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REVIEW

Silent atrial fibrillation: epidemiology, diagnosis, and clinical impact

Polychronis E. Dilaveris[1] | **Harold L. Kennedy**[2,3]

[1]1st University Department of Cardiology, Hippokration Hospital, Athens, Greece

[2]Department of Medicine & Cardiovascular Diseases, University of Missouri, Columbia, Missouri

[3]The Cardiovascular Research Foundation, St. Louis, Missouri

Correspondence
Polychronis E. Dilaveris, MD, 22 Miltiadou Street, 155 61 Athens, Greece
Email: hrodil1@yahoo.com

Silent or subclinical asymptomatic atrial fibrillation (SAF) has currently gained wide interest in the epidemiologic, neurologic, and cardiovascular communities. It is well known that the electrophysiological and mechanical effects of symptomatic and silent atrial fibrillation (AF) are the same. It is probable that because "AF begets AF," progression from paroxysmal to persistent or permanent AF might be more rapid in patients with long-term unrecognized and untreated SAF, because no treatment is sought by or provided to such patients. Moreover, SAF is common and has significant clinical implications. The clinical consequences of SAF, which include emboli (silent or symptomatic), heart failure, and early mortality, are of paramount importance. Consequently, SAF should be considered in estimating the prevalence of the disease and its impact on morbidity, mortality, and quality of life. Several diagnostic methods of arrhythmia detection utilizing the surface electrocardiogram (ECG), subcutaneous ECG, or intracardiac devices have been utilized to seek meaningful arrhythmic markers of SAF. Whereas a wide range of clinical risk factors of SAF have been validated in the literature, there is an ongoing search for those arrhythmic risk factors that precisely identify and prognosticate outcome events in diverse populations at risk of SAF. Modern diagnostic modalities for the identification of SAF exist, but should be further explored, validated, and tailored to each patient needs. The scientific community should undertake the clinical challenge of identifying and treating SAF.

KEYWORDS

silent atrial fibrillation, atrial fibrillation burden, diagnosis, epidemiology, clinical consequences

1 | INTRODUCTION

Atrial fibrillation (AF) was discovered more than 100 years ago.[1] It is currently recognized as the most prevalent cardiac arrhythmia and is associated with substantial complications and healthcare costs. The importance of clinical AF to all physicians has emerged during the last decade.[2,3] Recently, the Global Burden of Disease study has demonstrated a prevalence of 33.5 million persons affecting 2.5% to 3.2% of populations across all countries on many continents.[2] Five million new cases of AF are added annually. Aging of the population is a key factor for the AF "epidemic," due to the inverse pyramid demographics of the populations of the modern era. Improvements in survival resulting from improved medical therapies have also contributed to the enlarging elderly population. The higher prevalence rates of AF are found in developed countries, especially those of North America, whereas the lowest were found for both men and women in the Asia–Pacific area.[2]

In one-third of all AF occurrences, surgery, infection, or myocardial infarction may account for the precipitation of the arrhythmia.[4,5] The clinical consequences of AF, which include emboli, heart failure, and early mortality, are of paramount importance. Cerebral emboli leading to ischemic stroke and cognitive decline are the most emotionally dreaded events by both patient and physician,[6] and account for 25% to 30% of all acute ischemic strokes (Figure 1).[2] AF presents a 5-fold risk for a stroke, and has been demonstrated to increase both cardiovascular and all-cause mortality.[6] In the United States, stroke is the fifth leading cause of death, and a leading cause of chronic severe disability.[7] Thus, it is mandatory that physicians focus their attention and efforts on the detection, prevention, and therapy of AF.

The gold standard for the diagnosis of AF is the visual inspection of the electrocardiogram (ECG). An irregular pulse may raise suspicion for AF, but an ECG is necessary to diagnose AF.[6,8] The problem of early recognition of AF is greatly aggravated by the often silent nature of the rhythm disturbance.[9] In about one-third of patients

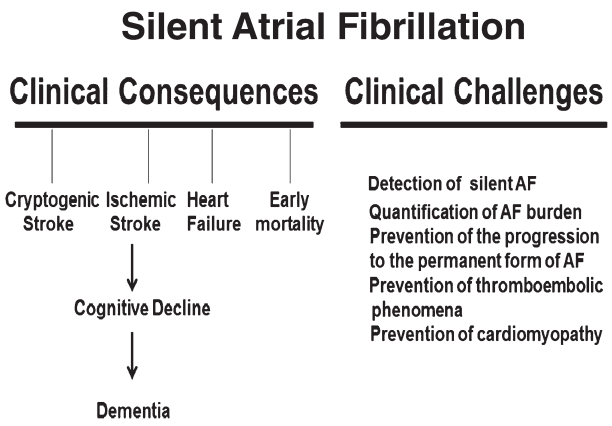

FIGURE 1 Clinical consequences of silent atrial fibrillation and issues to be addressed for the diagnosis and therapeutic handling of this arrhythmia. Abbreviations: AF, atrial fibrillation.

with this arrhythmia, patients are not aware of the presence of AF. Therefore, the term silent atrial fibrillation (SAF), which refers to the occurrence and detection of subclinical asymptomatic episodes of paroxysmal AF, emerged. To quantitate such episodes of SAF, the concept of atrial fibrillation burden (AFB) was introduced. AFB can be defined as the time spent in AF per unit of time (eg, day, week, month).[10] Although AFB is not part of any risk stratification scoring system, it has been represented by various arrhythmic markers, predominantly supraventricular arrhythmias, which prognosticate the development of AF and/or its outcomes.[11] Whereas patients with symptomatic AF are usually discovered by medical attention resulting from symptoms associated with hemodynamic complaints, unfortunately SAF may only present after the most serious of complications such as ischemic stroke or heart failure. A much earlier detection of AF might allow the timely introduction of therapies to protect patients not only from the consequences of the arrhythmia but also from progression of AF from an easily treated condition to an utterly refractory problem (Figure 1).

2 | ARRHYTHMIA DETECTION IN SAF POPULATIONS

The populations of SAF and AFB are diverse and have contributed to the confounding of clear interpretation of the data. A myriad of mechanisms that lead to atrial changes through atrial myopathy mechanisms, inflammation, direct invasion, or volume overload may contribute to AF pathophysiology.[2,11,12] Thus, there has been a plethora of scientific reports emanating from different disciplines, such as epidemiology, neurology, and cardiology. SAF detection currently seems most directed at a wide variety of arrhythmic markers that collectively or independently can identify a critical AFB or the occurrence of persistent or permanent AF.[11] This detection employs a host of approaches that include physical examination, surface ECG recordings, or invasive ECG devices.[13]

Routine self-monitoring of the pulse for diagnosing SAF in patients over 65 years of age is a class I recommendation in the European Society of Cardiology guidelines for the management of AF.[14] However, less than half of the electrophysiologists who responded to the European Heart Rhythm Association survey include this method in their common practice.[15] The preferred methods for identifying SAF are single 12-lead ECG recordings at outpatient visits and 24-hour Holter ECG recordings, frequently in patients who suffered a cryptogenic stroke.[15] The EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) study, compared new AF detection by noninvasive ambulatory ECG monitoring with either a 30-day event-triggered recorder (intervention group) or a conventional 24-hour monitor (control group) in 572 patients with cryptogenic stroke within the preceding 6 months, without a history of AF.[16] The investigators reported a greater than 5-fold increase (16.1% vs 3.2%; $P < 0.001$) in AF detection in the 30-day event monitor group.[16] The association between AF and cryptogenic stroke was strengthened by using implantable ECG loop recorders, which are seldom used in developing countries, but increasingly so in the United States.[15] Observations from clinical

TABLE 1 Incidence of newly detected AF in the population with implanted PPMs or ICDs

Year	Trial	Device Indication	Clinical Profile of Patients	Incidence of AF
2002	Gillis et al[37]	PPMs for SND	All	157/231 (68%)
2003	MOST[38]	PPMs for SND	All	156/312 (50%)
2010	TRENDS[21]	PPMs and ICDs for all indications	History of prior stroke, no history of AF, no OAC use, ≥1 stroke risk factor	45/163 (28%)
2012	TRENDS[39]	PPMs and ICDs for all indications	History of prior stroke, no history of AF, no OAC use, ≥1 stroke risk factor	416/1368 (30%)
2012	ASSERT[40]	PPMs and ICDs for all indications	History of hypertension, no history of AF, no OAC use	895/2580 (34.7%)
2013	Healey et al[41]	PPMs all indications	All	246/445 (55.3%)
2014	Gonzalez et al[42]	PPMs all indications	No history of AF	39/224 (17.4%)
2015	Benezet-Mazuecos et al[43]	PPMs and ICDs for all indications	All	28/109 (25.7%)
2015	Lima et al[44]	PPMs all indications	No history of AF	63/300 (21%)
2016	Benezet-Mazuecos et al[45]	PPMs and ICDs for all indications	History of hypertension	46/123 (37.3%)

Abbreviations: AF, atrial fibrillation; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; ICDs, implantable cardioverter-defibrillators; MOST, Mode Selection Trial; OAC, oral anticoagulants; PPMs, permanent pacemakers; SND, sinus node disease TRENDS, The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke.

trials in patients with recurrent AF,[17–19] analyses of atrial rhythm in patients with pacemakers or defibrillators (Table 1), and several single-center studies suggest that AF can be better detected by prolonged ECG recording. For this purpose, different recording methods such as continuous inpatient cardiac telemetry, external loop recorders, internal loop recorders, and mobile cardiac outpatient telemetry have been introduced. Because of chance variations in smaller series and different technologies for detection of undiagnosed AF, the diagnostic yield in these studies varies from 0% to 20%.[20–25]

After the discovery that implanted pacemakers and defibrillators can identify atrial arrhythmias in asymptomatic patients who had no prior AF history, it became clear that there may be a need for an implantable cardiac monitor whose sole purpose would be to detect previously undiagnosed arrhythmias such as AF. These monitors usually detect AF by analyzing the irregularity and incoherence of successive R-R intervals in a minimum required amount of time (typically 2 minutes). Several studies in the cryptogenic stroke population verified that more comprehensive arrhythmia monitoring strategies result in significantly higher AF detection rates than standard monitoring (Table 2). Obviously, the longer the monitoring is performed the more AF is discovered. However, the cost-effectiveness of prolonged ECG monitoring has been questioned.[26] Nevertheless, there has been a proliferation of new technologies and devices promising simple and accurate detection of AF in populations who carry a high burden of this disease (Table 3). However, the utility, acceptability, and cost-effectiveness of these approaches in real-world settings need to be explored.

3 | RISK FACTORS OF SAF AND AFB

Patients with cryptogenic stroke or other risk factors should be considered candidates for continuous ECG monitoring to detect SAF. Early diagnosis would trigger early treatment for primary or secondary stroke prevention. In clinical practice, there are several categories of patients at risk for SAF. The major risk factors are hypertension, age, elevated body mass index, diabetes mellitus, cigarette smoking, and previous cardiac disease (Table 4).[6,8,11] At very high risk are patients with chronic kidney disease who share several common risk factors among those for AF, such as hypertension, diabetes, previous cardiac disease, obesity, and metabolic syndrome.[27,28] Curiously, patients of blood group O seem to enjoy a reduced susceptibility to developing AF and its outcomes.[29] The clinical risk factors are inadvertently associated with arrhythmic risk markers of AFB (Table 4) and prognosticate outcome events in populations at risk. Age, patient population, and CHA_2DS_2-VASc (CHA_2DS_2-VASc, Congestive heart failure - Hypertension - Age ≥ 75 years - Diabetes - History of Stroke/Transient ischemic attack/Thromboembolism - Age 65–74 years - Vascular disease - Female sex) score are well-established factors to influence the AFB and outcome. AF monitoring may be attractive in patients with documented histories of paroxysmal AF treated with rhythm-control strategies, when the objective is treating AF for preventing stroke, not only symptoms. Patients with heart failure and paroxysmal AF might benefit from optimal rhythm control to prevent recurrences and optimal rate control to prevent hemodynamic impairment during AF episodes. The definitive criteria or the investigative algorithm to be employed in each diagnostic device within a specific population for a prespecified duration are not established. The above uncertainties are aggravated in the context of the currently available antithrombotic prophylaxis with the new oral anticoagulants. Even the time of examination in various populations, and an appreciation of the lack of temporal relationship between the examination and outcome event, further confound the complexity of investigation.[30] The investigative community must nevertheless take up and engage this clinical challenge.

4 | CLINICAL PERSPECTIVES

The magnitude of the problem reported in epidemiological studies of AF significantly underestimates AFB on society because asymptomatic arrhythmias are not included. It seems clear that SAF has the same prognostic impact as symptomatic AF. Cardiac electronic devices have revealed that a very large proportion of patients receiving these devices show unsuspected AF. This unique documentation of SAF episodes allows, on the one hand, therapeutic adjustments impossible otherwise to control arrhythmias, and on the other, the prevention of associated complications developed regardless of patient symptoms.[6] The electrophysiological and mechanical effects of symptomatic and silent AF are the same, and it is probable that because "AF begets AF," progression from paroxysmal to persistent or permanent AF might be more rapid in patients with long-term

TABLE 2 AF detected by implantable cardiac monitors in patients with cryptogenic stroke

Study	No. of Patients	AF Definition	Monitoring Duration	AF Detection Yield
Cotter et al[46]	51	2 minutes	Mean 229 (116) days	25.5%
Ritter et al[47]	60	2 minutes	1 year	16.7%
Etgen et al[48]	22	6 minutes	1 year	27.3%
Rojo-Martinez et al[49]	101	2 minutes	281 ± 212 days	33.7%
Jorfida et al[50]	54	5 minutes	6–28 months	46%
SURPRISE[51]	85	2 minutes	569 ± 310 days	16.1%
CRYSTAL AF[52,53]	221	>30 seconds	Minimum 6 months	8.9% at 6 months, 12.4% at 12 months, 30.0% at 36 months
Poli et al[54]	74, ≥1 AF risk factor	2 minutes	Minimum 6 months	28% at 6 months, 33.3% at 12 months

Abbreviations: AF, atrial fibrillation; CRYSTAL AF, Cryptogenic Stroke and Underlying Atrial Fibrillation; SURPRISE, Stroke Prior to Diagnosis of Atrial Fibrillation Using Long-term Observation with Implantable Cardiac Monitoring Apparatus Reveal.

TABLE 3 Novel technologies for atrial fibrillation detection

Study	Type of device	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)
Doliwa et al.[55]	Hand-held single-lead ECG with dry electrodes	100	92	96	96
Koleschke et al.[56]	Hand-held single-lead ECG with dry electrodes	508	99	96	92
Samol et al.[57]	Hand-held single-lead ECG with dry electrodes	132	100	100	
McManus et al.[58]	iPhone 4S application	76	96.2	97.5	
Lau et al.[59]	Smartphone case with dry electrodes	109	95-100%	90-94%	
Marazzi et al.[60]	Automated BP machine with AF detection algorithm	503	92	95	83
Wiesel et al.[61]	Automated BP machine with AF detection algorithm	139	100	90	52
Wiesel et al.[62]	Automated BP machine with AF detection algorithm	405	97	89	72
Turakhia et al.[63]	Wearable patch-based device	75			
Couderc et al.[64]	Contactless facial video monitoring	11	80	80	

AF: atrial fibrillation; BP: blood pressure; ECG: electrocardiogram

unrecognized and untreated SAF, because no treatment is sought by or provided to such patients. Significant exposure to SAF may expose a patient to the risk of further atrial remodeling or, in patients with relatively poor ventricular rate control, to tachycardia-induced cardiomyopathy. The latter may result in significant congestive heart failure and potentially life-threatening arrhythmias.

Given the well-documented presence of SAF in patients treated with antiarrhythmic agents, the efficacy of pharmacological interventions on clinical AFB may be overestimated. Many trials focus on symptomatic recurrence as a surrogate for arrhythmia recurrence. Whether antiarrhythmic therapy is appropriate for SAF remains unclear. Recent guidelines[14] attempt, for the first time, to provide recommendations about diagnostic criteria (atrial rate limit or duration of the atrial high-rate episodes [AHRE] for AF diagnosis) and further patient management. Obviously, reliance on symptoms may misguide a physician's assessment of stroke risk, resulting in unsafe cardioversions, delay of initiation of anticoagulation, and inappropriate withdrawal of anticoagulation in patients felt to be successfully rhythm controlled. The application of anticoagulation therapy in patients with device-detected AHRE is as yet unclear and challenging in the absence of randomized studies. To date, the only prospective, randomized trial to address this question was the IMPACT (Randomized Trial of Anticoagulation Guided by Remote Rhythm Monitoring in Patients With Implanted Cardioverter-Defibrillator and Resynchronization Devices) trial, which was stopped prematurely and not published.[31] Further studies are needed to establish the role of anticoagulation in these patients. In this aspect, the recently designed ARTESIA (Apixaban for the Reduction of Thromboembolism in Patients with Device-detected Subclinical Atrial Fibrillation) study will determine if treatment with apixaban, compared with aspirin, will reduce the risk of ischemic stroke and systemic embolism in pacemaker patients with subclinical AF and additional risk factors for stroke.[32] REACT.COM (The Rhythm Evaluation for Anticoagulation with Continuous Monitoring) pilot study showed that a targeted strategy of insertable cardiac monitor-guided intermittent novel anticoagulants administration is feasible, but larger studies are needed.[33] Based on the aforementioned studies, it is evident that any potential strategy of anticoagulation therapy should take into consideration not only the duration of AHRE, but also the individual's risk of stroke and thromboembolism, as defined by published stroke risk stratification schema.[34–36]

TABLE 4 Risk factors for SAF and AFB

Clinical	Arrhythmic
Age >75 years	>30 PAB/hour (24-hour Holter)
Cryptogenic stroke	>70 PAB/hour (24-hour Holter)
Ischemic stroke	>100 PAB/hour (30-day loop event recorder)
Neurological disease	SVT >3 beats <30 seconds (24-hour Holter)
Hypertension	SVT >30 seconds (24-hour Holter)
Diabetes mellitus	SVT >20 beats (48-hour Holter)
Obesity	AF >30 seconds (transtelephonic ECG)
Obstructive sleep apnea	Irregular R-R >30 beats (30-day loop event recorder)
RF ablation	Irregular R-R >30 sec (30-day loop event recorder)
ICD or pacemaker	Irregular irreg >10 seconds (28 days MCOT)
Post-AF precipitant	Irregular irreg >30 seconds (ILR)
Mitral valve disease	Atrial rate >190 bpm > 6 minutes (CIED)
High CHA_2DS_2-VASc score	Atrial tachy/AF >6 hours/day (CIED)

Abbreviations: AF, atrial fibrillation; AFB, atrial fibrillation burden; CHA_2DS_2-VASc, Congestive heart failure - Hypertension - Age ≥ 75 years - Diabetes - History of Stroke/Transient ischemic attack/Thromboembolism - Age 65–74 years - Vascular disease - Female sex CIED, cardiac implantable electronic device; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; ILR, implantable loop recorder; MCOT, mobile cardiac outpatient telemetry; PAB, premature atrial beat; RF, radiofrequency; SAF, silent atrial fibrillation; SVT, supraventricular tachycardia.

5 | FUTURE DIRECTIONS

Target populations at greatest risk for SAF and its complications should be identified and adequately assessed. Diagnostic algorithms and appropriate criteria should be defined. Although some populations can employ the most simple of diagnostic methods (ie, palpation of pulse), others should benefit from a gradient guideline of cost-effective diagnostic testing utilizing recommended surface or even implantable ECG techniques. Time of examination and its duration for meaningful and cost-effective detection of SAF and AFB should be standardized. Finally, definitive criteria for SAF and AFB should be

established. Perhaps a time-threshold effect could be defined, whereby a greater AFB or longer episodes of AF should confer a greater risk of adverse outcomes. Prevention and therapies would be better guided and adverse outcomes hopefully avoided.

6 | CONCLUSIONS

Asymptomatic AF is common and has significant clinical implications. Silent AF should be considered in estimating the prevalence of the disease and its impact on morbidity, mortality, and quality of life. Modern diagnostic modalities for the identification of SAF should be explored, validated, and tailored to each patient's needs. The scientific community should undertake the clinical challenge of identifying and treating SAF.

Conflicts of interest

The authors declare no potential conflicts of interest.

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