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Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT

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Background ASSERT demonstrated that subclinical atrial fibrillation (SCAF) is common in pacemaker patients without prior AF and is associated with increased risk of ischemic stroke or systemic embolism. SCAF episodes vary in duration and little is known about the incidence of different durations of SCAF, or their prognosis.

Methods and results ASSERT followed 2580 patients receiving a pacemaker or ICD, aged >65 years with hypertension, without prior AF. The effect of SCAF duration on subsequent risk of ischemic stroke or embolism was evaluated with time-dependent covariate Cox models. Patients in whom the longest SCAF was ≤6 min were excluded from the analysis (n=125). Among 2455 patients during mean follow-up of 2.5 years, the longest single episode of SCAF lasted >6 min to 6 h in 462 patients (18.8%), >6–24 h in 169 (6.9%), and >24 h in 262 (10.7%). SCAF duration >24 h was associated with a significant increased risk of subsequent stroke or systemic embolism (adjusted hazard ratio [HR] 3.24, 95% confidence interval [CI] 1.51–6.95, P=0.003). The risk of ischemic stroke or systemic embolism in patients with SCAF between 6 min and 24 h was not significantly different from patients without SCAF.

Conclusions SCAF >24 h is associated with an increased risk of ischemic stroke or systemic embolism.

Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke, heart failure, and mortality.[1,2] AF often manifests as a progressive disease defined as paroxysmal, self-terminating AF proceeding into persistent and finally permanent AF.[3–14] Recent data suggest that duration of clinical AF may be important prognostically; e.g. it has been reported that permanent AF is independently associated with increased risk of stroke compared with paroxysmal AF.[15–17]

There are now data linking *subclinical AF* (SCAF), detected by long-term continuous monitoring with pacemakers, and the risk of stroke and systemic embolism.[18–20] The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) study included older patients with a pacemaker or internal cardioverter defibrillator (ICD) *without* prior documented AF.[21,22] The pre-specified study outcome of the ASSERT, SCAF >6 min, was independently associated with a 2.5-fold increase in the risk of ischemic stroke and systemic embolism. An exploratory analysis of a similar study, TRENDS, suggested that an AF burden lasting more than 5.5 h was associated with double risk on embolic events.[19] However, the absolute risk of stroke in patients with SCAF in the ASSERT trial was only 1.7% per year, a rate that appears lower than usually reported in patients with clinical AF.[15,23]

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In the present analysis, we assess the incidence of different durations of SCAF and we aimed to determine whether longer durations of SCAF episodes were associated with a higher risk of ischemic stroke and systemic embolism, comparable to the rate reported in clinical AF.

Methods

The methods of the ASSERT trial have been previously published.[21,22] The ASSERT trial enrolled 2580 patients receiving a dual-chamber pacemaker or ICD, who were >65 years and had a history of hypertension, but no prior AF. All patients were programmed to dual-chamber pacing with atrio-ventricular delay programming optimized to reduce ventricular pacing frequency. Patients were followed for a mean of 2.5 years for the development of clinical AF, ischemic stroke or systemic embolism. All episodes of pacemaker-detected atrial tachyarrhythmias >6 min were documented and sent for independent adjudication by an expert committee. In the main ASSERT trial, pacemaker-detected SCAF lasting >6 min with an atrial rate of >190/min was prospectively defined as the threshold for significance.[22]

In the present analysis, we defined four mutually exclusive categories with no overlapping durations of episodes of SCAF: (1) no SCAF; (2) SCAF with duration >6 min–6 h; (3) SCAF between >6 h and 24 h, and (4) SCAF >24 h. These cut-offs were defined prior to the analysis, based on the categories into which the St. Jude pacemakers and defibrillators in the ASSERT trial sort SCAF.

Because duration of SCAF episodes could change over time, we introduced time-dependent covariates to assess the influence of SCAF duration on the study outcome. Patients with the longest SCAF ≤6 min were excluded from the present main analysis (n=125). The novelty of this study is that we now constructed one single time-dependent model using all patients and categorizing each SCAF episode into mutually exclusive groups according to the duration. In addition, we also (1) explored the short-term effect of SCAF (30 days window) and (2) reduced the bias in estimating SCAF effect by adjusting for potential baseline confounding factors. Furthermore, the association between SCAF duration and clinical outcome was further explored by conditional landmark analysis (see later).

Study outcomes

As in the main ASSERT trial, the primary outcome was ischemic stroke or systemic embolism. Strokes were adjudicated by a committee of experts. Ischemic stroke was defined as sudden onset of a focal deficit consistent with occlusion of a major cerebral artery (documented by means of imaging) and categorized as ischemic. Signs or symptoms must last >24 h, unless supported by clear evidence of cerebral infarction on diffusion-weighted MRI imaging. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ as documented with the use of imaging, surgery, or autopsy.

Statistical analysis

Patients were classified into 4 groups in baseline characteristics according to the longest duration of SCAF during follow-up as mentioned above. Continuous variables were reported as means/standard deviation and categorical variables as frequency/percentage.

The cumulative incidence of SCAF of different durations was illustrated using standard Kaplan–Meier method. Considering time-varying nature of SCAF episodes, we created a time-dependent covariate to track the change of duration of SCAF episodes over time for every patient. Each SCAF episode was classified into one of three categories based on its duration (>6min–6h, >6–24h, >24h). The time-dependent covariate was constructed through two different approaches: (1) Long-term effect (primary analysis): at onset of study all patients were considered as 'no SCAF'. When encountering the first episode, patient would be reclassified to the corresponding category and remain the status until end of follow-up unless a subsequent episode with longer duration was detected, in which case, SCAF status would be 'up-classified' to the new category. The time-dependent covariate took the most current duration at time of the first clinical event or end of follow-up. (2) Short-term effect (secondary analysis): similar to the first method, but the effect of SCAF on stroke was restricted to 30 days after each SCAF episode. At the end of 30-day period, SCAF status was switched back to 'no SCAF'. The effects of SCAF duration on risk of clinical outcomes were thereafter analyzed by time-dependent Cox proportional hazards model with 'no SCAF' as reference group, adjusting for baseline risk factors: age, sex, body mass index, heart failure, prior stroke or transient ischemic attack, diabetes, peripheral artery disease, and sinus node disease. Proportional hazards assumption of adjusted covariates and linearity of continuous variables were examined using Kolmogorov-type supremum test and restricted cubic spline plot respectively. No evidence of violation was detected. The risk of stroke and systemic embolism was compared in a pairwise manner among SCAF categories using Wald test of parameter estimates in a time-dependent Cox model. Two sensitivity analyses were conducted for primary Cox model: (1) oral anticoagulation use during follow-up period was entered into the model as a time-varying confounder; (2) 125 patients with longest SCAF duration<6min were treated as 'no SCAF' and included in Cox regression analysis.

An extended Kaplan–Meier approach, developed by Snapinn et al. 2005,[24] was implemented to plot hazard curves according to time-dependent SCAF durations. To further explore the association between SCAF duration and risk of clinical outcome, we performed a conditional landmark analysis,[25] where landmark time was set at time of 12-month visit. SCAF status of each patient was determined by the longest SCAF episode between enrollment and landmark time. Survival time was defined as the time from landmark time to either the first clinical outcome or end of study. Patients who ended follow-up prior to 12-month visit were excluded from the analysis. All P-values reported in this study were two-sided with significance at P<0.05. Statistical analyses were conducted with the use of SAS 9.2 software (SAS Institute, Inc., Cary, NC, USA).

Results

Incidence of different durations of SCAF during follow up

The primary analysis included 2455 patients. During a mean follow-up of 2.5 years, 462 (18.8%) patients developed SCAF, with the longest single episode lasting >6 min–6 h, 169 (6.9%), with SCAF lasting from >6 to 24 h, and 262 (10.7%) with SCAF >24 h. The other 1562 patients did not develop SCAF (*Table 1*). The Kaplan–Meier estimates of the cumulative incidence of the first episode of SCAF >6 min, SCAF >6 h and >24 h is depicted in *Figure 1*. At year 3, the cumulative incidence for SCAF >6 min is 39%, >6 h 19%, and >24 h 11%. There were 27 of

Table 1 Baseline characteristics according to the longest duration of SCAF

	No SCAF (*N*=1562)	SCAF >6 min–6 h (*N*=462)	SCAF >6 h—24 h (*N*=169)	SCAF >24 h (*N*=262)
Age (years), mean ± SD	76.0 ± 6.7	76.9 ± 6.5	76.2 ± 6.9	77.2 ± 7.0
Male, *n* (%)	887 (56.8)	254 (55.0)	104 (61.5)	183 (69.8)
Systolic blood pressure (sitting, mmHg), mean ± SD	137.8 ± 19.4	139.0 ± 19.5	139.5 ± 19.8	136.3 ± 19.1
Heart rate (bpm), mean ± SD	70.0 ± 11.7	70.1 ± 12.0	68.7 ± 10.3	67.7 ± 11.2
BMI (kg/m^2), mean ± SD	27.3 ± 4.8	27.5 ± 4.9	27.4 ± 5.2	28.3 ± 5.0
Prior stroke, *n* (%)	116 (7.4)	30 (6.5)	15 (8.9)	16 (6.1)
Prior TIA, *n* (%)	77 (4.9)	21 (4.5)	9 (5.3)	13 (5.0)
History heart failure, *n* (%)	222 (14.2)	70 (15.2)	27 (16.0)	43 (16.4)
Diabetes mellitus, *n* (%)	470 (30.1)	110 (23.8)	48 (28.4)	77 (29.4)
Prior MI, *n* (%)	300 (19.2)	68 (14.7)	30 (17.8)	48 (18.3)
$CHADS_2$ score, mean ± SD	2.3 ± 1.0	2.2 ± 1.0	2.3 ± 1.0	2.3 ± 1.0
CHA_2DS_2-VASc score, mean ± SD	4.0 ± 1.3	3.9 ± 1.3	4.0 ± 1.4	4.0 ± 1.2
Sinus node disease with or without atrioventricular-node disease, *n* (%)	668 (42.8)	194 (42.0)	74 (43.8)	120 (45.8)
Atrioventricular node disease without sinus-node disease, *n* (%)	776 (49.7)	240 (51.9)	87 (51.5)	129 (49.2)
Atrial lead septal position, *n* (%)	66 (4.2)	25 (5.4)	3 (1.8)	10 (3.8)
Duration hypertension >10 years, *n* (%)	629 (40.3)	208 (45.0)	72 (42.6)	119 (45.4)
Aspirin, *n* (%)	987 (63.2)	267 (57.8)	102 (60.4)	168 (64.1)
Beta-blocker, n (%)	599 (38.3)	138 (29.9)	67 (39.6)	104 (39.7)
Statin, n (%)	773 (49.5)	200 (43.3)	87 (51.5)	124 (47.3)

BMI, body mass index; MI, myocardial infarction; TIA, transient ischemic attack.

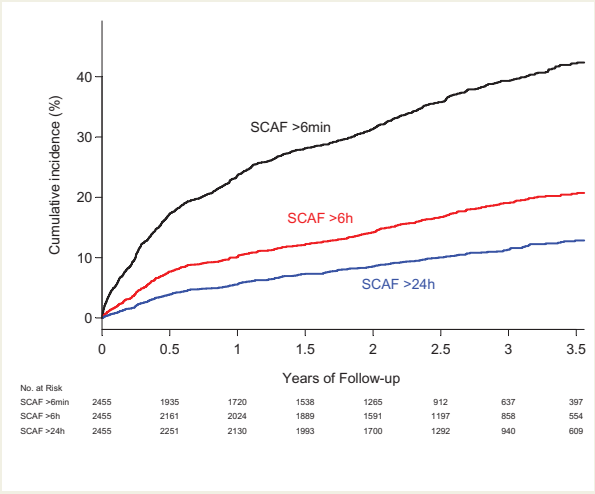


Figure 1 Kaplan–Meier estimates of cumulative incidence of SCAF >6 min, >6 h, and >24 h.

310 (8.7%) patients with SCAF lasting >6 min–6 h during the first year who developed an episode lasting >24 h and 33 of 105 patients (31%) patients with SCAF >6–24 h who developed SCAF >24 h (*Table 2*).

Association between SCAF duration and clinical outcomes

Time-dependent Cox regression analysis was used to assess the effect of duration of SCAF on the primary outcome. In the primary analysis, SCAF duration was considered to have a long-term effect on risk of the primary outcome. Patient follow up occurring after occurrence of SCAF >24 h was associated with an increased risk of the primary outcome compared to patient follow up time without (or prior to) any SCAF (adjusted HR 3.24, 95% CI 1.51–6.95, *P*=0.003, *Table 3 [Panel A]*, *Summarizing Figure*, *Figure 2*). Patient follow up occurring after SCAF >6min–6h and >6–24h was not associated with increased risk of the primary outcome compared to patients follow up time without any SCAF. A comparison between SCAF groups showed a significant higher risk of the primary outcome associated with SCAF >24 h compared to SCAF >6 min–6 h (*P*-value=0.009).

Two sensitivity analyses, one by adjusting OAC use and the other including 125 patients with a longest SCAF duration <6 min yielded similar results (see Supplementary material online, *Tables SA and SB*).

Table 2 Number of patients in respective groups developing SCAF >24 h after first year of follow-up

AF duration within 1st year	No. of patients	No. of patients with >24 h SCAF after 1 year	Percentage
No SCAF	1811	67	3.70
>6 min–6 h	310	27	8.71
>6 h–24 h	105	33	31.43
>24 h	129	71	55.04

Table 3 Time-dependent Cox regression analysis of AF duration on risk of ischemic stroke/systemic embolism with long-term effect (panel A) and short-term effect (panel B)

SCAF duration	Unadjusted		Adjusted[a]	
	Hazard ratio[b] (95% CI)	*P*-value	Hazard ratio[b](95% CI)	*P*-value
Panel A				
No SCAF	1	–	1	–
>6 min–6 h	0.93 (0.39–2.25)	0.880	0.75 (0.29–1.96)	0.562
>6 h—24 h	1.39 (0.42–4.57)	0.585	1.32 (0.40–4.37)	0.646
>24 h	3.86 (1.91–7.78)	<0.001	3.24 (1.51–6.95)	0.003
Panel B				
No SCAF	1	–	1	–
>6 min–6 h	0.78 (0.11–5.62)	0.802	0.83 (0.11–6.01)	0.851
>6–24 h	2.43 (0.34–17.65)	0.379	2.54 (0.35–18.55)	0.357
>24 h	5.60 (1.74–18.01)	0.004	3.86 (0.93–15.98)	0.063

[a]Adjusted for age, sex, BMI, heart failure, prior stroke/transient ischemic attack, diabetes, sinus node disease, peripheral/coronary artery disease.
[b]Reference group are patients with no SCAF.

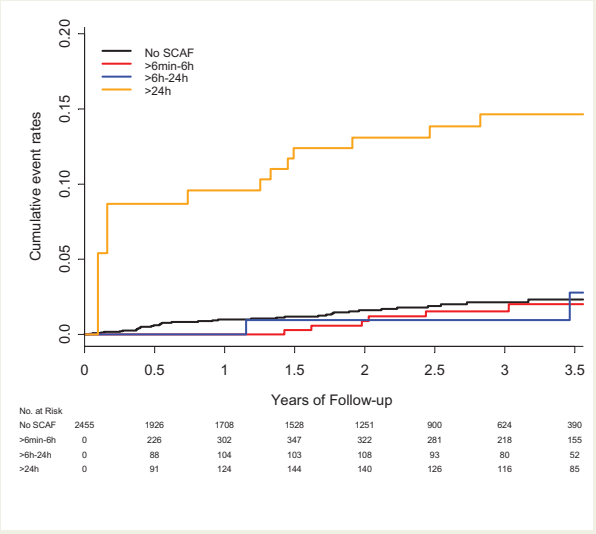


Figure 2 Extended Kaplan–Meier curves of ischemic stroke/systemic embolism stratified by time-dependent durations of SCAF with long-term effect.

The time-dependent analysis of SCAF with effect duration ≤30 days showed that the association between SCAF >24 h and stroke was qualitatively similar but no longer significant (*Table 3 [Panel B]*).

A conditional landmark analysis in which 100 patients with <1 year follow-up were excluded assessed the relationship between duration of SCAF occurring between baseline and the 12-month visit, and the risk of the primary outcome subsequent to the 12-month visit. The 129 patients who developed SCAF >24h showed a significantly higher risk of subsequent stroke or systemic embolism compared with those not experiencing SCAF in the first year (3.1 vs. 0.5%/year, adjusted HR 5.37, 95% CI 2.08–13.87, *P*<0.001, *Table 4*). Other durations of SCAF were not associated with an increased risk.

Discussion

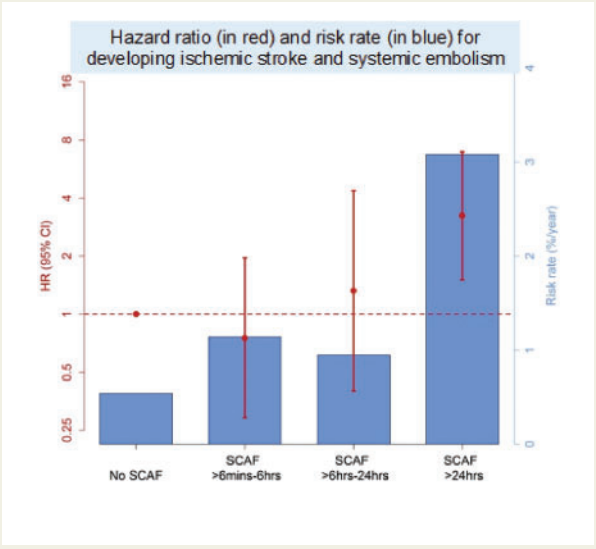
This analysis extends data of ASSERT with several new findings. First, we now report data on incidence of different durations of SCAF. During a follow-up of 2.5 years longest episodes of SCAF lasting >6–24 h occurred in 7% of patients and episodes lasting >24 h in 11% of patients. Further, and most importantly, we now show that patients with SCAF >24 h had a significantly higher subsequent risk of ischemic stroke or systemic embolism (absolute risk 3.1% per year, comparable to the risk of clinical AF) as compared to patients with no SCAF, while the risk of stroke and systemic embolism in patients with SCAF of shorter duration was not significantly different from patients without SCAF.

Clinical AF is associated with an increased stroke risk and other vascular events like myocardial infarction and heart failure. A recent analysis showed that baseline AF was associated with a 31% higher risk of any vascular event (HR 1.31, 95% CI 1.28-1.34) and a 89% higher risk of a fatal vascular event.[26] Several studies have reported an increased risk of embolic events with device-detected atrial arrhythmias.[18–20] A retrospective analysis of 312 patients from the MOde Selection Trial showed that the risk of death or stroke was increased by a factor of 2.5 in patients who had at least one episode of high atrial rate lasting >5 min.[18] An exploratory analysis of data on 2480 patients with a pacemaker or ICD suggested that the risk of thromboembolic complications was a quantitative function of AF burden. An AF burden >5.5 h in a 30-day window was associated with double the risk of embolic events.[19] Capucci *et al.* showed in 725 patients with a pacemaker and a history of symptomatic AF that device detected AF > 24 h in addition to stroke risk factors was independently associated with embolic events.[27] Botto *et al.* reported in 586 patients with a pacemaker and a history of AF being monitored for 1 year that AF duration in addition to the $CHADS_2$ score improved risk prediction for thromboembolic events.[20] The ASSERT trial was the only study that included patients *without* prior clinically documented AF and with blinded adjudication for the device electrograms and events.[21,22] The main study outcome showed that the prespecified finding of SCAF >6 min was associated with an increase of the risk of ischemic stroke and peripheral embolism by a factor of

Table 4 Landmark analysis showing ischemic stroke/systemic embolism occurring after 1 year follow-up, according to SCAF durations between enrollment and 1 year follow-up[a]

SCAF duration	Number events/patients	Event rate (%/year)	Unadjusted		Adjusted[b]	
			Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
No SCAF	19/1811	0.54	1	–	1	–
>6 min–6 h	7/310	1.14	2.11 (0.89–5.02)	0.091	1.75 (0.69–4.44)	0.242
>6–24 h	2/105	0.95	1.79 (0.42–7.69)	0.433	1.85 (0.43–8.01)	0.413
>24 h	7/129	3.08	5.73 (2.41–13.64)	<0.001	5.37 (2.08–13.87)	<0.001

[a]Only patients with minimum follow up of 1 year included.
[b]Adjusted for age, sex, BMI, heart failure, prior stroke/transient ischemic attack, diabetes, sinus node disease, peripheral/coronary artery disease.



Summarizing Figure SCAF >24 h is associated with comparable risk of ischemic stroke and systemic embolism as clinical AF. In this figure the hazard ratio from time dependent Cox model (long term effect, red) and the risk rate from the landmark analysis (blue) of ischemic stroke and systemic embolism are depicted.

2.5.[22] In the main ASSERT manuscript stratification of patients with SCAF in quartiles revealed that patients with SCAF in the highest quartile (>17.72 h) had significantly higher stroke rates as compared to those with shorter episodes of SCAF. Our present analysis, however, is much more detailed and strong.

The role of AF duration on stroke risk, however, is controversial.[18–20,28] Several studies have reported that persistent and permanent AF patients have higher stroke rates as compared with paroxysmal AF.[6,7,10,12] However, it is not possible to be sure that this is causal and not due to confounders as patients with shorter forms of AF tend to have fewer other risk factors. SCAF, however, differs from clinical AF in being often of short duration and often being asymptomatic. In the trials on the beneficial effects of anticoagulation in patients with AF only a few patients with SCAF have been included. At present no data from randomized trials are available to indicate whether patients with SCAF should receive anticoagulation. The present data may help to decide whether or not and when to start anticoagulation, awaiting the results of randomized trials.

The significance is that duration of SCAF appears to play a role in the risk of stroke or systemic embolism, and that SCAF >24 h may be a threshold for a higher stroke risk. Yet, it still may be questioned whether AF is causal or just another associated risk marker.[28–31] Several analyses showed that only a few patients with SCAF-associated embolic events had evidence of SCAF during the last month prior to their embolic event.[28,29,31] In the present study, patients with longer SCAF also were more likely to have other stroke risk factors suggesting that confounding factors, other than SCAF duration, might be responsible for the increased risk of adverse outcomes. Future studies investigating the association between duration of SCAF and embolic events are highly desirable.[32]

Although we assessed so called 'atrial high rate episodes,' we use the term 'SCAF'. We feel this is justified since all electrocardiograms were adjudicated implying that all are true atrial tachyarrhythmias. Indeed these atrial arrhythmias do not only represent AF but also atrial flutter and tachycardia. Although the data of the risk of stroke in these patients is limited, they are considered to have comparable risk of stroke as patients with AF.

Limitations

Limitations include the observational study design, precluding definite conclusions on cause-effect relations and unmeasured confounding factors. Further, the results are limited to a group of older patients with hypertension with a pacemaker or defibrillator. Although the report includes more patients with SCAF than any single previous prospective series, the total number of patients and events is small. Unfortunately, we have no data of AF burden. Nevertheless, we feel that these data importantly contribute to the understanding how AF may influence stroke.

Conclusions

SCAF is common in patients with pacemakers or ICDs and varies in duration. There is a relationship between duration of SCAF and stroke risk with a higher risk being associated with longer episodes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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