

# **Seek and ye shall find... subclinical atrial fibrillation in high-risk elderly patients.**

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Atrial fibrillation (AF) is a rapidly growing public health and economic burden<sup>1</sup>. The global number of individuals with clinically diagnosed AF was estimated to be 33 million in 2010 and is expected to double by 2050 due to demographic changes and the rising prevalence of risk factors for AF, such as obesity, diabetes and hypertension. AF is associated with substantial morbidity and mortality (mostly secondary to an increased risk of stroke), reduced quality of life, and considerable costs<sup>1</sup>. Yet, these figures are likely to underestimate the true prevalence of AF, as prolonged ECG monitoring detects clinically silent subclinical AF (SCAF) in a variable proportion of subjects presenting in sinus rhythm, depending on the type and duration of monitoring, the characteristics of the study population (in particular, age and medical history), and the definition of AF<sup>2</sup>.

SCAF could have a significant impact on health and disability in that it may be linked to a significant proportion of strokes of undetermined origin<sup>3, 4</sup>. In this regard, patients with an implanted cardiac device (e.g. pacemaker or defibrillator) that includes an atrial lead have provided novel data on the prevalence and potential clinical significance of atrial high rate episodes (AHRE), which largely represent SCAF (but may also include artifacts, atrial flutter, or re-entrant supraventricular tachycardia). In particular, in the ASSERT study, continuous ECG recording for 3 months by an implanted pacemaker (n=2451) or defibrillator (n=129) identified episodes of AHRE (defined as rapid atrial rate >190 bpm lasting >6 min) in 10% of patients (mean age ~76 years) who were in sinus rhythm and had no history of AF<sup>5</sup>. Compared with sinus rhythm, the presence of AHRE was associated with a hazard ratio for stroke and embolic events of 2.5 (95% CI, 1.3 to 4.9; P=0.007) over a 2.5-year follow-up period<sup>5</sup>. Although the prevalence of AHRE suggests that clinical AF may just be the tip of a large submerged iceberg of undiagnosed AF in the general population, it is possible that the medical conditions that resulted in implantation of a cardiac device were also driving the high rate of atrial arrhythmias in these patients. Similar concerns apply to evidence indicating that prolonged cardiac monitoring in patients who have experienced cryptogenic stroke reveals a high prevalence of SCAF<sup>3, 4</sup>.

In this issue of *Circulation*, Healey and co-workers report results from the ASSERT-II study<sup>6</sup>, which was designed to investigate the prevalence of SCAF (including atrial flutter/tachycardia) using subcutaneous implantable monitors in a cohort of high-risk patients with no history or symptoms suggestive of AF. This prospective multicenter study

recruited patients from cardiology and neurology clinics who were  $\geq 65$  years old and had either a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ , a BMI  $>30$  kg/m<sup>2</sup>, or a clinical diagnosis of obstructive sleep apnea. To be eligible, patients also had to have at least mild left atrial dilatation on echocardiography, or an elevated NT-proBNP ( $\geq 290$  pg/mL). A minimum duration of 5 minutes was required for a SCAF episode to be captured by the implanted device, and logs and electrograms from all detected episodes were adjudicated by at least one reader, with dual reporting and/or committee review in cases where the diagnosis was not certain.

A total of 256 patients underwent implantation of a cardiac monitor, with a total of 347 person-years of follow-up. As expected from the inclusion criteria, the recruited population was at high risk of both stroke and development of AF: mean age was  $\sim 74$  years, mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was  $\sim 4$ , and nearly half had a previous history of stroke, TIA or systemic embolism. Perhaps predictably given these baseline characteristics, the main finding was a rate of SCAF of 34.4% per year – i.e., over the course of a year, approximately 1 in 3 such patients experienced at least one SCAF episode lasting at least 5 minutes. Longer durations of SCAF were also common, with annual rates of SCAF  $\geq 30$  minutes,  $\geq 6$  hours and  $\geq 24$  hours being  $\sim 22\%$ ,  $\sim 7\%$ , and  $\sim 3\%$ , respectively. Yet these episodes were typically very infrequent, with an average time of 5 months to the detection of the first episode, and a weekly burden of SCAF of just 3 minutes. Clinical AF was detected by conventional surface ECG in 26 patients, at a rate of 7.9% per year;  $\sim 70\%$  of these individuals had SCAF recorded prior to the detection of clinical AF. Independent predictors of SCAF were older age and left atrial dilatation, and less expectedly, lower systolic blood pressure.

What does ASSERT-II add to our understanding of SCAF? Firstly, it confirms that SCAF is common in high-risk elderly patients without a pacemaker or defibrillator, and that risk factors known to predict clinical AF (such as age and left atrial size) also predict SCAF. This is consistent with clinical AF and SCAF being part of the same spectrum, and in keeping with the recently reported findings from the REVEAL-AF study, where the rate of detection of SCAF episodes lasting  $\geq 6$  minutes in a similar high-risk elderly population was 29.3% at 18 months follow-up, increasing to 40% by 30 months<sup>7</sup>. Secondly, these data imply that, at least in this age group, the majority of patients experience SCAF before a diagnosis of clinical AF is made. In ASSERT-II the median interval between the first episode of SCAF and clinical diagnosis of AF was only about 3 months; however, these figures may underestimate

the corresponding interval in routine clinical practice, since participation in ASSERT-II might have increased patient awareness and the likelihood of detecting AF by surface ECG. Finally, the pattern of SCAF episodes in ASSERT-II confirms that the typical duration of ECG monitoring (i.e., from 24 hours to 7 days) would only capture SCAF in a small proportion of patients.

While these messages are important, and undoubtedly advance our understanding of SCAF, several unanswered questions remain. From a clinical perspective, perhaps the most important relates to the optimal management of AHRE and SCAF. Large-scale trials of anticoagulation did not seek to identify and recruit patients with SCAF<sup>8</sup>. ASSERT-II was not designed or powered to investigate the link between SCAF and future thromboembolic events or to detect a difference in the prevalence of SCAF between patients who had a prior TIA/stroke and those who had not. More broadly, there are limited high-quality clinical data delineating the relationship between AF pattern and burden, and thromboembolic risk. Practice guidelines recommend anticoagulation based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and independently of AF burden, yet a recent meta-analysis of prospectively collected data in >99,000 patients indicates that paroxysmal AF is associated with a significantly lower risk of stroke/systemic embolism as well as better long-term survival compared to non-paroxysmal AF<sup>9</sup>. While many clinicians may feel uncomfortable not considering anticoagulation once SCAF has been identified, the relationship between SCAF duration and stroke risk is unclear<sup>10</sup>. A recent analysis of the ASSERT dataset suggests that only AHRE lasting ≥24 hours are associated with increased stroke risk<sup>11</sup>; however, a meta-analysis of the studies that explored the thromboembolic risk of SCAF does not support the existence of a threshold but points to a continuous relationship between risk and SCAF duration<sup>12</sup>. Ongoing randomized trials of oral anticoagulants in patients with device-detected SCAF may be instructive in this regard. Even so, since rivaroxaban has recently been reported to be superior to aspirin in preventing major adverse cardiovascular events (including cardiovascular death, myocardial infarction and stroke) in patients with coronary or peripheral vascular disease (COMPASS Trial news release), the presence of AF may not be a necessary prerequisite for a beneficial effect of anticoagulation in high risk patients.

Finally, study of individuals with SCAF has also yielded intriguing observations that suggest the current paradigm of stroke pathophysiology in AF patients may be overly

simplistic. Despite the clear link between SCAF and ischemic stroke, the temporal relationship between the conditions is not straightforward, with a further analysis of the ASSERT dataset suggesting that up to half of AHRE only occurred *after* the presumed embolic event<sup>10</sup>. This raises the possibility that systemic or local factors increase the embolic risk independently of (or additionally to) atrial arrhythmia in some individuals, with SCAF representing an accessible biomarker of this process rather than the vital precipitant to cardiac thrombus formation. This may also have wider relevance to patients with clinical AF, since CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring does not identify pathophysiologic factors specific to thrombus development, but rather includes clusters of upstream cardiovascular risk factors that also predict the incidence of stroke, thromboembolism and mortality in patients without AF<sup>13</sup>. Indeed, these same cardiovascular risk factors are also powerful predictors of the development of new-onset AF<sup>14</sup>, suggesting that CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring may not capture the *additional* stroke risk conferred by abnormal atrial structure and function in AF, but rather relies predominantly on the overlap between risk factors predisposing to both AF and embolic stroke. This is pertinent when considering the relatively poor predictive value of CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring in individual patients (median C-statistic 0.67<sup>15</sup>), and suggests that integration with clinical parameters (including symptomatology and AF burden), systemic biomarkers and cardiovascular imaging could offer a clinically meaningful improvement in stroke risk prediction.

In conclusion, emerging data reveal that SCAF is very common in high-risk elderly patients, and while usually infrequent and short-lasting, it often precedes clinical AF. The clinical significance and optimal management of SCAF are largely unknown; in particular, further studies are needed to determine whether SCAF is a potentially treatable risk factor, an accessible biomarker, or indeed both.

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