Stroke Type and Severity in Patients with Sub-Clinical Atrial Fibrillation: An analysis from the ASSERT trial

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Short title: Stroke Type and Severity in Sub-Clinical AF

Word count: Abstract – 251 Text – 1619

Tables - 2 Figures - 1

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ABSTRACT

Background:

The ASSERT trial demonstrated that sub-clinical atrial fibrillation (SCAF) was associated with a 2.5-fold increased risk of stroke. However, the absolute stroke rate was only 1.7% per year and fewer than 20% patients suffering SCAF-associated stroke had evidence of SCAF in the preceding 30 days. This raises the possibility that SCAF is merely a risk marker for stroke, rather than the cause. Systematic characterization of stroke sub-types among patients with SCAF would help to clarify this issue.

Methods:

All ischemic strokes which occurred in the ASSERT trial were blindly adjudicated by stroke neurologists, and classified as cortical vs. sub-cortical, and sub-typed using modified TOAST criteria. Stroke severity was measured using the modified Rankin Score (mRS).

Results:

Of the 44 participants who suffered an ischemic stroke, 15 had SCAF prior to stroke. Among these patients, 26.3% of strokes were judged to be cardioembolic, 26.3% to be lacunar, 5.3% to be large artery disease and 42.1% type uncertain. Although the proportion of cardioembolic strokes in patients with SCAF was higher than in patients without SCAF prior to stroke (8.0%), this difference was not statistically significant ($p=0.21$). Similarly, the proportion of strokes judged to be cortical was 52.6% among patients with SCAF and 36.0% among those without ($p=0.27$). The mRS at 30 days was similar between patients with (2.9 ± 1.7) and without SCAF (2.5 ± 1.9, $p=0.52$).

Conclusions:

In patients with SCAF, only one-quarter of strokes appear cardioembolic, and one-third are, clearly due to other mechanisms. Strokes appear less severe than in studies of clinical AF.

Background:

Approximately 25% of patients suffering ischemic stroke have a history of atrial fibrillation (AF) (1,2,3), and patients with AF typically have strokes that are more severe. (4,5) AF is often associated with large, cortically-based infarcts which have a 30-day mortality rate as high as 24% among patients not taking any antithrombotic therapy (6), and result in severe morbidity among survivors. (4,5) More than one third of patients with AF associated strokes are left with major neurological sequel that prevent them from independent living, categorized as 3 or 4 using the modified Rankin score (mRS). Another 10% of patients are left with total dependency (classified as an mRS of 5). Oral anticoagulation can prevent approximately 65% of strokes in patients with AF. (7,8) However: this conclusion is based on randomized trials, which included mostly patients with persistent or permanent AF, who appear to be at a higher risk of ischemic stroke than patients with paroxysmal AF. (9)

Device-detected SCAF is detected in up to 40% of individuals with implantable pacemakers and defibrillators capable of long-term continuous heart rhythm monitoring. (10, 11) It is characterized by one or more runs of rapid atrial arrhythmia detected by the device without symptoms and without any clinical AF detected by the usual methods, (i.e. electrocardiogram, Holter monitor, etc.). While these pacemaker patients with SCAF have a 2.5-fold increase in their risk of stroke, the absolute risk of stroke among this cohort with a CHADS2 score of 2.2+/-1.1, was only 1.7% per year;(10) a rate that is lower than the stroke rates of 4.0 (95% CI,3.1-5.1) per 100 patient years that were seen in patients with clinical AF with a CHADS2

score of 2. (12) As well, fewer than 20% individuals with SCAF who suffered stroke during the ASSERT study had evidence of SCAF in the 30 days preceding the stroke, raising the possibility that in many cases, SCAF may simply be a risk marker for stroke, and that stroke mechanism may be different than for clinical AF. (13)

Unlike with clinical AF, (4,5) there are currently no comprehensive data on stroke topography, sub-type and severity of strokes associated with SCAF. Understanding these characteristics of SCAF-associated ischemic stroke is critical to understanding if SCAF is a causal factor or a risk marker for ischemic stroke. Patients in the ASSERT trial had careful characterization of all SCAF and strokes and provides a large prospective dataset to evaluate these relationships.

Methods:

The design and main results of ASSERT have been published previously. (14) The study enrolled 2580 patients, aged ≥65 years, with a history of hypertension that underwent 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 primary outcome of the study was ischemic stroke or systemic embolism, with a mean follow- up duration of 2.5 years.

For the present analysis, all stroke events were adjudicated by two stroke neurologists, blinded to SCAF status. Differences in adjudication were resolved by consensus. All ischemic strokes were classified into cortical vs. sub-cortical, and sub-typed into cardio-embolic, lacunar,

large-artery and type uncertain, using modified TOAST criteria (15) (fig 1) These criteria were modified to remove the sick sinus syndrome and AF criteria for cardio-embolic stroke, given the very high prevalence of sick sinus syndrome in this pacemaker population and the desire to study the association between SCAF and stroke sub-type. Strokes were classified as cardio-embolic if patients had clinical AF or had other moderate or high-risk cardioembolic sources. The cardio-embolic sources compromised of clinical AF, akinetic or hypokinetic left ventricular segment, mitral annulus calcification, moderate to severe mitral stenosis, and atrial septum defect.

Stroke severity was measured at 7 and 30 days post-stroke using the modified Rankin Score (mRS). Only patients who had SCAF detected before their ischemic stroke were allocated to the SCAF group. Adjudication of stroke events was done individually with differences been resolved by consensus. Stroke sub type, topography, and 7 and 30 day mRS was compared between patients with and without SCAF.

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 standard deviation 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 44 patients experienced ischemic strokes during ASSERT study. Of these, 14 patients had SCAF prior to their ischemic stroke. There was no difference between baseline characteristics of the patients with SCAF vs no-SCAF. (Table1) The mean age in the 2 groups was 82.1(±6.4) and 78.5(±8.1) years, respectively. Approximately 20% in both groups had prior stroke and 50% of patients in the SCAF group were on anti-thrombotic agents prior to their index stroke compared to 63% in the non-SCAF group (Table 1). Three patients in the SCAF group were on OAC therapy compared to none in the no-SCAF group, and 64% patients in the SCAF group and 87% patients in the no-SCAF group were on antiplatelet therapy at the time of their stroke.

There were no significant differences noted in stroke subtype, topography or mRS between patients with vs. without SCAF. (Table 2). Cardio-embolic strokes were present in 26% of SCAF patients when compared to 8% in the non-SCAF group. Both groups had a similar number of lacunar strokes (26% vs 28%). The 30 day mRS was similar in SCAF vs non-SCAF groups (2.9±1.7 vs. 2.5±1.9)

SCAF Occurring Within 30 Days Before Stroke

Of the five patients who had SCAF detected within 30 days prior to their index stroke, 4 (80%) had cardioembolic and 1 (20%) had lacunar stroke. The average duration of SCAF in these patients was 4.9±5.8 hours/day. Only one patient had SCAF at the time of the stroke, this patient experienced a cardioembolic stroke with cortical localization and the 7-day mRS of this patient was one.

Discussion:

The present analysis of ASSERT data shows that over one-third of SCAF-associated strokes are sub-cortical, and over one-quarter are lacunar. Both findings suggest that a substantial fraction of strokes in patients with SCAF are not due to cardio-embolism. Furthermore, there was no difference in 7-day and 30-day mRS in patients with SCAF and without SCAF and the median mRS scores seen in these patients were lower than observed with strokes among patients with clinical AF. (4,5) These findings call into question our current understanding of the relationship between SCAF and stroke. 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. The fact that 4 of 5 patients with SCAF occurring within 30 days of a stroke suffered a cardioembolic stroke suggests that a proportion of strokes in patients with SCAF are indeed due to cardiac thromboembolism. However; many other episodes may be due to chronic endothelial changes due to multiple prior AF episodes; and some may be due to non-AF mechanisms (e.g. hypertension-associated lacunar stroke) for which AF may be just a risk marker. (16)

Of the patients in the ASSERT study who had ischemic stroke, 30% had SCAF detected only after their strokes, with all of them having an average of >1 year of negative monitoring before their stroke. (13) In the TRENDS study among the 20 patients with SCAF before their embolic event, only 30% had SCAF within the month before their embolic event, and the most recent episode of SCAF was an average of 166±189 days before. (11) Thus, the assumption that

atrial fibrillation detected after cryptogenic stroke is the cause of the embolic event may not always be correct.

In current practices fewer than 25% of patients with stroke risk factors and device-detected SCAF are treated with anticoagulation. (17) This may reflect the clinical equipoise that exits among physicians about best management of these patients. Given the lower absolute stroke rate in SCAF patients compared to clinical AF patients and the older age of these pacemaker population the risk benefit of oral anticoagulation need to be firmly established in this group. The demonstration of different stroke subtypes and lesser severity of strokes in this clinical cohort does suggest that SCAF may be a risk marker for cardioembolic stroke for many but perhaps for not all of these patients. This calls into question whether oral anticoagulation can be expected to prevent stroke in SCAF to the same extent as in clinical AF. A recent study that randomized 2718 patients with dual-chamber and biventricular defibrillator detected AF to anticoagulation vs. was stopped for futility, as there was no difference in the primary endpoints of thromboembolism and bleeding. (18) Two randomized trials, ARTESIA (NCT01938248) and NOAH (NCT02618577) are currently underway to determine whether patients with SCAF benefit more from anticoagulant therapy vs antiplatelet therapy. Results of these trials are anticipated in 3-4 years.

Limitations:

Although this is the largest prospective report on patients with SCAF and ischemic stroke, the total number of patients was small, precluding adequately-powered comparisons between patients with and without SCAF. As well, since none of the pacemakers and defibrillators used

in ASSERT were magnetic resonance imaging conditional, MRI studies were not available to help sub-type ischemic strokes. However it must be acknowledged that accurate subtyping of stroke may not be possible in all cases of stroke even with advanced neuroimaging and vascular imaging techniques and that some "lacunar" strokes could have cardio embolic or atheroembolic sources. (19)

Conclusions:

Although an association between SCAF and ischemic stroke has been established, short episodes of SCAF on long-term arrhythmia monitoring does not confer causality as the putative mechanism. In patients with SCAF, only one-quarter of strokes appear cardioembolic, and one-third were, clearly due to other mechanisms. Strokes appear less severe than in studies of clinical AF. Thus, in many cases, SCAF may be a risk marker for stroke, rather than causal.

Acknowledgements

Dr. Healey was supported by a personnel award from the Heart and Stroke Foundation, Ontario, Canada (MC7450) and the Population Health Research Institute Chair in Cardiology Research at McMaster University.

Disclosures

Dr. Healey has received research grants and speaking fees from St. Jude Medical, Boston Scientific and Medtronic.

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Table 1. Baseline characteristics based on the presence of SCAF

	NO SCAF (N=30)	SCAF (N=14)	P Value†
Baseline characteristics:			
Age, mean ±SD	78.5±8.1	82.1±6.4	0.117
Gender (Male), n(%)	20 (66.7)	6 (42.9)	0.135
Hypertension, n(%)	30 (100.00)	14 (100.00)	-
Prior stroke, n(%)	6 (20.0)	3 (21.4)	>0.999
Prior TIA, n(%)	5 (16.7)	0 (0.0)	0.161
History of Heart failure, n(%)	3 (10.0)	4 (28.6)	0.184
Diabetes, n(%)	10 (33.3)	4 (28.6)	>0.999
CAD, n(%)	10 (33.3)	2 (14.3)	0.282
$CHADS_2$ score, mean±SD	2.9±1.1	2.9±1.2	0.980
CHA_2DS_2-VASc score, mean±SD	4.6±1.4	4.7±0.9	0.677
Anthithrombotic Rx, n(%)	19 (63.3)	7 (50.0)	0.402
Antiplatelets, n(%)	26 (86.7)	9 (64.3)	?
Oral Anticoagulants n(%)	0 (0)	3 (21.4)	?
BP medications, n(%)	28 (93.3)	14 (100)	>0.999
Statins, n(%)	11 (36.7)	4 (28.6)	0.738

Table 2: Stroke subtype, topography and mRS score according to SCAF status

	NO SCAF (N=30)	SCAF (N=14)	P Value†
Stroke Subtype			
Cardio-embolic, n(%)	2 (8.0)	5 (26.3)	0.210
Large artery disease n(%)	0 (0.0)	1 (5.3)	0.432
Lacuna n(%)	7 (28.0)	5 (26.3)	0.901
Uncertain n(%)	16 (64.0)	8 (42.1)	0.149
Stroke Localization			
Cortical n(%)	9 (36.0)	10 (52.6)	0.270
Subcortical n(%)	12 (48.0)	7 (36.8)	0.459
Uncertain n(%)	4 (16.0)	2 (10.5)	0.684
Stroke Severity			
7-Day mRS score, mean±SD	3.2±1.8	3.4±1.9	0.642
30-Day mRS score, mean±SD	2.5±1.9	2.9±1.7	0.518

Figure 1:

TOAST Classification of High- and Medium-Risk Sources of Cardioembolism

High-risk sources

Mechanical prosthetic valve
Mitral stenosis with atrial fibrillation
Atrial fibrillation (other than lone atrial fibrillation)
Left atrial/atrial appendage thrombus
Sick sinus syndrome
Recent myocardial infarction (<4 weeks)
Left ventricular thrombus
Dilated cardiomyopathy
Akinetic left ventricular segment
Atrial myxoma
Infective endocarditis

Medium-risk sources

Mitral valve prolapse
Mitral annulus calcification
Mitral stenosis without atrial fibrillation
Left atrial turbulence (smoke)
Atrial septal aneurysm
Patent foramen ovale
Atrial flutter
Lone atrial fibrillation
Bioprosthetic cardiac valve
Nonbacterial thrombotic endocarditis
Congestive heart failure
Hypokinetic left ventricular segment
Myocardial infarction (>4 weeks, <6 months)