Subclinical atrial fibrillation and stroke: insights from continuous monitoring by implanted cardiac electronic devices

Chu-Pak Lau1,2,3*, Chung-Wah Siu1,2, Kai-Hang Yiu1,2, Kathy Lai-Fun Lee1, Yap-Hang Chan1, and Hung-Fat Tse1,2

1Cardiology Division, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China; 2Research Center of Heart, Brain, Hormone and Healthy Ageing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; and 3Cardiac Health Heart Centre, Suite 1303, Central Building, 1 Pedder Street, Central, Hong Kong

Received 26 February 2015; accepted after revision 8 June 2015

Nearly one out of five strokes is associated with atrial fibrillation (AF). Atrial fibrillation is often intermittent and asymptomatic. Detection of AF after cryptogenic stroke will likely change therapy from antiplatelet to oral anticoagulation agents for secondary stroke prevention. A critical step is to convert ‘covert’ AF into electrocardiogram documented AF. External rhythm recording devices have registered a high incidence of AF to occur after a cryptogenic stroke, but are limited by short duration of continuous recordings. Invasive cardiac monitoring using insertable leadless cardiac monitors are sensitive means to identify subclinical AF (SCAF) after cryptogenic stroke, and AF has been reported to occur in 8.9% of these patients by 6 months in one study. It will be more attractive to identify SCAF before a stroke occurs. Recent series in pacemaker and implantable cardioverter-defibrillator (ICD) recipients showed that short episodes of SCAF increased stroke risk, with odds ratio $\approx 2.2–3.1$ compared with those without SCAF recorded. However, temporal sequence of recorded SCAF and stroke occurrence was uncertain, and the overall stroke risk was lower compared with patients with clinical AF at similar risk scores. This article reviews the incidence and clinical role of using implanted devices to detect SCAF and discusses the implication of SCAF so detected in primary and secondary stroke prevention.

Keywords
Atrial fibrillation • Implanted pacemaker • Implantable cardioverter-defibrillator • Insertable cardiac monitor • Stroke • Cryptogenic • Atrial high rate

Introduction
Epidemiological evidence suggests that atrial fibrillation (AF) increase ischaemic stroke risk by 5- to 6-fold independent of other risk factors.1 Atrial fibrillation-related stroke tends to be more severe,2 and mortality rate is higher (70–80%) compared with stroke without AF. There is also a high recurrence rate.3

Atrial fibrillation episodes are often asymptomatic, and AF may present for the first time with complications such as thromboembolism or heart failure. A recent meta-analysis4 on 6563 aspirin-treated patients suggests that the yearly stroke rates are 2.1, 3.0, and 4.2% for paroxysmal, persistent, and permanent AF, respectively. While there may be an impact of AF type on stroke risk, the stroke rate for paroxysmal AF remains significant. About 25% of strokes have no detectable underlying cerebrovascular disease or other stroke risk factors. Atrial fibrillation is an important underlying mechanism for cardioembolism in these patients. Apart from overt neurological deficits, recurrent cerebral emboli can cause cognitive dysfunction and dementia.5

In the absence of documented AF, secondary and primary prophylaxis of stroke relies on the use of antiplatelet agents. If AF is the cause of stroke, aspirin can reduce stroke risk by 22% compared with placebo. However, oral anticoagulation using warfarin can additionally reduce this risk by 38–63% compared with aspirin.6 More recently, non-vitamin K-dependent oral anticoagulation agents (NOACs) have been shown to be at least non-inferior to warfarin and have a lower incidence of major haemorrhagic complications, thus improving the risk–benefit ratio of stroke prevention in AF. This background makes primary and secondary prophylaxis of AF-related stroke attractive. A critical first step is to document underlying AF.
**Atrial fibrillation documentation**

Owing to the intermittent occurrence and often asymptomatic presentation of AF, routine electrocardiogram, 24-h Holter, and patient-triggered recording devices have low detection rate of AF. Several types of external monitors with attached electrodes have enabled more prolonged monitoring with better patient tolerability. Electrodes used include wet or dry electrodes. These provide not only patient-triggered recordings, but also automatic recording if AF occurs.

Longer term recording of cardiac rhythm is possible with implantable leadless cardiac monitors (ICMs), such as the Medtronic Reveal XT™. As P waves are not well detected in ICMs, irregularity of RR interval is used as a surrogate for AF, the so-called Lorentz plot is arithmetically used to register AF. The XPECT Trial patients with high AF burden received the Reveal XT™ showed a sensitivity, specificity, positive predictive value, and negative predictive value of the Reveal XT™ to identify AF of 96.1, 85.4, 79.3, and 97.4% respectively, with an accuracy of 98.5%. Further, false-positive is reduced by superimposing the R waves to examine for a possible P wave. Apart from the Reveal XT™, other devices such as Confirm™ (St. Jude Medical Inc.) and BioMonitor™ (Biotronik) ICMs are available. The LINK™ (Medtronic Inc.) is a miniaturized version of Reveal XT™ that can be implanted with an injection mechanism.

Obviously, cardiovascular implantable electronic devices (CIEDs) with implanted atrial electrodes provide excellent AF recording. Table 1 shows the requirement to maximize sensitivity and specificity to detect AF in CIEDs. Accurate recording requires a closely spaced atrial bipolar (<1 cm), an appropriate atrial sensitivity setting, post-ventricular atrial refractory period (PVARP), and post-ventricular atrial blanking (PVAB) adjustment.

In 5769 CIED-detected atrial high rate episodes (AHREs), Kaufman et al. examined the relative contribution of programmed cut-off detection rate and duration on accuracy of AF detection. An increase in cut-off detection rate from 190 to 250 b.p.m. reduces false-positive detection, especially if shorter AF detection rates were programmed. A cut-off detection duration of >6 min will have a 17.3% false-positive detection rate, compared with 3.3% if detection duration of >6 h was programmed. It was concluded that validation by atrial electrograms (AEGMs) will be important for shorter detected AF episodes of between 6 min and ≤6 h, whereas this become less critical for longer episodes >6 h. As most studies do not vigorously relate symptoms with device-detected AF episodes, this review use the term subclinical AF (SCAF) for AF detected by implanted CIEDs, to distinguish them from the occurrence of clinical AF.

**Secondary prevention in cryptogenic stroke**

Kishore et al. summarized 32 trials which have used either external monitors or ICMs to detect AF in patients after ischaemic stroke or transient ischemic attack (TIA), and documented an overall detection rate of 11.5%. A large prospective study recruited 572 ambulatory patients with a mean age of 55 years at a mean of 75 days after a stroke or TIA. Patients were randomized to receive either a 30 days event-triggered external recorder using dry electrodes or with another 24-h Holter recording. The primary endpoint was detected AF >30 s, which was reached in 16.1% of patients vs. 3.2% using Holter only, and had led to an increase in oral anticoagulation use (18.6 vs. 11.1%). Clinical AF was only detected in 0.5% of patients after 90 days, and AF was more often detected if the device was administered within 30 days of the index stroke. In the CRYSTAL AF study, 441 patients at a mean of 38 days after a cryptogenic stroke received either an external Holter or ICM (Reveal XT™) to assess the time of first occurrence of AF >30 s (Figure 1). Atrial fibrillation was detected in 8.9% in the ICM group compared with 1.4% in the Holter only group (P < 0.001) at 6 months, the time for primary endpoint of the study. This resulted in more oral anticoagulation use (14.7 vs. 6.0%, P < 0.007) at 12 months, and a trend

<table>
<thead>
<tr>
<th>Table 1 Optimization of AF detection accuracy using implanted atrial leads</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Implantation</strong></td>
</tr>
<tr>
<td>Atrial lead position (e.g. appendage vs. low septum)</td>
</tr>
<tr>
<td>Maximize A to V ratio</td>
</tr>
<tr>
<td>Choice of closely spaced atrial bipolar (e.g. 5 mm interelectrode distance)</td>
</tr>
<tr>
<td>Programming atrial sensing</td>
</tr>
<tr>
<td>Appropriate high atrial sensitivity without noise detection (e.g. 0.1–0.5 mV)</td>
</tr>
<tr>
<td>Short PVARP</td>
</tr>
<tr>
<td>Long PVAB (e.g. ≥25 ms)</td>
</tr>
<tr>
<td>Enhancing specificity for AF</td>
</tr>
<tr>
<td>AEGM validation</td>
</tr>
<tr>
<td>High atrial rate (e.g. 220 vs. 180 b.p.m.)</td>
</tr>
<tr>
<td>Long AHRE duration (e.g. ≥6 min)</td>
</tr>
<tr>
<td>Avoid competition atrial pacing or RNRVAS</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; AHRE, atrial high rate episode; PVAB, post-ventricular atrial blanking; PVARP, post-ventricular atrial refractory period; RNRVAS, repetitive non-re-entrant ventricular atrial synchrony.

**Figure 1** Insertable leadless cardiac monitor vs. Holter recording to detect AF in patients after cryptogenic stroke. Atrial fibrillation was detected in 8.9, 12.4, and 30% by ICMs at 6, 12, and 36 months, respectively. Redrawn from data of Refs 7, 14.
to a lower recurrent stroke rate (7.1 vs. 9.1%). At 3 years, the device projected battery life, AF was detected in 30% of patients. Most of the episodes of detected AF were asymptomatic (74 and 79% at 6 and 12 months, respectively). The lower rates of AF detected in the CRYSTAL AF compared with EMBRACE may be due to difference in baseline risk factors and timing of recording in relation to stroke. The recently concluded SURPRISE study has shown new AF detected in 18.6% in 3 years in similar patients.

Taken together, AF is a common occurrence in an embolic stroke of undetermined source and its detection will likely affect antithrombotic treatment. Since AF is detected in a significant proportion of such patients, arguably antithrombotic therapy with NOACs may be considered even in patients without AF documentation. This is the subject of several prospective randomized studies (see below).

**Primary prevention of stroke by early subclinical atrial fibrillation detection using implanted devices**

The strong association between clinical AF and ischaemic stroke, and the proven benefit of anticoagulation prophylaxis make early AF detection of clinical interest. The relationship of SCAF detected by CIEDs and future clinical AF and stroke provides important background information for the clinical importance of SCAF.

**Frequency of subclinical atrial fibrillation detected by cardiovascular implantable electronic device and relation to clinical atrial fibrillation**

In patients with sick sinus syndrome and a previous history of paroxysmal AF, a recent study reported persistent AF to develop at a rate of 8.3%/year, that was independent of the site or rate of atrial pacing. Gillis and Morck reported SCAF to be detected in 68% of 231 patients with sinus node disease, and an incidence of 50.6% of SCAF was documented in 617 patients with DDD pacemakers. An incidence of 44% of AF was detected in 226 patients during a long follow-up period of 7 years with a much higher incidence of AF in patients with a prior history of AF than those without (87 vs. 22%). Independent of prior history, AF detection was associated with a 10-fold increase in incidence of persistent AF and 2.5-fold increase in major cardiovascular events. With AEGM validation, a 55% incidence of SCAF was recorded in 254 patients in whom 54% had sinus node disease. Several studies have also shown an incidence of SCAF in 69–79% in patients with prior history of AF and 25–45% in patients without prior history. Two studies have examined the relationship of SCAF detected by device and the development of clinical AF (Table 2).

In the retrospective MOST study, patients with SCAF (defined as AHRE ≥ 220/min, duration >5 min) increased risk of clinical AF by 5.9 times. The ASSERT study prospectively evaluated 2580 patients without prior history of AF and found a 10.1% incidence of SCAF (atrial rate ≥ 190/min lasting ≥6 min) at 3 months. The presence of SCAF increases the risk of clinical AF by 5.6 times.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Mean age (years)</th>
<th>FU (months)</th>
<th>Prior AF (%)</th>
<th>Atrial activation duration</th>
<th>Clinical AF</th>
<th>Prior OAC (%)</th>
<th>CHADS2</th>
<th>Number of pts with OAC (%)</th>
<th>SCAF (&lt;190/min)</th>
<th>Annual TE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOST20</td>
<td>312</td>
<td>74</td>
<td>27</td>
<td>60</td>
<td>Atrial AF ≥ 220/min, ≥ 1 day</td>
<td>5.9</td>
<td>0.0001 20</td>
<td></td>
<td>24</td>
<td>110</td>
<td>2.8</td>
</tr>
<tr>
<td>Capucci22</td>
<td>725</td>
<td>71</td>
<td>22</td>
<td>100</td>
<td>AT/AF ≥ 1 day</td>
<td>1.80</td>
<td>32</td>
<td>1.8</td>
<td>14</td>
<td>10</td>
<td>1.4</td>
</tr>
<tr>
<td>Botto21</td>
<td>568</td>
<td>70</td>
<td>12</td>
<td>100</td>
<td>AT/AF ≥ 1 day</td>
<td>1.40</td>
<td>56</td>
<td>40</td>
<td>10</td>
<td>22</td>
<td>5.3</td>
</tr>
<tr>
<td>TRENDS26</td>
<td>2486</td>
<td>71</td>
<td>17</td>
<td>20</td>
<td>AT/AF burden</td>
<td>13.40</td>
<td>200</td>
<td>20</td>
<td>12</td>
<td>22</td>
<td>2.2</td>
</tr>
<tr>
<td>ASSERT27</td>
<td>2580</td>
<td>76</td>
<td>34</td>
<td>0</td>
<td>AT ≥ 190/min</td>
<td>18.6</td>
<td>120</td>
<td>34</td>
<td>18</td>
<td>25</td>
<td>170</td>
</tr>
</tbody>
</table>

FU, follow-up; OAC, oral anticoagulation; RR, relative risk; pts, patients; SCAF, subclinical atrial fibrillation; TE, thromboembolism.
Subclinical atrial fibrillation in predicting stroke and other thromboembolism

Five large studies have examined the relationship of CIED recorded SCAF and future thrombo-embolic risk (Table 2).20–22,26,27 With the exception of the ASSERT, all studies had included some or all patients with prior history of clinical AF. Oral anticoagulation (primarily vitamin K antagonist) was used in 18–32%, with the aspirin use in over half of the remaining patients. Prior thrombo-embolic events occurred in 1.4–20%, in a population with an overall CHADS2 score of 1–2.2. The definition of SCAF recorded by CIEDs ranged from >5 min or as SCAF burden ≥5.5 h/day.

The number of thrombo-embolic events in these studies is relatively small, with 51 events occurring in largest ASSERT trial that had recruited 2580 patients, and only 14 events among 725 patients in Capucci’s study.22 The overall annual thrombo-embolic rate ranges from 0.89 to 2.5%.21 Subclinical atrial fibrillation detected by the device increased the relative risk for thromboembolism by a factor of 2.2–5.3 compared with no SCAF detected. Annual thromboembolic rates were similarly higher in those patients with detected SCAF vs. those without.

Subclinical atrial fibrillation duration and CHADS2 scores in relation to thromboembolism

In a retrospective analysis, Botto et al.21 had attempted to stratify thrombo-embolic risk in a cohort of 567 patients with a total number of 14 events. There was a relationship between duration of SCAF and CHADS2 score with a stroke event. At a CHADS2 score of 1, only AF ≥24 h would increase the annual stroke rate to 4% compared with 0.6% for SCAF that lasted shorter. At a CHADS2 score of 2, any SCAF >5 min resulted in a 4% stroke rate. In the TRENDS study, only SCAF burden >5.5 h/day increased thrombo-embolic rate to 2.4%/year, in a population of CHADS2 score of 2.2. Likewise, the thrombo-embolic risk in ASSERT became significant only when SCAF was >17.72 h.

In a pooled analysis of over 10,000 patients, Boriani et al.28 compared the duration of CIED recorded SCAF and stroke risk (Figure 2). The hazard ratio of SCAF >5 min was similar to the impact of having sustained AF, and progressively increased with SCAF duration up to 24 h.

The annual risk for thromboembolism in these studies is lower than expected when compared with patients with clinical AF with similar CHADS2 scores (Table 3). Possibilities include: patients with CIEDs are different from clinical AF patients, that atrial leads might have generated a different type of AF, or SCAF may represent less severe or early AF that requires time to become an establish risk. Finally, a substantial per cent of patients in these studies were on antithrombotic therapy which would have reduced thromboembolic risk.

Is subclinical atrial fibrillation only a risk marker for stroke?

The traditional belief is that AF results in cardioembolic events from atrial clots due to mechanical stasis in the atrium. Indeed, in transesophageal echocardiographic studies, substantial risk for left atrial thrombosis occurred when AF lasted >48 h.30 However, recent studies suggest that transient episodes of AF or high atrial rates induced by atrial pacing can lead to increased platelet activation and thrombin generation.31,32

With an implanted CIED, it is possible to relate the temporal occurrence of SCAF and stroke and other thrombo-embolic events. Daoud et al.31 analysed the device recordings of the 40 patients who developed thromboembolism in the TRENDS study, and showed SCAF occurred in about half before the event. Of these, only half had SCAF 30 days before the thromboembolism to suggest a causative mechanism. Overall, 29/40 (72.5%) of patients may be considered to have stroke due to non-cardioembolic causes. The only factors that predicted SCAF to occur before a thromboembolic event are patients with a long duration of entry into the

![Figure 2](https://academic.oup.com/europace/article/17/suppl_2/ii40/2802581)

### Table 3 Annual stroke (and other thrombo-embolic) risk (in %) at different CHADS2 scores compared with the reported risk in patients with clinical AF

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>&lt;2</th>
<th>2</th>
<th>&gt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCAF detected</td>
<td>0.56%</td>
<td>1.29%</td>
<td>3.78%</td>
</tr>
<tr>
<td>SCAF not detected</td>
<td>0.28%</td>
<td>0.70%</td>
<td>0.97%</td>
</tr>
<tr>
<td>Clinical AF in reference population</td>
<td>2.8%</td>
<td>4.0%</td>
<td>&gt;5.8%</td>
</tr>
</tbody>
</table>

Although SCAF increased risk of events, the risk remained substantially lower than the occurrence of clinical AF (data from Refs.27,29).
study (485 ± 273 vs. 251 ± 221 days, *P* < 0.01) and a higher mean and maximum AF burden.

In a similar analysis, the ASSERT investigators showed that only 51% (26/51) patients with stroke (or other thromboembolism) had SCAF occurring before, and only 8% of the overall cohort had SCAF within 1 month of the event (Figure 3). This suggests that in patients without prior AF, as many as 92% of the stroke do not have a SCAF 30 days before the stroke occurrence.

Taken together, SCAF detected by CIEDs predicted the occurrence of clinical AF and increased the risk of stroke. However, especially in studies in which most patients did not have AF at the baseline, the annual risk for stroke when SCAF was detected is lower than expected from clinical AF with equal risk factors. A close temporal relationship between SCAF occurrence and stroke was plausible only in a minority. These suggest that either AF has a different temporal relationship to stroke or AF is simply a vascular maker, or both.

### When should subclinical atrial fibrillation be anticoagulated

The IMPACT trial is a prospective randomized trial that randomized over 2000 patients with an ICD or CRTD to receive warfarin or not based on the CHADS2 score, and the presence or absence of SCAF as detected by CIED and monitored by remote monitoring. The moderate risk group (CHADS2 ≤ 4) was randomized to receive warfarin in the presence of SCAF or to terminate warfarin when SCAF became undetected. The primary endpoint was a composite of stroke, embolism, or major bleed. Early results were presented and suggested anticoagulation guided by SCAF detected by CIED to be equal to routine clinical care. The reasons for the neutral result are not certain, and the full report is awaited.

After validation of device recorded SCAF to be accurate AF registration, it seems reasonable now to consider the patient’s thromboembolic risk to decide for anticoagulation. In patients with prior clinical AF, they should be anticoagulated according to their CHADS2 or CHA2DS2-VASc scores as suggested by current guideline. It should be noted that in patients without clinical AF, the ASSERT trial has reported a significantly lower rate of stroke compared with published registry. Indeed, as pointed out by Chen-Scarabelli et al., when compared with the National Registry of AF, the HRS of stroke risk in ASSERT is significantly lower (4.0 vs. 1.82). This may be due to the significantly higher percentage of female and prior stroke or TIA in the NRAF compared with the ASSERT despite similar overall CHADS2 score. The yearly stroke rates of current AF population compared with current clinical AF patients are tabulated in Table 3.

There is no consensus of the role of oral anticoagulation in patients with only device-detected AF episodes. Only the Canadian Cardiovascular Society Guidelines for the management of AF has suggested that it is reasonable to prescribe oral anticoagulation for patients ≥65 years or CHADS2 score ≥1 who have episodes of SCAF ≥24 h, or shorter episodes in high-risk patients (such as those with a recent cryptogenic stroke) as a conditional recommendation with low-quality evidence. Several trials are underway to
examine the role of anticoagulation such as Apixaban for Reduction of Thrombo-Embolism due to Sub-Clinical AF (ARTEMIA) (Clinical Trials.gov NCT 01938248). The Randomized Evaluation in Secondary stroke PreVention Comparing the Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in Embolic Stroke of Undetermined Source (RE-SPECT ESUS™) in 6000 patients. Similarly, the NAVIGATE ESUS study will randomize 7000 patients either to rivaroxaban (15 mg) or aspirin 100 mg daily in ESUS patients. These new trials will guide our antithrombotic management of patients with SCAF or ESUS. At present, the following may be a probable scheme (Table 3). For CHADS2 = 0, SCAF requires no anticoagulant, whereas most clinicians would start oral anticoagulants for CHADS2 ≥ 3. For CHADS2 = 1, based on the ASSERT trial, the risk of stroke probably is outweighed by the risk of warfarin. At CHADS2 = 2, warfarin is likely indicated. Longer episodes of SCAF (especially close to 24 h) increase stroke risk. When NOACs are considered, it seems reasonable to initiate anticoagulation at a lower CHADS2 score or shorter AF duration.

Conclusion
In the presence of a cryptogenic stroke, SCAF of up to 30% in 3 years can be recorded by an ICM. While there is no randomized data, most would consider the use of oral anticoagulation instead of aspirin therapy in secondary prevention for recurrent stroke. More controversy centred about SCAF recorded by implanted CIEDs. Recorded SCAF predicted clinical AF. However, recorded SCAF, while increasing stroke (and other thrombo-embolic risk) occurred at a magnitude that is substantially less than what occurred when AF developed clinically. In addition, a temporal relationship between SCAF and stroke occurred only in a minority of patients. Until more data become available, the use of oral anticoagulation in this cohort remains expert opinion, although CHADS2 score and duration of AF may help to identify a group of patients who may be such candidates.

Funding

Conflict of interest: none declared.

References


