Treatment of Subclinical Atrial Fibrillation

Does One Plus One Always Equal Two?

Michael R. Gold, MD, PhD

Atrial fibrillation (AF) is the most common pathological arrhythmia observed in clinical practice and it is associated with stroke, heart failure, and increased mortality. Multiple pivotal, randomized trials established the role of anticoagulation to reduce the risk of stroke among patients with AF with an elevated risk profile, as assessed by the $CHADS_2$ or CHA_2DS_2-VASc scoring systems. As such, anticoagulation with warfarin or novel oral anticoagulants is a class I indication in the treatment of patients with AF by all major societies, even though these agents are consistently underutilized because of fear of hemorrhagic complications. Retrospective analyses of large, multicenter trials have more recently showed that stroke risk is somewhat higher with chronic in comparison with paroxysmal AF, but this difference is not sufficiently large to affect anticoagulation recommendations.

The studies of anticoagulation use to prevent stroke, as well as most other treatments of AF are based on clinical documentation of the arrhythmia. Typically, this is driven by symptoms such as palpitations, syncope, dyspnea, or chest pain, but sometimes asymptomatic and incidentally discovered. The presence of arrhythmia-related symptoms does not appear to change the stroke risk, so anticoagulation recommendations are unaffected.

Although pacemakers have been implanted for >50 years, the development of algorithms to detect arrhythmias automatically and accurately more recently allows for the assessment of occult atrial tachyarrhythmias. Among patients with no history of these arrhythmias, the term subclinical AF has been coined. Subclinical AF can also be detected with implantable defibrillators, implantable cardiac monitors, and a rapidly growing number of wearable monitors. Studies of these devices have revealed that subclinical AF is common, particularly in elderly patients, and the prevalence increases with longer duration of monitoring.

Several large multicenter trials of subclinical AF have led to a dramatic change in clinical practice, particularly with regard to anticoagulation. The TRENDS study (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) of AF detected by pacemaker data logs showed that AF >5.5 hours/d in any 30-day period was associated with double the risk of stroke in comparison with patients with no AF or a lower arrhythmia burden.[1] The ASSERT study (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) evaluated elderly, hypertensive patients with pacemakers or implantable cardioverter defibrillators and no indication for anticoagulation. During a 3-month monitoring period post–device implantation, any episode of AF >6 minutes in duration was associated with ≈2.5-fold increase in subsequent stroke.[2]

It is not surprising that the results of TRENDS and ASSERT have led to an increased use of anticoagulation for subclinical AF. The logic for these clinical decisions appears straightforward. Clinical AF is associated with stroke whether symp-

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tomatic or asymptomatic and whether paroxysmal or persistent. Anticoagulation markedly reduces stroke risk in such patients with risk factors, so why should this be different for subclinical AF? Such logic in the absence of data showing therapeutic benefit has led to overtreatment and, at times, harm in other scenarios. For instance, most concerning are the now almost forgotten data on the treatment of premature ventricular contractions following myocardial infarction. Ventricular arrhythmias are associated with increased mortality, but antiarrhythmic drugs to suppress these arrhythmias further increase mortality.

Follow up-studies of subclinical AF raise even more confusion regarding optimal care of these patients. Analyses from TRENDS, ASSERT, and IMPACT (Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk)[3] all show essentially no temporal association between AF episodes and stroke. A majority of strokes had no AF recorded in the preceding month, and, in many instances, AF occurred only after stroke and not before. Does this imply that AF is not causative but only a marker of high-risk patients? In addition, whereas duration cutoffs of 30 seconds, 6 minutes, or 5.5 hours were predefined for the studies noted above, subsequent analysis from ASSERT on the relationship between the duration of AF on embolic events suggests that the risk of stroke only increases significantly with episodes of at least 24 hours in duration.[4] Thus, what is the best therapeutic decision for the treatment of a 6-hour episode of AF noted on a pacemaker interrogation of a patient with a CHA_2DS_2-VASc score of 3 or a 10-minute episode recorded from an implantable cardiac monitor in a patient following cryptogenic stroke?

Despite the rapid progression in technology to detect subclinical AF, equipoise exists regarding the role of anticoagulation, and even less is known regarding the value of the diagnostic evaluation of sleep apnea or ischemic heart disease that is now routine for clinical AF. My own clinical practice for subclinical AF is not to simply mimic the guidelines for clinical AF. Because the risk of subclinical AF is lower in most trials, I tend to recommend anticoagulation only in patients with a CHA_2DS_2-VASc of ≥3 and then only with prolonged episodes lasting hours and not minutes. It is important to note that I always have a discussion with the patient with regard to the pros and cons of treatment options acknowledging the uncertainties in this field. This is yet another example of technological advances raising as many questions as problems are solved.

It is fortunate that several studies are now underway to evaluate the role of anticoagulation of device-based AF in high-risk patients, including the ARTESiA study (The Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial fibrillation; ClinicalTrials.gov. Unique identifier: NCT01938248) and the NOAH-AFNET 6 trial (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes Trial; ClinicalTrials.gov. Unique identifier: NCT02618577). It will be several years until we have the results of these trials, so, in the interim, we need to decide for each of our patients with subclinical AF if one plus one equals two.

DISCLOSURES

Dr Gold is a Steering Committee Member of ASSERT and ATRESIA without remuneration.

AFFILIATION

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FOOTNOTES

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