Atrial high-rate episodes

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REVIEW

Atrial high-rate episodes: prevalence, stroke risk, implications for management, and clinical gaps in evidence

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Self-terminating atrial arrhythmias are commonly detected on continuous rhythm monitoring, e.g. by pacemakers or defibrillators. It is unclear whether the presence of these arrhythmias has therapeutic consequences. We sought to summarize evidence on the prevalence of atrial high-rate episodes (AHREs) and their impact on risk of stroke. We performed a comprehensive, tabulated review of published literature on the prevalence of AHRE. In patients with AHRE, but without atrial fibrillation (AF), we reviewed the stroke risk and the potential risk/benefit of oral anticoagulation. Atrial high-rate episodes are found in 10–30% of AF-free patients. Presence of AHRE slightly increases stroke risk (0.8% to 1%/year) compared with patients without AHRE. Atrial high-rate episode of longer duration (e.g. those >24 h) could be associated with a higher stroke risk. Oral anticoagulation has the potential to reduce stroke risk in patients with AHRE but is associated with a rate of major bleeding of 2%/year. Oral anticoagulation is not effective in patients with heart failure or survivors of a stroke without AF. It remains unclear whether anticoagulation is effective and safe in patients with AHRE. Atrial high-rate episodes are common and confer a slight increase in stroke risk. There is true equipoise on the best way to reduce stroke risk in patients with AHRE. Two ongoing trials (NOAH-AFNET 6 and ARTESiA) will provide much-needed information on the effectiveness and safety of oral anticoagulation using non-vitamin K antagonist oral anticoagulants in patients with AHRE.

Keywords Atrial fibrillation • Atrial high-rate episodes • Pacemaker • Stroke • Anticoagulation • Continuous monitoring

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Introduction

The increased use of cardiac implantable electronic devices (CIED) and their technical ability to monitor atrial rhythm and to identify even very short episodes of atrial arrhythmias has transformed our understanding of these events in the last 10–15 years. Having an atrial lead implanted, CIED can detect episodes of atrial tachyarrhythmias including atrial tachycardia, atrial flutter, and atrial fibrillation (AF). These episodes, which are commonly asymptomatic and only detected through long-term continuous rhythm monitoring by a CIED, are described as atrial high-rate episodes (AHREs) and must be distinguished from asymptomatic episodes of paroxysmal AF, which are diagnosed through surface electrocardiographic methods[1–4]: Some AHRE do not represent true atrial tachyarrhythmias, but reflect artefacts.[5] In addition, the biological relevance of very rare AHRE, which will usually not be detected by occasional electrocardiograms (ECGs), remains unknown.

Here, we provide a comprehensive review of the prevalence of AHRE, their impact on stroke risk and current implications for management. While other have used the term 'sub-clinical AF', we use AHRE in this review, partially reflecting the diagnostic uncertainty, the high prevalence of AHRE compared with ECG-documented AF, and their spurious association with overt AF and with AF-related outcomes.

Prevalence of atrial high-rate episodes in patients undergoing continuous atrial rhythm monitoring

Atrial high-rate episodes have been reported in several large observational studies with different design, cohort size, patient characteristics, duration of follow-up, detection algorithms, and definition of AHRE in terms of atrial rate and duration (*Table 1*). Most of these studies included unselected patients with common indications for pacemaker or implantable cardioverter-defibrillator,[6–15] while others analysed populations with heart failure or risk factors for stroke.[16–23] Most studies used an atrial rate limit of >175 or >180 to define an AHRE,[6,11,12,16–18,20] while a few others used atrial rates that were even higher.[7,19,21] Atrial high-rate episodes were reported in 10% in the SAFE registry and in 70% in the analysis of data from the Veterans Administration Health Care System (*Table 1*). Importantly, studies including patients with the clinical diagnosis AF, which *per se* have a higher frequency of atrial arrhythmias, found AHRE in 40–70%.[1,6–9,11,13,16,20,21,23] Studies excluding patients with known AF have found AHRE in 10–30% of patients % (*Figure 1*).[10,12,14,17–19,22]

The minimal duration of AHRE varied from three premature atrial complexes—much below the threshold for a sustained atrial arrhythmia in the view of most experts—in the RATE Registry to up to 14 min in the pooled analysis from the HOME Care and EVEREST trials,[15,20] with the majority of studies using an episode duration longer than 5–6 min to define AHRE.[7,9,10,12,14,17–19,22,23] This duration seems to be a 'diagnostic sweet spot' that allows most algorithms detecting AHRE to distinguish artefacts from true atrial arrhythmias. This duration has not been selected based on biological relevance (e.g. association with stroke risk). There is a clear relation between the detection of AHRE and the duration of monitoring, e.g. illustrated in the ASSERT trial that found AHRE in 10% of patients within the first 3 months after enrolment, and in an additional 24.5% during the subsequent mean follow-up of 2.5 years.[19,24]

The high AHRE detection rates spurred discussion whether these rates are generalizable, e.g. reflecting that these patients all had arrhythmias requiring a CIED which may also create a substrate for AHRE[3,25] and potentially a proarrhythmic effect in the first few weeks after implantation of a new atrial lead.[12,26] Several studies using subcutaneous implantable loop recorders (ILRs) have largely refuted these considerations, at least in patients with stroke risk factors. These devices detect QRS complexes and determine AHRE using similar algorithms based on ventricular rate and its regularity.[27,28] Implantation of an ILR in stroke survivors, often after usual work-up for AF including Holter monitoring, found AHRE in 4–34% of patients, depending on monitoring duration and patient characteristics (*Table 2*).[29–40] Implantable loop recorders also detect AHREs in 21–58% of patients with cardiovascular conditions, but without an indication for rhythm monitoring (*Table 3*),[41–45] i.e. with comparable rates as in pacemaker populations. Thus, these data suggest that AHRE are common in patients with cardiovascular conditions undergoing long-term continuous monitoring of atrial rhythm.

Patients with atrial fibrillation, including those with paroxysmal atrial fibrillation, are at sufficient risk for cardioembolic stroke to benefit from oral anticoagulation for stroke prevention

Atrial fibrillation in rheumatic heart disease was recognized as a factor that predisposes to systemic embolism in 1951.[46] Left atrial emboli causing ischaemic stroke were described a decade later.[47] In the Framingham Heart Study, AF was associated with a five-fold long-term increased risk of stroke.[48,49] Prospective randomized studies from the late 1980s reported a dramatic and highly significant reduction in stroke in patients with AF treated with warfarin. The randomized AFASAK,[50] SPAF,[51] and BAATAF[52] studies were among the first to demonstrate that dose-adjusted warfarin prevented strokes effectively in patients with AF, confirmed in a later meta-analysis.[53]

Until recently, the risk of thromboembolism has been considered to be independent of AF type.[54–57] Previous systematic reviews of risk factors for stroke in AF patients have not identified AF type as an important prognostic risk factor for thromboembolism.[58–60] Atrial fibrillation stroke risk prediction models have, in general, not included AF type[61–64] perhaps because of absence of AF pattern information in hospitalization/discharge databases that were used for their derivation and validation. This consensus of risk equivalence between AF patterns is reflected by Class I and IIa recommendations in current European[55] and North American[54] guidelines.

Vanassche *et al.*[65] pooled the data on aspirin-treated patients ($n = 6573$) from the ACTIVE-A and AVERROES trials. Atrial fibrillation pattern was a strong independent predictor of risk for

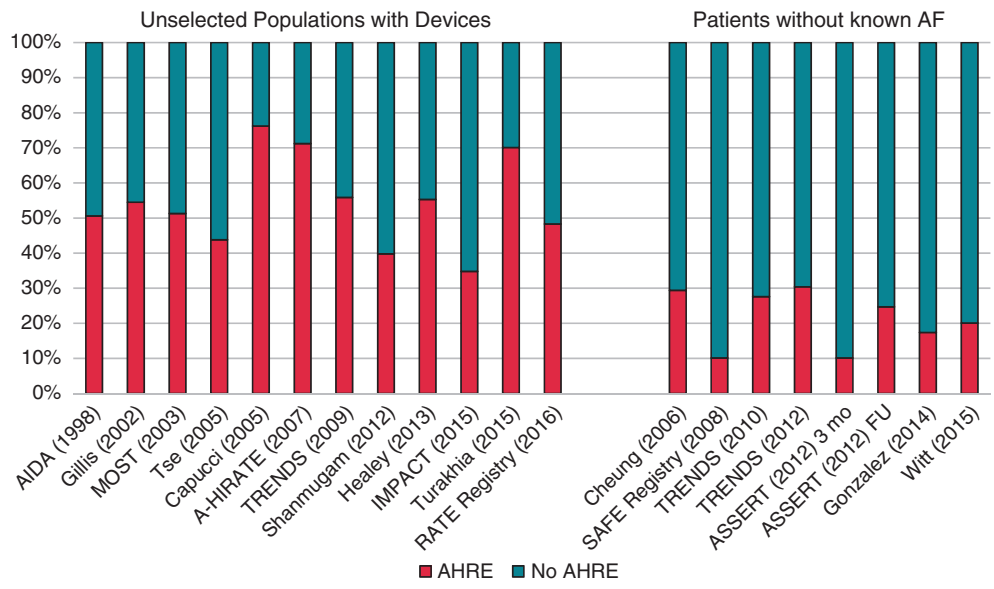

Figure 1 Percentage of AHRE in patients with (left panel) and without (right panel) known AF. AF, atrial fibrillation; AHRE, atrial high-rate episode.

Table 1 Incidence of CIED-detected AHRE

Study	Number of patients	Mean age (years)	% male	Duration of follow-up	Definition of AHRE	Patients with AHRE
AIDA (1998)	617	70 ± 11	62%	28 days	≥1 min (the AIDA algorithm)	179/354 (50.6%)
Gillis *et al.* (2002)	231	70 ± 12	52%	718 ± 383 days	Atrial rate >180 b.p.m. for ≥1 min; sustained AF >250 b.p.m. for >1 min	126/231 (54.5%) (AF)
MOST (2003)	312	74	45%	Median 27 months	Atrial rate >220 b.p.m. for >5 min	160/312 (51.3%)
Tse *et al.* (2005)	226	72 ± 10 in patients with detected AF; 70 ± 10 in patients without detected AF	39%	84 ± 16 months	Any AT detected by the device	99/226 (43.8%)
Capucci *et al.* (2005)	725	71 ± 11	50%	Median 22 months (16–30)	AF >5 min; AF >1 day	76.2%; 56.3%
Cheung *et al.* (2006)	262	74 ± 12	54%	596 ± 344 days	AHRE ≥5 min	77/262 (29%)
A-HIRATE (2007)	427	75 ± 9	56%	24 months	Atrial rate >180 b.p.m. for ≥1 min	53.8% in patients without previous AT; 88.6% in patients with previous AT
SAFE registry (2008)	1482	74 ± 12	56%	Median 349 ± 147 days	Atrial rate ≥180 b.p.m. for ≥5 min	150/1482 (10.1%)
TRENDS (2009)	2486	71 ± 11	66.4%	Median 1.4 years (0.1–3.3)	Atrial rate >175 b.p.m. for ≥20 s	1389/2486 (55.9%)

Continued

Table 1 *Continued*

Study	Number of patients	Mean age (years)	% male	Duration of follow-up	Definition of AHRE	Patients with AHRE
TRENDS (2010)	163	74.0 ± 9.1 in patients with AHRE; 72.8 ± 9.9 in patients without AHRE	71.1% in patients with AHRE; 62.7% in patients without AHRE	1.1 ± 0.7 years	Atrial rate >175 b.p.m. for ≥5 min	45/163 (27.6%)
TRENDS (2012)	1368	70.2 ± 11.8	66.2%	1.1 ± 0.7 years	Atrial rate >175 b.p.m. for ≥5 min	416/1368 (30.4%)
ASSERT (2012)	2580	77 ± 7 in patients with AHRE; 76 ± 7 in patients without AHRE	56.3% in patients with AHRE; 58.6% in patients without AHRE	Mean 2.5 years	Atrial rate ≥190 b.p.m. for >6 min; all episodes confirmed by manual expert review of electrograms	261/2580 (10.1%) within 3 months after device implantation; 633/2566 (24.6%) during further follow-up
Shanmugam *et al.* (2012)	560	66 ± 10	77.4%	Median 370 days (253–390)	Atrial rate >180 b.p.m. for ≥14 min	223/560 (39.8%); 126/382 without history of AF, 97/178 with history of AF
Healey *et al.* (2013)	445	74.3 ± 13.7 in patients with AHRE; 71.7 ± 14.4 in patients without AHRE	58% in patients with AHRE, 59% in patients without AHRE	51.5 ± 39.7 months	Any PM detected AF (manufacturer-specific nominal settings for AF detection)	246/445 (55.3%)
Gonzalez *et al.* (2014)	224	74 ± 12	53%	6 months after PM implantation	Any device-detected AHRE ≥5 min	39/224 (17.4%)
IMPACT (2015)	2718	Median 64.4	73.7%	Median 701 days	Atrial rate ≥200 b.p.m. for ≥36 of 48 atrial beats	945/2718 (34.8%)
Witt *et al.* (2015)	394	Median 67 years (59–74)	74%	Median 4.2 years (2.5–6.6)	Manufacturer-specific nominal settings for AF detection; AHREs >6 min	79/394 (20.0%)
Turakhia *et al.* (2015)	187	68 ± 8.4	99.5%	120 days	AF ≥6 min	70.1% (26.2% ≥6 min of AF; 24.6% ≥1 h of AF; 19.3% ≥5.5 h of AF)
RATE Registry (2016)	5379	73.6 ± 11.8 in patients with PM; 64.5 ± 12.6 in patients with ICD	54.1% with PM; 72.4% with ICD	Median 22.9 months	≥3 premature atrial complexes	145/300 (48%) with PM and 155/300 (52%) with ICD of the representative random sample studied

AF, atrial fibrillation; AHRE, atrial high-rate episode; AT, atrial tachycardia; CIED, cardiac implantable electronic devices; ICD, implantable cardioverter-defibrillator; PM, pacemaker.

embolic event (ischaemic or unspecified stroke or systemic embolism). The ACTIVE-W trial found a trend towards higher stroke (and systemic embolism) rates in persistent/permanent compared with paroxysmal AF in non-anticoagulated patients but not in warfarin-treated patients.[57] Similarly, the data from Friberg *et al.*[66] did not show a significant overall difference in stroke rates according to AF pattern, but found an increase in ischaemic stroke in the subgroup of non-anticoagulated patients with permanent compared with

Table 2 Incidence of ILR-detected subclinical AF in patients with cryptogenic stroke or transient ischaemic attack

Study	Number of patients included	Mean age (years)	% male	Mean CHA_2DS_2-VASc score	Duration of follow-up	Definition of AHRE	Patients with AHRE	Time to first AHRE episode
Dion *et al.* (2010)	24	49 ± 13.6	62.5%	NR	Mean 14.5 months	Ventricular rate >165 b.p.m. for >32 complexes	1/24 (4.2%) with AF <30 s	NR
Cotter *et al.* (2013)	51	51.5 ± 13.9	54.9%	Median 3 (2–4)	Mean 229 ± 112 days in patients without AHRE	AF >2 min	13/51 (25.5%)	Median 48 days (0–154)
Ritter *et al.* (2013)	60	Median 63 (48.5–72.0)	56.7%	Median 4 (3–5) without AHRE; median 4 (3–5) with AHRE	Median 397 days (337–504) without AHRE; median 312 days (242–397) with AHRE	AF >2 min	10/60 (16.7%)	Median 64 days (1–556)
Etgen *et al.* (2013)	22	60.0 without AF; 65.8 with AF	43.8% without AF; 66.7% with AF	NR	12 months	AF ≥6 min	6/22 (27.3%)	Mean 152.8
Rojo-Martinez *et al.* (2013)	101	67	46.5%	NR	281 ± 212 days	AF >2 min	34/101 (33.7%)	Median 102 days (26–240)
SURPRISE (2014)	85	54.0 without AF; 66.9 with AF	58.0% without AF; 44.4% with AF	Median 3 without AHRE; median 4 with AHRE	569 ± 310 days	AF >2 min	18/85 (20.7%)	109 ± 48 days
CRYSTAL AF (2014)	441 (208 ICM)	61.5 ± 11.3	63.5%	NR	12 months	AF >2 min	8.9% at 6 months; 12.4% at 12 months	Median 41 days (14–84)
CRYSTAL AF (2016)	48 (24 ICM)?	61.6 ± 11.4	?	NR	36 months	AF >2 min	30%	?
Poli *et al.* (2016)	74	66.4 ± 12.5	47%	Median 5 (4–6)	12 months	AF >2 min	21/74 (28.4%) at 6 months; 25/74 (33.8%) at 12 months	105 ± 135 days
Israel *et al.* (2017)	123	65.0 ± 9.4	60.2%	4.5 ± 1.3	12.7 ± 5.5 months	AF ≥2 min	29/123 (23.6%)	Average 3.6 months
Reinke *et al.* (2018)	105	64.4 ± 12.6	56.2%	Median 4 (3–6)	?	AF >2 min	19/105 (18%)	Median 217 days (72.5–338)
Pedersen *et al.* (2018)	105	Median 65.4 (27.1–80.8)	45.7%	Median 4 (2–7)	Median 381 days (371–390)	AF ≥2 min	7/105 (6.7%)	Median 21 days (5–146)

?, not reported; AF, atrial fibrillation; AHRE, atrial high-rate episode; ILR, implantable loop recorders; ICM, intracardiac monitor; NR, not recorded.

Table 3 Incidence of ILR-detected subclinical AF in patients at high risk of stroke

Study	Number of patients	Mean age (years)	% male	Duration of follow-up	Definition of AHRE	Patients with AHRE	Time to first AHRE
ASSERT-II (2017)	273	73.9 ± 6.2	65.6%	16.3 ± 3.8 months	AF including AFL and AT ≥5 min	90/256 (35.2%)	5.1 ± 5.5 months
REVEAL AF (2017)	446	71.5 ± 9.9	52.3%	22.5 ± 7.7 months	AF ≥6 min	29.3% at 18 months; 6.2%, 20.4%, 27.1%, 33.6%, and 40.0% at 1, 6, 12, 24, and 30 months	Median 123 days (41–330)
PREDATE AF (2017)	245	74.3 ± 7.7	58.8%	18 months; mean follow-up 451 ± 185 days	AF ≥6 min	55/245 (22.4%)	141.3 ± 139.5 days
Philippsen *et al.* (2017)	82	71 ± 4.0	63%	Median 588 days (453–712)	AF ≥2 min	17/82 (20.7%); 14/82 (17%) AF ≥6 min	Median 91 days (41–251)
Romanov *et al.* (2018)	50	57.8 ± 8.3	88%	≥24 months	AF ≥2 min	29/50 (58%) at 24 months; 16%, 40%, 50%, and 54% at 3, 6, 12, and 18 months	Median 4.8 months

AF, atrial fibrillation; AFL, atrial flutter; AHRE, atrial high-rate episode; ILR, implantable loop recorders.

paroxysmal AF. Recent trials in anticoagulated AF patients reported lower stroke rates in paroxysmal vs. non-paroxysmal AF patients (SPORTIF,[67] ARISTOTLE,[68] and ENGAGE-AF[69]). A meta-analysis combining data from >95 000 patients[70] appears to confirm that stroke risk may be slightly lower in patients with paroxysmal AF compared with those with chronic AF.

Patients at high stroke risk without atrial fibrillation do not benefit from oral anticoagulation

Oral anticoagulation using either vitamin K antagonists such as warfarin or non-vitamin K antagonist oral anticoagulants (NOACs) has been tested in several conditions predisposing for stroke other than AF usually without evidence for effectiveness.

Anticoagulants in survivors of a stroke without atrial fibrillation

Conducted almost 20 years ago, the WARSS trial could not detect a clinical benefit of warfarin [target international normalized ratio (INR) 1.4–2.8] over 325 mg aspirin per day after a non-cardioembolic ischaemic stroke in patients without AF within 2 years.[71] In patients with a recent embolic stroke of undetermined source, the NAVIGATE ESUS trial has been stopped in 2017 due to no efficacy improvement of 15 mg rivaroxaban over 100 mg aspirin daily, with an increased risk of bleeding in patients randomized to rivaroxaban.[72] A similar trial with dabigatran, the RE-SPECT ESUS study, similarly reported no reduction in stroke rates in patients randomized to dabigatran, with increased clinically relevant major bleedings compared to aspirin.[73]

Anticoagulants in patients with other neurological disorders

The CADISS trial tested warfarin vs. aspirin in patients with symptomatic carotid and vertebral artery dissection.[74] No difference was detected between oral anticoagulation or single antiplatelet treatment. The WASID trial compared warfarin (target INR 2.0–3.0) with high-dose aspirin (1300 mg per day) in patients with transient ischaemic attack or stroke caused by a 50–99% stenosis of a major intracranial artery.[75] This study was stopped prematurely after 569 patients because of a significantly higher bleeding rate without any benefit in the warfarin arm.

Anticoagulation in patients with heart failure, but without atrial fibrillation

The WARCEF trial showed no difference between long-term warfarin and aspirin treatment in 2305 patients with a left ventricular ejection fraction below 35% and sinus rhythm.[76] The primary composite endpoint (ischaemic stroke, intracerebral haemorrhage, and death from any cause) comprised 7.47 events per 100 patient-years in the warfarin group and 7.93 in the aspirin group. COMMANDER-HF confirmed that rivaroxaban, albeit at a lower dose than the dose approved for stroke prevention in AF, was not effective in prevention of strokes compared with no anticoagulation in a similar heart failure population.[77]

Risk of bleeding in patients treated with oral anticoagulants

The benefit of oral anticoagulation in patients with AF can so far only be achieved by exposing patients to an increased bleeding risk.[72,78] Non-vitamin K antagonist oral anticoagulant treatment is associated with a markedly lower rate of intracranial haemorrhage and lower mortality than Vitamin K antagonist therapy,[79] but the bleeding rate on NOACs is still important (ca. 2% per year of exposure), both in clinical trials[79] and in patients exposed to NOACs under routine care conditions.[80–83] In summary, the bleeding rates associated with different NOACs in real-world patients vary from 1.9% to 4.3% per year of treatment. Absolute rates depend on patient characteristics such as age. Notably, these findings on the rates of major bleeding with NOACs are comparable with the major bleeding rates reported in the pivotal randomized clinical trials.

The average atrial high-rate episodes burden is only a few hours per year, and the majority of patients with atrial high-rate episodes never receive a clinical diagnosis of atrial fibrillation

Current anticoagulation guidelines in non-valvular AF are supported by studies in patients with ECG-documented AF episodes, whether symptomatic or not.[84,85] Clinical diagnosis of AF in patients with AHRE was evaluated more than 10 years ago in the Ancillary MOST substudy,[7] performed in 312 patients included in the MOST study.[86] The population was heterogeneous, and patients with previously documented AF were not excluded. Selected patients had a pacemaker implanted due to sinus node dysfunction but were in sinus rhythm at randomization, and the analysis was retrospective and observational. During a median follow-up of 27 months, AHREs were detected in 160 patients (51.3%). Twenty of these patients had AF history documented before AHRE detection. Of the remaining 140 patients without previous AF, 36 (25.7%) had AF documented during follow-up. Similar or lower rates of AF detection were found in the ASSERT and ASSERT II studies.

Hence, although AHRE renders detection of ECG-documented AF more likely, the majority (>75%) of patients with AHRE never develop ECG-documented AF in the subsequent years, probably due to the infrequent and short nature of AHRE episodes in most patients.

Stroke risk in atrial high-rate episode patients is lower than in patients with paroxysmal atrial fibrillation

There is a growing body of evidence on the stroke risk in patients with AHREs. In the ASSERT study, the annual thromboembolic event rate was 1.7% in patients with AHRE within 3 months after inclusion,

compared with 0.7% in patients who did not show AHRE within 3 months after inclusion. These numbers are comparable to a recent systematic review where patients with AHRE had an annual stroke rate of 1.9%, compared with 0.9% in patients without AHRE.[88] Recently, a subanalysis from ASSERT focused on the longest AHRE episode found that only AHRE >24 h was associated with an increased risk of stroke compared with absence of AHRE.[87] This is much lower than the stroke risk that can be expected in patients with a similar stroke risk profile and ECG documented AF. Interestingly, strokes occur equally during periods with and without AHRE in patients with AHRE suffering a stroke.[89] Furthermore, the current licences of NOACs do not explicitly allow their use in patients with AHRE. Thus, also in view of the bleeding risk associated with anticoagulation, we do not know whether to use oral anticoagulation in patients with AHRE.

Summary: equipoise for oral anticoagulation in patients with atrial high-rate episode

Most modern pacemakers, defibrillators, and cardiac resynchronization devices provide automated algorithms alerting to AHRE. A growing body of clinical data supports the hypothesis that AHREs are associated with an elevated risk of developing further clinical AF and stroke, but the stroke risk is substantially lower than in patients with ECG-detected AF, most likely due to the very rare and short nature of AHRE episodes.[90] In view of the small but substantial risk of major bleeding in patients treated with oral anticoagulants, including NOACs, there is currently no justification for oral anticoagulation in patients with AHRE. Two ongoing studies, NOAH-AFNET 6[91] and ARTESiA,[92] will address the key question of whether patients with AHRE benefit from oral anticoagulation. ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical AF) aims to enroll 4000 high-risk (CHA_2DS_2-VASc score ≥3) participants with permanent pacemakers, defibrillators, or resynchronization device, and at least one AHRE episode of 6 min to 24 h duration (atrial rate >175/min if an atrial lead is present).[92] Patients will be randomized to receive apixaban or aspirin. The primary efficacy outcome is ischaemic stroke or systemic embolism; the primary safety outcome is major bleeds. The NOAH-AFNET 6 study (NOAC in patients with AHRE) trial is recruiting ca 3000 patients aged >65 years with one additional CHA_2DS_2-VASc factor and AHRE documented by CIED (≥170 b.p.m. atrial rate and ≥6 min duration).[91] These patients will be randomized to edoxaban or aspirin/placebo, depending on the indications for antiplatelet therapy. The primary outcome parameter of NOAH-AFNET 6 is a composite of stroke, systemic embolism, or cardiovascular death.

The results of these two trials have the potential to inform future guidance on the management of patients with atrial arrhythmias detected by implantable devices. Until these trials have reported, treatment with oral anticoagulants should be limited to rare individual decisions in patients with AHRE, but without ECG-diagnosed AF, to avoid the substantial bleeding risk on anticoagulation.

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