New Horizons in Atrial Fibrillation

Stroke Prevention in Atrial Fibrillation

The ADOPT Trial and Direct Factor Xa Inhibitors

Anticoagulation Therapy: New Opportunities, New Challenges

CONTINUING MEDICAL EDUCATION: 1.5 CREDITS AVAILABLE
Selected Reports from the 2011 Scientific Sessions of the American Heart Association

Christopher P. Cannon, MD, Guest Editor

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Payal Kohli, MD
TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts

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Suraj Kapa, MD
Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

**CME Post Test and Evaluation**
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RATIONALE AND PURPOSE
Since the early 1950s, long-term, warfarin-based anticoagulation has protected countless patients with atrial fibrillation from having a stroke, as well as patients at risk of deep venous thrombosis and embolism. Nevertheless, because of its narrow therapeutic window, the need for frequent laboratory monitoring and dosage adjustments, and multiple food and drug interactions, patients and their physicians often find the use of this vitamin K antagonist to be cumbersome and inconvenient, leading to physician underutilization of oral anticoagulation therapy and poor adherence on the part of patients. This picture changed in 2009 with the introduction of a new class of oral anticoagulants offering fixed dosing and no requirement for frequent blood tests, with safety and efficacy similar to, and perhaps even better than, those of warfarin.

This edition of The Cardiology Report focuses on the mechanisms of action of warfarin and the newer oral anticoagulants; the pathophysiology and treatment of atrial fibrillation; the evidence supporting the use of oral anticoagulants in patients with atrial fibrillation, as well as those with deep venous thrombosis and pulmonary embolism; and the issues surrounding their use in clinical practice—particularly the translation of data from pivotal clinical trials to everyday practice. In the absence of information from direct head-to-head comparisons among these newer agents and the lack of guidance from nationally recognized bodies, many questions remain as to the choice of an oral anticoagulant for individual patients with atrial fibrillation or thromboembolic disease or whether such patients should be switched from warfarin to one of the newer drugs. The authors of this monograph detail the advantages and disadvantages of using warfarin, the direct thrombin inhibitor dabigatran, and two factor Xa inhibitors—rivaroxaban and apixaban—and describe the current state of the art in prescribing oral anticoagulants for different patient populations. These summaries are followed by a look forward to more convenient, effective approaches to monitoring patients using warfarin and improving adherence (perhaps the most important aspect of using this drug long term) and a brief description of what’s on the horizon in oral anticoagulation, including ways of monitoring the activity of novel anticoagulants and predicting patient response. The articles within are based upon presentations delivered during the 2011 Scientific Sessions of the American Heart Association, held in Orlando, Florida, November 12–16, 2011.

The articles in this issue, written from the academic perspective of physicians in training at leading medical institutions, summarize the import of these new findings and place them into clinical context. This activity has been developed and approved by a planning committee of nationally recognized thought leaders to meet a perceived educational need to provide cardiologists and other physicians with diagnostic and therapeutic strategies to help them perform their medical roles.

LEARNING OBJECTIVES
After studying this issue of The Cardiology Report, participants in this educational activity should be able to:

• Interpret the results of clinical studies comparing the efficacy and safety of novel oral anticoagulants with those of warfarin.
• Summarize the pros and cons of using novel oral anticoagulants as warfarin substitutes in clinical practice.

TARGET AUDIENCE
Cardiologists and other physicians significantly involved in the management of atrial fibrillation and stroke prevention should find participating in this educational activity valuable.

ACCREDITATION AND CREDIT DESIGNATION
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Cincinnati and Direct One Communications, Inc. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians. The University of Cincinnati designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CREDIT AVAILABILITY
Activity release date: February 10, 2012
Expiration date: February 11, 2013

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read the CME information on these two pages, including the learning objectives and disclosure statements, as well as the full content of this monograph, and then complete the post test and evaluation form online at www.CardiologyReport.com. Upon successful completion of the post test (80% correct) and evaluation form, a CME certificate of participation will be awarded automatically. The certificate may be printed directly from the Web site or e-mailed and printed later.

There are no fees for participating in or receiving credit for this activity.

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Christopher P. Cannon, MD, is a Senior Investigator in the TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital, and Professor of Medicine, Harvard Medical School, Boston, Massachusetts. He has received research support from Accumetrics, AstraZeneca, GlaxoSmithKline, Merck, and Takeda and honoraria for developing independent educational symposia from AstraZeneca and Pfizer. In addition, he has an ownership interest in Automedics Medical Systems and has served as an advisor or consultant to Alnylam, Bristol-Myers Squibb, Novartis, and sanofi-aventis (but funds donated to charity).

Payal Kohli, MD, a Research Fellow in the TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, has nothing to disclose.

Ravi Marfatia, MD, a Hypertension Research Fellow in the Division of Hypertension and Clinical Pharmacology, Pat and Jim Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, Connecticut, has nothing to disclose.

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In this issue of The Cardiology Report, Dr. Marfatia discusses studies of apixaban, an investigational oral anticoagulant, and briefly refers to ongoing clinical trials of two other investigational drugs, betrixaban and edoxaban. Dr. Sarma mentions otamixaban and melagatan, neither of which have been approved by the FDA. Finally, Dr. Kapa briefly describes unapproved/off-label uses of recombinant factor VIIa and prothrombin complex concentrate.

CONTACT INFORMATION
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Introduction

Selected Reports from the 2011 Scientific Sessions of the American Heart Association

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The American Heart Association (AHA)’s Scientific Sessions is one of the largest annual meetings in the United States of scientists, researchers, physicians, nurses, and other healthcare workers involved in studying or treating patients with cardiovascular disease and stroke. Each year, over 17,000 health professionals and 22,000 total attendees receive and share information emerging from basic research, laboratory studies, and clinical trials. Experts speaking at the November 2011 gathering in Orlando, Florida, delivered over 4,000 presentations covering the prevention, diagnosis, and treatment of cardiovascular disease and its sequelae from the perspectives of different researchers and healthcare providers.

This edition of The Cardiology Report focuses on the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF) and management of deep venous thrombosis (DVT) and other thrombotic disorders in patients at risk. The authors of this report—all senior cardiology fellows at leading medical institutions—cover the physiologic phenomena that ultimately lead to stroke and describe current strategies for preventing thrombotic disease in patients with AF via surgical techniques and anticoagulation therapy. Further, they summarize the results of important clinical trials that have contributed immeasurably to our understanding of thrombosis-based disease and its optimal treatment. Finally, these reports offer a glimpse at future therapies and research directions.

NEW HORIZONS IN ATRIAL FIBRILLATION

Understanding the impact and origins of thrombotic disease provides the background necessary for clinicians to offer their patients the best care possible. Payal Kohli, MD, from Brigham and Women’s Hospital and Harvard Medical School in Boston, provides an overview of the impact of AF in the United States and around the world. This report covers current knowledge about the triggers of AF and the body’s responses to these catalysts. Dr. Kohli shares information on the electrophysiologic mechanisms of AF and the efficacy of ablative techniques in correcting the arrhythmia. In addition, the article describes the advantages and disadvantages of rhythm and rate control in managing AF and the use of anticoagulants as a main strategy to prevent stroke and thromboembolism.

STROKE PREVENTION IN ATRIAL FIBRILLATION

Ravi Marfatia, MD, from the University of Connecticut School of Medicine in Farmington, follows this theme with a summary of presentations devoted to anticoagulation in treating patients with AF. This report begins with currently used risk-stratifying schemes and the considerable differences in management recommendations that physicians find when they weigh therapeutic options. After discussing factors that discourage warfarin therapy, Dr. Marfatia describes the actions of the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, betrixaban, and edoxaban and discusses the results of clinical studies comparing the safety and efficacy of these drugs with those of warfarin.

THE ADOPT TRIAL AND DIRECT FACTOR Xa INHIBITORS

A closer look at the newer anticoagulants approved by the US Food and Drug Administration and in late stages of clinical development provides insight into the future of AF therapy. Satyam Sarma, MD, from Northwestern University’s Feinberg School of Medicine in Chicago, reports on the usefulness of direct factor Xa inhibitors in providing oral anticoagulation without the need for frequent and continued blood monitoring. Direct thrombin inhibitors allow convenient oral administration and offer a more predictable dose response than do vitamin K antagonists such as warfarin. Comparisons of direct factor Xa inhibitors with warfarin...
help differentiate these drugs. Recently published studies provide crucial information on anticoagulants used in patients with AF, DVT, and pulmonary embolism and the advantages and disadvantages of different drug types. In addition, Dr. Sarma summarizes findings from the recently completed Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial, which compared the ability of apixaban with that of enoxaparin in preventing DVT and pulmonary embolism by prolonging prophylaxis of venous thromboembolism in patients at high risk.

**ANTICOAGULATION THERAPY: NEW OPPORTUNITIES AND NEW CHALLENGES**

These first three articles set the stage for a glimpse into the future of anticoagulation therapy as reported by Suraj Kapa, MD, from the Hospital of the University of Pennsylvania in Philadelphia. Clinicians often are torn between short-and long-term anticoagulation schemes. The need for close monitoring during warfarin therapy, owing to its narrow therapeutic window and multiple food and drug interactions, has resulted in the underutilization of oral anticoagulant therapy and poor patient adherence.

Newer oral anticoagulants are more targeted and cause more predictable responses than warfarin, and clinical trials comparing these drugs to warfarin have produced interesting and promising results. Dr. Kapa reviews the known advantages and disadvantages of these agents, their mechanisms of action, and ongoing research into how their anticoagulant effects can be reversed when needed. In addition, Dr. Kapa recounts how warfarin therapy may become more patient-friendly, what factors must be considered when switching patients from warfarin to a newer anticoagulant, and why these novel drugs may become the standard of care for treating AF and DVT.

We are grateful to these authors for attending the AHA’s 2011 Scientific Sessions and providing us with a vivid picture of the present and future status of anticoagulant and antithrombotic therapies. Future editions of *The Cardiology Report* certainly will continue to educate readers about innovative methods to prevent stroke and systemic embolism in patients with AF or who have recently undergone major orthopedic procedures.
New Horizons in Atrial Fibrillation

Payal Kohli, MD
TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts

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 Krannert 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.

I. 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.

II. 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

Dr. Kohli is a Research Fellow in the TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts.
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 *PITX2* (paired-like homeodomain 2), a gene involved in cardiac development, that doubles the risk of developing AF. Transgenic mice with *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 CHADS2, (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 bradyarrhythmia 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-
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.2 In addition, drug interactions between both dabigatran and rivaroxaban with other 

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
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<tr>
<td>Target</td>
<td>Factor IIa (thrombin)</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
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<tr>
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<td>Yes</td>
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<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

**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>P &lt; 0.001*</td>
</tr>
<tr>
<td></td>
<td>Dabigatran (150 mg)</td>
<td>1.11%/yr</td>
<td>0.66</td>
<td>P &lt; 0.001*</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>P &lt; 0.001*</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>2.2%/yr</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE19</td>
<td>Apixaban (5 mg)</td>
<td>1.27%/yr</td>
<td>0.79</td>
<td>P &lt; 0.001*</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>1.6%/yr</td>
<td>0.79</td>
<td></td>
</tr>
</tbody>
</table>

*Stroke/systemic embolism

**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


Stroke Prevention in Atrial Fibrillation

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Abstract Despite the proven ability of anticoagulation therapy to significantly reduce morbidity and mortality in patients with atrial fibrillation (AF), it frequently is underutilized. The goal of stroke and bleeding risk-stratifying schemes is to assist clinicians in selecting appropriate antithrombotic therapy to prevent stroke in patients with AF while minimizing the risk of hemorrhagic complications. Clinical trials have demonstrated that newer oral anticoagulant agents are at least noninferior to warfarin in reducing thromboembolic events and may provide a safer risk profile for bleeding. However, results of prolonged studies that have assessed long-term safety issues are not yet available.

Atrial fibrillation (AF) is associated with a fivefold increase in the risk of stroke and is a major risk factor for thromboembolism. Ischemic strokes secondary to AF are associated with significantly higher morbidity and mortality when compared with strokes due to other causes.

Chronic antithrombotic therapy is an appropriate preventative strategy in most patients with AF. Various risk-stratification schemes have been developed to identify and treat patients at highest risk of stroke and to protect low-risk patients from the bleeding complications of antithrombotic therapy. The many clinicians who are unaware of these various schemes tend to underestimate the risk-benefit ratio of antithrombotic therapy and overestimate its bleeding risks. As a result, anticoagulation therapy is often underutilized; reportedly, it is given to just 30%–60% of eligible patients with AF. Risk-stratifying schemes that categorize patients into low-, moderate-, and high-risk groups have been developed (Table 1). Risk-defining parameters largely have been derived from cohorts of patients enrolled in clinical trials who did not receive anticoagulation therapy and for whom various potential risk factors were not documented. Validation studies in large “real-world” cohorts have indicated that contemporary risk-stratifying schemes have a comparable, yet limited, predictive value of thromboembolic risk in AF, but the choice of antithrombotic therapy may significantly vary from one patient to another depending upon the scheme applied.

Current guidelines recommend anticoagulation with vitamin K antagonists in patients categorized as being at high risk, the use of vitamin K antagonists or aspirin in those at intermediate risk, and the administration of aspirin alone in patients considered to be at low risk. However, anticoagulation therapy using vitamin K antagonists has been shown to be superior to the use of aspirin in reducing ischemic stroke and systemic thromboembolic events in “intermediate-risk” AF patients. Additionally, the benefit of using aspirin to prevent thromboembolic events in “low-risk” AF patients is questionable. Thus, identifying truly low-risk patients in whom bleeding risks would outweigh the benefits of antithrombotic therapy is imperative.

Simplicity is what has made the CHADS2 score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and previous stroke/transient ischemic attack [double risk]) index the most commonly used risk-stratifying scheme. It is derived from the Atrial Fibrillation Investigators (AFI) and Stroke Prevention in Atrial Fibrillation (SPAF I–III) studies, and it has been validated in the National Registry of AF cohort.

The CHADS2 score is limited, in that it classifies a large proportion of patients as being at intermediate-risk and excludes other known stroke risk factors (namely, female gender, age 65–74 years, and vascular disease), which could improve the identification of “truly low-risk” patients. The CHA2DS2-VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus and previous stroke/transient ischemic attack [double risk], vascular disease, age = 65–74 years, sex category) index, which was recently proposed to augment the CHADS2 score, includes these risk factors. Its predictive value is similar to that of existing schemes; however, it allows...
improved identification of truly low-risk patients.9,20

Assessment of Bleeding Risk

Risk factors for bleeding during anticoagulation therapy are similar to those for stroke risk—as the risk for stroke increases, so does the risk for bleeding.21 Practical bleeding risk schemes could offer a simple tool to assist clinicians in making decisions regarding anticoagulation therapy in AF patients. For example, high-dose dabigatran therapy, which has demonstrated superiority over warfarin in reducing the risk of stroke but a similar risk of bleeding,22 could be used in patients with low bleeding scores. Use of low-dose dabigatran, which has been shown to be noninferior to warfarin therapy for stroke reduction but has had a preferable risk profile for bleeding,23 could be chosen for patients having higher bleeding risk scores in countries where the lower dose is available. The 110-mg dose currently is not approved for use in the United States.

Of several bleeding risk-stratifying schemes, two are relatively simple, have been validated in large “real-world” cohorts, and could provide a practical and complementary role for stroke risk assessment. The first scheme, HAS-BLED,23 assigns 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio (INR), advanced age, and drug or alcohol consumption. The maximum score is 9; a patient having a score > 3 is considered to be at high risk of bleeding. This score has had a consistent predictive accuracy over 1 year across different populations (C-statistic, 0.72). The second risk-stratifying scheme, ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation),24 derived a simple 5-variable risk score from a large community-based cohort of patients with AF; 3 points were assigned to anemia and severe renal disease, 2 points to age ≥ 75 years, and 1 point each to previous hemorrhage or a history of hypertension. The risk score was collapsed to a three-category scheme in which “low-risk” (0–3 points) and “high-risk” (5–10 points) patients had hemorrhage rates of < 1% and > 5% per year, respectively.

Newer Anticoagulants

Warfarin has been the mainstay of long-term anticoagulation therapy, because it significantly reduces the occurrence of stroke in patients with AF.25 The optimal benefit of stroke prevention in nonvalvular AF patients that does not enhance the risk of hemorrhagic complications occurs at an INR range of 2.0–3.0.26

Factors such as diet, comorbidities,
drug-drug interactions, and genetic predisposition lead to a highly variable response to warfarin in many individuals. This variation necessitates frequent monitoring of the INR and subsequent dose adjustments that may limit patient adherence to therapy. In addition, patients spend only approximately 55% of their time within the therapeutic INR range, on average. These numbers vary depending upon whether the patient is cared for by healthcare professionals in a primary care office, anticoagulation clinic, or a randomized controlled trial.

A wave of newer oral anticoaguants has recently become available that requires less laboratory monitoring than warfarin, with similar or even better efficacy and safety.

**Direct Thrombin Inhibitors**

Dabigatran etexilate is an oral, synthetic prodrug that undergoes plasma and hepatic esterase-catalyzed hydrolysis into its active form, dabigatran, which is a competitive and reversible direct thrombin inhibitor. Its actions are more predictable than those of warfarin. For example, the actions of dabigatran are reversible, and it binds thrombin with high selectivity and potency. The activity of dabigatran in the blood can be detected by prolongation of the thrombin clotting time and the ecarin clotting time, which are sensitive coagulation assays.

Dabigatran therapy was compared with warfarin therapy in patients with nonvalvular AF in the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial. This prospective, randomized, multicenter study compared low-dose (110 mg twice daily) and high-dose (150 mg twice daily) dabigatran with warfarin (target INR, 2–3) in patients with nonvalvular AF. The primary outcome was a composite of stroke or systemic embolism. Patients had a mean CHADS2 score of 2.1, and those in the warfarin group spent a mean 64% of their time within the therapeutic INR range.

Use of high-dose dabigatran was superior to warfarin (1.11% vs 1.69% events per year; \( P < 0.001 \)), whereas low-dose dabigatran was noninferior to warfarin therapy (1.53% vs 1.69% events per year; \( P = 0.34 \)). Low-dose dabigatran therapy was associated with a lower rate of major bleeding than warfarin therapy (2.71% vs 3.36% per year; \( P = 0.003 \)), whereas the rate of major bleeding was similar with high-dose dabigatran and warfarin (3.11% vs 3.36% per year; \( P = 0.31 \)). Both doses of dabigatran also caused significantly fewer intracranial hemorrhagic complications than warfarin (\( P < 0.001 \)). Although a higher rate of myocardial infarction was observed with both doses of dabigatran, as compared with warfarin therapy, a post hoc analysis with additional outcomes that were not reported in the initial study showed that these differences were not statistically significant. Moreover; overall vascular mortality was reduced with dabigatran therapy, although the true significance of this finding is unknown. Dyspepsia, a major side effect of dabigatran, occurred at a significantly higher rate with both doses of the drug (110 mg, 11.3%; 150 mg, 11.8%) than with warfarin (5.8%; \( P < 0.001 \)).

Dabigatran is approved by the US Food and Drug Administration (FDA) as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular AF. Recommended doses are 150 mg twice daily for patients with a creatinine clearance (CrCl) > 30 mL/min and 75 mg twice daily for those with a CrCl = 15–30 mL/min. It should be noted that patients in the pivotal RE-LY trial were excluded if they had a CrCl < 30 mL/min. Thus, use of the lower dose of 75 mg twice daily is not supported by clinical trial data but, rather, is an extrapolation of the pharmacokinetic studies on this drug. Although the 110-mg dose has not been approved for use in the United States, European guidelines recommend 150 mg of dabigatran twice daily for patients having a low (HAS-BLED score = 0–2) or 110 mg of dabigatran twice daily for patients having a high (HAS-BLED score ≥ 3) bleeding risk. Canadian guidelines recommend dabigatran as an alternative to warfarin at both doses.

**Factor Xa Inhibitors**

Rivaroxaban and apixaban—oral, direct selective inhibitors of factor Xa in the coagulation cascade—have both been studied in large phase III trials. Rivaroxaban is given once daily; it recently was approved in both the United States and Europe to prevent stroke in patients with nonvalvular AF. Phase III clinical trials of apixaban, which is given twice daily, to prevent stroke in patients with AF have been completed, and possible approval of the drug currently is being reviewed by the FDA.

Rivaroxaban was compared with warfarin in high-risk patients with nonvalvular AF in the prospective, double-blind, multicenter ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial. Patients were randomized to receive 20 mg of rivaroxaban once daily (reduced to 15 mg once daily for those with a CrCl = 30–49 mL/min) or dose-adjusted warfarin (target INR, 2–3). The primary composite outcome was stroke or systemic embolism. Patients in the ROCKET AF trial, with a mean CHADS2 score of 3.5, were at a higher risk of stroke than were those in the RE-LY study. In addition, patients randomized to warfarin therapy spent an average of 55% of their time within the therapeutic INR range, which was a smaller percentage than that observed among the warfarin group in the RE-LY trial (64%).

Rivaroxaban was noninferior to warfarin for stroke prevention in this high-
risk population (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.74–1.03; \( P = 0.12 \)). The rates of major and clinically relevant nonmajor bleeding were similar among patients treated with rivaroxaban and those given warfarin, whereas the rate of intracranial hemorrhage was significantly lower among patients given rivaroxaban than in the warfarin group (0.49% vs 0.74%; \( P = 0.02 \)).

Apixaban therapy was compared with aspirin use for the prevention of stroke in patients with AF who were unable to tolerate warfarin or failed to respond to the drug in the prospective, multicenter AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Reduce the Risk of Stroke) trial.\(^{30}\) The study was stopped abruptly due to a significant reduction (55%) in the occurrence of stroke and systemic thromboembolism in the apixaban group (HR, 0.45; 95% CI, 0.32–0.62; \( P < 0.001 \)), with no increased risk of major bleeding relative to aspirin.

Apixaban also was assessed for non-inferiority versus warfarin in the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) trial.\(^{37}\) This prospective, double-blind, multicenter trial compared 5 mg of apixaban given twice daily with dose-adjusted warfarin (target INR, 2–3). Patients had a stroke risk similar to that of the RE-LY cohort; they had a mean CHADS\(_2\) score of 2.1, and those on warfarin spent a mean of 62% of their time within the therapeutic INR range.

Use of apixaban resulted in a similar clinical benefit to that achieved with warfarin in reducing the risk of ischemic stroke, but its superiority to warfarin was shown by a 21% overall reduction of stroke and thromboembolic events, which was secondary to a 50% reduction in hemorrhagic stroke. Major hemorrhagic complications and all-cause mortality also were significantly lower in the apixaban arm than in the warfarin arm (31% and 11%, respectively).

Betrixaban and edoxaban are oral factor Xa inhibitors that are in the early stages of development. EXPLORE-Xa (Phase 2 Study of the Safety, Tolerability and Pilot Efficacy of Oral Factor Xa Inhibitor Betrixaban Compared to Warfarin) is a recently completed phase II trial that is comparing use of three blinded doses of betrixaban (40, 60, and 80 mg) with warfarin administration for stroke prevention in patients with nonvalvular AF.\(^{38}\) ENGAGE AF-TIMI 48 (Global Study to Assess the Safety and Effectiveness of DU-176b vs Standard Practice of Dosing with Warfarin in Patients with Atrial Fibrillation) is a phase III clinical trial that is assessing the noninferiority of edoxaban given at high (60 mg) and low (30 mg) doses when compared with warfarin therapy in reducing stroke and thromboembolic events in high-risk AF patients (CHADS\(_2\) score > 2).\(^{39}\)

**REFERENCES**


The ADOPT Trial and Direct Factor Xa Inhibitors
Satyam Sarma, MD
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Abstract Vitamin K antagonists and heparin-based compounds have formed the cornerstone of anticoagulation therapy for decades. Although they are effective in treating a myriad of thrombosis-based diseases, these agents have considerable disadvantages in terms of side-effect profiles, drug-drug interactions, and dose-response variability. In recent years, however, a number of new antithrombotic compounds have been developed to overcome these limitations. Direct factor Xa inhibitors have evolved from intravenous formulations used primarily to treat heparin-induced thrombocytopenia to oral compounds, which have been compared with vitamin K antagonists and low-molecular-weight heparins in various clinical scenarios. This review provides a background on the new antithrombotic agents and covers findings from the Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial.

Over the past decade, new oral anticoagulants have been developed to overtake the mantle of heparin and vitamin K antagonist-based therapies. Promising convenient fixed dosing, fewer food and drug interactions, improved side-effect profiles, and efficacy at least equal to that of warfarin, these compounds have revolutionized the treatment of thrombotic diseases by overcoming the unpredictability and dose variability of older anticoagulant options. Some of these novel compounds have been studied under a range of clinical conditions and have been used with varied success when compared with established therapy. They fall primarily into two major classes: direct factor Xa inhibitors and direct thrombin inhibitors. As summarized in Table 1, they have been evaluated clinically for the prophylaxis of deep venous thrombosis (DVT) in patients undergoing orthopedic surgery and the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF) and acute coronary syndrome; they also are being tested to treat acute venous thromboembolism (VTE).

MECHANISMS OF ACTION
Unlike vitamin K antagonists, direct factor Xa and direct thrombin inhibitors target specific links in the coagulation chain to theoretically confer a more predictable dose-response relationship. Activated factor X converts prothrombin to thrombin; it is an important focal point of the coagulation cascade linking extrinsic and intrinsic pathways. Direct factor Xa inhibitors bind directly to the catalytic site of factor X in a 1:1 stoichiometric ratio. Unlike indirect inhibitors (eg, enoxaparin and fondaparinux), direct factor Xa inhibitors do not require antithrombin III as a mediating factor to exert their anticoagulant effects.

Direct thrombin inhibitors (eg, ximelagatran and dabigatran) block the effects of thrombin and limit the generation of fibrin from fibrinogen, but they also affect the actions of thrombin on non-coagulation cascade pathways by inhibiting both thrombin-mediated platelet activation and activation of factors V, VIII, XI, and XIII. Development of ximelagatran ceased in 2006 after a high incidence of hepatotoxicity was related to its use, leaving dabigatran as the only oral direct thrombin inhibitor currently available for clinical use.

Although the mechanism of action of direct factor Xa and direct thrombin inhibitors seems straightforward, considerable variability in the effective bioavailability of factor X and thrombin exists, affecting the in vivo actions of these drugs. Both factor X and thrombin can be freely circulating or fibrin bound. Factor Xa complexes with factor Va on the platelet surface to form the prothrombinase complex, increasing the catalytic activity of factor Xa as compared with unbound factor Xa and allowing for highly efficient thrombin activation. The direct inhibitors are able to access the catalytic sites of the respective targets, whether in the circulation or in spatially confined locations (eg, dense clot).

Efficacy
Unlike testing of vitamin K antagonists, assays used to test the potency of direct factor Xa and direct thrombin inhibitors depend on thrombin availability and configuration, which makes standardized clinical screening problematic. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) rely on normal concentrations of clotting factors. In the case of PT, factor VII is the critical factor that catalyzes clot formation.

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after the in vitro addition of tissue factor. For aPTT, a number of factors need to be at physiologic levels to allow a clot to form after in vitro addition of phospholipids. Addition of direct or indirect inhibitors also can affect aPTT, even in the presence of normal concentrations of clotting factors, if plasma levels of the inhibitors remain high enough to affect normal phospholipid activation of the coagulation cascade.

For direct inhibitors, routine measurement of PT and aPTT is not recommended, because these drugs may have unpredictable and unclear effects on assay results, depending upon plasma concentration and dose timing.27 For dabigatran and rivaroxaban, aPTT may offer a qualitative measure of activity; normal levels suggest inadequate anticoagulant levels.28,29 PT results are more unreliable due to variability in the reagents used. Thrombin time and activated factor Xa level are more direct measures of plasma anticoagulant activity for direct thrombin and direct factor Xa inhibitors, respectively, but their measurement is not readily available in most clinical laboratories.

Comparing compounds in a standardized assay can supply helpful insight into their relative potency. Gray and Fareed40 compared the direct inhibitory effects on thrombin activation of rivaroxaban, otamixaban, apixaban, dabigatran, and melagatran. In an isolated tissue factor-activated prothrombin assay system, the inhibitory effects of rivaroxaban were most potent, followed by those of otamixaban, apixaban, melagatran, and dabigatran. When assessed using traditional plasma-based assay systems, direct factor Xa inhibitors were less potent in altering PT and aPTT measures than were the direct thrombin inhibitors. These results suggested that the actions of these drug classes in complex systems are not completely understood and that they likely extend beyond the simple inhibition of thrombin and factor Xa.

Clinical results discussed during the 2011 Scientific Sessions of the American Heart Association, including those from the Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial,20 offered cardiologists and other health professionals a glimpse of the great promise that newly approved drugs and agents now being developed have for patients in need of safe and effective anticoagulation.

### CLINICAL USE

Currently, only rivaroxaban and dabigatran are approved by the US Food and Drug Administration (FDA) for prevention of stroke and systemic embolism in patients with nonvalvular AF. In addition, only rivaroxaban is FDA approved for prevention of DVT in patients undergoing knee or hip replacement surgery. However, a number of other oral anticoagulants are in phase II or phase III clinical trials for these indications and for use beyond DVT prevention after orthopedic surgery or for the prevention of stroke or emboli in patients with AF or acute coronary syndromes. A relatively unexplored and potentially effective application of newer anticoagulants is the prevention of post-discharge DVT in medically ill patients.

DVT and pulmonary embolism (PE) are significant causes of morbidity and mortality in nonsurgical hospitalized patients, and the risk persists into the post-discharge period. Anticoagulant use effectively prevents DVT and PE; anticoagulation, primarily using warfarin or enoxaparin, has dramatically decreased mortality from PE in patients hospitalized for hip and knee surgery and has become the standard of care.31 In addition, routine DVT prophylaxis during hospitalization has reduced the rates of DVT and fatal PE among patients who were hospitalized for medical illness and suffered a loss of mobility.21

However, a large number of patients suffer DVT and PE after hospital discharge, and few studies have assessed the efficacy of extending antithrombotic therapy into the postdischarge period in patients hospitalized for medical illnesses. A recent study of extended-duration DVT prophylaxis in nonsurgical patients given subcutaneous (SC) enoxaparin for 28 days did not show a significant net benefit due to an increase in bleeding that counterbalanced the decrease in VTE incidence.33

Direct factor Xa and direct thrombin inhibitors, however, offer the opportunity for a better prophylactic agent post discharge because they are given orally and have a more predictable dose response.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Dosinga</th>
<th>Clinical trials</th>
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<td>Ximelagran</td>
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DTI = direct thrombin inhibitor; bid = twice daily, DVT = deep venous thrombosis; VTE = venous thromboembolism, FXa = factor Xa inhibitor; IV = intravenous
'a Oral administration except where noted

### TABLE 1: Clinically Studied Oral Factor Xa and Direct Thrombin Inhibitors

Satyam Sarma, MD  The ADOPT Trial and Direct Factor Xa Inhibitors
when compared with heparin and vitamin K antagonist-based therapies. Prior studies of these compounds in patients with AF showed a lower incidence of bleeding when compared with warfarin, and this benefit was expected to translate into a net clinical advantage for direct factor Xa and thrombin inhibitors in medically ill patients post discharge. The MAGELLAN study first examined extended-duration DVT prophylaxis using an oral factor Xa inhibitor and compared rivaroxaban given for 35 days with enoxaparin administered for 10 days post discharge. Patients treated with rivaroxaban had a decreased incidence of DVT and PE (4.4% vs 5.7% for enoxaparin; relative risk [RR], 0.771; \( P = 0.0211 \)), but, unfortunately, the benefits of this drug were substantially outweighed by increased bleeding rates (4.1% for rivaroxaban vs 1.7% for enoxaparin; RR, 2.5; \( P < 0.0001 \)).

**THE ADOPT TRIAL**

Apixaban, the second direct factor Xa inhibitor developed after rivaroxaban, is the latest compound to be evaluated in advanced clinical studies in this patient population. Apixaban and rivaroxaban share a number of similarities. Apixaban has an oral bioavailability > 66% and a half-life of 8–13 hours, compared with an oral bioavailability of 80% and a half-life of 7–13 hours for rivaroxaban. In the ROCKET AF trial, rivaroxaban therapy was statistically noninferior to warfarin therapy, with the two drugs showing similar rates of major bleeding. Results of studies investigating the use of apixaban and/or rivaroxaban are summarized in Table 2.

The double-blind, double-dummy, placebo-controlled ADOPT trial compared use of apixaban with enoxaparin therapy for preventing acute DVT and PE in medically ill patients discharged from the hospital. Similar to the group conducting the MAGELLAN study, these investigators hypothesized that prolonging VTE prophylaxis into the postdischarge period would prevent occurrence of DVT or PE in high-risk patients.

**Methods**

Inclusion criteria for patients included hospitalization for either congestive heart failure (CHF) or acute respiratory failure, with an expected hospital stay of at least 3 days. In addition, patients could be eligible if they were hospitalized for an infection, inflammatory bowel disorder, or acute rheumatic disorder and had a VTE risk factor, which included age ≥ 75 years, body mass index > 30 kg/m², history of VTE, or estrogen use. Patients also had to have moderately (ie, walking within the room) to severely limited (ie, primarily bed-bound) mobility. Patients were excluded if they had a confirmed VTE; required use of anticoagulation for other indications; were on dual antiplatelet therapy; or had renal dysfunction, anemia (hemoglobin level < 9 mg/dL), abnormal liver function tests, or a high risk of bleeding.

Patients were randomized during initial hospitalization to receive either 2.5 mg of apixaban administered orally twice daily for 30 days or 40 mg of enoxaparin SC once daily for 6–14 days, with the duration of enoxaparin therapy determined by the investigator. Subjects randomized to the apixaban arm of the study received placebo injections of enoxaparin for at least 6 days to preserve blinding.

The primary efficacy outcome was a 30-day composite endpoint of death from VTE, fatal or nonfatal PE, and occurrence of symptomatic or asymptomatic VTE detected by lower extremity duplex sonography within the 30-day treatment period. Secondary endpoints included (1) death from any cause within the 30- or 90-day study period, (2) composite of death or occurrence of VTE within the 6–14 days of enoxaparin therapy, or (3) symptomatic VTE or nonfatal PE within 60 days.

The primary safety outcome was major bleeding, clinically relevant nonmajor bleeding, and all bleeding reported by investigators; MI; stroke; thrombocytopenia; and death from any cause. Major bleeding was defined as fatal or overt if at least one of the following applied: decrease in hemoglobin level of ≥ 2 g/dL over 24 hours; transfusion of ≥ 2 units of packed red cells; bleeding that occurred in an operated joint that required reoperation or intervention; or intramuscular bleeding with the compartment syndrome; or intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding. Nonmajor bleeding was defined as bleeding that did not meet the major criteria.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Results of Selected Rivaroxaban and Apixaban Clinical Trials</th>
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<tr>
<td>Post total knee arthroplasty</td>
<td>RVX × 35 days</td>
</tr>
<tr>
<td></td>
<td>APX × 35 days</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>RVX</td>
</tr>
<tr>
<td></td>
<td>APX</td>
</tr>
</tbody>
</table>

RVX = rivaroxaban; EXP = enoxaparin; DVT = deep venous thrombosis; PE = pulmonary embolism; CVD = cardiovascular death; MI = myocardial infarction; CVA = cerebral vascular accident; APX = apixaban

*Values shown in bold represent outcomes or results obtained in patients who received either rivaroxaban or apixaban.*
but that caused epistaxis, gastrointestinal bleeding, hemoptysis, hematuria, or unusual bruising.

Results

In all, 6,528 acutely ill patients were randomized initially to receive short-term enoxaparin prophylaxis or extended apixaban prophylaxis. Approximately 2,000 patients were excluded for nonevaluable or missing lower extremity venous ultrasonograms during the 30-day treatment period. The baseline characteristics of the patients in the two groups did not differ. The median age of patients was 68 years for those given apixaban and 67 years for those given enoxaparin. Over 60% were > 65 years of age. Approximately 80% of enrolled subjects were hospitalized for CHF or respiratory failure equally, with the remainder of patients primarily hospitalized for infectious causes without septic shock. In all, 10% had a history of cancer, of which 3% had an active malignancy. In addition, 4% of patients had a history of VTE. The average length of hospital stay was 5 days, and the duration of therapy for patients randomized to receive treatment with apixaban or enoxaparin was 24.9 ± 10.0 (standard deviation) days and 7.3 ± 4.0 days, respectively.

In all, data on 4,495 patients were analyzed for the primary outcome. At 30 days, there were no differences in event rates for the primary outcome between the apixaban and enoxaparin arms (2.71% vs 3.06%, respectively; RR with apixaban, 0.87; 95% confidence interval [CI], 0.62–1.23; \( P = 0.44 \)). There was a significant increase in major bleeding in the apixaban group as compared with the enoxaparin group (0.47% vs 0.19%; RR with apixaban, 2.58; 95% CI, 1.04–7.24; \( P = 0.04 \)). There were more patients with a decrease in hemoglobin level ≥ 2 g/dL in the apixaban group, which accounted for the primary difference in major bleeding between the groups. There were two fatal hemorrhages and intracranial bleeds each in the enoxaparin arm and none in the apixaban group. Total rates of bleeding (including major and nonmajor bleeds) were not statistically different between the two groups (7.73% vs 6.81%; RR, 1.13; 95% CI, 0.95–1.34; \( P = 0.18 \)).

The key secondary outcome of VTE or death during the period prior to discontinuation of enoxaparin (6–14 days) was also similar between both groups (1.73% vs 1.61%; RR, 1.06; 95% CI, 0.69–1.63). There was a nonsignificant trend toward the combined endpoint of decreased symptomatic VTE and VTE-related death in patients treated with apixaban after enoxaparin therapy was discontinued (0.25% vs 0.58%; RR, 0.44; 95% CI, 0.19–1.00). The primary driver of the difference was a reduction in symptomatic VTE among patients given extended thromboprophylaxis with apixaban when compared with those given enoxaparin (0.15% vs 0.49%), which was not statistically significant.

Mortality in both groups of patients was 4.1% during the 90-day study period. Within the early post-discharge period (< 14 days), when both groups received antithrombotic therapy, no patients died of VTE-related complications in either study arm. During the later follow-up period after enoxaparin therapy was stopped, there were two and three VTE-related deaths in the apixaban and enoxaparin arms, respectively. The most common event over the 30-day treatment period was development of symptomatic VTE. The average length of hospital stay was 4.1% during the 90-day study period. The average length of hospital stay was 4.1% during the 90-day study period. Within the early post-discharge period (< 14 days), when both groups received antithrombotic therapy, no patients died of VTE-related complications in either study arm. During the later follow-up period after enoxaparin therapy was stopped, there were two and three VTE-related deaths in the apixaban and enoxaparin arms, respectively. The most common event over the 30-day treatment period was development of proximal DVT, which occurred in 2.4% of patients receiving apixaban and 2.5% receiving enoxaparin, respectively.

Discussion

Results concerning the primary endpoint of the ADOPT trial did not show a benefit from extended apixaban therapy when compared with enoxaparin use, but it did reveal a trend toward decreased symptomatic VTE and VTE-related deaths in the apixaban-treated group after discontinuation of enoxaparin therapy. There were no differences in total bleeding events between the groups, but there was an increase in major bleeds in patients treated with apixaban. Although the overall findings were not statistically significant, there were many limitations to the final analysis. The primary endpoint was underpowered due to the exclusion of approximately 2,000 patients for inadequate follow-up ultrasonography. The comparator arm also was not representative of real-world practice, as treatment with enoxaparin for 6–14 days is not routine in post-discharge care. Furthermore, screening for DVT at 10 days post discharge is not routine; thus, the natural history and occurrence of VTE-related events in the study period likely were altered.

The findings from the ADOPT trial do not support a strategy favoring extended-duration apixaban use over short-term enoxaparin therapy in treating patients at high risk for developing VTE or PE post discharge. Unanswered questions regarding the strategy of extending DVT prophylaxis into the post-discharge period remain. A better understanding of clinical factors that identify high-risk patients is necessary to balance the risk-benefit ratio. The increased risk of bleeding seen in prior studies using enoxaparin and rivaroxaban for extended DVT prophylaxis also was observed in the ADOPT trial.

To date, the use of direct factor Xa inhibitors have not substantially mitigated the risk for bleeding when compared with enoxaparin therapy in the medically ill patient population. However, with proper identification of patients at high risk for post-discharge DVT, both apixaban and rivaroxaban may yet have a role in this undertreated population. Further, direct thrombin inhibitors offer the advantage of oral administration when compared with injected low-molecular-weight heparins and a more predictable dose response when compared with vitamin K antagonists.

CONCLUSION

Direct factor Xa and direct thrombin inhibitors have introduced new options for treatment of thrombotic diseases. Their clinical efficacy has been studied in multiple trials of patients with AF, acute coronary syndromes, and prophylaxis and acute treatment of DVT. Development of new direct inhibitors has focused primarily on direct factor Xa inhibitors, with a number of new compounds being examined through phase III studies. Whereas their safety profiles with regard to occurrence of major bleeding have not been as robust as hoped, their clinical efficacy
when compared with vitamin K antagonists and low-molecular-weight heparins has been well validated. Because of their oral route of administration and few drug interactions, these new antithrombotic compounds may find new indications for short-term anticoagulant therapy in patients at high risk for thrombotic complications.

REFERENCES


Anticoagulation Therapy: New Opportunities, New Challenges

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Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Abstract Short- and long-term anticoagulation strategies are important in caring for patients with a variety of cardiovascular diseases, including atrial fibrillation, deep venous thrombosis, and pulmonary embolism. Management of these patients, whether upon initiation of anticoagulation therapy, perioperatively, or in terms of when and how long to treat them, has been the subject of numerous clinical trials and several guideline statements. Until recently, the options for oral outpatient anticoagulation have been limited to warfarin, a vitamin K antagonist used since the mid-1950s, which is encumbered by a narrow therapeutic window and multiple dietary and pharmacologic interactions. A variety of randomized clinical trials have been published in the past year supporting the use of several novel oral anticoagulants as alternatives to warfarin for both short- and long-term outpatient anticoagulation in different clinical settings. This review focuses on these newer oral anticoagulants; the clinical data supporting their use for different indications; their potential impact on current clinical care; and the controversies that surround how, when, and for whom they should be prescribed.

Multiple clinical trials and guideline statements support the use of long-term anticoagulation for stroke prevention in high-risk patients with atrial fibrillation (AF).1–4 Long-term anticoagulation is also a mainstay in the management of patients with mechanical heart valves, deep venous thrombosis (DVT), and pulmonary embolism.

Until recently, warfarin has been the standard of care for oral outpatient anticoagulation. Although the efficacy of warfarin therapy has been well established, its use entails several difficulties related to day-to-day management. Specifically, warfarin therapy requires control of patients’ prothrombin time or international normalized ratio (INR) within a narrow therapeutic range. Warfarin levels above the therapeutic range lead to an increased risk of life-threatening bleeding, and levels below the therapeutic range obviate any potential benefits from the drug. In turn, ensuring maintenance of therapeutic INRs requires frequent blood testing, whether patients use more recently established home-monitoring methods or undergo blood draws through a clinical laboratory. The multiple dietary and pharmacologic interactions that can potentiate or inhibit warfarin’s anticoagulant effects may complicate the maintenance of a therapeutic INR.5,6 Indeed, several studies have suggested that in clinical practice, patients maintain therapeutic INRs less than 50% of the time.7

These issues and the increasing size of the patient population who could benefit from oral anticoagulant therapy have led to the development of multiple novel oral anticoagulants that may offer the same clinical benefit as warfarin with little increased risk. However, implementation of these new agents requires consideration of both their impact on clinical practice as well as what is best for individual patients.

This review focuses on the use of oral anticoagulation in patients with AF and DVT, compares the relative utility of warfarin with that of newer oral anticoagulants, and considers the controversies surrounding the day-to-day management of patients requiring long-term outpatient anticoagulation. It is based on a program presented at the 2011 Scientific Sessions of the American Heart Association, held November 12–16, 2011, in Orlando, Florida. The session was moderated by James B. Froehlich, MD, MPH, Associate Professor of Internal Medicine, Director of Vascular Medicine, and Director of the Anticoagulation Clinic at the University of Michigan Medical School, Ann Arbor, and Toby Trujillo, PharmD, BCPS, Associate Professor of Pharmacy at the University of Colorado–Denver School of Pharmacy and Director of the Inpatient Anticoagulation–Thrombosis Management Service at the University of Colorado Hospital in Aurora.

ANTICOAGULANTS: WHAT ARE THEY? HOW DO THEY WORK?

Based on a presentation by Richard Becker, MD, Director of the Cardiovascular Thrombosis Center at Duke University Medical Center, Durham, North Carolina.

Thrombus formation involves a departure from the delicate balance that exists between thrombotic and antithrombotic tendencies in biologic systems. The cell-based model of coagulation has been well studied and used to identify therapeutic targets for anticoagulation.8,9 In AF, the extrinsic, or tissue factor, pathway is the primary target for preventing thrombus formation and stroke.10,11 In the most basic sense, thrombus formation involves

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tissue factor-bearing cells that come into contact with circulating coagulation factors. As factor VII comes into contact with tissue factor on these cells, an activated complex forms, which triggers factors IX and X. Factor Xa and factor Va then form prothrombinase complexes that activate prothrombin to thrombin, which then stimulates factor VII and other components of the coagulation cascade (Figure 1). The complex feedback mechanisms involved in this cascade include multiple biologic means of turning “off” the pathway. These concepts have been well described in previous reviews.12,13

Different anticoagulants interrupt the coagulation cascade at various points. Newer anticoagulants target specific points in the coagulation cascade (Figure 1). The goal of novel oral anticoagulants is, in part, to offer more specific targeting and to afford more predictable responses than current therapies such as warfarin can offer. Parenteral alternatives to warfarin have existed for several years to decades, but logistical concerns and patient comfort related to self-injection or maintenance of parenteral medications make their use difficult. Ideally, an oral anticoagulant would require no remote monitoring, have little interaction with other substances, offer good safety profiles with regard to bleeding risk and similar efficacy to warfarin in reducing thromboembolic events, and reach therapeutic levels within several hours. A discussion of pharmacologic considerations related to the use of warfarin and other novel anticoagulants illustrates the advantages and disadvantages of each therapeutic agent.

**Warfarin**

Warfarin has been approved by the US Food and Drug Administration for use as an anticoagulant since 1954.16 This drug inhibits vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K to its reduced form after it participates in the carboxylation of several blood coagulation proteins, including prothrombin and factor VII. Carboxylation is needed for calcium and phospholipid binding, a key factor in activating the blood clotting factors involved in creating the right environment for thrombus formation. However, when warfarin therapy is initiated, anticoagulation is not achieved immediately. Often, several days must pass before clotting factors naturally disappear in the circulation.

The duration of action of a single warfarin dose is 2–5 days. The therapeutic effect of warfarin exists within a narrow therapeutic window as dictated by the INR, and considerable inter- and intraindividual dose variability may be affected by a wide range of physiologic (eg, liver and thyroid function), genetic, and environmental (eg, diet, other drugs) factors.5,10 Thus, regular monitoring is required to avoid excessive or insufficient anticoagulation. If needed, the anticoagulant effects of warfarin may be reversed via a variety of means, ranging from parenteral administration of vitamin K (which may take several hours to reverse the effects of warfarin) to intravenous infusion of clotting factors (which may offer faster reversal).

**Dabigatran**

Dabigatran etexilate is a direct thrombin inhibitor that is given at a fixed oral dose without the need for INR monitoring.17,18 Because of potential P-glycoprotein interactions, its absorption may be decreased if dabigatran is taken with a proton pump inhibitor.19 Excretion through P-glycoprotein pumps may be slowed in patients taking P-glycoprotein pump inhibitors such as quinidine, verapamil, or amiodarone, thus raising plasma levels of dabigatran.19

The drug has a relatively short half-life when compared with warfarin (12–17 hours vs 2–5 days, respectively). Its therapeutic effect may be affected by renal function; patients with acute or chronic renal

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**FIGURE 1** Coagulation cascade along the tissue factor pathway and the targets of direct factor Xa and thrombin inhibitors. The vitamin K antagonist warfarin typically works on several calcium-dependent clotting factors, including factors II, VII, IX (not shown), and X.
failure may require dose reductions, and dialysis may reduce dabigatran levels by as much as 66% within 2 hours.\(^\text{17,18}\)

Once a bottle of dabigatran is opened, the medication expires after 30 days due to the effects of humidity on the drug.\(^\text{17,18}\)

Rivaroxaban and Apixaban

Rivaroxaban and apixaban are direct factor Xa inhibitors that are oxazolidinone derivatives.\(^\text{20–23}\) Both drugs are C-shaped molecules with arylation moieties and methoxyphenol pores. Their interaction with factor X involves both an S1 binding site and an S4 specificity pocket. The two drugs interact slightly differently with the S4 region of factor X.

Both rivaroxaban and apixaban bind to the catalytic/active site of factor X and directly interfere with the coagulation cascade. They have predictable pharmacokinetics and allow for fixed oral dosing. Similar to dabigatran, their half-lives are under 12 hours. No means to reverse their anticoagulant effects are available currently.

Several other related drugs are under active clinical development.\(^\text{24}\)

### OUTPATIENT USE OF WARFARIN AND POTENTIAL IMPACT OF SWITCHING TO NEWER ANTICOAGULANTS

Based on a presentation by Jack E. Ansell, MD, Chairman of the Department of Medicine at Lenox Hill Hospital, New York, New York.

Several models exist for treating patients requiring long-term anticoagulation.\(^\text{25–27}\) Management of these patients may be complex, and traditional models of care have relied almost exclusively on warfarin and close monitoring of INRs to adjust doses. Several issues related to warfarin therapy follow:

- There is a narrow therapeutic window of effectiveness and safety.
- Many factors, including diet and the use of other drugs, can influence the level of warfarin, resulting in either excessive or ineffectual anticoagulation.
- Frequent monitoring of prothrombin time or the INR with blood tests is required to maintain patients within warfarin’s therapeutic window.

- Monitoring is labor-intensive and complex and requires expert dosing decisions.
- Because of these complexities, some clinicians may experience high rates of complications and therefore avoid using warfarin, resulting in undertreatment of patients who might benefit from it.

Several models of care have emerged as a result of the difficulties associated with using warfarin for short- and long-term anticoagulation. The most basic of these models is routine medical care, wherein a physician or office staff manage warfarin dosing based on INRs obtained from blood draws in a laboratory or via a point-of-care device in the clinic. Several larger clinics and hospital services have moved to anticoagulation clinics that are managed by dedicated pharmacists, physicians, registered nurses, or other healthcare professionals and that have systematic policies to manage and dose patients, again using either point-of-care or laboratory-based INRs.\(^\text{25–27}\) A third, more recent model has patients using a point-of-care monitor at home to measure their INRs and then reporting back to the personnel in a clinic to alter the dose.\(^\text{28,29}\)

This model may be taken to the point of patient self-management, in which patients manage their own anticoagulant doses in response to home-tested INRs.

The move from warfarin to novel oral anticoagulants may greatly impact current paradigms of routine clinical care requiring outpatient anticoagulation. A number of questions may be raised about a switch from warfarin therapy to the use of newer fixed-dose oral anticoagulants. One key issue is the lack of validated tests to measure the anticoagulant effect of these novel anticoagulants. For example, activated factor Xa levels that may be used to assess the therapeutic impact of factor Xa inhibitors are not readily available in all centers.\(^\text{30}\) Furthermore, there is no antidote for most of these agents, and it is more difficult to assess patient compliance with new agents than with vitamin K antagonists such as warfarin.

These concerns are tempered by the fact that less monitoring is required for patients on newer oral anticoagulants. The decision to switch may be difficult due to the lack of clear data on long-term adverse effects beyond bleeding and the need for head-to-head studies comparing the new agents. These drugs have been compared generally with warfarin in noninferiority trials, but no study has compared them directly to one another. In turn, given concerns about the impact of impaired liver function on the use of rivaroxaban or apixaban and of impaired renal function on the use of dabigatran, the role of monitoring renal and liver function in such patients is unclear.

In the past, the main roles of anticoagulation services were to monitor INR levels to adjust warfarin dosing, manage periprocedural issues related to warfarin use, assure compliance by educating patients, and prevent adverse events by achieving stable INR levels within a nar-

<table>
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<tr>
<th>Characteristic</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
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<tr>
<td>Site of action</td>
<td>Vitamin K antagonist</td>
<td>Direct thrombin inhibitor (Ila)</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
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<tr>
<td>Maximum time to onset</td>
<td>2–5 days</td>
<td>2 hours</td>
<td>2.5–4 hours</td>
<td>3 hours</td>
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<tr>
<td>Half-life</td>
<td>2–5 days</td>
<td>14–17 hours</td>
<td>5–9 hours in healthy patients; 9–12 hours in elderly patients</td>
<td>8–15 hours</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Acetaminophen; aspirin; NSAIDs; anti-infectives; SSRI; phenytoin; multiple other drugs (and diet)</td>
<td>P-gp inducers (eg, rifampin); dronedarone; ketoconazole; aspirin; NSAIDs; clopidogrel</td>
<td>Strong inhibitors and inducers of CYP3A4 and P-gp; aspirin; NSAIDs; clopidogrel</td>
<td>Aspirin; clopidogrel; potentially, strong inhibitors and inducers of CYP3A4 and P-gp</td>
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NSAIDs = nonsteroidal anti-inflammatory drugs; SSRI = selective serotonin reuptake inhibitors (antidepressants); P-gp = P-glycoprotein
row therapeutic window. However, new anticoagulants introduce new paradigms of therapy. Peaks and troughs in anticoagulation levels may result from the relatively shorter half-lives of these agents and their faster times to onset of action (Table 1). Further, the dosing of these drugs is fixed, so there is no easy way to measure the “therapeutic” effects of these drugs using specific blood tests, and there is little to educate patients about beyond compliance. Anticoagulation clinics will play key roles for patients still on warfarin or who may be switched between different agents, and additional monitoring of liver and renal function may be needed to ensure that dose adjustments or switching of agents is not required.

**SHOULD NEW ORAL ANTICOAGULANTS BE THE STANDARD OF CARE FOR AF?**

Based on presentations by Kenneth W. Mahaffey, MD, Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, North Carolina, and Henry I. Bussey, Jr, PharmD, Professor of Pharmacy, Division of Pharmacotherapy, College of Pharmacy, The University of Texas Health Science Center, San Antonio, Texas.

Stroke associated with AF has substantial morbidity and mortality. Patients with AF-related stroke have a 1.8-fold increase in mortality when compared with those who experience a stroke unrelated to AF, possibly because AF-related strokes tend to be larger in size and more often lead to hemorrhagic transformation. Recent guidelines suggest thromboembolic prophylaxis for patients having risk factors for stroke. Multiple studies have supported the use of INR-adjusted warfarin via head-to-head comparisons with placebo, aspirin, aspirin plus fixed-dose warfarin, and dual antiplatelet therapy. Although patients with AF and at least two additional risk factors for stroke benefit from warfarin therapy, many patients and their physicians resist using warfarin because of concerns related to INR monitoring, the risk of falls, and the potential for bleeding and intracranial hemorrhage.

These numerous challenges in managing patients on warfarin have led to multiple randomized clinical trials comparing dabigatran, apixaban, and rivaroxaban with warfarin. The results of these studies have shown a strong trend toward the superiority of these novel drugs in preventing stroke and in reducing the rate of intracranial hemorrhage. Results from these trials and the ease of using agents that do not require blood work to ensure therapeutic effect and safety have led to great hope for easing the management of patients with AF who need long-term oral anticoagulant therapy.

However, these trials have revealed several issues related to switching a patient to a new oral anticoagulant. Of greatest concern is the brief percentage of time that patients using warfarin actually are maintained in a therapeutic range. Data from systematic overviews suggest that patients are managed at a therapeutic INR only 63% of the time at best, with even worse results being observed in community practices. The importance of staying at a minimum INR of 2.0 to obtain effective stroke prevention has been well defined. Analyses of data from the ROCKET AF, RE-LY, and ARISTOTLE studies have suggested that even when considering quartiles based on how well the INR was managed or centers that had the best INR management of patients given warfarin, there was no significant difference in stroke outcomes between patients given a novel oral anticoagulant and those using warfarin. However, RE-LY data showed that 50% of patients using warfarin who had a therapeutic INR at least 67% of the time had a composite event rate of 5.48, which was lower than the event rates among patients using two different doses of dabigatran. On the other hand, patients who were in the therapeutic range less than 54% of the time had an event rate of 12.32, which was much worse than those for patients in both dabigatran arms.

The importance of keeping patients in the therapeutic range is further supported by results of the SPORTIF trial, in which 25% of patients who had the greatest percentage of time in the therapeutic range had the lowest event rates; however, patients who were in the therapeutic range less than 60% of the time had much higher event rates (ie, up to 11.5 events/1,000 patients per year). In the ATRIA study, there was an 8-fold increase in ischemic events with any drop in the INR < 1.3 if the INR was > 4.0, there was a 12-fold increase in intracranial hemorrhage. Some professionals believe that the relative observed benefit of newer anticoagulants may have been overly influenced by adverse events seen in patients who were suboptimally managed on warfarin.

Self-testing may provide a better way to maintain INR levels within a narrow therapeutic window. Results from the THINRS trial suggested a trend toward benefit in mortality, major bleeding, and stroke when patients performed self-testing rather than relying on specific clinics for monitoring and managing their anticoagulation. Similarly, in the STOARM2 trial, group and individual INR management improved with automated self-monitoring, with INR values < 1.5 or > 5 seen in only 0.47% of patients. Findings from other studies have suggested that anticoagulation clinics run by clinical pharmacists may reduce major events, hospitalizations, and emergency visits by 60%–80% when compared with usual clinic-based management of warfarin and that weekly INR self-testing and self-management may reduce major events by as much as 70% and mortality by as much as 61%.

**Weekly INR self-testing and self-management may reduce major events by as much as 70% and mortality by as much as 61%.”**
patients per year on apixaban versus 2.9 events/1,000 patients per year on warfarin, and 6.9 events/1,000 patients per year on dabigatran versus 4.0 events/1,000 patients per year for warfarin. This theory suggests that there would be a relative benefit to being on optimally managed warfarin. Thus, some contend that the primary issue is to fix how we are managing patients using warfarin rather than to switch patients to another agent.

Another key concern about switching patients to newer oral anticoagulants is the cost. Cost-effectiveness analyses of the newer anticoagulants are limited. At a cost of $7–$9/day (two capsules), dabigatran use may cost an estimated $10,000 per year of life saved.\(^{52-54}\) However, this analysis does not consider direct comparisons against the cost of maintaining patients on warfarin. Further studies are needed to better analyze the relative cost-effectiveness of warfarin against any of these newer oral anticoagulants, particularly as it pertains to the cost of improving current models of care for INR management.

Newer agents also have issues not shared with warfarin, including a shorter half-life with rapid offset and potential attendant clotting risk, the need for a reversal agent in case of acute bleeding or at the time of emergent procedures, and the lack of laboratory monitoring to evaluate patient adherence.\(^{55}\) These newer agents are easy to use, and patients can benefit from lower stroke risk without needing repeated blood tests for INR monitoring, so the potential benefits are obvious.

To truly assess the relative benefit of optimal warfarin control against the use of newer agents, a number of factors must be considered. Optimal control is not achieved in all patients, and implementation of new models of anticoagulation care is costly. Further, the relative superiority of either approach is difficult to define without results from a head-to-head trial of optimally controlled warfarin versus other oral anticoagulants. Thus, efficacy, safety, and ease of use must be considered, and decisions related to cost, individual patients, and the ability of centers to manage patients’ INR levels must be made.

**SHOULD NEW ORAL ANTICOAGULANTS BE THE STANDARD OF CARE FOR DVT?**

Based on presentations by William E. Dager, PharmD, BCPS (AQ Cardiology), FCCP, FASHP, FCSHP, FCCM, Pharmacist Specialist at the University of California Davis Medical Center, Sacramento; Stuart T. Haines, PharmD, BCPS, BC-ADM, FCCP, FASHP; FAPhA, Professor and Vice Chair for Clinical Services and Pharmacotherapy Specialist in the Department of Pharmacy Practice and Science at the University of Maryland School of Pharmacy, Baltimore; and Michael S. McMurtry, MD, PhD, FACHE, partially supported by a grant from AstraZeneca, Professor and Vice Chair for Clinical Services at the University of Maryland School of Pharmacy, Baltimore; and Michael S. McMurtry, MD, PhD, FACHE, Assistant Professor of Medicine, Division of Cardiology, at the University of Alberta, Edmonton, Alberta, Canada.

The role of novel anticoagulants in treating patients with DVT parallels that in patients with AF. The same concerns related to INR monitoring, the narrow therapeutic window of warfarin, and the wide array of dietary and pharmacologic interactions with warfarin still exist. In patients with DVT, one key difference is that the goal is treating an existing problem rather than preventing a potential one. However, the decision to treat as an outpatient versus as an inpatient becomes more difficult, because the time to reach an effective therapeutic range on warfarin varies from 2 to 5 days; in the interim, either injectable low-molecular-weight heparin or parenteral unfractionated heparin would be needed.\(^{56,57}\)

Newer anticoagulants have shorter times to onset with presumably fewer drug interactions than warfarin has. In the EINSTEIN DVT trial, which compared rivaroxaban use with warfarin therapy, and in an extension of the EINSTEIN trial, which examined prevention of recurrent venous thromboembolism with rivaroxaban, a nonsignificant decrease in mortality was noted with rivaroxaban therapy.\(^{58,59}\) Similarly, in the RE-COVER trial, dabigatran use was noninferior to warfarin therapy in treating acute DVT.\(^{60}\)

Further, several major limitations existed in both the EINSTEIN and RE-COVER trials. In EINSTEIN, the percentage of concurrent use of aspirin and/or clopidogrel was not reported, and the study population excluded use of interacting medications (strong CYP3A4 inhibitors and inducers) and patients with significantly elevated liver function tests or renal impairment. Similarly, in RE-COVER, the study population excluded patients if they had recent unstable cardiovascular disease, baseline liver function test results more than twice the upper limit of normal, or significant renal impairment. As with the AF trials, patients in both trials were within the therapeutic range less than 60% of the time.

Thus, considerations related to the choice of initial anticoagulant for patients with acute DVT need to be similar to those used for those with AF, namely, the ability to keep the patient on warfarin within therapeutic levels, the costs of individual agents, the unknown long-term risks related to novel anticoagulants, and the lack of clarity regarding efficacy in patients with significant liver or renal impairment.

**ADVANCES IN PATIENT MONITORING AND DEVELOPING REVERSAL AGENTS**

Based on a presentation by Samuel Z. Goldhaber, MD, Professor of Medicine, Harvard Medical School, and Director of the Venous Thromboembolism Research Group at Brigham and Women's Hospital, Boston, Massachusetts.

Warfarin may be easily monitored using the INR, but the same is not true for dabigatran or the factor Xa inhibitors. Dabigatran can raise the INR, activated partial thromboplastin time, and thrombin time, although the degree of elevation has not been clearly associated with the therapeutic effect of this drug.\(^{52}\) One method that has been suggested is the ecarin clotting time (ECT), in which a known quantity of ecarin is added to the patient's plasma and the time to clotting is evaluated.\(^{61}\) The ECT is notably unaffected by heparin or warfarin. Recently developed chromogenic dabigatran assays may allow for monitoring serum dabigatran levels.\(^{62}\) Similarly, an anti-factor Xa level may be used to evaluate the therapeutic effects of rivaroxaban or apixaban. However, these assays are not as quickly obtained or as widely available as is the INR. Furthermore, therapeutic ranges for these assays remain to be determined.

In terms of managing bleeding complications in patients treated with novel
oral anticoagulants, there is some evidence that the anticoagulant actions of both dabigatran and rivaroxaban may be reversible.82–85 Preclinical studies in animal models of bleeding suggest that both recombinant factor VIIa and prothrombin complex concentrate (PCC) can reverse the effects of dabigatran and rivaroxaban on bleeding time and activated partial thromboplastin time (aPTT). In a randomized, double-blind, placebo-controlled crossover trial, administration of a single bolus (50 IU/kg) of PCC immediately reversed the anticoagulant activity of rivaroxaban in 12 healthy human volunteers but had no effect on dabigatran-induced increases in aPTT, ECT, or thrombin time.82 To date, there have been no reports, anecdotal or otherwise, on how these blood products might function in actual emergent clinical situations. Obviously, more study is needed.

CONCLUSION

The new era of anticoagulant therapy has resulted in a milieu of studies and evolving guidelines to help refine the optimum use of these novel agents as more convenient and possibly safer therapeutic alternatives to warfarin. Although the introduction of such oral anticoagulants as rivaroxaban, apixaban, and dabigatran has the potential to revolutionize the day-to-day care of patients who require oral anticoagulation therapy, the best use of these drugs may need to be determined on a patient-by-patient and center-by-center basis. This is especially true in light of how novel these agents are and the lack of clarity on their long-term risks.

All of these issues—including individual centers’ efficacy in managing INRs, the ability to safely maintain a therapeutic range in individual patients on warfarin, and the current lack of a clear methodology for monitoring or reversing the anticoagulant effects of novel agents (although this may change soon)—must be taken into account when a patient is switched from warfarin to one of these other drugs. Future studies to examine the cost-effectiveness of these agents and their impact on individual patients and systems-based care, as well as head-to-head comparisons of novel oral anticoagulants, will be the key to understanding how these novel agents may enter the current lexicon of anticoagulation.

REFERENCES

CME Post Test

Using this page as a worksheet, select the best answer to each question based upon your reading of the articles in this issue of The Cardiology Report, then complete the evaluation form on the facing page and see the instructions below it to obtain CME credit for completing this activity.

1. The most common risk factor for the development of atrial fibrillation (AF) is:
   a. Rheumatic heart disease
   b. Patient age
   c. Obstructive sleep apnea
   d. Hypertension

2. Which of the following is the principal electrical aberration that can trigger AF?
   a. Increased pulmonary vein arrhythmogenicity
   b. Dysregulation of the autonomic nervous system
   c. Severe reduction in sodium current density
   d. Anisotropic, high-frequency re-entrant sources ("rotors") throughout the atria

3. Based on positive results from the phase III AVERROES and ARISTOTLE trials, the US Food and Drug Administration has given priority review status to:
   a. Otamixaban
   b. Ximelagatran
   c. Betrixaban
   d. Apixaban

4. Current therapeutic guidelines recommend long-term anticoagulation therapy using which of the following in AF patients at high risk of having a stroke?
   a. Direct factor Xa inhibitors
   b. Direct thrombin inhibitors
   c. Vitamin K antagonists
   d. Heparin or a derivative substance

5. Results from the ROCKET AF trial showed that among patients with AF at high risk of having a stroke, those who used rivaroxaban, compared with those who had taken warfarin, had a lower rate of:
   a. Intracranial hemorrhage
   b. Major bleeding
   c. Clinically relevant nonmajor bleeding
   d. All of the above

6. According to Gray and Fareed, which of the following oral anticoagulants exhibits the most potent direct inhibition of thrombin activation?
   a. Melagatran
   b. Rivaroxaban
   c. Dabigatran
   d. Apixaban

7. In the ADOPT trial, which compared apixaban with enoxaparin for preventing acute deep vein thrombosis (DVT) and pulmonary embolism (PE), patients using apixaban showed:
   a. A significant decrease in the incidence of DVT and PE
   b. A significant decrease in major bleeding
   c. A significant decrease in nonmajor bleeding
   d. No fatal hemorrhages or intracranial bleeds

8. Which of the following statements is true?
   a. The tissue factor coagulation pathway is the primary target for preventing thrombus formation and preventing stroke in patients with AF.
   b. The duration of action of a single warfarin dose is typically 5–7 days.
   c. The absorption of dabigatran may be increased by taking it with a proton pump inhibitor.
   d. Anticoagulation is achieved immediately when warfarin therapy is initiated.

9. To achieve effective stroke prevention, AF patients taking warfarin should maintain a minimum international normalized ratio (INR) of:
   a. 1.0
   b. 2.0
   c. 3.0
   d. 4.0

10. One difference in using novel oral anticoagulants in patients with DVT as compared with individuals with AF is that in patients with DVT:
    a. INR monitoring is unnecessary.
    b. The therapeutic window is considerably wider.
    c. The risk of drug interactions is significantly less.
    d. The goal is treatment rather than prophylaxis.
Evaluation

Your candid and thorough completion of this evaluation will help the University of Cincinnati improve the quality of its CME activities. Thank you for your participation.

1. As a result of this activity, I am more knowledgeable about the …
   a. Electrophysiologic mechanisms of atrial fibrillation, the rationale for using oral anticoagulants to prevent stroke, and risk stratification.
   b. Mechanisms of action of vitamin K antagonists, direct thrombin inhibitors, and direct factor Xa inhibitors.
   c. Factors that discourage patients from adhering to warfarin anticoagulation therapy and ways to overcome them.
   d. Results of clinical studies comparing the efficacy and safety of novel oral anticoagulants with those of warfarin.
   e. Pros and cons of using novel oral anticoagulants as warfarin substitutes in clinical practice.

2. I found the content of this educational activity …
   a. Clearly written and well organized.
   b. Accurate and timely.
   c. Related to its overall objectives.
   d. Free from commercial bias.
   e. Relevant to my own clinical practice.

3. Did the information you received from this CME activity:
   a. Confirm the way you currently manage your patients?
   b. Suggest new options for managing your patients that you might apply in the future?

4. I used the information in this issue for … (check all that apply)

5. Approximately how long did it take you to complete this activity, including this evaluation?

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- Using page 28 as a worksheet, answer all of the post-test questions based on the content of the articles.
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