Atrial High Rate Episodes (AHRE) – what are they and how should we approach them?

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Take Home Messages

- AHRE are common asymptomatic atrial tachyarrhythmias detected by an implanted cardiac device
- Patients with AHRE > 6 mins are 3 – 4 times more likely to develop clinical AF: consider it a marker of atrial myopathy and tackle cardiovascular risk factors early, especially hypertension
- Increasing burden of AHRE is associated with increased thromboembolism and episodes ≥ 24h should be considered for anticoagulation in high-risk patients
- Two new RCTs (ARTESIA and NOAH-AFNET 6) agree that anticoagulation for AHRE 6 min – 24h reduces ischaemic stroke risk (RR 0.68), but at the expense of increased major bleeding (RR 1.62)

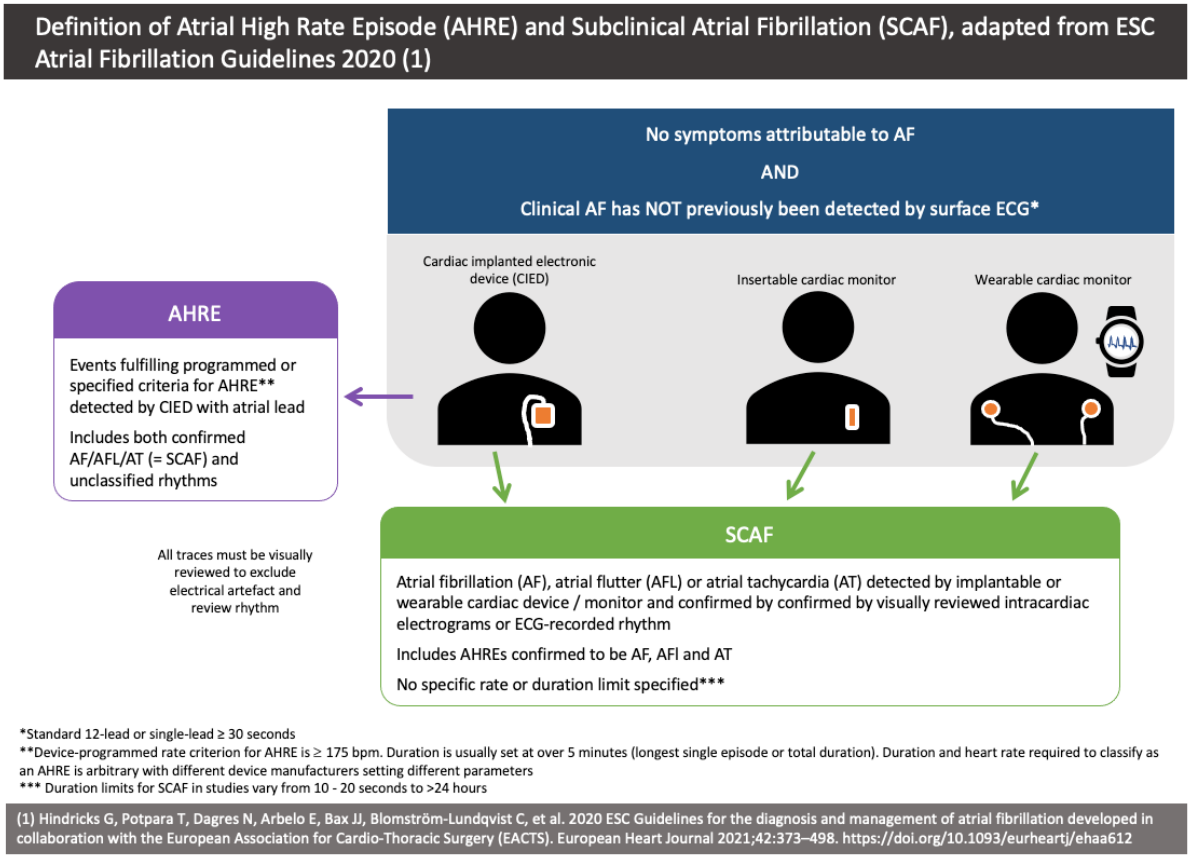
Introduction

Atrial High Rate Episodes (AHRE) are asymptomatic flurries of increased atrial rates detected by a cardiac implanted electronic device (CIED) in patients without history of clinical atrial fibrillation (AF). They are common, detected in around a third of hypertensive over 65-year-olds within the first 2.5 years of pacemaker implant (1). Their clinical significance is unclear. Should AHRE be seen as a precursor to AF? Do they contribute to thromboembolic risk? And if so, should we offer anticoagulation to these patients even in the absence of surface ECG confirmation of AF?

AHRE vs. Subclinical AF (SCAF)

Definitions vary widely clinically and academically (2) so caution is needed when reviewing the literature. **Figure 1** depicts definitions from European Society of Cardiology (ESC) AF guidelines in which the authors concede amalgamation to 'AHRE/Subclinical AF' due to limited evidence base (3).

Figure 1. Definition of Atrial High Rate Episode and Subclinical Atrial Fibrillation, adapted from (3)



Essentially, AHRE are episodes of fast atrial rates detected a CIED (officially an atrial lead), whether there is an identifiable underlying rhythm or not, whereas SCAF is a general term encompassing AF, Atrial Tachycardia (AT) or Atrial Flutter (AFl) detected by implanted ***or*** wearable monitoring. Atrial rate / duration are better defined for AHRE than SCAF but remain arbitrary and inconsistent (2).

By comparison, ***clinical*** AF is declared if AF is detected on surface ECG (12-lead or ≥30 seconds on single-lead rhythm strip). Perhaps counterintuitively, defining the arrhythmia as 'clinical' relies on obtaining sufficient surface ECG evidence rather than symptoms or clinical sequalae (3) (4). Note that the ESC discourage use of 'AHRE or 'SCAF' in patients with known clinical AF and that crucially, much of our AF clinical trial data is unapplicable to this collective cohort.

Visual inspection is essential to exclude artefact such as myopotential oversensing, electromagnetic interference or lead failure (5). The clinical distinction between the two terms may be nuanced (6) but the derived cohorts differ considerably: SCAF may be identified in an otherwise healthy smart-watch wearer whereas AHRE refers exclusively to cardiac device patients.

A precursor to Atrial Fibrillation?

Patients with ≥ 5 – 6 minutes of AHRE (as defined in **Fig. 1**) in any given 24h period are more likely to be diagnosed with clinical atrial fibrillation than those without, with relative risk of 3 – 4 reported in meta-analyses (7) (8) (9). However, AHRE can also represent other supraventricular arrhythmias (4) (5) so it may be more appropriate to consider AHRE an indicator of underlying atrial myopathy than pre-curser to AF per se.

Do AHRE cause thromboembolic strokes?

Allowing for wide heterogeneity in AHRE studies, the overall thromboembolism risk in patients with AHRE (as defined in **Fig.1**) appears to be around 2 – 2.5 times those without (1) (7) (8) (5) (10) (11) (12), with evidence strongest for single episodes ≥ 24h (2) (3) (4) (11) (13). Hypertension is a key confounder along with other CHA2DS2-Vasc scoring criteria (older age, heart failure, previous stroke/TIA) and left atrial volume (9) (14).

Mechanism-wise, it seems plausible that embolic events could result from stasis related to dysfunctional atrial contraction. However, the relationship between AF and thromboembolic stroke is now appreciated to be more complex than first imagined (3) (4) (15). **Table 2** shows examples of the epidemiological basis for refuting a simplistic causal relationship.

Table 1 – Epidemiologist Bradford Hill's criteria of causation and the AF – stroke relationship, adapted from (15)

Bradford Hill criterion	How it refutes a causative AF – Stroke relationship
Specificity	There is also a link between AF and non-cardioembolic strokes
Temporality	AF itself does not always precede the stroke
Biological Gradient	The burden of AF is not reliably associated with risk of stroke

Abnormal atrial substrate takes centre-stage in Kamel et al's modernised AF – stroke mechanistic model, with vascular and metabolic risk factors also playing key roles (15).

To anticoagulate or not?

The ESC and European Heart Rhythm Association (EHRA) both recommend considering anticoagulation in select patients with AHRE/SCAF ≥ 24h but not for shorter durations due to insufficient evidence (3) (4). Two new RCTs trialling anticoagulation in AHRE/SCAF 6 min – 24h have since been published with **Table 2** summarising NOAH-AFNET 6 (edoxaban vs. placebo) and ARTESIA (apixaban vs. aspirin) side-by-side. Both included older patients at high risk for stroke with no surface ECG-diagnosed AF.

Table 2. RCTs on anticoagulation in AHRE/SCAF: NOAH-AFNET 6 (2023) (16) and ARTESIA (2024) (17)

	NOAH-AFNET 6	**ARTESIA**
Inclusion criteria	No clinical AF ≥65y and at least one stroke risk factor of heart failure, hypertension, diabetes, prior stroke, vascular disease Or ≥75y	No clinical AF ≥55y and CHA2DS2-VASc score ≥ 3 Or ≥75y Or History of stroke
AHRE duration	≥ 6 minutes to 24h (Pacemaker, ICD, ILR)	≥ 6 minutes to 24h (Pacemaker, ICD, ILR)
N	2536	4012
Mean age	78	77
CHA2DS2-VASc	4 (median)	3.9 (mean)
Trial drug	Edoxaban 60mg od (or 30mg od)	Apixaban 5mg bd (or 2.5mg bd)
Control	Placebo	Aspirin 81mg OD
Follow up duration	21 months (median) – terminated early	42 months (mean)
Primary efficacy outcome Incidence, % per patient year	**Composite of cardiovascular death, stroke or systemic embolism** Treatment group 3.2% Control group 4.0% HR 0.81; 95% CI 0.60 to 1.08; P=0.15	**Stroke or systemic embolism** Treatment group 0.78% Control group 1.24% HR 0.63; 95% CI 0.45 to 0.88; P=0.007
Primary safety outcome Incidence, % per patient year	**Composite of death from any cause or major bleeding** Treatment group 5.9% Control group 4.5% HR 1.31; 95% CI 1.02 to 1.67; P=0.03	**Major bleeding** Treatment group 1.71% Control group 0.94% HR 1.80; 95% CI 1.26 to 2.57; P=0.001
ICD = Implantable cardiac defibrillator, ILR = Implantable Loop Recorder, HR = Hazard Ratio, CI = Confidence Interval		

At first glance, the results appear contradictory. NOAH-AFNET 6 was terminated early due to safety concerns and treatment futility (16), whereas ARTESIA demonstrated reduced incidence of stroke or systemic embolism with anticoagulation (0.78 % vs. 1.24%, HR 0.63), albeit with increased major bleeding (17). Note however that NOAH-AFNET 6 included cardiovascular death in its primary efficacy outcome, perhaps diluting treatment effect.

In a meta-analysis of the two trials, oral anticoagulation was found to reduce ischaemic stroke (RR 0.68, 95% CI 0.50-0.92) with no reduction in cardiovascular death or all-cause mortality (18). Incidence of major bleeding was higher with anticoagulation (RR 1.62, 95% CI 1.05-2.5) (18), despite aspirin being the control in ARTESIA. There was surprisingly low absolute stroke risk of around 1% per patient year in treatment and control groups of both trials (despite average CHA2DS2-VASC score 4), perhaps supporting a more conservative approach in this cohort.

Summary

Collectively, AHRE and subclinical AF are asymptomatic atrial tachyarrhythmias detected by intracardiac devices or wearable monitors with no surface ECG confirmation of rhythm. Increasing burden of AHRE/SCAF is associated with increasing incidence of thromboembolism (albeit to a lesser degree than clinical AF), and episodes lasting ≥ 24h warrant anticoagulation in high CHA2DS2-VASC scorers. Net benefit of anticoagulation to reduce stroke risk in AHRE ≤ 24h is not clearcut but management of other stroke risk factors and regular reassessment for emergence of longer duration AHRE or clinical AF is sensible (3) (4).

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