Atrial fibrillation (AF) quintuples the risk of stroke, and patients with stroke and AF are the most likely to be left dead or permanently disabled. More than 5 million people in the United States and >8 million people in the European Union were estimated to have AF in 2010. The lifetime risk of AF is high, with a quarter of 40-year-old patients expected to develop AF during the course of their lifetime. Because of aging populations, the prevalence of AF in the United States is expected to exceed 12 million by 2030, whereas in the European Union estimates 17.9 million cases by 2060. The risk of stroke can be stratified by various scores, including CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus [1 point], and previous stroke or transient ischemic attack [TIA; 2 points]) and the CHA2DS2-VASc score (congestive heart failure/left ventricular dysfunction, hypertension [1 point], age ≥75 years [2 points], diabetes mellitus [1 point], previous stroke or TIA [2 points], vascular disease, age 65–75 years, and female sex [1 point]). Multiple trials have demonstrated the efficacy of anticoagulation in reducing the risk of stroke by 65% to 80% in patients with clinically detected AF and other risk factors.

AF burden can be defined as the time spent in AF per unit of time (day, week, month, etc). It is noteworthy that the burden of AF is not part of any risk stratification scoring system. In fact, current practice views AF as a dichotomous variable; one that is either present—or whether paroxysmal, persistent, or permanent—or absent. Implicit in this perspective is an assumption that the burden AF is not relevant to stroke risk. This assumption is based on results from older cohort studies and anticoagulation trials that showed that paroxysmal AF carries the same stroke risk, and responds as well to anticoagulation as persistent or permanent AF. This perspective is reinforced by major guidelines that do not distinguish stroke risk based on whether AF is paroxysmal (AF that terminates spontaneously or with intervention within 7 days of onset), persistent (continuous AF that is sustained >7 days), or permanent (ie, when the patient and clinician make a joint decision to stop further attempts to restore or maintain sinus rhythm), or whether AF burden has been decreased or eliminated with antiarrhythmic drugs, ablation, or surgery.

Stroke neurologists are increasingly asked to make anticoagulation recommendations for patients with exceedingly brief and isolated episodes of AF. This makes it crucial for neurologists to understand the gaps in knowledge about the significance of these brief episodes of AF, the risk of stroke associated with these episodes, and the implications for stroke prevention. Rather than thinking of AF as a dichotomous variable (present or absent), neurologists may have to view AF as a continuous variable, with different amounts (burdens) of AF carrying different stroke risks and treatment implications. This article seeks to update stroke neurologists on this new way of thinking about AF. Ongoing clinical trials should clarify the use of this view of AF, and this review prepares neurologists to critically appraise these trials.

The current practice of treating AF as a dichotomous variable—of not stratifying stroke risk or choosing antithrombotic therapy based on burden—is an outgrowth of data collected at a time when only high-burden AF was detectable. For example, the AF described in the Framingham study was detected by routine ECG, physical examination, or at the time of symptoms. In contrast, the advent of implantable cardiac rhythm management devices (ie, dual-chamber pacemakers, implantable cardiac defibrillators [ICDs], and implantable cardiac monitors [ICMs]) with automatic AF detection, have now made it possible to detect AF that occurs only a few times per year and as briefly as a minute or two in duration. Patients with this de minimus AF may be biologically different than those with the high-burden AF studied in older landmark trials, but this possibility has not been systematically studied.

We think it is the time to reexamine the assumptions about AF burden that underlie current practice and guidelines because ongoing trials may overturn them.

**Brief History of AF and Stroke**

In the first half of the 20th century, autopsy series of patients with rheumatic mitral valve disease and chronic AF by Harvey and Levine determined that auricular fibrillation definitely increases the incidence of auricular thrombosis. A second
autopsy series performed by Hay and Levine found that the presence of AF in patients with mitral stenosis significantly increased the risk of cardiac thrombus formation compared with those without known AF. In the 1970s, the Framingham study was the first to demonstrate that the risk of stroke extended to those with AF and without mitral stenosis, although the risk was substantially lower in the former (5- versus 17-fold). The 1980s brought early attempts to delineate the association between paroxysmal AF and stroke, but were limited by AF detection by electrocardiogram and symptoms. Takahashi et al found embolic complications in 8 of 94 patients with paroxysmal atrial fibrillation, and a Danish study reviewing data accumulated between 1940 and 1957 showed a yearly incidence of emboli in 2.0% of patients with paroxysmal atrial fibrillation and 5.1% of those with chronic AF. The clear connection between paroxysmal AF and stroke, but were limited by AF duration. In a substudy of the Stroke Prevention in Atrial Fibrillation (SPAF) I–III trials performed between 1987 and 1997, stroke risk was compared in aspirin-treated patients with paroxysmal and persistent or permanent AF and found near-identical strokes risks between the 2 groups (3.2% versus 3.3% per year).

These data formed the basis of current recommendations that ignore AF burden when risk-stratifying patients for stroke. However, these data may be outdated because of secular trends including better control of hypertension and other stroke risk factors, which may lower the stroke risk in patients with AF. For example, an analysis of the stroke rates in 6563 aspirin-treated patients with AF from the contemporary ACTIVE-A/AVERROES databases showed that the risk of stroke, after adjusting for known risk factors, was 2.1, 3.0, and 4.2% for paroxysmal, persistent, and permanent AF, respectively (P=0.05 for all comparisons). In fact, AF pattern (a gross reflection of burden) was the second strongest predictor of stroke after previous stroke or TIA. This finding shows that the risk of stroke correlates with burden, and suggests that efforts at stroke prevention may have to take burden into account.

If AF burden is important, then assessing burden becomes critical. Unfortunately, neither symptoms nor short-term monitoring are reliable in determining who has AF, or how much AF they have. Approximately 40% of patients with AF are completely asymptomatic and those who do experience symptoms are aware of only 5% to 20% of episodes. The relevance of this for stroke neurologists is that one quarter of all AF does not become symptomatic except by causing a stroke. Long-term monitoring with implantable devices provide a unique opportunity to detect and quantitate AF burden, correlate AF duration with stroke occurrence, and potentially manage decision making surrounding anticoagulation in a select subset of patients with AF.

**Device-Detected Atrial High Rate Episodes Correlate With True Atrial Tachyarrhythmias**

Pacemakers and ICDs with atrial leads can detect local atrial depolarizations at the endocardial surface. Atrial rates above a certain cut-off (typically 170–220 bpm) can be categorized as atrial high rate episodes (AHRE). AHRE detection can be triggered by any of the atrial tachyarrhythmias, including AF, atrial flutter, or atrial tachycardia, with AF and atrial flutter representing the most common arrhythmias. Current pacemakers and ICDs have been shown to detect AF with a high degree of accuracy. AHRE detection by mode switching algorithms designed to prevent ventricular tracking of prolonged atrial tachyarrhythmias have a sensitivity and specificity of 98% and 100%, respectively. In contrast to pacemakers and defibrillators with leads in the right atrium, leadless ICMs detect AF based on incoherence of the R–R interval. The overall accuracy of the ICM for AF duration is 98.5%.

**Association Between Device-Detected AHRE and Stroke**

AHRE are definitely associated with stroke. However, the burden of AHRE sufficient to raise stroke risk is unclear, with various studies suggesting AF duration anywhere from 5 minutes to >24 hours is associated with increased stroke risk. Furthermore, no study has yet determined if anticoagulation of AHRE reduces the risk of stroke to a similar degree as it does in clinically manifest AF. Complicating this analysis, most studies linking AHRE to stroke did not make any attempt to determine the mechanism of AHRE-associated stroke. These studies are summarized in Table.

In an ancillary study of the Mode Selection Trial (MOST), 312 patients with a median age of 74 years who had pacemakers placed for sinus node dysfunction were prospectively studied for a median of 27 months. Their pacemakers were programmed to log AHRE when the atrial rate was >220 bpm for >5 consecutive minutes. The incidence of AHRE during the study was 51.3%. Multivariate analysis showed that the presence of any AHRE >5 minutes in duration was an independent predictor of death or nonfatal stroke, with a hazard ratio of 2.8 (95% confidence interval [CI], 1.5–5.2) compared with those without any AHRE. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) study showed that subclinical AHRE were not only common in patients with implantable cardiac devices but also associated with an increased risk of stroke, similar to that seen in the MOST trial. In this study, 2580 patients with no history of AF who were ≥65 years of age and had a history of hypertension, in whom a dual-chamber pacemaker or ICD had been recently placed, were monitored for 3 months for the presence of AHRE (defined as an atrial rate of >190 bpm for >6 minutes). They were then followed for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. At 3 months, 10.1% of patients demonstrated subclinical AHRE. Having any subclinical AHRE >6 minutes was significantly associated with the primary outcome of ischemic stroke or systemic embolism with a hazard ratio of 2.49 (95% CI, 1.28–4.85), although the annual rates of stroke and systemic embolization did not become statistically significant until an AF duration of ~18 hours was reached when the patients with AHRE were stratified according to duration quartiles of the longest AHRE episode.
A higher burden of AF was found to significantly increase the risk of stroke in the TRENDS study (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implantable Device Diagnostics). This trial was a prospective cohort study of patients with ≥1 stroke risk factor (heart failure, hypertension, age ≥65 years, diabetes mellitus, or previous thromboembolic event) who were scheduled for a dual-chamber pacemaker or ICD with atrial monitoring capabilities. The primary outcome of the study was the incidence of stroke, TIA, or thromboembolic event. AHRE were defined as atrial rates >175 bpm lasting ≥20 s. The AHRE burden was defined as the maximum number of hours of AHRE on any 1 day during a 30-day period, and may have included >1 episode of AHRE per day. The median burden of AHRE among all 30-day rolling windows that contained AHRE was 5.5 hours. Patients were divided into 3 groups for analysis: those with zero AHRE, those with <5.5 hours of AHRE, and those with ≥5.5 hours of AHRE during any 30-day period. The annualized risk of stroke, TIA, or thromboembolism was 1.1%, 1.1%, and 2.4% for patients with zero, <5.5 hours, and ≥5.5 hours of AHRE, respectively. Compared with patients who had a zero AHRE burden, patients with <5.5 hours of AHRE had a hazard ratio of 0.98 (95% CI: 0.34–2.82) for stroke, TIA, or thromboembolism. Those with ≥5.5 hours of AHRE had a hazard ratio of 2.20 (95% CI: 0.96–5.05). Thus, in this study, patients with ≥5.5 hours of AHRE were roughly twice as likely to have a stroke, TIA, or thromboembolism as those without AHRE, whereas those with <5.5 hours of AHRE were at no increased risk.

Finally, a longer duration of device-detected AF was required to significantly increase stroke risk in a study by Capucci et al that assessed the incidence of arterial embolism in 725 patients with bradycardia, a history of symptomatic AF (either paroxysmal or persistent), and an indication for a dual-chamber pacemaker. The incidence of arterial embolism during the median follow-up time of 22 months was 1.9%. The risk of embolism, adjusted for other known risk factors, was found to be 3.1x higher (95% CI: 1.1–10.5) in patients with device-detected AF lasting ≥24 hours compared with those with <24 hours of AF or no AF. In fact, the occurrence of
device-detected AF lasting >5 minutes but <24 hours was not associated with a significantly higher risk of embolic events compared with those with no AF in this study. These studies are summarized in the Table.

In sum, these studies demonstrate an association between the burden of AHRE and stroke risk, but offer no consensus on a threshold effect between the 2. Furthermore, these studies did not explicitly investigate an interaction between traditional stroke risk factors, AF burden, and stroke risk. This potential interaction was studied by Botto et al., who evaluated the combination of duration of device-detected AHRE and CHADS2 score on stroke risk. The study evaluated 568 patients with pacemakers and a history of AF during a 1-year period. There was a 2.5% stroke rate during the 1-year follow-up. Patients were divided into groups based on duration of device-detected AHRE (none, between 5 minutes and 24 hours, and >24 hours) and CHADS2 score (0, 1, 2, or ≥3). Two subpopulations of patients were identified with significantly different stroke risks. A low stroke risk of 0.8% per year was identified in patients who had zero AHRE with CHADS2 ≤2, had <24 hours of AHRE with CHADS2 ≤1, or had >24 hours of AHRE with CHADS2 ≥0. A high stroke risk of 5% (P=0.035 compared with the first patient population) was identified in patients who had zero AHRE but with CHADS2 >2, had <24 hours of AHRE with CHADS2 >1, or had >24 hours of AHRE with CHADS2 ≥1. This study suggests that AHRE burden may be most helpful in differentiating stroke risk in patients with an intermediate CHADS2 score (1 or 2). Although patients with a low CHADS2 score of 0 are at low risk regardless of AF duration, and patients with a high CHADS2 score of ≥3 are at high risk regardless of AF duration. Of note, those patients with a CHADS2 score of 1 or 2 and a history of AF but no documented recurrences had a stroke risk similar to that of a CHADS2 0 patient. This concept is illustrated schematically in the Figure.

Temporal Association of AHRE and Stroke
Substudies of the 2 trials showing an association between AHRE and stroke, TRENDS and ASSERT, have paradoxically shown that AHRE are not necessarily temporally related to stroke occurrence. In a substudy of the TRENDS trial, the 40 patients enrolled in TRENDS who experienced stroke or TIA and who had at least 30 days of monitoring before the occurrence of an ischemic event were evaluated.10 AHRE of at least 5 minutes were detected before stroke in 20 (50%) of the 40 patients. In contrast, 9 (45%) of the 20 patients with AHRE detected before stroke did not have any AHRE detected in the 30 days preceding stroke. Thus, 29 (73%) of the 40 patients with stroke had no AHRE within the 30 days before their event. Of the 20 patients who had AHRE before stroke, only 6 (30%) had AHRE at the time of stroke. In the 14 patients who had AHRE before stroke, the mean time from the last recorded AHRE and stroke was relatively long at 168±199 days (range, 3–642 days). Still, those patients who had ≥5.5 hours of AF were more than twice as likely to have a thromboembolism event within 30 days because those with shorter AF durations and no recorded AF, and the 30-day stroke risk was higher even within the same individual after a longer AF episode. This suggests that there may be a temporal association only between longer AHRE episodes with stroke.

A substudy of the ASSERT trial showed similar results.31 Of the 51 patients in ASSERT with stroke, subclinical AF was detected in 26 (51%). Of these patients, only 18 (35%) had subclinical AF before stroke. Only 4 (8%) had subclinical AF within 30 days before stroke, and only 1 patient (2%) had subclinical AF at the time of stroke. In patients with AF >30 days before stroke, AF occurred a median of 339 days (25th–75th percentile, 211–619 days) before stroke. AF was detected only after stroke in 8 (16%) patients.

These analyses suggest that AHRE burden correlates with stroke risk, but may not always be directly causative of stroke. There are several potential explanations for this latter finding. First, the link between AHRE burden and stroke could be an epiphenomenon: patients with more AHRE may have more severe vascular risk factors.32 Second, it may be that many patients had strokes because of causes other than AF. Finally, the event rate may have been insufficient to demonstrate a temporal association. Consistent with this last point, the largest study to date which enrolled 9850 patients with implanted devices showed that the odds ratio for the risk of stroke within 30 days of an AHRE lasting ≥5.5 hours was 5.2 compared with a control period 90 to 120 days before.33

On the basis of the available data, subclinical AHRE that would likely go otherwise undetected are clearly associated with stroke. However, it remains unclear if this association is causative or simply a marker of overall risk. If in fact AF is an epiphenomenon, then maintaining sinus rhythm will not completely protect against strokes, particularly in patients with multiple other risk factors.

Treatment Based on Burden: Anticoagulation Based on Remote Monitoring
Most implantable cardiac rhythm management devices now have the ability to send transmissions remotely either manually or automatically. These transmissions, which can occur as often as once a day, include detailed information about ambient arrhythmias and device function, allowing for continuous monitoring of the cardiac rhythm. Several studies have shown the ability of remote monitoring to decrease the time from AHRE occurrence to detection and treatment when compared with conventional monitoring with periodic remote or in-office device interrogations at fixed intervals in an outpatient clinic.34–36 These studies lead to the possibility that early
recognition and treatment of subclinical AF could decrease stroke while minimizing exposure to anticoagulation.

In an analysis of the Comparative Follow Up Schedule With Home Monitoring (COMPAS) trial, patients showed a trend toward lower stroke rates when followed by continuous remote monitoring compared with standard in-office follow-up. However, this study was designed primarily to determine the safety of remote monitoring and was neither powered to show a difference in stroke rates between groups nor designed to specify an intervention protocol once AF was discovered. Similarly, the Lumos-T Safely Reduces Routine Office Device Follow-Up (TRUST) study showed a nonsignificant trend toward a lower stroke rate in the group of patients with continuous remote monitoring compared with those monitored with standard in-office follow-up, although again the study was not designed to look at specific interventions for device-detected AHRE.

The IMPACT (Randomized Trial of Anticoagulation Guided by Remote Rhythm monitoring in Patients with ICD and Resynchronization Devices) trial attempted to address the question of management of device-detected AF. This trial was designed to investigate the use of remote monitoring combined with a predefined anticoagulation strategy compared with conventional device evaluation and physician-directed anticoagulation in patients with dual-chamber ICDs or cardiac resynchronization therapy devices. Warfarin was the anticoagulant used in the vast majority of patients. Patients with a CHADS2 score $\geq 1$ with or without a history of paroxysmal AF were randomized in a 1:1 fashion to 1 of 2 arms. In the standard-of-care arm, patients received in-office follow-up with physician-directed anticoagulation if AF was detected. Patients in the treatment arm were monitored remotely for device-detected AHRE ($\geq 200$ bpm for 36 of 48 beats) and anticoagulation was started and stopped based on a combination of CHADS2 score and duration of AHRE. Patients with a CHADS2 score $<2$ were started on anticoagulation with warfarin if they had $>48$ continuous hours of AHRE, and warfarin was stopped if AHRE were not detected for 30 consecutive days. Patients with a CHADS2 score of 3 to 4 started anticoagulation with warfarin if they had $>24$ hours of AHRE within a 48-hour window, and warfarin was stopped if AHRE were not detected for 90 consecutive days. Finally, patients with a CHADS2 score of 5 to 6 were started on anticoagulation with warfarin if they had any duration of AHRE. Once started, warfarin was not stopped in this group. The primary end point of the study was freedom from the composite of stroke, systemic embolism, or major bleeding. A total of 2718 patients were randomized and followed for $\leq 5$ years. However, there was no significant difference between groups in the primary outcome, and the trial was terminated early because of futility. At 5 years, the Kaplan–Meier estimate of the primary end point was 86.8% in the remote monitored group and 87.9% in the standard of care group ($P=0.73$). One major limitation of this study is that warfarin was used for anticoagulation in the majority of patients. Because warfarin can take 5 to 7 days to become therapeutic, patients in the treatment arm who had device-detected AF may not have been anticoagulated during the critical window immediately after the detection of AF. In addition, international normalized ratio levels were subtherapeutic about a third of the time, and many patients were not treated according to the study protocol. Event rates during the trial were lower than expected and the combined end point of stroke and stroke may have obscured any benefit for stroke prevention in this study.

Several ongoing and planned studies test the link between device-detected episodes of subclinical AF, stroke, and the impact of anticoagulation. The Apixaban for the Reduction of Thrombo-Embolism in patients with device-detected Sub-Clinical Atrial fibrillation (ARTESiA) study has been designed to look specifically at the treatment of patients with subclinical device-detected AF, with no history of clinical AF (clinicaltrials.gov NCT01938248). The trial has begun enrollment, with a goal of enrolling 4000 patients. Patients with device-detected subclinical AF will be randomized to treatment with either aspirin or apixaban. Patients will be followed for an estimated 3 years for the primary end point of stroke or systemic embolism. This study will be one of the first randomized trials to evaluate treatment for patient with subclinical AF and may elucidate whether anticoagulation for device-detected AF reduces stroke risk in the same way it does for clinical AF.

Although much recent attention has been paid to the association between device-detected subclinical AF episodes and stroke, the same technology used to identify AF could potentially also be used to limit oral anticoagulation exposure in patients with a history of AF but with low or absent AF burdens either spontaneously or as the result of a rhythm control intervention, such as ablation or antiarrhythmic therapies. The REACT.COM study used daily home monitoring from an ICM (Reveal XT, Medtronic Inc) and used an AF duration of $>1$ hour as the threshold to initiate oral anticoagulation for 30 days. The pilot study showed a 94% reduction in time on oral anticoagulation compared with expected. In contrast to the IMPACT trial, this pilot study focused on lower risk (ie, CHADS2 score 1 or 2) patients and used rapid onset novel oral anticoagulations instead of warfarin. The planned REACT-AF trial will randomize CHADS2-VASc 1 to 4 patients with nonpermanent AF to either chronic novel oral anticoagulation therapy or targeted therapy using an ICM.

All these studies implicitly test the link between AF (or AHRE) burden and stroke by only anticoagulating patients with AF when they have the arrhythmia documented by an implantable device. If this strategy is successful, it would suggest that AF is not a dichotomous variable, that anticoagulation is only needed when the arrhythmia is present, and that maintenance of sinus rhythm might indeed lower stroke risk enough to obviate the need for anticoagulation.

**Areas of Uncertainty**

Although it seems clear that AHRE detected by ICMs and other implanted are associated with stroke, several major areas of uncertainty remain. First, whether there is a particular burden of AHRE needed to raise the risk of stroke is unclear. The studies presented above have demonstrated a wide range of durations ($>5$ minutes to $>24$ hours) needed to significantly increase the risk of stroke. Interestingly, all the studies showing an association between AHRE and stroke have shown an association with durations of $<48$ hours, which has traditionally been the cut-off used before cardioversion to determine if...
the stroke risk with cardioversion is high enough to warrant either cardioversion anticoagulation or a transesophageal echocardiogram to rule out left atrial appendage thrombus. It may also be that the duration of AF in combination with other clinical risk factors, such as the CHADS, or the CHA2DS2-VASc score, may be a better predictor of stroke risk than the presence and duration of AF alone. Second, the mechanism of stroke in patients with device-detected AF remains to be determined. The temporal dissociation of most AHRE from stroke observed in some, but not all, studies raises the possibility that AHRE may not be the direct cause of stroke in all patients and that for some patients the possibility exists that short episodes of AF are simply a marker for other stroke mechanisms. Further research into this area is needed. Finally, whether treatment with anticoagulation for subclinical device-detected AHRE reduces stroke risk as it does for clinical AF is currently unknown. Planned and ongoing studies can be expected to answer most if not all of these questions in the not too distant future. It is important to stress, however, that at present, there is no clear clinical trial evidence that AF burden should influence anticoagulation decisions.

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