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Complexities in the Atrial Fibrillation-Stroke Relationship: Improving Comprehension of Temporal Discordance, Magnitude Synergism, and Subclinical Atrial Fibrillation -- Three Sources of Consternation for Physicians Who Care for Patients with Atrial Fibrillation

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Abstract

That clinically-documented atrial fibrillation (AF) in association with a variety of elevated clinical/laboratory risk markers is associated with an increased risk of stroke is well known – regardless of whether the AF is paroxysmal, persistent, or permanent. Moreover, data is accumulating to suggest that the absolute rate of stroke should be expectedly higher with a greater burden of AF and greater degree of comorbid contributors. Relatedly, stroke prevention with chronic oral anticoagulation (OAC) is recommended for AF patients with appropriate risk markers by all major medical, cardiologic, and surgical guideline-writing organizations. However, at least two major clinical concerns about the above AF-stroke statements remain. First, if AF is related to stroke, why then is there not a consistent temporal relationship between a stroke and AF? Second, is there importance to and what should we do about device-detected AF (so-called subclinical AF [SCAF]) in the absence of clinically-recognized AF? This paper is designed to enhance the understanding of these issues and reduce the consternation of physicians who care for patients with AF with respect to them.

Introduction

That clinically-documented atrial fibrillation (AF) in association with a variety of elevated clinical/laboratory risk markers[1] is associated with an increased risk of stroke is well known -- regardless of whether the AF is paroxysmal, persistent, or permanent. Moreover, data is accumulating to suggest that the absolute rate of stroke should be expectedly higher with a greater burden of AF and greater degree of comorbid contributors[4-7]. Relatedly, stroke prevention with chronic oral anticoagulation (OAC) is recommended for AF patients with appropriate risk markers by all major medical, cardiologic, and surgical guideline-writing organizations. However, at least two major clinical concerns about the above AF-stroke statements remain. First, if AF is related to stroke, why then is there not a consistent temporal relationship between a stroke and AF? Second, is there importance to and what should we do about device-detected AF (so-called subclinical AF [SCAF]) in the absence of clinically-recognized AF?[8].

Discordance of Temporal Relationship Between AF and Stroke:

[1] If stroke in high-risk-marker-present AF patients is related to the AF, then why can such strokes be temporally unrelated to the timing of AF? In some studies, the last AF event prior to a stroke has been noted to occur >30 days before, while in others, AF is first demonstrated on continuous monitoring (initiated post stroke) one or more years post stroke. Additionally, if AF is causative of strokes in high-risk-marker patients, then why is not properly administered OAC preventative in 25% of cases or more? Is our model wrong, or have we oversimplified it? For several reasons I, among others, [9] strongly suspect the latter.

(a) AF in the absence of co-morbidities, has an incredibly low risk of stroke. So, the story cannot be AF in and of itself. Moreover, many of the high-risk-marker comorbidities, such as hypertension, diabetes, vascular disease, are themselves associated with an increased risk for stroke, independent of AF. Thus, a stroke in an AF patient may be a consequence of comorbid disorders and not directly due to AF. AF may simply be a marker of greater atrial myopathy with the latter the proximate cause of thrombus formation. Accordingly, is it ever possible to know if AF was causative of a stroke or just a marker of a thrombogenic comorbidity? When AF is present at the time of an imaging-documented embolic stroke, being causative seems likely. But, temporal discordance does not exclude AF as a factor just as an embolic event from a comorbidity in a patient who happens to be in AF does not absolutely indicate AF was the cause (see below). Thus, we should temper our statements regarding causality and our therapeutic expectations re: OAC protection. A stroke in an anticoagulated AF patient may not mean the OAC failed. Moreover,

Key Words

Atrial Fibrillation, Magnitude Synergism, Temporal Discordance, Subclinical Atrial Fibrillation

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the absence of laboratory measurement of anticoagulant activity with the non-vitamin K OACs at the time of a thromboembolic event further limits our ability to assess this relationship.

(b) AF induced strokes are ischemic, consequent to thromboembolism. However, a stroke in an AF patient can also be non-embolic, embolic but not from the left atrium (e.g., aorta, carotid, patent foramen, etc.), hemorrhagic (due to the OAC or not), or lacunar. Thus, OAC should not be expected to prevent all strokes in AF patients. Lumping together all strokes as a single outcome event in clinical trials, as is usually/often done may be a disservice re: their interpretation[10].

(c) In patients with AF and stroke-risk comorbidities, including older age, hypertension, diabetes, heart failure, and more, the left atria are not normal. Rather, there are endothelial, metabolic, anatomic, histopathologic, and contractile alterations in the atria that can be prothrombotic – including endothelial dysfunction, atrial dilation, and hypocontractility. These contributory dysfunctions can result from the comorbidities present as well as from any superimposed atrial tachycardic myopathy consequent to the AF itself and should contribute to thromboembolic risk synergistically[4-11]. Importantly, any component due to the AF may not resolve either immediately or completely upon cessation of AF (whether paroxysmal AF, cardioverted AF, or SCAF). Post-ablation and post-cardioversion imaging studies have demonstrated this clearly. Moreover, if a clot forms during a period of AF, it need not resolve or embolize synchronously with the termination of AF. Conceptually, it may even be more likely to embolize after some improvement of atrial contractile function following AF cessation. Thus, AF may contribute to causation but not be present at the time of thromboembolism. Understanding this allows us to recognize why there can be a temporal disconnect between the timing of AF and the timing of an AF-mediated stroke – though in a given patient at the time of a stroke, a causative relationship between the stroke and somewhat remote AF can never be certain.

Sub-Clinical Atrial Fibrillation – Is It Really a Dilemma?

[2] SCAF is of growing interest with respect to the above issues. Is SCAF of relevance and if so, when? It is only recently that SCAF has become a concern. A Medline search on the term "subclinical atrial fibrillation" produced no entries between 1990 and 2009 but 49 (including letters) between 2010 and the present, with 34 of the latter between 2016 and now. Notably, the importance of SCAF as a factor in thromboembolic risk originally grew out of observations made in patients implanted with pacemakers or defibrillators (P/ICD) but has been expanded by the recent trials utilizing insertable cardiac monitors in patients without known AF but identified as being at AF risk by demographic, echocardiographic, and/or laboratory risk markers. The P/ICD trials, using a variety of AF durations to define SCAF, clearly revealed an epidemiological link to increased stroke risk[1,8]. Some have suggested that the risk is greater the longer the duration of AF (a contributor to overall AF burden). My own belief (with clinical trial support) is that there cannot be an absolute threshold for SCAF duration and embolic risk; rather, the risk must be dependent upon the AF burden and the number and magnitude of the comorbidities present[4-7]. The greater the atrial pathophysiology created by the synergism of AF and underlying disease, the greater the risk. Hence the concept of magnitude synergism should be applied to understanding SCAF and considered when designing future clinical trials and interpreting their results[1,4]. It is not enough to just note the presence of SCAF and its longest duration; rather, a quantitative description of the setting in which it occurs is also a necessity (quantitative and qualitative comorbidity) and an assessment of AF burden should also be considered[4,7]. The recent KP-RHYTHM study [3] demonstrated that AF burden, not just the presence of AF, is important in quantitating the risk for stroke. In the KP-RHYTHM study: "the highest tertile of atrial fibrillation burden was associated with a more than 3-fold higher adjusted rate of thromboembolism….compared with the combined lower 2 tertiles…" Importantly, currently ongoing anticoagulation trials in device-detected SCAF patients [12,13] will add a great deal regarding the importance and treatment of SCAF.

Certainly, there is much more to debate about AF, stroke, clinical trials of such, and therapies. But given the discussion in recent times about the above two issues in particular, a better understanding of them can only improve upon our forward direction.

Disclosures

In the past 36 months, Dr. Reiffel has served as Principal Investigator of the REVEAL-AF trial, sponsored by Medtronic; as a member of the steering committee of the ORBIT AF trials and of CABANA; as a consultant to Janssen, Portola, Sanofi, Acesion, InCardia Therapeutics; on the speaker's bureau for Janssen; and as a member of the AF SCREEN program.

References

1. Reiffel JA. Optimum Risk Assessment for Stroke in Atrial Fibrillation: Should We Hold the Status Quo or Consider Magnitude Synergism and Left Atrial Appendage Anatomy?. Arrhythm Electrophysiol Rev. 2017;6 (4):161–166.
2. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL, McCabe P, Noseworthy PA, Perez MV, Turakhia MP. Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity: A Scientific Statement From the American Heart Association. Circulation. 2018;137 (20):e623–e644.
3. Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, Harrison TN, Liu TI, Solomon MD. Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation: The KP-RHYTHM Study. JAMA Cardiol. 2018;3 (7):601–608.
4. Reiffel JA. If it were only that simple. Eur. Heart J. 2016;37 (20):1603–5.
5. Lin YS, Chen YL, Chen TH. Comparison of clinical outcomes among patients with atrial fibrillation or atrial flutter stratified by CHA2DS2-Vasc score. JAMA Network Open, 2018; 1:e180941. 2018.
6. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D. Catheter Ablation for Atrial Fibrillation with Heart Failure. N. Engl. J. Med. 2018;378 (5):417–427.
7. Zoler ML. Beats of burden: AF ablation success gets new standard. Cardiology News,. 2018;16:1–4.
8. Di Cori A, Lilli A, Zucchelli G, Zaca V. Role of cardiac electronic implantable device in the stratification and management of embolic risk of silent atrial fibrillation: are all atrial fibrillations created equal?. Expert Rev Cardiovasc Ther. 2018;16 (3):175–181.

9. Passman R. Atrial fibrillation and stroke: The more we learn, the less we understand. Am. Heart J. 2018;201 ():158–159.
10. Perera KS, Sharma M, Connolly SJ, Wang J, Gold MR, Hohnloser SH, Lau CP, Van GI, Morillo C, Capucci A, Israel CW, Botto G, Healey JS. Stroke type and severity in patients with subclinical atrial fibrillation: An analysis from the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT). Am. Heart J. 2018;201 ():160–163.
11. Kamel H, Healey JS. Cardioembolic Stroke. Circ. Res. 2017;120 (3):514–526.
12. Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA).. https://clinicaltrials. gov/ct2/show/NCT01938248.
13. Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH). https://clinicaltrials.gov/ct2/show/ NCT02618577.