Atrial Fibrillation in Cryptogenic Stroke

Look Harder, Look Longer, But Just Keep Looking

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Despite atrial fibrillation (AF) being the most common cardiac arrhythmia, its asymptomatic (and sometimes, paroxysmal) nature makes subsequent detection and diagnosis challenging. Ischemic stroke as a result of AF is usually more severe and results in greater functional loss, and patients with undetected AF will undoubtedly be at greater risk of recurrent stroke. The failure to diagnose AF after stroke also relegates this particularly vulnerable group to using antiplatelet agents, which are known to be only minimally effective in established AF, while placing them at similar risk of hemorrhagic complications as with oral anticoagulation therapy.

Current guidelines (both European and American) recommend the use of short-term (usually 24 hours) cardiac monitoring among stroke and patients with transient ischemic attack for whom occult AF or paroxysmal AF is suspected, and no other causes for stroke are found. However, even in selected high-risk patient group (such as the elderly, cryptogenic stroke patients, etc), the use of 24-hour ECGs only improve new AF detection rates to just >10%, whereas extended monitoring (>24 hours) with external loop recorder or implantable device can further increase detection rates to >14%. This would suggest that longer cardiac monitoring among patients with cryptogenic stroke is indicated and would have important therapeutic and clinical implications. Therefore, current guidelines and strategies for AF detection may need to be reviewed.

Until recently, the evidence-base for protracted cardiac monitoring among such patients relied on relatively small cohort studies that lacked a control group and, therefore, it was not possible to conclude whether extended monitoring would actually improve AF diagnosis over current practice. However, 2 randomized controlled trials recently published in the *New England Journal of Medicine* have provided compelling evidence in favor of longer ECG monitoring among patients with cryptogenic stroke.

The first of these, the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) trial, included 441 patients newly diagnosed with cryptogenic stroke. Half of whom were subsequently provided with an implantable cardiac monitor for continuous monitoring for 26 months, the others received usual care. The second study, the 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) trial, involved 572 patients with cryptogenic stroke and subsequently randomized them to receive a 30-day event trigger cardiac monitor or 24-hour cardiac monitor. In both trials, patients were extensively investigated before a diagnosis of cryptogenic stroke was made, and before enrollment and randomization all patients underwent initial 24-hour ECG monitoring to detect the presence of AF.

In the CRYSTAL AF trial, by the sixth month, new AF was detected in 8.9% of patients with implantable cardiac monitor when compared with 1.4% among those receiving standard follow-up, increasing further to 12.4% by 12 months (versus 2.0% in controls). A similar trend was observed in the EMBRACE trial, in which new AF was detected in 16.1% of patients who received with 30-day event recorder, versus only 3.2% by 24-hour monitor.

Further analysis of data from CRYSTAL AF trial shows that the majority of patients (≤79%) who subsequently developed AF were asymptomatic, and ≤92% of patients had a maximum of 1-day duration of AF lasting >6 minutes. Extrapolating from these results, <10 patients would need to be screened by extended cardiac monitoring to detect 1 new diagnosis of AF among those with cryptogenic stroke (number needed to treat=8 in EMBRACE trial), and even more protracted monitoring over time equates to improve detection rate (as shown by the 6-month versus 12-month results in CRYSTAL AF). Such detection of AF allows greater numbers of patients to benefit from oral anticoagulation therapy, with a potential reduction in recurrent strokes and a reduced morbidity and mortality.

In short, both the CRYSTAL AF and EMBRACE trials demonstrate the effectiveness of extended cardiac monitoring over contemporary practice of a single 24-hour ECG in post-ischaemic stroke patients. The rate of AF detections by implantable cardiac monitor and external cardiac monitor is in accordance with results from previous studies. The higher new AF detection rate in EMBRACE trial may be explained by the older patient group (>70 years) when compared with younger patients (age =60s) in CRYSTAL AF.

The main limitation of both trials lies in the delay between the index event of ischemic stroke or transient ischemic attack and the start of extended cardiac monitoring, varying from 38 days in CRYSTAL AF to 75 days in EMBRACE. This may have significant impact because sensitivity of detection of causative arrhythmia decreases over time, and the increases in subsequent detection of AF may simply reflect the increased...
propensity of AF in the at-risk group of patients. Thus, the association of AF with stroke versus the causation of index stroke by undetected paroxysmal AF becomes less clear.

Nonetheless, these trials demonstrate the need for extended cardiac monitoring, be it 30-day external or implantable devices, to improve detection of new AF. In addition, both trials also highlight that most patients who subsequently develop AF are unaware of it, thus making symptom-driven detection of AF unreliable. Furthermore, a daily burden of AF of ≥6 minutes was evident in 92% of new AF detected. This is important given that the Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial (ASSERT) and Mode Selection Trial (MOST) trials have demonstrated that subclinical atrial arrhythmias of even this duration are independently associated with increased risk of stroke, death, and development of permanent AF by upward of 2-fold.

In conclusion, we need to look harder and longer to detect AF, especially in patients with incident (cryptogenic) stroke. One might argue that cryptogenic stroke is only a diagnosis of exclusion, after vigorous efforts to exclude AF by (very?) prolonged monitoring—that is, we need to just keep on looking for AF. Continuous monitoring would result in newly detected AF in approximately one third of patients with multiple stroke risk factors during a year’s follow-up, and given that many such patients are asymptomatic, the development of AF in the context of associated stroke risk factors would lead to the first presentation of AF with an acute stroke. Beyond detecting episodes of silent AF, another study suggests that quantification of AF burden can improve the predictive value of clinical risk stratification scores. Overall, better detection of AF would allow for the identification of poststroke patients who could benefit from oral anticoagulation therapy, thus allowing for the best possible reduction of future recurrent cerebral events and the associated morbidity and mortality.

Disclosures
Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis. Dr Lane reports an investigator-initiated educational grant from Boehringer Ingelheim and honoraria from Boehringer Ingelheim, Bristol-Myers-Squibb/Pfizer and Bayer for lectures at educational meetings. Dr Lane is also on the Steering Committee of a Phase IV clinical trial sponsored by Bristol-Myers-Squibb. Y.C. Lau reports no conflicts.

References

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