Anticoagulation in device-detected atrial fibrillation: Challenges in stroke prevention and heart failure management

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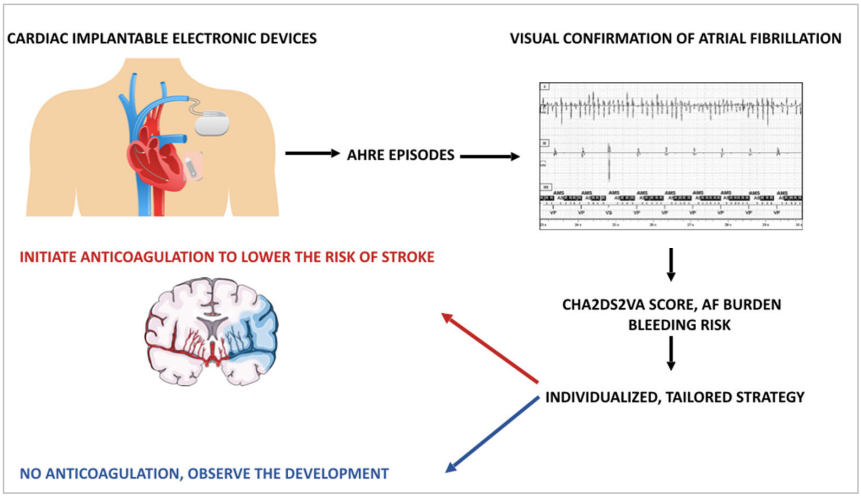
Atrial fibrillation (AF), the most common cardiac arrhythmia globally, contributes significantly to morbidity and mortality. With advancements in implantable devices like pacemakers, defibrillators, and loop recorders, incidental detection of AF as device-detected AF (DDAF) or subclinical AF (SCAF) has become common. This asymptomatic AF presents unique management challenges, particularly in anticoagulation decisions for stroke prevention. Evidence from recent trials, notably NOAH-AFNET 6 and ARTESiA, indicates a complex risk-benefit profile for anticoagulation in DDAF. In ARTESiA, anticoagulation modestly reduced stroke and systemic embolism rates, though this effect did not reach statistical significance. The NOAH-AFNET 6 trial found no significant reduction in a composite of cardiovascular death, stroke, or systemic embolism with anticoagulation compared to placebo. Both trials revealed an increased bleeding risk, underscoring the need to carefully weigh stroke prevention against bleeding risks in DDAF. The 2024 European Society of Cardiology guidelines reflect this nuanced approach by advocating a tailored, risk-based strategy. Emerging evidence also shows that AF burden impacts heart failure (HF) outcomes, with a five-fold increase in HF hospitalizations associated with higher AF burden. This highlights the importance of rhythm or rate control to reduce HF progression, particularly in patients with both AF and HF, where reducing AF burden is associated with better prognosis and fewer hospitalizations. Future research should focus on refining anticoagulation strategies, especially for patients with low AF burden, and exploring novel approaches like intermittent anticoagulation and advanced monitoring to support personalized DDAF management.

Anticoagulation in Device-Detected Atrial Fibrillation: Challenges in Stroke Prevention and Heart Failure Management



In this review, we evaluate the unique challenges associated with assessing stroke risk and determining the need for anticoagulation therapy in patients with device-detected atrial fibrillation.

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Graphical Abstract

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a significant impact on morbidity and mortality[1]. The incidence of AF is doubling every few decades and is associated with a significantly increased risk of stroke[2,3]. The risk is primarily due to thrombi that most often form within the left atrial appendage due to blood stasis from ineffective atrial contraction. Automated continuous rhythm monitoring has become feasible with the widespread use of cardiac implantable electronic devices (CIED). A common observation in devices with atrial sensing capabilities is the occurrence of atrial high-rate episodes (AHREs). Although definitions vary across studies, AHREs are typically described as episodes of atrial tachyarrhythmias with rates exceeding 175 beats per minute and lasting longer than 5 minutes[4-6]. False positives are not uncommon, often resulting from artifacts, electrical noise, or far-field R-wave signals[7]. Subclinical atrial fibrillation (SCAF), or device-detected AF (DDAF) that better describes the entity, refers to mainly asymptomatic AHREs detected by the device that are subsequently confirmed as AF, atrial flutter, or atrial tachycardia following a visual review of CIED tracings. In contrast, clinical AF is defined as AF lasting at least 30 seconds, symptomatic or asymptomatic, as documented by a surface electrocardiogram (ECG) (ref.[8]). While the clinical implications of clinical AF are well-known, DDAF presents unique challenges. These episodes vary in duration and frequency, raising questions about the association with stroke risk and the need for anticoagulation therapy. Some evidence indicates that even brief AF episodes, sometimes as short as a few minutes, may elevate stroke risk, especially in high-risk individuals with conditions like hypertension and diabetes[9]. Guidelines for anticoagulation therapy in clinical AF rely on scoring systems like CHA_2DS_2-VA; however, the management of device-detected AF is less clear. Previous studies have shown that, although stroke risk for patients with DDAF is higher than those without, it is lower than for patients with clinical AF (ref.[9-11]). Recent evidence, notably from the NOAH-AFNET 6 and ARTESiA trials, suggests that in device-detected AF, anticoagulation therapy poses a complex risk-benefit profile. In ARTESiA, there was a reduction in the primary outcome of stroke and systemic embolism with anticoagulation, though this did not reach statistical significance. In NOAH-AFNET 6, anticoagulation therapy did not significantly reduce the incidence of a composite of cardiovascular death, stroke or systemic embolism compared with placebo. Both trials highlighted an increased bleeding risk associated with anticoagulation, raising concerns about the balance between potential stroke prevention benefits and the heightened bleeding risk[12,13]. This review provides a comprehensive overview of current evidence on DDAF, stroke risk assessment, emphasizing anticoagulation strategies, and new avenues for personalized management.

Epidemiology and detection of DDAF

The prevalence of clinical AF has increased significantly over recent decades, driven by longer life expectancy and advancements in diagnostic methods. The estimated global prevalence of AF is almost 60 million patients in 2019 (ref.[1]). The prevalence of DDAF varies according to the patient population and type of monitoring (Fig. 1). Studies have shown that around 10–30% of patients with implantable cardiac devices experience DDAF, the incidence increasing with longer monitoring durations and patient age[6,9,14]. For instance, the ASSERT study found that about 10% of patients with pacemakers or ICDs developed asymptomatic AF episodes over a 2.5-

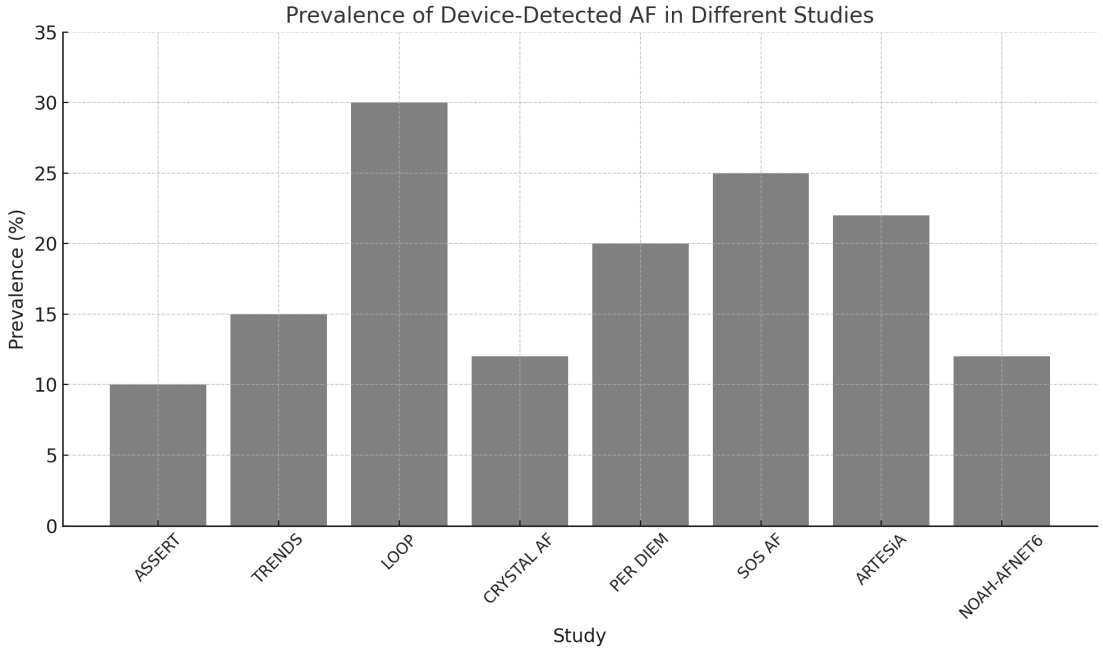

Fig. 1. Prevalence of Device-detected atrial fibrillation in different studies.

year follow-up[9]. The TRENDS study further identified a 15% incidence of DDAF in patients followed for 1.5 years, demonstrating the role of prolonged monitoring in AF detection[6]. Among elderly patients, the LOOP study using insertable loop recorders (ILRs) found that approximately 30% developed device-detected AF over three years[15]. This highlights the high prevalence of subclinical AF in older populations, particularly those with cardiovascular risk factors. The risk factors for DDAF largely mirror those for symptomatic AF, with age, hypertension, heart disease, and diabetes being prominent. Additionally, men have a higher likelihood of developing AF, although DDAF is also increasingly diagnosed in women with expanding device use[16,17]. Studies like ASSERT have shown that patients with DDAF lasting as short as six minutes have an elevated stroke risk, prompting consideration of AF burden and episode duration in clinical decision-making. It has been also postulated that the risk of stroke is related to the duration and burden of DDAF. Longer duration of DDAF episodes between 12 and 23 h is independently associated with the risk of clinical AF (ref.[18]). The MOST study demonstrated an elevated risk of stroke, cardiovascular mortality, and all-cause mortality in patients with DDAF (ref.[19]). Although wearable devices, including smartwatches, are primarily used for preliminary AF screening, they are limited by battery life and the ability to monitor continuously. However, these devices have become valuable tools for initial AF detection and may complement implantable devices in identifying high-risk patients for further monitoring[20,21].

Pathophysiology of Device-Detected AF

DDAF develops through mechanisms similar to symptomatic AF, involving structural, electrical, and autonomic remodeling of atrial tissue. These changes lead to irregular atrial contractions and blood stasis, particularly in the left atrial appendage, which can predispose individuals to thromboembolic events[22]. Structural remodeling in the atria often involves the development of fibrosis, or scarring, that disrupts normal electrical pathways and promotes reentrant circuits, which can sustain AF. Studies have shown that fibrotic remodeling is driven by chronic inflammation, genetic factors, and comorbid conditions like hypertension, diabetes, and heart failure[23-25]. In DDAF, structural remodeling is often asymptomatic but still contributes to stroke risk through similar mechanisms of blood stasis and thrombus formation seen in clinical AF. Studies using cardiac imaging, such as delayed enhancement magnetic resonance imaging (DE-MRI), have visualized this fibrotic burden in patients with both symptomatic and subclinical AF, linking it to AF persistence and stroke risk[26]. Repeated AF episodes lead to electrical remodeling, wherein shortened atrial refractory periods and action potential durations facilitate a self-perpetuating cycle of arrhythmogenicity. This contributes to the likelihood of recurrent episodes, even in patients with DDAF (ref.[27,28]). Research on electrical remodeling in AF has demonstrated that persistent changes in ion channel function and cellular signaling pathways contribute to AF maintenance in both symptomatic and asymptomatic populations[29,30]. The autonomic nervous system, particularly increased sympathetic tone, can create focal triggers for AF initiation. This is especially prevalent in areas like the pulmonary veins, which are known to contribute to arrhythmogenicity in AF (ref.[31,32]). Autonomic triggers are relevant in both device-detected and symptomatic AF, as they can provoke isolated AF episodes that go undetected without continuous monitoring. The significance of

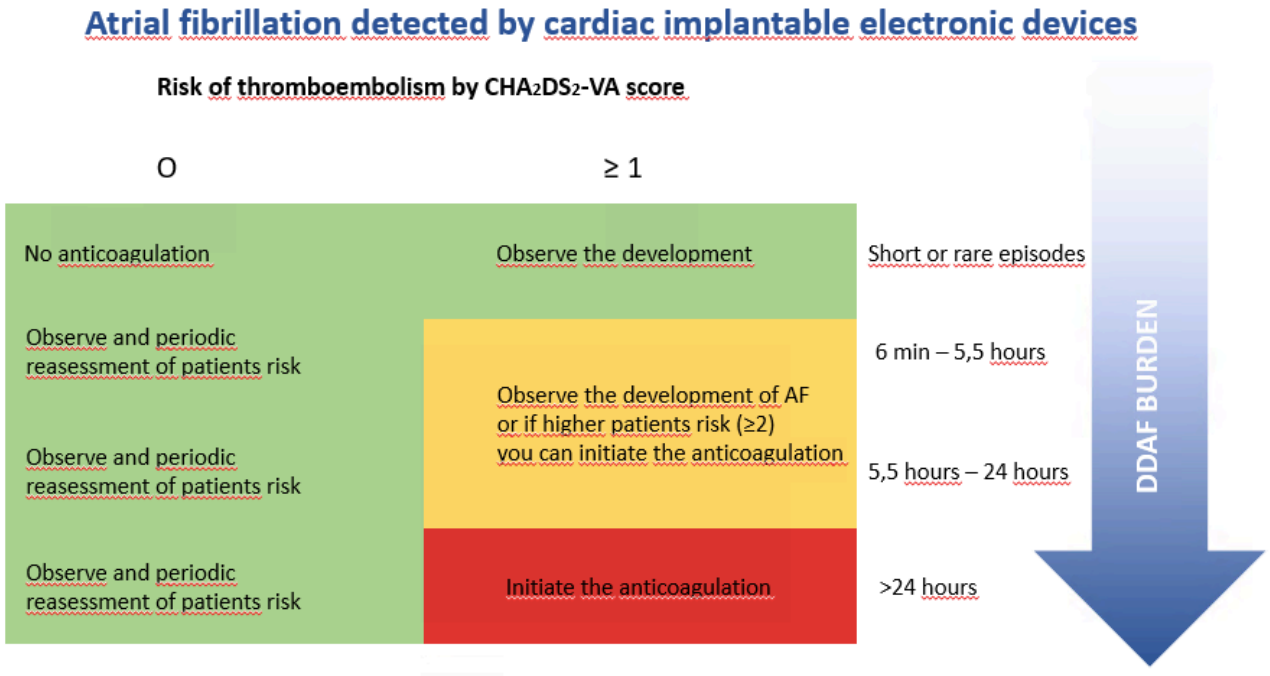

Fig. 2. Algorithm for anticoagulation initiation in patients with device-detected atrial fibrillation (DDAF). Modified from Joglar JA et al. Circulation. 2024;149(1):e1-e156.

autonomic influence is highlighted by studies indicating that vagal and sympathetic stimulation can potentiate AF by modulating atrial electrical properties and enhancing ectopic activity[33,34].

Anticoagulation strategies for DDAF

With the recent published 2024 European society of cardiology (ESC) guidelines for AF, the approach to managing DDAF for stroke prevention is becoming refined[8]. These guidelines address the unique challenges associated with DDAF, which is often asymptomatic and varies greatly in episode duration and frequency. Although traditional guidelines have focused on clinical AF, the new ESC recommendations offer guidance on initiating anticoagulation therapy for patients with DDAF, emphasizing a tailored, risk-based approach informed by recent trial data and patient-specific risk profiles. Recent findings from pivotal trials like NOAH-AFNET 6 and ARTESiA are central to this updated perspective. The NOAH-AFNET 6 trial aimed to assess whether anticoagulation with edoxaban could reduce thromboembolic events in patients with AHRE detected by devices without meeting the criteria for clinical AF. The study included elderly participants with a median CHA_2DS_2-VASc score of 4, putting them at elevated stroke risk. However, the results did not meet the primary efficacy endpoint of reducing cardiovascular death, stroke, or systemic embolism. The trial was stopped early due to a combination of safety concerns and a lack of efficacy. Specifically, patients in the edoxaban group experienced a higher incidence of major bleeding compared to the placebo group, without a significant reduction in stroke rates. This suggests that anticoagulation in patients with AHRE but no confirmed AF may not be beneficial and could lead to a higher risk of bleeding complications. The median AF burden was approximately 2.8 hours, with 89% of patients experiencing AHRE lasting under 24 hours, while around 11% had episodes extending beyond 24 hours, highlighting variability in AF burden among participants[12]. The ARTESiA trial demonstrated that anticoagulation with apixaban significantly reduced the risk of stroke and systemic embolism in patients with SCAF compared to aspirin. Specifically, apixaban lowered the annual stroke risk by approximately 37% in this population. However, this benefit was counterbalanced by a notable increase in major bleeding incidents, with bleeding rates almost doubling those in the aspirin group. The study showed that the number needed to treat (NNT) to prevent one stroke was considerably higher than the number needed to harm (NNH) due to bleeding, raising questions about the risk-benefit balance for routine anticoagulation in patients with DDAF who lack other clinical AF criteria. The AF burden was relatively low, with episodes detected by devices being mostly brief and asymptomatic, and a significant proportion of patients had episodes lasting less than 24 hours[13]. According to the 2024 ESC guidelines, the optimal duration and burden of SCAF that could justify the use of oral DOAC remains unclear[35]. It is not only the duration of the longest AF episode or AF burden that impacts stroke risk, rather, there is a more complex interplay between patient comorbidities and AF duration. Recent studies illustrate this interaction between stroke risk factors and AF burden, showing that both factors together, rather than in isolation, influence outcomes significantly[36,37]. Regardless of whether OAC is initiated, these guidelines emphasize that patients with DDAF should be closely monitored and managed for comprehensive AF care. This is critical because these patients have a 6–9% annual risk of developing clinical AF, which heightens stroke risk and necessitates more direct AF interventions, including rhythm and rate control and potentially lifestyle or risk factor management. In real-world practice, physicians require tools to help them decide whether to initiate anticoagulation. Since the ESC guidelines do not provide a guiding schema, the schema presented in the American College of Cardiology (ACC) guidelines, which is based on AF burden and the risk score, can be utilized. This schema has been simplified and modified, with sex being excluded from the risk score (Fig. 2) (ref.[38]).

Choosing between direct oral anticoagulants and vitamin K antagonists

Direct oral anticoagulants (DOACs), including apixaban, rivaroxaban, edoxaban, and dabigatran, have become the preferred choice over vitamin K antagonists (VKAs) for stroke prevention in AF due to their superior safety profile and ease of use. Unlike VKAs, DOACs do not require routine international normalized ratio monitoring, have fewer dietary restrictions, and offer a more consistent anticoagulant effect. Important trials although primarily focused on symptomatic AF, indicate that DOACs are generally safer and are for long-term anticoagulation. In device-detected AF, DOACs are also often favored, especially for patients with high AF burden and elevated CHA_2DS_2-VA scores[39-42]. It is also important to mention, that maintaining VKA treatment rather than switching to a DOAC may be considered in patients aged ≥75 years on clinically stable therapeutic VKA with polypharmacy to prevent excess bleeding risk[43].

DDAF and heart failure

In AF management, preventing ischemic stroke has long been a primary goal, but the importance of addressing heart failure (HF) risk is increasingly recognized. HF is a prevalent and often life-threatening complication among AF patients, which can sometimes overshadow the risk of stroke[44]. For those with DDAF, this risk is especially pronounced: as the burden of DDAF increases, studies have shown that the likelihood of HF-related hospitalizations rises substantially by up to five times[45]. This elevated risk emphasizes the need for proactive management strategies, even in patients without overt AF symptoms. To address this risk, early intervention targeting AF burden is crucial. For many patients, rhythm control strategies can be beneficial by maintaining normal sinus rhythm and reducing the progression of AF burden. In cases where DDAF burden is particularly high, rate control may be appropriate to prevent tachycardia-mediated cardiomyopathy, a type of HF driven by persistently elevated heart rates. By maintaining a more stable heart

rhythm and controlling the rate, these approaches aim to mitigate the strain on the heart, thereby reducing HF progression risk. This approach is especially significant in patients where AF and HF coexist. Managing AF burden in HF patients is associated with improved clinical outcomes. Evidence suggests that well-controlled AF in these patients not only reduces the immediate strain on the heart but may also slow or even prevent further HF progression, thereby offering a more favorable prognosis and enhancing quality of life for affected individuals[46,47].

CONCLUSION

The management of DDAF has evolved significantly, driven by advancements in monitoring and insights from recent trials. AF remains a leading cause of morbidity and mortality, primarily due to its associations with stroke and heart failure. The increasing detection of AF through implantable devices has revealed a unique population with asymptomatic, device-detected episodes that vary in duration and frequency, challenging traditional approaches to AF management. Recent trials, including NOAH-AFNET 6 and ARTESiA, underscore the complexity of anticoagulation in DDAF patients. The NOAH-AFNET 6 trial, which aimed to assess the benefits of anticoagulation with edoxaban in patients with AHRE, was terminated early due to safety concerns, with findings indicating no significant reduction in cardiovascular death, stroke, or systemic embolism. Instead, anticoagulation increased the incidence of major bleeding, raising concerns about its routine use in patients without documented AF. Similarly, the ARTESiA trial, which studied apixaban in DDAF patients, showed a modest reduction in stroke risk but was also marked by a notable increase in major bleeding events, emphasizing the delicate balance between stroke prevention and bleeding risk in these patients. The 2024 ESC guidelines reflect this nuanced approach by advocating a tailored, risk-based strategy. While DOACs are favored over VKAs due to their improved safety profile, the precise threshold of AF burden to justify DOAC use remains uncertain in the DDAF population. Moreover, evidence now shows that AF burden significantly impacts heart failure outcomes, with a five-fold increase in HF-related hospitalizations associated with higher AF burden. This underscores the need for proactive rhythm or rate control strategies to mitigate HF progression, particularly in patients with coexisting AF and HF, where reducing AF burden has been linked to a favorable prognosis and reduced hospitalizations. Future research should aim to refine anticoagulation strategies, particularly in patients with low AF burden, and explore emerging approaches such as intermittent anticoagulation and advanced monitoring technologies to enable more personalized treatment. As AF management advances toward individualized care, integrating these clinical insights with technological innovation will be essential for optimizing outcomes in DDAF patients.

Search strategy and selection criteria: Our research strategy focused on evaluating studies assessing the risk of stroke in patients with device-detected atrial fibrillation. We conducted a comprehensive search of scientific articles published since 2002 using the PubMed and Web of Science databases. The search terms included “atrial fibrillation”, “device-detected atrial fibrillation”, “subclinical atrial fibrillation”, “device-detected atrial fibrillation and heart failure” and “subclinical atrial fibrillation and bleeding risk.”

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