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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Device-Detected Atrial Fibrillation

What to Do With Asymptomatic Patients?

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ABSTRACT

Atrial fibrillation (AF) is the most common clinically significant arrhythmia and conveys an increased risk of stroke, regardless of whether it is symptomatic. Despite multiple studies supporting an association between subclinical atrial tachyarrhythmias (ATs) detected by cardiac implantable electronic devices and increased risk of thromboembolic events, clinical intervention for device-detected AT remains sluggish, with some clinicians delaying treatment and instead opting for continued surveillance for additional or longer episodes. However, the 2014 updated clinical practice guidelines on AF recommend use of the CHA_2DS_2-VASc stroke risk score for nonvalvular AF, with oral anticoagulation recommended for scores ≥2, regardless of whether AF is paroxysmal, persistent, or permanent. This paper reviews the epidemiology of AF and mechanisms of stroke in AF, and discusses device-detected AF and its clinical implications. (J Am Coll Cardiol 2015; 65:281–94) © 2015 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is the most common clinically significant heart rhythm disorder (1), with an estimated lifetime risk of 22% to 26% or about a lifetime risk of 1 in 4 (2). It has been diagnosed in >2.5 million people in the United States alone (3). In 2010, the incidence of diagnosed AF in the United States was 1.2 million, and its prevalence is projected to increase to >12 million cases by 2030 (4). In the European Union, there were 8.8 million adults >55 years of age with AF in 2010, with an expected increase to 17.9 million by 2060 (5). Globally, AF incidence in 2010 was estimated at 33.5 million (20.9 million men and 12.6 million women). Despite a higher incidence in men, mortality associated with AF is greater in women, doubling between 1990 and 2010 (6). These statistics do not account for silent or undiagnosed AF, which is thought to affect as many as one-third of the U.S. population (3).

MECHANISMS OF AF

The pathophysiology of AF is multifactorial and complex, including both genetic and neural mechanisms. The main mechanism by which autonomic activation triggers AF is activation of the sympathetic and parasympathetic nervous system, which likely interact with the pulmonary vein-left atrial (LA) junction to trigger atrial ectopy (7). Genetic mechanisms linked to AF development include alterations in potassium or sodium channels, connexin expression or function (2), and microRNAs (8). Four major mechanisms that promote focal ectopic firing and reentry substrate formation have been implicated in

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AHRE = atrial high rate episodes

AT = atrial tachyarrhythmia

CIED = cardiac implantable electronic device

CRT = cardiac resynchronization therapy

CS = cryptogenic stroke

ECG = electrocardiogram

EGM = intracardiac electrogram

ICM = implantable cardiac monitor

LA = left atrium/atrial

LAA = left atrial appendage

TE = thromboembolic event(s)

AF: 1) ion channel dysfunction; 2) calcium handling abnormalities; 3) structural remodeling (primarily atrial fibrosis); and 4) autonomic neural dysregulation (2,8). These 4 conditions not only trigger AF, but may also result from episodes of AF, supporting the concept that "atrial fibrillation begets atrial fibrillation," first reported in an early animal study documenting atrial electrical remodeling in AF (9). Further advances in knowledge of the pathophysiology of AF have revealed that electrical remodeling in AF is not limited to the atria. More pronounced remodeling after brief episodes of induced AF has been documented in the pulmonary veins (10), thereby extending the concept to "AF begets AF in the pulmonary veins".

AF AND STROKE

AF is a major independent predictor of ischemic stroke, resulting in a 5-fold increase in risk (1). Each year, approximately 795,000 people experience strokes, of which 610,000 are first strokes and approximately 87% are ischemic. In the United States, someone suffers a stroke every 40 s (that is, approximately 90 people/h) (1). Among patients with AF, it is estimated that every hour, 15 will have a stroke (11), and such AF-related strokes impose a higher mortality than strokes unrelated to AF (12). The prevalence of AF and associated stroke risk are highest among elderly patients, with stroke risk independent of whether AF is paroxysmal, persistent, or permanent (1). A large number of earlier clinical trials (13–15) demonstrated that systemic anticoagulation is highly efficacious for stroke prevention in patients with AF (16), with a recent meta-analysis documenting the efficacy of both direct thrombin inhibitors and vitamin K antagonists in stroke prevention in nonvalvular AF (17).

The association between AF and cryptogenic stroke (CS) was recently documented using an implantable cardiac monitor (ICM). The CRYSTAL-AF (CRYptogenic Stroke and underlying Atrial Fibrillation) trial, a prospective, randomized, multicenter, global study, in which long-term cardiac monitoring using an ICM was compared to conventional electrocardiogram (ECG) monitoring (ECG, 24-h Holter, or event monitor) for detection of AF in 441 patients with CS, demonstrated that AF was detected in 8.9% of ICM patients (compared to 1.4% in the ECG control group) at 6 months. Furthermore, on long-term conventional ECG group (18). Although anticoagulant prescription for AF was higher in the ICM group versus the routine ECG monitoring group (10.1% vs. 4.6%) at 6 months, 97.0% of patients with detected AF were receiving oral anticoagulant agents by the 12-month follow-up (18).

A similar study, the EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) study, compared new AF detection by noninvasive ambulatory ECG monitoring with either a 30-day event-triggered recorder (intervention group) or a conventional 24-h monitor (control group) in 572 patients with CS within the preceding 6 months, without a history of AF (19). The investigators reported a greater than 5-fold increase (16.1% vs. 3.2%; $p < 0.001$) in AF detection in the 30-day event monitor group, with a subsequent significant increase in anticoagulation prescription (18.6% vs. 11.1%; $p = 0.01$) among the 30-day event monitor group. At the 90-day follow-up, 87% of patients with AF in the event monitor group and 100% of patients with AF in the control group were on anticoagulant therapy (19). Thus, both the CRYSTAL-AF and EMBRACE studies documented a significant increase in anticoagulant prescription in CS patients with newly detected AF. However, anticoagulation treatment rates are significantly lower for patients without a prior history of stroke with newly detected AF on cardiac implantable electronic devices (CIEDs). One retrospective study reported a 50% incidence of pacemaker-detected AF, yet <25% of these patients with pacemaker-detected AF were treated with anticoagulant agents (20). The temporal relationship between atrial fibrillation and stroke is not as well understood, and in some patients, episodes of AF are not detected until months after a stroke.

MECHANISMS OF STROKE IN AF

Although AF-related stroke is commonly attributed to clot formation resulting from blood stasis in the poorly contracting LA during AF, the mechanisms of thrombogenesis in AF are much more complex, implicating Virchow's triad reviewed by Watson et al. (21) and Iwasaki et al. (22).

In AF, endothelial and endocardial damage in the left atrial appendage (LAA), the presence of complex aortic plaque (≥4 mm, ulcerated, or mobile) (23), and abnormal extracellular matrix turnover (which can induce fibrosis) all contribute to vessel wall changes. Abnormal blood stasis in the LA and LAA (which

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(activation of platelets and the coagulation cascade), complete Virchow's triad (21). Virchow's triad (described by the German physician, Rudolf Virchow), identified 3 main factors contributing to thrombosis: alterations in blood flow (stasis), the vessel wall (injury to the vascular endothelium), and blood constituents (hypercoagulability). When applied to thrombogenesis in AF, blood stasis occurs in the LA/LAA, atrial structural remodeling (including endothelial damage) ensues, and there is hypercoagulability due to activation of platelets and the coagulation cascade. Atrial hypocontractility and loss of atrial kick, along with LA enlargement, lead to blood stasis, which promotes endothelial damage and hypercoagulability. Up-regulation of inflammatory and growth factors leads to endothelial damage, which in turn, promotes hypercoagulability with subsequent abnormal fibrinolysis (22).

Due to its anatomical morphology, the LAA, a vestigial remnant of the original embryonic LA, has a predilection for thrombus formation. In fact, the LAA is the most common site of thrombus formation in patients with nonvalvular AF (24), accounting for >90% of thrombi (**Figure 1**). This thrombogenic tendency has led to targeted interventions to occlude the LAA in an attempt to reduce stroke risk in AF, as reported in trials such as the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) trial in 2002 (25) and, most recently, the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) study, which documented noninferiority of LAA occlusion to systemic anticoagulation (26). In fact, the PROTECT AF trial was credited with being the first trial to demonstrate involvement of the LAA in the pathogenesis of stroke in AF (27).

Significant safety concerns for WATCHMAN implantation, including pericardial effusions and device embolization, were addressed in a subsequent trial, the PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial, which documented a significantly lower rate of adverse events compared to the PROTECT AF trial (4.2% vs. 8.7%; $p = 0.004$) (28). Although the third review by the Food and Drug Administration Circulatory System Devices Advisory Panel in October 2014 (29) resulted in a unanimous vote on safety of the device, analysis of the updated June 2014 PREVAIL dataset demonstrated new ischemic strokes occurring more than 1 year after WATCHMAN device implant. Furthermore, neither the first primary endpoint of the PREVAIL trial second primary endpoint (composite 18-month rate of stroke and systemic embolism) were met, raising the question regarding long-term efficacy, with the committee split on the benefit-risk profile. At the present time, the fate of the WATCHMAN device remains uncertain (29).

Recent studies reported a significant association between the type of LAA morphology and silent cerebral ischemia as well as stroke risk, suggesting a potential role for LAA morphology in stroke risk stratification schemes. Among the 4 major types of LAA morphology (chicken wing, cactus, windsock, and cauliflower), cauliflower LAA morphology carried the highest risk of stroke, whereas chicken wing carried the lowest in a study of 932 patients undergoing catheter ablation of AF (30). A significant association between LAA morphology and burden of silent cerebral ischemia was reported in 348 patients undergoing catheter ablation of AF (31). Although LAA exclusion does not prevent AF-related strokes due to other causes (i.e., noncardioembolic origin), because the LAA accounts for >90% of thrombi in AF (25), it may be a significant strategy in stroke prevention in nonvalvular AF.

DEVICE-DETECTED AF

Subclinical atrial tachyarrhythmias (AT) can be detected by various cardiac monitoring methods, including external surface monitoring (e.g., standard 12-lead electrocardiogram, ambulatory Holter monitors, event monitors) and by CIEDs (e.g., implantable cardiac monitors, dual-chamber pacemakers, dual-chamber implantable cardioverter-defibrillators, cardiac resynchronization therapy [CRT] devices), many of which enable remote monitoring. This review addresses only CIEDs, given their continuous monitoring capability. AT commonly occurs in patients with CIEDs and is associated with an increased risk of thromboembolism (TE) (1). Several studies have correlated TE risk with the total duration or burden of device-detected AT (32–34). However, there are presently no published randomized clinical studies investigating treatment of AT detected by CIEDs.

All cardiac rhythm recordings obtained from CIEDs require adjudication or review by a qualified clinician to verify diagnostic accuracy. Retrospective review of device-derived data has confirmed that most of these tachyarrhythmias represent paroxysmal AF or atrial flutter. However, false detection may occur due to far-field R-wave (**Figure 2**) oversensing by the atrial lead (35–37) or runs of premature atrial complexes.

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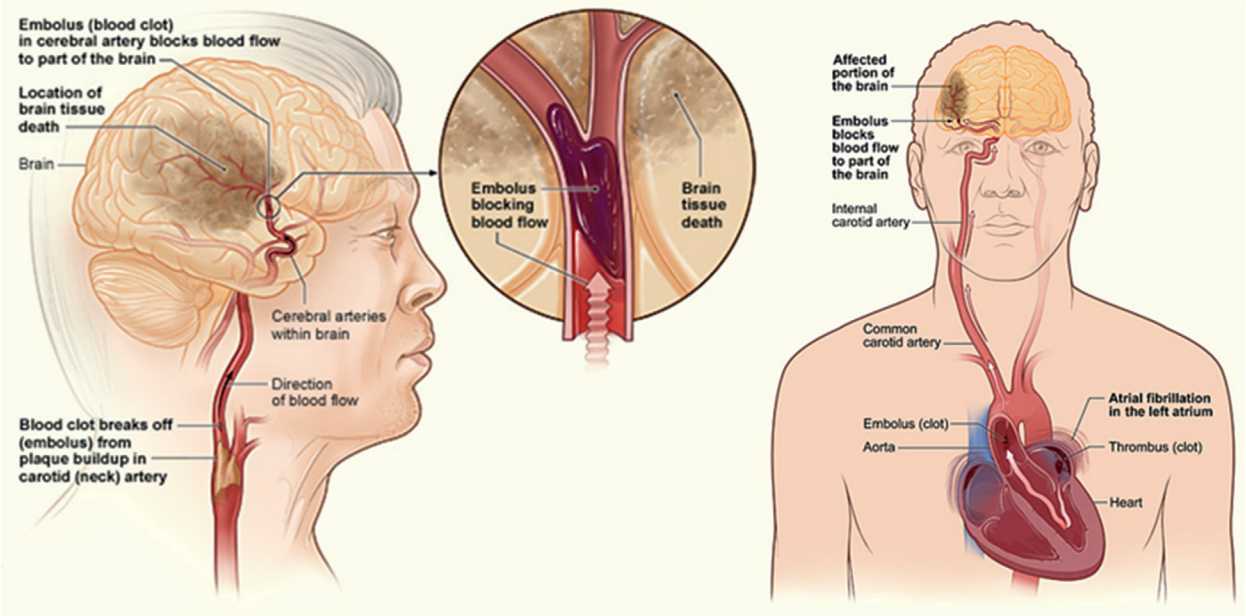
antitachycardia responses of CIEDs are not specific for AF (35,37) and may be triggered by other forms of AT, including atrial tachycardia or atrial flutter. Thus, intracardiac electrograms (EGMs) must be reviewed to verify the accuracy of the device diagnostics. Device-stored data based solely on marker channels, without EGMs, cannot be used to verify AF due to the potential for diagnostic errors caused by oversensing or undersensing by the atrial lead. Furthermore, atrial tachycardia detection rate programming and the duration of the post-ventricular atrial blanking interval can also influence the number of automatic mode-switching episodes in the setting of AT (38). Although ICM are also susceptible to false AF detection due to oversensing or missed AF detection due to undersensing, 2 ICM with AF algorithms (Medtronic Reveal XT, Model 9529, Medtronic Inc., Minneapolis, Minnesota, and, SJM Confirm Implantable Cardiac Monitor Model DM2102, St. Jude Medical, Inc., Sunnyvale, California) are currently available on the market, with the Medtronic Reveal XT reported to have an overall accuracy of 98.5% in AF detection (39) (**Figure 3**). Although atrial high rate episodes (AHRE) have been used as a surrogate for AF, the data must be interpreted with caution. In the ASSERT (ASymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing) trial, the positive predictive value of AHREs for EGM-confirmed AF was examined in 2,850 subjects with implanted pacemakers. In 17.3% of cases, AHRE episodes at >190 beats/min lasting >6 min were found to be falsely positive, due predominantly to repetitive non-re-entrant ventriculoatrial synchrony (40), also known as atrioventricular-desynchronization arrhythmia (**Figure 4**). Repetitive non-re-entrant ventriculoatrial synchrony is triggered by retrograde ventriculoatrial conduction with functional atrial undersensing. It results from retrograde atrial activation during the post-ventricular atrial refractory period and functional atrial non-capture due to atrial stimulation during the absolute refractory period, with the potential to trigger mode switching (41–45).

REVIEW OF PUBLICATIONS ON DEVICE-DETECTED AF

Because the advent of dual-chamber devices and ventricular leads with atrial sensing capability, the clinical implications of device-detected AT have been considered in the context of anticoagulation for stroke prevention (46), but the question of what to

FIGURE 1 Mechanisms of Stroke in Atrial Fibrillation



Cardioembolic sources, almost exclusively represented by left atrial appendage thrombi, account for >90% of embolic events. Noncardioembolic origin, more often embolic material dislodged from thoracic and or carotid plaques, account for the remaining 10% of events. Graphics source: National Institutes of Health/National Heart,

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