodes with atrial rate above 190 bpm, without however specifying a minimum duration limit; the ESC guidelines of 2020 on the diagnosis and treatment of AF instead propose an atrial rate of at least 175 beats/min for at least 5 min as a criterion. The presence of a duration criterion has the advantage of minimizing the possible inclusion of artifacts/electrical noise recorded by the atrial catheter, as well as other forms of short duration arrhythmias.

The incidence of AHRE varies significantly between the various studies and is between 10 and 70%.

Such variability can be justified considering that the data in the literature also come from very different works (prospective and retrospective studies, registries and case studies) that involved different populations (in particular only a minority of the studies excluded patients with a history of AF) and who, as mentioned above, have adopted different definitions of AHRE. In the ASSERT study, the only large study that excluded patients with a history of AF, the incidence of AHRE was 25% at 2.5 years of observation, with an increase linearly related to the duration of follow-up. This data is in line with what reported by a sub-analysis of the TRENDS study which, excluding patients with previous AF or use of anticoagulants/antiarrhythmics, reports an incidence of AHRE of 31%, identifying, however, a higher incidence of AHRE of long duration (> 6 h) higher CHADS score in patients.

With all the limitations due to the heterogeneity of the available data and the poor comparability of the studies, it seems that the main factors influencing the incidence of these arrhythmias are, in addition to the history of AF (which also facilitates interpretation and management episodes), advanced age, high blood pressure and Type II diabetes mellitus. According to other papers, the original indication for implantation (e.g. for sinus node disease vs. AV node disorders), as well as the high percentage of pacing, both atrial and ventricular, appear to be associated with a higher incidence by AHRE. (Figure 1)

Atrial high rate episode and embolic risk

Several publications have associated the finding of AHRE with thromboembolic events. The ASSERT study demonstrated that, in a follow-up of almost 3 years, patients who had experienced episodes of high atrial rate in the first months of enrolment had a significantly higher incidence of ischaemic stroke and systemic embolisms than others patients, with a hazard ratio (HR) of 2.49 (95% CI: 1.28-4.85; P = 0.007). This increased risk was substantially preserved both by censoring patients diagnosed with manifest AF (HR: 2.41; 95% CI: 1.21-4.83; P = 0.01) and by stratifying patients by CHADS2 score. Subdividing the episodes by duration also showed a stronger association for episodes of longer duration (HR, respectively, 1.7 for all episodes > 6 min, 2.9 for those> 6 h and 4.9 for those> 24 h, compared with the group without arrhythmia). Also in the TRENDS study, a higher incidence of stroke is reported in the group of patients with AHRE > 5.5 h compared with the others; however, it should be noted that patients with a history of AF in medical history were not excluded from the study.

Many other papers, as well as a recent meta-analysis, report an AHRE-embolism association suggesting overall a greater risk for episodes of longer duration and in patients with a higher CHADS2 score. On the other hand, it is more complex to define the possible association between embolic events and AHRE of short duration (which, moreover, represent the majority of the episodes that are encountered daily when checking implantable devices): while an analysis of the
When to set anticoagulant therapy in asymptomatic AF?

RATE register, which evaluated a cohort of over 5000 PM/ICD patients, found no such association during the 2-year follow-up, a more recent meta-analysis, which considered 27 studies for a total of nearly 62,000 patients, reports an association with thromboembolic events for AHRE lasting more than 30 s.

Temporal relationship between atrial high rate episode and thromboembolic events

Although there is an association between AHRE and an increased risk of thromboembolism, the mechanisms by which this occurs are not clear.

It is known that the embolic risk of AF is given by the tendency to thrombus formation inside the left atrium, especially in the left auricle, caused by a reduced contractility (this mechanism also explains the increased incidence of embolic events following cardioversion). By analyzing patients hospitalized for ischemic stroke and with implantable devices, it emerged, however, that the temporal association between silent atrial arrhythmia and embolism is very weak if not completely absent. In a sub-analysis of the TRENDS study which included only patients with thromboembolic event (encephalic or systemic) it was reported that only 50% of the patients involved had documentation of AHRE before the index event, and of these only a small part was in arrhythmia during the embolic event (15%) or in the previous month (25%). Similarly, in the ASSERT study, only 12% of embolisms were preceded by AHRE in the previous month and 2% of patients were experiencing the arrhythmia during the event.

Precursors of atrial fibrillation?

Episodes of short duration AHRE often evolve in the same patient into episodes of longer duration. Several studies have shown a significant increase in the incidence of AF (clinical) in patients with AHRE: ASSERT reports an incidence of AF of 15% in patients in whom an episode of AHRE was identified vs. 3% of patients in the group without AHRE (HR: 5.5). Similar results also emerged from the subgroup of patients of the MOST study (AHREs detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial) without a history of AF before enrolment (39 vs. 2%).

However, some considerations must be made: although a higher incidence of AF emerged, this only affected a minority of patients with AHRE (85% of patients with AHRE in the ASSERT study did not have a diagnosis AF during follow-up). Furthermore, the incidence of embolic events, although increased, is much lower than that of patients with AF. Finally, as mentioned previously, the lack of temporal correlation with thromboembolic events suggests that AHREs represent a risk indicator for embolisms rather than a causal factor.

Treatment of atrial high rate episodes

While anticoagulant therapy plays a fundamental role in the prevention of embolic events and allows a reduction in mortality in patients with AF, there is no evidence to date that justifies its use in patients with AHRE. The decision to undertake anti-thrombotic prophylaxis with anticoagulant drugs in these patients therefore remains at the discretion of the individual clinician and represents a daily problem for the cardiologist who deals with the control and programming of pacemakers and defibrillators. Some factors that can influence this choice are the number and duration of arrhythmic episodes, the total arrhythmia burden and also the patient’s basal embolic risk (given by age, comorbidities, and CHADSVASc score).

A recent survey involving doctors from all over the world (80% cardiologists) found that more than one third of the participants considered a single episode of asymptomatic arrhythmia lasting more than 5 min to be sufficient for the prescription of OACs (oral anticoagulants), whereas the 16 and 18% considered that an arrhythmia burden greater than 5.5 and 24 h, respectively, was necessary. When patients with a previous stroke or TIA were considered, almost all doctors agreed in prescribing anticoagulant prophylaxis.
The association between AHRE and thromboembolic events certainly makes anticoagulant prophylaxis ‘inviting’, but it is not in itself sufficient to justify it. We find a similar example in a couple of studies\textsuperscript{13,14} aimed at evaluating the efficacy of OAC therapy in preventing relapses in patients with a history of thromboembolic ischaemic stroke and without AF documentation: both works failed to demonstrate superiority of OAC over standard therapy (with ASA, aspirin) in preventing relapse and reported more clinically relevant bleeding episodes in the OAC-treated group.

To date, two randomized trials are underway aimed at identifying the efficacy of anticoagulant prophylaxis in patients with AHRE (ARTESiA: apixaban vs. aspirin; \(n = 4000\) –ClinicalTrials.gov identifier: NCT01938248; and NOAH: edoxaban vs. aspirin; \(n = 3400\) pcs–ClinicalTrials.gov Identifier: NCT02618577) with composite endpoint of ischaemic stroke, systemic embolism, and cardiovascular mortality.

Given the association with episodes of AF, it is reasonable to perform a 12-lead ECG together with a clinical evaluation with estimation of the embolic risk (CHA\textsubscript{2}DS\textsubscript{VA}Sc) whenever there is documentation of AHRE. These patients must also be followed-up with close checks (even in remote control mode) in order to be able to identify early progression towards prolonged forms of arrhythmia (especially identifying episodes lasting more than 24 h).

A previous consensus document EHRA (Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—2017) had identified a daily burden greater than 5.5 as a risk cut off, therefore as a threshold beyond which to prescribe anticoagulant therapy in prophylaxis. According to the most recent ESC guidelines on the diagnosis and management of atrial fibrillation (ESC Guidelines for the diagnosis and management of atrial fibrillation—2020), the use of anticoagulants can be considered (Class of recommendation IIA) in patients with long-lasting episodes (\(\geq 24\) h) when associated with an estimate of high embolic risk (CHA\textsubscript{2}DS\textsubscript{VA}Sc score \(\geq 3\)), after discussion of potential risks and benefits with the patient. (Figure 2)

**Conclusions**

Pharmacological treatment of AF is effective and safe in the prevention of embolic complications and in prolonging patient survival.

The extensive use of ICDs (implantable pacemakers/defibrillators), which allow continuous monitoring of the heart rhythm, has brought to light an enormous number of patients with subclinical atrial arrhythmias (about 8 times higher than the manifest forms), generating the problem of their correct interpretation and treatment. Further complicating the decision-making process is
the fact that these arrhythmias are independently associated with the risk of clinical AF, as well as with an increased incidence of ischaemic stroke and systemic embolisms. To date, we have no data to justify the prescription of anticoagulant therapy in all patients with AHRE: pending the publication of the two studies now in progress (ARTEsIA and NOAH), European guidelines recommend close monitoring of the rhythm in order to identify early progression in AF. The initiation of anticoagulant prophylaxis can be considered in selected patients, characterized by a high overall arrhythmic burden and a high embolic risk profile.

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