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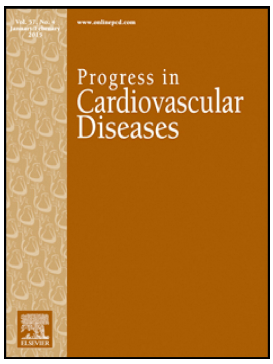

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Quantifying Time in Atrial Fibrillation and the Need for Anticoagulation

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ABSTRACT

Atrial fibrillation (AF) is one of the major cardiovascular diseases, and the number of patients with AF is predicted to increase markedly in the coming years. Despite recent advance in management of patients with AF, AF remains one of the main causes of stroke or systemic embolism. Application of simple stroke risk-stratification schemes, such as the CHA_2DS_2-VASc score has been introduced to identify patients who mostly benefit from oral anticoagulants (OACs) for stroke prevention. Current medical devices allow the detection of short and asymptomatic episodes of AF, termed atrial high rate episodes (AHREs), which are also associated with an increased risk of thromboembolism. Early diagnosis of AF has clinical importance for a timely initiation of OAC, while strokes often occur without AHRE detected within 30 days before the event. Consequently, it is unclear whether any AHRE imply the same therapeutic requirements as clinical AF. The exact estimation of AF burden and correct risk stratification in patients with asymptomatic AF and AHRE remains a challenge in clinical practice.

Keywords
Atrial fibrillation burden; Diagnosis; Clinical outcomes; Anticoagulation

Alphabetical List of Abbreviations:

AF = atrial fibrillation; AHRE = atrial high rate episode; CI = confidence interval; CIED = cardiac implantable electronic device; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; NOAC = non-vitamin K antagonist oral anticoagulant; NSR = normal sinus rhythm; OAC = oral anticoagulant; VKA = vitamin K antagonist

Introduction

Atrial fibrillation (AF) is globally the most common cardiac arrhythmia, with a prevalence of 2.5 to 3.2% of the population.[1] Although the management of patients with AF has been increasing in the last decade, AF remains a major cause of stroke, heart failure (HF), sudden death, unplanned hospital admissions[2, 3] and leads to an impaired quality of life.[4] Thus, AF is associated with a 5-fold greater risk of ischemic stroke or systemic embolism compared with normal sinus rhythm.[3, 5]

AF-related stroke is particularly more likely to be fatal or severely disabling.[6] Thus, stroke prevention is the cornerstone of the management of patients with AF.

Risk factors of stroke in patients with AF have been widely described[7] and oral anticoagulation (OAC) is well established as effective stroke prevention. The Vitamin K antagonists (VKAs, e.g. warfarin) are still used in many countries as first choice OAC. Treatment with warfarin can reduce the risk of stroke by 60%-70%.[8] More recently, the non-vitamin K antagonist oral anticoagulants (NOACs) have been approved and introduced in the market. The NOACs demonstrate relative efficacy, safety and convenience in comparison to warfarin in 4 phase-3 large randomized controlled trials,[9-12] particularly with a significantly lower risk of intracranial haemorrhage, which is the most feared complication of OAC. Indeed, NOACs provide more convenient therapeutic options compared to warfarin and are increasingly adopted in clinical practice.

Patients with AF may have a variety of symptoms with different levels of severity of palpitations, dyspnea, chest discomfort, and syncope. Among patients with AF, the prevalence of those having no or few symptoms related to AF, termed silent or asymptomatic AF, was reported to be up to 40% in one previous study.[13] Even in the same patient, AF sometimes presents with symptoms, whereas some others may be asymptomatic.

In clinical practice, AF is known to progress from short, infrequent and self-limiting episodes to longer and more sustained episodes. Current accepted definition of AF include 1) 'Paroxysmal AF' that spontaneously terminates in most cases within 48

hours, and lasts for up to 7 days; 2) 'Persistent AF' that is not self-terminating, and is sustained longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion or ablation after7 days or more; 3) ' Permanent AF,' previously referred to as 'chronic AF', is sustained longer than 1 year, and implicates a shared decision between physician and patient to adopt a rate control strategy with no further attempt to restore sinus rhythm. AF proceeds from paroxysmal into persistent, and eventually into permanent AF, with an annual rate reaching 15% at 1 year.[14] Some studies have suggested that permanent AF may be associated with a higher risk of stroke and mortality compared to paroxysmal AF[15-17], but there is no general agreement on this aspect.[18] Patients with silent or asymptomatic AF rarely undertake some medical examinations in clinical practice, and they are noticed incidentally through a wide variety of methods including routine physical examination, pre-operative assessments or population surveys. Some patients are sometimes first diagnosed with AF after presentation with severe complications such as ischemic stroke and HF. In >15% of patients presenting with cryptogenic stroke, underlying silent paroxysmal AF may be present.[19]

Current medical devices using the latest technology can provide useful information to detect AF early and initiate medical intervention. However, silent or asymptomatic AF has not been sufficiently evaluated for its clinical impact. Therefore, the accurate evaluation of AF in 'at risk' populations should be explored. Early recognition of AF allows the clinicians to initiate the treatments for AF, leading to not only suppression of AF progression, but also prevention from AF-related complications.

The purpose of this review is to provide an overview of 1) methods to detect the presence of silent or asymptomatic AF, 2) rates of ischemic stroke and 3) anticoagulation strategies in patients with AF.

Detection of Silent or Asymptomatic AF

Surface 12-lead electrocardiography (ECG) and 24-hour Holter ECG are golden standard tools recommended for the diagnosis of AF.[20] However, silent or asymptomatic AF is unlikely to be detected by these 'brief' temporal ECG recordings. As a result, it is likely that AF would remain undiagnosed and undertreated with conventional methods.

Therefore, longer continuous ECG monitoring is needed for detection of silent or asymptomatic AF. The latest medical devices using novel technology have enabled us to monitor cardiac rhythm for long-term and to detect AF that was not diagnosed in routine clinical practice. Furthermore, recent studies indicate that quantifying the duration or burden of AF would lead to a basis for therapeutic indication for silent AF.[21]

Cardiac implantable electronic devices (CIED) including pacemaker, and implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy (CRT) have been introduced for the management of symptomatic bradycardias and pauses, life-threatening tachyarrhythmias, and heart failure with reduced ejection fraction. In addition to their main functions, these devices are also capable of automatic long-term recording and storing of episodes of spontaneous atrial high rate episodes (AHREs).

CIEDs with an atrial lead allow continuous monitoring of atrial rhythm and can record AHREs with the programmable detection criteria, which can be manually adjusted. Although mechanical problems such as lead-related noise, far-field oversensing, and some false positive recordings due to other tachyarrhythmias,[22, 23] more recent CIEDs have well-programmed technologies, which can discriminate whether the high rate episodes are likely to be attributable to AF or not.

For the detection of AHRE, previous studies adopted as cut-off settings for the atrial tachycardia, a rate between 170 and 225 bpm, with the duration of the episode of more than 20 seconds (Table 1).[24-32] In these studies, the AHREs were detected in a variable range from 20% to 70% of patients with CIEDs (Table 1). In the Italian AT500 registry, which included 725 patients with pacemaker indication for bradycardia and a history of atrial tachyarrhythmias, the AHREs lasting more than 5 minutes were found in 73.8% of the patients over a median 22-month follow-up.[26] On the other hand, the ASSERT study, which included 2580 patients with CIEDs and no history of AF, demonstrated that the AHREs lasting more than 6 minutes were found in 34.7% of the patients over a mean follow-up of 2.5 years.[29]

These different reported incidences of AHREs may be dependent on the underlying heart diseases and the period of follow-up. However, these results suggested that

there is a considerable number of patients with CIEDs who are incidentally diagnosed with AF.

The implantable loop recorder (ILR), which is a subcutaneous, single-lead, ECG monitoring device, is used for AF detection in patients who have recurrent unexplained episodes of palpitation or syncope, and/or a history of cryptogenic stroke.[33] This device usually recognizes AF by detecting the irregularity of successive R-R intervals. In particular, AF that is first diagnosed after cryptogenic stroke occurs is most often asymptomatic and paroxysmal, and is unlikely to be detected by strategies based on symptom-driven monitoring or short-term recordings.

The ILR has been validated for more comprehensive arrhythmia monitoring in patients with cryptogenic stroke (Table 2).[34-39] In the CRYSTAL-AF study, AF was more commonly detected in patients with ILR compared to those with conventional strategies (hazard ratio (HR), 7.3; 95% confidence interval (CI), 2.6 to 20.8; P<0.001).[38] These studies indicate that ILR is beneficial for detection of silent or asymptomatic AF, but ILR devices are not always available and indications for ILR implantation require further standardization. On the other hand, the external ambulatory continuous ECG monitoring, such as a wearable non-adhesive dry-electrode belt and a wearable-patch has been introduced for AF detection in general population (Table 2).[19, 40] Although the monitoring duration of these devices are shorter (2 to 4 weeks) compared to the implantable devices, these devices are less invasive and convenient than the implantable devices, and the feasibility for the detection of AF in general population has been verified in previous studies (Table 2).

Furthermore, novel technologies have been developed and applied for the screening of AF. The new screening devices using blood pressure monitors and smartphone can detect AF based on pulse irregularity and specific algorithms with high sensitivity and specificity (Table 3).[41-47] Patients can routinely and readily operate at home, whereas the utility for AF detection strongly depends on patients' compliance. In the future, the acceptability, and cost-effectiveness of these methods must be explored in clinical practice.

Stroke in Patients with Silent or Asymptomatic AF

Adverse stroke outcomes in relation to silent or asymptomatic AF have been reported in previous studies. In a community-based study, which enrolled 4,618 patients who were newly diagnosed with AF, 25% had no symptoms and were 3 times more likely to have had an ischemic stroke preceding their AF diagnosis. Another study demonstrated that 33.8% out of 467 patients had asymptomatic AF at the time of the first AF diagnosis, and asymptomatic AF was associated with an increased risk for cardiovascular (HR, 3.12; 95% CI, 1.50 - 6.45) and all-cause mortality (HR, 2.96; 95% CI, 1.89 - 4.64) compared to those with typical AF symptoms even after adjustment for CHA_2DS_2-VASc score and age.[48]

Previous studies regarding AHRE detected in patients with CIEDs have suggested that AHRE is associated with an increased stroke rate (Table 4). In the ASSERT study, for example, the presence of AHRE was associated with an increased risk of ischemic stroke or systemic embolism (HR 2.49; 95% CI 1.28 - 4.85; P = 0.007). However, the risk of stroke seems to be lower in patients with AHREs than those with clinically ECG-detected AF and similar $CHADS_2$ or CHA_2DS_2-VASc scores and probably depends on the fact that patients with CIEDs often have already been on medical treatment or support before AF-related complications occurred, thus reducing the incidence of thromboembolism.

Moreover, the threshold time used to define AHREs was different in previous studies, providing variable rates of ischemic stroke. In the TRENDS study, which included 2486 patients with $\geqq$1 stroke risk factor, adjusted HRs were 0.98 (95% CI, 0.34- 2.82; P = 0.97) in patents with AHREs <5.5 hours, and 2.20 (95% CI, 0.96- 5.05; P = 0.06) with AHREs $\geqq$5.5 hours, compared to those without AHREs.[27] On the other hand, the recent subanalysis of the ASSERT study, suggested that adjusted HRs were 0.75 (95% CI, 0.29-1.96; P = 0.56) in patents with AHREs >6 minutes to 6 hours, 1.32 (95% CI, 0.40- 4.37; P = 0.65) with AHREs >6 to 24 hours, and 3.24 (95% CI, 1.51 – 6.95; P = 0.003) AHREs >24 hours, compared to those without AHREs.[49] Therefore, the threshold to define AHRE remains uncertain, and randomized control trials are needed for quantifying duration time of AHRE that is associated with an increased thromboembolic risk.

Anticoagulation for Silent AF

Anticoagulant therapy has been an established treatment for reducing stroke, systemic embolism, and all-cause mortality in patients with AF.[50] However, inadequate therapeutic anticoagulation preceding stroke is prevalent in patients with AF even in specialized clinics for anticoagulation, where at least one third of patients had suboptimal anticoagulation control.[51] Frequently patients without symptoms, especially those in normal sinus rhythm (NSR), may stop anticoagulation over time[52]; this is relevant as the cessation of OAC is independently associated with an increased risk of stroke, adverse cardiovascular events and mortality.[53, 54] However, this issue seems to be partially overcome by the increasing use of NOACs[55]

In a previous study, among patients admitted with acute ischemic stroke who had a history of AF, 83.6% of 94,474 patients were not receiving therapeutic anticoagulation; 13.5% had subtherapeutic warfarin anticoagulation (INR <2) at stroke, 39.9% were receiving antiplatelet therapy only, and 30.3% were receiving no anticoagulant therapy. Moreover, patients with therapeutic anticoagulation had lower odds of moderate or severe stroke (NIHSS score 16) than those without therapeutic anticoagulation.[56] In a cohort study of 5,555 patients without symptoms who were diagnosed with AF incidentally in general practice, the adjusted stroke and mortality rates at 1.5 years in patients receiving anticoagulant therapy were lower than in those receiving no anticoagulant therapy (1.3% *vs.* 3.9%, 4.2% *vs.* 7.2%, respectively).[57] One recent multicentre study including 59 patients with a history of non-permanent AF and ILRs indicated that intermittent NOAC administration based on the presence of AF lasting more than 24 hours is feasible.[58]

Although these results suggest that anticoagulant therapy may be beneficial in patients with silent AF as well as clinically ECG-detected AF, a randomized control trial demonstrated that anticoagulant therapy based on remote rhythm monitoring in patients with CIEDs did not show the improvement of thromboembolism compared to usual office-based follow-up (HR 1.06; 95% CI 0.75 - 1.51; P = 0.732).[32] Investigators of this study showed that the main limitation of this strategy is the poor compliance with OAC in patients with remote rhythm monitoring follow-up. In addition, it remains unclear whether AHREs detected in patients with CIEDs imply the same therapeutic

requirements as clinically ECG-detected AF.

Future Prospective

Continuous long-term ECG monitoring and the new modalities of non-invasive ECG recording seem to be effective for the detection of silent or asymptomatic AF, however, there is still room for improvement on the utility, adherence, and cost-effectiveness for screening of silent AF in general population. Randomized control trials with larger sample size must be conducted to test the associations between ECG-detected silent AF and adverse outcomes.

The major studies regarding silent or asymptomatic AF performed thus far are not comparable as they included inhomogeneous populations, such as patients with and without a history of prior AF at baseline. Furthermore, there was a lack of characterization/definition of clinical endpoints such as for ischemic stroke, i.e. cardioembolic, atherothrombotic, or lacunar infarction. Therefore, the association between newly detected silent AF and clinical outcomes should be further investigated.

Although CIEDs-detected AHRE was shown to be significantly associated with an increased risk of thromboembolic events, the temporal relationship between AHREs and thromboembolic events remains uncertain. In previous studies, the majority of patients with AHRE detected by implantable devices, who experienced an ischemic stroke or systemic embolism, did not have any AT/AF or subclinical AF in the 30 days prior to the event, questioning the causal relationship between AHRE and thromboembolism.[59, 60] Patients with AHREs may have transient blood stasis due to low flow in left atrial appendage and changes in atrial endothelium, leading to increased risk of thromboembolism. Consequently, the criteria of AHREs requiring medical intervention and the stratified stroke risk factors in patients with CIEDs must be fully explored.

What trials will inform clinical practice? The ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; NCT01938248) and NOAH (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; NCT02618577) trials are ongoing studies on the benefit

of NOAC in patients with CIEDs, and will provide useful information on quantifying duration time of AHREs.

Conclusions

Silent or asymptomatic AF is still an under-recognized disease in the general population and is detectable in 25-35% of patients presenting with ischemic stroke. The use of diagnostic devices lead to a more accurate and early detection of AF, allowing a prompt initiation of OAC before the occurrence of severe and disabling events. CIEDs-detected AHREs were shown to be associated with an increased risk of stroke and frequently precede clinically overt AF.

AHREs may represent an additional risk factor for stroke in patients with paroxysmal AF and sinus rhythm. Thus, these patients could benefit from an early initiation of OAC when AHREs are identified.[61] However, there is still uncertainty and evidence gap in the management of patients with silent AF and AHREs, such as the number and /or length of AHREs to be considered as clinically relevant to start OAC. Appropriate management algorithms to estimate AF burden in the general population and to stratify the risk of thromboembolism should be further developed.

Conflict of Interest

There are no financial disclosures and acknowledgments directly related to this manuscript.

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Table 1. Summary of the definition and incidence of AHRE in patients with CIEDs.

Year	Study	Atrial detection rate	Detection time	Incidence of AHRE
2002	Gillis AM, et al[23]	>180 bpm	>1 minutes	157/231 (68%)
2003	MOST[24]	>220 bpm	>5 minutes	156/312 (50%)
2005	Italian AT500 Registry[25]	>170 bpm	n/a	524/725 (73.8%)
2009	TRENDS[26]	>175 bpm	>20 seconds	1389/2486 (55.9%)
2012	Shanmugam N, et al[27]	>180 bpm	>14 minutes	223/560 (39.8%)
2012	ASSERT[28]	>190 bpm	>6 minutes	895/2580 (34.7%)
2014	Gonzalez M, et al[29]	>178 bpm	>5 minutes	39/224 (17.4%)
2015	Benezet-Mazuecos J, et al[30]	>225 bpm	>5 minutes	28/109 (25.7%)
2015	IMPACT[31]	>200 bpm	n/a	945/2718 (34.8%)

AHRE, atrial high rate episode; MOST, Mode Selection Trial; TRENDS, The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; IMPACT, Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices.

Table 2. Summary of the implantable and external devices for the detection of AF.

Year	Study	Detection time	Follow-up period	Incidence of AF
Implantable ECG monitoring				
2013	Cotter PE, et al[33]	2 minutes	229 days (mean)	13/51 (25.5 %)
2013	Ritter MA, et al[34]	2 minutes	382 days (median)	10/60 (16.7 %)
2013	Etgen T, et al[35]	6 minutes	1 year	6/22 (27.3 %)
2014	SURPRISE[36]	2 minutes	569 days (mean)	14/85 (16.1 %)
2014	CRYSTAL-AF[37]	30 seconds	>6 months	29/221 (12.4 %, 12 months)
2016	Poli S, et al[38]	2 minutes	>6 months	25/75 (33.3 %, 12 months)
External ECG monitoring				
2014	EMBRACE[39]	30 seconds	30 days	45/280 (16.1%)
2015	STUDY-AF[40]	30 seconds	14 days	4/75 (5.3%)

SURPRISE, Stroke Prior to Diagnosis of Atrial Fibrillation using Longterm Observation with Implantable Cardiac Monitoring Apparatus Reveal; CRYSTAL-AF, Cryptogenic Stroke and Underlying Atrial Fibrillation; EMBRACE, Atrial Fibrillation in Patients with Cryptogenic Stroke; STUDY-AF, The Screening Study for Undiagnosed Atrial Fibrillation.

Table 3. Summary of the new devices for AF screening.

Year	Study	Device	Sensitivity (%)	Specificity (%)
2009	Doliwa PS, et al[41]	Handheld single-lead ECG	92	96
2009	Samol A, et al[42]	Handheld single-lead ECG	100	100
2012	Marazzi G, et al[43]	Blood pressure monitor	92	95
2013	Wiesel J et al[44]	Blood pressure monitor	97	90
2014	Kearly K, et al[45]	Blood pressure monitor	95	90
2011	Lewis M, et al[46]	Plethysmograph	100	92
2016	McManus DD, et al[47]	Plethysmograph	97	94

Table 4. Summary of thromboembolic rate in patients with CIEDs.

Year	Study	Follow-up period	Cut-off burden of AHREs	Annualized TE rate (95% CI)	Hazard ratio (95% CI)
2003	MOST[24]	27 months	<5min	0.58%	
			>5min	2.22%	6.7 (P=0.02)
2005	Italian AT500 Registry[25]	22 months	<5min	0.9%	
			>5min	0.2%	
			>24 h	1.8%	3.1 (1.1-10.5; P=0.04)
2009	TRENDS[26]	1.4 years	None	1.1% (0.8-1.6)	
			<5.5 h	1.1% (0.4-2.8)	0.98 (0.34-2.82; P=0.97)
			>5.5 h	2.4% (1.2-4.5)	2.2 (0.96-5.05; P=0.06)
2012	Shanmugam N, et al[27]	370 days	<14min	2% (overall)	
			>14min-3.8h		4.3(0.73-26.2; P=0.11)
			>3.8 h		9.4 (1.8-47.0; P=0.01)
2012	ASSERT[28]	2.5 years	<6min	0.69%	
			>6 min	1.69%	2.49 (1.28-4.89; P=0.01)
2017	Van Gelder IC, et al[50]	2.5 years	<6min	n/a	
			>6 min-6 h		0.75 (0.29–1.96; P=0.56)
			>6 h-24 h		1.32 (0.40–4.37; P=0.65)
			>24 h		3.24 (1.51–6.95; P<0.01)

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