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REVIEW ARTICLE

Clinical relevance and management of atrial high-rate episodes: a narrative review

Relevancia clínica y manejo de los episodios de alta frecuencia auricular: una revisión narrativa

Juan D. Orozco-Burbano[1], Camilo J. Chara-Salazar[2], Dairo L. Vargas-Zabala[2], Juan S. Castillo-Concha[3], Juan F. Agudelo-Uribe[4], and Juan D. Ramírez-Barrera[4]*

[1]Cardiology Unit, CardíoVID Clinic, UPB, Medellin; [2]Internal Medicine Unit, Hospital Universitario San José, Popayán; [3]General Medicine, Universidad del Quindío, Armenia; [4]Electrophysiology Service, CardioVID Clinic, UPB, Medellín. Colombia

Abstract

Atrial high-rate episodes (AHREs) are atrial tachyarrhythmias detected by cardiac implantable electronic devices when the atrial rate exceeds the device's programmed detection threshold. The frequency and duration of these episodes vary, with those lasting more than 5 min generally considered clinically significant. The occurrence of AHREs has been associated, in multiple clinical trials, with an increased risk of progression to overt atrial fibrillation (AF) and a higher incidence of thromboembolic events, particularly ischemic stroke. Several studies have demonstrated that the strength of these associations is directly proportional to AHREs duration and is further influenced by comorbidities such as advanced age, hypertension, and a history of heart failure. Despite the elevated embolic risk, clinical uncertainty persists regarding the optimal timing and indication for initiating long-term oral anticoagulation in patients with AHREs. Consequently, this narrative review aims to outline a contemporary clinical approach and propose a treatment algorithm for AHREs, grounded in the current body of evidence.

Keywords: *Atrial fibrillation. Embolic stroke. Anticoagulants. Artificial pacemaker. Implantable defibrillator.*

Resumen

Los episodios de alta frecuencia auricular se definen como eventos auriculares que superan el límite programado de frecuencia de detección establecido por los dispositivos electrónicos cardiacos implantables. La periodicidad y la duración de estos episodios son variables, considerándose clínicamente relevantes los que duran más de 5 minutos. En numerosos estudios, su presencia se ha asociado a la progresión a largo plazo a fibrilación auricular clínica y un mayor riesgo de ictus embólico. Los estudios han establecido que estas asociaciones están directamente relacionadas con la duración de los episodios de alta frecuencia auricular, junto con factores de riesgo como la edad, la hipertensión y los antecedentes de insuficiencia cardiaca. A pesar de existir un riesgo elevado de eventos embólicos, sigue existiendo incertidumbre respecto al inicio de la anticoagulación a largo plazo y los beneficios clínicos de dicho tratamiento. Por ello, esta revisión narrativa busca ofrecer una aproximación clínica actual y proponer un algoritmo de tratamiento para los episodios de alta frecuencia auricular según la evidencia actual.

Palabras clave: *Fibrilación auricular. Accidente cerebrovascular embólico. Anticoagulantes. Marcapaso artificial. Desfibrilador implantable.*

***Correspondence:**
Juan D. Orozco-Burbano
E-mail: juan.orozcob@upb.edu.co

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Background

Among cardiac arrhythmias, particularly supraventricular tachyarrhythmias, atrial fibrillation (AF) is recognized as the most prevalent sustained rhythm disorder in the adult population[1,2]. This condition substantially increases the risk of embolic stroke, thereby contributing to the overall morbidity and mortality burden associated with cardiovascular disease[2-4].

AHREs are defined as atrial tachyarrhythmias that exceed the detection rate threshold programmed in cardiac implantable electronic devices (CIEDs)[1]. These devices are capable of detecting a range of atrial arrhythmias, including AF, atrial flutter, and atrial tachycardia[5], typically characterized by an atrial rate > 170 beats per minute (bpm), with a mean rate of approximately 190 bpm, and a minimum duration of 30 s[6,7]. AHREs are considered clinically significant when they last more than 5 min, as they have been associated with a higher risk of progression to sustained AF and an increased incidence of thromboembolic events when compared to individuals without such episodes[1,3,8].

Despite these established associations, there is ongoing debate regarding the optimal strategies for diagnosis, risk stratification, and longitudinal management of AHREs. Furthermore, evidence remains limited concerning their predictive value for major adverse cardiovascular events in affected patients[9-11]. Therefore, this review aims to deepen the understanding of AHREs and to provide an evidence-based perspective on their clinical management.

Materials and methods

A narrative review of the literature was performed using the PubMed and Google Scholar databases, covering publications from January 1, 2010, to August 1, 2024. The following keywords were used: "atrial fibrillation," "atrial high-rate episodes," "embolic stroke," "oral anticoagulants," "artificial pacemaker," and "implantable defibrillator." A total of 40 articles were selected based on relevance to the topic, the authors' judgment, and consultation with subject matter experts.

Epidemiology

The incidence of atrial high-rate episodes (AHREs) varies considerably depending on the studied population. Most available data come from observational registries, which estimate a prevalence of up to 28.1% (95% confidence interval [CI]: 24.3-32.1%) and an overall incidence of 17.56 cases/100 person-years (95% CI: 8.61-35.79; I^2 = 99%). Notably, in episodes lasting longer than 6 min, the incidence increases to 36.95 cases/100 person-years (95% CI: 31.78-42.97; I^2 = 51%)[12].

The detection of AHREs may occur at variable time points following CIED implantation, particularly in patients without a prior history of AF but with suspected embolic events. Cumulative detection rates have been reported in up to 25% of patients within the 1st year and 35% at 2-year follow-up[9]. Although the causal relationship between AHREs and the development of clinical AF remains incompletely understood, current evidence suggests that the presence of AHREs is associated with a 4.45-fold increased risk of developing AF (95% CI: 2.87-6.91)[12].

Several clinical and demographic factors have been implicated in the onset and progression of AHREs, particularly in the transition to sustained AF. These include advanced age, hypertension, diabetes mellitus, heart failure, alcohol consumption, smoking history, and ischemic heart disease[1,13]. These comorbidities may promote structural and electrical atrial remodeling, facilitating arrhythmogenesis. While most patients remain asymptomatic during AHREs, some studies have identified a correlation between AHREs and increased risk of embolic complications. In an analysis from the AF Follow-up Investigation of Rhythm Management trial, 12% of patients with documented ischemic stroke had been asymptomatic before the event[14].

Pathophysiology

Although the underlying pathophysiological mechanisms of AHREs are not entirely understood, and further research is warranted to clarify them[15], a potential relationship between AHREs and the subsequent development of clinical AF should be considered. It is essential to examine the mechanisms and factors that may facilitate the onset and maintenance of AF[9].

Several theories have been proposed to explain AHRE, including the presence of ectopic depolarizing foci, structural atrial remodeling, and abnormal conduction properties[16,17]. In addition, both environmental and genetic predispositions may contribute to its occurrence[1,18].

Electrophysiological disturbances may be the root cause, as ectopic foci can generate disorganized and asynchronous electrical impulses, promoting AHREs development[19]. Under normal physiological conditions, the Bachmann bundle transmits the electrical impulse from the right to the left atrium. However, ectopic impulses arising from atrial cardiomyocytes – particularly

transmitted erratically via the sensitive central portion of the Bachmann bundle – can lead to disordered conduction[18]. The pulmonary vein ostia (and less commonly the vena cava, coronary sinus, and ligament of Marshall)[19] are key sites implicated in ectopic activity due to abrupt changes in myocardial fiber architecture, extracellular matrix composition, and heightened ion channel sensitivity in adjacent cells[16]. This may result in asynchronous impulses at the sinoatrial node, characterized by shortened refractory periods or delayed conduction[19].

Moreover, action potential abnormalities have been described in atrial myocytes at these sites, possibly linked to genetic mutations in sodium, potassium, and calcium channels, which impact cellular electrophysiology[17,20]. These changes contribute to altered refractory periods and promote re-entry mechanisms[16,18].

Pathological conditions also induce structural changes within the atria, particularly through fibrosis mediated by increased type I and III collagen deposition. Fibroblasts and myofibroblasts – stimulated by signaling molecules such as angiotensin II, matrix metalloproteinases, transforming growth factor-β1, connective tissue growth factor, and platelet-derived growth factor – are key players in this process[19]. These molecules also impair connexin function within intercalated discs, fostering a substrate for impaired electrical coupling and facilitating fibrotic remodeling[21].

AHREs and risk of embolic events

AHREs have been associated with a heightened risk of embolic stroke. Some series report that up to 2.4% of patients who experienced ischemic stroke had documented AHRE[1,22]. However, uncertainty remains regarding the initiation of oral anticoagulation (OAC) in this population. While direct oral anticoagulants (DOACs) have demonstrated efficacy in reducing embolic events in patients with clinical AF and high thromboembolic risk[23], data in patients with AHREs remain limited. Nonetheless, up to 25% of AHRE cases detected by CIEDs might warrant anticoagulation[24].

A sub-analysis of the mode selection trial (MOST) examined 312 patients with sinus node dysfunction and pacemaker implantation. It showed that individuals with AHREs > 220 bpm lasting more than 5 min had an increased risk of stroke over 27 months (hazard ratio [HR] = 2.79, 95% CI: 1.51-5.15, p = 0.0011) and of developing AF (HR: 5.93, 95% CI: 2.88-12.2, p = 0.0001)[22]. These findings were later supported by the ASSERT trial, which reported that patients with AHREs > 190 bpm and duration > 6 min had a higher risk of stroke or systemic embolism (HR: 2.49, 95% CI: 1.28-4.85; p = 0.007)[25]. Similarly, Will et al. found an elevated risk of stroke in patients with cardiac resynchronization therapy and AHREs > 24 h (HR: 2.30, 95% CI: 1.09-4.83; p = 0.028)[26].

The role of arrhythmic burden was further explored in the TRENDS study, an observational cohort of 2,486 patients followed for 1.4 years. This study found that atrial arrhythmias persisting for more than 5.5 h over 30 days doubled the risk of thromboembolic events[27].

A 2021 systematic review and meta-analysis that included 23 studies confirmed that AHREs duration correlates with thromboembolic risk. It found a significant increase in risk even for AHREs durations > 30 s (HR: 4.41, 95% CI: 2.32–8.39; I^2 = 5.5%)[6].

More recently, a 2024 meta-analysis by Ahmed et al. evaluated nine studies with 7440 patients with AHREs but no prior AF. The findings confirmed increased risks of clinical AF (RR = 3.33, 95% CI: 1.99-5.57; p < 0.0001) and thromboembolism (RR = 2.21, 95% CI: 1.72-2.85; p < 0.0001), though no significant difference in all-cause mortality was observed[28].

Risk factors for the development of AHREs

The likelihood of detecting AHREs in patients with CIEDs depends on several risk factors. The literature categorizes these patients into two main groups: (1) those with a known history of AF, in whom AHREs occur in 40-70%, and (2) those without prior AF, in whom detection rates range from 10-30%[23].

A sub-analysis of the IMPACT trial stratified AHREs duration into < 6 min, 6 min-6 h, 6-24 h, and > 24 h. Risk factors for AHREs > 6 min included age ≥ 65 years (odds ratio [OR] = 1.54, 95% CI: 1.21-1.97; p < 0.001) and prior AF history (OR = 2.50, 95% CI: 1.83-3.43; p < 0.001). Hypertension was associated with prolonged AHREs > 24 h (HR: 2.13, 95% CI: 1.24-3.65; p = 0.006). Interestingly, female sex was associated with a lower likelihood of experiencing AHREs lasting > 6 min but ≤ 6 h (HR: 0.72, 95% CI: 0.54-0.96; p = 0.027). Embolic risk, as measured by the CHADS2 score, also correlated with AHREs duration: patients with CHADS2 ≥ 3 had higher AHREs incidence ≥ 6 h (RR = 1.244, 95% CI: 1.029-1.504) and ≥ 24 h (RR = 1.476, 95% CI: 1.113-1.957)[29].

Another study involving 500 patients with CIEDs identified the following risk factors for AHREs > 24 h: male sex (HR: 2.14, 95% CI: 1.08-4.23; p = 0.029),

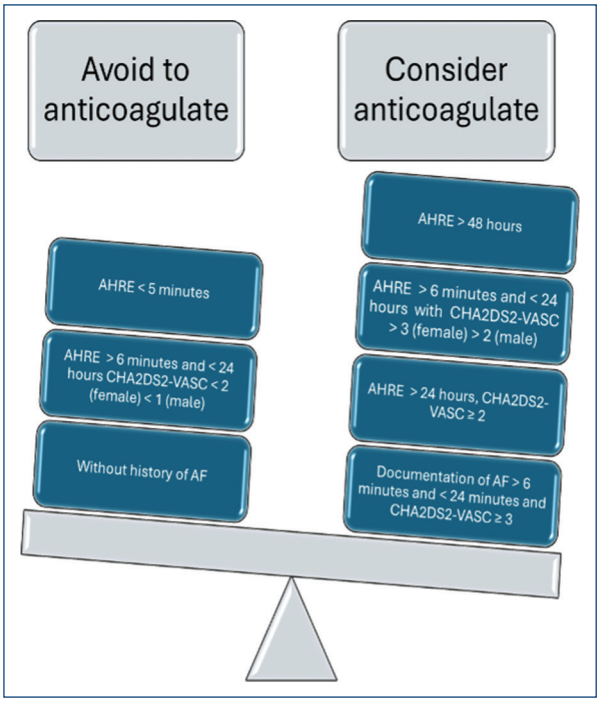

Figure 1. An approach to starting or avoiding anticoagulation based on atrial high-frequency episode intervals (*adapted from Joglar et al.[1] and Ding et al.[31]*).

age > 75 years (HR: 2.93, 95% CI: 1.57-5.45; p = 0.001), and heart failure (HR: 4.02, 95% CI: 1.43-11.26; p = 0.008). Larger left atrial diameter and volume were also associated with AHREs occurrence (p = 0.021 and p = 0.011, respectively)[23].

Direct atrial lead stimulation may have a proarrhythmic effect. Atrial arrhythmic events often occur in the early post-implantation period, with 50% detected within the 1st month; events usually stabilize after 1 year. These early-onset patients tend to be older than those with persistent AHREs over time[24,30].

In patients without a prior AF diagnosis who receive ventricular pacing > 50%, the risk of AHREs is increased – possibly due to ventricular dyssynchrony causing elevated filling pressures and subsequent left atrial remodeling[15].

AHREs management

There are currently two major areas of controversy in the clinical approach to AHREs, which will be addressed based on the most up-to-date evidence.

Rate or rhythm control?

At present, there is limited evidence supporting either rate or rhythm control as the optimal management strategy for patients with AHREs. A randomized study of 307 patients with AHREs exceeding 200 bpm for ≥ 24 h, and without a prior diagnosis of AF, compared pharmacologic intervention (n = 169) versus no treatment (n = 138). The intervention group received either Class IC antiarrhythmics (n = 54), beta-blockers (n = 58), or amiodarone (n = 57), aiming to evaluate AF progression. During a 20-month follow-up, 50 patients developed clinical AF: 11 in the Class IC group, 25 in the beta-blocker group, and 5 in the amiodarone group (p < 0.001). Time to AF progression was significantly longer in the intervention arm compared to controls (17.7, 17.2, and 19.0 vs. 15.9 months, respectively; p < 0.001). Furthermore, amiodarone demonstrated superior efficacy in reducing AHRE burden during follow-up[32]. Despite these findings, current guidelines do not recommend routine initiation of long-term antiarrhythmic therapy due to concerns over drug-related adverse effects, and further randomized trials are warranted.

In addition, atrial pacing has been shown in some studies to reduce the incidence of AF compared to ventricular pacing[33,34]. However, results from the MOST, which assessed dual-chamber pacing, did not demonstrate a significant difference in AF development[22]. Therefore, pacing strategy remains an area of ongoing investigation.

The great debate: should these patients be anticoagulated?

One of the most contentious issues in AHREs management is the role of OAC (Fig. 1). Two recent randomized, double-blind clinical trials – NOAH-AFNET 6 and ARTESIA – evaluated the efficacy and safety of DOACs in patients with AHREs. Notably, the two trials differed in their definitions and thresholds for AHREs inclusion. Both trials reported comparable composite outcomes for efficacy and safety, yet drew divergent conclusions: one trial favored anticoagulation, while the other highlighted an increased risk of major bleeding without clear benefit. Key results from these studies are summarized in table 1[35,36].

According to the 2023 American College of Cardiology/AHA/Heart Rhythm Society Guidelines on AF, OAC may be considered in patients with AHREs lasting > 24 h and a CHA_2DS_2-VASc score ≥ 2 in men or ≥ 3

Table 1. Comparison of ARTESIA and NOAH-AFNET trials

Population	2,538 patients: 1,306 assigned to edoxaban 60 mg every 24 h	4,012 patients: 2,015 assigned to apixaban 5 mg every 12 h
Comparator	Placebo	Aspirin 85 mg
Methods	Double-blind – double-dummy. Intention to treat	Double-blind – double-dummy. Intention to treat
Inclusion criteria	65 years before CIED (2 months before randomization) AHRE > 2 months after CIED implantation AHRE defined by > 170 bpm > 6 minutes duration 65 years ≥ 1 risk factor: HF, AHT, DB, prior stroke or TIA, vascular endocarditis 75 years without risk factors	Subclinical AF > 6 min < 24 h detected by CIED with subsequent electrocardiographic confirmation > 55 years or > 75 years with a history of stroke CHA_2DS_2-VASc ≥ 4
Exclusion criteria	Previously documented AF PCI or CABG < 30 days Life expectancy < 12 months Contraindication to anticoagulation DAPT GFR < 15 ml/min	History of clinical AF documented by electrocardiogram Indications for oral anticoagulation Mechanical valve Uncorrected major bleeding < 6 months GFR < 25 ml/min
Primary endpoint	Efficacy: occurrence of CV death, stroke, systemic embolism Safety: major bleeding compound ISTH	Efficacy: stroke composite (stroke+TIA), systemic embolism Safety: major bleeding by ISTH criteria
Mean CHA_2DS_2-VASc	4 (IQ 3-5)	3.9 ± 1.1
Results	No prevention of cardiovascular events increased the bleeding risk	Anticoagulation in favor of apixaban with increased bleeding risk
Consider anticoagulation	No	Yes

AF: atrial fibrillation; AHRE: atrial high-frequency episodes; CIED: cardiac implantable electronic device; HF: heart failure.

in women. This carries a Class IIa recommendation, based on limited but emerging evidence.

However, uncertainty persists in patients with shorter episodes (< 24 h), regardless of thromboembolic risk. AHREs burden appears to be a critical determinant. An observational cohort of 356 device-implanted patients found that those with AHREs episodes ≥ 48 h had a significantly higher risk of embolic events (HR: 10.77; 95% CI: 3.22-55.12; p = 0.030)[31]. Thus, individualized risk stratification incorporating clinical comorbidities – such as hypertension, diabetes, prior stroke, or heart failure – should guide the decision to initiate OAC[37].

Recent advances have explored the use of artificial intelligence to predict clinically relevant AHREs (defined as episodes > 6 min). In a cohort of 104 patients, 14.4% developed relevant AHREs. Independent predictors included beta-blocker use, prior stroke or TIA, increased left atrial diameter, and > 1% premature atrial contractions before pacemaker implantation[38]. These factors may aid in identifying low-CHA_2DS_2-VASc patients who could still benefit from anticoagulation.

In elderly populations (> 75 years), the decision to start OAC remains particularly challenging due to concurrent elevated risks of both embolic and hemorrhagic events. Some expert groups suggest initiating OAC for AHREs lasting ≥ 5.5 h in older adults without frailty. Ultimately, the choice to prescribe anticoagulation should weigh the absolute annual risk of stroke (generally > 1%) against bleeding risk, incorporating shared decision-making between clinicians and patients[39,40].

Conclusion

The detection of AHREs is increasingly common, largely due to the widespread use of CIEDs. Multiple studies have established a strong association between AHREs and the subsequent development of clinical AF as well as an elevated risk of embolic stroke. The decision to initiate OAC should be individualized, particularly in patients with AHREs lasting longer than 24 h and in those with elevated thromboembolic risk as defined by validated scoring systems such as $CHADS_2$

and CHA_2DS_2-VASc. However, significant evidence gaps remain regarding the benefits and risks of OAC in patients with shorter AHRE episodes (< 24 h) and older adults. Further prospective studies are warranted to refine risk stratification and guide evidence-based management in these populations.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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