

ATRIAL FIBRILLATION

Could subclinical AF be a missing link in the etiology of cryptogenic stroke?

Subclinical atrial fibrillation (AF) is associated with a 2.5-fold increase in the risk of ischemic stroke or systemic embolism. This finding from the prospective, observational study ASSERT has been reported by Dr Jeff Healey and colleagues in the *New England Journal of Medicine*.

The link between AF and stroke is well established; however, a substantial proportion of strokes cannot be attributed to either AF or to cerebrovascular disease. Determining the etiology of these so-called cryptogenic strokes is an ongoing clinical challenge. The theory that such events might be linked to subclinical AF is not new, but monitoring patients for asymptomatic atrial arrhythmias is difficult and the issue remains unresolved. The strategy used by the ASSERT investigators was to harness the analytical technology of pacemakers and implantable cardioverter-defibrillators to assess the incidence of subclinical AF and stroke in patients with hypertension and sinus-node or atrioventricular-node disease.

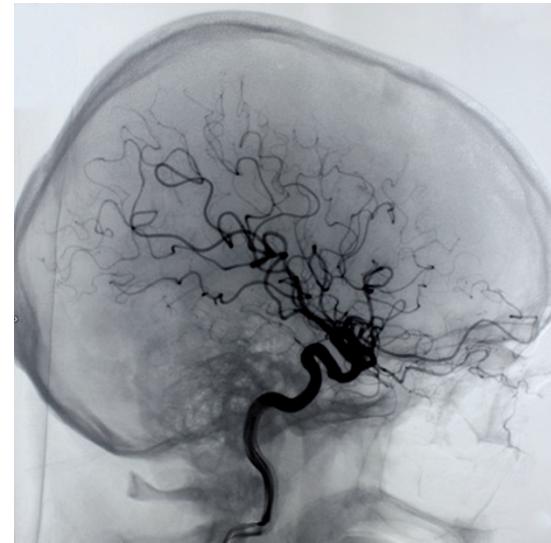
Over a 5-year period, 2,451 patients aged ≥ 65 years were enrolled, none of whom had a history of AF. All participants had undergone implantation of a pacemaker or cardioverter-defibrillator in the preceding 8 weeks. At study entry, these devices were programmed to detect atrial tachyarrhythmias that exceeded 190 bpm for ≥ 6 min. Data were retrieved from the implanted devices after 3 months. At this point, patients with pacemakers were randomly assigned to have their devices

turned 'on' or 'off' for continuous atrial overdrive pacing to determine whether prevention of AF has an effect on outcomes.

During the first 3 months of the study, subclinical atrial tachyarrhythmias occurred in 261 patients (10.1%). Over the course of follow-up (mean 2.5 years), the rates of subsequent clinically notable AF (15.7% vs 3.1%; HR 5.56, 95% CI 3.78–8.17, $P < 0.001$) and ischemic stroke or systemic embolism (4.2% vs 1.7%; HR 2.49, 95% CI 1.28–4.85, $P = 0.007$) were higher among patients who had experienced a subclinical arrhythmic episode in the first 3 months than among those who had not. The risk of stroke or embolism was highest in patients with other risk factors for stroke—almost 4% per year among those with a CHADS₂ score of > 2 , compared with 1.8% per year for a score of 2 and, paradoxically, 2.1% per year for a score of 1.

Unfortunately, the second aspect of ASSERT did not yield such intriguing data. The strategy of continuous atrial overdrive pacing did not reduce the incidence of AF, which was low in both groups.

Healey *et al.* point out that, although these findings suggest a link between subclinical AF and cryptogenic stroke, "long-term continuous monitoring, like that available with a pacemaker, is currently not practical". In an Editorial that accompanies the ASSERT paper, Dr Gervasio Lamas, who was not involved in the study, comments that "questions remain ... about cause and effect, as well as about clinical significance". He proposes



several hypotheses, including that short episodes of subclinical AF are precursors to the longer ones that pose a true risk of stroke; that these short episodes are merely a marker of stroke risk and have no causative effect; and that a pre-existing proinflammatory state could underlie both stroke and subclinical AF. Further trials of the 'at-risk' population are required to shed light on these possibilities.

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Original article Healey, J. S. *et al.* Subclinical atrial fibrillation and the risk of stroke. *N. Engl. J. Med.* **366**, 120–129 (2012)