Role of Atrial Fibrillation Burden in Assessing Thromboembolic Risk

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Stroke represents the most devastating complication of atrial fibrillation (AF). Our understanding of the pathophysiology of thromboembolism in patients with AF remains incomplete, and as such, our assessment and management of this risk is imperfect. Current guidelines regard the risk of thromboembolism as independent of the frequency or duration of AF. Paradoxically, standard practice in the pericardiogram version period considers thromboembolic risk to accrue after 48 hours of AF. This recommendation, however, is based on limited data, including an observational study of 357 patients which demonstrated that the risk of thromboembolic events was <1% in patients with AF lasting <48 hours who cardioverted without prolonged anticoagulation therapy or a transesophageal echocardiogram. No strong randomized control trial data exist to specifically support a 48-hour safety cut-off, and recent data suggest that the duration of AF associated with a significantly increased risk of stroke may in fact be less. The emergence of technology to allow absolute quantification of the frequency and duration, or burden, of AF offers the opportunity to refine our assessment and management of thromboembolic risk associated with AF.

Historical Association Between AF and Thromboembolic Risk

It has been 200 years since William Wood described a ball thrombus in the left atrium of a patient with mitral stenosis and 170 years since Virchow identified the critical components required for thrombus formation. It took until 1930 for Harvey and Levine to first declare that “auricular fibrillation definitely increases the incidence of auricular thrombosis” in an autopsy series of patients with mural thrombi. Uncertainty as to whether nonneumatic AF resulted in stroke continued for the next 40 plus years until Wolfe and colleagues, in their landmark analysis using the Framingham population data, identified a 5.6-fold increased risk of stroke in patients with chronic nonvalvular AF. With time it would become apparent that paroxysmal as well as continuous AF were associated with increased thromboembolic risk, although the mechanism of this association continues to remain an area of uncertainty. Nonetheless, the critical therapeutic introduction of warfarin therapy for patients with AF resulted in a roughly 65% reduction in the risk of stroke. The anticipated increase in the prevalence of AF with the aging of the worldwide population and advances in our ability to detect AF portends a marked expansion in the number of patients who will meet current criteria for lifelong anticoagulation. It is our challenge to further refine our understanding of who is at risk for thromboembolism and develop ways to reduce the burden of the therapies used to reduce this risk.

Risk Factors for Stroke and Criteria for Thromboembolic Prophylaxis in Patients With AF

The validated CHADS2 scoring system has long been the standard for thromboembolic risk stratification in AF. Until recently, the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines used the CHADS2 components with additional consideration for anticoagulation in patients between the age of 65 and 74 with concomitant diabetes mellitus, coronary artery disease, or congestive heart failure. The CHADS2-VASc system represents a further refinement of the CHADS2 system and has been adapted into the European and now the American AF guidelines. In both the American and European guidelines, >1 risk factor qualifies for lifelong anticoagulation with warfarin or one of the new oral anticoagulants. For patients with a CHA2DS2-VASc score of 1, the European guidelines recommend anticoagulation, whereas the American guidelines differ and consider aspirin, oral anticoagulation, or no therapy as equally appropriate. In the European guidelines, aspirin has also been removed as a recommended therapeutic option in low- and moderate-risk patients. One of the important strengths of the CHA2DS2-VASc system is the identification of a low-risk population with a score of 0 who might be able to safely avoid anticoagulation; however, this group represents only 5% to 10% of the world’s 35 million individuals with AF.

The CHADS2 and CHA2DS2-VASc systems are arguably the most widely used risk scoring tools for any cardiovascular disease in clinical practice, yet compliance with these guidelines remains poor. In fact, a major component of noncompliance relates to the counterintuitive absence of distinction between paroxysmal and continuous AF in these scoring systems. Questions inevitably arise from patients and physicians alike—why must one be anticoagulated if AF is believed to be absent.
fully suppressed, or potentially cured? And furthermore, if episodes of <48 hours duration are considered safe for cardioversion without antecedent transesophageal echocardiogram or anticoagulation, why is anticoagulation required for maintenance therapy in patients with short duration AF recurrences?

The equivalent thromboembolic risk of paroxysmal and permanent AF has been an observation rather than a prespecified hypothesis in several therapeutic trials of different anticoagulation regimens. Some secondary analyses of large trials have, however, demonstrated a lower risk of thromboembolic events in patients with paroxysmal AF compared with persistent/permanent AF. This inconsistency does, however, pose the fundamental question of whether AF is the direct cause of thrombosis or merely an associated condition, and, if it is a direct cause of thrombosis, how much AF is needed to generate this risk. Specifically, can the burden (frequency and duration of AF episodes) further guide thromboembolic risk stratification?

Data That Support AF Burden as a Risk for Thromboembolism

It has long been recognized that intermittent monitoring of patients with known AF provides an incomplete assessment of AF frequency. The ability to accurately define AF burden has now been improved by advances in pacemaker, implantable cardioverter-defibrillator (ICD), and implantable monitor technology with remote monitoring capabilities (Figure 1), and data from a multitude of device studies have identified a significant thromboembolic risk associated with asymptomatic and frequently short duration episodes of AF (Table). These studies generally required an AF episode to last ≥5 to 6 minutes to be accurately classified as AF. A meta-analysis of over 10000 patients in 3 of these studies identified 43% with ≥5 minutes of AF, and, after correcting for CHADS2 score and anticoagulation status, there was a 2-fold increased risk of stroke associated with as little as 1 hour of AF with increasing risk associated with increasing AF burden.

The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) study of 2580 patients (median age 76 years, 58% male, 6.6% with prior stroke, mean CHADS2 score 2.3) with dual chamber pacemakers or ICDs and newly identified, asymptomatic AF found a 2.5-fold increased hazard of stroke associated with episodes >6 minutes in duration. In particular, there was a nearly 5-fold increased risk of stroke associated with episodes of >17.7 hours compared with a 1.3-fold risk in those with <17.7 hours of AF. The total number of AF episodes did not correlate with stroke risk, suggesting that episode duration rather than frequency was the more critical component of AF burden.

Of note was that the absolute risk of stroke or systemic embolism among all patients who had subclinical AF detected was 1.69%/year (with a range between 0.56%/year for patients with a CHADS2 score of 1, to 3.78%/year for patients with a CHADS2 score >2). This absolute risk is lower than has been observed in some studies investigating the risk of thromboembolism in clinically documented AF. It is difficult to draw direct comparisons between the absolute thromboembolic risk in ASSERT and other modern AF trials because anticoagulation has become the standard of care for clinically detected AF, and only 18% of patients in ASSERT who had subclinical AF detected were on oral anticoagulants.

Data That Challenge the Association of AF Burden With Risk of Thromboembolism

Two studies referenced above have also provided data to potentially refute the association of AF burden with stroke risk. The TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) study of 2486 patients (median age 71 years, 66% male, 13.4% with prior thromboembolic event, mean CHADS2 score 2.2) with a history of AF and a dual chamber pacemaker or ICD found a trend toward increased stroke risk with AF episodes lasting ≥5 hours. However, further analysis revealed that only 11 out of the 40 patients in that study who developed a thromboembolic complication had an episode of AF within a month of the event.

In the ASSERT study, 51 patients had a nonhemorrhagic stroke or embolic complication, but only 51% (n=26) of these patients had subclinical AF identified before or after the event. Of the 26 patients with identified AF, only 4 had AF within 30 days and only 1 had AF at the time of stroke (Figure 2). Importantly, the CHADS2 and CHA2DS2-VASc scores in these ASSERT stroke patients were 2.8±1.1 and 4.5±1.2, respectively.

Similarly, in a study of 560 patients with biventricular pacemakers or ICDs, despite a 4-fold increased risk of stroke among those with AF compared with those without AF, only 27% of patients were in AF at the time of stroke. In all of these studies, the number of strokes was remarkably low. Nonetheless, these data suggest that at least in patients with multiple risk factors for stroke (ie, CHADS2 scores >2), a causal link between AF frequency/duration and stroke risk may not clearly exist.

Is There a Way to Reconcile the Data for and Against an Association of AF Burden and Stroke Risk?

It has become clear that it is far too simplistic to presume that thrombus formation is produced only by AF. Multiple potential mechanisms of thrombosis have been proposed in
AF patients which can be associated with, but not necessarily caused by, proximate arrhythmia occurrence. In addition, it is clear that our current risk scoring systems also identify patients at risk for stroke independent of the presence of AF. In one study of 860 patients with AF and a history of stroke, 39% had other potential cardiac sources of embolism beyond AF and 27% had a concomitant possible atherothrombotic mechanism of stroke. The association of these alternative sources of stroke in patients with AF was significantly correlated with increasing CHADS2/CHA2S2-VASc scores. Other

### Table. Studies Showing A Correlation Between AF Burden and Stroke or Systemic Embolism

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patients (n)</th>
<th>Study Type</th>
<th>AF Monitoring</th>
<th>Follow-Up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glotzer et al (2003)</td>
<td>312</td>
<td>Secondary analysis of multcenter RCT (MOST)</td>
<td>Dual-chamber PPM Median 27 mo</td>
<td>10 patients (3.2%) developed stroke AHRE lasting ≥5 min associated with HR of 2.79 for death or nonfatal stroke (P=0.0011)</td>
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<tr>
<td>Capucci et al (2005)</td>
<td>725</td>
<td>Prospective registry (AT500 Registry)</td>
<td>Dual-chamber PPM Median 22 mo</td>
<td>14 patients (1.9%) developed a thromboembolic event (11 were stroke or TIA) AF episodes lasting &gt;24 h associated with adjusted HR of 3.1 for thromboembolic event (P=0.044) AF episodes lasting between 5 min and 24 h were not associated with a significant increase in thromboembolic risk</td>
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<tr>
<td>Botto et al (2009)</td>
<td>568</td>
<td>Prospective observational study</td>
<td>Dual-chamber PPM 1 y</td>
<td>14 patients (2.5%) developed stroke or systemic embolism When patients were stratified into multiple groups based on CHADS2 score (0, 1, 2, or ≥3) and duration of AF episodes over 24 h (~5 min, 5 min to 24 h, and 24 h continuously), this allowed selection of 2 patient populations with significantly different annual rates of thromboembolic events (0.8% vs 5%) Patients with a high CHADS2 score and any burden of AF and patients with a low CHADS2 score and a high burden of AF had increased rates of thromboembolism.</td>
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<tr>
<td>Glotzer et al (2009)</td>
<td>2486</td>
<td>Prospective observational study (TRENDS)</td>
<td>Dual-chamber PPM or ICD Mean 1.4 y</td>
<td>Annual thromboembolic risk was 1.1% for patients with no AF, 1.1% for patients with AF episodes lasting &lt;5.5 h (low burden), and 2.1% for patients with AF episodes lasting ≥5.5 h (high burden) No statistically significant difference in thromboembolic events between no AF, low burden, and high burden groups, although P value of borderline significance in comparison between high burden and zero burden (HR 2.20, P=0.06) 30-day cumulative AF burden ≥10.8 h showed a trend toward association with an increased risk of thromboembolism (HR 2.22, P=0.06)</td>
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<tr>
<td>Healey et al (2012)</td>
<td>2580</td>
<td>Primary analysis of RCT (ASSERT)</td>
<td>Dual-chamber PPM or ICD Mean 2.5 y</td>
<td>Annual rate of thromboembolism 1.69% in patients with atrial tachyarrhythmia episodes lasting &gt;6 min compared with 0.69% in patients with episodes &lt;6 min (HR 1.76, P=0.05) Longest atrial tachyarrhythmia &lt;17.7 h—an annual rate of stroke or systemic embolism was 1.2% Longest atrial tachyarrhythmia &gt;17.7 h—an annual rate of stroke or systemic embolism was 4.9%</td>
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<tr>
<td>Shanmugan et al (2012)</td>
<td>560</td>
<td>Secondary analysis of 2 prospective, multcenter, observational studies (Home CARE &amp; everesT)</td>
<td>Biventricular PPM or ICD Mean 370 days</td>
<td>11 patients (2%) had a thromboembolic event AHRE ≥3.8 h/d were associated with HR 9.4, P=0.006 for stroke or systemic embolism compared with patients without arrhythmia</td>
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<tr>
<td>Boriani et al (2014)</td>
<td>10 016</td>
<td>Pooled analysis of 3 prospective studies (TRENDS, PANORAMA &amp; Italian ClinicalService® Registry</td>
<td>PPM or ICD with atrial lead Mean 24 mo</td>
<td>95 patients (0.39%/y) experienced stroke or systemic embolism AF burden was independently associated with thromboembolism at multiple cutoff points AF episodes &gt;1 h were associated with HR of 2.11, P=0.008 for ischemic stroke AF episodes &gt;5 min were associated with HR 1.76, P=0.041 for ischemic stroke For every hour of AF in a 24 h period, the relative risk for stroke increased by 3%</td>
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AHRE indicates atrial high rate episodes; AF, atrial fibrillation; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; PPM, permanent pacemaker; and RCT, randomized control trial.
markers of stroke risk, such as left atrial dysfunction, can be identified in patients without documented AF, correlate with increasing CHADS$_2$/CHA$_2$DS$_2$-VASc scores, and represent potential contributors to embolic stroke risk in patients with intermittent AF.$^{37}$ Additionally, patients can have nonthromboembolic strokes because of multiple factors, including hypertension or in situ thrombosis, which have no mechanistic relationship with AF. Therefore, it should not come as a surprise that patients with a history of AF can have thromboembolic events without proximate AF episodes. It is also important to realize that although thromboembolic events were adjudicated in both the ASSERT and TRENDS studies, the diagnosis was based primarily on clinical symptoms rather than detailed brain imaging, and given that all patients had pacemakers or ICDs, brain MRI would not be routinely used for stroke diagnosis.

Pacemakers and ICDs are also only able to detect AF by measuring the rate of atrial activation at the site where the right atrial lead is positioned, and this adds a layer of complexity to the association between device-detected AF and subsequent thromboembolic events. AF detected in the right atrium from a pacing lead can be associated with organized atrial activity at a range of rates as slow as 200 beats per minute, even when the surface ECG demonstrates absent atrial activity. As a result, AF detection algorithms rely predominantly on detecting an atrial rate above a set threshold (eg, 200 beats per minute). Therefore, all device-detected episodes of atrial tachycardia may not be AF, particularly when the rate cutoff for identification of AF is set well below 200 beats per minute. On the other hand, subclinical atrial tachycardia other than AF may still be associated with an increased risk of stroke, and some studies have even demonstrated an association between short runs of atrial tachycardia and subsequent stroke.$^{40}$ Whether this association is related directly to the arrhythmia itself and association of these other arrhythmias with AF requires further study.

One attractive hypothesis proposes that AF burden dictates stroke risk in patients with an otherwise low risk of stroke (low CHADS$_2$ score). Conversely, as the CHADS$_2$ score increases, the influence of AF burden on stroke risk diminishes. Botto et al evaluated 568 patients after dual chamber pacemaker implantation. Thromboembolism developed in 14 patients (2.5%) over 1 year of follow up with a linear increase in risk related to increased AF burden across all CHADS$_2$ scores. In this analysis, patients were stratified by AF burden (duration of AF episodes per 24 hour period: <5 minutes, 5 minutes to 24 hours, and 24 hours continuously) and CHADS$_2$ score (0, 1, 2, or $\geq 3$). A relationship between AF burden and CHADS$_2$ score existed for those patients with intermediate CHADS$_2$ scores (1–2) but not for those with high scores ($\geq 3$) and low scores (0). The thromboembolic risk was similar (5.0%) for a patient with a CHADS$_2$ score of 1 and continuous AF and a patient with CHADS$_2$ $\geq 3$, regardless of the AF burden. Conversely, the risk was 0.8% for patients with a CHADS$_2$ score of 0 to 2 with no AF (Figure 3).$^{33}$ These data support the hypothesis that patients with a low burden of AF and a low to intermediate stroke risk may be safe without continuous anticoagulation.

**Remote Monitoring to Guide Anticoagulation in Patients With AF**

The IMPACT (Multicenter randomized study of anticoagulation guided by remote rhythm monitoring in patients with implantable cardioverter-defibrillator and CRT-D devices) study
Risk of thromboembolic events

- 0.8% to 5.0%
- P = 0.035
- 58 Pts No AF
- 80 Pts No AF
- 24 Pts No AF
- 4 Pts No AF
- 54 Pts AF >5 min
- 76 Pts AF >5 min
- 42 Pts AF >5 min
- 7 Pts AF >5 min
- 59 Pts AF >24 h
- 113 Pts AF >24 h
- 45 Pts AF >24 h
- 6 Pts AF >24 h

Figure 3. Thromboembolic risk stratified by atrial fibrillation (AF) duration and CHADS2 score. Combination of AF burden and CHADS2 score separated the study population into 2 groups with significantly different thromboembolic risk (0.8% vs 5.0%). Columns correspond to CHADS2 scores and rows correspond to AF duration over the course of 1 day (none, >5 min, and 24 h continuous). Reprinted from Botto et al33 with permission of the publisher. Copyright ©2009, Wiley Periodicals, Inc.

represented an initial foray into the concept of intermittent, tailored anticoagulation based on the presence or absence of AF. This was a randomized control trial of remote monitoring to identify and guide anticoagulation in patients with previously implanted dual chamber and biventricular ICDs. Importantly, patients did not have to have a history of AF to enroll in the study. Patients with a CHADS2 score of 1 to 2 and previously identified noncontinuous AF for stroke risk. If there is a population for whom AF burden of 6 hours. Patients resume anticoagulation as soon as these criteria are no longer met.

The REACT.COM (Rhythm Evaluation for AntiCoagulaTion with COntinuous Monitoring) study (Clinicaltrials.gov identifier NCT 01706146) is a multicenter pilot study of 75 patients with a Medtronic REVEAL XT™ implanted for AF surveillance. As with the TACTIC study, patients with infrequent AF and a CHADS2 score of 1 to 2 who can tolerate a new oral anticoagulant are monitored with the goal of reducing the amount of time they spend on anticoagulation. Enrollment can occur when there has been <1 hour of continuous AF for 2 consecutive months. Patients transmit data to their physician every morning at a prespecified time and with symptoms compatible with AF. Anticoagulation is discontinued after 30 consecutive days with <1 hour of AF and is resumed for a continuous AF episode of ≥1 hour. If these 2 pilot studies prove feasible, larger definitive trials will be required to determine if anticoagulation can be safely started and stopped based on AF burden.

Summary

Currently available data have demonstrated that many patients without a clinical history of AF will have short episodes of AF detected on pacemaker and ICD interrogations. The clinical implications of short (lasting seconds to minutes) subclinical episodes of AF and the optimal cutoff time for treating device-detected AF episodes remain unclear. It is likely, however, that continuous AF episodes lasting more than a few hours, but <48 hours, do carry an increased risk of thromboembolic stroke, with a risk profile that likely varies based on a patient’s underlying substrate and thromboembolic risk factors.

Our current approach to thromboembolic prophylaxis is fraught with uncertainty and contradiction. The time honored assumption that 48 hours of AF is required for thrombus development has formed a first principle of AF management for decades. Emerging data have challenged this premise and, in fact, have drawn into question the importance of proximate AF for stroke risk. If there is a population for whom AF burden significantly contributes to stroke risk, it is likely those patients with few non-AF–related stroke risk factors. The availability of sophisticated, continuous remote monitoring and new, rapidly acting oral anticoagulants affords the opportunity to formally test a strategy of tailored anticoagulation and the hypothesis that some lower-risk patients may be able to stop and start anticoagulation based on the pattern of AF.
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