Temporal Relationship between Subclinical Atrial Fibrillation and Embolic Events

Running title: Brambatti et al.; Subclinical atrial fibrillation and stroke

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Abstract

**Background**—Among patients with implantable pacemakers and defibrillators, sub-clinical atrial fibrillation (SCAF) is associated with an increased risk of stroke; however, there is limited understanding of their temporal relationship.

**Methods and Results**—The ASSERT trial enrolled 2580 pacemaker and defibrillator patients ≥ 65 years old, with a history of hypertension, but without a history of atrial fibrillation. Pacemakers and ICDs precisely logged the time and duration of all episodes of SCAF and recorded electrograms which were adjudicated by experts. We examined the temporal relationship between SCAF > 6 minutes in duration and stroke or systemic embolism. Of 51 patients who experienced stroke or systemic embolism during follow-up; 26 (51%) had SCAF. In 18 patients (35%) SCAF was detected prior to stroke or systemic embolism. However, only 4 patients (8%) had SCAF detected within 30 days prior and only one of these 4 patients was experiencing SCAF at the time of their stroke. In the 14 patients with SCAF detected more than 30 days prior to stroke or systemic embolism, the most recent episode occurred at a median interval of 339 days (P25-P75: 211-619) earlier. Eight patients (16%) had SCAF detected only after their stroke, despite continuous monitoring for median duration of 228 (P25-P75: 202-719) days prior to their event.

**Conclusions**—Although SCAF is associated with an increased risk of stroke and embolism, very few patients had SCAF in the month prior to their event.

**Clinical Trial Registration**—http://www.clinicaltrials.gov. Identifier: NCT00256152.

**Key words:** arrhythmia; stroke; pacemakers
Atrial Fibrillation (AF) is a common arrhythmia and a well-known risk factor for ischemic stroke and systemic embolism\textsuperscript{1,2}. With the development of continuous long-term monitoring, it is now apparent that many patients have evidence of AF without recognizable symptoms\textsuperscript{3-8}. We have called this phenomenon sub-clinical atrial fibrillation (SCAF). SCAF is often recognized after stroke has occurred using intensive electrocardiographic monitoring\textsuperscript{3-7}. Implanted dual-chamber pacemakers and defibrillators (ICD) represent the most sensitive means for SCAF detection, as they can continuously monitor cardiac rhythm for many years, precisely characterizing the time and duration of AF and storing intracardiac electrograms\textsuperscript{8,9,10}. The ASSERT trial demonstrated that over 2.5 years, SCAF of 6 minutes duration or longer, is observed in over 40\% of pacemaker patients without a prior history of AF, but leads to clinical, ECG-documented AF in fewer than 15\% of cases\textsuperscript{8}.

We have recently reported that SCAF is associated with a 2.5-fold increased risk of stroke or systemic embolism\textsuperscript{8}. However; the relationship between SCAF and embolism is not clearly understood, although several interpretations are possible. One possible interpretation is that SCAF might be associated with thromboembolic events without any causality or SCAF may be directly causing stroke. In the latter scenario, stasis due to low flow in the fibrillating atrial appendage might increase the risk of stroke or systemic embolism very shortly after the onset of SCAF\textsuperscript{11}. Alternately, SCAF may cause changes in the atrial endothelium that increase the risk of stroke or systemic embolism. These alterations may be transitory or persistent\textsuperscript{12-16}. Finally, SCAF may simply be a marker of risk and not causally linked to the occurrence of stroke.

To better understand the relationship between SCAF and embolic events, it is critical to understand the temporal relationship between SCAF episodes and stroke or systemic embolism. The TRENDS study group has published data on 40 patients who suffered a stroke, systemic
embolism or transient ischemic attack during that trial. Among the 20 patients with atrial fibrillation prior to their embolic event, only 30% had atrial fibrillation within the month prior to their embolic event and the most recent episode of atrial fibrillation was an average of 166 ± 189 days prior. However; this population is very different than ASSERT, as nearly half of the patients in the TRENDS analysis had a history of clinical atrial fibrillation prior to study enrolment. The present analysis from the ASSERT trial permits a deeper understanding of this relationship by examining the more robust outcome of stroke or systemic embolism; by using only data on adjudicated episodes of SCAF; by including a larger number of patients and by limiting this analysis to patients without a prior history of clinical atrial fibrillation.

Methods

The design and main results of ASSERT have been published previously. The study enrolled 2580 patients, 65 years or older, with a history of hypertension who underwent initial implantation of a St Jude Medical (St. Paul, Minnesota, USA) dual-chamber pacemaker or ICD. Patients were excluded if they had a history of clinical AF or atrial flutter lasting more than 5 minutes or if they required oral anticoagulant therapy for any reason. The study was approved by an institutional review committee at each participating centre and all patients provided written informed consent. After implant, devices were programmed according to study protocol with high atrial sensitivity (0.1–0.5 mV). There was central adjudication of all available device electrograms showing SCAF (atrial rate > 190 beats per minute for > 6 minutes), and all embolic events. The primary outcome of the study was ischemic stroke or systemic embolism and the mean follow-up duration was 2.5 years.

For the current analysis, stored device data including the date, time of onset and the
duration of all SCAF episodes detected over the entire follow up period were examined. For each day, the total number of hours spent in SCAF was calculated. CHADS2 and CHA2DS2-VASC scores were calculated for each patient\textsuperscript{19-21}. The clinical outcome of interest was ischemic stroke or systemic embolism. To ensure a minimum of 3 months of continuous monitoring prior to any systemic embolism and to maintain consistency with the methodology of the main ASSERT study \textsuperscript{8}, only embolic events occurring more than 3 months following study enrolment were examined.

**Statistical Analysis**

The normality of continuous variables was assessed graphically, given the small number of patients in this report. Data are presented using the mean and standard deviation or median and percentiles (25\textsuperscript{th} - 75\textsuperscript{th}), as appropriate, with the comparison between groups performed using the T-test or Wilcoxon rank-sum test, respectively. Categorical variables are summarized using counts and proportions with groups compared using the Fisher’s exact test.

**Results**

A total of 59 patients experienced ischemic stroke or systemic embolism during the ASSERT trial. Of the 51 patients who experienced these events after the 3-month visit, 26 (51\%) patients had SCAF either before or after the embolic event (**Figure 1**). The median CHA2DS2-VASc scores were 5 (P25-P75: 4-5) in the group with and 5 (P25-P75: 3-5) in the group without SCAF (**Table 1**). Aspirin was used by 57.7\% and 52\% of patients respectively and none of patients were receiving oral anticoagulation at baseline (**Table 1**). The median duration of continuous device monitoring before embolic events was greater than 1.7 years (P25-P75: 0.8-2.4 years) (**Table 1**).
In 18 patients (35%), SCAF was detected prior to the stroke or systemic embolism; however, in only 4 patients (8%) was SCAF detected within 30 days prior to such an event (Figure 1). Only 1 patient experienced a continuous episode of SCAF at the time of his stroke, which lasted a total of 2.7 hours. In the remaining 14 patients (27%), who had SCAF detected more than 30 days prior to their embolic event, the most recent episode of SCAF occurred at a median interval of 339 days (P25-P75: 211-619 days) before and the median duration of the most recent episode of SCAF was 4.2 hours (P25-P75: 0.80–466 hours). Over the entire follow-up, 10 of 18 patients with SCAF prior to an embolic event (55%) had an episode of SCAF lasting more than 24 hours prior to their event. However, only one patient had such an episode within 30 days prior to their stroke or embolism and AF was clinically diagnosed in only one other patient.

In 8 patients with both SCAF and an embolic event (16%), SCAF was detected only after the stroke or embolism; at a median interval of 101 days (P25-P75: 14-196 days) later. This was despite continuous monitoring for a median duration of 228.5 days (P25-P75: 202-719 days) prior to their stroke. Among these patients, the median maximum duration of SCAF on a single day was 6.3 hours (P25-P75: 1.9-10.3 hours) and none of these patients developed SCAF of more than 24 hours in continuous duration.

The detailed temporal relationship between the total daily burden of SCAF and the occurrence of a stroke or systemic embolism for each of the 18 patients with SCAF detected within one year before or after their embolic event is presented in Figures 2a, 2b and 2c. Of the remaining 8 patients (out of 26 with both SCAF and embolic events), 1 had their first episode of SCAF more than one year after their embolic event and 7 patients had SCAF detected more than one year prior to their stroke or embolism, without further episodes during the interval.

**SCAF occurring within 30 days prior to Stroke or Embolism**
A higher-resolution detail of SCAF occurring within 30 days of stroke or systemic embolism is displayed in Figure 2b. Patient # 8 experienced a long-lasting (125 hours) episode of SCAF 3 months before and then 3 brief episodes (the last one 6 minutes in duration) 11 days before his ischemic stroke. Patient # 9 experienced several episodes of SCAF longer than 24 hours, 11 months before his stroke and then a 2.7-hour episode on the day of his stroke. Patient # 10 had his last episode of SCAF (lasting 88.7 hours) detected 6 days before his stroke and had a longer episode of 6 days duration detected 39 days earlier. Finally, patient # 11 had a 12.5 hour episode of SCAF 15 days before his stroke, but had several episodes lasting more than 24 hours detected about 11 months earlier.

**Antithrombotic therapy in the study population**

Over the course of the follow up period, 6 patients with SCAF received an oral anticoagulant: 1 after clinical evidence of AF (detected by surface ECG) and 5 as a result of SCAF alone (Details of timing of oral anticoagulant use for 4 patients are shown in Figure 2a). Two patients experienced an embolic event following discontinuation of oral anticoagulation after SCAF had not recurred for 1 and 8 months. Two patients were receiving oral anticoagulation at the time of their embolic events; however, we unfortunately did not capture details regarding INR control. In the remaining 2 patients, oral anticoagulation was introduced only after their embolic event occurred.

**Discussion**

The ASSERT trial demonstrated that SCAF is common in elderly patients with either pacemakers or ICD and a history of hypertension and was associated with a 2.5-fold increase in the risk of embolic events. However; the present analysis shows that only 15% of patients with
SCAF-associated embolic events had evidence of SCAF > 6 minutes in duration within the month prior to their stroke or systemic embolism. Furthermore, most SCAF occurring prior to embolic events was far shorter than 48 hours in duration, which is commonly believed to be the minimum duration required for thrombus to form in the left atrial appendage prior to cardioversion \(^{22,23}\). Finally, this analysis shows that in most cases, patients with 6-minutes episodes of SCAF did not require the development of long-lasting episodes of SCAF for stroke or systemic embolism to occur.

All of these findings call into question our current understanding of how AF causes embolic events; at least among patients with isolated SCAF. It is likely that this relationship, if indeed causal, is far more complex than a simple matter of prolonged AF leading to atrial stasis, clot formation and then embolism \(^{14}\). Some thromboembolic events may indeed be due to stasis from an actual AF episode; some may be due to chronic endothelial changes due to multiple prior AF episodes; and some may be due to non-AF mechanisms (i.e. hypertension-associated lacunar stroke) for which AF may be just a risk marker. Our understanding of the mechanistic relationship between stroke or systemic embolism and AF must therefore evolve; particularly as it pertains to SCAF, which is becoming increasingly recognized with the growing popularity of prolonged cardiac monitoring \(^{24,25}\).

There are several possible explanations for the lack of temporal association between SCAF and stroke or systemic embolism observed in ASSERT. Among patients having electrical and pharmacological cardioversion of AF, echocardiographic studies have shown that mechanical atrial contraction may not resume for hours to days following electrical cardioversion from AF to sinus rhythm \(^{26}\). This might explain a delay between AF and a presumed cardioembolism. However; it is unclear if a similar process is plausible in the case of SCAF as
evidence suggests that this electro-mechanical delay is more common for longer-lasting episodes of persistent AF\textsuperscript{27}. As well, the majority of patients with SCAF-associated systemic embolism in ASSERT had their embolic event well more than one month after the most recent episode of SCAF, far longer than the typical duration of atrial mechanical stunning following cardioversion\textsuperscript{23}. The second possible explanation is that SCAF itself does not cause embolism, but rather is a marker of cardio-embolic risk. There is abundant evidence that AF causes changes in atrial structure and in endothelial function\textsuperscript{12}. AF is also associated with biochemical evidence of inflammation\textsuperscript{13} markers of hyper-coagulability\textsuperscript{14, 15} and evidence of left atrial spontaneous echo contrast\textsuperscript{16}. Thus, the occurrence of even brief episodes of SCAF may trigger chronic changes in the atria which lead to thrombus formation sometime after the actual occurrence of SCAF.

Finally, it is possible that the association between SCAF and stroke seen in ASSERT\textsuperscript{8} was simply due to chance, given the relatively small number of events observed.

Although ASSERT demonstrated an association between SCAF and embolic events\textsuperscript{8}, ASSERT does not provide any evidence that oral anticoagulation will have the same effectiveness in this population as it does for patients with clinical AF, so many are suggesting that randomized trials are needed\textsuperscript{8, 28, 29}. Some clinicians appear to agree, as recent surveys suggest that oral anticoagulation is typically not prescribed to patients with isolated SCAF\textsuperscript{30, 31}. This analysis from ASSERT also has an important implication for the clinical strategy of intensive cardiac rhythm monitoring among patients who have suffered cryptogenic stroke\textsuperscript{7}. Thirty percent of ASSERT patients with SCAF and ischemic stroke or systemic embolism had SCAF detected only after their embolic event. This was despite over 1 year of negative monitoring prior to their embolism. Thus, the assumption that the detection of AF after a cryptogenic stroke always implies that AF caused the stroke is questionable, and may
overestimate the number of cryptogenic strokes truly caused by AF.

An earlier report from the TRENDS study also demonstrated that most patients did not have AF within the month prior to their AF-associated embolism; however; this report from ASSERT adds substantially to our understanding. Among the TRENDS patients with pacemaker-detected AF and embolism, 55% already had an established clinical diagnosis of AF, which may explain their higher (50%) proportion of patients with SCAF prior to their embolic event and the higher (15%) proportion of patients with a continuous episode of AF at the time of their embolic event. The ASSERT trial excluded all patients with a prior history of AF, allowing a more precise analysis of the relationship between isolated SCAF and embolic events. Moreover, adjudication of device detected high rate episodes was not performed in TRENDS, so it is unclear if the reported events all represent AF.

Limitations
Although this report contains data on more patients with SCAF and stroke than any other prospective series, the total number of patients remains small. As well, since none of the pacemakers and defibrillators used in ASSERT was MRI-conditional, we were not able to subclassify ischemic strokes. Finally, we were not able to adjudicate all episodes of SCAF of less than 6 minutes in duration, limiting our ability to comment on the association of these briefer episodes and stroke.

Conclusions
Although SCAF was associated with an increased risk of ischemic stroke and systemic embolism in the ASSERT study, very few patients had SCAF in the month prior to their stroke. Thus, SCAF may simply be a risk marker for stroke; or if it is causal, then it is related via an indirect mechanism which is more complex than previously appreciated.
**Funding Sources:** The ASSERT Trial was funded by St. Jude Medical

**Conflict of Interest Disclosures:** Dr. Healey has a personnel award from the Heart and Stroke Foundation, Ontario Provincial office (MC7450).

**References:**


Table 1. Baseline characteristics of the patients who had a stroke or embolism in ASSERT.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SCAF not detected (n=25)</th>
<th>SCAF detected (n=26)</th>
<th>Overall (n=51)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex —no. (%)</td>
<td>20 (80)</td>
<td>8 (31)</td>
<td>28 (55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age — years</td>
<td>Mean (SD)</td>
<td>75.4 ± 6.7</td>
<td>80.3 ± 7.1</td>
<td>0.015</td>
</tr>
<tr>
<td>Body-mass index— kg/m2</td>
<td>Mean (SD)</td>
<td>26.8 ± 3.3</td>
<td>25.8 ± 5.7</td>
<td>0.451</td>
</tr>
<tr>
<td>Systolic Blood Pressure —mmHg</td>
<td>Mean (SD)</td>
<td>136 ± 22.6</td>
<td>144 ± 20.4</td>
<td>0.161</td>
</tr>
<tr>
<td>CHADS2 score †</td>
<td>Mean (SD)</td>
<td>2.8 ± 1.2</td>
<td>2.7 ± 1.1</td>
<td>0.944</td>
</tr>
<tr>
<td>CHA2DS2-VASc ‡</td>
<td>Mean (SD)</td>
<td>4.3 ± 1.4</td>
<td>4.7 ± 1.0</td>
<td>0.331</td>
</tr>
<tr>
<td>Risk factors for stroke —no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke</td>
<td>5 (20)</td>
<td>4 (15)</td>
<td>9 (18)</td>
<td>0.726</td>
</tr>
<tr>
<td>Prior transient ischemic attack</td>
<td>4 (16)</td>
<td>2 (8)</td>
<td>6 (12)</td>
<td>0.418</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>2 (8)</td>
<td>5 (19)</td>
<td>7 (14)</td>
<td>0.418</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (36)</td>
<td>7 (27)</td>
<td>16 (31)</td>
<td>0.555</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>6 (24)</td>
<td>1 (4)</td>
<td>7 (14)</td>
<td>0.049</td>
</tr>
<tr>
<td>Sinus node disease, with or without atrioventricular node disease —no. (%)</td>
<td>11 (44)</td>
<td>12 (46)</td>
<td>23 (45)</td>
<td>1.000</td>
</tr>
<tr>
<td>Aspirin —no. (%)</td>
<td>13 (52)</td>
<td>15 (58)</td>
<td>28 (55)</td>
<td>0.781</td>
</tr>
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<td>Clinical event type —no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>21 (84)</td>
<td>25 (96)</td>
<td>46 (90)</td>
<td>0.190</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>4 (16)</td>
<td>1 (4)</td>
<td>5 (10)</td>
<td>0.190</td>
</tr>
<tr>
<td>Time from device implantation to primary outcome —days</td>
<td>Mean (SD)</td>
<td>580 ± 357</td>
<td>703 ± 394</td>
<td>643 ± 377</td>
</tr>
<tr>
<td>Time from primary outcome to last follow up —days</td>
<td>Mean (SD)</td>
<td>570 (263-816)</td>
<td>670 (456-900)</td>
<td>612 (293-890)</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± SD
† The CHADS2 score is used to estimate the risk of stroke in AF. The score is derived from the sum of point values of individual stroke risk factors (congestive heart failure, hypertension, age ≥ 75, diabetes (1 point each), and prior stroke or transient ischemic attack (2 points)) \(^{19,20}\)
‡ CHA2DS2-VASc score was developed to refine risk stratification for predicting stroke in AF. Major improvements were assigning 2 points to previous stroke or transient ischemic attack, and age ≥75 years and 1 point to congestive heart failure, hypertension, diabetes mellitus, vascular disease, female gender, and age 65–74 years \(^{21}\)
Figure Legends:

Figure 1. Study flow chart. SCAF= subclinical atrial fibrillation.

Figure 2. A. Summary of SCAF occurring within one year of stroke or systemic embolism. Each row represents data collected from each of 18 patients who had SCAF occurred within one year before and/or after the event. There are 8 patients with SCAF and either stroke or systemic embolism who are not shown on this graph: 7 who had SCAF more than 1 year prior to their event and 1 who had SCAF more than 1 year after their event. Total hours of atrial episodes per day are denoted by the height of each red vertical line. Gray shaded areas correspond to the period of continuous monitoring with cardiac device. Stars (*) and black dashed line denote use and period of oral anticoagulation therapy. SCAF= subclinical atrial fibrillation. B. Summary of SCAF events occurring within 30 days prior to stroke or systemic embolism. Each row represents data collected from each of 4 patients who had the last SCAF occurred within 30 days prior to the event. Total hours of atrial episodes per day are denoted by the height of each red vertical line. Gray shaded areas correspond to the period of continuous monitoring with cardiac device. Stars (*) and black dashed lines denote use and period of oral anticoagulation therapy. SCAF= subclinical atrial fibrillation. C. Summary of SCAF events occurring only after the stroke or systemic embolism. Each row represents data collected from each of 7 patients who had SCAF within one year after the event. Total hours of atrial episodes per day are denoted by the height of each red vertical line. Gray shaded areas correspond to the period of continuous monitoring with cardiac device. SCAF= subclinical atrial fibrillation.
Figure 1
Figure 2C
Temporal Relationship between Subclinical Atrial Fibrillation and Embolic Events
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