Approach to device-detected subclinical atrial fibrillation

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ABSTRACT

Subclinical atrial fibrillation, a commonly encountered entity in patients with implantable devices, has been associated with a number of adverse outcomes – the most important of which is thromboembolism. Through the detection of atrial high rate episodes, implanted devices offer a method to monitor for atrial fibrillation over extended periods of time. Several studies have demonstrated that patients with device-detected atrial tachyarrhythmias have an increased incidence of stroke, especially in the presence of additional risk factors. Yet, there are many uncertainties with limited evidence from randomised clinical studies and no formal guidelines to inform management in this population. This contributes to marked practice heterogeneity, under-recognition and missed opportunities for stroke prevention. We propose a logical approach to management of patients with device-detected atrial high rate episodes pending additional data from ongoing trials. SAHeart 2017;14:86-95

INTRODUCTION

Cardiac implantable electronic devices (CIEDs) are becoming more and more common due to an aging global population and expanded criteria for implantation. During 2009, over 1.3 million new or replaced implantable cardiac devices were implanted worldwide, with around a quarter of these occurring in the United States (US) alone.[1,2] South Africa has experienced substantial growth with an almost 25% rise in CIEDs implanted between 2005 and 2009, as opposed to only 8% in the US.[1] In addition, there is a greater availability of external surface monitoring and implantable loop recorders (ILR). Out of this vast increase in continuous arrhythmia monitoring arises the challenge of how to approach the abundance of data that identifies subclinical arrhythmia, and germane to this discussion, atrial fibrillation (AF).

As the most pervasive sustained arrhythmia encountered in clinical practice, AF has risen in age-adjusted incidence over the last half century – a trend which may be plateauing over the last decade.[3,4] After age 40 the lifetime risk of developing AF is almost 1 in 4.[2] As many as 40% of patients are entirely asymptomatic – also termed subclinical AF – and the arrhythmia may only come to the attention of the patient and provider as an incidental finding.[5] Population screening of those over 65 years of age would detect subclinical AF in an estimated 1.4% of patients – of whom, more than two thirds would be at high risk for stroke based on clinical risk prediction models.[6] AF shares many risk factors – including age, male gender, heart failure and coronary disease – with indications for a permanent pacemaker or implantable cardioverter defibrillator (ICD) and,

as such, the detection of clinically silent paroxysms of AF by device interrogation is not uncommon. In patients with CIEDs placed for unrelated indications, without a prior history of permanent AF, 43% had 5 minutes or more of AF detected over 2 years of follow-up in a pooled analysis of 5 large prospective trials (n=10 016).[7] Therefore, adoption of a strategy for dealing with device-detected subclinical AF is vital for clinicians.

In the midst of several studies which demonstrate the consequences of device-detected AF, many uncertainties currently exist regarding its management. Is device-detected AF associated with the same stroke risk as AF diagnosed by conventional means? Is the presence of device-detected AF enough to warrant oral anticoagulation (OAC) or do additional stroke risk factors need to be taken into account? Should OAC be given continuously or is it safe to interrupt treatment during periods of sinus rhythm? What threshold of device-detected AF should prompt initiation of OAC and should this first be confirmed by surface monitoring? Does OAC reduce the risk of thromboembolic events in patients with subclinical device-detected AF? In addition to elaborating on the available evidence, this review also highlights what remains unknown and warrants further study.

ATRIAL FIBRILLATION AS A VASCULAR DISEASE

In order to convey the clinical relevance of device-detected atrial fibrillation, an overall understanding of the pathobiology and potential consequences of AF in general is important. Although probably not the only mechanism, AF has classically and conceptually been associated with an elevated risk of ischaemic stroke through a stasis-induced formation of thrombus in the left atrial appendage (LAA) which may dislodge and embolise to the central nervous system. Subsequently, several observations have suggested that additional mechanisms may be at work when considering AF as a marker of risk, for not only stroke, but a wide range of vascular outcomes.[8] A large meta-analysis involving over half a million patients with AF over a median follow-up period ranging from 3 - 6 years, highlights that this arrhythmia is associated with increased absolute risk of heart failure (11.1 events/1 000 person-years), chronic kidney disease (6.6/1 000), stroke (3.6/1 000) and ischaemic heart disease (1.4/1 000) as well as excess cardiovascular (2.6/1 000) and all-cause mortality (3.8/1 000).[9] Certainly this association does not imply direct causality but it does question why a correlation with excess mortality and morbidity from both cardiovascular and non-cardiovascular causes exists.

Although the exact pathophysiology is complex, atrial remodeling with dilatation and fibrosis is a central feature underlying longstanding AF. Atrial ischaemia, hypertension, diabetes mellitus, systemic inflammation, hypertension, valvular disease and senescence can all contribute to atrial stretch, dilatation and injury. Atrial myocyte apoptosis leads to activation of fibroblasts via several mediators (including calpain, angiotensin II and transforming growth factor beta-1) resulting in collagen deposition and fibrosis.[8] Genomic studies have also identified genetic variants associated with a susceptibility for primary atrial fibrosis.[10] Atrial fibrosis disrupts diastolic function and electrical conduction. The chamber becomes predisposed to electrical reentry and anisotropy which then permits ectopy and irregular wave fronts.[11] Successful surgical ablation of AF does not eradicate progression of fibrosis, suggesting that the process occurs irrespective of the presence of arrhythmia.[12] Impairment in diastolic function leads to increased left atrial (LA) volume which, in turn, has been independently associated with an increased risk of myocardial infarction, congestive heart failure, coronary revascularisation and stroke.[13,14]

Yet many of these variables which contribute to LA fibrosis are also associated with an increased risk of cardiovascular disease in general and AF may simply be a surrogate marker of vascular disease burden. This is supported by the finding that AF in the absence of other risk factors for stroke in patients under 60 years of age, otherwise referred to as lone AF, does not significantly increase stroke risk or overall mortality.[15,16] Furthermore, in patients with additional stroke risk factors, the risk remains elevated with paroxysmal AF even when in sinus- or paced-atrial rhythms.[17-19] The PREVAIL (WATCHMAN LAA closure device in patients with atrial fibrillation vs. long term warfarin therapy) trial was designed to follow-up on the positive data of PROTECT AF (WATCHMAN left atrial appendage system for embolic PROTECTion in patients with atrial fibrillation) – and with failure to meet non-inferiority over 18 months has also brought into question the long-term efficacy of percutaneous LAA closure devices in stroke pre-vention without systemic anticoagulation.[20] Also to be considered, the LA cavity rather than the appendage can be the site of thrombus formation in more than half of patients with valvular AF and 1 in 9 with nonvalvular AF.[21]

Endothelial dysfunction, systemic inflammatory response and atrial hypocontractility as cause and consequence of a fibrotic atrial cardiomyopathy have been implicated as the drivers of a hypercoagulable state in AF.[8] These factors do not abate in the absence of arrhythmia and advocate that AF, whether persistent or paroxysmal, could itself be viewed as a vascular disease (Figure 1). Considering these basic principles is crucial when formulating an approach to device-detected AF.

INTERPRETATION OF DEVICE-DETECTED ATRIAL TACHYARRHYTHMIAS

Device-detection of subclinical AF may occur intentionally – for example, via cardiac monitoring following cryptogenic stroke – or incidentally as a result of cardiac monitoring for an unrelated indication. Various methods exist for detecting subclinical atrial tachyarrhythmias including ambulatory surface monitoring and CIEDs (ILRs, pacemakers and ICDs). Unlike pacemakers or ICDs which rely on one or more transvenously implanted leads to sense, the subcutaneous ILR records cardiac signals transmitted through the chest wall. Significant advantages of implantable devices are the ability to perform long-term continuous monitoring and improved compliance – the latter of which can be less than 50% with prolonged ambulatory surface monitoring, even in the setting of a clinical trial.[22] The obvious disadvantages of implantable devices include cost, the need for a minimally-invasive procedure and data fatigue with an abundance of information recorded over extended periods of time.

Historically, leadless ILRs and single-chamber pacemakers only had the ability to detect AF using irregular and incoherent R-R intervals. When compared to simultaneous external Holter monitor recordings in patients with known paroxysmal AF, these algorithms falsely classified AF resulting in suboptimal specificities of around 85% while retaining a sensitivity of over 95%.[23] False positives occurred as a result of premature atrial or ventricular complexes, irregular sinus rhythm, ventricular bigeminy and other atrial arrhythmias. Newer generation leadless devices have an AF detection algorithm which can filter P waves in order to reduce false positives by 46%, thereby raising both specificity and sensitivity to around 97%.[24]
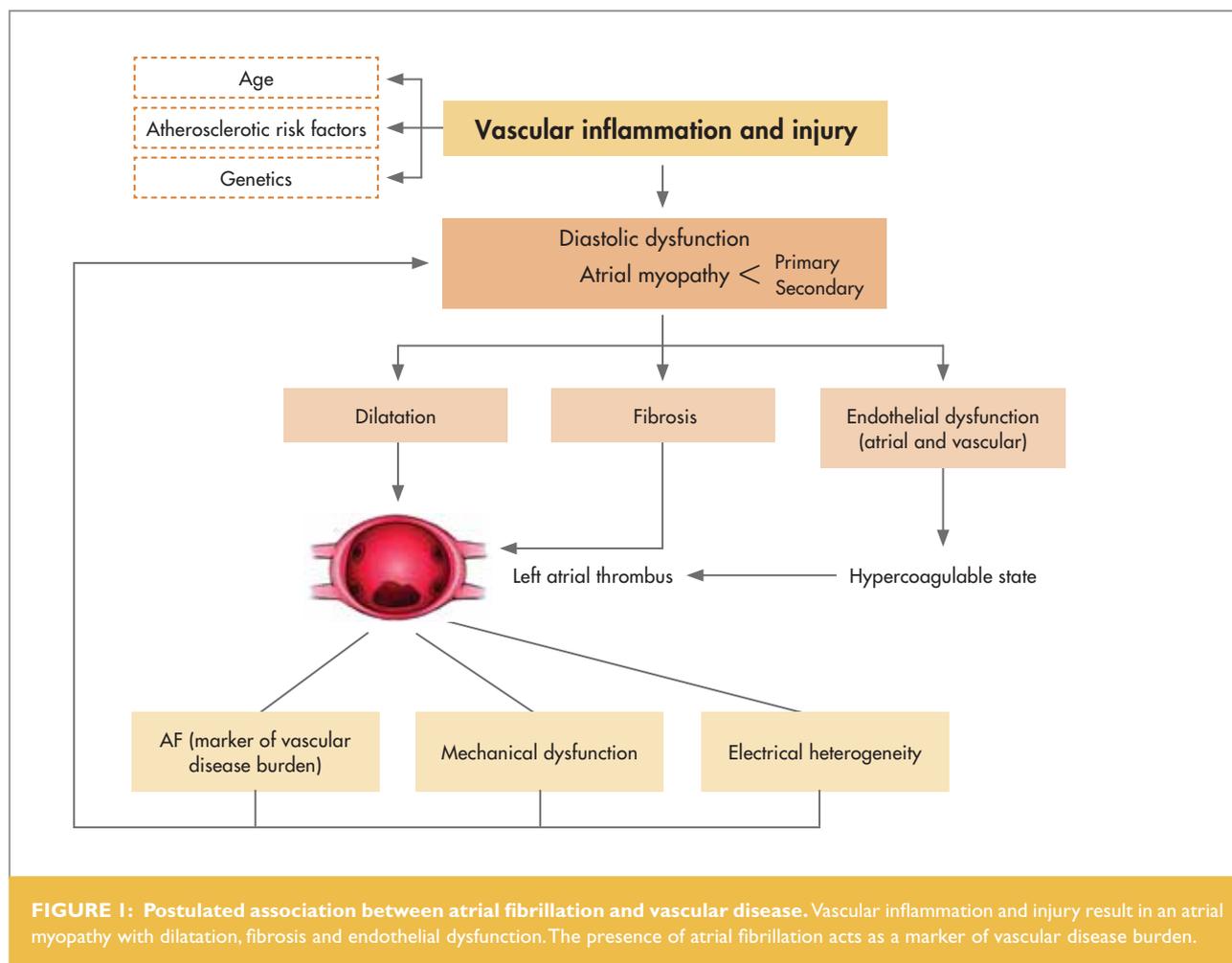
FIGURE 1: Postulated association between atrial fibrillation and vascular disease. Vascular inflammation and injury result in an atrial myopathy with dilatation, fibrosis and endothelial dysfunction. The presence of atrial fibrillation acts as a marker of vascular disease burden.

In devices with atrial sensing capability, such as dual-chamber permanent pacemakers, detection of an atrial high rate episode (AHRE) is often used as a surrogate for atrial tachyarrhythmia and AF. Modern devices may automatically identify and store these events as atrial flutter or fibrillation depending on whether or not the rhythm is regular or irregular, respectively. Sensitivity for AF with device AHRE algorithms is high; ranging from 94% - 100%.[25-27] False negatives, although uncommon, primarily occur with AF of durations of less than 30 seconds and occasionally with misclassification of short duration AF to atrial flutter, sinus tachycardia or premature atrial complexes.[26,27] As discussed later in this review, the clinical significance of short duration AF episodes remains uncertain.

Using device-detected AHREs to diagnose AF is imperfect. Of almost 6 000 AHREs (>190 beats per minute for >6 minutes), 17% were false positives when intracardiac electrograms were reviewed independently by researchers in the Asymptomatic AF and stroke evaluation in pacemaker patients and the AF reduction atrial pacing trial (ASSERT) of 2 580 patients.[28] False detections occur as a consequence of far field oversensing of R waves, retrograde ventriculoatrial conduction, noise and

frequent atrial ectopy.[28-30] As such, adjudication by a qualified clinician remains essential prior to making a diagnosis of AF based on device interrogation data.

Storing electrograms reduces the battery life of devices and may be limited by device memory. In some cases, this information may not be available requiring an alternate means of discriminating between true and false AF detection. The most recent guidelines from the European Society of Cardiology (ESC) provides a class IB recommendation for further electrocardiogram (ECG) monitoring to confirm AF in all patients found to have an AHRE.[31] Duration and timing of an AHRE may also help discriminate. In the ASSERT trial, positive predictive value for AF increased from 83% - 97% when the duration threshold of AHREs was increased from 6 minutes to 6 hours at >190 beats per minute.[28] Hence, in the case of long duration AHREs, further investigation is unlikely to improve diagnostic accuracy. After the first 12 months, new inappropriate detections were also rare (3%) over nearly 2 years of additional follow-up.[28] This data would suggest that short AHREs, lasting less than 6 hours within the first 12 months following device placement, requires further con-

firmation of AF either by review of available electrograms, reprogramming of devices to allow storing of electrograms during AHREs or with an additional ECG monitoring modality, such as Holter.

THE RELATIONSHIP BETWEEN STROKE AND DEVICE-DETECTED ATRIAL FIBRILLATION

Several trials have demonstrated an association between device-detected AHREs and elevated stroke risk. The first large scale study to demonstrate this was a sub group analysis published in 2003 of 312 patients from the landmark mode selection trial (MOST) of dual-chamber vs. single-chamber pacing in patients with sinus node dysfunction. Over a mean of 27 months, 51% of patients from this sub group had at least one device-detected AHRE (>220 beats/minute for 10 consecutive beats) lasting longer than 5 minutes. These AHREs were not adjudicated to confirm AF and one-third of these had confirmed AF prior to development of an AHRE. Nonetheless, the presence of an AHRE was associated with a near 3-fold increase in composite end-point of death or stroke and a 6-fold increase in AF diagnosis.[25]

To follow-up on the previous association, the relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risks study (TRENDS) enrolled over 2 000 patients with CIEDs and at least 1 stroke risk factor in an observational prospective trial. Over a mean follow-up of 1.4 years, a quarter of patients had an AHRE detected (defined as >120 beats/minute for ≥20 minutes). Patients were twice as likely to sustain a stroke or TIA within 30 days with a maximum daily AHRE burden of at least 5.5 hours compared to those without AHRE. Interestingly, and in contrast to the MOST study, an AHRE burden of less than 5.5 hours but more than 5 minutes per day exhibited no significant difference when compared to those with a zero burden. This trial, however, had included patients with prior AF and AHREs were not adjudicated. Furthermore, the study entailed limited follow-up and a small number of outcome events.[32]

Subsequently, the landmark ASSERT trial was primarily designed to investigate the association between AHRE and stroke incidence by prospectively analysing more than 2 500 CIED patients over the age of 65 with hypertension. In contrast to TRENDS, patients with a previous history of atrial tachy-arrhythmias were excluded and intracardiac electrograms were adjudicated to confirm AF for each AHRE. At least 1 AHRE (defined as ≥190 beats/minute lasting greater than 6 minutes) was detected in a tenth of patients at 3 months and in more than a third of patients over a median follow-up of 2.5 years. Subclinical AF was recognised as being 8 times more common than clinical AF. Subclinical AHREs, detected during the first 3 months, were independently associated with a 2.5-fold increased risk of ischaemic stroke or systemic embolism, even when adjusted for baseline stroke risk factors. In ASSERT, both longer AHRE duration and higher number of episodes were

associated with an increased risk of thromboembolism. Hazard ratios were 2, 3 and 5 for AHRE durations of >6 minutes, >6 hours and >24 hours, respectively.[33]

RISK STRATIFICATION IN PATIENTS WITH DEVICE-DETECTED ATRIAL FIBRILLATION

The critical threshold AHRE duration associated with an increased stroke risk varied greatly from trial to trial: >5 minutes in MOST, >6 minutes in ASSERT and >5.5 hours cumulative daily in TRENDS.[25,32,33] The variability stems from differences in study technique and technical parameters including adjudication to confirm AF, AF detection algorithm, length of follow-up, baseline stroke risk and sample size. A pooled analysis was aimed at determining the effect of AHRE burden on stroke risk. The Stroke prevention Strategies based on Atrial Fibrillation information from implanted devices (SOS AF) study included 5 prospective studies (including TRENDS) and cumulatively involved over 10 thousand patients. An AHRE lasting 5 minutes or more occurred in 43% of patients during the median follow-up of 24 months. An increased risk of ischaemic stroke was significantly associated with a maximum daily AHRE threshold of ≥5 minutes (hazard ratio 1.76, p=0.04) but the highest risk was found with ≥1 hour (hazard ratio 2.11, p=0.008). When controlling for $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack) score risk factors and oral anticoagulation used at baseline, the hazard ratio remained elevated at almost 2 (p=0.049) for a burden of ≥1 hour compared to <1 hour. The authors concluded that, when AHRE burden was assessed as a continuous variable, every additional hour increase led to a 3% increase in the relative risk for stroke or TIA.[7] Similarly, a recently published reanalysis of ASSERT data found that, even when controlling for other stroke risk factors (age, sex, BMI, heart failure, prior stroke, diabetes and arterial disease) a continuous AF burden of more than 24 hours was associated with increased risk of stroke or systemic embolism (hazard ratio 3.24, p=0.003) with no significant difference when comparing shorter durations to no AF.[34] Higher AF burden appears to be associated with higher risk of stroke, at least in part due to the finding that longer duration AHREs have a higher positive predictive for true AF.[28]

Risk stratification using clinical risk prediction scores for patients with device-detected AF has been studied. Data from the SOS AF trial suggested that AF burden was predictive of stroke, even in patients with a low $CHADS_2$ score.[7] In the ASSERT trial, the absolute risk of stroke approached a rate of nearly 4% in the presence of AF with a $CHADS_2$ score of greater than 2 but with lower $CHADS_2$ scores there were no significant association.[33] In a separate retrospective study, data from remote CIED interrogation in over 500 patients was retrospectively analysed over a follow-up period of 1 year. Patient risk was categorised based on $CHADS_2$ score in addition

to a minimum AHRE burden over a 1 day period (Figure 2). High risk patients had 24 hours of AHRE burden and a $CHADS_2$ score of 1, >5 minutes and a $CHADS_2$ score of 2, or a $CHADS_2$ score of >2. Patients with a $CHADS_2$ score of 0 were found to be low risk regardless of burden; however, this conclusion was limited by short follow-up and a low incidence of outcome thromboembolic events (2.5% in total).[35]

Interestingly, the annual stroke rates for AF patients with a $CHADS_2$ score of 2 were lower (around 2%) in ASSERT and other device-detected AF trials than the 4% found in the national registry of atrial fibrillation (NRAF) trial which originally validated this clinical risk prediction score in 2001.[33,35,36] The NRAF validation trial has been criticised for including high risk patients with a high prevalence of congestive heart failure as well as prior stroke and TIA, thereby skewing the comparison.[37] This finding may also reflect the reduction in stroke incidence in developed countries over the last decade and that neither trial controlled for anticoagulation use at baseline.[38] Nonetheless, the available data suggests that in the device-detected AF population – similar to those with AF detected through other modalities – clinical risk prediction scores are most helpful at the extremes with uncertainty surrounding the intermediate scores.

It is crucial to recognise though, that no clear temporal relationship between stroke and device-detected AHRE has been established in the majority of studies. In a sub group analysis of TRENDS: only half of those who experienced a stroke or TIA had an AHRE episode recorded prior to the event; a quarter were linked to an AHRE within a month of the event and only 15% were associated with an AHRE during the event.[17] Findings were very similar with the ASSERT data: only half of the patients sustained AF prior to their thromboembolic stroke event; only 12% within 30 days and only a single patient (2%) during the event.[18] Furthermore, none of the patients in this study sustained AF lasting longer than 24 hours continuously; recognising that current consensus opinion and anticoagulation guidelines are predicated on a minimum duration of 48 hours of AF as the requisite duration for intra-atrial thrombus formation.[18,39] As alluded to previously in this review, temporal dissociation suggests that a mechanism beyond pure cardiogenic thromboembolism may play a role in stroke in some AF patients, particularly among those with additional risk factors.

A temporal association was, however, demonstrated in an observational study involving nearly 10 000 patients in the US Veterans dministration with CIEDs of which 187 suffered an ischaemic stroke. An AF burden of 5.5 hours within a day was not met by the majority (85%) in the 30 days before stroke, yet a small subset of 13 patients (7%) did have a positive AF burden in the 30 days before stroke. This conferred an odds ratio for stroke of more than 17 (p <0.0001) for the first 5 days after

onset of AF which gradually returned to 1 as the period reached beyond 30 days.[40]

The majority of studies had classified patients with AHREs lasting less than 5 minutes as having no AF and potential exists for missing clinically important events in this group. Recently published data from the RATE registry (registry of atrial tachycardia and atrial fibrillation episodes) – a multicentre prospective observational study aimed at following outcomes of over 5 000 patients with device-detected AF of any duration – demonstrated that short episodes of AF terminating within a single adjudicated electrogram (usually less than 20 seconds) did not increase the risk of a composite outcome of stroke, TIA, hospitalisation or mortality. Importantly, approximately one half of these patients did go on to develop longer episodes of AF over 2 years of follow-up. Longer episodes were associated with a hazard ratio of 1.5 (p=0.03) for stroke or TIA and 1.7 (p<0.001) for the composite outcome.[41] These results suggest that very brief AHREs may not be clinically significant in isolation but, given a propensity for these patients to have longer episodes over time, close surveillance remains important. Furthermore, whether multiple shorter events are clinically equivalent to a single longer event of a similar cumulative duration and whether events longer than 20 seconds but less than 5 minutes in duration are clinically significant when compared to no events has yet to be determined.
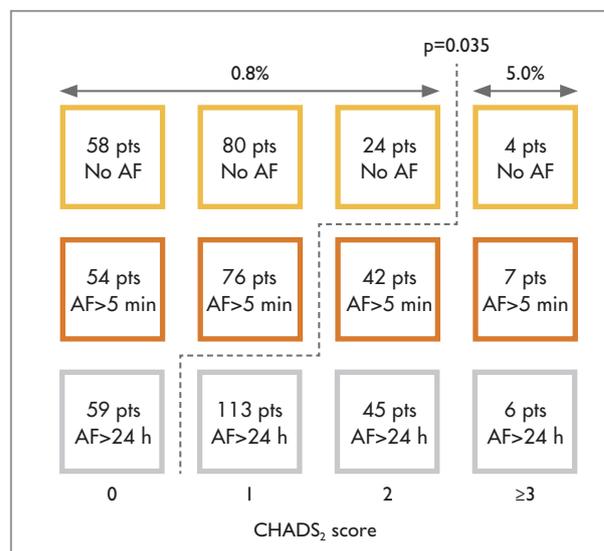

FIGURE 2: Thromboembolic risk stratified by atrial fibrillation duration and $CHADS_2$ score. Combination of AF burden and $CHADS_2$ score separated the study population into 2 groups with significantly different thromboembolic risk (0.8% vs 5.0%). Columns correspond to $CHADS_2$ scores and rows correspond to AF duration over the course of 1 day (none, >5min, and 24h continuous).
Reprinted with permission from Botto, et al.[33]

AF = Atrial Fibrillation, $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes Mellitus, Stroke or transient ischaemic attack.

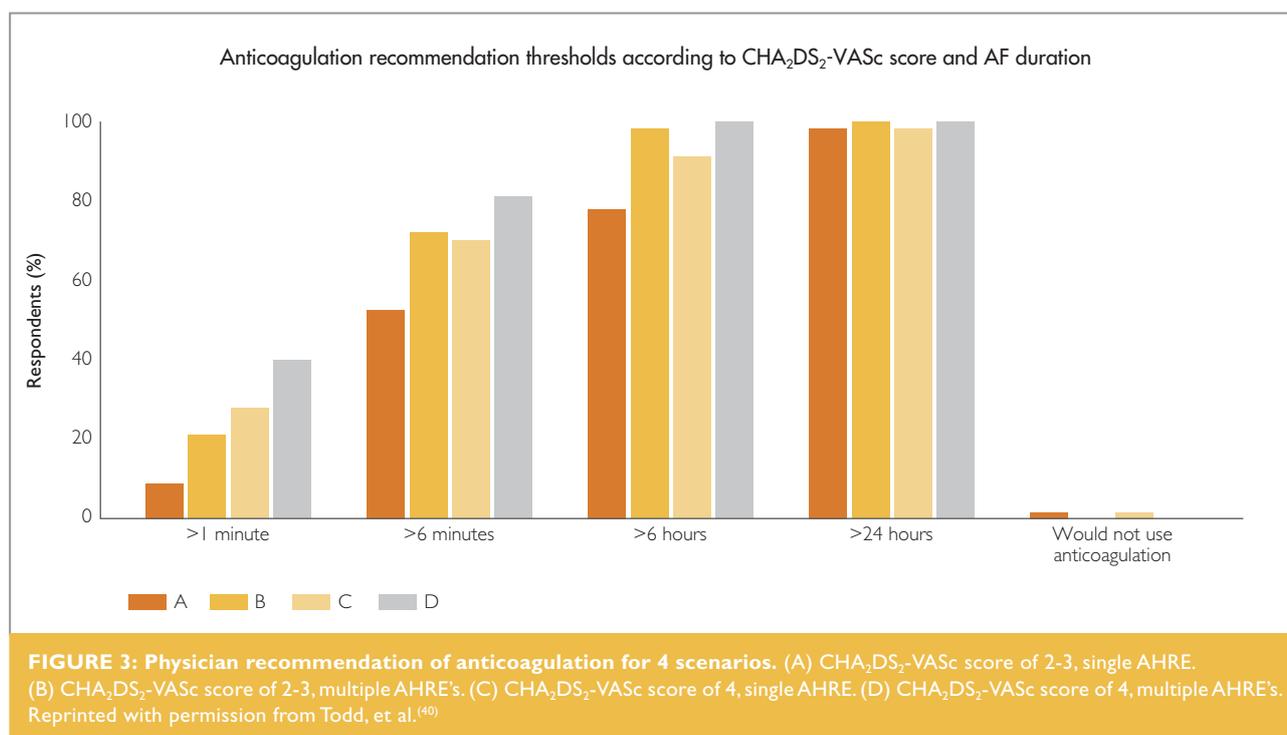## CURRENT CLINICAL PRACTICES FOR DEVICE-DETECTED ATRIAL FIBRILLATION

At present, there is limited evidence from randomised clinical studies to inform management of subclinical AF detected by CIEDs. The topic was only recently included in guidelines released by the ESC but remains absent from North American consensus statements. This stems from ambiguity regarding stroke risk stratification with regards to accuracy of AF detection, burden of AF, individual stroke risk and validity of clinical risk prediction scores such as $CHADS_2$ or CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65 - 74, female sex category) in this patient population.[36] Therefore, the approach to device-detected AF varies greatly between clinicians.

A European Heart Rhythm Association survey involving 46 primarily medium-high volume European device-implanting centres captured the current practice heterogeneity (Figure 3). When presented with a patient scenario where a single AHRE was detected lasting more than 6 minutes, 53% of cardiologists recommended anticoagulation when CHA_2DS_2-VASc score was 2 - 3 as opposed to 70% when CHA_2DS_2-VASc was 4. Overall, a trend was shown towards favouring anticoagulation in patients with higher CHA_2DS_2-VASc scores, multiple AHREs and longer duration episodes.[42]

In the setting of recent stroke, data from randomised trials suggests a higher likelihood of OAC prescription patterns in patients with device-detected AF. In the landmark cryptogenic stroke and underlying AF (CRYSTAL AF) trial, the number of patients on OAC at 6 and 12 months was more than double in a group randomised to receive an ILR following stroke when compared to controls who received monitoring by conventional strategies (pulse palpation, ECG, Holter or event monitors). At 12 months, 97% of patients with device-detected AF were receiving OAC at 12 month follow-up, despite the study protocol not mandating treatment of AF.[43] Although providers may recognise the importance of secondary stroke prevention, the potential for primary prevention from device-detected subclinical AF may still be underappreciated. In a retrospective study of 445 patients with CIEDs, 53% had device-detected AF but, in those without a history of clinical AF, less than one-quarter were prescribed OAC despite 88% having a $CHADS_2$ score of 1 or more. Patients with clinical AF were more than twice as likely to receive OAC.[44] These findings suggest that a more unified approach towards management of device-detected AF for primary prevention is required.

An open-label prospective multicentre study is currently underway which aims to implant an ILR in patients at high risk for AF in order to understand how patients with device-detected AF are managed. The REVEAL AF trial (NCT01727297) plans to follow 400 patients for a minimum of 18 months to assess time to first episode of AF lasting more than 6 minutes, clinical predictors for AF, and observations of physician actions in response to awareness of AF.

FIGURE 3: Physician recommendation of anticoagulation for 4 scenarios. (A) CHA_2DS_2-VASc score of 2-3, single AHRE. (B) CHA_2DS_2-VASc score of 2-3, multiple AHRE's. (C) CHA_2DS_2-VASc score of 4, single AHRE. (D) CHA_2DS_2-VASc score of 4, multiple AHRE's. Reprinted with permission from Todd, et al.[40]

AHRE = Atrial High Rate Episodes, AF = Atrial Fibrillation CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes Mellitus, Stroke or transient ischaemic attack, Vascular disease, Age 65 - 74, female Sex category.

MANAGEMENT STRATEGIES AND STROKE PREVENTION IN DEVICE-DETECTED ATRIAL FIBRILLATION: EXISTING EVIDENCE

Currently, limited data exits to support the use of OAC in subclinical AF. An observational study from the UK involving more than 5 000 patients visiting outpatient clinics for reasons unrelated to AF, those with an incidental first AF diagnosis demonstrated more than double the stroke rate and all-cause mortality rate when matched to controls without AF. Of these patients, nearly half received OAC during follow-up and experienced a significant reduction in both stroke (by two-thirds) and all-cause mortality (by one-third).[45] As such, OAC has been shown to be effective at reducing stroke even in those with incidentally-diagnosed subclinical AF, but not necessarily in those with AF detected by an implanted device.

A single randomised prospective trial with several principal flaws has been published which evaluated OAC in device-detected AF. The highly controversial premise of intermittent anticoagulation stems from the hypothesis that patients who are free from AF for a period of time could safely stop their OAC due to a presumed temporal reduction in stroke risk. The randomised trial of anticoagulation guided by remote rhythm monitoring in patients with implanted cardioverter-defibrillator and resynchronisation devices (IMPACT) was primarily aimed at utilising remote monitoring to guide inter-mittent anticoagulation in almost 3 000 patients with dual-chamber or biventricular ICDs. The trial was terminated pre-maturely due to a lack of benefit of intermittent anticoagulation with regards to thromboembolism, hemorrhagic stroke, major bleeding and mortality.[46] Several limitations may have con-tributed to the results of this study. An AHRE duration threshold of 24 hours was used to initiate OAC in the intervention group when much shorter durations have been associated with significant stroke risk in other studies.[25,32,33,35] Finally, this trial also preceded many of the studies that have demonstrated a temporal dissociation between AHRE and thromboembolism; notably, a third of AHREs were detected only after the event in this investigation. The provocative conclusion of this trial and the concern from opponents of intermittent OAC use is that the presence of AHRE is a marker of risk rather than the direct cause of thromboembo-lism – arguing for maintenance of therapeutic anticoagulation without interruption in all at risk individuals.[46]

Which patients will benefit most from OAC has yet to be determined by a randomised trial. The CRYSTAL AF study did demonstrate improved OAC prescription for secondary prevention in those patients with devices, and although not powered to detect this end point, demonstrated a trend towards lower recurrent stroke and TIA in the device group when compared to controls utilising conventional monitoring (5% vs. 9%).[43] Three trials are currently recruiting to evaluate efficacy of OAC in stroke prevention of patients with device-detected AF: subclinical atrial fibrillation and stroke (SILENT – NCT02004509), Non-vitamin K antagonist oral anticoagulants in patients with atrial high rate episodes (NOAH – NCT02618577) and apixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA – NCT01938248). To initiate OAC in the intervention groups, SILENT will use a threshold AF burden of >5.5 hours with ARTESiA and NOAH planning to use >6 minutes. An additional 2 randomised studies will attempt to reanalyse the safety of intermittent OAC in patients with various AF burdens and CHADS$_2$ scores: Safety study on stopping anticoagulation medication in patients with a history of atrial fibrillation (TACTIC AF – NCT 01650298) and rhythm evaluation for anticoagulation with continuous monitoring (REACT.COM – NCT01706146).

In patients with contraindications to systemic anticoagulation, LAA appendage occlusion and ligation for stroke prevention could potentially be considered, yet the risk-benefit ratio will need to be scrutinised for these invasive procedures.[20]
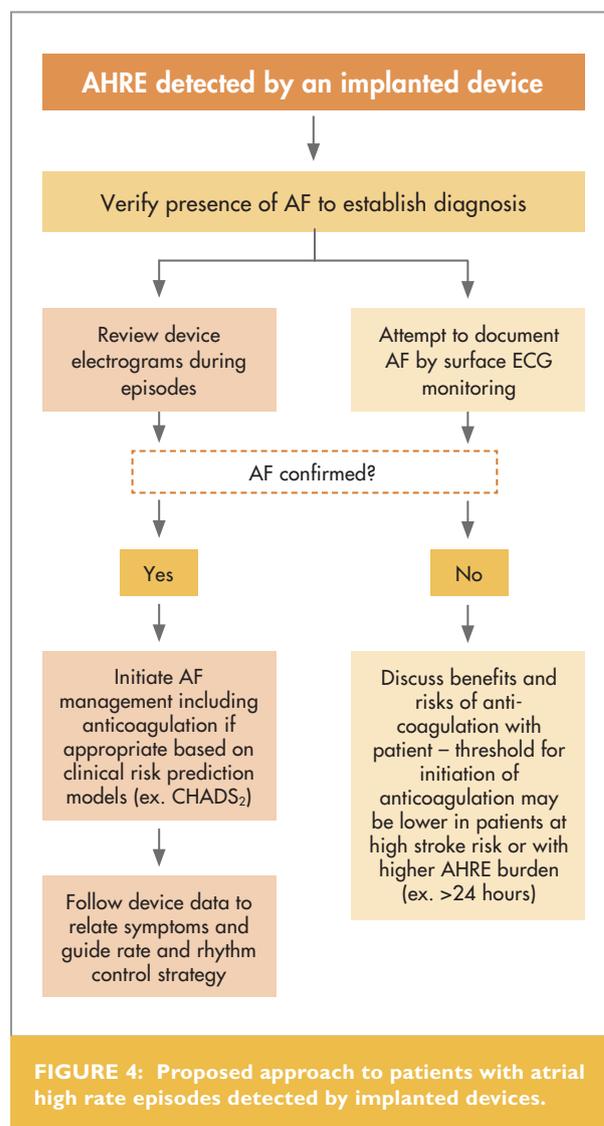

FIGURE 4: Proposed approach to patients with atrial high rate episodes detected by implanted devices.

AHRE = Atrial High Rate Episode, AF = Atrial Fibrillation.

TABLE 1: A summation of the large prospective trials examining the relationship between device-detected atrial high rate episodes and thromboembolic events.

Study	n	Main findings	Conclusion
MOST	312 patient subgroup with sinus node dysfunction and pacemakers programmed to log AHRE	Median follow-up, 2.3 years	Patients with AHREs exceeding 5 minutes in duration are more than twice as likely to die or have a stroke and 6 times as likely to develop atrial fibrillation
		The presence of any AHRE was an independent predictor of the following: Total mortality (HR, 2.48; 95% CI, 1.25-4.91; p=0.0092); death or nonfatal stroke (HR, 2.79; 95% CI, 1.51-5.15; p=0.0011); and atrial fibrillation (HR, 5.93; 95% CI, 2.88- 2.2; p=0.0001)	
TRENDS	2 486 patients with ≥1 stroke risk factors with pacemakers or defibrillators	Mean follow-up, 1.4 years	Thromboembolism risk is a quantitative function of AHRE burden
		Annual thromboembolism risk was 1.1% for no-burden, 1.1% for low-burden, and 2.4% for high-burden subsets of 30-d windows	AHRE burden ≥5.5 h on any of 30 prior days doubled thromboembolism risk
ASSERT	2 580 patients ≥65 years of age with hypertension and no history of AF, with pacemaker or ICD	Mean follow-up, 2.5 years	Subclinical atrial tachyarrhythmias, without clinical AF, occurred frequently in patients with pacemakers and were associated with a significantly increased risk of ischaemic stroke or systemic embolism
		Subclinical atrial tachyarrhythmias were associated with an increased risk of ischaemic stroke or systemic thromboembolism (HR, 2.49; 95% CI, 1.28-4.85; p=0.007) even after adjustment for predictors of stroke (HR, 2.50; 95% CI, 1.28-4.89; p=0.008)	
IMPACT	2 718 patients with dual-chamber and biventricular defibrillators	Median follow-up, 2 years	Intermittent anticoagulation based on remotely detected AHRE did not prevent thromboembolism
	2-Arm RCT: (1) start and stop anticoagulation on the basis of remote rhythm monitoring vs. (2) usual office-based follow-up	Primary events (2.4 vs. 2.3 per 100 patient-years) did not differ between trial arms (HR, 1.06; 95% CI, 0.75–1.51; p=0.732); in patients with AHRE, thromboembolism rate was 1.0 vs 1.6 per 100 patient-y (p=0.251); no temporal relationship between AHRE and stroke was seen	
SOS AF	Pooled analysis of data from 5 prospective studies; 10 016 patients with pacemakers and ICDs without permanent AF, with at least 3 months of follow-up	Median follow-up, 2 years	Daily AHRE burden is associated with an increased risk of thromboembolism even after adjustment for anticoagulant use and CHADS₂ score
		Increased risk of stroke was associated with a maximum daily AHRE threshold of ≥5 minutes (HR, 1.76; 95% CI, 1.02-3.02; p=0.041) but the highest risk was with ≥1 hour (HR, 2.11; 95% CI, 1.22-3.64; p=0.008); when controlling for stroke risk factors and oral anticoagulation use at baseline, the risk persisted (HR, 1.90; 95% CI, 1.00-3.61; p=0.0487)	
RATE	5 379 patients with pacemakers or ICDs	Median follow-up, 1.9 years	Adjudicated short AHREs (terminating within a single electrogram) were not associated with increased risk of clinical events when compared to no AHRE
		Patients with only short AHREs were associated with lower adjusted incidence of composite clinical events including stroke (HR, 0.86; 95% CI, 0.77-0.97; p=0.01) when compared to no AHRE; long AHREs were associated with incident clinical events (HR, 1.68; 95% CI, 1.49-1.88; p<0.001) and stroke orTIA (HR, 1.51; 95% CI, 1.03–2.21; p=0.03)	Long AHREs (extending beyond a single electrogram) were associated with an increased incidence of stroke

AF = atrial fibrillation, AHRE = atrial high rate episode, ASSERT = asymptomatic atrial fibrillation and stroke evaluation in pacemaker patients and the atrial fibrillation reduction atrial pacing trial, AT = atrial tachycardia, CI = confidence interval, HR = hazard ratio, ICD = implantable cardioverter-defibrillator, IMPACT = multicenter, randomised study of anticoagulation guided by remote rhythm monitoring in patients with implantable cardioverter-defibrillator and resynchronisation devices, MOST = mode selection trial, RATE = registry of atrial tachycardia and atrial fibrillation episodes, RCT = randomised, controlled trial, SOS AF = stroke prevention strategies based on atrial fibrillation information from implanted devices, TRENDS = the relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke.

CONCLUSION

Subclinical AF is commonly recognised in patients with CIEDs and its relationship to systemic thromboembolism and ischaemic stroke presents a significant clinical management dilemma. Given the lack of standardised and validated AF detection algorithms, at this stage it behooves the clinician to review the intracardiac recordings. If any uncertainty exists, in concordance with recent ESC guidelines, acquiring additional surface ECG monitoring to confirm that the recorded AHRE is a veritable atrial tachyarrhythmia is crucial.[31] Once AF is diagnosed, a logical methodology to patient-specific intervention is necessary and we propose the following approach (Figure 4).[47]

In summary, despite subtle differences in design, all studies presently confirm that device-detected AF positively correlates with thromboembolic stroke, especially in patients with additional stroke risk factors (Table 1).[7,25,32,33,35,41,46] Clinical risk prediction scores, such as $CHADS_2$, have been studied in this population and demonstrate value in supporting clinical decisions.[33,35] Uncertainty still exists regarding the exact burden of AF that portends the highest risk, yet a minimum threshold associated with clinically events may be in the range of 5 or 6 minutes.[7,25,33,35,41] The detection of shorter episodes should not be ignored as these herald a risk for developing a more significant AF burden over time and further study is required to identify stroke risk associated with these events.[41] It is also striking that the majority of AF appears not to be linked with thromboembolic events in a temporal manner, suggesting that atrial arrhythmias are markers of a propensity towards stroke as opposed to a direct etiology of left atrial thrombus.

A reduction in stroke risk with the use of anticoagulation has yet to be demonstrated in the subclinical device-detected AF population and several trials are currently underway to address this question. While awaiting further data, the excess stroke risk in these patients should not go unheeded. Recent data suggests an excess stroke risk in patients with more than 24 hours of continuous AF even when controlling for other stroke risk factors.[34] We would recommend utilising clinical judgement to balance the risk of the risk of bleeding with initiation of systemic anticoagulation with the thromboembolism based on higher AF burden and presence of additional risk factors.

Additional research is imperative in order to guide standardisation of AF detection algorithms and criteria for stroke prevention by exploiting the evolving technology of implantable devices. In addition to stroke prevention, the detection of AF should draw attention to the arrhythmia, its consequences and its comorbidities – prompting clinicians to review rate and rhythm control strategies as well as optimisation of cardiovascular risk factors.

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