European Heart Journal Supplements (2024) **26** (Supplement 1), i123–i126
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae029

Management of atrial arrhythmias identified by cardiac devices

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KEYWORDS
Subclinical atrial fibrillation;
Atrial high-rate events;
Oral anticoagulant therapy;
Thrombo-embolic risk stratification

Implantable cardiac devices have shown that atrial fibrillation (AF) is more frequent than previously assumed, with subclinical, asymptomatic, self-limiting manifestations called atrial high-rate events (AHREs) or subclinical AF. The clinical significance and correct therapeutic management of these episodes of subclinical AF is less well defined than in the case of clinically manifest AF. Two important randomized studies on the topic have recently been published, NOAH-AFNET 6 and ARTESIA, which, however, have not definitively clarified the topic. In patients with AHRE or subclinical AF, the average thrombo-embolic risk is lower than that in patients with clinically manifest AF and is ∼1%. For this reason, in these patients, the possibility that the benefit of anticoagulant therapy is overshadowed by the risk of bleeding is very high. Therefore, while waiting for new tools that allow a better stratification of low-risk patients, we must rely on individual clinical evaluation and overcome the qualitative dichotomy (AHRE yes vs. AHRE no), preferring instead an approach that is as quantitative as possible and takes into account the number of episodes, their duration, and the patient's CHADSVASC score, before deciding, in each individual case, whether or not to use anticoagulant therapy.

Introduction

The use of oral anticoagulant therapy (OAT) for antithrombotic prophylaxis in patients with clinically manifest atrial fibrillation (AF) has been extensively studied in numerous clinical trials, and overall, this therapy has proved effective, reducing the risk of stroke by 64% and the risk of death by 25%.[1] The ever-increasing use of implantable cardiac devices, pacemakers (PMKs), implantable converter defibrillator (ICD), and implantable loop recorder (ILR), and now also wearables (smart watches), which allow a continuous monitoring of the heart rhythm, has, however, shown that AF is much more frequent than previously hypothesized, with subclinical, asymptomatic, self-limiting manifestations, of which the patient is often unaware. These episodes are called atrial high-rate events (AHREs) or subclinical AF. Crystal AF (cryptogenic stroke and underlying AF) data,[1] e.g. in a population of 221 patients with cryptogenic stroke or transient ischaemic attack (TIA), without a previous history of AF, undergoing ILR implantation, in fact, have demonstrated that 6 months after implantation of the device, at least one episode of AF is observed in 8.9% of subjects; this percentage rises to 12.4% after 12 months and to 30% if the follow-up is extended up to 36 months. These data have ample confirmation in the literature. Studies conducted in patients undergoing PMK or ICD implantation provide comparable results: 10% of AF at 3 months and 35% at 30 months in the ASSERT (Atrial Fibrillation Reduction Atrial Pacing Trial),[2] 30% of AF at 1 year in TRENDS (The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk),[3] 43% at 24 months in the SOS AF (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices),[4] and 51% at 27 months in the MOST (MOde Selection Trial).[5]

Particularly noteworthy is the fact that many of the episodes diagnosed in these studies are asymptomatic. In Crystal AF,[1] where episodes lasting at least 30 s were considered, 74% of the episodes were asymptomatic, and

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in ASSERT,[2] which included AF episodes lasting at least 6 min, 84% of the episodes were asymptomatic. These data, as mentioned, all derive from case series of patients with cardiac devices and therefore may not be fully transferable to the general population; nevertheless, they show that the presence of short-term arrhythmic episodes is certainly frequent, although perhaps with different percentages in different types of patients, and that the majority of these episodes is asymptomatic.

The clinical significance and correct therapeutic management of these episodes of subclinical AF is less well defined than in the case of clinically manifest AF.

Clinical significance of atrial fibrillation episodes detected by cardiac devices

The ASSERT study[2] enrolled 2451 hypertensive subjects, without a history of AF, who underwent PMK or ICD implantation. Thrombo-embolic events occurred in 4.2% of patients with evidence of AF episodes (to be considered as such had to last >6 min and have a heart rate >190 b.p.m.) and in 1.7% of subjects without AF, with a hazard ratio (HR) of 2.49. In the MOST study,[5] 312 patients with PMK were followed for 27 months. The combined endpoint of death or non-fatal stroke occurred in 20.6% of subjects with AF episodes (duration >5 min) and in 10.5% of those who were free from arrhythmic events (HR 2.79). In the SOS AF study,[4] which accumulated data from 3 different clinical studies analysing 10 016 patients, those who had episodes of AF >5 min had an HR for stroke or TIA of 2.04 compared with those who had no episodes. Also in Capucci *et al.*'s study,[6] the presence of AF episodes >24 h increased the probability of a thrombo-embolic event by 3.1 times. However, episodes that lasted between 5 min and 24 h did not induce an increased probability of thromboembolism. In TRENDS,[3] those who had AF episodes lasting >5.5 h had a 2.2-fold increase in the risk of thrombo-embolic events compared with those without arrhythmias.[7]

These studies certainly present numerous limitations: they included heterogeneous populations, with variable percentages of patients in OAT; in some cases, they classified the arrhythmia based on the duration of the individual episodes, while in others, they took into account the total arrhythmic load ('burden'), and, finally, they provided variable results on the cut-off duration of the arrhythmia capable of having repercussions on the thrombo-embolic risk. Even taking these limitations into account, the studies as a whole have demonstrated that in the populations studied, a thrombo-embolic risk exists, even if it is low; that episodes of AF, even if short-lived, even if asymptomatic, still increase this thrombo-embolic risk; that the longer the duration of the arrhythmia, the higher the risk; and that, finally, it is not currently possible to identify a minimum limit of duration of AF episodes that can be said to be safe and without effects on the risk of thrombo-embolic events.

Temporal relationship between atrial fibrillation episodes and thrombo-embolic events

Our cultural paradigm according to which AF increases the risk of stroke only because it causes blood stasis in the atria, which, in turn, facilitates the formation of clots from which emboli can detach, has been challenged by the data emerging from continuous monitoring of the heart rhythm operated by cardiac devices. In fact, the continuous recording of the cardiac rhythm allows us to establish, in subjects presenting thrombo-embolic phenomena, the temporal relationship between arrhythmia and clinical events. In Shanmugam *et al.*'s study,[8] e.g. the last episode of AF occurred at an average of 46.7 ± 72 days before the thrombo-embolic event. In TRENDS,[8] 40 patients presented an arrhythmic episode before a thrombo-embolic event, but in 73% of these, AF was not present in the 30 days preceding the embolic event. Also in the IMPACT (Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices),[9] no temporal association emerged between AF and clinical events. Considering both groups of the study, 69 thromboembolisms occurred: 20 of these occurred between 1 and 489 days after an episode of AF, 9 occurred before the onset of AF, and 40 occurred in the absence of arrhythmic episodes. Also interesting in this context are the ASSERT data[10]: of the 51 embolic events that occurred after the first 3 months of the study, only 26 episodes of AF were observed. In 8 of these 26 patients, however, the arrhythmic events appeared only after the stroke had already occurred. In the 18 subjects in which, however, the arrhythmia preceded the embolism, the distance between the two events was >30 days in 14 patients, with therefore only 4 patients in whom an episode of AF was recorded within 30 days preceding the embolic episode.

In the light of these data, it is therefore not clear whether the finding of short-term episodes of AF should be considered a further indicator of increased thrombo-embolic risk to be added to the clinical stratification of the individual patient or be interpreted as a direct cause of stroke or peripheral embolism.

Does oral anticoagulant therapy in patients with atrial arrhythmias identified by cardiac devices reduce the risk of stroke and confer an overall clinical benefit?

Two important randomized studies on the topic have recently been published, NOAH-AFNET 6 (anticoagulation with edoxaban in patients with atrial high-rate episodes)[11] and ARTESIA (apixaban for stroke prevention in subclinical AF),[12] which, however, did not definitively clarify the issue.

NOAH-AFNET 6[11] enrolled, between 2016 and 2022, patients aged at least 65 years, without clinically manifest AF, wearing cardiac devices, with AHRE episodes of at least 6 min duration (without maximum limit) and with at least one thrombo-embolic risk factor (heart failure, hypertension, diabetes, previous stroke or TIA, vascular disease, or age >75 years). The patients were then randomized to edoxaban ($n = 1270$, 28.7% taking the reduced dose) or placebo ($n = 1266$, 53.9% still taking aspirin). The primary efficacy outcome was the combination of cardiovascular death, stroke, or systemic embolism. The safety outcome was the

Table 1 Anticoagulant trial in atrial fibrillation

	NOAH-AFNET 6, edoxaban vs. placebo (%)	ARTESIA, apixaban vs. ASA (%)	AVERROES, ASA (%)	ENGAGE, edoxaban (%)
Stroke and embolism	1.0 vs. 1.5	0.79 vs. 1.24		
Stroke	0.9 vs. 1.1	0.78 vs. 1.21	3.7	1.49
Embolism	0.5 vs. 1.1	–		
Cardiovascular death	2.0 vs. 2.2	1.47 vs. 1.55		
Death	4.3 vs. 3.7	5.06 vs. 4.82		
Major bleeding episodes	2.1 vs. 1.0	1.53 vs. 1.12		

ASA, acetylsalicylic acid.

combination of death from any cause or major bleeding. The median age of patients was 78 years, the median duration of AHRE was 2.8 h, the median number of AHRE episodes was 2.8, and the median CHADSVASC was 4 (thus identifying a population with a high cardio-embolic risk profile). The study was stopped early after a median follow-up of 21 months due to safety concerns. The primary efficacy outcome occurred in 83 patients in the edoxaban group (3.2% per year) and in 101 in the placebo arm (4.0% per year; HR 0.81, $P = 0.15$). The outcome safety was instead detected in 149 (5.9% per year) and 114 patients (4.5% per year), respectively (HR 1.31, $P = 0.03$). Stroke occurred in 22 and 27 patients (0.9 vs. 1.1% per year, HR 0.79), systemic embolism in 14 and 28 patients (0.5 vs. 1.1% per year, HR 0.51), the combination of stroke and systemic embolism in 25 and 38 patients (1.0 vs. 1.5%, HR 0.65), cardiovascular death in 52 and 57 patients (2.0 vs. 2.2% per year, HR 0.90), major bleeding in 53 and 25 patients (2.1 vs. 1.0%, HR 2.1), and death from any cause in 111 and 94 patients (4.3 vs. 3.7%, HR 1.16).

ARTESIA[12] enrolled, between 2015 and 2021, patients aged at least 55 years, without clinically manifest AF, wearing cardiac devices, with at least one episode of subclinical AF lasting at least 6 min but <24 h and with a CHADSVASC score of 3 or greater. The patients were then randomized to apixaban ($n = 2015$, 9.4% taking the reduced dose) or 81 mg aspirin ($n = 1997$). The primary efficacy outcome was the combination of stroke or systemic embolism. The safety outcome was major bleeding. The average age of the patients was 76.8 years, the median duration of the longest AF episode was 1.47 h, the median CHADSVASC was 3.9 (therefore identifying a population with a high cardio-embolic risk profile), and the mean duration of follow-up was 3.5 years. The primary efficacy outcome occurred in 55 patients in the apixaban group (0.78% per year) and in 86 in the aspirin arm (1.24% per year; HR 0.63, $P = 0.007$). The safety outcome was instead detected (on-treatment population) in, respectively, 86 (1.71% per year) and 47 patients (0.94% per year; HR 1.80, $P = 0.001$). Stroke occurred in 55 and 84 patients (0.78 vs. 1.21% per year, HR 0.64), systemic embolism in 0 and 2 (0 vs. 0.03% per year), cardiovascular death in 105 and 108 (1.47 vs. 1.53 per year, HR 0.96), and death from any cause in 362 and 341 (HR 1.04). Anticoagulant therapy reduced the risk of the stroke being disabling or fatal by 49% compared with aspirin. In the study, therefore, apixaban reduced the risk of stroke and systemic embolism by 37% and the risk of fatal or disabling stroke by 49% despite, however, an 80% increase in major bleeding, mostly of gastrointestinal origin. However, transfusions, cerebral haemorrhages, and fatal bleeding did not present statistically significant differences between the two treatment groups, and 90% of haemorrhages were managed conservatively.

The results of the two studies appear substantially consistent with each other, despite the fact that in the first of them, the statistical significance of the primary efficacy outcome was not reached, probably due to the early interruption of the trial and also to the inclusion of cardiovascular death, an endpoint difficult to reach and therefore potentially capable of diluting the beneficial effect of the anticoagulant. Furthermore, in both of them, the use of aspirin may have underestimated the actual increase in bleeding risk induced by the anticoagulant.

The fundamental fact of the two trials is that, in both, the incidence of stroke was lower than expected. Patients without anticoagulant therapy had, in fact, a lower incidence of stroke than the group treated with aspirin in the AVERROES (Apixaban in Patients with Atrial Fibrillation) study[13] and the group treated with edoxaban in the ENGAGE AF-TIMI 48 study (Edoxaban vs. Warfarin in Patients with Atrial Fibrillation)[14] (Table 1). The haemorrhage rate was instead in line with expectations and with the results of both previous trials and clinical practices. Consequently, in absolute terms, according to a subsequent meta-analysis of the two studies,[15] anticoagulant treatment prevents three ischaemic strokes every thousand patients/year at the cost of seven major bleedings every thousand patients/year.

Conclusions

The only certain statement that can be made is that in patients with subclinical AF or AHRE, anticoagulant therapy does not reduce mortality. For the rest, anticoagulant therapy does its job: it decreases thrombotic events and increases haemorrhagic events. Whether this exchange is acceptable or not in the individual patient depends on what his thrombotic and haemorrhagic risk is, as well as on individual preferences. In fact, every therapeutic intervention has

an effect that depends on its ability to reduce a certain event and on the basic probability that that event can occur. The greater these two variables are, the greater the benefit induced by the therapeutic intervention in question. The problem in patients with AHRE or subclinical AF is that their average thrombo-embolic risk, although not zero, is lower than that in patients with clinically manifest AF and is ∼1%. With such a value, being able to obtain a benefit with anticoagulant therapy is difficult because the risk that the benefit (reduction of thromboembolism) is overshadowed by the inevitable risk of bleeding is very high. Anticoagulant therapy, therefore, should be used in patients who have a thrombotic risk >1%, especially in those with a low bleeding risk, and avoided in those who have a risk <1%, especially in those with a high bleeding risk. The problem is the lack, at the moment, of tools that allow the recognition of both. While waiting for new risk calculators that allow a better stratification of low-risk patients, we must rely on individual clinical evaluation, taking into account the patient's previous history (age >75 years and a previous thrombotic event in particular but also previous haemorrhagic episodes or a history of gastrointestinal diseases, in the light of the most frequent site of bleeding), the individual preferences, the risk profile expressed by the CHADSVASC score, and the characteristics of the AF episodes. The burden of the arrhythmia weighs heavily and is probably responsible for the lower thrombotic risk of these patients compared with those with clinically manifest arrhythmia. A single arrhythmic episode lasting a few minutes does not have the same value as numerous events lasting many hours, and the two cases cannot therefore be treated in the same way. It is therefore necessary to overcome a purely qualitative dichotomy (AHRE yes vs. AHRE no) and prefer an approach that is as quantitative as possible and takes into account the number of episodes, their duration, and the patient's CHADSVASC score before deciding, in each individual case, whether or not to use anticoagulant therapy.

Funding

No funding provided.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

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