JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 3, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.10.045

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Device-Detected Atrial Fibrillation

What to Do With Asymptomatic Patients?

Carol Chen-Scarabelli, PHD,* Tiziano M. Scarabelli, MD, PHD,† Kenneth A. Ellenbogen, MD,‡ Jonathan L. Halperin, MD†

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

From the *Veterans Affairs Ann Arbor Health Care System, University of Michigan, Ann Arbor, Michigan; †Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai Medical Center, New York, New York; and the ‡Department of Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia. Dr. Ellenbogen has served as a consultant for Medtronic, Boston Scientific and St. Jude Medical, and has received research, honorarium, and fellowship support from Medtronic and Boston Scientific. Dr. Halperin has served as a consultant for Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Inc., Biotronik, Boston Scientific, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Ellenbogen and Halperin contributed equally to this work as senior authors. Sumeet Chugh, MD, served as Guest Editor for this paper.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

You can also listen to this issue's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received June 29, 2014; revised manuscript received October 14, 2014, accepted October 14, 2014.

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)

promote focal ectopic firing and reentry substrate formation have been implicated in 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 follow-up at 3 years, AF was detected in 30% of patients by ICM, compared to only 3% in the 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 is promoted by and further worsens LA dilation), along with abnormal hemostasis and coagulation