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Silent Atrial Fibrillation: A Critical Review

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Abstract

Atrial fibrillation (AF) in the most common cardiac arrhythmia, and is associated with an increased risk of thromboembolic events. Silent AF is an asymptomatic form of AF incidentally diagnosed during a routine test or manifesting as an arrhythmia-related complication. Although recent trials have clearly demonstrated that patients with sub-clinical AF are at increased risk of stroke, the real incidence of this form of AF is still unknown. In fact, studies about silent AF had been performed only in specific subgroups of patients such as those with implantable cardiac devices, with recent cryptogenic stroke or transient ischemic attack, and recently undergoing AF ablation. Continuous ECG-monitoring in patients without implantable cardiac devices may improve silent AF detection but its cost-effectiveness actually is not well established in all kind of patients. Moreover, recent data have revealed that only a small number of these patients may have sub-clinical AF within the month prior to their stroke suggesting a lack of temporal relationship between the stroke and the AF episode.

This paper will review available data on different diagnostic tools for silent AF detection with a focus on their cost-effectiveness, analyzing the direct correlation between the arrhythmia and embolic events, and discussing areas of uncertainty where further research is required.

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and is associated with an increased risk of ischemic stroke and systemic embolism.[1]

While many patients with AF may complain of palpitations, dyspnea and fatigue, some patients report no symptoms. Silent AF (SAF) is an asymptomatic form of AF incidentally diagnosed during routine examination or manifesting as an AF-related complication, such as ischemic stroke or tachycardiomyopathy.[2] The real incidence of SAF in general population is still unknown, and this can be considered a major healthcare problem since the SAF paroxysms have been correlated with the same increased risk of ischemic stroke as symptomatic episodes.[3–5]

Recently, implementation of new technologies such as long-term ECG-Holter monitoring or new detection algorithms in implantable cardiac devices allowed an improvement in the recording rates of SAF.[5,6]

The aim of the present paper is to review clinical and diagnostic tools that can be helpful in detecting SAF, and consequent strategies aimed at reducing morbidity and mortality.

Key Words:

Atrial Fibrillation, Silent Atrial Fibrillation, Stroke, Tia, Thromboembolism, Holter-Monitoring, Cardiac Implantable Electronic Devices, Stroke, Transient Ischemic Attack, Detection Algorithms, Loop-Recorder.

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None.

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Silent AF: Difference Between Clinical Trials And "Real World" Population

One of the main issues regarding SAF is that the vast majority of patients enrolled in the longer clinical trials dealing with AF detection and burden assessment had very peculiar characteristics, which are seldom represented in the real world population. The prevalence of arterial hypertension varies from 50[7] to 87%[8] in some of the most recent clinical trials on AF, while its true prevalence is around 65%, according to recent registry data.[9] Moreover, some cardiac comorbidities such as coronary artery disease (CAD) and heart failure (HF), while not uncommon in every day clinical practice, are usually excluded or under-represented in major clinical trials.[10–12]

In more recent real world population prevalence of SAF was around 1.4% in all patients ≥ 65 years screened for AF, and reach 13.3% in patients with a known diagnosis of AF.[13,14] The first real world study aimed to detect the real risk profile of SAF was the BELGRADE-AF study,[14] which showed significant baseline differences between symptomatic and asymptomatic AF, as well as significant increase in progression to permanent AF and ischemic stroke in SAF. The authors concluded that asymptomatic presentation of incident AF could require more attentions in every day clinical practice.

However, most of the recent clinical trials on SAF were not aimed to the whole picture but rather focused the attention on just three main subgroups: patients with an implantable devices,[3–5,15] patients with cryptogenic acute stroke or transient ischemic attack (TIA),[6] and patients undergoing AF ablation.[16]

Cardiac Implantable Electronic Devices (CIED)

Implantable devices allow a continuous ECG recording of cardiac

Table 1: summary of main studies in patients with CIEDs

	Year	N. of patients	Type of device	Type of patients
Gillis et al.[17]	2002	231	PMK	Standard indication to pacing
MOST trial.[15]	2003	312	PMK	Patients with SND
Israel. et al. [18]	2004	678	PMK	Patients with SND or atri-ventricular block
Capucci et al.[3]	2005	725	PMK	Patients suffering from bradycardia and a history of symptomatic atrial tachyarrhythmias (AT)
Orlov et al.[19]	2007	427	PMK	Patients with stardard indication for pacing
TRENDS[5]	2009	2486	PMK or ICD	Patients with indication for Pacing, ICD, or CRT with or whitout AF history
ASSERT[4]	2012	2580	PMK or ICD	Sinus node or AV node disease, not previous history of AF
Shanmugam et al.[45]	2012	560	CRT	Patients with CRT and home-monitoring system

PMK-Pacemaker, SND- sinus node disease.

activity, and therefore are privileged in this context. An overview of the major clinical CIED trials dealing with SAF is presented in Table 1.

Glotzer et al.[15] found a prevalence of 51% of Atrial High Rate Episodes (AHRE) in a cohort of 312 patients implanted for sinus node disease (SND). Similar incidence rates were shown by Gillis et al. in another study, with similar population.[17]

Regarding patients with prior history of AF Israel et al.[18] showed in a group of 110 implanted patients (for SND or atrio-ventricular block) an high recurrence of AF despite optimal medical therapy; moreover a significant proportion of these patients were asymptomatic during the 3.5 year follow-up. Similar data were found by Capucci et al.[3] in a group of patients implanted with pacemaker for bradycardia with previous history of ATs (74% recurrence of AF episodes lasting at least more than 5 min during a median follow-up of 22 months).

In 2007, Orlov et al.[19] compared 427 patients with an implantable device divided according to the presence or absence of an history of atrial tachyarrhythmias (AT) such as AF or atrial flutter (AFL). They found a high occurrence of AHRE in both groups, slightly higher in those with previous history of AT (88.5% vs. 53.8% at 24 months post implant; $p < 0.001$).

Finally, in the ASSERT trial,[4] Healey and colleagues found an incidence of at least one AHRE in 34.7% of patients without any previous history of AF during 2.5 year of follow-up.

Algorithms for discrimination of ventricular tachycardia (VT) from supraventricular tachycardia (SVT) were originally designed in order to avoid inappropriate shocks in patients with implanted cardioverter defibrillator (ICD). In single-chamber devices, the detection is made using four different parameters: RR onset, RR stability, ventricular electrocardiogram morphology (VEGM) and sustained rate duration. The combination of these features ensures appropriate therapy of sustained VT at the expense of decreased specificity for SVT rejection. On the other hand, dual-chamber devices offer the possibility of sensing directly the right atrial chamber. While this feature does not seem to add a lot in terms of VT discrimination specificity when compared with single lead devices,[20] it surely represents a major breakthrough in AF detection capability. These advanced algorithms are the main reason whereby dual-chamber pacemakers have a much higher sensitivity and specificity than 24-hour Holter ECG monitoring in AF diagnosis.[15, 16, 21]

Differently from pacemakers and ICDs, implantable loop recorder (ILR) devices cannot sense endocardial atrial activity therefore RR intervals variation is used as the main variable for AF diagnosis.[22]

A recent clinical study (XPECT trial) showed that a subcutaneous device provided with AF detection algorithm had a good accuracy (98.5%) in AF burden quantification, and high sensitivity (96.4%) in AF identification, independently of symptoms.[23]

Cryptogenic Stroke

Cryptogenic stroke is defined as a stroke caused by unknown, undetermined or unclear cause, and accounts for 25-30% of all ischemic strokes.[24] SAF is often suspected to be the underlying cause of stroke in these patients[25] and screening for SAF episodes is mandatory for therapeutic reasons.

A single 12-lead ECG has very poor sensitivity for paroxysmal AF detection. A 24-hour ECG recording (Holter monitoring) is often used and allows the detection of previously unrecognized AF in only 2% of stroke patients.[26–28]

Moreover, the use of 7-day ambulatory ECG monitoring with the new event-loop recording system (ELR) demonstrated a further improvement of sensitivity in recognizing SAF in patients with stroke or TIA (Table 2).

Jabaudon et al.[6] enrolled 149 patients with acute stoke or TIA, evaluated with standard 12-lead ECG and, if not diagnostic, a 24-hour Holter monitoring. In case the Holter was not diagnostic too they underwent a 7-day ambulatory ECG monitoring. The 7-day monitoring was able to detect SAF in an additional 5.7% of patients despite standard ECG and 24-hour Holter found no evidence of AF (5/88 patients).

A further improvement in SAF diagnosis after an acute cerebral ischemic episode derived from ILRs. In fact, those devices allow a much longer ECG monitoring with a consequent big increase in sensitivity. Ritter et al.[29] showed that ILR was superior to 7-days ECG monitoring in SAF detection (17% vs. 1.7%; p=0.008) in patients with cryptogenic stroke.

Even Cotter and colleagues[30] found also in a cohort of 51 patients with cryptogenic stroke that AF was detected by ILR in 25.5% of cases. Continuous ECG monitoring (CEM) with telemetry in stroke unit plays also a central role in diagnosis of AF paroxysms that may be asymptomatic.[31]

Cryptogenic stroke and underlying atrial fibrillation (CRYSTAL-AF) study[32] showed that continuous ECG monitoring with ILRs is superior to conventional follow-up methods in detection AF after a cryptogenic stroke or TIA. Moreover, most of AF episodes detected in the CRYSTAL-AF were asymptomatic (74% in ILR group at 6 months follow-up).

Unfortunately, this study was underpowered to find a stroke or TIA recurrence reduction.

Finally, the recent EMBRACE trial[33] demonstrated that non invasive ambulatory 30-day ECG monitoring improved the detection of SAF by 5-fold and nearly doubled the rate of anticoagulant therapy

Table 2: summary of studies with different cardiac monitoring systems in patients with cryptogenic stroke or TIA.

	Year	N. of patients	Method	Type of patients
Koudstaal et al.[27]	1986	100	24 hour Holter ECG	Patients with TIA
Kessler et al.[26]	1995	100	ECG	Patients with stroke
Jabadoun et al.[6]	2004	149	Ambulatory 7-day ECG monitoring	Patients with acute stroke or TIA and negative standard ECG-Holter
Douen et al.[28]	2008	144	Inpatient serial ECG vs 24-hour Holter ECG	Patients with stroke
Rizos et al.[31]	2012	832	Continous ECG monitoring vs 24-hour ECG Holter	Patients with stroke
Cotter et al.[30]	2013	51	ILR	Patients with cryptogenic stroke
Ritter et al.[29]	2013	60	ILR vs 7-day ECG	Patients with cryptogenic stroke
CRYSTAL AF[32]	2014	441	ILR	Patients with cryptogenic stroke or TIA
EMBRACE[33]	2014	572	24-hour ECG Holter vs 30 day trigger ELR	Patients with cryptogenic strike or TIA in previous 6 months

where compared to standard ECG-monitoring. The detection rates of AF were 16.1% vs 3.2%, and 9.9% vs 2.5% when a cut-off of ≥30 seconds and ≥2.5 minutes was used respectively.

AF Ablation

ECG monitoring plays an important role in evaluating the asymptomatic recurrences after AF ablation. This therapeutic strategy may in fact favor a shift from symptomatic to asymptomatic form of AF,[34] and it is well known that symptoms evaluation alone is not useful in monitoring AF ablation success.[35]

In the large majority of trials the monitoring strategy was based on 24–72 hours of Holter monitoring, which unfortunately does not provide accurate heart rhythm status, particularly after AF ablation (Table 3). Hanke et al.[21] enrolled 45 patients with previous AF history, who underwent surgical AF ablation and subsequent implant of ILR. Patient follow-up was scheduled at 3, 6, 9, and 12 months postoperatively and then every 2 years with a clinical visit and 24-hour ECG Holter. While 24-hour Holter readings indicated sinus rhythm in 53 instances, a simultaneous telemetry allowed AF recurrence recording in 19 of these 53, suggesting an overall 34% 24-hour Holter failure ($p<0.0001$) in detecting SAF. This reflects a low 24-hour Holter sensitivity (0.60) and a low negative predictive value (0.64).

Pokushalov et al.[36] also demonstrated that a continuous monitoring with ILRs after AF catheter ablation is useful in early detection of AF recurrence and may guide to perform an early second ablation. Similar results were recently found by Mangianello et al.[37]

Unfortunately ILR are invasive, have limited memory storage and have a lifespan of only 3 years. External loop recorders (ELRs) with AF detection algorithms may be another option in SAF recurrence detection.[38]

Unfortunately, most of the patients commonly seen in clinical practice do not belong to one of these three aforementioned categories. Therefore, AF may long remain undiagnosed[39] as many patients with SAF have no reason to perform an ECG, or present a normal sinus rhythm during ECG routine control. For example we have no available data for prevalence of SAF in otherwise-healthy, hypertensive patients, which is the most frequent risk factor in AF population.[9] Similarly, some particular subtypes of AF, such as late postoperative AF, could benefit from the increased detection rates provided by ILRs and ELRs in order to avoid short- and long-term complications associated with this disease.[40]

Is SAF Monitoring Cost-Effective? And When?

We have seen how continuous ECG monitoring may improve SAF recurrences detection.

However, is it cost-effective? And, even if it is, is that true for every kind of patient?

Unfortunately, in literature there are not enough data in order to give a clear answer.

In patients with CIED, the possibility of continuous monitoring is surely an added benefit. In these patients, utilization of remote monitoring (RM) may provide a risk reduction for stroke, compare with standard ambulatory monitoring, because it allows an early detection of AF paroxysms while reducing follow-up costs.[41]

A meta-analysis from Kamel et al. showed that one-week continuous monitoring is cost-effective in diagnosis of SAF in order to prevent ischemic events recurrence in patients with ischemic stroke.[42] Similar results were found by Felix and colleagues with 7-day ECG monitoring, in a similar population.[43]

The real challenge is to extend the possibility of continuous monitoring to other sub-groups of patients with AF risk factors or predisposition. For all these reasons, more studies and new evidence are needed.

On the other hand, one time community screening using single-lead ECG recording with handheld devices showed some promising results in the recent SEARCH-AF study.[44] In this study ten pharmacies across Sidney where trained in order to screen for AF using specific software on a handheld devices. While the proportion of newly diagnosed AF was in line to what already known (1.3%) the authors found that this type of screening brought an incremental cost-effectiveness ratio of 3142€ per QALY gained and 15993€ per stroke avoided. This findings are especially important when compared with the cost of a hospitalization for stroke which was assumed by the authors to account for 34036€ in a ten-year time horizon. Moreover, the algorithm using by the software to detect AF had a very good sensitivity (98.5%) and specificity (91.4%).

AF Burden, Temporal Association And Risk Of Systemic Thromboembolism

In the last few years, many studies involving patients with implantable devices evaluated the correlation between AF burden and the risk of thromboembolic events.

The MOST trial in 2003[15] showed that the presence of pacemaker-detected AHREs lasting at least 5 minutes were associated with a more than doubled risk of death or stroke and 6-fold increased risk of developing AF. Despite these results, a direct cause-effect relationship between AHRE and mortality seems unlikely as the authors added that patients with AHRE also had more severe

Table 3: studies in follow-up after AF ablation

	Year	N. of patients	Method
Hanke et al.[21]	2009	45	24 hour Holter ECG vs ILR
Pokushalov et al.[33]	2011	286	ILR
Joshi et al.[38]	2009	72	ELR
Manganiello et al.[37]	2014	113	12-lead ECG vs ILR

structural heart disease. Another important study from Capucci et al. conducted in 725 patients with previous history of AF and implanted with dual-chamber pacemakers for bradycardia, found that device-detected recurrence of AF lasting more than 24 hours was associated with a 3-fold increased risk of embolic events.[3] Unfortunately, in this study patients with episodes < 24 hours were in the same group as with patients with no AF burden, thus making difficult to define a clinically useful cut-off of daily AT/AF burden that raises the risk of thromboembolic events.

Glotzer et al. in the TRENDS study[5] followed-up 2486 patients with implantable cardiac rhythm device to evaluate the AT/AF burden (defined as the longest total AT/AF duration on any given day during the prior 30-day period). Those patients were divided into 3 groups: zero, low (<5.5 hours), and high burden (>5.5 hours). A major finding was that patients with a >5.5 hours daily AT/AF burden had a double risk of systemic thromboembolism. Two main limitations of this study were the unexpectedly low event rates and the absence of ECG tracings to verify AF episodes.[5]

Similarly to what previously exposed, Shangmugan and colleagues found in a cohort of HF patients that daily AF burden >3.8 hours over 24 hours was associated with a significant increase in thromboembolic event rate.[45]

Finally, the Subclinical Atrial Fibrillation and the Risk of Stroke trial (ASSERT)[4] enrolled a total of 2451 patients with a newly implanted pacemaker (for SND or atrio-ventricular blocks) and 129 patients with a newly implanted ICD. Those patients had no previous history of AF or AFL lasting more than 5 minutes, and were not in oral anticoagulation therapy.

Episodes of AT were detected at least once during a mean follow-up of 2.5 years in about one third of the patients. One major finding was that subclinical AT (lasting more than 6 minutes) were independently associated with 2.5-fold risk of ischemic stroke or systemic independently of other risk factors and on the presence of AF symptoms. A limitation was that this trial did not analyze device-detected events of 6 minutes or less, which occurred frequently and potentially important from a clinical point of view.

Although there is evidence of an association between AF burden and thromboembolic events, their temporal relationship is still poor understood. A sub-analysis from the ASSERT trial showed that only 15% of patients with an embolic event had evidence of subclinical AF (SCAF) >6 minutes in the previous month. Moreover, the majority of SCAF events occurring prior to the embolic event were far shorter than 48 hours, which is commonly believed to be the minimum duration required for thrombus formation in the left atrial appendage.[46] Shangmugan et al.[45] in their study reached a similar conclusion. In fact, mean time from last AHRE and thromboembolic event was 46.7±71.9 days. Moreover only 27.3% of patients with detected atrial burden, who suffered a thromboembolism complication, were in AT at the time of diagnosis. Furthermore, one third of those who developed thrombotic events had no prior atrial arrhythmia recorded.

These data suggest that subclinical AF may be related to embolic events via indirect mechanism or could be only a risk marker.

Conclusion:

Despite all the current efforts, SAF is still widely under-diagnosed in every day clinical practice. Unfortunately, prevalence of this disease is not trivial and enough data suggest that SAF could predispose to a higher risk of thromboembolic events.

Fortunately, new and advanced diagnostic tools are now widely available and can help to detect SAF in a good proportion of patients, thus potentially improving anticoagulation therapy and quality of life. The cost-effectiveness and the heterogeneity of population at risk for SAF are still limiting contemporary detection rates of this invisible enemy.

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