Seek and Ye Shall Find Fibrillations

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aw No. 10 in the satirical book House of God states, “If you don’t take a temperature, you can’t find a fever.” In essence, do not go looking for problems. However, what if finding that fever led to ordering a limb ultrasound, discovering a deep vein thrombosis, prescribing anticoagulation, and averting life-threatening pulmonary emboli?

Similar logic now applies for atrial fibrillation (AF). It has been known for decades that AF directly causes ischemic stroke as fibrin-rich clots form in the left atrium, flicking off into the brain. However, AF is often paroxysmal and, hence, uncaptured on 12-lead ECG or inpatient telemetry—so what if, just a few days or weeks after stroke, finding that AF led to prescribing anticoagulation and averting massive, debilitating strokes?

In a longitudinal cohort study, Edwards et al compiled over a decade of data (2003–2013) from the Ontario Stroke Registry—patients in normal sinus rhythm, without known AF, after ischemic stroke or TIA.2 Outcomes included the proportion who received at least 24-hour Holter cardiac monitoring within 30 and 90 days. They found that after adjusting for potential confounders, the majority of the registry’s 17,398 subjects did not receive even a 24-hour monitor at either time point. Almost none (<1%) underwent prolonged monitoring (over 60 hours). They conclude that this woeful underuse of cardiac monitoring has likely caused a population-wide overdiagnosis of cryptogenic strokes and underdiagnosis of AF.2

AF currently affects ≈5 million Americans and has a lifetime risk of 1:4 over age 40.3 Compared with those without AF, those with AF carry a 5-fold higher future stroke risk,4 and unanticoagulated AF doubles recurrent stroke risk.5 AF represents 15% to 20% of all ischemic strokes and half from cardiac etiology.6 Besides this substantial morbidity, the mortality of AF-related strokes is 24% by 1 month and 50% at 1 year.5,7 Thus, guidelines recommend at least 24 hours of ECG telemetry after stroke but encourage longer monitoring: the American Academy of Neurology in 2014 stated, “Clinicians may obtain rhythm studies for prolonged periods (eg, 1 or more weeks) instead of shorter periods (eg, 24 hours) in cryptogenic stroke without known AF, to increase yield of identification of occult AF” and the American Heart/Stroke Association in 2011 advocated, “For patients who have stroke with no apparent cause, prolonged rhythm monitoring (>30 days) for AF is reasonable within 6 months of the event.”8,9

But do physicians adhere to this or instead follow House of God, doing nothing?9

Edwards et al admonish hasty, nihilistic stroke-etiology decision-making.2 Quickly decreeing patients’ cryptogenic without further monitoring seems ubiquitous, especially given its prevalence of ≈30% of all strokes.10 Yet, compared with conventional methods, long-term monitoring after stroke significantly increases detection of AF; decreasing cryptogenics.11 In an analysis of 17 studies of long-term monitoring, the AF detection rate jumped as high as 23% in cryptogenics, with longer monitoring demonstrating greater yield.8,9 In 2016, armed with our cornucopia of high-tech, wi-fi, mobile cardiac telemetry systems (transdermal devices wearable for weeks, subcutaneously inserted loop recorders logging rhythms for years, and previously installed pacemakers and defibrillators, interrogated readily), any rush to conclude cryptogenic seems impetuous. Perhaps including long-term monitoring in standard evaluation instead of advanced evaluation of stroke could motivate lethargic physicians?10

Anchor bias and premature closure involve fixating upon one diagnosis and avoiding auxiliary evidence. After an unrevealing standard evaluation in a third of stroke patients, that pesky cryptogenic moniker anchors in our mind, stuffing these patients into a diagnostic grab bag. Good luck, take an aspirin. We say this after a limited hospitalization stay, excluding only a few of the 200 known causes of stroke10 and despite the panoply of detection technologies available. Do not end the search at discharge!

Is not the point of screening to uncover true positives, provide appropriate therapy and prevent disease recurrence? Clearly, fewer monitors are ordered than indicated. There are barriers. First, cumbersome logistics: many patients, discharged from tertiary stroke centers and transferred by helicopter from distant smaller hospitals, may lack transportation, physical ability, or means to follow up. Second, physicians may decline monitoring because of its weighty responsibility: fastidiously interpreting results, coordinating interdisciplinary opinions, initiating treatment, checking laboratories, and exposing to anticoagulating liabilities (namely intracerebral hemorrhage). Third, long-term monitoring requires ancillary staff to educate patients on device instruction. Fourth, patients may disuse the monitor (claiming “it fell off” or even “I don’t like/need/want it”), but this nonadherence is probably alike other tests, laboratories, and medications.

What biomarkers augment AF yield with monitoring?

Older age, strokes in multiple brain territories, especially the cortex, and echocardiography showing left atrial dilatation, strain, big appendage, and single-lobe morphology.10
ECG hints include p wave dispersion and frequent atrial premature beats.\textsuperscript{10} Our favorite pearl is symptoms: dizziness (D), palpitations (P), and syncope (S); we coined the mnemonic “Ask For DiPS” at our institution. Nurses, fellows, residents, and medical students “Ask For DiPs” in stroke patients. If they screen DiPs-positive with negative standard work-up, then we order 3-week monitoring on discharge. Non-DiPSters may undergo other advanced evaluation,\textsuperscript{10} but ultimately may receive long-term cardiac monitoring in outpatient stroke clinic anyway because many AF patients are asymptomatic. But some insurance companies require DiPS symptoms to authorize outpatient monitoring; others consider monitoring investigational. However, as Edwards et al suggest, monitoring is cost-effective by preventing recurrent strokes.\textsuperscript{2}

Critics of this approach deem low-burden paroxysmal AF less risky than high-burden or chronic AF.\textsuperscript{10}\textsuperscript{11} However, 2 studies demonstrated that low-burden AF was still associated with 2-fold stroke risk versus those without AF.\textsuperscript{12,13} If monitoring identifies 15\% of low-burden AF,\textsuperscript{10} then of the ≈180000 Americans with cryptogenic stroke, we could unearth an extra 36000 AF-provoked stroke patients annually.

Unfortunately, stroke patients with AF (versus other stroke etiologies) more often are discharged to skilled nursing facilities or expire than go home or to rehabilitation.\textsuperscript{5,14} In a stroke registry here in Florida and Puerto Rico, we found this discrepancy applies to women with versus without AF, but interestingly men with stroke and AF had similar discharge disposition compared with men with stroke without AF.\textsuperscript{14} This apparent sex disparity may be multifactorial, but perhaps physicians are underscreening and undertreating women for AF.

Recent trials evaluating novel oral anticoagulants (NOACs) have shown noninferiority or superiority to warfarin in stroke prevention, with less intracranial hemorrhage. Subjects in these trials received their anticoagulant 7 to 14 days after stroke.\textsuperscript{15–17} At our university, the Cardiology and Neurology departments have jointly started the AREST trial (Apxiban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation). Our intent is to see if early NOAC use after AF-associated stroke shows a decreased risk for recurrent events without excess intracerebral hemorrhage. When to start NOAC depends on the ischemic stroke size on neuroimaging, and the comparator arm is conventional treatment with warfarin at 14 days.

Another study we are participating in is RESPECT-ESUS (Dabigatran Etxilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source), the randomized, double-blind, evaluation of the NOAC dabigatran versus aspirin to prevent stroke recurrence after Embolic Stroke of Undetermined Source (ESUS). RESPECT-ESUS and the other ongoing trial NAVIGATE-ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) (with the NOAC rivaroxaban) both exclude AF. However, the prerequisite for cardiac monitoring in these trials is only ≈23 hours. Enrolling and randomizing subjects to anticoagulation before prolonged heart monitoring will include patients initially labeled ESUS who actually would be diagnosed with paroxysmal AF had they been monitored for a few days or weeks after stroke. Monitoring would increase the yield of truly positive ESUS subjects for the trial and exclude those with AF who will, therefore, get the appropriate therapy—anticoagulation—instead of being potentially randomized to antiplatelet, which is inferior.

Given the danger of AF, its well-known morbidity/mortality risk—higher than most etiologies of ischemic stroke—physicians must avoid anchoring bias, perform long-term cardiac monitoring, follow-up the results, appropriately anticoagulate AF, particularly women, and then, if the patient truly seems cryptogenic, contemplate ESUS and enroll them into a trial.

Disclosures

Dr Rose is on speakers’ bureau for Chiesi-USA and Boehringer-Ingelheim. Drs Falcaio and Martin report no conflicts.

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