

Temporal Relationship Between Subclinical Atrial Fibrillation and Embolic Events

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

Methods and Results—The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) enrolled 2580 pacemaker and defibrillator patients aged ≥ 65 years with a history of hypertension but without a history of atrial fibrillation. Pacemakers and implantable cardioverter-defibrillators precisely logged the time and duration of all episodes of SCAF and recorded electrograms that 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 before stroke or systemic embolism. However, only 4 patients (8%) had SCAF detected within 30 days before stroke or systemic embolism, and only 1 of these 4 patients was experiencing SCAF at the time of the stroke. In the 14 patients with SCAF detected >30 days before stroke or systemic embolism, the most recent episode occurred at a median interval of 339 days (25th to 75th percentile, 211–619) earlier. Eight patients (16%) had SCAF detected only after their stroke, despite continuous monitoring for a median duration of 228 days (25th to 75th percentile, 202–719) before their event.

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

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Key Words: arrhythmia ■ pacemaker ■ stroke

Atrial fibrillation (AF) is a common arrhythmia and a well-known risk factor for ischemic stroke and systemic embolism.^{1,2} With the development of continuous long-term monitoring, it is now apparent that many patients have evidence of AF without recognizable symptoms.^{3–8} We have termed this phenomenon *subclinical atrial fibrillation* (SCAF). SCAF is often recognized after stroke has occurred with the use of intensive ECG monitoring.^{3–7} Implanted dual-chamber pacemakers and implantable cardioverter-defibrillators represent the most sensitive means for SCAF detection because they can continuously monitor cardiac rhythm for many years, precisely characterizing the time and duration of AF and storing intracardiac electrograms.^{8–10} The Asymptomatic Atrial Fibrillation and Stroke

Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) demonstrated that over 2.5 years, SCAF of ≥ 6 minutes' duration is observed in $>40\%$ of pacemaker patients without a prior history of AF but leads to clinical, ECG-documented AF in $<15\%$ of cases.⁸

Clinical Perspective on p 2099

We reported recently that SCAF is associated with a 2.5-fold increased risk of stroke or systemic embolism.⁸ However, the relationship between SCAF and embolism is not clearly understood, although several interpretations are possible. One possible interpretation is that SCAF may be associated with thromboembolic events without any causality or that SCAF may be directly causing stroke. In the latter scenario, stasis due

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to low flow in the fibrillating atrial appendage may increase the risk of stroke or systemic embolism very shortly after the onset of SCAF.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.^{12–16} Finally, SCAF may simply be a marker of risk and may not be 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.¹⁷ Among the 20 patients with AF before their embolic event, only 30% had AF within the month before their embolic event, and the most recent episode of AF was an average of 166 ± 189 days before.¹⁷ However, this population is very different than that of ASSERT⁸ because nearly half of the patients in the TRENDS analysis had a history of clinical AF before study enrollment.¹⁷ The present analysis from the ASSERT study 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 AF.⁸

Methods

The design and main results of ASSERT have been published previously.^{8,18} The study enrolled 2580 patients, aged ≥ 65 years, with a history of hypertension who underwent initial implantation of a St Jude Medical (St Paul, MN) dual-chamber pacemaker or implantable cardioverter-defibrillator. Patients were excluded if they had a history of clinical AF or atrial flutter lasting >5 minutes or if they required oral anticoagulant therapy for any reason. The study was approved by an institutional review committee at each participating center, and all patients provided written informed consent. After implantation, devices were programmed according to study protocol¹⁸ with high atrial sensitivity (0.1–0.5 mV). There was central adjudication of all available device electrograms showing SCAF (atrial rate >190 bpm 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 present analysis, stored device data including the date, time of onset, and 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.^{19–21} The clinical outcome of interest was ischemic stroke or systemic embolism. To ensure a minimum of 3 months of continuous monitoring before any systemic embolism and to maintain consistency with the methodology of the main ASSERT study,⁸ only embolic events occurring >3 months after study enrollment were examined.

Statistical Analysis

The normality of continuous variables was assessed graphically, given the small number of patients in this report. Data are presented as mean and SD or median and percentiles (25th to 75th), as appropriate, with the comparison between groups performed with the *t* test or Wilcoxon rank-sum test, respectively. Categorical variables are summarized with the use of counts and proportions, with groups compared with the Fisher exact test.

Results

A total of 59 patients experienced ischemic stroke or systemic embolism during the ASSERT study. Of the 51 patients who experienced these events after the 3-month visit, 26 patients

(51%) had SCAF either before or after the embolic event (Figure 1). The median CHA₂DS₂-VASc scores were 5 (25th to 75th percentile, 4–5) in the group with SCAF and 5 (25th to 75th percentile, 3–5) in the group without SCAF (Table). Aspirin was used by 57.7% and 52% of patients, respectively, and no patients were receiving oral anticoagulation at baseline (Table). The median duration of continuous device monitoring before embolic events was >1.7 years (25th to 75th percentile, 0.8–2.4 years) (Table).

In 18 patients (35%), SCAF was detected before the stroke or systemic embolism; however, in only 4 patients (8%) was SCAF detected within 30 days before such an event (Figure 1). Only 1 patient experienced a continuous episode of SCAF at the time of stroke, which lasted a total of 2.7 hours. In the remaining 14 patients (27%), who had SCAF detected >30 days before their embolic event, the most recent episode of SCAF occurred at a median interval of 339 days (25th to 75th percentile, 211–619 days) before, and the median duration of the most recent episode of SCAF was 4.2 hours (25th to 75th percentile, 0.80–466 hours). Over the entire follow-up, 10 of 18 patients with SCAF before an embolic event (55%) had an episode of SCAF lasting >24 hours before their event. However, only 1 patient had such an episode within 30 days before stroke or embolism, and AF was clinically diagnosed in only 1 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 (25th to 75th percentile, 14–196 days) later. This was despite continuous monitoring for a median duration of 228.5 days (25th to 75th percentile, 202–719 days) before their stroke. Among these patients, the median maximum duration of SCAF on a single day was 6.3 hours (25th to 75th percentile, 1.9–10.3 hours), and none of these patients developed SCAF of >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 1 year before or after their embolic event is presented in Figure 2. Of the remaining 8 patients (of 26 with both SCAF and embolic events), 1 had a first episode of SCAF >1 year after the embolic event, and 7 patients had SCAF detected >1 year before the stroke or embolism, without further episodes during the interval.

SCAF Occurring Within 30 Days Before 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 his ischemic stroke 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 lasting >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 >24 hours detected ≈ 11 months earlier.

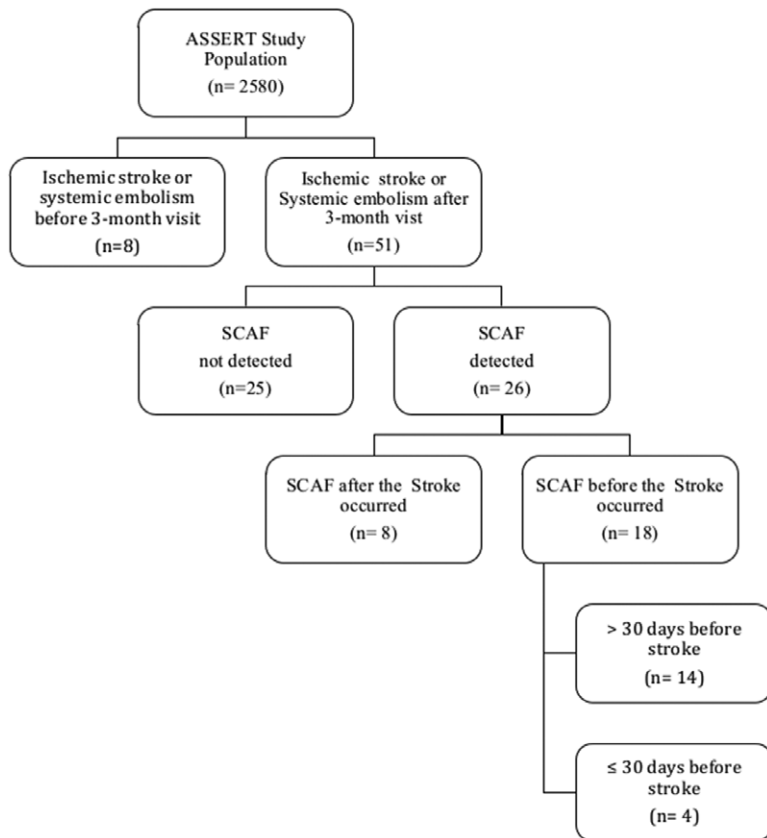


Figure 1. Study flow chart. ASSERT indicates Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; and SCAF, subclinical atrial fibrillation.

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 after 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 international normalized ratio control. In the remaining 2 patients, oral anticoagulation was introduced only after the embolic event occurred.

Discussion

The ASSERT study demonstrated that SCAF is common in elderly patients with either pacemakers or implantable cardioverter-defibrillators and a history of hypertension and was associated with a 2.5-fold increase in the risk of embolic events.⁸ 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 before their stroke or systemic embolism. Furthermore, most SCAF occurring before 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 before cardioversion.^{22,23} Finally, this analysis shows that, in most cases, patients with 6-minute 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 (ie, 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 electric and pharmacological cardioversion of AF, echocardiographic studies have shown that mechanical atrial contraction may not resume for hours to days after electric cardioversion from AF to sinus rhythm.²⁶ This might explain a delay between AF and a presumed cardioembolism. However, it is unclear whether a similar process is plausible in the case of SCAF because evidence suggests that this electromechanical delay is more common for longer-lasting episodes of persistent AF.²⁷ As well, the majority of patients with SCAF-associated systemic embolism in ASSERT had their embolic event >1 month after the most recent episode of SCAF, far longer than the typical duration of atrial mechanical stunning after cardioversion.²³

Table. Baseline Characteristics of Patients Who Had a Stroke or Embolism in ASSERT

Characteristics		SCAF Not Detected (n=25)	SCAF Detected (n=26)	Overall (n=51)	P Value
Male sex, No. (%)		20 (80)	8 (31)	28 (55)	<0.001
Age, y	Mean±SD	75.4±6.7	80.3±7.1	77.9±7.3	0.015
Body mass index, kg/m ²	Mean±SD	26.8±3.3	25.8±5.7	26.3±4.6	0.451
Systolic blood pressure, mm Hg	Mean±SD	136±22.6	144±20.4	140±21.7	0.161
CHADS ₂ score*	Mean±SD	2.8±1.2	2.7±1.1	2.8±1.1	0.944
	Median (P25–P75)	2 (2–4)	2 (2–4)	2 (2–4)	
CHA ₂ DS ₂ -VASc score†	Mean±SD	4.3±1.4	4.7±1.0	4.5±1.2	0.331
	Median (P25–P75)	5 (3–5)	5 (4–5)	5 (4–5)	
Risk factors for stroke, No. (%)					
Prior stroke		5 (20)	4 (15)	9 (18)	0.726
Prior transient ischemic attack		4 (16)	2 (8)	6 (12)	0.418
History of heart failure		2 (8)	5 (19)	7 (14)	0.418
Diabetes mellitus		9 (36)	7 (27)	16 (31)	0.555
Prior myocardial infarction		6 (24)	1 (4)	7 (14)	0.049
Sinus node disease, with or without atrioventricular node disease, No. (%)		11 (44)	12 (46)	23 (45)	1.000
Aspirin, No. (%)		13 (52)	15 (58)	28 (55)	0.781
Clinical event type, No. (%)					
Ischemic stroke		21 (84)	25 (96)	46 (90)	0.190
Systemic embolism		4 (16)	1 (4)	5 (10)	0.190
Time from device implantation to primary outcome, d	Mean±SD	580±357	703±394	643±377	0.270
	Median (P25–P75)	570 (263–816)	670 (456–900)	612 (293–890)	
Time from primary outcome to last follow-up, d	Mean±SD	477±399	452±480	464±438	0.565
	Median (P25–P75)	404 (93–866)	350 (41–731)	398 (71–825)	

ASSERT indicates Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; P25–P75, 25th to 75th percentile; and SCAF, subclinical atrial fibrillation.

*The CHADS₂ score is used to estimate the risk of stroke in atrial fibrillation. The score is derived from the sum of point values of individual stroke risk factors (congestive heart failure, hypertension, age ≥75 y, diabetes mellitus [1 point each], and prior stroke or transient ischemic attack [2 points]).^{19,20}

†The CHA₂DS₂-VASc score was developed to refine risk stratification for predicting stroke in atrial fibrillation. Major improvements were assigning 2 points to previous stroke or transient ischemic attack and age ≥75 y and 1 point to congestive heart failure, hypertension, diabetes mellitus, vascular disease, female sex, and age 65–74 y.²¹

The second possible explanation is that SCAF itself does not cause embolism but rather is a marker of cardioembolic risk. There is abundant evidence that AF causes changes in atrial structure and endothelial function.¹² AF is also associated with biochemical evidence of inflammation,¹³ markers of hypercoagulability,^{14,15} and evidence of left atrial spontaneous echo contrast.¹⁶ Thus, the occurrence of even brief episodes of SCAF may trigger chronic changes in the atria that lead to thrombus formation sometime after the actual occurrence of SCAF. Finally, it is possible that the association between SCAF and stroke seen in ASSERT⁸ was simply due to chance, given the relatively small number of events observed.

Although ASSERT demonstrated an association between SCAF and embolic events,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, and therefore many investigators are suggesting that randomized trials are needed.^{8,28,29} Some clinicians appear to agree because recent surveys suggest that oral anticoagulation is typically not prescribed to patients with isolated SCAF.^{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.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 >1 year of negative monitoring before 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 before their AF-associated embolism¹⁷; 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 the higher (50%) proportion of patients with SCAF before their embolic event and the higher (15%) proportion of patients with a continuous episode of AF at the time of their embolic event.¹⁷ The ASSERT study excluded all patients

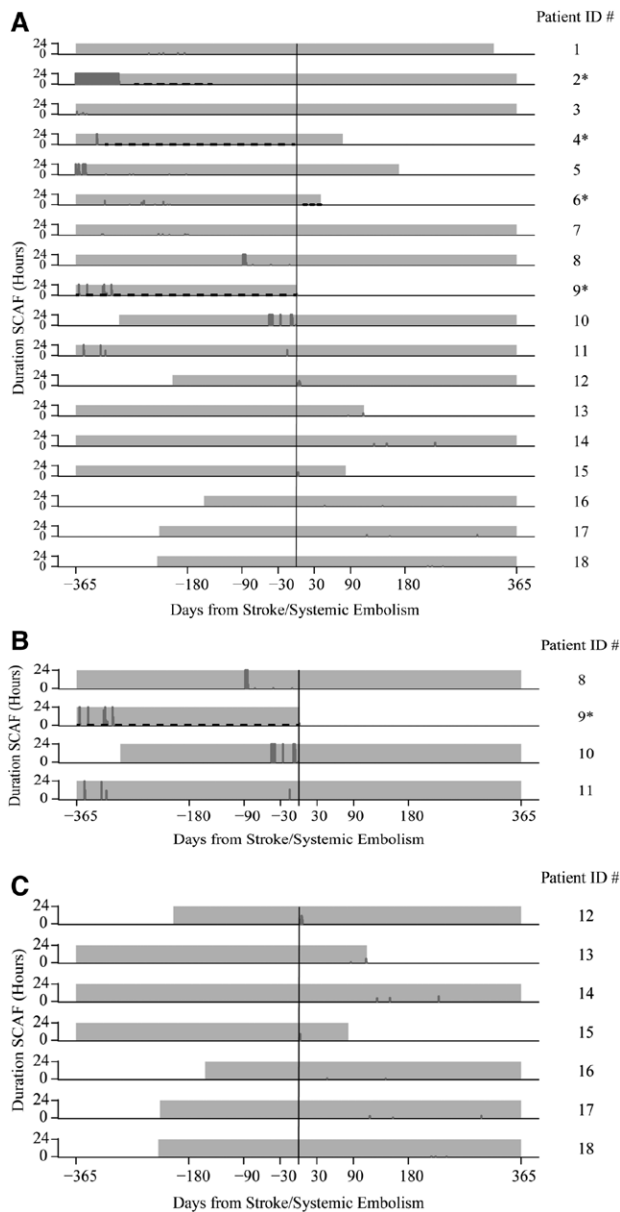


Figure 2. A, Summary of subclinical atrial fibrillation (SCAF) occurring within 1 year of stroke or systemic embolism. Each row represents data collected from each of 18 patients who had SCAF within 1 year before or after the event. Eight patients with SCAF and either stroke or systemic embolism are not shown on this graph: 7 who had SCAF >1 year before the event and 1 who had SCAF >1 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. Asterisks and black dashed lines denote use and period of oral anticoagulation therapy. ID indicates identification. B, Summary of SCAF events occurring within 30 days before stroke or systemic embolism. Each row represents data collected from each of 4 patients who had the last SCAF within 30 days before 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. Asterisks and black dashed lines denote use and period of oral anticoagulation therapy. 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 1 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.

with a prior history of AF,¹⁸ 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,¹⁷ and therefore it is unclear whether 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, because none of the pacemakers and defibrillators used in ASSERT were magnetic resonance imaging conditional, we were not able to subclassify ischemic strokes. Finally, we were not able to adjudicate all episodes of SCAF of <6 minutes in duration, limiting our ability to comment on the association between 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 before 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 that is more complex than previously appreciated.

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Disclosures

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CLINICAL PERSPECTIVE

This analysis from the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) provides important new insights into the mechanism of stroke in pacemaker and implantable cardioverter-defibrillator patients with subclinical atrial fibrillation (SCAF) and helps to guide our clinical management of atrial fibrillation. Our analysis is consistent with that of other groups because it fails to show a temporal relationship between SCAF and stroke in the majority of patients. Thus, SCAF may simply be a risk marker for stroke. If it is causal, then the relationship between SCAF and stroke is far more complex than the conventional paradigm of long-lasting atrial fibrillation leading to atrial stasis and clot formation after 24 to 48 hours with the risk of stroke increasing shortly thereafter. These findings raise questions regarding the clinical practice of performing cardioversion of atrial fibrillation without anticoagulation. In ASSERT, most cases of SCAF occurring before stroke were asymptomatic and far shorter than 48 hours, calling into question that a minimum duration is required for stroke risk to increase. As well, our findings have implications for patients with cryptogenic stroke and the interpretation of the recent Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL-AF) trial. Thirty percent of ASSERT patients with SCAF and ischemic stroke or systemic embolism had SCAF detected only after their stroke or embolism, with >1 year of negative monitoring before their stroke or embolism. Thus, the assumption that atrial fibrillation detected after cryptogenic stroke is the cause of the embolic event may not always be correct, although from a practical perspective, the use of oral anticoagulation would still be indicated in most cases.