New Horizons in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) represents a growing medical problem that affects older individuals and those with a genetic predisposition to this condition. Speakers at the 2011 Scientific Sessions of the American Heart Association (AHA) described risk factors for AF as well as current best practice for treating affected patients. Ablation is a common treatment option, although researchers continue to test other procedures in their quest to optimize patient outcomes. The US Food and Drug Administration has approved several new anticoagulants recently, and other new agents that may be useful in treating patients with AF are in development.

The incidence of atrial fibrillation (AF), a complex disease with multifactorial etiologies, has been increasing worldwide. Newer treatment options, including ablation and oral anticoagulation, are now available, yet management of this disease continues to consume significant health care resources annually, and its morbidity and mortality remain high. As the population ages, physicians face ongoing challenges in managing this disease, its complications, and associated comorbidities. Tremendous progress has been made in the past several decades in treating AF, yet mortality has not improved, and the incidence of AF continues to rise. An understanding of the underlying mechanisms of AF is instrumental to improving its treatment.

This review of AF is based on a symposium offered during the 2011 Scientific Sessions of the American Heart Association, held November 12–16, 2011, in Orlando, Florida. The session was moderated by Douglas P. Zipes, MD, Distinguished Professor Emeritus of Medicine and former Director of the Cardiology Division and Knarrert Institute of Cardiology at Indiana University, Indianapolis, and Alan Camm, QHP, BSc, MD, FRCP, FRCP, FESC, FACC, FAHA, FCGC, Professor of Cardiology at St. George’s Hospital and Medical School, London, UK. The presentations spanned the full spectrum of AF, from epidemiology and global impact to biology, genetic factors, and treatment options.

EPIDEMIOLOGY AND IMPACT OF AF ON GLOBAL HEALTH

Based on a presentation by Gregory Y.H. Lip, MD, Professor of Cardiovascular Medicine, University of Birmingham, and Consultant Cardiologist and Director, Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK.

With an overall prevalence of 0.4%–1%, AF is the most common arrhythmia encountered in clinical practice, with a dramatic increase in incidence with increasing age; it also accounts for one third of hospitalizations for cardiac rhythm disturbances. Over the past two decades, the aging US population has experienced a 66% increase in hospitalizations for AF. The annual cost per patient to treat AF is $3,600, and it is anticipated that 12–15 million patients worldwide will be diagnosed with AF by the year 2050. This global epidemic affects various populations and ethnic groups and carries a high risk of stroke, all-cause mortality, heart failure, and associated hospitalizations.

In Chinese patients of the Guangzhou Biobank Cohort, obesity (as defined by waist circumference or body mass index) was independently associated with a substantial risk of developing AF. Furthermore, the reported prevalence of AF in geographic regions of China is highly variable (unpublished observations). Although most studies of AF are hospital-based, there is a growing need for more community-based investigations, which likely would better represent the general population.

TREATMENT OF AF AND CLINICAL OUTCOMES

Despite major advances in the diagnosis, risk stratification, and management of AF over the past two decades, mortality due to AF remains unchanged. In a community-based study of 4,618 residents of Olmstead County, Minnesota, who were diagnosed with AF between 1980 and 2000, there was no evidence of improvement in overall mortality, early or late mortality, or mortality among patients with no preexisting cardiovascular conditions. The reasons for these results are complex and may be a combination of (1) the increased prevalence of AF, which, in turn, has increased the overall incidence of stroke; and (2) the introduction of potent antithrombotic therapies, which physicians use in place of anticoagulants. Thus, our understanding of AF and its treatment has improved, yet the disease burden remains high, and ongoing research is needed to improve clinical outcomes.

BIOLOGY AND GENETICS OF AF

Based on a presentation by Stanley Nattel, MD, Professor and Paul-David Chair in Cardiac Electrophysiology, University of Montreal, Montreal, Quebec, Canada.

Atrial fibrillation results from increased ectopic activity in the atria, which can trigger susceptible substrates and lead...
to reentrant arrhythmia. These triggers and substrates can result from a variety of causes, including environmental and genetic factors (eg, ischemic heart disease, hypertension, alcohol consumption, obstructive sleep apnea; Figure 1). The most common risk factors are patient age and history of myocardial infarction (MI).

**Biologic Factors**

Age appears to be the strongest risk factor for the development of AF. This arrhythmia is now becoming an epidemic, especially among the growing elderly population. Both acute and chronic coronary atherosclerotic disease confers risk. Observational data from a large cohort (n = 3,983) demonstrated a 3.6-fold increase in the risk of AF post MI after adjustment for age and other prognostic variables.

In a canine model of coronary artery disease (CAD) affecting the atria, investigators noted an increase of calcium sparks (or irritable foci) within the atria of affected dogs, as compared with control animals. When affected dogs sustained atrial ischemia/infarction after ligation of coronary vessels, these calcium sparks were converted into calcium waves, resulting in persistent ectopic activity as well as substrates for reentry. Myocardial ischemia, therefore, appears to produce both the trigger and the substrate for ectopic activity.

**Genetic Factors**

Genetic factors also may confer significant risk of AF by altering thresholds for triggers and by altering substrates. Mendelian mutations are rare, but their presence suggests that this mode of inheritance plays a dominant role in the genetic predisposition for developing AF. In contrast, genome-wide association studies have identified a number of polymorphisms, which exist in a variety of genes. Examples of these polymorphisms are calcium-dependent potassium channels or transcription factors, which are relatively more common but which have lower attributable risk for AF.

A mutation on chromosome 4q25 changes the function of \textit{PITX2} (paired-like homeodomain 2), a gene involved in cardiac development, that doubles the risk of developing AF. Transgenic mice with \textit{Pitx2} mutations have a loss of myocardial pacemaker cells around the pulmonary veins, leading to increased susceptibility to atrial arrhythmia.

**Ablation of AF: How and When**

Based on a presentation by Hakan Oral, MD, Professor of Internal Medicine, Director of the Cardiac Electrophysiology Service, and Frederick G.L. Huetwell Research Professor of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor.

With an improved understanding of electrophysiologic pathways resulting in AF and mounting challenges in maintaining adequate rate control and appropriate anticoagulation, the trend toward alternative treatment options, such as catheter ablation, has been rising. Choosing the appropriate patient population to maximize the efficacy and success of this intervention is controversial.

**Electrophysiologic Mechanisms**

Atrial fibrillation results from four principal electrical aberrations: (1) increased arrhythmogenicity related to the pulmonary vein and other thoracic veins; (2) autonomic dysregulation; (3) fixed and functional reentry substrates, especially anisotropic high-frequency reentrant sources (termed “rotors”) throughout the atria; and (4) electroanatomical remodeling of myocardial structures. Given the
heterogeneous nature of this arrhythmia (Figure 2), one or more mechanisms simultaneously may be responsible for its generation, making ablation more challenging option if the etiology is multifactorial.

Most commonly, pulmonary vein arrhythmogenicity triggers AF. For this reason, ablation efforts mostly have focused on targeting pulmonary vein tissue and the myocardial tissue cuff adjacent to these structures. In addition to the pulmonary vein antrum, however, rotors, ganglionated plexi, and other triggers also exist. Techniques such as complex fractionated atrial electrograms (CFAEs) and isoproterenol infusions can be used to identify such structures. These methods must be used cautiously, however, because they can trigger passive activation of foci not responsible for generation and propagation of this arrhythmia, which would result in false-positive results. Furthermore, these diagnostic strategies actually may lead to the initiation of an arrhythmia or may induce contractile dysfunction.

Catheter Ablation: Technique, Complications, and Indications

Isolation of the pulmonary veins followed by isolation of the superior vena cava and the coronary sinus and then linear ablation (Figure 3) remains the most commonly used technique for catheter-based ablation. Although surgical ablation also is an option, the invasive nature of this procedure makes it less preferable.

Despite many recent advances, ablation may result in embolic stroke, pulmonary vein stenosis, atrioesophageal fistula, atrial flutter, complete heart block, or recurrent arrhythmia. Use of such risk-prediction tools as the CHADS, (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke/transient ischemic attack) score has been validated for predicting thromboembolic risk of ablation, but careful selection of patients for this treatment is critical because ablation rarely is considered to be a first-line therapy. American College of Cardiology/AHA/Heart Rhythm Society indications for ablation include symptomatic AF with Wolff-Parkinson-White syndrome, symptomatic AF in the presence of persistent symptoms and failure of antiarrhythmic medications, and AF in the presence of heart failure or decreased ejection fraction. Special consideration for ablation should be given to the following: young patients, who have a high likelihood of needing antiarrhythmic agents and anticoagulants for the rest of their lives; patients with tachycardia-mediated cardiomyopathy; patients with liver or renal disease that may complicate medical therapy; and patients with structural heart disease.

RHYTHM VS RATE CONTROL IN THE NEXT DECADE

Based on a presentation by Isabelle Van Gelder, MD, Professor of Cardiology, Interuniversity Cardiology Institute and University of Groningen, Groningen, the Netherlands.

A physician who chooses not to use ablation for managing patients with AF may need to ponder the relative effectiveness of rate control versus rhythm control. The choice to control rate or rhythm should be individualized for each patient and depends upon the patient’s age, type of symptoms, duration of disease, and the presence of additional comorbidities and stroke risk factors.

In the AFFIRM study, 4,060 patients with AF were randomized to undergo rate control or rhythm control. The results suggested that rhythm control offered no survival benefit but was linked to a higher incidence of drug-related side effects. Since then, the findings of a number of other studies (eg, RACE, PIAF, HOT CAFE, AF-CHF, and J-RHYTHM) have demonstrated no benefit of rhythm control over rate control. Data from the AF-CHF study even suggested an increase in hospitalizations secondary to bradycardia-rhythmia in the rhythm-control arm.

Data from the RACE-II trial suggested that rate control does not need to be as strict as previously thought necessary and that lenient rate control (heart rate < 110 beats/min, resting and exercise) is as effective as strict rate control (resting heart rate < 80 beats/min; exercise heart rate < 110 beats/min) and easier to achieve. Therefore, rate control likely is the most effective strategy, especially in elderly patients who have minimal symptoms.

When to Use Rhythm Control

In some situations, rhythm control is preferable. For example, some patients who are especially susceptible to the long-term adverse effects of electroanatomical remodeling of the atria may benefit from maintenance of sinus rhythm. Sinus rhythm is, indeed, a marker for improved survival. For this group, ablation (prefer-
ably catheter-based pulmonary-vein isolation) with or without the use of adjunctive antiarrhythmic drugs is the recommended strategy. Because such remodeling is time dependent, this strategy should be employed early, after the decision to use rhythm control has been made.

**ANTICOAGULATION FOR AF**

Based on a presentation by Elaine M. Hylek, MD, MPH, Associate Professor of Medicine, Section of General Internal Medicine, Boston University, Boston, Massachusetts.

In addition to rate versus rhythm control, anticoagulation is central to the management of AF. Use of the CHADS2 score to determine which patients are appropriate candidates for anticoagulation therapy has been well established. Nevertheless, Waldo and others16 reported that 55% of hospitalized patients at high risk for thromboembolic disease were not receiving anticoagulation therapy with warfarin.

Explanations for the underuse of warfarin are multifactorial, most commonly advanced age, which is highly correlated with increased intracranial hemorrhage, and previous bleeding diathesis (eg, gastrointestinal bleeding). However, the most likely explanation relates to the complex dosing, intensive monitoring, and multiple drug-drug interactions associated with warfarin therapy. For these reasons, great effort has been devoted to the study of novel oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban to treat patients with AF.

**Novel Oral Anticoagulants in AF**

The results of these trials have emphasized the delicate balance between effective anticoagulation and the risk of hemorrhagic and thrombotic complications (Figure 4, Table 1). Based on the results of the RE-LY study, the US Food and Drug Administration (FDA) recently approved the use of dabigatran to prevent stroke in patients with nonvalvular AF, when given at a dose of 150 mg twice daily for patients with a creatinine clearance (CrCl) > 30 mL/min and at a dose of 75 mg twice daily for those with a CrCl = 15–30 mL/min.17 Likewise, the FDA recently approved the use of rivaroxaban to reduce the risk of stroke in patients with AF, based on the results of the ROCKET-AF trial.18 The recommended dose for this purpose is 20 mg once daily for patients with a CrCl > 50 mL/min and 10 mg once daily for those with a CrCl = 30–50 mL/min. In addition, the FDA is giving priority review to the use of 5 mg of apixaban given twice daily based on positive results from the phase III AVERROES and ARISTOTLE trials.19 Considering these developments, a new era in anticoagulation for AF has dawned.20 Another drug being investigated in patients with AF is edoxaban, which is being compared with warfarin in the ENGAGE-TIMI 48 study.

These studies have provided a wealth of data (Table 2) that demonstrate the efficacy of oral anticoagulation therapy with minimal monitoring of the international normalized ratio (INR) in patients with AF and a range of CHADS2 scores.

Postmarketing surveillance of dabigatran is ongoing. The FDA has issued warnings about increased bleeding related to the use of the drug in patients older than 75 years of age and the risk of rebound thromboses in patients who are transitioning from rivaroxaban to warfarin. Overall, however, these agents appear to be well tolerated.

Concerns persist regarding the usefulness and cost-effectiveness of these agents in the setting of excellent control of the INR.21 In addition, drug interactions between both dabigatran and riva-

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**TABLE 1**

**Characteristics of Novel Oral Anticoagulants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor IIa (thrombin)</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Time to Cmax, hours</td>
<td>2</td>
<td>2–4</td>
<td>1–3</td>
<td>1–2</td>
</tr>
<tr>
<td>CYP metabolism</td>
<td>None</td>
<td>32%</td>
<td>15%</td>
<td>&lt;4%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>7%</td>
<td>80%</td>
<td>66%</td>
<td>62%</td>
</tr>
<tr>
<td>Transporters</td>
<td>P-gp</td>
<td>P-gp/BCRP</td>
<td>P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>&gt; 90%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td>Half-life, hours</td>
<td>12–14</td>
<td>9–13</td>
<td>8–15</td>
<td>8–10</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>80%</td>
<td>66%</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>Linear pharmacokinetics</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Cmax = maximum serum concentration; P-gp = P-glycoprotein; BCRP = breast cancer resistance protein; CYP = cytochrome P450

Adapted from a presentation by Robert P. Giugliano, MD, at an Investigator Meeting for the TIMI Study Group, 2011 Scientific Sessions of the American Heart Association

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**TABLE 2**

**Primary Endpoint Results of RE-LY, ROCKET-AF, and ARISTOTLE Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug (dose)</th>
<th>Primary endpoint</th>
<th>Hazard ratio</th>
<th>Noninferiority P vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY17</td>
<td>Dabigatran (110 mg)</td>
<td>1.53%/yr</td>
<td>0.91</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>Dabigatran (150 mg)</td>
<td>1.11%/yr</td>
<td>0.66</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>1.69%/yr</td>
<td>0.79</td>
<td>-</td>
</tr>
<tr>
<td>ROCKET-AF18</td>
<td>Rivaroxaban (20 mg)</td>
<td>1.7%/yr</td>
<td>0.79</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>2.2%/yr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ARISTOTLE19</td>
<td>Apixaban (5 mg)</td>
<td>1.27%/yr</td>
<td>0.79</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>1.6%/yr</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a Stroke/systemic embolism
b Intention-to-treat analysis
c Modified intention-to-treat analysis
Adapted from a presentation by C. Michael Gibson, MD, at the 2011 Scientific Sessions of the American Heart Association

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**Figure 4** The balance between hemorrhage and thrombosis in atrial fibrillation is delicate. If anticoagulation is appropriate, the agent must be carefully chosen to prevent tipping the scale in either direction.
roxaban with P-glycoprotein inhibitors (eg, dronedarone, ketoconazole) are of concern. Finally, many questions remain unanswered regarding the ability to reverse the anticoagulant effects of these drugs, patient monitoring, and the risks/benefits of using these agents against a background of potent antiplatelet therapy and in patients with AF and acute coronary syndromes.21

The transition of a new class of drugs from the clinical trial arena into clinical practice is often fraught with regulatory and logistic concerns. Often, safety warnings are issued after FDA approval; further, the addition of a new drug to other drugs a patient is already taking may compromise compliance. Overall, however, the newer oral anticoagulants provide growing options within the medical arsenal, which will improve patient care and outcomes.

REFERENCES