



Should Atrial Fibrillation Burden Be A Feature to Guide Thromboembolism Prophylaxis?

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Abstract

Atrial fibrillation (AF) is a well-known risk factor for cerebrovascular events and systemic emboli. However, the frequency and duration of AF necessary to be considered at risk for thrombus formation is unknown. This review summarizes the literature regarding AF burden and risk for thromboembolism. Previously, no distinction was made between patients who had paroxysmal versus persistent AF in regards to initiation of anticoagulation. Recently though, given an enhanced ability to detect even very brief paroxysms of AF via stored device diagnostics, the issue has been readdressed. However, despite multiple studies no clear threshold for AF burden to mandate anticoagulation has been established. In addition, there is a growing body of evidence which suggests that the pathophysiology of thrombus formation in AF involves mechanisms beyond just stasis due to protracted episodes of discoordinate atrial contraction. Therefore, once AF has been diagnosed and the risk-benefit ratio favors anticoagulation, therapy should be initiated and continued indefinitely unless a bleeding contraindication develops.

Abbreviations: AF = atrial fibrillation, AT = atrial tachycardia, LAA = left atrial appendage, PAF = paroxysmal atrial fibrillation, SE = systemic emboli.

Keywords: atrial fibrillation, stroke, cerebrovascular accident, implantable device.

Introduction

Atrial fibrillation (AF) is a well known risk factor for cerebrovascular events and systemic emboli (SE).¹⁻⁴ Embolization can occur with all forms of AF and has been associated with a high level of morbidity and mortality. Most practitioners rely on the well validated risk assessment tools, CHADS₂ and CHA2DS-2VAsC, to select the appropriate prophylaxis for SE with either aspirin, or an anticoagulant. Remarkably, AF burden, when categorized as paroxysmal, persistent or permanent, has not been demonstrated to be a relevant distinction for SE risk. Data support-

ing this conclusion has been based upon patient reporting of symptoms and/or physician determination of AF frequency. However, it is unclear if AF burden, categorized by frequency and duration of episodes when documented by stored electrograms from intracardiac devices, would be an additional risk factor for AF-related SE.

Background & Prior Studies

It is often presumed that patients with brief episodes of AF are less likely to experience SE. Consensus statements recommend anticoagulation

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for AF of at least 48 hours. By extrapolation, the AF guidelines do not mandate anticoagulation prior to cardioversion for AF of less than 48 hours.⁵ The rationale for this recommendation is the presumption that prolonged episodes of discoordinate atrial contraction are necessary to generate stasis and thus a thrombogenic left atrial milieu.⁶

This paradigm is based on multiple older studies which have noted fewer SE in patients with paroxysmal AF (PAF) as compared to "chronic AF". The definition of chronic AF in many older studies implies more sustained episodes of AF with no clear distinction made between long standing persistent and permanent AF. Specifically, in the Framingham study, the risk of stroke was 5.4% among patients with chronic AF and 1.3% in PAF patients.⁷ A similar conclusion and nearly identical SE incidence rates was also reported by Peterson et al. They analyzed the incidence of embolic complications among 426 patients with initial PAF. After transition from PAF to persistent AF, the incidence of SE rose from 2% to 5.6%, a nearly 3-fold increase.⁸ Also, Shimomura et al. reported a systemic embolism rate of 15 per 1,000 patient years with PAF, which was significantly lower than a embolization rate of 28 per 1,000 patient years reported with chronic AF.^{8,9}

The outcomes of more recent studies contradict prior results, showing that patients with PAF and persistent AF may have a similar risk of stroke. In the Stroke Prevention in Atrial Fibrillation trial, there was no significant difference in the yearly stroke rate for patients with paroxysmal versus sustained AF (5.6 versus 5.9 percent without aspirin and 3.2 versus 3.3 percent on aspirin).¹⁰

The Boston Area Anticoagulation Trial in Atrial Fibrillation also found a similar incidence of stroke in both groups - 13% in intermittent AF versus 17% in sustained AF.¹¹ In addition, a subset meta-analysis found that the reduction in ischemic stroke with oral anticoagulation in patients with PAF (1.5 events per 100 patient-years on coumadin versus 4.7 events on aspirin) was similar to that in patients with persistent AF (2.2 events per 100 patient-years on coumadin versus 4.2 events on aspirin).¹² Additional evidence of the embolic risk associated with PAF comes from AFFIRM and RACE trials that compared rhythm to rate control in patients with paroxysmal or sustained

AF. These studies demonstrated that embolization occurred with equal frequency whether a rhythm control or a rate control strategy was adopted.^{13,14}

A major limitation of each of these trials is that the design was not intended to specifically evaluate the impact of AF frequency and duration, which was incomplete/unavailable. Furthermore, patients with presumably low AF burden, PAF, represented only a small percent (<15%) of the study population.

AF Burden

Despite seemingly contradictory results, the current standard of care is that decisions regarding initiation of anticoagulation do not differentiate paroxysmal or persistent AF. That is, AF patients with high risk features (CHADS₂ score ≥ 2), are generally prescribed anticoagulants, irrespective of AF burden. This approach however, has been challenged. Stored electrograms retrieved from implanted cardiac devices provide diagnostic information for even asymptomatic, short-duration, and infrequent AF. Unlike the common presentation of AF, either by symptoms or incidental discovery, AF of even a mere few seconds is being identified among patients with an implanted device. However, it is unclear if patients with low AF burden, but with high CHADS₂ score require anticoagulation. Is their risk of SE similar to patients with longer/more frequent episodes AF? Is there a lower AF burden threshold that would mandate initiation of anticoagulation therapy?

In 2003, Glotzer et. al evaluated a 312 patient subgroup of the MOST (Mode Selection Trial) study with 27 months of follow-up. Their analysis demonstrated that the presence of any atrial high rate episode lasting >5 minutes was an independent predictor of death or nonfatal stroke.¹⁵ However, in 2005 Capucci et. al evaluated 725 patients with pacemakers, and found that AF episodes of 5 minutes to 1 day in duration were not associated with a significantly higher risk of SE. The risk of SE in patients with AF episodes of longer than one day though, was 3.1 times higher than patients with no/brief AF episodes, after adjustment for known risk factors.¹⁶

More recently, the TRENDS study evaluated the relationship between AF burden and stroke events. In this observational study, 3045 patients requir-

ing device therapy with an implantable atrial lead (pacemaker or defibrillator) were enrolled from 116 clinical sites. Utilizing stored electrogram data retrieved from routine device interrogation, the AF burden (duration of AF per day) was calculated and correlated to clinical SE. Low atrial tachycardia/fibrillation (AT/AF) burden (defined as < 5.5 hours on any single day in the preceding 30 days) conferred a risk for SE similar to having no AT/AF, whereas an AT/AF burden of >5.5 hours on any day during the antecedent 30 days doubles the risk for thromboembolism.¹⁷ This finding of a correlation between AF burden and stroke risk was also noted in the similarly designed ASSERT trial (Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial). Greater than 2000 patients with no history of AF in whom a device was implanted were evaluated over the course of 3 months. Those with atrial high rate episodes lasting > 6 minutes were more than twice as likely to suffer a stroke even after controlling for other stroke risk factors.¹⁸

Based on these studies, there is growing evidence that a quantitative relationship may exist between AT/AF burden and SE. This correlation would then imply that AF burden should be considered as a feature to guide anticoagulant therapy. To this end, when a retrospective study incorporated AF burden into risk stratification scheme, the specificity, but not sensitivity, for predicting SE was improved.¹⁹ An important study that will evaluate the clinical impact of AF burden on SE is the recently initiated IMPACT study. This multicenter, prospective, randomized study will utilize detection of AF by remote monitoring to guide initiation of anticoagulation therapy.²⁰

Mechanism of Stroke in Atrial Fibrillation

In addition to AF burden, there is further appreciation that the pathophysiology of SE in patients with AF may involve mechanisms more than merely protracted episodes of AF. In a recently published sub-study of the 40 patients in the TRENDS study who sustained an embolic event, 29 of 40 (73%) patients had zero AT/AF within the 30 days prior to the event. Hence, in the majority of the TRENDS population, there was no temporal relationship between AT/AF episodes and SE. This suggests that the mechanism for AF-related embolic events was not solely due to AT/AF episodes leading to pro-

longed stasis in a poorly contractile left atrium.²¹

Furthermore, the overall rate of SE in patients with AF enrolled in TRENDS was only 1.1% for patients with low AT/AF burden and 2.4% for those with a higher burden. All subsets were far below the 4% annual rate predicted based on older studies. Similar low rates of SE in patients with AF have been reported in multiple other more recent studies. Investigators have suggested that the lower stroke rates found in more recent studies may be due to improved therapies for stroke risk factors including hypertension and diabetes, further supporting the concept that SE in AF is not simply due to the presence of AF.¹⁷ It is noteworthy that the risk factors for SE in AF reflected by the CHADS₂ and CHA₂DS₂VASc scoring systems primarily reflect risk factors associated with vascular disease.

Emolic events in AF are likely due to a complex interplay of atrial tachyarrhythmias, endothelial dysfunction, systemic hypercoagulable state, and atherosclerotic disease. Atrial fibrillation has been implicated as a risk factor for endothelial dysfunction by increasing oxidative stress and proinflammatory agents. Mechanistically, AF impairs acetylcholine-mediated augmentation of blood flow, reduces plasma nitrite/nitrate levels, and thus facilitates endothelial dysfunction.²² A systemic hypercoagulable state is also evident in patients with AF, with upregulation of multiple coagulation factors, including prothrombin fragments 1 and 2, thrombin-antithrombin complexes, D-dimers, and fibrinogen.²³ Multiple investigators have also noted an increased atherosclerotic plaque burden in patients with AF. This increase is most readily identified in the thoracic aorta with transesophageal imaging. In the echocardiographic substudy of the SPAF III trial, 57% of patients were noted to have thoracic aortic plaque.²⁴ Furthermore, patients who do not have aortic plaque are noted to have lower than expected stroke rates (1.2%/year, 95% CI 0.2% to 8.7%) despite the presence of other known risk factors for stroke.²⁵

Left Atrial Appendage Occlusion and Anticoagulation

Among patients with nonvalvular AF, many investigators have observed that the vast majority of

atrial thrombi are located in the left atrial appendage (LAA).²⁶ Thus, occluding the LAA through either surgical ligation or use of the recently developed Watchman device (a self-expanding nitinol cage designed to completely occlude the LAA) may be attractive alternatives to chronic anticoagulation for reducing SE in patients with AF.²⁷ However, in addition to inconclusive data to support LAA occlusion (surgical or device) over anticoagulation,²⁸ the fundamental question regarding this strategy is if AF-related SE is solely related to thrombi originating from the LAA. As discussed above, merely a history of AF may tip the balance to increase the risk of stroke arising from sources other than LAA thrombi. Stopping anticoagulation in a patient in whom the LAA is occluded, but who has a high CHADS₂ score may paradoxically enhance the risk for stroke.

Anticoagulation after AF ablation

Recently, ablation has emerged as a potential method for eliminating symptomatic AF. A recent meta-analysis of over 15,000 patients revealed a success rate of 74% after more than 6 months of follow-up.²⁹ However, the appropriate management of anticoagulation post successful ablation remains uncertain. Since AF may promote stroke through mechanisms other than merely due to prolonged stasis in a poorly contractile left atrium, the risk of SE in a patient who is "cured" of AF may still be elevated. Yet, many clinicians contend that in the absence of recurrent AF post ablation, anticoagulation can be safely discontinued.³⁰ Current recommendations suggest that the management of anticoagulation after successful AF ablation be guided by the CHADS₂ point system.³¹

Conclusions

To date, risk assessment scoring tools such as CHADS₂ and the more recent CHA₂DS₂-VASc, are conventional and accepted methods used to help guide initiation of anticoagulation in AF. However, these acronyms likely over-simplify the complex pathophysiology of AF-related SE. Data from devices that provide continuous monitoring have further elucidated the relationship between AF and stroke and provide the growing evidence that a correlation exists between stroke risk and AF bur-

den. However, calculating and incorporating AF burden into clinical practice and the exact threshold that confers increased risk for SE and signals the need for initiation of anticoagulation remains uncertain. The authors are currently utilizing the TRENDS data of > 5.5 hours in a single day during a 30-day monitoring period as a risk factor for SE¹⁷. However, paradoxically, simply because a patient has not had any recent episodes of AF, does not imply that anticoagulation can be safely discontinued, as noted in the TRENDS stroke sub-study.²¹ The pathophysiology of stroke in AF patients likely involves more than just AF-induced stasis. Hence, once AF is diagnosed and the risk-benefit ratio favors anticoagulation, therapy should likely be continued indefinitely unless a bleeding contraindication develops. The role of anticoagulation after successful elimination of AF by ablation or deployment of a LAA closure device remains to be determined.

Disclosures

- Molly Sachdev - none.
- Emile Daoud- Consultant: Medtronic, St. Jude and Biosense Webster Research support: Medtronic, St. Jude, Biosense Webster, and Boston Scientific

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