ATRIAL FIBRILLATION: ATRIAL HIGH RATE EVENTS (AHREs):

LOOK AND YOU WILL FIND - THEN WHAT?

By

Albert L. Waldo, MD, PhD (Hon), A. John Camm, MD,

The paper by Halcox et al. describes the Assessment of Remote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibfillation (REHEARSE-AF) Study, a randomized trial of screening for atrial fibrillation (AF) using a smartphone-based single lead ECG capture system in 1,001 patients ≥ 65 years, with a CHA2DS2-VASc score of ≥ 2, and without a previous history of AF(1). Patients were randomized either to bi-weekly ECG recordings using the iPhone device (iECG group, n=500), or to routine care (control group, n=501) over a 12-month period. Not surprisingly, patients with AF were identified, more in the iECG group (n=19) than in the control group (n=5).

The data from this study confirm results from studies with implanted pacemakers, ICDs, and loop recorders (2-9) and other AF screening studies (10,11) that in patients unknown to have AF, particularly those with cardiovascular comorbidities, the more you look for AF, the more you will find it. As Sophocles mused more generally, “look and you will find - what is unsought will go undetected.” But is there a need to know about asymptomatic episodes of so-called “subclinical AF” (SCAF)? What are the implications of such a finding?

Clinical AF is associated with increased rates of stroke, heart failure, mortality, hospitalization, and cognitive decline, much of which may present suddenly, and constitute irretrievable harm (12). Therefore, there is a strong *prima facie* argument that it would help to know the onset of AF as soon as possible, but that is true only if we have therapeutic strategies which can prevent the adverse consequences of AF both safely and effectively. Anticoagulation for AF leads to a reduction in stroke and mortality, and perhaps halts the decline of cognitive function and the onset of dementia. It seems that a solid case might be made to look for AF, and to react to its discovery by recommending anticoagulation. But is it that simple?

The AF detected by continuous monitoring with implanted devices, or frequent ECG sampling, as in the REHEARSE-AF study, may not have the same adverse consequences as in patients who present with clinically symptomatic AF. We have learned that paroxysmal, and perhaps persistent forms of AF, may have less risk of stroke than permanent AF (13,14). There also seems to be a direct relationship between stroke and the duration of episodes of AF, or the overall burden of AF. Do the possibly short and infrequent bouts of Atrial High Rate Events (AHREs), or SCAF, imply a clinically significant incidence of adverse consequences?

There are several studies in patients with implantable devices that have tried to quantify the duration of AF that would merit OAC based on the incidence of stroke or systemic embolism. They all showed an increased rate of stroke associated with AHREs. Representative data from these studies indicate that the duration of the AF is of particular importance. The MOST study (retrospective) found that AF as short as five minutes was associated with an increased risk of stroke (5). The TRENDS study, in which nearly half of the patients had a history of clinical AF before study enrollment,found that patients with moderate stroke risk and AHREs ≥ 5.5 hours per day in a 30-day period appeared to double thromboembolic risk (6). The ASSERT study in hypertensive patients found that episodes of AF lasting more than six minutes, as compared to no episodes, were associated with a 2.5 fold risk of ischemic stroke or systemic embolism (15). Then, the Detection of AHREs by Continuous Home Monitoring study in heart failure patients found that, compared with patients without detected AHREs, patients with detected AHREs > 3.8 hours over a day were nine times more likely to develop a thromboembolism (16). Most recently, a revisit of the ASSERT study data examined the duration of device-detected SCAF and the occurrence of stroke. They found that the risk of ischemic stroke or systemic embolism in patients with SCAF duration between six minutes and 24 hours was not significantly different from patients without SCAF. Only SCAF > 24 hours was associated with an increased risk of ischemic stroke or systemic embolism (17). It was concluded thatSCAF > 24 hours was associated with an increased risk of ischemic stroke or systemic embolism. And despite all of the above, importantly, there is the recognition that short AHREs are sometimes/often only a prelude to becoming longer episodes, most recently reported by the RATEF Registry study (7).

Another puzzle is that asymptomatic episodes of SCAF detected by continuous monitoring, in many, if not most studies, seem not to correlate closely with the timing of stroke (4,6-8,15). It may be that AF and thrombus formation might occur some days, weeks, or even months, before the clot dislodges from the atrium, and causes an embolic stroke, but it is difficult to incriminate AF as the stroke mechanism when the AF only occurs after the stroke. And, importantly, there are many causes of ischemic stroke, other than AF, none of which are unlikely in patients with AF. However, one large study (19), which combined a clinical database and a data-monitoring database, clearly demonstrated that there was a much higher likelihood of finding AF ≥ 5.5 hours duration within the days preceding the stroke than at other times.

If we accept that episodes of AHREs or SCAFs revealed by monitoring increase the risk of stroke, and may be mechanistically involved, the next question is whether these embolic events occur frequently enough and long enough to justify attempting stroke prevention with anticoagulant therapy. For all the above studies, the absolute risk of stroke was much lower than expected (19). For instance, in the relatively longer ASSERT study (mean three year follow up), the number of patients with a thromboembolic even was 1.20%, and the number of patients with AF detected before their thromboembolic event was 0.70%. Modeling studies have concluded that an ischemic event rate of ≥ 0.9%/year (direct oral anticoagulants) and 1.7%year (vitamin K antagonist therapy) are needed to justify anticoagulation for AF because of the major bleeding associated with anticoagulant therapy (20). It is, therefore, far from clear that anticoagulation is justified, especially for episodes of AF shorter than 24 hours in duration.

Two randomized controlled trials are currently underway to explore this issue. ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Sub-Clinical Atrial Fibrillation; NCT01938248) (21) randomizes apixaban against aspirin in patients with AHRE, and NOAH (Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes; NCT02618577) (22) in which similar patients receive edoxaban or placebo, with blind aspirin treatment available for placebo patients with an indication for aspirin. Neither trial will report for some years, which leaves the clinician still uncertain as to how to manage these patients (23). European guidelines have strongly recommend using the discovery of AHREs to “undergo further ECG monitoring to document AF before initiating AF therapy”, unless the thrombogenic risk of the patient, or patient preference, warrants anticoagulation (24).

How does the REHEARSE-AF study help? Halcox and his colleagues used bi-weekly, short recordings to identify AF in patients at risk of thrombogenesis. Is this a “poor man’s” version of arrhythmia monitoring, utilizing intermittent, short iECG recordings, rather than implantable device monitoring? Certainly, the frequent iECG recording, well outside the clinical norm will tend to reveal infrequent arrhythmia, but the short recording period gives little idea of the duration of the arrhythmia – mere identification is not enough. Finally, the results of the REHEARSE-AF study also serve to focus on issues seen in virtually all the previous AHRE studies. First, the adverse event rate (stroke, and systemic embolism) in the 1,001 participants was quite low (0.02%). Second, of the 16 total strokes, 14 were either causally unrelated to AF, or of undetermined etiology.

As far as choosing whether to anticoagulate the patient, we might as well follow the advice of Yogi Berra: “When you come to a fork in the road [decision], take it [guess].” Perhaps, it is better not to look for it – after all “what is left unsought will not be discovered.” But we can’t leave it there, thinking “out of sight, out of mind,” since what Victor Hugo actually wrote was “When a man is out of [his] sight [blind], it is not too long before he is out of [his] mind” [crazy],, and we would not want that, and all the other adverse complications of AF, to come tumbling down on our patients just because we were not prepared to look, find, and further evaluate what can be discovered using simple clinical techniques. Clearly, we have more work to do.

REFERENCES

1. Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, Gravenor MB: Assessment of REmote HEArt Rhythm Sampling using the AliveCor heart monitor to screen for Atrial Fibrillation: The REHEARSE-AF study. Circulation 2017;?????
2. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, Pouliot MS, Ziegler PD on behalf of the REVEAL AF Investigators: Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: The REVEAL AF study. JAMA Cardiol 2017;2:1-8
3. Healey JS, Alings M, Leong-Sit P, de Graaf J, Birnie D, Freericks M, Ha AH, Verma A, Leong D, Dokainish H, Philippon F, Barake W, Simek K, Hill M, Wang J, Carlson M, McIntyre W, Connolly S: Prevalence of sub-clinical atrial fibrillation using an implantable cardiac monitor in patients with cardiovascular risk factors: ASSERT II. Circulation, 2016;134:e714.
4. Nasir JM, Pomeroy W, Marler A, Hann M, Baykaner T, Jones R, Stoll R, Hursey K, Meadows A, Walker J, Kindsvater S: Predicting determinants of atrial fibrillation or flutter for therapy elucidation in patients at risk for thromboembolic events (PREDATE AF) Study. Heart Rhythm 2017; 7:955-961.
5. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA, MOST investigators: Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the Mode Selection Trial (MOST). Circulation 2003:107:1614-1619.
6. Glotzer TV, Daoud EG, Wyse DB, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia bur den from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol 2009:2:474-480.
7. Swiryn S, Orlov MV, Benditt DG, DiMarco JP, Lloyd-Jones DM, Karst E, Qu F, Slawsksy MT, Turkel M, Waldo AL: RATE Registry Investigators: Clinical implications of brief device-detected atrial tachyarrhythmias in a cardiac rhythm management device population: results from the Registry of Atrial Tachycardia, and Atrial Fibrillation episodes. Circulation 2016;134:1130-1140.
8. Martin DT, Bersohn MM, Waldo AL, Wathen MD, Choucair WK, Lip GY, Ip J, Holcomb AR, Akar JG, Halperin JL: IMPACT Investigators: Randomization trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. Eur Heart J, 2015;36:1660-1668.
9. Camm AJ, Simantirakis E, Goette A, Lip GY, Vardas P, Chlouverakis G, Diener HD, Kirchhof P: Atrial high-rate episodes and stroke prevention. Europace 2017;19:169-179.
10. Svenberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. Circulation 2015;131:2176-2184.
11. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Brifffa T, Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW, Freedman SB: Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation use iPhone ECG in pharmacies. The SEARCH-AF Study. Thromb Haemost 2014;111:1167-1176
12. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW: ACC/AHA Task Force members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:e199-e267. Doi: 10.1161/Cir.00000000000000041.
13. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Diaz R, Hohnloser SH, Lewis BS, Shestakovska O, Wang J, Connolly SJ: Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6,563 aspirin-treated patients in ACTIVE-A and AVERROES, Eur Heart J, 2015;36:2821-287a
14. Link MS, Giugliano RP, Rupp CT, Scirica BM, Huikuri H, Oto A, Crompton AE, Murphy SA, Lanz H, Mercuri MF, Antman EM, Braunwald E: ENGAGE AF-TIMI 48 Investigators: Stroke and mortality risk in patients with various patterns of atrial fibrillation: Results from the ENGAGE AF-TIMI 48 Trial (Effective anticoagulation with Factor Xa next generation in atrial fibrillation – thrombolysis in myocardial infarction 48). Circ Arrhythm Electrophysiol, 2017;10: pii: e004267. Doi 10.1161/CIRCEP 116 004267.
15. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators: Subclinical atrial fibrillation and the risk of stroke N Engl J Med 2012;366:120-129.
16. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK, Bauer WR, Paul V, Sack S: Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. Europace 2012;14:230-237.
17. Van Gelder IC, Healey JS, Crijns HJGM, Wang J, Hohnloser SH, Gold MR, Capucci A, Lau CP, Morillo CA, Hobbelt AH, Rienstra M, Connolly SJ: Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J 22017; 38:1339-1344.
18. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J. than CT, Keung EK, Singer DE: Atrial fibrillation b urden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. Circ Arrhythm Electrophysiol 2015;8:1040-1047.
19. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, Boriani G, Brachmann J, Brandes A, Chao T-F, Conen D, Engdahl J, Fauchier L, Fitzmaurice DA, Friberg L, Gersh BJ, Gladstone DJ, Glotzer TV, Gwynne K, Hankey GJ, Harbison J, Hillis GS, Hills MT, Kamel H, Kirchhof P, Kowey PR, Krieger D, Lee VWY, Levin L-A, Lip GYH, Lobban T, Lowres N, Mairesse GH, Martinez C, Neubeck L, Orchard J, Piccini JP, Poppe K, Potpara TS, Puererfellner H, Rienstra M, Sandhu RK, Schnabel RB, Siu C-W, Steinhubl S, Svendsen JH, Svennberg E, Themistoclakis S, Tieleman RG, Turakhia MP, Tveit A, Uittenbogaart SB, Van Gelder IC, Verma A, Wachter R, Yan BP: Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. Circulation 2017;135:1851-1867.
20. Eckman MH, Singer DE, Rosand J, Greenberg SM: Moving the tipping point: the decision to anticoagulated patients with atrial. Circ Cardiovasc Qual Outcomes. 2011;4:14-21.
21. NOAH (Non vitamin K Antagonist oral anticoagulants in patients with atrial high rate episodes: NCT02618577.
22. Healey JS, Martin JL, Duncan A, Connolly SJ, Ha AH, Morillo CA, Nair GM, Eikelboom J, Divakaramenon S, Kokainish H: Pacemaker detected atrial fibrillation in patients with pacemakers: prevalence, predictors, and current use of oral anticoagulation. Can J Card 2013;29:224-228.
23. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HD, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Po Butte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman E, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimmons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano J, Zeppenfeld K: 2016 guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J, 2016;37:2893-2962.
24. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Buenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893-2962.