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Clinical Insights

Detection of subclinical atrial fibrillation with cardiac implanted electronic devices: What decision making on anticoagulation after the NOAH and ARTESiA trials?☆

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ABSTRACT

Atrial fibrillation (AF) may be asymptomatic and the extensive monitoring capabilities of cardiac implantable electronic devices (CIEDs) revealed asymptomatic atrial tachi-arrhythmias of short duration (minutes-hours) occurring in patients with no prior history of AF and without AF detection at a conventional surface ECG. Both the terms "AHRE" (Atrial High-Rate Episodes) and subclinical AF were used in a series of prior studies, that evidenced the association with an increased risk of stroke. Two randomized controlled studies were planned in order to assess the risk-benefit profile of anticoagulation in patients with AHRE/subclinical AF: the NOAH and ARTESiA trials. The results of these two trials (6548 patients enrolled, overall) show that the risk of stroke/systemic embolism associated with AHRE/subclinical AF is in the range of 1–1.2 % per patient-year, but with an important proportion of severe/fatal strokes occurring in non-anticoagulated patients. The apparent discordance between ARTESiA and NOAH results may be approached by considering the related study-level meta-analysis, which highlights a consistent reduction of ischemic stroke with oral anticoagulants vs. aspirin/placebo (relative risk [RR] 0.68, 95 % CI 0.50–0.92). Oral anticoagulation was found to increase major bleeding (RR 1.62, 95 % CI 1.05–2.5), but no difference was found in fatal bleeding (RR 0.79, 95 % CI 0.37–1.69). Additionally, no difference was found in cardiovascular death or all-cause mortality. Taking into account these results, clinical decision-making for patients with AHRE/subclinical AF at risk of stroke, according to CHA_2DS_2-VASc, can now be evidence-based, considering the benefits and related risks of oral anticoagulants, to be shared with appropriately informed patients.

Atrial fibrillation (AF) is a quite heterogenous disease presenting either as a symptomatic arrythmia or, quite frequently, as an asymptomatic event [1,2], detected occasionally through a 12-lead ECG, a Holter recording or, nowadays, even with smartphones or smartwatches, so called wearables [3–5]. According to AF guidelines of the European Society of Cardiology (ESC), when AF is documented at 12-lead ECG or through an electrocardiographic rhythm strip documenting at least 30 s of AF, we can make the diagnosis of "clinical AF" [6,7]. Even if the arrhythmia is asymptomatic or associated with atypical symptoms, physicians must clinically evaluate the patient, his/her underlying cardiac condition, as well as the associated comorbidities to assess the risk of stroke and thromboembolic events. This approach has been proposed as A.B.C. (Avoid stroke with Anticoagulation, Better patient-centred symptom-directed decisions on rate or rhythm control, Cardiovascular risk factor and comorbidity optimization, including lifestyle changes) pathway in the 2020 ESC guidelines [6,8–10] and as S. O.S. (Stroke risk assessment, Optimizing all modifiable risk factors, Symptoms management) pathway in the recent ACC/AHA guidelines [11].

In patients with clinical AF the risk of stroke and adverse outcomes is

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independent on the presence/absence of AF-related symptoms [12]. This information, coupled with the high prevalence of AF at advanced age has fueled initiatives and studies on AF screening to reduce the burden of AF associated stroke [13,14].

The most extensive possibilities of monitoring the cardiac rhythm are provided by cardiac implantable electronic devices (CIEDs) with atrial sensing capabilities [13]. Most of the knowledge on atrial tachi-arrhythmias detected by CIEDs is based on pacemakers, ICDs and CRT devices with atrial sensing, but some data have also been obtained by implantable loop recorders [7,15].

The ESC guidelines have clarified the terminology to be used when an atrial tachi-arrhythmia is detected by CIED with EGMs available in device memory for analysis and exclusion of noise, artifacts, double counting [6,7]. The term "AHRE" (Atrial High-Rate Episodes) has been proposed when an atrial tachi-arrhythmia is detected by a CIED, and three negative conditions are all satisfied:

1) no prior history of AF;
2) absence of symptoms typical of AF;
3) no detection of AF at a conventional 12-lead ECG.

In other terms AHRE, as well as subclinical AF (corresponding to AHRE confirmed to be a true arrhythmia and not an artifact) are clinical entities diagnosed only thanks to the extensive monitoring capabilities of CIEDs.

In the last 15 years a series of observational studies clearly outlined what follows:

- AHRE/subclinical AF are quite common, especially in elderly patients, with up to 30 % experiencing AHRE $\geq$ 5–6 min during follow-up ranging from 1 to 3 years [15];
- AHRE $\geq$ 5–6 min area associated with an increased risk of stroke, even if the increase in risk corresponds to around a 2-fold increase in the risk of stroke, thromboembolism, thus differing from the 5-fold increase in stroke risk reported for clinical AF [16];
- Patients with AHRE have a substantial risk of evolving to clinical AF or to a high maximum daily burden $>$ 24 h and this has been reported to occur in up to 30 % of the patients at 2 years, more frequently when the burden at baseline is higher, especially when it is between 12 and 24 h [17,18].
- The risk of stroke/systemic embolism increases according to AF burden and CHA_2DS_2-VASc but the precise cut-off of single AF episode duration or of daily AF burden associated with a substantial increase in the risk of associated stroke was not established in observational studies, since thresholds ranging from 5 to 6 min to 1 hour, to 5.5 h or even 24 h were identified [19–23].
- In general, according to the observational studies published in the literature, the risk of stroke appeared significantly increased when AF episodes duration or AF burden $>$ 23–24 h are detected and, even in the absence of RCTs, oral anticoagulants were considered as a reasonable option by many authors and by many practicing cardiologists [24,25].
- Using continuous monitoring through CIEDs a series of studies highlighted that there is an association between history of AF and stroke, but stroke may occur at distance of days-weeks from AF episodes, suggesting that AHRE and subclinical AF may be in many cases markers of increased risk, but without the expected cause-effect relationship implying the sequence AF-atrial thrombus-cardioembolism-stroke [18,26].

In consideration of the uncertainty regarding the indication to anticoagulation in patients with AHRE and the need to assess the risk-benefit ratio of oral anticoagulants in this setting, two randomized controlled trials were planned 8–10 years ago, the ARTESiA trial (Apixaban for the Reduction of Thrombo-Embolism in Patients with Device detected Subclinical Atrial fibrillation) and the NOAH-AFNET 6 (Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High-Rate Episodes) trial [27,28].

Indeed, all the guidelines released on AF management in the last years did not provide recommendations based on evidence [29], but rather recommended individualized decision making, while waiting for the results of these two RCTs [6,30].

ARTESiA and NOAH substantially differed for the entry criteria for AHRE (between 6 min and 24 h in ARTESiA, $>$ 6 min in NOAH without an upper limit of AHRE duration), for the oral anticoagulant tested in the intervention arm (apixaban in ARTESiA, edoxaban in NOAH) and also for the control arm (ASA 81 mg in ARTESiA [31], aspirin or placebo, at the discretion of investigators, in NOAH, which however included aspirin in around half of enrolled patients) [32]. As shown in Table 1, also the primary end-point was substantially different, since cardiovascular mortality was associated to the classical end-point of stroke/systemic embolism in NOAH, but not in ARTESiA.

The NOAH-AFNET 6 trial recruited 2536 subjects with subclinical AF randomized to receive either edoxaban or placebo [32]. The average age of participants was 78 years, and the average duration of AF episodes was 2.8 h. The primary endpoint of the study consisted of death from cardiovascular causes, stroke, or systemic embolism. After a mean follow-up of 21 months, the study was stopped prematurely, on the basis of recommendations from the data and safety monitoring board and the steering committee, owing to safety concerns and on the basis of the results of an informal assessment of futility for the efficacy of edoxaban. At the time of trial termination, the primary endpoint occurred in 3.2 % of the treated group and 4 % of the placebo group (hazard ratio, 0.81; 95 % CI:0.60 to 1.08; $P = 0.15$). In both groups, the incidence of stroke was approximately 1 % per patient-year. The choice to include cardiovascular death in the primary end-point of this trial is actually questionable, since cardiovascular death is largely dependent on underlying heart disease and comorbidities [33] and fewer than 10 % of all deaths may be related to stroke, thus reducing the chances of a positive impact of anticoagulants [34]. The composite endpoint of total mortality and major bleeding occurred in 5.9 % of the edoxaban group and 4.5 % of the placebo group (HR 1.31; 95 %CI 1.02 – 1.67; $P = 0.03$). The risk of major bleeding was doubled in the group of patients treated with edoxaban (Table 1), with a mean number of bleeding events of 0.06±0.35 per patient-year. All-cause mortality did not differ between edoxaban-treated and placebo-treated patients. Clinical AF developed in 18.2 % of the enrolled patients (8.7 % per patient-year). The authors of the NOAH trial concluded that in patients with AHRE treated with edoxaban the incidence of a composite of cardiovascular death, stroke, or systemic embolism did not differ from placebo, but treatment with edoxaban led to a higher incidence of the composite end-point of death or major bleeding.

The results of the ARTESiA trial were communicated and published 75 days after the results of NOAH and at first look may appear quite discordant [31]. In the ARTESiA study 4012 patients (mean age 77 years) with device-detected subclinical AF lasting between 6 min and 24 h (median duration of the longest episode of 1.5 h) were randomized to receive either apixaban (2.5 or 5 mg twice daily) or aspirin (81 mg daily). In patients with AF lasting more than 24 h or developing clinical AF, trial medications were discontinued, with initiation of oral anticoagulants, as open treatment, and this occurred in around 24 % of the patients, after a median time after randomization of 18.3 months [31]. The primary endpoint was stroke or systemic embolism (Table 1). After a mean follow-up of 3.5 years, the primary endpoint occurred in 55 patients in the apixaban group and 86 in the aspirin group (corresponding to 0.78 and 1.24 % per patient-year, HR 0.63; 95 % CI 0.45–0.88, $P = 0.007$). Of note, the occurrence of moderately disabling to fatal strokes, as evaluated by the modified Rankin Scale ranging between 3 and 6, was halved in patients treated with apixaban. No difference was found in the occurrence of death. The other end-points are shown in Table 1.

Major bleeding, assessed with an on-treatment analysis, occurred more frequently in the apixaban group (HR 1.81; 95 % CI 1.26–2.57, P

Table 1
Characteristics and results of the NOAH [32] and ARTESiA [31] randomized controlled trials and of the study-level meta-analysis based on these trials, according to intention-to-treat [34].

	NOAH-AFNET 6 trial	ARTESiA trial	Study level meta-analysis including NOAH and ARTESiA trials
Patients eligibility criteria	Patients with age ≥65 yr and >1 additional CHA_2DS_2-VASc risk factor (except sex) or age ≥75 yr and with SCAF episodes ≥6 min detected on CIEDs	Patients with age ≥55 yr, CHA_2DS_2-VASc score ≥3, and SCAF episodes ≥6 min to <24 hr detected on CIEDs	
AHRE/SCAF duration	At least one episode (atrial rate ≥170/min) ≥6 min, no upper limit	At least one episode (atrial rate ≥175/min) ≥6 min, but no single episode ≥24 h	
Intervention	Edo 60 mg (30 mg with prespecified dose reduction criteria) once daily	Api 5 mg (2.5 mg with prespecified dose reduction criteria) twice daily	DOAC (Edo or Api)
Control	Pla or Asa 100 mg once daily (when clinically indicated)	Asa 81 mg once daily	Pla or Asa
Treatment with Asa	In 54 % of the Pla group	In 57 % of the patients as open-label	
N° of patients	2536 1270 Edo analysed 1266 Pla analysed	4012 2015 Api analysed 1997 Asa analysed	6548
Follow-up	Median 21 months	Mean 3.5 ± 1.8 years	
Enrollment period	2016–2022	2015–2021	
Primary efficacy endpoint	Composite of stroke or systemic embolism or CV death	Composite of stroke or systemic embolism	
Primary safety endpoint	Composite of death from any cause or major bleeding	Major bleeding	
Ischemic stroke N° patients (% per patient-yr for the trials, % for the meta-analysis)	22 Edo (0.9 %) - 27 Pla (1.1 %) HR 0.79 (0.45 to 1.39)	45 Api (0.64 %) - 71 Asa (1.02 %) HR 0.62 (0.43 to 0.91)	67 DOAC (2.0 %) - 98 Pla/Asa (3.0 %) RR 0.68 (0.50 to 0.92)
All-cause stroke or systemic embolism N° patients (%)	23 Edo (1.8 %) - 33 Pla (2.6 %) RR 0.69 (0.41 to 1.18)	55 Api (2.7 %) - 86 Asa (4.3 %) RR 0.63 (0.45 to 0.88)	78 DOAC (2.4 %) - 119 Pla/Asa (3.6 %) RR 0.65 (0.49 to 0.86)
Major bleeding (% per patient-yr for the trials, % for the meta-analysis)	53 Edo (2.1 %) - 25 Pla (1.0 %) HR 2.10 (1.30 to 3.38)	106 Api (1.53 %) - 78 Asa (1.12 %) HR 1.36 (1.01 to 1.82)	159 DOAC (4.8 %) - 103 Pla/Asa (3.2 %) RR 1.62 (1.05 to 2.50)
Fatal bleeding N° patients (%)	2 Edo (0.2 %) - 1 Pla (0.1 %) RR 1.99 (0.18 to 21.96)	10 Api (0.5 %) - 14 Asa (0.7 %) RR 0.7 (0.32 to 1.59)	12 DOAC (0.4 %) - 15 Pla/Asa (0.5 %) RR 0.79 (0.37 to 1.69)
Cardiovascular death N° patients (%)	52 Edo (4.1 %) - 57 Pla (4.5 %) RR 0.91 (0.63 to 1.31)	105 Api (5.2 %) - 108 Asa (5.4 %) RR 0.96 (0.74 to 1.25)	157 DOAC (4.8 %) - 165 Pla/Asa (5.1 %) RR 0.95 (0.76 to 1.17)
All-cause death (% per patient-yr for the trials, % for the meta-analysis)	111 Edo (4.3 %) - 94 Pla (3.7 %) HR 1.16 (0.88 to 1.53)	362 Api (5.06 %) - 341 (4.82 %) HR 1.04 (0.90 to 1.21)	473 DOAC (14.4 %) - 435 Pla/Asa (13.3 %) RR 1.08 (0.96 to 1.21)

Legend: Api: apixaban; Asa: acetylsalicylic acid; CIED: cardiac implantable electronic device; CV: cardiovascular; DOAC: direct oral anticoagulant; Edo: edoxaban; HR: hazard ratio; Pla: placebo; RR: relative risk; yr: year.

= 0.04). The same was found for gastro-intestinal bleeding (HR 1.76, 95 % CI 1.13–2.74). However, no significant differences were found in the occurrence of fatal bleeding or of symptomatic intracranial haemorrhages. Most cases of major bleeding responded promptly to supportive care and haemodynamic instability was uncommon.

An important finding of both ARTESiA and NOAH is that the risk of stroke /systemic embolism associated with AHRE/subclinical AF is in the range of 1–1.2 % per patient-year, so lower than the risk associated with clinical AF, but this should not minimize the impact on patients' outcome, since 43 % of the strokes occurring during aspirin in ARTESiA resulted in important disability or death. Indeed, in interpreting the risk-benefit ratio of anticoagulants in patients with AHRE/subclinical AF we should not put at the same level the reduction in stroke risk and the increase in major bleeding. A series of studies have revealed disparities in the assessment of stroke and bleeding risks between patients and physicians, since physicians tend to perceive bleeding risks as a more significant event, whereas patients place greater importance on stroke risk as compared to physicians' perceptions [35]. With this regard it is

noteworthy that in a time trade-off analysis on patient values and preferences, 45 % of patients considered a major stroke to be a worse outcome than death [36].

According to ESC guidelines, which adopted the CHA_2DS_2-VASc score since 2010 and chose the threshold of 1 point for recommending anticoagulation, it results that the threshold of stroke incidence considered to justify oral anticoagulation was set at a roughly 1 % per year [37], thus corresponding to the actual risk of stroke found in AHRE/subclinical AF under placebo or aspirin in NOAH and ARTESiA. Also the very recent ACC/AHA guidelines on AF report that an estimated annual stroke risk of about 1 % may be considered as a reasonable threshold for instituting treatment with direct oral anticoagulants [11].

In numerical terms and in an intention-to-treat perspective the results of ARTESiA indicate that oral anticoagulation results in 4.6 fewer strokes/embolic events (per thousand patient-years), even if at the expense of 4.1 more major bleeding events (per thousand patient-years). However, we should carefully consider, in a perspective of patient values, that the positive results of ARTESiA, with a marked reduction of disabling strokes vs. aspirin, are much more important, for the patients, their families and the community, than the clinical implications of major bleeding, which were increased by apixaban, but were managed conservatively in 90 % of cases, using transfusions when needed, and without increase in fatal bleedings or deaths [31].

Any interpretation of the apparent discordance between ARTESiA and NOAH should consider that the conclusions of the latter study were largely conditioned by its premature termination and the consequent negative impact on trial statistical power. However, an important clarification comes from the study-level meta-analysis based on ARTESiA and NOAH, published by McIntyre et al., that involved authors of both trials [34]. This meta-analysis, including the data from NOAH-AFNET 6 (2536 participants) and ARTESiA (4012 participants) (Table 1) actually showed that the results of the two trials with regard to reduction of ischemic stroke by oral anticoagulants are consistent (I^2 statistic for heterogeneity=0 %, relative risk [RR] 0.68, 95 % CI 0.50–0.92; high-quality evidence). Additionally, oral anticoagulation was found to reduce the composite of cardiovascular death, all-cause stroke, peripheral arterial embolism, myocardial infarction or pulmonary embolism (RR 0.85, 95 % CI 0.73–1.00, I^2=0 %; moderate-quality evidence). The meta-analysis found no difference in cardiovascular death (RR 0.95, 95 % CI 0.76–1.17, I^2=0 %; moderate-quality evidence) or all-cause mortality (RR 1.08, 95 % CI 0.96–1.21 I^2=0 %; moderate-quality evidence). Oral anticoagulation was found to increase major bleeding (RR 1.62, 95 % CI 1.05–2.5 I^2=61 %; high-quality evidence), but no difference was found in fatal bleeding (RR 0.79, 95 % CI 0.37–1.69, I^2=0 %, moderate-quality evidence) [34].

The availability of two randomized controlled trials is considered as a key requirement for evidence-based decision making [29]. According to current knowledge, we think that in patients with AHRE/subclinical AF detected through an implanted device decision making should be individualized, taking into consideration that in patients at risk of stroke according to CHA_2DS_2-VASc score, anticoagulants substantially reduce the risk of stroke, and particularly the risk of disabling or fatal stroke. This favourable effect is associated with an increased risk of major bleeding, but this can be managed conservatively in 90 % of cases and there is not an increase in fatal bleeding or death.

In this context, patients with AHRE/subclinical AF should be adequately informed about the expected benefit and the risk-benefit ratio of anticoagulation, with shared decision-making between clinicians and patients, taking into account individual values and preferences, coupled with appropriate management of associated conditions and comorbidities, as well as correction of modifiable risk factors for bleeding [11].

Additionally, clinical decision making should also consider that, on average, around one out of 5 patients with device-detected AF (traditionally named AHRE or subclinical AF) will experience progression to clinical AF or long-duration AHRE (>24hours) during a 2-year follow up. This progression implies per se a increased risk of stroke, that may be even more pronounced in patients with a higher $CHADS_2$ or CHA_2DS_2-VASc and/or with a higher AF burden at baseline [17,18]. Data from the NOAH trial confirm that progression to clinical AF is more common when device detected AHRE have a duration of more than 24 h, with a doubling of the progression rate to clinical AF (17 % per patient-year), as compared with shorter AHRE [38].

Remote monitoring of CIEDs has the ability to provide detailed notification on the presence and duration of AHREs/subclinical AF episodes, providing tracings with arrhythmia electrograms, and therefore its contribution and its organization have gained increasing clinical value, both in patients with and without heart failure [39–42].

It is expected that future analyses of ARTESiA and NOAH data will provide additional information on other subgroups of patients with a high chance of evolution to clinical AF, as well as on the profile of patients that can achieve the maximal net benefit from anticoagulation, based on clinical characterization at baseline. Finally, it will be of great importance, from the clinical point of view, to assess what is the relationship between AHRE/subclinical AF and atrial cardiomyopathy and whether assessment of the extent of derangement in atrial function and structure may better predict the associated risk of stroke, as well as the dynamics of progression from short duration AHRE/subclinical AF to longer duration episodes of clinical AF [43–47].

In summary, after the NOAH and ARTESiA trials we have new evidence-based information for guiding decision-making in daily practice. Indeed, reduction of strokes, and particularly of disabling strokes through appropriate treatment with oral anticoagulants in patients with AF is a major goal of clinical medicine, of great value for the patients and the community, and recent evidence shows that this important goal can be obtained also in patients with AF detected by means of the extended diagnostics of CIEDs. Achievement of this goal requires a clinically oriented, patient-centred management of AF and of associated conditions and comorbidities, and implies appropriate, individualized evaluations of the risks and benefits of oral anticoagulants, to be shared with appropriately informed and empowered patients.

Declaration of competing interest

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