CLINICIAN UPDATE

How to Manage Occult Atrial Fibrillation Detected on Long-Term Monitoring
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Illustrative Case: A 60-year-old asymptomatic man with a cardiac resynchronization therapy device previously implanted for dilated cardiomyopathy returns for a device checkup. At his last cardiac resynchronization therapy check, atrial high-rate episodes were detected with an overall arrhythmia burden of 30%. His blood pressure is 124/80 mmHg, and there is no history of diabetes mellitus or other cardiovascular risk factors. His last recorded left ventricular ejection fraction was 40%, and the left atrial diameter on transthoracic echocardiography was 42 mm. His CHA2DS2-VASc score is 1, and his HAS-BLED score is 0. Current medications include aspirin, angiotensin-converting enzyme inhibitor, statin, and β-blocker. How do we manage this patient, and should we anticoagulate him? Does atrial fibrillation (AF) burden matter?

Introduction
AF predisposes to an increased risk of stroke and thromboembolism, which is associated with greater fatality and disability compared with non--AF-related stroke.

The more common stroke risk factors seen in clinical practice are defined by the CHA2DS2-VASc score acronym, which is now used in many clinical guidelines. Even paroxysmal AF is related to a higher risk of stroke when associated stroke risk factors are present. Current guidelines recommend that stroke prevention is needed regardless of type of AF (paroxysmal or not) and whether rate or rhythm control is used.

Even so-called cryptogenic stroke (currently referred to as embolic stroke of uncertain source) is frequently associated with a high detection rate of AF if detection efforts are continued for a prolonged time period. Thus, long-term continuous electrocardiographic recording by an implantable cardiac monitor should be considered in patients presenting with embolic stroke of uncertain source for the detection of asymptomatic AF.

Many sophisticated implanted monitoring devices with the capability to detect AF are available. Apart from these devices (eg, implanted loop recorders), many pacemakers have the increasing capability to detect atrial high-rate episodes, many of which (but not all) are probably AF. These atrial tachyarrhythmias, often asymptomatic, are referred to as subclinical atrial tachyarrhythmias.

The Relationship Between Occult AF Detected on Long-Term Monitoring and Thromboembolism
Occult AF may be found in many settings. The patient with no prior AF may have various cardiovascular risk factors for developing AF and is initially asymptomatic or has mildly symptomatic paroxysmal AF. Eventually, this patient may progress to symptomatic (persistent or permanent) AF. A greater probability of detecting AF occurs with more prolonged monitoring with, say, up to 14 days of Holter monitoring. In some cases of unexplained palpitations, when a subcutaneous implanted loop recorder is implanted, AF detection is even more likely as a result of more prolonged monitoring.

Another example is the patient with no known AF who develops asymptomatic paroxysmal AF and presents for the first time with a new-onset stroke but could be in sinus rhythm at

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presentation. AF may not be detected during inpatient ECGs (or the limited monitoring in the acute stroke unit), but when more prolonged cardiac monitoring is performed with an implanted loop recorder, AF is evident.3

In the 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) study, there was a strong relationship between the proportion of patients with AF detected with more prolonged electrocardiographic monitoring: 2.2%, 7.4%, 11.6%, and 14.8% at 24 hours and 1, 2, and 4 weeks, respectively.4 AF might be newly detected in nearly a quarter of patients presenting with a stroke or transient ischemic attack.5

What Do Observational Studies and Clinical Trials Tell Us?
Numerous observational studies have addressed the impact of asymptomatic AF and outcomes.3 In an analysis from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial, asymptomatic patients tended to have less serious heart disease and more cerebrovascular disease, but the absence of AF symptoms did not confer a more favorable prognosis.6

The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) shows how device-detected atrial tachyarrhythmias can be strongly related to stroke/systemic embolism and the presence of clinical AF or flutter. This risk was related to stroke risk factors, being 2.14%/y in patients with a CHADS2 score ≥2 and only 0.19%/y in those with a CHADS2 score of 1 and no atrial tachyarrhythmias detected.7 However, the event rates with overt AF seemed to be much higher than corresponding event rates with subclinical atrial tachyarrhythmias. For example at a CHADS2 score of 0, the event rate was 1.9%/y in the National Registry of Atrial Fibrillation cohort8 but only 0.56%/y in the ASSERT trial.7

In the Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke (TRENDS) trial, ASSERT, and the Multicenter, Randomized Study of Anticoagulation Guided By Remote Rhythm Monitoring in Patients With Implantable Cardioverter-Defibrillator and Resynchronization Devices (IMPACT; Table),7,9,10 there was a high prevalence of any AF detected before thromboembolism, although the proportion of AF detected in the 30 days before the thromboembolic event was high only in TRENDS but low in ASSERT and IMPACT (Table). AF detected after thromboembolism was between 13% and 16% in the 3 studies. There was often no clear temporal relationship between the atrial tachyarrhythmia and the thromboembolic event, suggesting that other mechanisms may pathophysiologically explain this enhanced risk. One could hypothesize that transient AF would suffice to cause enough stasis for thrombus to form within the left atrial appendage to result in thromboembolism which then embolizes at a timepoint which may be remote from the atrial tachyarrhythmia.

How much AF is needed to cause thromboembolism? Prior studies have suggested a graded relationship between increasing AF (or atrial high-rate episodes) and thromboembolism risk.10,11 In the Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke (CRYSTAL-AF) trial,12 94.9% of patients in the implantable cardiac monitoring arm had a maximum 1-day AF burden of >6 minutes, and 59.0% had a maximum 1-day AF burden of >6 hours.

In the ASSERT trial,7 there was a clear time-dependent relationship of ischemic stroke or systemic embolism to duration of atrial tachyarrhythmias. This ranged from a relative risk of 1.77 (95% confidence interval, 1.01–3.10) with a duration of atrial tachyarrhythmia of ≥6 minutes to a relative risk of 4.96 (95% confidence interval, 2.39–10.3) at ≥24 hours. However, what may be a particular duration of atrial tachyarrhythmia in a particular monitoring period may not be the same duration in the following period, given the variability of AF and its time course.

Sapos et al13 found that among all patients with poststroke AF, 56.3% had poststroke AF episodes of <30 seconds during diagnostic evaluation. However, the clinical and prognostic significance of poststroke AF episodes of <30 seconds is uncertain.

Cryptogenic Stroke (Embolic Stroke of Uncertain Source) and Occult AF
Electrocardiographic monitoring is recommended for at least 24 hours after an ischemic stroke to rule out AF. The most effective duration and type of monitoring remain uncertain, and the cause of ischemic stroke remains uncertain despite a complete diagnostic evaluation.

In the Oxford Vascular Study (OXVASC), Li et al4 reported that among 2555 patients, 812 (32%) had cryptogenic events (incidence of cryptogenic stroke, 0.36 per 1000 population per year). Death or dependency at 6 months was high and similar after cryptogenic stroke and noncardioembolic stroke (23% versus 27% for large-artery and small-vessel subtypes combined; P=0.26), as was the 10-year risk of recurrence (32% versus 27%; P=0.91). Compared with large-artery and small-vessel stroke subtypes combined, those patients with cryptogenic events had no excess of paroxysmal AF (6% versus 10%; P=0.17) at baseline or of new AF (adjusted hazard ratio, 1.23; 95% confidence interval, 0.78–1.95; P=0.37).

Detection of AF is common and more likely (≈30%) among patients >60 years of age with prior cortical/cerebellar stroke.14 Thus, long-term continuous electrocardiographic recording by an implantable cardiac monitor should be considered in patients presenting with embolic stroke of uncertain source for the detection of asymptomatic AF.

The CRYSTAL-AF trial12 was a randomized, controlled study of 441
patients to assess whether long-term monitoring with an insertable cardiac monitor is more effective than conventional follow-up (control) for detecting AF in patients with cryptogenic stroke. By 12 months, AF had been detected in 12.4% of patients in the insertable cardiac monitor group (n=29) compared with 2.0% of patients in the control group (n=4 patients; hazard ratio, 7.3; 95% confidence interval, 2.6–20.8; P<0.001). Importantly, 75% of first episodes of AF were asymptomatic. Thus, electrocardiographic monitoring with an insertable cardiac monitor was superior to conventional follow-up for detecting AF after cryptogenic stroke.

In summary, subclinical atrial tachyarrhythmias are associated with an increased risk of ischemic stroke or systemic thromboembolism. Specific randomized trials are lacking in the patient population in which occult atrial tachyarrhythmias are detected with devices or prolonged monitoring, but the presence of (often multiple) stroke risk factors may be a persuasive reason for starting oral anticoagulants (OACs). Ongoing randomized, controlled trials will specifically address this question.

### Does Having Just 1 Stroke Risk Factor Merit an OAC?

Recent studies have addressed the issue of the necessity of an OAC in patients with AF and a CHA2DS2-VASc score of 1. Chao et al16 reported that the ischemic stroke rate in patients with 1 stroke risk factor (ie, CHA2DS2-VASc score of 1 in men and 2 in women) overall was 2.5 to 2.7%/y if untreated. With a single stroke risk factor, not all the stroke risk factors carry equal weight, and in our patient with moderate left ventricular systolic impairment,
the C criterion of CHA2DS2-VASc had an ischemic stroke rate of 2.4%/y.

In Europe, the Danish nationwide cohort study reported an overall ischemic stroke rate of 1.5% with 1 stroke risk factor of the CHA2DS2-VASc score if untreated, which was lowered by the use of OAC but not lowered with aspirin.17

Mortality was increased (≈11%) in patients with 1 stroke risk factor using the CHA2DS2-VASc score (ie, 1 in men and 2 in women), and this rate was reduced to 4% among OAC users (Figure 1). This observation is corroborated by the historical trials in which OAC versus control/placebo reduced stroke/systemic embolism by 64% and all-cause mortality by 26%.19 In addition, a high residual risk of mortality remains despite the use of an effective OAC that reduces stroke rates.20

Even with 1 stroke risk factor (ie, CHA2DS2-VASc score 1 in men and 2 in women), the net clinical benefit of OAC compared with untreated and OAC compared with aspirin. However, the net clinical benefit was neutral or negative for aspirin compared with untreated.18,21 Indeed, the evidence for aspirin for stroke prevention in AF is weak. Aspirin has a limited impact on stroke prevention, and it increases the rate of serious bleeding.22 For those with no stroke risk factors (ie, CHA2DS2-VASc score 0 in men and 1 in women), the net clinical benefit was neutral for aspirin or OAC, consistent with the European Society of Cardiology (ESC) guideline recommendations.21

Hence, rather than a categorical approach to stroke risk stratification (ie, dividing patients into low, moderate,
and high risk) and basing treatments on this artificial categorization, the better approach should be to initially identify low-risk patients (step 1) who are defined as having a CHA₂DS₂-VASc score of 0 in men and 1 in women, for whom no antithrombotic therapy is recommended. The subsequent step (step 2) is to offer effective stroke prevention to those with ≥1 stroke risk factors. In a newly diagnosed anticoagulation-naïve patient, the SAMe-TT₂R₂ score* can help decision making between a non–vitamin K antagonist OAC (NOAC) or vitamin K antagonist, without recourse to a trial of warfarin (Figure 2).

Patient values and preferences should be considered, and most patients would be keen to avoid an ischemic stroke, even at the cost of 4 major bleeding events.23

Take-Home Messages

- Asymptomatic AF is common and may confer an even poorer prognosis than symptomatic AF.
- Device-detected AF is common, whether detected by implanted loop recorders or increasingly sophisticated pacemakers, and is manifest by asymptomatic (and short) episodes of atrial tachyarrhythmias.
- Current evidence strongly associates such subclinical atrial tachyarrhythmias with an increased risk of stroke and systemic thromboembolism.
- In the presence of stroke risk factors, it would be preferable to offer stroke prevention, which is OAC with a vitamin K antagonist (with time in therapeutic range >70%) or a NOAC.

Management of the Patient in Our Illustrative Case

Our patient has a CHA₂DS₂-VASc score of 1, and the 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines24 recommend that OAC, aspirin, or no therapy can be considered. In contrast, the ESC guidelines recommend that OAC should be considered in such a patient (Class IIa recommendation), considering patient values and preferences. OAC refers to use of a vitamin K antagonist (with good-quality anticoagulation control, as reflected by a time in therapeutic range >70%) or an NOAC.

After discussion and counseling, our patient was keen on stroke prevention and was treated with an NOAC, specifically apixaban 5 mg twice daily. He discontinued aspirin.

Disclosures

Dr Lip reports the following disclosures: ESC guidelines on AF, 2010 and focused update, 2012; ESC guidelines on heart failure, 2012; American College of Chest Physicians Antithrombotic Therapy guidelines for AF, 2012; National Institute for Health and Care Excellence (NICE) guidelines on AF, 2006 and 2014; NICE quality standards on AF 2015; ESC Cardio- oncology Task Force, 2015; ESC Working Group on Thrombosis position documents (2011–present); chair, Scientific Documents Committee, European Heart Rhythm Association (EHRA); reviewer for various guidelines and position statements from ESC, EHRA, NICE, etc; steering committees for various phase II and III studies, Health Economics & Outcomes Research, etc; investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in AF, acute coronary syndrome, lipids, etc; consultant for Bayer/Jensen Johnson & Jensen, Beleev K, Beckman K, Vidaliet H, Kron J, Safford R, Mickel M, Barrell P; AFFIRM Investigators. Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Am Heart J. 2000;149:657–663. doi: 10.1067/mhj.2004.06.032.


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