Subclinical Atrial Fibrillation in Older Patients

Editorial, see p 1284

Jeff S. Healey, MD, MSc et al

BACKGROUND: Long-term continuous electrocardiographic monitoring shows a substantial prevalence of asymptomatic, subclinical atrial fibrillation (SCAF) in patients with pacemakers and patients with cryptogenic stroke. Whether SCAF is also common in other patients without these conditions is unknown.

METHODS: We implanted subcutaneous electrocardiographic monitors (St. Jude CONFIRM-AF) in patients ≥65 years of age attending cardiovascular or neurology outpatient clinics if they had no history of atrial fibrillation but had any of the following: CHA_2DS_2-VASc score of ≥2, sleep apnea, or body mass index >30 kg/m^2. Eligibility also required either left atrial enlargement (≥4.4 cm or volume ≥58 mL) or increased (≥290 pg/mL) serum NT-proBNP (N-terminal pro–B-type natriuretic peptide). Patients were monitored for SCAF lasting ≥5 minutes.

RESULTS: Two hundred fifty-six patients were followed up for 16.3±3.8 months. Baseline age was 74±6 years; mean CHA_2DS_2-VASc score was 4.1±1.4; left atrial diameter averaged 4.7±0.8 cm; and 48% had a prior stroke, transient ischemic attack, or systemic embolism. SCAF ≥5 minutes was detected in 90 patients (detection rate, 34.4%/y; 95% confidence interval [CI], 27.7–42.3). Baseline predictors of SCAF were increased age (hazard ratio [HR] per decade, 1.55; 95% CI, 1.11–2.15), left atrial dimension (HR per centimeter diameter, 1.43; 95% CI, 1.09–1.86), and blood pressure (HR per 10 mm Hg, 0.87; 95% CI, 0.78–0.98), but not prior stroke. The rate of occurrence of SCAF in those with a history of stroke, systemic embolism, or transient ischemic attack was 39.4%/y versus 30.3%/y without (*P*=0.32). The cumulative SCAF detection rate was higher (51.9%/y) in those with left atrial volume above the median value of 73.5 mL.

CONCLUSIONS: SCAF is frequently detected by continuous electrocardiographic monitoring in older patients without a history of atrial fibrillation who are attending outpatient cardiology and neurology clinics. Its clinical significance is unclear.

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The full author list is available on p 1282

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Clinical Perspective

What Is New?

- In patients with implanted pacemakers and defibrillators, prior studies have established that subclinical atrial fibrillation (SCAF) lasting at least 5 minutes in duration is very common and is associated with an increased risk of stroke.
- The results of the ASSERT-II trial (Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor) now demonstrate that this finding is not unique to patients with implanted pacemakers and defibrillators but is similarly common among individuals ≥65 years of age who have cardiovascular and stroke risk factors.

What Are the Clinical Implications?

- Given the effectiveness of oral anticoagulation at preventing stroke in patients with clinical atrial fibrillation, screening for SCAF in high-risk individuals could be a viable strategy to prevent stroke in a large number of individuals.
- However, given the relatively low absolute risk of stroke with SCAF and debate as to whether SCAF is simply a stroke risk marker, ongoing clinical trials will need to demonstrate that the use of oral anticoagulation in patients with SCAF reduces stroke in a cost-effective fashion before more widespread screening for SCAF can be recommended.

Atrial fibrillation (AF)–related stroke is an important cause of death and disability, and AF prevalence will double by 2050 as a result of population aging.[1] Until recently, the diagnosis of AF was made primarily by surface ECG either in patients with permanent AF or at the time of symptoms in those with paroxysmal AF. The advent of new technologies that permit continuous long-term electrocardiographic monitoring has revealed a high prevalence of asymptomatic, subclinical AF (SCAF) in selected populations. Long-term intracardiac monitoring in patients with pacemakers and implantable defibrillators detects SCAF in 25% to 50% of these patients within the first 1 to 3 years after implantation, despite the fact that they have no history of AF.[2–6]

More recently, long-term electrocardiographic monitoring has been performed in older patients with cryptogenic ischemic stroke and has detected SCAF in many patients.[7,8] In 1 study, 90 days of monitoring with a surface electrocardiographic monitor found SCAF of ≥30 seconds in 16.1% of patients,[8] and another study using subcutaneous implantable cardiac monitors (ICMs) detected SCAF of ≥30 seconds in 8.9% of patients by 6 months.[7] However, neither of these studies included a control group of patients without stroke.

We hypothesized that a high rate of SCAF detection by long-term continuous electrocardiographic monitoring is not unique to the pacemaker and stroke populations but rather that SCAF is broadly prevalent in older patients. We therefore sought to determine the rate of detection of SCAF in older at-risk patients attending outpatient cardiology and neurology clinics by means of subcutaneous implantable monitors.

METHODS

The ASSERT-II trial (Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor; NCT01694394) was a prospective cohort study conducted at 26 sites in Canada and the Netherlands, the goal of which was to define the prevalence of SCAF in patients attending outpatient cardiovascular clinics. The study population included patients ≥65 years old with a CHA_2DS_2-VASc score of ≥2, a clinical diagnosis of obstructive sleep apnea, or a body mass index >30 kg/m^2 and either evidence of left atrial enlargement (either a left atrial volume ≥58 mL[9] or diameter ≥4.4 cm) or an elevated NT-proBNP (N-terminal pro–B-type natriuretic peptide) ≥290 pg/mL.[10] Patients were not eligible for enrollment if they had a documented history of AF or atrial flutter or were presenting with symptoms attributable to arrhythmias such as palpitations. Patients were also ineligible if they had a chronic indication for oral anticoagulation, had an implanted pacemaker or defibrillator, or had cardiac surgery planned in the next 6 months. Patients were recruited from cardiology and neurology clinics, including catheterization laboratories, preoperative assessment clinics, and cardiac rehabilitation clinics (Appendix I in the online-only Data Supplement). The study was approved by the ethics committee of each participating hospital, and all patients provided written informed consent.

Clinical details were collected from eligible and consenting patients, and serum levels of NT-proBNP and troponin T were measured. Patients were then scheduled for implantation of a St. Jude Medical CONFIRM-AF device (DM2100). Consenting patients who did not undergo implantation had no further follow-up. Preoperative mapping was performed according to the device labeling to identify an orientation with maximal visualization of p waves.[11] The ICM was implanted in an operating room or catheterization or electrophysiological laboratory, and care was taken to ensure that the ICM was placed directly on the muscular fascia and that the pocket was small enough to minimize ICM mobility. The ICM was programmed for AF detection only and had all tachycardia, bradycardia, and patient-activated detections turned off to maximize available ICM memory. The minimum duration for AF detection was set to 5 minutes, with recordings obtained for 10 seconds before and 60 seconds after each detection. All other settings were detailed in a programming manual (Appendix II in the online-only Data Supplement).

Patients were scheduled for study visits at 3, 6, and 9 months after ICM implantation, with a final study visit at 18 months or after the last enrolled patient completed 9 months of follow-up, whichever came first. At each visit, details of clinical events were captured, including device-related complications, clinical atrial arrhythmias, stroke, systemic embolism, heart failure hospitalizations, bleeding, and anticoagulant

use. A routine 12-lead ECG was also performed at each study visit. Printouts of all automatically detected episodes, including logs and electrograms, were sent for central adjudication by a committee of device experts. Using a standardized method, the committee adjudicated events as AF, atrial flutter/tachycardia, or an inappropriate detection. Events adjudicated as definite underwent review by only a single reader, whereas episodes reviewed as probable underwent a second review by another reader. If there was disagreement between the 2 readers, the case was submitted for committee review; 82.5% of cases received review by a single expert, 13.5% by 2 experts, and 4.0% by committee. Blinded, duplicate adjudication of 50 cases of AF or atrial flutter and 50 cases with other diagnoses was performed, and the rate of between-observer agreement was 88%. The primary study outcome was device-detected SCAF, including atrial flutter/tachycardia, lasting ≥5 minutes. This duration was chosen to be consistent with the methodology of the ASSERT and TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) studies,[2,6] which demonstrated the association between SCAF lasting at least 5[6] or 6[2] minutes and stroke.

Statistics and Data Analysis

The rate of detection of SCAF was estimated before the study to be 12% on the basis of previous studies.[11,12] To achieve 4% precision 95% of the time, a sample size of 254 patients was required.

Baseline clinical characteristics were summarized as frequency (percentage) for categorical variables and mean (SD) or median (interquartile range [IQR]) for continuous variables. Comparison between patients with and without SCAF during follow-up was made with the Pearson χ^2 or Fisher exact test for categorical variables and 2-sample *t* test or Wilcoxon rank-sum test for continuous variables. The events of interest were observed from ICM implantation until either the end of the study or death, whichever came first. The 95% confidence intervals (CIs) for incidence rates were derived from a Poisson distribution. Cumulative incidences of SCAF with different durations were plotted with the Kaplan-Meier method. Subgroup analyses were prespecified for age, NT-proBNP, CHA_2DS_2-VASc score, and atrial volume above versus below the median value and for patients with versus without sleep apnea. Potential predictors of SCAF ≥5 minutes in duration were selected from univariate analysis on the basis of clinical and statistical significance ($P<0.2$) and were included in a multivariable Cox model. NT-proBNP was logarithm transformed to normalize the distribution. Linearity of continuous predictors and proportional hazards assumption were examined with restricted cubic spline plot and Kolmogorov-type supremum test, respectively. No violation was detected. Results were reported as hazard ratios with associated 95% profile-likelihood CIs. A nonparametric moving-average plot with a locally weighted smoothing curve was constructed to further explore the relationship of continuous predictors with the risk of SCAF ≥5 minutes. Sequentially overlapping subpopulations were created with a sliding window approach.[13] Each subpopulation included 30 patients with the following subpopulation changing by 10 patients. The incidence rate of SCAF was calculated and plotted against the corresponding median value of the continuous predictor for each subpopulation. All analyses were performed with SAS 9.4 software for SunOS (SAS Institute Inc, Cary, NC). All tests of significance were 2 sided with an α level of 0.05.

RESULTS

Between December 2012 and December 2015, two hundred seventy-three patients were enrolled, of whom 256 underwent implantation of an ICM. Seventeen patients did not receive an ICM: 12 withdrew consent, 4 became ineligible before implantation, and 1 enrollee did not receive one as a result of a physician decision (Figure I in the online-only Data Supplement). At base-

Table 1. Baseline Clinical Characteristics

	Overall (n=256)	SCAF (n=90)	No SCAF (n=166)	*P* Value
Age, y (SD)	73.9 (6.2)	75.3 (6.9)	73.1 (5.7)	0.008
Female sex, n (%)	88 (34.4)	33 (36.7)	55 (33.1)	0.57
White, n (%)	246 (96.1)	89 (98.9)	157 (94.6)	0.17
History of hypertension, n (%)	188 (73.4)	62 (68.9)	126 (75.9)	0.23
Systolic blood pressure, mm Hg (SD)	137.9 (19.2)	134.6 (18.5)	139.7 (19.4)	0.043
Resting sinus rate, bpm (SD)	64.6 (10.2)	65.7 (9.6)	64.0 (10.5)	0.19
History of heart failure, n (%)	22 (8.6)	3 (3.3)	19 (11.4)	0.027
Diabetes mellitus, n (%)	64 (25.0)	16 (17.8)	48 (28.9)	0.049
Prior stroke, TIA, or systemic embolism, n (%)	123 (48.0)	47 (52.2)	76 (45.8)	0.33
Vascular disease, n (%)	82 (32.0)	22 (24.4)	60 (36.1)	0.06
Sleep apnea, n (%)	29 (11.3)	9 (10.0)	20 (12.0)	0.62
BMI, kg/m^2	28.7 (4.6)	28.6 (5.3)	28.8 (4.3)	0.79
Valve disease, n (%)	37 (14.5)	12 (13.3)	25 (15.1)	0.71
CHA_2DS_2-VASc score	4.1 (1.4)	4.1 (1.4)	4.2 (1.4)	0.48
LA diameter, cm	4.7 (0.8)	4.9 (0.9)	4.7 (0.7)	0.02
LA volume, mL	76.5 (20.6)	79.4 (22.4)	74.8 (19.4)	0.17
LVEF, %	59.8 (10.6)	58.5 (8.0)	60.5 (11.9)	0.19
NT-proBNP, pg/mL	143 (55–393)	161 (81–393)	137 (51–393)	0.32
Troponin T, ng/mL	2.0 (6.4)	3.9 (11.7)	1.5 (4.3)	0.55

Data are mean (SD) or median (IQR) as appropriate.

BMI indicates body mass index; LA, left atrial; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SCAF, subclinical atrial fibrillation; and TIA, transient ischemic attack.

line, the average age of participants was 73.9±6.2 years, their average CHA_2DS_2-VASc score was 4.1±1.4, and 48% had a history of stroke, systemic embolism, or transient ischemic attack (Table 1).

Rates of Detection of SCAF and Clinical AF

The average follow-up was 16.3±3.8 months; 98.4% completed the minimum 9 months of monitoring, and 65% of patients completed 18 months, giving a total of 347.1 person-years of follow-up. SCAF ≥5 minutes occurred at an incidence rate of 34.4% per person-year (95% CI, 27.7–42.3), with Kaplan-Meier cumulative incidence at 12 months of 31.0% (Figure 1). In patients with SCAF ≥5 minutes, the median number of SCAF episodes was 6.5 (IQR, 1–24), the median duration of the longest SCAF episode was 62 minutes (IQR, 24–401 minutes), and the median weekly burden of SCAF was 3.4 minutes (IQR, 0.6–20 minutes). The rate of detection of SCAF ≥30 minutes was 21.8%/y (95% CI, 16.7–27.8); ≥6 hours, 7.1%/y (95% CI, 4.5–10.6); and ≥24 hours, 2.7%/y (95% CI, 1.2–5.0) (Figure 1).

Of the 90 patients in whom SCAF ≥5 minutes was detected, 34% were detected in the first 30 days, 64% within the first 6 months, and 87% within the first year. The mean time from ICM insertion to the detection of SCAF ≥5 minutes was 5.1±5.5 months. In addition to SCAF, clinical AF or atrial flutter was detected by conventional surface electrocardiographic methods in 26 patients, with an annual rate of 7.9%/y. Of the patients with clinically detected AF or atrial flutter, 18 (69%) of them had SCAF detected before clinical AF a median of 82.5 days (IQR, 2–250 days) earlier.

Patients in whom SCAF was detected were older, had a larger left atrial diameter, and had a lower systolic blood pressure and prevalence of heart failure and diabetes mellitus (Table 1). There were no differences between those with and without SCAF detected in the baseline prevalence of prior stroke, resting sinus rate, CHA_2DS_2-VASc score, or serum NT-proBNP or troponin levels (Table 1).

Predictors of SCAF and Patient Subgroups

The independent predictors for detection of SCAF ≥5 minutes were increased age, increased left atrial diameter, and lower systolic blood pressure (Table 2). Figure 2 shows the relationship between rate of detection of SCAF and increasing age (Figure 2A). It also shows the relationship between rate of detection of SCAF and increasing left atrial diameter (Figure 2B). The rate of detection of SCAF was not significantly different among patients with a history of stroke, systemic embolism, or transient ischemic attack compared with those without such a history (Figure 3).

Clinical Outcomes

During follow-up, 8 patients died (2.3%/y), 5 of nonvascular causes, and 5 patients were hospitalized for heart failure (1.5%/y). Ischemic stroke occurred in 4 patients, none of whom had had SCAF detected. Hemorrhagic stroke occurred in 1 patient who had been detected to have SCAF and who was being treated with anticoagulation. Transient ischemic attack and systemic embolism occurred in 1 patient each, neither of whom had SCAF. Oral anticoagulation was started during the study at the discretion of treating physicians in 67 patients (26.2%): in 15 because of clinically detected AF, in 45 as a result of detection of SCAF by the ICM, and in 7 for other indications.

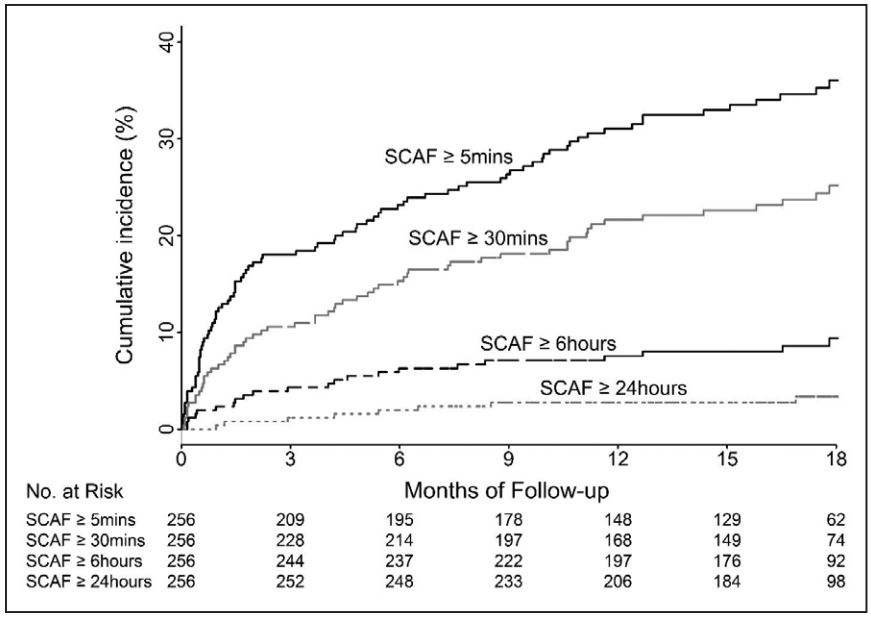

Figure 1. Cumulative rate of detection of different durations of subclinical atrial fibrillation (SCAF).

Table 2. Univariate and Multivariable Cox Regression Analyses of Subclinical Atrial Fibrillation Risk Factors

Factor	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, per 10-y increment	1.64 (1.18–2.27)	0.004	1.55 (1.11–2.15)	0.011
Resting sinus rate, per 10-bpm increment	1.18 (0.97–1.44)	0.10	1.23 (0.99–1.53)	0.060
Systolic blood pressure, per 10–mm Hg increment	0.89 (0.79–0.99)	0.04	0.87 (0.78–0.98)	0.023
LA diameter, per 1-cm increment	1.40 (1.07–1.82)	0.02	1.43 (1.09–1.86)	0.009
NT-proBNP, per 10% increase	1.01 (0.99–1.03)	0.40		
Heart failure	0.34 (0.08–0.91)	0.03	0.42 (0.10–1.13)	0.092
Diabetes mellitus	0.59 (0.33–0.98)	0.04	0.71 (0.39–1.22)	0.223
Vascular disease	0.64 (0.39–1.02)	0.06	0.78 (0.46–1.27)	0.332

CI indicates confidence interval; HR, hazard ratio; LA, left atrial; and NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Adverse Events

Five patients (2.0%) experienced implantation complications: 2 had minor bleeding; 1 had a transient, nonstroke speech disorder; 1 required a second device because the original device could not be appropriately programmed; and 1 developed a pneumothorax. During follow-up, 1 patient (0.4%) required ICM removal because of infection and another because of suspected ICM allergy. No patients died as a result of ICM implantation or developed a major pocket hematoma.

DISCUSSION

The main finding of this study is that long-term continuous electrocardiographic monitoring with an ICM frequently detected asymptomatic SCAF of ≥5 minutes in older patients with cardiovascular risk factors who were attending outpatient cardiology and neurology clinics. By 1 year of follow-up, more than one third of patients had had at least 1 episode of SCAF ≥5 minutes and 7% had had an episode lasting ≥6 hours. SCAF episodes were typically very infrequent, with an average time of 5 months to detection of the first episode and with a median weekly burden of SCAF of 3 minutes. Thus, only a minority of these episodes would have been detected with typical 24-hour and 1-week ambulatory cardiac monitors. Although some patients with SCAF also developed clinical AF, diagnosis of clinical AF was made in only 20% of patients with SCAF, and clinical AF diagnosis often occurred well after SCAF was first identified.

The patients in this study were recruited primarily from outpatient cardiovascular and neurology clinics and were typical of many patients attending such clinics in that they were elderly and had risk factors for cardiovascular disease and stroke. We designed the study to enrich the study population with patients at a somewhat increased risk of having SCAF by specifying that, in addition to a minimum age of 65 years, most patients would have some degree of left atrial enlargement. We selected patients who had a left atrial volume of ≥58 mL because this represents the upper limit of normal for left atrial size[14] and the median value among a random sample of patients referred for echocardiography who were ≥65 years of age without AF, pacemaker, valve surgery, congenital heart disease, or stroke.[9] Patients could also be included in the study if they had elevated NT-proBNP without left atrial enlargement. One can appreciate from Figure 2A that, although increasing left atrial size is associated with increased risk of detection of SCAF, there is still a substantial annual rate

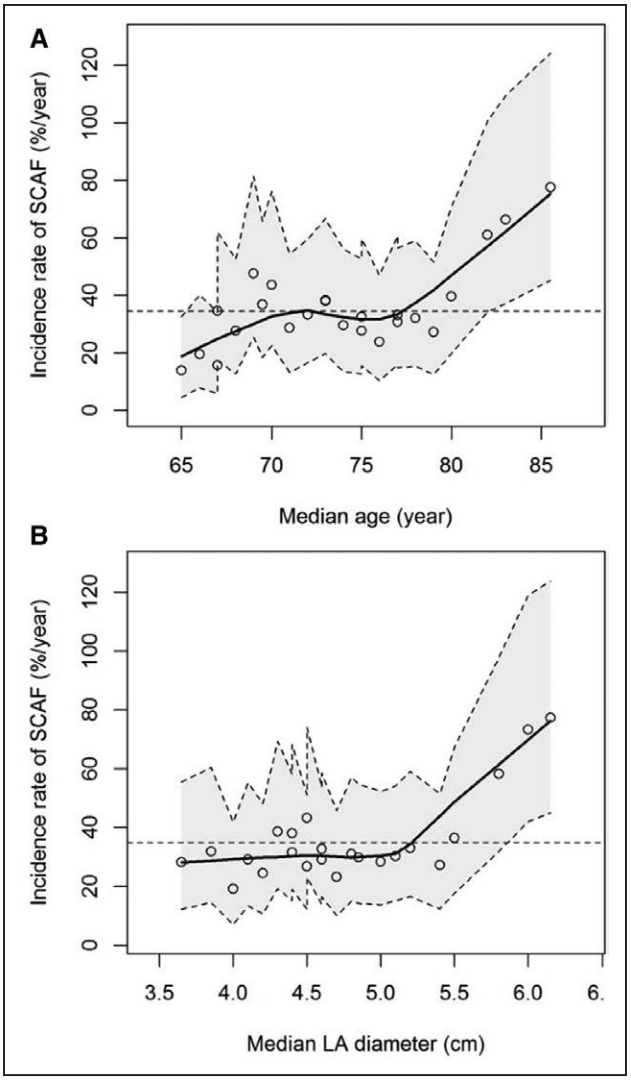

Figure 2. Relationship between subclinical atrial fibrillation (SCAF) lasting ≥5 minutes and (A) age and (B) left atrial diameter.
LA indicates left atrial.

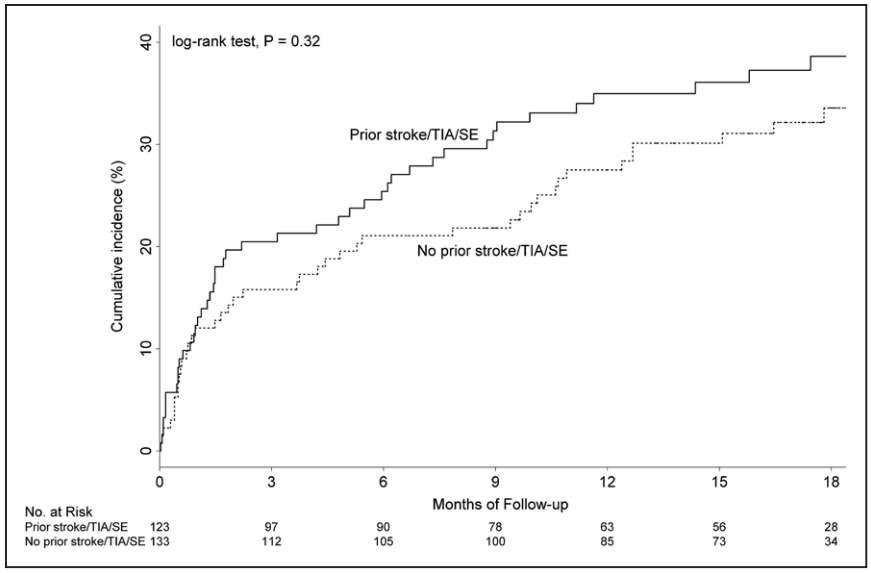

Figure 3. Cumulative rate of detection of subclinical atrial fibrillation ≥5 minutes in duration in patients with and without prior stroke, transient ischemic attack (TIA), or systemic embolism (SE).

of detection of SCAF (>20%) in patients whose left atrial diameter is within the normal range.

SCAF of at least 5 minutes' duration was detected in ASSERT-II at a rate 3 times higher than SCAF of only ≥30 seconds detected in CRYSTAL-AF (Cryptogenic Stroke and Underlying Atrial Fibrillation).[7] The high rate of detection of SCAF in ASSERT-II raises questions about how to interpret the detection of SCAF by means of long-term electrocardiographic monitoring of patients with recent cryptogenic stroke.[7,8] In our study, about half of the patients had had a prior stroke and half did not, and there was not a significant difference between these 2 groups in the rate of detection of SCAF. Our study also shows that detection of SCAF with long-term monitoring is common in older patients with cardiovascular risk factors, which indicates that we should be cautious in ascribing a causal relation between SCAF and stroke, even when SCAF is detected (by long-term monitoring) after recent cryptogenic stroke. The hypothesis that anticoagulation is of benefit in patients with recent stroke in whom SCAF is detected by long-term continuous electrocardiographic monitoring should be tested in a randomized clinical trial.

It is difficult to directly compare the rates of SCAF between recent studies because of differences in the definition of the minimum duration of SCAF, which was 30 seconds in CRYSTAL-AF[7] and EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event)[8] and 5 minutes in ASSERT-II. Nonetheless, the rate in CRYSTAL-AF (12.4% at 12 months) appears to be lower than in EMBRACE (16.1% at 90 days) and even lower than in the present study (31.0% at 12 months). These differences may be explained in part by the differences in mean age between these studies (CRYSTAL-AF, 61.5 years; EMBRACE, 73 years; ASSERT-II, 75 years) because our data also indicate that increasing age and increasing left atrial size are predictors of SCAF.

The present study was not designed to assess the risk of stroke in patients with SCAF. In patients with pacemakers and implanted defibrillators, we have previously reported that detection of SCAF within 3 months of device implantation is associated with an increased risk of ischemic stroke or systemic embolism.[2] Currently, there is no recommendation to use oral anticoagulation to treat SCAF detected by a cardiac rhythm device[5,15,16]; however, 3 large-scale clinical trials of anticoagulation for patients with device-detected SCAF are underway: the ARTESiA trial (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; NCT01938248), the NOAH trial (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; NCT02618577), and the Danish Loop study (Atrial Fibrillation Detected by Continuous ECG Monitoring; NCT02036450).

Limitations

This cohort study includes nonconsecutive outpatients meeting specific eligibility criteria who thus are not representative of the population at large. Although the need for echocardiography to select patients might appear limiting, recent data suggest that ≈20% of Medicare recipients in the United States undergo at least 1 echocardiogram each year.[17] Although care was taken to exclude patients with symptoms that could be suggestive of AF, it remains possible that physicians somehow selected patients with such minimal symptoms. ASSERT-II was not designed to determine the stroke risk associated with SCAF in this population, given its small size and the fact that approximately half of the patients who developed SCAF received oral anticoagulant therapy.

ASSERT-II had only modest statistical power to compare subgroups of patients such as those with and without a history of stroke. In contrast, the counterintuitive

observation among patients with SCAF of a lower blood pressure and a lower prevalence of heart failure may suggest some degree of patient selection, perhaps as a result of patients with heart failure and hypertension being more likely to have prior investigations that would have identified AF, making them ineligible to participate. Finally, we may have modestly underestimated SCAF burden in this study because we did not perform remote ICM monitoring; thus, device counters may have been saturated in a small number of patients. However, the upper quartile for SCAF burden in ASSERT-II was only 24 episodes, so this issue likely did not have a major impact.

Conclusions

SCAF is common in older individuals with cardiovascular risk factors, particularly in those with some left atrial enlargement. The clinical importance of the detection of SCAF is unclear, and randomized trials of anticoagulation for the prevention of first or recurrent stroke in patients with SCAF are needed.

AUTHORS

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FOOTNOTES

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