

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.¹ Paradoxically, standard practice in the pericardioversion period considers thromboembolic risk to accrue after 48 hours of AF.¹ 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.² 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.³⁻⁸ 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 stenosis⁹ and 170 years since Virchow identified the critical components required for thrombus formation.¹⁰ 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.¹¹ Uncertainty as to whether nonrheumatic 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.¹² 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.¹³ The anticipated increase in the prevalence of AF with the aging of the worldwide population^{14,15} 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.¹⁶ 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.¹⁷ The CHA₂DS₂-VASc system¹⁸ represents a further refinement of the CHADS₂ system and has been adopted into the European¹⁹ and now the American AF guidelines.¹ 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.²⁰⁻²²

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.²³ 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,

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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.^{24,25} 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.²⁶ 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.^{4,5,27–31} 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^{3–8,33} (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.⁶

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 AF 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.⁴

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).⁴ This absolute risk is lower than has been observed in some studies investigating the risk of thromboembolism in clinically documented AF.³⁴ 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.³ 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.³⁵ 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 \pm 1.1 and 4.5 \pm 1.2, respectively.³⁶

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.⁸ 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

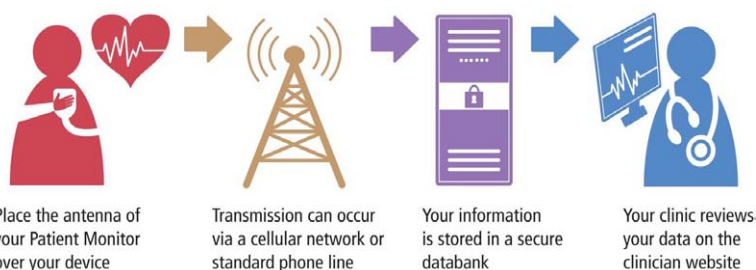


Figure 1. Remote transmission of arrhythmia data. Reproduced with permission from Zimetbaum et al. Copyright ©2013, The Authors. Journal compilation ©2013 Wiley Periodicals, Inc.³²

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

Author (year)	Patients (n)	Study Type	AF Monitoring	Follow-Up	Outcome
Glotzer et al (2003) ⁵	312	Secondary analysis of multicenter RCT (MOST)	Dual-chamber PPM	Median 27 mo	10 patients (3.2%) developed stroke AHRE lasting ≥5 min associated with HR of 2.79 for death or nonfatal stroke (<i>P</i> =0.0011)
Capucci et al (2005) ⁷	725	Prospective registry (AT500 Registry)	Dual-chamber PPM	Median 22 mo	14 patients (1.9%) developed a thromboembolic event (11 were stroke or TIA) AF episodes lasting >24 h associated with adjusted HR of 3.1 for thromboembolic event (<i>P</i> =0.044) AF episodes lasting between 5 min and 24 h were not associated with a significant increase in thromboembolic risk
Botto et al (2009) ³³	568	Prospective observational study	Dual-chamber PPM	1 y	14 patients (2.5%) developed stroke or systemic embolism When patients were stratified into multiple groups based on CHADS ₂ 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 CHADS ₂ score and any burden of AF and patients with a low CHADS ₂ score and a high burden of AF had increased rates of thromboembolism.
Glotzer et al (2009) ³	2486	Prospective observational study (TRENDS)	Dual-chamber PPM or ICD	Mean 1.4 y	Annual thromboembolic risk was 1.1% for patients with no AF, 1.1% for patients with AF episodes lasting <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 <i>P</i> value of borderline significance in comparison between high burden and zero burden (HR 2.20, <i>P</i> =0.06) 30-day cumulative AF burden ≥10.8 h showed a trend toward association with an increased risk of thromboembolism (HR 2.22, <i>P</i> =0.06)
Healey et al (2012) ⁴	2580	Primary analysis of RCT (ASSERT)	Dual-chamber PPM or ICD	Mean 2.5 y	Annual rate of thromboembolism 1.69% in patients with atrial tachyarrhythmia episodes lasting >6 min compared with 0.69% in patients with episodes <6 min (HR 1.76, <i>P</i> =0.05) Longest atrial tachyarrhythmia <17.7 h—annual rate of stroke or systemic embolism was 1.2% Longest atrial tachyarrhythmia >17.7 h—annual rate of stroke or systemic embolism was 4.9%
Shanmugan et al (2012) ⁸	560	Secondary analysis of 2 prospective, multicenter, observational studies (Home CARE & everest)	Biventricular PPM or ICD	Median 370 days	11 patients (2%) had a thromboembolic event AHRE ≥3.8 h/d were associated with HR 9.4, <i>P</i> =0.006 for stroke or systemic embolism compared with patients without arrhythmia
Boriani et al (2014) ⁶	10016	Pooled analysis of 3 prospective studies (TRENDS, PANORAMA & Italian ClinicalService® Registry)	PPM or ICD with atrial lead	Median of 24 mo	95 patients (0.39%/y) experienced stroke or systemic embolism AF burden was independently associated with thromboembolism at multiple cutoff points AF episodes >1 h were associated with HR of 2.11, <i>P</i> =0.008 for ischemic stroke AF episodes >5 min were associated with HR 1.76, <i>P</i> =0.041 for ischemic stroke For every hour of AF in a 24 h period, the relative risk for stroke increased by 3%

AHRE indicates atrial high rate episodes; AF, atrial fibrillation; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; PPM, permanent pacemaker; and RCT, randomized control trial.

AF patients which can be associated with, but not necessarily caused by, proximate arrhythmia occurrence.^{37,38} In addition, it is clear that our current risk scoring systems also identify patients at risk for stroke independent of the presence of AF.³⁹ 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.³⁸ Other

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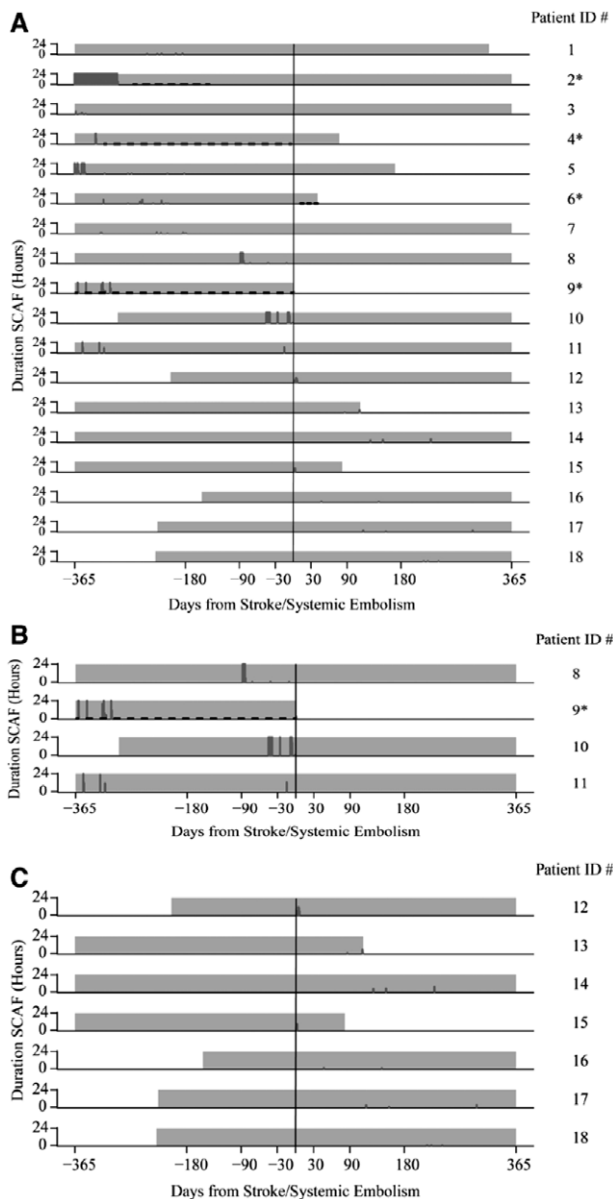


Figure 2. Summary of subclinical atrial fibrillation (AF) burden and its temporal relationship to stroke and systemic embolism in the ASSERT trial. Light gray shaded areas represent the period of continuous rhythm monitoring with a pacemaker or implantable cardioverter-defibrillator (ICD). The height of the dark gray bars represents the total number of hours of AF per day. Asterisks denote patients who were on anticoagulation therapy and black dashed lines denote the period of anticoagulant use. **A**, Summary of subclinical AF occurring within 1 year of stroke or systemic embolism. Each row represents data collected from each of 18 patients who had subclinical AF within 1 year of their thromboembolic event. Eight patients who had subclinical AF >1 year before or after their thromboembolic event are not shown. **B**, Summary of subclinical AF episodes in 4 patients who had subclinical AF detected within 30 days of their thromboembolic event. **C**, Summary of subclinical AF episodes in 7 patients who had subclinical AF detected within 1 year after a thromboembolic event. Reprinted from Brambatti et al³⁶ with permission of the publisher. Copyright ©2014, Wolters Kluwer Health.

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 tachycarrhythmias 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 tachycarrhythmias 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 CHADS₂ score). Conversely, as the CHADS₂ 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 CHADS₂ 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 CHADS₂ score (0, 1, 2, or ≥3). A relationship between AF burden and CHADS₂ score existed for those patients with intermediate CHADS₂ scores (1–2) but not for those with high scores (>2) and low scores (0). The thromboembolic risk was similar (5.0%) for a patient with a CHADS₂ score of 1 and continuous AF and a patient with CHADS₂ ≥3, regardless of the AF burden. Conversely, the risk was 0.8% for patients with a CHADS₂ 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

markers of stroke risk, such as left atrial dysfunction, can be identified in patients without documented AF, correlate with increasing CHADS₂/CHA₂DS₂-VASc scores, and represent

Risk of thromboembolic events

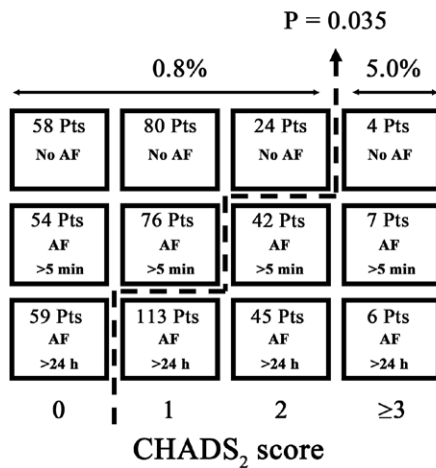


Figure 3. Thromboembolic risk stratified by atrial fibrillation (AF) duration and CHADS₂ score. Combination of AF burden and CHADS₂ score separated the study population into 2 groups with significantly different thromboembolic risk (0.8% vs 5.0%). Columns correspond to CHADS₂ scores and rows correspond 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 48 hours of continuous AF were started on warfarin. Anticoagulation was discontinued in this intermediate risk group after 30 consecutive days without AF. Patients with high stroke risk (CHADS₂ 3–4) required 24 hours of AF to initiate warfarin and 90 consecutive days free of AF to discontinue it, whereas high risk patients (CHADS₂ 5–6) remained on anticoagulation regardless of AF burden.⁴¹ The study was discontinued prematurely because of an absence of benefit associated with an intermittent strategy of anticoagulation. The vast majority of patients received warfarin rather than new oral anticoagulants, and the time in therapeutic range was suboptimal at ≈59%. In addition, out of the 2718 patients enrolled, only 241 had AF during the study, and only 69 had a thromboembolic event.⁴²

Two additional pilot studies are underway to further define whether tailored anticoagulation is feasible in patients with AF. Both of these studies only use the newer oral anticoagulants (dabigatran, rivaroxiban, and apixaban) because of the ease and safety of rapid anticoagulation and include only patients with a CHADS₂ score of ≤2 and previously identified noncontinuous AF.

TACTIC-AF (Tailored Anticoagulation for Non-continuous Atrial Fibrillation) (Clinicaltrials.gov identifier NCT01650298) is an ongoing multicenter randomized control pilot study of remote monitoring via dual chamber pacemakers and ICDs to allow intermittent use of anticoagulation in patients with infrequent episodes of AF. Eligible patients must tolerate a new oral

anticoagulant and have a preexisting dual chamber pacemaker or ICD which has documented a low burden of AF (<30 minutes per day and <6 continuous minutes per episode for ≥30 days before enrollment). Patients are randomized to a control arm (continuous anticoagulation regardless of rhythm) or the device-tailored treatment arm, which requires that patients transmit AF burden data to their physician twice a week on a defined schedule. In addition, any AF episodes that last >30 minutes are automatically transmitted. In the tailored therapy arm, anticoagulation is discontinued after 30 days of freedom from both a single AF episode of ≥6 minutes and a total daily 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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KEY WORDS: anticoagulation ■ atrial fibrillation ■ ischemic ■ stroke ■ thromboembolism

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