JAOA
Supplement 2 Volume 112 Number 9 September 2012
http://www.osteopathic.org/JAOA
Supplement to JAOA—The Journal of the American Osteopathic Association

A New Era of Anticoagulation Therapy:

Optimizing Outcomes for Atrial Fibrillation

This supplement is supported by an independent educational grant from Bristol-Myers Squibb and Pfizer.

AN OFFICIAL PUBLICATION OF THE AMERICAN **OSTEOPATHIC** ASSOCIATION

JAOA
Supplement to JAOA—
The Journal of the American Osteopathic Association

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JAOA Supplement 2 Volume 112 Number 9

September 2012

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This supplement was produced in collaboration with Impact Education, LLC. It is supported by an independent educational grant from Bristol-Myers Squibb and Pfizer.

Editor's Message

Individualized Care for Improved Outcomes in Patients With Atrial Fibrillation

Stuart A. Winston, DO

This supplement to *JAOA—The Journal of the American Osteopathic Association* includes a timely review[1] and expert panel discussion[2] of the most important goal for the treatment of patients with atrial fibrillation (AF): that is, the prevention of stroke.

With an aging population and the age-related prevalence of AF highlighted by the authors and discussants,[1,2] all of us, whether we are primary care physicians or specialists, will be seeing more and more patients with AF. It may be that our patients have had singular AF episodes, multiple paroxysmal episodes, or multiple AF episodes that require intervention; or, our patients may have permanent AF. Regardless of the type of AF, and with few exceptions, all of these patients' risk for thromboembolic complications is higher than that of similar patients without AF.

The care for these patients can be complex. Appropriate choices regarding either a rate-control strategy or a rhythm-control strategy can be challenging. These decisions are clearly individually specific and often require initial and then ongoing collaboration between primary care physicians and cardiologists. Antiarrhythmic drug regimens, cardioversion strategies, and percutaneous or surgical ablation options are available, but these treatments are designed to reduce AF-related symptoms. In most cases, these treatments do not mitigate the risk of stroke.

Stroke risk for patients with AF depends on the presence of concomitant clinical factors. The authors describe the 2 most commonly used scoring systems for thromboembolic risk for patients with nonvalvular AF. The $CHADS_2$ score incorporates the risk associated with a history of congestive heart failure, hypertension, age, diabetes mellitus, and prior stroke.[3] The CHA_2DS_2-VASc score adds the factors of gender, the presence of vascular disease, and a more stringent addressing of age-related risk.[4]

These scoring systems are summarized well in the following 2 articles,[1,2] which highlight the required individualization of risk assessment balanced by the risk of bleeding associated with anticoagulation therapy.

In assessing risk, however, it needs to be emphasized that the scoring systems are based on statistical analyses of clinical studies of populations. As

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Financial Disclosures: None reported.

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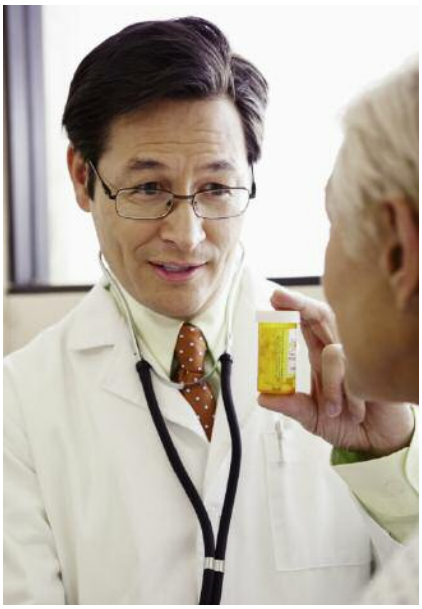
This supplement is supported by an independent educational grant from Bristol-Myers Squibb and Pfizer.

a reminder, a $CHADS_2$ score of 0 still renders an individual with AF a 1.9% per year risk of stroke.[3] On the basis of the balance between benefit and risk of treatment, guidelines permit consideration of either no antithrombotic therapy or treatment with aspirin for patients with nonvalvular AF and a $CHADS_2$ score of 0.[5] We may be reassured by the fact that our elderly patient (let's say with a $CHADS_2$ score of 3), for whom we felt anticoagulation therapy rendered him or her at too high of a risk for bleeding, has not had a stroke while taking aspirin alone. But we can, at the next moment, be devastated by the younger patient with the $CHADS_2$ score of 0 who then has a stroke.

The devastation of such a patient's negative experience can indeed unduly affect us. However, the authors and discussants in this supplement to the *JAOA* emphasize the importance of the systematic prospective application of these risk assessments and the opportunity for improving the care we provide. The data they cite remind us that there is much to be done to increase the number of patients with AF who receive the appropriate stroke-preventing medications.

With the addition of newer anticoagulants, prescribing and monitoring anticoagulation therapy may become easier. Warfarin's advantages and challenges are well known. Our contributors describe some of the liabilities related to warfarin and patients' associated difficulty with adherence to its related rigorous monitoring. Dabigatran, a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor, are now approved by the US Food and Drug Administration, and others are on the way. I recommend that readers study their advantages and disadvantages carefully.

For each patient with AF that is before us, we have an obligation to first assess his or her individual risk of stroke. Then, we need to discuss with him or her the potential hazards and



benefits of the anticoagulation regimen indicated by the patient's risk of stroke. The choices we have now are most appropriately implemented according to each and every patient's particular set of clinical characteristics and his or her preferences. Our authors go a long way in helping us think about how we can hard wire these processes into our practices.

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JAOA—The Journal of the American Osteopathic Association (ISSN 0098-6151).

JAOA Supplement 2 Vol 112 No 9 September 2012

Printed in the USA.

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Stroke Prevention in Patients With Atrial Fibrillation: Disease Burden and Unmet Medical Needs

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The incidence of atrial fibrillation (AF), as well as the related morbidity and mortality, is increasing in step with the aging of the US population. Frequently, AF leads to untoward outcomes, including a 5-fold increased risk of stroke, hospitalization, impaired quality of life, and decreased work productivity. Therapeutic decision making for patients with AF at risk for stroke is a process that varies from one physician to the next. This lack of consistency in care is compounded by disrupted communication among caregivers coupled with barriers to health care resources. Improved application of evidence-based treatment guidelines for the diagnosis, staging, and tracking of AF-associated stroke is needed, especially because patients with AF are at high risk. In addition to affecting practice guidelines, the latest anticoagulants are poised to change the standard of care for preventing stroke in patients with AF. These novel agents, with their greater safety and ease of administration, have the potential to improve treatment outcomes.

J Am Osteopath Assoc. 2012;112(9 suppl 2):eS2-eS8

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Financial Disclosures: Drs Ciervo and Schaller report no financial interest or relationship relating to the topic of this activity. Dr Granger receives grant or research funding from Astellas Pharma US Inc; AstraZeneca; Boehringer Ingelheim Pharmaceuticals GmbH; Bristol-Myers Squibb Company; GlaxoSmithKline plc; Medtronic Inc; Merck & Co, Inc; sanofi-aventis; and The Medicines Company. He receives consultant fees from AstraZeneca, Boehringer Ingelheim Pharmaceuticals GmbH, GlaxoSmithKline plc, Hoffman-La Roche Inc, Novartis AG, Otsuka Pharmaceutical and Development & Commercialization Inc, sanofi-aventis, and The Medicines Company.

This article was developed with assistance from Impact Education, LLC. Steve Casebeer, MBA, acted as the project planner. He reports no financial interest or relationship relating to the topic of this activity.

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A trial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice, affecting an estimated 2.6 million to 3 million Americans.[1,2] More than 529,000 hospitalizations for AF occur each year,[3] with adults carrying a lifetime risk of 1 in 4.[2,4,5] The prevalence of AF increases with age, with 10% of individuals aged 80 years or older having AF. As a large segment of the US population reaches age 65 years or older, prevalence is expected to double by 2020[2,4-6] (*Figure 1*). Atrial fibrillation often triggers stroke, impairs quality of life, decreases work productivity, and increases hospitalization rates and mortality.

The cost of managing AF itself combined with the cost of managing AF-related hospitalizations and long-term complications such as stroke places a substantial financial burden on patients and the health care system. Total annual treatment costs are estimated to be $6.65 billion, including $3 billion for hospitalizations directly related to AF diagnoses, $1.95 billion for inpatient management of AF as a comorbid diagnosis, $1.53 billion for outpatient management of AF, and $235 million for prescription drugs[7] (*Figure 2*). The costs of care are comparable with those of other chronic conditions such as diabetes mellitus.[8] A comorbid diagnosis of stroke increased the cost to $12 billion in 2006, primarily because of the costs of rehabilitation, long-term care, and lost income.[7,9]

This supplement is supported by an independent educational grant from Bristol-Myers Squibb and Pfizer.

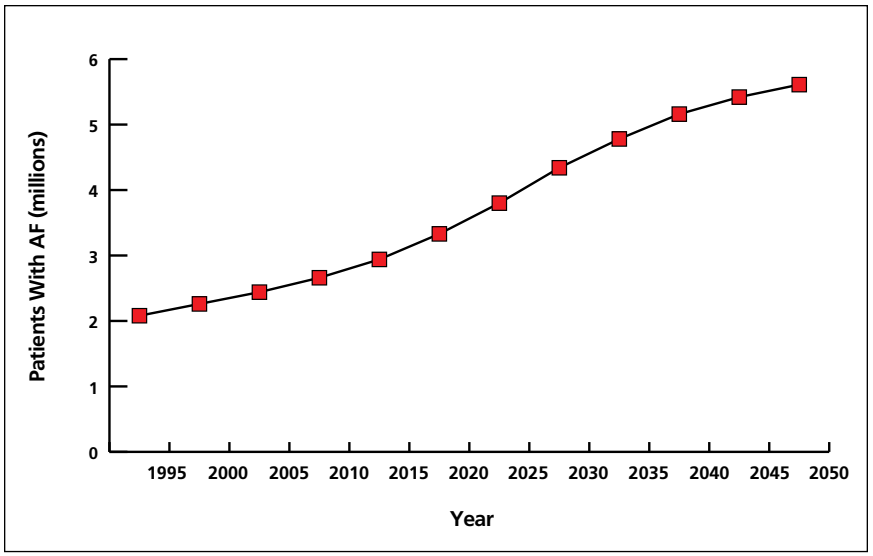

Figure 1. *Projected number of adults with atrial fibrillation (AF) in the United States between 1995 and 2050. An estimated 6 million Americans will be affected by AF by 2050. Adapted from Go et al.*[6]

AF and Stroke

Stroke risk in patients with AF increases when stagnant blood in the fibrillating atrium forms a thrombus that can embolize and enter cerebral circulation, blocking arterial blood flow and causing ischemic injury.[1] This surge in risk exists apart from other cardiovascular abnormalities and is why AF causes 15% to 20% of all cerebrovascular events.[1] Data from the Framingham Heart Study indicate that nonvalvular AF is associated with an annual stroke rate that is approximately 5.6 times greater than that in those without AF.[10] The presence of significant valvular disease in patients with AF increases the risk of stroke more dramatically, by 17-fold.[11] Further, the data indicate that stroke risk attributable to AF escalates with age, rising from 1.5% in patients aged 50 to 59 years to 23.5% for patients aged 80 to 89 years.[11,12] Consequently, it is the elderly—in whom AF is most prevalent—who are at greatest risk for stroke and its clinical, economic, and social burdens.

The consequences of AF-related stroke can be devastating. Outcomes in patients with AF-associated thromboembolic infarctions are often poor, leading to severe permanent neurologic deficit or death.[13] Results from population-based studies[12,14] indicate that the presence of AF in patients with ischemic stroke is associated with higher 30-day and 1-year fatality rates. The 1-year mortality rate for AF-related stroke is approximately 50%.[14] Strokes related to AF have a 12% risk of recurrence and are more severe, predisposing patients to longer hospital stays, higher degrees of disability, increased need for nursing home care, and higher direct and indirect costs.[15]

Atrial fibrillation was also associated with a statistically significant higher rate of recurrent stroke within the first year of follow-up and with a worse survival rate after an average follow-up of almost 4 years.[14] Among stroke survivors, the average hospital stay for patients with AF was significantly higher than that for patients without AF (50 days vs 40 days), with worse neurologic and functional outcomes.[16]

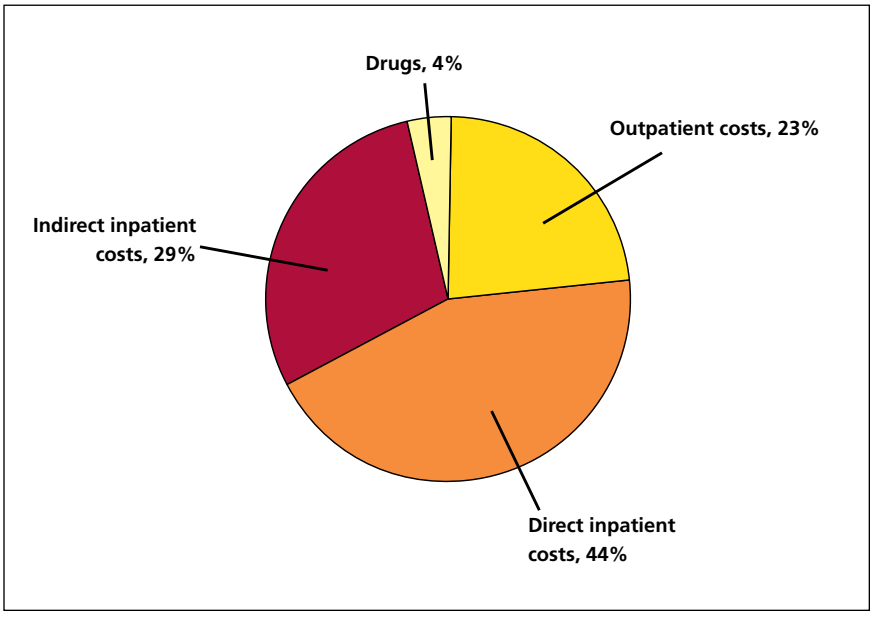

Figure 2. *Distribution of direct and indirect costs for treating atrial fibrillation (AF). Total annual treatment costs for AF are approximately $6.65 billion, including $3 billion for hospitalizations directly attributable to an AF diagnosis, $1.95 billion for inpatient management of AF as a comorbid diagnosis, $1.53 billion for outpatient treatment of AF, and $235 million for prescription drugs. Adapted from Coyne et al.*[7]

Stroke Prophylaxis in Patients With AF

Anticoagulation therapy has been shown to reduce the risk of stroke in patients with AF by about two-thirds.[17-19] An evidence-based guideline[17] developed by the American College of Cardiology, American Heart Association, and European Society of Cardiology recommends that treatment selection be made on the basis of stroke

risk stratification and bleeding risk assessment.

Stratification of stroke risk uses scoring systems—including $CHADS_2$ (congestive heart failure, hypertension, age ⩾75 years, diabetes mellitus, and stroke or transient ischemic attack [2 points]) or CHA_2DS_2-VASc (addition of vascular disease, age 65 to 74 years, sex category)—and is an important first step in guiding selection of anticoagulation therapy (*Table 1* and *Table 2*). These scores estimate risk by allocating points to patients on the basis of their past and current medical conditions. For example, $CHADS_2$ records factors such as history of prior stroke or transient ischemic attack, patient age, and presence of hypertension and diabetes mellitus. Risk is then categorized as low, moderate, or high.[20] The CHA_2DS_2-VASc score complements the $CHADS_2$ score by adding other "stroke risk modifier" factors: lower age bracket (65-74 years), female sex, and vascular disease. In addition, the CHA_2DS_2-VASc assigns an extra point if a patient is aged 75 years or older.[21]

Table 1.
$CHADS_2$ Scoring System[a]

Risk Factor		Points
C	Congestive heart failure	1
H	Hypertension (blood pressure >140/90 mm Hg or on medication)	1
A	Age ⩾75 years	1
D	Diabetes mellitus	1
S_2	Prior stroke or transient ischemic attack	2

[a] Risk Categories by total points: 0, low risk; 1 or 2, moderate risk; ⩾3, high risk.

Table 2.
CHA_2DS_2-VASc Scoring System[a]

Risk Factor		Points
C	Congestive heart failure	1
H	Hypertension (blood pressure >140/90 mm Hg or on medication)	1
A_2	Age ⩾75 years[b]	1
D	Diabetes mellitus	1
S_2	Prior stroke, transient ischemic attack, or thromboembolism	2
V	Vascular disease[c]	1
A	Age 65-74 years[b]	1
Sc	Sex category[d]	1

[a] Risk categories by total points: 0, low risk; 1, moderate risk; ⩾2, high risk.

[b] One point is added if the patient is aged between 65 and 75 years, and a second point is added if patient is aged 75 years or older.

[c] Vascular disease defined as previous myocardial infarction, peripheral artery disease, or aortic plaque.

[d] One point is added if patient is a woman.

In November 2010, a scoring system to assess the risk of developing bleeding complications while receiving anticoagulation therapy was validated.[22] This system, called HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [age >65 years], and drugs or alcohol), assigns 1 point to each component (*Table 3*). Higher scores indicate a greater risk for a bleeding event while receiving anticoagulant therapy. An important issue to consider with HAS-BLED is the overlap of risk factors for both stroke and bleeding, wherein excessive focus on bleeding avoidance will result in failing to reduce stroke for patients at higher risk.

Historically, aspirin or vitamin K antagonists (eg, warfarin) have been the primary therapeutic options for the prevention of thromboembolism.[17] Aspirin, although modestly effective in reducing the risk of stroke for patients with AF, is inferior to warfarin and is reserved for patients at low risk for stroke.[17] Warfarin is highly effective, reducing the stroke risk for patients with AF by about two-thirds.[18,23] Yet, despite the well-established benefits of warfarin treatment, anticoagulant therapy is underused and is inconsistently prescribed for patients with AF, even if those patients are at highest risk for stroke.[24-28] In a systematic review,[28] 25 of the 29 studies reported undertreatment (defined as treatment in less than 70% of high-risk patients) of AF patients with a history of stroke or TIA who were deemed eligible for oral anticoagulation therapy according to published guidelines. Even patients with a $CHADS_2$ score of 2 or higher were suboptimally treated.

Table 3.
HAS-BLED Scoring System[a]

Risk Factor		Points
H	Hypertension	1
A	Abnormal liver or renal function[b]	1 or 2
S	Stroke	1
B	Bleeding tendency	1
L	Labile international normalized ratio[c]	1
E	Elderly[d]	1
D	Drugs or alcohol[b,e]	1 or 2

[a] Risk categories by total points: 0, low risk; ⩾2, high risk.

[b] One point awarded for each.

[c] Defined as a therapeutic time in range of less than 60%.

[d] Defined as age 65 years or older.

[e] For example, antiplatelet agents or nonsteroidal anti-inflammatory drugs.

Source: Adapted from Pisters et al.[22]

A meta-analysis[29] of 8 studies assessed warfarin control among patients with AF and found that patients spent an average of only 55% of their time within the therapeutic INR range. However, when the data were stratified by treatment setting, the authors found that patients with AF receiving care in a community-based physician practice spent 11% less time within target INR range (ie, a lower limit INR between 1.8 and 2.0 and an upper limit INR between 3.0 and 3.5) compared with patients treated in a specialized anticoagulation clinic. Thus, fewer than half of patients with AF receiving warfarin are achieving and maintaining their target blood levels.

Unmet Needs in Stroke Prophylaxis

Left unmanaged or undermanaged, AF results in substantial morbidity and mortality. However, even traditional warfarin regimens create prescribing challenges for physicians who care for patients with AF (*Figure 3*). The complex pharmacokinetics and pharmacodynamics of warfarin interact with many medications and foods.[30] Furthermore, warfarin is difficult to use because of a narrow therapeutic window and the need for ongoing laboratory monitoring to avoid the risk of major bleeding events and minimize the risk of inadequate anticoagulation.

- Requires frequent monitoring and regular clinic visits
- Narrow therapeutic window
- Slow onset/offset of action; requires 3 to 6 days to achieve therapeutic levels
- Long half-life
- Multiple drug-drug and drug-food interactions
- Genetic polymorphisms exist that confer increased sensitivity or resistance
- Highly variable pharmacokinetics and dynamics; inter- and intra-individual variability in dosing and metabolism common

Figure 3. *Limitations of warfarin. Reprinted with permission from Libertas Academica Ltd.*[30]

Management challenges associated with anticoagulation therapy are exacerbated by difficulties in accurately identifying the patients who are at the highest risk for stroke or bleeding.[31] In fact, many practicing physicians identify concerns about excessive bleeding as the primary barrier to more widespread use of anticoagulation therapy.[31,32]

These issues, in addition to risks associated with patient nonadherence, have spurred efforts to improve the safety, efficacy, and convenience of anticoagulation therapy by targeting specific steps in the coagulation cascade, with a goal of reducing the number of potential adverse effects. Emerging anticoagulants may overcome the limitations of warfarin, potentially improving overall patient outcomes while more closely fitting the profile of the "ideal anticoagulant" (*Figure 4*). There remains an unmet clinical need for treatments that do not require intensive monitoring and frequent dose adjustments—2 of the shortcomings of traditional anticoagulation therapy. However, many osteopathic primary care physicians may be unable to fully evaluate the available clinical trial data on emerging thromboprophylactic treatments, particularly data on hazards and benefits of anticoagulants.[32]

The approach to stroke prevention for patients with AF is changing now that effective alternatives to warfarin are available. Two new classes of oral anticoagulants have recently been shown to be at least equivalent to warfarin in preventing stroke or systemic embolism.[33-35] Factor Xa inhibitors and direct thrombin inhibitors (DTIs), whether approved or under investigation, offer a rapid onset of action and predictable pharmacokinetics and pharmacodynamics, though they are not without potential limitations (*Figure 5*).

Factor Xa agents act directly on factor X in the coagulation cascade and, unlike low–molecular weight heparins, do not require antithrombin as a mediator. The highly selective mechanism of action of factor Xa agents limits the number of effects outside of the clotting cascade that theoretically may result in fewer adverse events overall than observed with vitamin K antagonists.[36] As of this writing, 1 factor Xa agent, rivaroxaban, has been approved by the US Food and Drug Administration (FDA) and 2, apixaban and edoxaban, are in development. As indicated in *Table 4*, rivaroxaban is an oral, reversible, direct factor Xa inhibitor that has a rapid onset of action and high oral bioavailability.[37] It is rapidly absorbed, with a half-life of 5 to 9 hours in patients aged 20 to 45 years and 11 to 13 hours in patients aged 65 years or older.[38] The pharmacokinetics of rivaroxaban are dose-proportional and generally unaffected by sex or body weight.[38] Although rivaroxaban can be affected by drugs that interact with CYP3A4, a low potential for clinically significant drug interactions has been reported.[38]

- At least equivalent efficacy to warfarin
- Better safety profile than warfarin, including less intracranial hemorrhage
- Predictable response
- Wide therapeutic window
- Low inter- and intrapatient variability
- Simple oral dosing, ideally once daily
- Low potential for drug-drug and drug-food interactions
- No need for regular monitoring
- Rapid onset and relatively short half-life to result in short offset
- Low incidence and severity of adverse events

Figure 4. *Features of the "ideal anticoagulant." Reprinted with permission from Libertas Academica Ltd.*[30]

- No clinically proven antidote
- Lack of validated tests to monitor anticoagulant effect
- Unknown long-term safety profile
- Lack of features of regular monitoring to enhance adherence
- High cost

Figure 5. *Potential limitations of the new oral anticoagulants. Reprinted with permission from Libertas Academica Ltd.*[30]

Apixaban is an oral, selective, reversible, direct factor Xa inhibitor also with a high oral bioavailability and an onset of action of within 3 hours.[39] Apixaban has a half-life of about 12 hours and is cleared via multiple pathways (about 25% by renal elimination).[40] Data indicate that apixaban does not inhibit or induce cytochrome P450 enzymes, and its absorption is not impacted by food.[41] Edoxaban is a potent, selective factor Xa inhibitor that, like the other factor Xa inhibitors, has good oral bioavailability.[42] It is rapidly absorbed, with a half-life ranging from 9 to 11 hours. Neither food-related effects nor dose-dependent increases in adverse events have been observed with edoxaban.

Dabigatran etexilate, a drug that directly targets the thrombin enzyme, was the first FDA-approved alternative to warfarin. It is absorbed as the dabigatran etexilate ester that is con-

Table 4.
Comparison of Pharmacokinetics Profiles of Warfarin and of the New Oral Anticoagulants

Profile	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Vitamin K-dependent factors	Thrombin	Factor Xa	Factor Xa	Factor Xa
Administration	Oral	Oral	Oral	Oral	Oral
Dose	Variable	150 mg twice daily	20 mg once daily	5 mg twice daily	30-60 mg once daily
Half-life, h	40	12-17	5-9 (age 20-45 y); 11-13 (age ⩾65 y)	12	9-11
Time to peak plasma level	3-5 d	1 h	2.5-4 h	3 h	1-2 h
Renal clearance, %	0	80	35	25	40
Interactions	CYP2C9; 1A2; 3A4	Inhibitors of P-glycoprotein transporter[a]	Inhibitors of CYP3A4 and P-glycoprotein transporter[b]	Inhibitors of CYP3A4 and P-glycoprotein transporter[b]	Inhibitors of CYP3A4 and prostaglandin transporter[b]
Monitoring required	Yes	No	No	No	No
Antidote	Vitamin K	None	None	None	None

a Includes amiodarone (cautions with interaction) and verapamil.

b Includes antifungals and protease inhibitors.

Abbreviation: CYP, cytochrome P450.

verted in the liver to its active compound, dabigatran.[43] As a competitive, direct, and reversible inhibitor of thrombin, dabigatran inhibits fibrin production.[43] It also prevents thrombin-mediated activation of factors V, VIII, XI, and XIII and thrombin-induced platelet aggregation.[44] The peak onset of action of dabigatran occurs within 1 hour, and the half-life with multiple doses is approximately 12 to 17 hours.[43] Dabigatran is predominantly (80%) cleared by the kidneys.[43] The P-glycoprotein transporter pathway is involved in the pharmacodynamics of dabigatran and other factor Xa inhibitors; thus, plasma levels of dabigatran will increase modestly when used in combination with drugs such as amiodarone and verapamil. Neither the prodrug nor its metabolite exerts an effect on the cytochrome P450 system; thus, dabigatran is associated with fewer drug-drug and drug-food interactions than is warfarin. Absorption of dabigatran may be delayed by food, and there is an age effect on pharmacokinetic parameters but no reported gender effect.[43]

Although factor Xa and DTI agents appear to circumvent many of the disadvantages of warfarin (*Table 4*), the most important role these drugs play are in improving clinical outcomes, as revealed in the large randomized trials comparing them to warfarin. In the RE-LY,[33] ROCKET-AF,[34] and ARISTOTLE[35] trials, the novel agents were each shown to be at least as effective as warfarin in preventing stroke, and their use resulted in substantial (30% to 70%) reduction in intracranial hemorrhage[33-35,45] (*Table 5*).

Role of Osteopathic Physicians in the Management of Stroke Prophylaxis

Osteopathic physicians, who often have large patient panels, are in an excellent position to improve outcomes for patients with AF who are at risk for stroke. By ensuring that all eligible patients are treated with oral anticoagulants and by improving the coordination of care and adherence, osteopathic physicians can begin to reduce the disability and mortality caused by AF-associated strokes. In addition, osteopathic physicians can be instrumental in the effort to manage patients' expectations and minimize aversion to potentially burdensome anticoagulation therapy regimens.

Most patients with multiple comorbidities receive care from several physicians within the same year.[46] Fragmentation of care and its relationship to rapidly rising health care costs are well documented.[46] Coordination of the entire patient care team—from specialists to nurses to pharmacists—is important for optimizing anticoagulation therapy.[32,47] An integrated approach to health care can improve patient adherence to recommended treatment; reduce unnecessary hospitalizations, office visits, tests, and procedures; minimize use of expensive technology or treatments when less expensive options are equally effective; and enhance patient safety.[47]

Like other health care providers, osteopathic physicians must evolve with the health care system. A patient with AF who is at risk for stroke benefits greatly from a coordinated, patient-centered approach to anticoagulation therapy. By adopting a model in which continuity of care supersedes episodic office visits, osteopathic physicians can ensure optimal outcomes and reinforce the risk-reducing benefits of regular anticoagulation therapy.

Conclusion

Anticoagulation therapy plays a crucial role in the prevention of stroke in patients with AF. Until 2011, the only oral anticoagulant approved in the United States for treating patients with

Table 5.
Results of Large Randomized Controlled Trials Comparing New Oral Anticoagulants With Warfarin

Profile	Trial		
	Re-LY[33]	ROCKET-AF[34]	ARISTOTLE[35]
Drug	Dabigatran	Rivaroxaban	Apixaban
Dosage	150 mg twice daily	20 mg once daily	5 mg twice daily
Stroke or systemic embolism	Superior	ITT cohort: noninferior; On Rx cohort: superior	Superior
Major bleeding event	Similar	Similar	Lower
Mortality	Similar (*P*=.051)	Similar	Superior (*P*=.047)
Ischemic or uncertain stroke	Lower	Similar	Similar
Mean time in therapeutic range, %	62	55	62
Stopped Drug, %	21	23	23
Withdrew Consent, %	2.3	8.7	1.1

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ITT, intent-to-treat; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; 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.

AF at risk for stroke was warfarin. Although warfarin is effective for preventing ischemic stroke, reducing the incidence by as much as 65%, it has a number of disadvantages that have led to its underuse. Recent advances in anticoagulation medication have provided clinicians with new evidence on which to base treatment guidelines and improvements in management strategies, risk stratification schemes, and anticoagulation therapy. The emergence of novel anticoagulation therapies means that warfarin is no longer the only choice for effective stroke prophylaxis. Physicians must recognize and comprehend the strengths and weaknesses of new therapeutic options before employing them in clinical settings.

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A New Era of Anticoagulation Treatment: Optimizing Outcomes for Atrial Fibrillation

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Atrial fibrillation is a common condition that is associated with a high risk of stroke. In the present article, which is based on a roundtable discussion held on February 8, 2012 , the faculty discuss various aspects of caring for patients with atrial fibrillation. These topics include the burden of the disease, stroke risk assessment, use of stroke prophylaxis, and improvement of outcomes.

J Am Osteopath Assoc. 2012;112(9 suppl 2):eS9-eS21

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Financial Disclosures: Drs Ciervo, Dr Schaller, and Dr Engelke, report no financial interest or relationship relating to the topic of this activity. Dr Granger reports that he receives grant or research funding from Astellas Pharma US, AstraZeneca, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic Foundation, Merck & Company, sanofi-aventis, and The Medicines Company; he receives consultant fees from AstraZeneca, Boehringer Ingelheim Pharmaceuticals Inc, GlaxoSmithKline, Hoffman-La Roche, Novartis Pharmaceuticals Company, Otsuka Pharmaceutical and Development & Commercialization Inc, sanofi-aventis, and The Medicines Company.

This article was developed with assistance from Impact Education, LLC. Steve Casebeer, MBA, acted as the project planner. He reports no financial interest or relationship relating to the topic of this activity.

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Moderator: *My name is Keith Engelke, PhD, host of today's activity, and I would like to welcome you to the roundtable discussion entitled A New Era of Anticoagulation Treatment: Optimizing Outcomes for Atrial Fibrillation. I am pleased to be a part of such a distinguished group of scientists and clinicians. Thanks to each of you for your willingness to participate in this discussion.*

I would like to start our discussion with a case study. Here is a brief overview of the patient, Robert:

- *68-year-old man; long-time patient in your office*
- *no current complaints; appears healthy and states he is physically active*
- *reports he sought treatment at an urgent care center after falling while on vacation in another city (resulting in a large hematoma on his thigh)*
- *medical history: positive for atrial fibrillation (AF) (mild palpitations lasting approximately 3 hours and occurring 5 or 6 times per year), positive for long-standing hypertension (for which he takes lisinopril, 20 mg every day) and diabetes mellitus (for which he takes metformin, 500 mg by mouth twice daily)*
- *presents for follow-up of anticoagulation therapy for stroke prophylaxis*
- *anticoagulation regimen was adjusted multiple times in the previous 12 months because of supra- and subtherapeutic international normalized ratios (INRs)*
- *current stroke prophylaxis regimen: warfarin 5 mg 4 times per week and 2.5 mg 3 times per week*
- *current INR: 6.7*

Burden of Atrial Fibrillation and Stroke

Moderator: *What appears to be Robert's primary medical challenge?*

Dr Schaller: I think Robert demonstrates a really good example of one of the most difficult issues with paroxysmal AF, and that is management of the medication. We do not know the circumstances of his fall and hopefully it

This supplement is supported by an independent educational grant from Bristol-Myers Squibb and Pfizer.

was just a mechanical fall and not something associated with syncope. But apart from that, this is a relatively young person who has not apparently been able to manage warfarin therapy with a reasonable and sustainable INR.

My greatest concern with this patient is to identify what happened—why is his INR 6.7? Obviously there is a whole gamut of possibilities inclusive of compliance issues and interactions between prescribed and over-the-counter (OTC) drugs, particularly if he has not informed his managing physician which OTC medications he is taking. However, in any case a person who is 68 years old and is capable of getting around and living life and being active should be able to maintain a reasonably controlled INR with proper compliance with the guidelines.

Beyond that we have the other standard risks of him experiencing paroxysmal AF. One of the biggest concerns I have about paroxysmal AF is that if we depend solely on symptomatic expression to make a diagnosis, we are missing an awful lot of disease. We do not really know how often our patients experience symptomatic paroxysms. In this case, Robert reported he had symptomatic paroxysms 5 to 6 times per year, but he may have many more asymptomatic events that he is not aware of—maybe as often as weekly. These asymptomatic events are an important contributor to the AF burden and can even increase the risk of further thromboembolism, especially if the INR is not adequately maintained.

Dr Ciervo: I agree with Dr Schaller about the need to understand why the INR is all over the place. As a primary care physician, in addition to effectively managing his hypertension and diabetes mellitus, my concern—and in all honesty, my concern long before this visit—is why has his INR been so inconsistent over the past 12 months? Are there medication interactions? Did he make changes in his diet that affected his INR? I need to make sure to have a conversation with him about these and other things that impact his INR.

But as Robert's primary care physician, my immediate concern—particularly now that he has had a fall—is what is it that I am not doing? During the past 12 months, his INRs have been all over the place, putting him at increased risk of stroke. Also, I am concerned about his hematoma: Is it going to get larger? How is it going to progress? Because of these issues, I would seriously consider a referral for a cardiology consultation to figure out a better course of action.

Dr Granger: I think all these are good comments. I will just highlight a couple of facts about the importance of effective anticoagulation therapy and about keeping the INR in a target range between 2 and 3. A quick calculation suggests that the patient in this case has a $CHADS_2$ (congestive heart failure, hypertension, age ⩾75 years, diabetes mellitus, and stroke or transient ischemic attack [TIA]) score of 2. This score places him at high risk and gives him about a 4% estimated risk of stroke per year. Effective treatment with an oral anticoagulant will reduce this risk by about two-thirds.

We also know that patients who spend less time in the target INR range are at higher risk of both stroke and bleeding. For every 10% reduction of time spent in the target range during the course of a year, there is a 1% increased risk of stroke. So keeping patients in the target range is obviously important.

Moderator: *What stroke risk factors are present in Robert's profile, and how does his risk for stroke compare with that of individuals without a history of AF?*

Dr Granger: As I mentioned a moment ago, the classic approach to estimating stroke risk in patients with AF is to use the $CHADS_2$ score. The $CHADS_2$ score takes into account the presence—or absence—of 5 factors: congestive heart failure, hypertension, age greater than or equal to 75 years, diabetes mellitus, and history of stroke or TIA. All the variables except a history of stroke or TIA are assigned a value of 1; history of stroke or TIA is assigned a value of 2. To determine the $CHADS_2$ score, simply add up the points assigned to the variables. So the patient in our current case, who presents with hypertension and diabetes mellitus, has a $CHADS_2$ score of 2.

It should be noted that the $CHADS_2$ score is actually not particularly accurate—there are limitations to it—but nevertheless it has been shown to be both clinically useful and reasonable, and it forms the foundation of our efforts to identify stroke risk in patients with AF.

Dr Schaller: Dr Granger, I absolutely agree. The only thing I would add is the CHA_2DS_2-VASc score (which adds a point each for female sex and vascular disease and includes a second age category), particularly because the European Society of Cardiology is using this scoring system for patients with AF and we are starting to see it mentioned more frequently in journals and at meetings. So, I think it is important to be aware of both of those scoring systems.

Dr Granger: I agree. The CHA_2DS_2-VASc has been a hot topic of conversation in cardiology recently. Frankly, those of us who spend a lot of our lives considering these issues can sometimes get carried away with complex scoring systems and fail to appreciate whether they are relevant to nonacademic physicians and other health care providers.

I know I cannot remember much more than 5 things for any disease state, and I would not be surprised if people's eyes glaze over when they hear us talk about yet another stroke risk scoring system for our patients with AF. Perhaps the introduction of new scoring systems will be easier once we have the ability to better integrate these elements into electronic decision support tools.

Dr Ciervo: Anecdotally, I think there is a decent level of familiarity with the $CHADS_2$ score among primary care physicians. That is not to say that every physician is determining the $CHADS_2$ score for every patient with AF who may be at risk for stroke.

Even though it sounds like we

should consider using it, I am not sure there is much familiarity with the CHA_2DS_2-VASc scoring system at the primary care level. However, I agree with you about the value of integrating these types of scoring systems into electronic medical records (EMRs). An increasing number of practices are using EMR systems that prompt physicians to collect data during the patient examination, and those data can then be used to calculate risk scores in real time. These metrics can guide a discussion with the patient and also help make treatment decisions.

Dr Schaller: Dr Ciervo, I agree. Just like yourself, I have the TIMI (Thrombosis in Myocardial Infarction) scores and Framingham scores and $CHADS_2$ scores—I have all these scores I am supposed to be using on every patient that comes in the door—it gets crazy. And I know primary care physicians are not going to be able to do all that unless we have a system that prompts us to collect these things.

Dr Granger, I have a question for you. One of the reasons I bring up the CHA_2DS_2-VASc is because I have always been uncomfortable with the age component of the $CHADS_2$ score. I am not sure if you have the same impression, but I have never been comfortable saying that a person older than 65 years but younger than 75 years has no additional risk for embolus. I think we have plenty of data to show this statement is probably not true, which is why I like the portion of the CHA_2DS_2-VASc that says, if nothing else, we should be mindful of the person younger than 75 years who also has other risk factors. Would you agree with that?

Dr Granger: I think that is an excellent point. There are a couple of other points I think are important as well. First is that with the introduction of novel oral anticoagulants, we are in a new era—and I think the guidelines are reflecting this—an era in which we probably should consider a lower threshold for initiating treatment with an oral anticoagulant to reduce the risk of stroke, particularly for our patients who deal with the liabilities of warfarin. Having CHA_2DS_2-VASc scores can help us get there.

Second, although scores are really important, we also need to be using clinical judgment, especially for the patient we just mentioned—the one with warfarin liabilities that we struggle to keep in the target INR range. It is very difficult to keep these patients adherent to their warfarin treatment plan, and it makes you a little bit less enthusiastic about the risks and benefits of the drug. We need to remember that a patient's struggle with warfarin is not reflected in a risk score, and we must use our clinical judgment when making treatment decisions for a patient like Robert.

Dr Schaller: Absolutely. We have a lot of trial data, but every patient is individual, and regardless of what our data tell us, we have to individualize it to each patient.

Moderator: *We have discussed $CHADS_2$ and CHA_2DS_2-VASc scoring, but we have not discussed a third tool—the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly [age >65 years], and Drugs/alcohol) score. Dr Ciervo, can you calculate the HAS-BLED score for Robert?*

Dr Ciervo: Sure. As the primary care physician, I went through the $CHADS_2$, which was something I do routinely. For his hypertension and his diabetes mellitus he got 1 point each. So his total score of 2 puts him at high risk. With the CHA_2DS_2-VASc, the patient received a point each for his hypertension and diabetes mellitus, and because he is aged between 65 and 74 years, he got a point for his age for a total of 3 points. For the HAS-BLED score, he gets 1 point each for hypertension, bleeding history, labile INRs, and age, as well as his medications that put him at risk for a total score of 6, again putting him at high risk for bleeding while receiving an anticoagulant.

Dr Granger: With a score of 6, the risk of bleeding becomes more relevant, although I have to say that even when I talk to cardiologists who are interested in this topic, there are very few who have ever calculated a HAS-BLED score. I think the HAS-BLED score in my opinion is helpful in that it identifies and reinforces some of the factors that common sense tells you are important.

Robert, with a history of labile INR and prior bleeding, is someone we are clearly concerned about for further bleeding. I may be a little bit provocative here in disagreeing with some of the guideline suggestions, but for the average patient many of us care for on a regular basis, the HAS-BLED score is not particularly helpful.

Moderator: *Let's move away from risk assessment and discuss the pathologic mechanisms underlying the increased risk for stroke in patients with AF. Why does AF place a patient at increased risk for stroke?*

Dr Granger: Atrial fibrillation is the rapid, irregular beating of the left atrium. Rapid, uncoordinated contractions slow the movement of blood through the atria, causing blood to stagnate, particularly in the left atrial appendage. Stagnant flow, or pooling of blood, increases the risk of clot formation. If a clot embolizes and travels to the brain, it can cause a stroke by blocking flow through cerebral arteries. The elderly appear to be at highest risk for stroke as a result of AF-related emboli.

For the majority of preventable strokes, the factors associated with AF include stiffness of the ventricle, heart failure, left atrial dilatation, genetic factors that play a role in increased thrombogenicity, and left atrial geometry that predisposes an individual to thrombus and embolization. The goal of oral anticoagulation therapy is to decrease the formation and embolization of thrombi from the left atrium. But it is a bit more complicated than it seems because many of these patients have vascular disease, cerebrovascular disease, or both, and there are other strokes that are occurring in these patients. These other strokes may also be a target for anticoagulation therapy.

Dr Schaller: I would just mention the additional problem of valvulopathies—another independent risk factor for thromboembolism. This is particularly true if the patient has an artificial valve prosthesis, but some extensive native valvulopathies have also been shown to be thrombogenic as well, especially rheumatic mitral stenosis. So, not just the AF itself but other associated factors have to be taken into consideration.

Moderator: *Let's turn our attention to the overall burden (clinical, social, economic, etc) of stroke. Obviously, this can be an entire dissertation, but let's briefly summarize the key points here.*

Dr Ciervo: As a primary care physician, I live this aspect of patient care. From a clinical standpoint, a patient who has had a stroke typically has an extended hospital stay. The best thing we can do is get this patient out of the hospital as quickly as possible.

Although clinical factors are most important, decision making is sometimes driven by economics. Unfortunately, sometimes it comes down to the fact that patients are not able to gain access to the services that they need because it is just not economically feasible, or it could be that we are not able to get them to services because they do not have an intact support structure.

When the person gets out of the hospital, there is a cost associated with rehabilitation, the extent of which depends on the severity of the stroke. Often a patient who has had a stroke needs prolonged care at a subacute care facility or requires outpatient physical, occupational, and speech therapy, all of which can get very expensive. In many cases, third-party payers are placing limits on the amount and types of rehabilitation services they will reimburse. After using up their benefit, many stroke patients are ultimately discharged to home. Unfortunately, the cost of rehabilitation is not limited to dollars and cents—there is a social cost involved, as well, that includes the whole process of caring for the patient and worrying about the cost of rehabilitation. Thus, stroke becomes a stressful event for everyone—the patient, the family, and the caregivers.

Moderator: *What is the general awareness of stroke risk with AF among primary care physicians and patients?*

Dr Ciervo: I think that there is substantial awareness of stroke with AF, but something that we in primary care often do is talk ourselves out of using anticoagulation therapy; we somehow exaggerate the risk of therapy and say, "Well, I'm worried about gastrointestinal bleeding," or, "I'm worried that if their gait becomes unstable, they're going to fall and fracture their hip and then have a major bleeding event."

Unfortunately, many of us talk ourselves into not prescribing a medication when clearly most of the evidence indicates that people like Robert really need to be given anticoagulation therapy. The awareness is there—I just don't feel that it is put into action.

Moderator: *From the perspective of a cardiologist, Dr Schaller and Dr Granger, anything to add?*

Dr Schaller: I agree—this is a critical issue. Our registry database suggests that about half of the people who should be given an oral anticoagulant are not receiving it. There has been a fair amount of research that attempts to tease out reasons why there is such a big gap; some of the reasons are explainable, but some of them, I think, are still somewhat of a mystery. Regardless, I think we all recognize—including from our own practice—that a substantial part of the hesitancy comes from patient and physician concern about the risks and challenges of using oral anticoagulation therapy.

The results of the AVERROES trial provide a little insight into why anticoagulation therapy is not used more widely. The investigators enrolled 5000 patients who were considered to be unsuitable for warfarin. One of the goals of the trial was to identify the reasons why patients were deemed unsuitable for warfarin therapy. One of the most common reasons anticoagulation therapy was not used was that neither the patient nor the physician thought that the patient was able to manage the monitoring and follow-up required with use of warfarin. Some of this hesitancy was related to concerns about risk. In other words, if the physician was not confident that the INR could be tracked on a regular basis, the decision was made that using warfarin was too risky.

Moderator: *It sounds like there is a disconnect between awareness of a problem and applying guidelines for recommended treatment.*

Dr Schaller: Just knowing about the problem does not always translate into adherence to the guidelines by the managing physicians. Certainly not all of that is a physician-directed problem—much of it is a patient-directed issue. This issue is certainly not unique to anticoagulation therapy—we have exactly the same problem in the management of hypertension and diabetes mellitus. All physicians know the risks of these 2 conditions, but we have had a great deal of difficulty getting blood pressure and hemoglobin A1C targets met, even in treated patients. Although we are getting better, adherence is still not where it should be.

But I would like to reinforce a point that Dr Granger made earlier. In our anticoagulation clinic , we have patients who are simply unable to understand or appreciate the dangers of not properly taking their medications, and they are not in an economic or social position where they can be placed elsewhere or have other health care providers administer their medications. This problem is a struggle we face virtually on a daily basis.

This situation ultimately becomes an ethical issue, which is very difficult to resolve. Do I take a patient who I know is likely to take 4 warfarin doses instead of 3 doses, thinking 1 of the doses is one of his or her other pills because he or she is confused, or unsure, or just does not remember, and place the patient at risk of bleeding to prevent the risk of stroke? How do you put a number on the risk of a patient falling, forgetting, or losing their medicine? We cannot really do that.

So there is an awful lot of subjectivity that comes into the risk vs benefit when treating patients whom you are truly concerned about as to whether they can manage a medication as dangerous as warfarin on their own. I do not have a solution to that; as I said earlier, we struggle with this every day.

Moderator: *Excellent points, which I am sure will resonate with many of your colleagues. We touched on the level of awareness and understanding of the risk of stroke among patients with AF and about physicians' concerns with the risk associated with use of warfarin. What other barriers limit the ability to reduce stroke risk in patients with AF?*

Dr Ciervo: To reiterate, I think physicians are generally aware of the risk of stroke in patients with AF. However, I would not necessarily say that all patients are aware. As a primary care physician, I think we really need to educate our patients about AF and stroke.

Regarding medications, when you talk to people in a primary care setting about the use of warfarin, you have to explain that this is a commitment. Our patients and their caregivers need to understand that this is something that must be followed on a regular basis. It also needs to be emphasized that all patients receiving anticoagulation therapy need a good support structure—both in our offices and remotely. Primary care physicians need to be able to reach out to patients to discuss INR results, dose adjustments, and related issues.

Some primary care physicians are comfortable with providing this support, whereas others would rather refer the patient to an anticoagulation clinic where he or she can receive anticoagulation-specific care and follow-up.

Dr Granger: I think that is right. We have pretty good evidence that follow-up at an anticoagulation clinic, or at least having some systematic and organized way to monitor patients and provide timely feedback, is important and necessary to improve the quality of anticoagulation care.

Moderator: *What about patient adherence with therapy? Dr Schaller, I believe it was you who made the point earlier that whether it is hypertension or diabetes mellitus, compliance with prescribed therapy continues to be a problem that dogs physicians and patients across the board.*

Dr Schaller: Right. I do not think this problem with anticoagulation therapy is any different than other situations. The biggest concern is that warfarin is a dangerous medicine. It comes with very high risks if it is not administered and monitored properly.

Dr Granger: I would like to also reiterate the issue of adherence. We have this enormous public health problem—every registry that I have looked at shows that about one-quarter of patients who start taking an oral anticoagulant for AF has stopped it by 1 year. It is similar to everything else—hypertension medications, cholesterol medications, whatever. But in patients with AF, it is particularly concerning because these patients are subject to a short-term substantial increased risk of stroke simply related to having stopped the therapy.

So I think this issue of adherence is an enormous one, and frankly, it is something that we are all concerned about with the new agents. Despite the challenges of using warfarin, there are at least 2 things about using this drug that helps us monitor adherence. The first is that with warfarin, we can measure adherence every month for a person who is coming back to the anticoagulation clinic.

The second is the opportunity for patients to interface with a variety of health care providers while in the clinic. So as we begin to use the new agents, we potentially lose this opportunity to monitor our patients on a regular basis. Consequently, physicians who prescribe the newer agents will need to be especially focused on monitoring and encouraging adherence.

Dr Schaller: I appreciate that, Dr Granger; that is an extremely important point you just made. The opportunity for physicians to monitor patients who are taking these potentially dangerous medicines is critical to preventing adverse outcomes. If we lose that interface because we do not need to see the patient for 3, 4, or 6 months in the primary care setting, it puts the patient at risk.

However, the other thing we have to remember is that these newer agents are very expensive, which can negatively affect adherence. Many of our patients have fixed or lower incomes, and many of them may choose not to fill their prescriptions. Or, if they fill it, they take their pills every other day to stretch them out because they are so expensive. And the worst part is they do not tell you they are doing this.

Dr Ciervo: That is something that we see in primary care—patients adjusting their use of medication because of cost. They also try to space out their visits, because even with Medicare, many of our patients have health insurance plans with co-pays. This all adds up and it becomes problematic.

Moderator: *Dr Granger, I believe you touched briefly on the fact that the guidelines and practice recommendations are evolving as additional therapies become available. Do you believe that the guidelines can be a barrier to effective treatment of these patients?*

Dr Granger: Yes, I think they can be. As we have talked about, although the guidelines are fairly clear, guidelines are only guidelines. A huge challenge is how to implement the concepts of the guidelines in the face of the complexities of our daily lives as physicians and patients.

Stroke Risk Assessment in Patients With AF

Moderator: *Let's discuss some of the tools that are available to assess the risk of stroke in patients with AF. I know we touched on these earlier, but let's elaborate a little bit more. How can a primary care physician quickly assess the risk of stroke in a patient with AF during an office visit? What tools are available to do this quickly in the office?*

Dr Ciervo: I think there is a general awareness of the association of stroke and hypertension and stroke and diabetes mellitus because physicians know that both conditions affect the vasculature. I would also say that the relationship between stroke and age and congestive heart failure is well understood by my colleagues. I do believe that even if primary care physicians are not calculating a $CHADS_2$ score, they are at least thinking about the components of the scoring system when they are assessing the stroke risk and determining if there is a need for anticoagulation therapy.

I would say that this practice is less common for the CHA_2DS_2-VASc score. As a primary care physician who interacts with a substantial number of other primary care physicians, unless you are using an EMR that flags the need for data on the components of the CHA_2DS_2-VASc scoring system as you do the examination, the stroke risk assessment may not come up.

Moderator: *Dr Ciervo, just to circle back, how widely are these specific tools actually used in practice?*

Dr Ciervo: We want to believe that they are used widely. Again I think it comes down to whether there is an awareness about the diseases associated with risk for stroke—diseases like AF, diabetes mellitus, heart failure, and previous stroke or TIA. So I think the $CHADS_2$ score is pretty widely used and accepted.

Moderator: *Thank you, Dr Ciervo. Let's move on to another aspect of risk assessment: the INR. What is a typical INR for a healthy patient not receiving anticoagulation therapy?*

Dr Granger: I will take that. The INR is a ratio of the patient's measure of anticoagulant effect vs control with no effect. Therefore, a person who is not receiving an oral anticoagulant and who has normal coagulation ability would have an INR of 1 or 1.0.

Moderator: *For a patient who is taking anticoagulation therapy, what might their INR be?*

Dr Granger: It depends on the target range. In our patients with AF without a prosthetic heart valve—just simply AF—the target INR is in the range of 2 to 3, recognizing that this range approximates what was shown to be effective when using vitamin K antagonists in randomized clinical trials. This range also fits with observational studies showing that once the INR drops below 2, the risk of stroke begins to increase, and once it goes above 3, the risk of bleeding increases.

Moderator: *You anticipated the next question—what is the relationship between INR and risk of stroke in a patient with AF? To what degree can anticoagulation therapy reduce the risk of stroke in these patients?*

Dr Granger: I mentioned that earlier. Hart and colleagues[1] published a nice summary of the primary and secondary prevention data, as well as the findings of several meta-analyses. Their review of the literature highlights the fact that vitamin K antagonists such as warfarin reduce the risk of stroke by about two-thirds.[1] So, warfarin is very effective at preventing stroke in patients with AF.

Moderator: *Dr Ciervo, what is the role of the primary care physician in the diagnosis and staging of stroke in these patients? When should a patient be referred to a specialist?*

Dr Ciervo: I think the primary care physician needs to be aware of those disease processes that put the patient at risk for stroke—heart failure, hypertension, diabetes mellitus—as well as being cognizant of the impact that age plays on stroke risk across the years. Incidentally, one of the advantages we have as primary care physicians is that we follow many of our patients for a long time.

When should the patient be referred? I think a lot of that depends on the physician's comfort level with his or her ability to be appropriately aggressive with treatment to prevent stroke. It is very important for all of us to know what we know, but perhaps more importantly, we should know what we do not know.

Moderator: *This may be obvious, but which specialty is typically the point of referral or is the referral made to?*

Dr Ciervo: I think the best referral is to a cardiologist, as this is the specialist responsible for staying most current on the data. They also have a wealth of clinical experience with patients with AF at risk for stroke. In fact, I frequently look to my cardiology colleagues for state-of-the-art approaches to caring for these patients.

Moderator: *Any comments from our cardiology colleagues on the panel?*

Dr Granger: It is a good question, and frankly, it would be interesting to have more evidence to guide us on how we use our evolving health care systems and environment to decide which of these patients really does need cardiology assessment.

It has been my experience—at least in my region of the country—that cardiologists get involved with most patients with new onset AF. This early involvement holds true even for those patients who are being treated with one of the newer anticoagulants; however, we anticipate that primary care will eventually develop an expertise and comfort level with these agents to where a cardiologist will not always get involved so early. Many cardiologists feel this way because the newer agents have many attributes that make them safer and easier to use than warfarin.

Dr Schaller: We staff a lot of warfarin clinics managed by nonphysician providers, so there is no magic in having a referral to a cardiologist just to monitor anticoagulation therapy.

In my experience, there are 2 different questions here for the cardiologist to be involved in. First, after the primary care physician has identified the patient at risk, a cardiologist may be needed to determine the answer to, "Should this person be given anticoagulation therapy?" Once that determination has been made, I think the

second question is, "Is this adequate for a primary care practice to follow, or does it need to be followed by a specialty clinic?"

I think the critical decision is not identifying the type of practitioner involved but understanding the type of service needed. A primary care physician who is comfortable with managing INRs with warfarin or managing these newer agents may have a nurse practitioner or a physician assistant in the office who routinely communicates with patients and who could very easily do as good a job as a cardiologist regarding communication with patients about coagulation issues.

In addition, there are data that indicate that if a cardiology practice does not have these services available to follow up with patients with heart failure,[2] chronic stable angina,[3] or even anticoagulation,[4] the outcomes in the cardiology practice are no different than those in a primary care practice.

So it is not so much the label of the physician as the quality of the service instituted. In addition, a shortage of skilled practitioners may have a real impact on patients in rural America. All of us on this panel work in metropolitan areas where there is lots of support. But what do you do when you are in a town with a population of 3000 and there is no cardiologist? These patients are not going to travel 100 miles just to have their INRs checked.

So I think it is the quality of follow-up and the structure of the supervision that is most critical to improving outcomes for these patients, more so than monitoring by a specific specialty. Would you agree, Dr Granger?

Dr Granger: I think those are key points. It is probably more important how the patient is cared for and the kind of infrastructure of the practice than who is doing it. Again, I think cardiology should be involved to some degree in the initial evaluation for the patients with new-onset AF. Also, a cardiology referral of a patient with AF may also be useful to help with longer-term strategies for the aspects of AF management separate from stroke prevention.

Dr Ciervo: I agree with you completely, Dr Schaller. The role of the specialist will most likely be determined by geography. One more point I would like to make: The team approach you described is incorporated into the patient-centered medical home concept—the physician, nurse practitioner, physician assistant—everybody working together to track a patient and his or her information to improve outcomes over the long term.

Management of Stroke Prophylaxis in Atrial Fibrillation

Moderator: *Excellent discussion, thank you. Now that we have established that our patient is at high risk, let's talk a little bit about the management of stroke prophylaxis in patients with AF. Dr Schaller, would you mind starting us off by telling us where we can find guidelines for stroke prevention in patients with AF?*

Dr Schaller: The most recent update of the treatment guidelines was just published by the American College of Cardiology (ACC) Foundation and the American Heart Association (AHA) in 2011.[5] The guidelines[5] are available and free to the public on the ACC Web site. They can also be accessed through the National Library of Medicine's PubMed database.

I would just like to make a comment regarding the timeliness of treatment guidelines. One of the reasons we get frustrated with guidelines is that by the time they get published they may already be out of date. To address this issue, the ACC and AHA periodically update specific issues within certain guidelines. This approach reduces turnaround time and helps keep the guidelines current with the published literature.

Moderator: *Thank you, Dr Schaller. Does anyone else have anything to add?*

Dr Granger: I think that is a good summary. I might add that there are 2 other organizations that have some relevance. I think sometimes we get "guideline-itis" because we have so many guidelines. But the 2 others to consider are the European Society of Cardiology,[6] which published their update in 2010, and the American College of Physicians, which published a comprehensive guideline on anticoagulation therapies in a supplement to *Chest* in February 2012.[7] What we hope, and I think it has been generally true, is that there is reasonable alignment among the guidelines because they are all based on the same evidence.

Moderator: *Dr Ciervo, what is the level of awareness of these guidelines in the primary care community?*

Dr Ciervo: Reflecting on some of the comments made by Drs Granger and Schaller about the number of eligible people who fail to receive anticoagulation therapy certainly makes you wonder about the level of awareness. I think most primary care physicians are aware of the ACC/AHA guidelines; however, I am not so confident in the level of awareness with guidelines from the other groups.

As Dr Granger said, we do get "guideline-itis" because it is not just in cardiology—it is in urology, in psychiatry, and in so many other areas that we are dealing with. That is why providing periodic updates is an excellent concept, particularly to primary care physicians. It is almost impossible to read through an entire set of guidelines every time new data become available.

Moderator: *Dr Ciervo, let me ask you this question as a follow-up: Is there a misalignment between institutional or payer guidelines for anticoagulation therapy and these national guidelines, and if so, how does this impact your ability to provide care?*

Dr Ciervo: I have not seen any issues with that as far as being able to use anticoagulation therapy—particularly warfarin, aspirin, or clopidogrel. However, with some of the newer therapies, I think we should anticipate that there will be payers who may not be willing to reimburse for some of the recommendations in the newer guidelines. As a matter of fact, I have already experienced this with 1 of the new anticoagulants.

Moderator: *Anybody else have anything to add regarding this potential misalignment, at least as it currently exists?*

Dr Schaller: The general support of warfarin therapy has been reasonable, although I really believe the monitoring of warfarin is underfunded. I am concerned about some of the newer agents because, for example, in our region we have a dominant single health care provider, and that provider is extremely reluctant to cover any of the newer agents for anticoagulation. So although we do not have much of a problem with warfarin, I do anticipate a problem with the newer agents solely on the basis of the fact that insurance plans may not support the use of these agents regardless of what we say.

Treatment of Patients With AF by Using Stroke Prophylaxis

Moderator: *Let's move on to some of these agents and talk about treatment approaches for these patients. What are the primary treatment goals for a patient with AF, like the one in our case?*

Dr Schaller: That is a complicated question. In the context of this discussion, we are concentrating more on anticoagulation therapy with a focus on stroke prophylaxis. I think the short answer is that all patients with AF are at an increased risk for thromboembolism, and most receive full-dose anticoagulation therapy on a permanent basis.

Dr Ciervo: In addition to stroke prophylaxis, as a primary care physician I would also be focused on tight control of their diabetes mellitus, hypertension, and other comorbid conditions, trying to maximize therapy as best as I could in those areas.

Dr Granger: I think that is a good approach. There have been good observational studies, including one by Hylek and colleagues[8] comparing the SPORTIF III and V trials, that suggest control of blood pressure as an important way to reduce risk of stroke in patients with AF.

Moderator: *We touched on this a little bit earlier regarding the use of anticoagulation therapy in these patients with AF, but can somebody remind us again what percentage of AF patients actually receive appropriate anticoagulation therapy?*

Dr Granger: Data from a number of registries[9,10] indicate that around 50% to 60% of eligible patients currently receive oral anticoagulation therapy.

Moderator: *Dr Ciervo, what is the role of the primary care physician in establishing and implementing the treatment plan in these patients?*

Dr Ciervo: I think primary care physicians can educate patients and their caregivers about the whole treatment process, including the necessary level of commitment, the risks of treatment—particularly those associated with warfarin—and the risk associated with choosing not to undergo treatment. By risk I mean the impact of an AF-related stroke on the patient's long-term morbidity and mortality.

Moderator: *What is the role of pharmacists, nurses, and other providers in this particular patient?*

Dr Schaller: Every person who interacts with the patient has the opportunity for what I call an educational vignette. So whether it is me, another physician, the pharmacist, the certified medical assistant in my office, or a nurse, everybody has the opportunity to reinforce the importance of adherence, particularly if the patient is being treated with warfarin.

Dr Granger: I agree completely with that statement. We could talk for hours about this topic, not just about oral anticoagulation for patients with AF, but for prevention of any type of condition.

And this gets back to our discussion of adherence. I think one of the things that we have to do, especially with these novel agents, is measure adherence. It is something we do not do—at least most of us do not do—in routine practice. We know it is important and yet we do not measure it, and if we do not measure something, we cannot improve it or intervene on it.

How do you measure adherence? Well there are a variety of ways. For example, follow fill and refill records provided by a pharmacy benefit manager or, if you work in a setting with the technology, check the electronic pharmacy records to see if the prescription was filled or refilled as prescribed. We can also ask the patient a variety of simple questions, some of which are well validated, such as "Do you forget to take your medicines? Do you have problems taking them? Do you understand what they're for?" In reality, these are things nurses and pharmacists are often much better at doing than are physicians.

Therapeutic Selection: Warfarin and Other Traditionally Used Therapies

Moderator: *Let's shift our attention to therapeutic selection and focus initially on warfarin and other long-standing therapies. Historically, what has been used for stroke prophylaxis in patients with AF, and what are their relative strengths and weaknesses?*

Dr Granger: I am happy to get us started with a brief overview. Compared with no treatment, we know that antiplatelet therapy results in about a 20% relative risk reduction in stroke.[1] These results are not particularly impressive and are accompanied by a risk of bleeding, but otherwise, antiplatelet agents are reasonably well tolerated.

Results of the ACTIVE A trial[11] indicated that when adding clopidogrel to aspirin, you get an additional 28% relative risk reduction in stroke, but this comes at the cost of a lot of bleeding. In fact, the excess bleeding with clopidogrel plus aspirin vs aspirin alone is very similar to what one sees with warfarin. So on the basis of these findings, we think that clopidogrel plus aspirin provides very little value to these patients. But if someone needs to be taking clopidogrel for another reason, there is some additional stroke risk reduction.

Compared with placebo, warfarin resulted in a 64% relative reduction in

stroke risk,[11] but it also has a substantial risk of bleeding, particularly intracranial hemorrhage. Warfarin is simply one of a number of vitamin K antagonists, but I think it is the only one relevant for this discussion.

Dr Schaller: That is a very good summary. I think there might be some confusion about whether aspirin therapy is an "alternative" to warfarin; this is not the case. So I just want to reiterate that aspirin is not a substitute for warfarin.

Dr Granger: Dr Schaller makes an excellent point—aspirin is not a substitute for or alternative to warfarin.

Dr Schaller: This might be a good time to discuss the combining of different anticoagulation agents. When aspirin and warfarin are used together, there appears to be a 50% higher risk of hemorrhage.[12] Concerns about using these agents together may be particularly relevant for our patients with active coronary artery disease. For example, all eligible patients after a myocardial infarction are prescribed aspirin. But it should be noted that when even a baby aspirin is added to warfarin, it most likely results in a meaningful increased risk of bleeding; therefore, one should be thoughtful about when the benefit outweighs the risk.

The risk of bleeding is even higher when clopidogrel, aspirin, and warfarin are used together; this combination may increase risk of major bleeding by as much as 4-fold.[12] Again, this strategy may be an appropriate approach for some patients—for example, if someone has a coronary stent placed and has a high $CHADS_2$ score with AF, then triple therapy is warranted. But it needs to be recognized that one should minimize the duration of triple therapy with these agents and recognize that there is a real cost in terms of bleeding risk.

Dr Ciervo: Another thing to consider is the use of OTC products by our patients. To some degree, we can control the use of drugs we prescribe, but many patients in this age category also have osteoarthritis, which they treat with OTC nonsteroidal anti-inflammatory drugs. So it is very important to make sure our patients understand the importance of avoiding nonsteroidal anti-inflammatory drugs if they are receiving any form of anticoagulation therapy for stroke prevention.

Therapeutic Selection: New Oral Anticoagulants

Moderator: *Let's now move on to a discussion of the new oral anticoagulants. What are the oral anticoagulants recently approved or in late-stage development for stroke in patients with AF? Dr Schaller, would you give us a quick overview of these agents?*

Dr Schaller: Sure. I am happy to see that some of these agents are finally approved. As we know, we have the direct thrombin inhibitor dabigatran approved for nonvalvular AF, and we also have rivaroxaban available.[13,14] Being a twice daily drug, dabigatran is a little less convenient than the single daily dosing of rivaroxaban, a factor Xa inhibitor. There are 2 other factor Xa inhibitors in development—apixaban and edoxaban—and as far as I know, they are still in their final approval stages. Is that correct, Dr Granger?

Dr Granger: That is right. There are 2 trials published on apixaban,[15,16] and results of ENGAGE-AF TIMI 48 with edoxaban[17] is expected to be reported at the European Society of Cardiology meeting later this year. Apixaban is currently going through the US Food and Drug Administration's approval process. I anticipate that it will be available soon, but we will have to wait and see. However, I am optimistic that eventually 4 novel agents will be approved.

Moderator: *Can someone provide a brief overview of how the mechanism of action of these agents differs from that of traditional therapy, specifically warfarin?*

Dr Granger: I am happy to address that. Each of the new oral anticoagulants is a small molecule and is a direct inhibitor of the coagulation system. Dabigatran is an oral direct thrombin inhibitor. It is actually a prodrug that is about 80% metabolized in the kidneys.[13] It has a relatively low bioavailability; consequently, it is formulated in a capsule that has an acid environment, which may explain why there is about a 5% incidence of gastrointestinal intolerance.[13]

Dabigatran was studied in 2 doses, 150 mg twice a day and 110 mg twice a day, but the 110 mg formulation is not available in the United States. There is also a 75 mg twice-a-day dose that is approved for patients who have renal insufficiency.[13]

Rivaroxaban, apixaban, and edoxaban are all oral-direct factor Xa inhibitors, so these have their effect more proximal in the coagulation cascade. All of the factor Xa inhibitors have about a 12-hour half-life, so it is interesting that apixaban[15,16] and dabigatran[13] are given twice a day and rivaroxaban is approved for once a day use.[14]

Dr Schaller: I think it is also important to add the time of onset of action. The problem with warfarin is that it is an indirect inactivator and you have to deplete your vitamin K–dependent factors before the medication demonstrates its effect. This can take anywhere between 48 and 72 hours. In contrast, the onset of action of these new drugs is quick; we do not have that delay.

Moderator: *How do these new agents compare with the current standard, in most cases warfarin, in terms of efficacy, safety, need for monitoring drug interactions, and adherence?*

Dr Granger: Having been pretty centrally involved in the development of these agents, I can start. I think it is a very exciting time for the clinical community because of the opportunities to improve care of patients with AF. The main reason for my optimism is because clinical trials with these agents have identified features that provide substantial advantages over warfarin.

The clinical trials I am referring to are the RE-LY,[18] ROCKET AF,[19] ARISTOTLE,[15] and AVERROES[16] trials. Each of these was a noninferiority trial by its initial design, and the hope was that

these agents would be as good as warfarin but with some practical advantages. In fact, each of these drugs is at least as good as warfarin for prevention of stroke or systemic embolism, which was the primary outcome, with dabigatran having a statistically significant 30% relative risk reduction,[18] rivaroxaban having a 12% nonsignificant risk reduction in the intent-to-treat arm,[19] and apixaban demonstrating a 21% significant relative risk reduction in the primary outcome.[15] But each of the drugs has a point estimate of a lower risk of stroke than the highly effective warfarin. So that is the first benefit—they are all effective in preventing stroke. Second, each of them had about a 50% reduction in intracranial hemorrhage when compared with warfarin. I think this reduction is one of the most exciting findings of these trials—these drugs are safer than warfarin with respect to the most serious type of bleeding. This finding has created all types of interesting hypotheses and has led to a search for an explanation for why this reduction occurred. Third, each of the new drugs does not need anticoagulation therapy monitoring and therefore has major practical advantages with respect to warfarin. And finally, there are no food interactions or issues with variability with dietary vitamin K affecting anticoagulation, and there is less of an issue with drug interactions, although there are some drug interactions.

Moderator: *Dr Granger, you mentioned earlier the value of monitoring for adherence purposes with no need for monitoring in these agents. Will this lack of monitoring have obvious effects on patient adherence in your view?*

Dr Granger: Yes, it can have a positive effect on adherence. But your question reminds me that it is also important for us to talk about the limitations of the new agents. Even though I enthusiastically believe these agents provide a major advantage in terms of improving care, there are also going to be challenges and limitations in their implementation.

These challenges include the fact that there is no specific antidote to the anticoagulation effect. There is also a lack of standardized measures regarding adherence that we touched on earlier. Each of these agents uses some renal metabolism, and so in the elderly population, especially those with renal insufficiency, we need to be careful. Also, some of these new drugs result in more gastrointestinal bleeding than warfarin does. And finally, there are financial barriers; these new drugs are expensive, and that is an issue, especially for our Medicare population.

Moderator: *Thank you, Dr Granger. Any additional thoughts from our other panelists regarding the safety, efficacy, and monitoring of these new agents?*

Dr Schaller: Dr Granger summarized the outcomes of the trials very effectively. What we have been looking for in an ideal agent is something that is effective, cost-effective, and easy to take and has a lower risk profile than does warfarin. At this point, it appears that these agents possess nearly all the features with the possible exception of cost-effectiveness. To see a significant reduction in intracerebral bleeding for the first time with an effective anticoagulant is a remarkable advancement, and I think that needs to be stressed.

Dr Ciervo: As Drs Granger and Schaller have summarized, the data on these new agents give us greater peace of mind. We can now treat our patients with medications that require much less follow-up and significantly decrease the risk of intracranial hemorrhaging—this is critical.

Moderator: *We have discussed how these agents compare with other interventions, but what about head-to-head comparison in terms of safety and efficacy? Are there any head-to-head trials, and if not, what has been the clinical experience in terms of their comparison with each other?*

Dr Granger: We get asked this a lot, and it is a legitimate question. Practitioners often say, "Okay, we have a couple of new agents and we will have more. How do we make decisions?"

It is challenging because we as clinical researchers want to be very careful making indirect comparisons because they tend to be unreliable. So I would reiterate that I think each of the new agents has important advantages over warfarin in that they cause less intracranial bleeding and each of them has a point estimate of about a 10% lower risk of death than warfarin—a nice integrated outcome to show the overall safety and efficacy of these drugs.

Beyond that, I would say a couple of things that I think are relevant, not comparing one agent to another, but just looking at some of the attributes of each agent. I think that dabigatran 150 mg twice a day is the dose that had the greatest effect on reducing ischemic stroke. The other trials did not show that. And it may be that 150 mg twice a day of dabigatran is a bit more potent of an antithrombotic regimen.

The investigators in the ROCKET trial[19] were very careful to examine the safety of rivaroxaban in patients with moderate renal impairment; that is, patients with a glomerular filtration rate of 50 down to 30 mL/min /1.73 m^2—using in that population a 15 mg daily dose. This population is really important because they tend to be at higher risk for AF-related stroke, and the clinical efficacy and safety of the drug at that dose were very impressive. In the ARISTOTLE[15] and AVERROES[16] trials, apixaban was studied at doses of 5 mg twice a day or 2.5 mg twice a day for patients who were at high risk on the basis of having 2 of 3 of the following characteristics: older age, low body weight, and elevated creatinine level. This dosing strategy was demonstrated to be very safe with a 31% relative risk reduction in major bleeding compared with warfarin. Apixaban was also effective and very well tolerated.

Moderator: *Any other thoughts from our other faculty on the comparison between the agents?*

Dr Schaller: I would like to add a comment to reinforce what Dr Granger just said about the 150 mg twice daily dose

of dabigatran possibly being a bit more potent as an antithrombotic regimen. Interestingly, the same dose was shown to have a lower incidence of hemorrhagic stroke as well. So I think it is important to note that if dabigatran is more potent, it is a safe potency, so to speak.

Moderator: *Dr Ciervo, from your perspective have any of these agents been incorporated into clinical practice?*

Dr Ciervo: Yes. I have seen dabigatran used in clinical practice, but at this point I have not seen much use of the other agents in primary care.

Moderator: *Drs Granger or Schaller, have any of these agents been incorporated into the guidelines? Any insights into when they might be included in future updates?*

Dr Schaller: The February 2011 American College of Cardiology Foundation, AHA, and Heart Rhythm Society guideline update on atrial fibrillation specifically addressed dabigatran in a general way, but the other newer agents have not yet been included in a version of the guidelines. I expect them to be included in the next update—they need to be included because they are substantially better than the other drugs. Dr Granger, do you think they will all be included in the next update?

Dr Granger: Yes, I think so. The European guidelines already comment that dabigatran is more effective than warfarin.

Rivaroxaban is not yet incorporated into any of the guidelines, and apixaban is not yet even approved. It is a fairly fast-moving field right now, which is exciting but challenging. It is a challenge because we need to be sharing information in a clear and concise yet clinically relevant way to the broad practice community that is involved with the care of patients with AF. However, there are many complexities to all the different scenarios and questions that come up about the use of oral anticoagulants in patients with AF. It is going to take us some time to sort out.

The common questions that we get include, What do you do when somebody has bleeding and they are taking a new agent? How do you tell whether they are having an important adverse effect? And how do you manage the bleeding? What do you do around cardioversion? What do you do when someone needs an urgent surgery or procedure?

These are all questions that we have some answers to. For example, the package insert for dabigatran has some guidance on how long before surgery you should stop the drug. And there is a publication on the issue of cardioversion.[20] So we do have some information, but these are the kind of practical questions that are so important to helping the community.

Cardiology is definitely challenged by a lack of data to guide decision making around these issues. I suspect the lack of guidance is even more challenging for primary care; we need to be getting this information out in a way that is understandable and usable to physicians.

Moderator: *Dr Ciervo, you mentioned that you have used one of the agents. What has been the patient response to the use of that agent?*

Dr Ciervo: My patients like the idea that they do not have to have the monitoring. It is safe and has been efficacious so far. I think the patient uptake will be good, but the key factor, and I believe it was Dr Schaller who mentioned it, is being able to provide safe, effective, and cost-effective care, and right now with the cost of these agents, that is going to be tough.

It is easy to get into the discussion about cost versus cost of care with these agents; certainly there are cost savings because there is less need for phlebotomy, fewer patient visits for monitoring, and saving on the cost of running laboratory tests. But patients still experience the big "wow" factor when they get to the pharmacy and see the price.

Dr Schaller: I do think that these agents are going to be very well received by patients, apart from their cost. We actually have a large number of patients who are requesting these newer agents. They are hearing about them, they are seeing advertisements, and they know that they are "easier to take" and that they "don't have to get those stupid blood tests." So I do think it is going to be well received.

Improving Outcomes in Patients With AF at Risk for Stroke

Moderator: *Let's now turn our attention to the challenge of improving outcomes in patients with AF at risk for stroke. Dr Ciervo, what is the role of the primary care physician in terms of improving overall outcomes for patients with AF at risk for stroke?*

Dr Ciervo: I think a big part of what we should be doing, and hopefully what we are doing effectively, in primary care is catching the patient as far upstream as possible—before a patient's condition worsens. In other words, we need to effectively recognize and manage the risk factors associated with stroke—things like controlling diabetes mellitus, managing hypertension in accordance with guidelines, and appropriately managing heart failure if it exists. The goal is to prevent some of the catastrophic events that can occur down the line.

That being said, however, we will continue to have patients show up with AF. So we must take the opportunity to discuss with them the risk of stroke and the risks and benefits associated with the available anticoagulation options.

I am a big fan of including patients in their own health care. For example, now that I use an EMR system, I can actually show patients how their variables influence their $CHADS_2$ score—rather than have the screen in front of me and the patients to my back, I actually put them next to me and show them how their blood pressure, diabetes mellitus, and other factors affect their score. In this way, I invite the patients to become part of the decision-making process.

I also work with patients to help them understand their role in the patient-centered medical home concept. In our system, we have a secure

patient portal that patients can use to e-mail questions about medications and other issues. This actively engages patients in their own health care more than they have been in the past.

Moderator: *Dr Granger, you raised the concept of EMRs earlier. What are your thoughts on incorporating the EMR and what role it might play in improving outcomes?*

Dr Granger: I see 2 major opportunities. One is to help identify patients by reminding physicians about the features of patients with AF who have an indication for oral anticoagulation therapy but who are not receiving it. The second is around adherence—using EMRs to measure how well patients are adhering to and persisting on their oral anticoagulation regimen.

Our hope is that the new anticoagulants will help us achieve better outcomes. But the biggest opportunity is still probably to make sure that everybody who has an indication for oral anticoagulation is taking an oral anticoagulant, understanding that even warfarin itself, with all its downsides, is still a very effective agent.

With regard to cost effectiveness, there have been at least 4 published cost-effectiveness analyses with dabigatran, and each study has a general conclusion that dabigatran is a cost-effective treatment when one looks at even the high cost of the medication, the events prevented, and the effect on patient outcomes.[21-24]

And perhaps the most helpful review is one from the well-respected National Institute for Health and Clinical Excellence—the NICE group from the United Kingdom. Their review was quite favorable toward dabigatran and presumably will be similarly for the other agents. So I think that is important, that at least on a societal level these drugs are cost effective.

There is another question that comes up a lot—what about the patient who has historically done well while taking warfarin? Is there any advantage to switching that patient to a new agent? This is actually a reasonable debate because we do not have a clear definitive answer to the question. My personal opinion here is that the weight of evidence suggests that a patient also gets a benefit from taking one of the new agents, including less risk of intracranial hemorrhage. However, I think new patients and patients having difficulties with warfarin will provide the greatest opportunity to improve outcomes with the novel agents.

Summary

Moderator: *In closing, I invite each of you to summarize your final thoughts and highlight what you think are the primary take-away messages from today's discussion about stroke prevention in patients with AF. Dr Schaller, would you like to start?*

Dr Schaller: I believe patients are responsible for managing their own health. However, patients are going to do what patients are going to do. I think the easier we make it for them to treat themselves properly, the more likely they are to do it. And therefore, patients at very high risk who are being treated with a dangerous drug and following a complicated and bothersome regimen will be more adherent and much more likely to have better outcomes with these newer, easier-to-use agents.

Dr Granger: It is an exciting time for both patients and physicians. We have these new agents with distinct and important advantages over warfarin. We hope that as a result, more attention will be paid to the clinical needs and some of the unmet needs for this patient population. These agents will allow us to treat a larger proportion of the eligible population with drugs that are well tolerated and that also possess some practical advantages over warfarin. However, we should also continue to focus on optimizing the application and use of warfarin.

Dr Ciervo: Both Drs Schaller and Granger summarized the key points very well. From a primary care standpoint, I would reiterate this is a really exciting time for us to be able to embrace new agents to manage the stroke risk associated with AF.

As more and more patients are treated with the newer, easier-to-use agents, perhaps some of the time we used to spend managing warfarin can be used to better educate our patients about their disease and how they can contribute to the management of their own health.

Ideally, we would implement an interdisciplinary care approach to achieve these goals. This means engaging cardiologists and other health care providers who interact with these patients to help provide treatment proven to improve outcomes.

Moderator: *That brings us to the end of our discussion. Thanks to each of you for an excellent discussion. We appreciate your willingness to share your expertise and provide excellent insights on this important topic.*

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For each of the questions below, place a checkmark in the box provided next to your answer so that you can easily verify your answers against the correct answers, which will be published in the October 2012 issue of the *JAOA*.

1. Which of the following adverse outcomes is associated with atrial fibrillation (AF):

☐ (a) stroke
☐ (b) impaired quality of life
☐ (c) decreased work productivity
☐ (d) increased hospitalization rates
☐ (e) all of the above

2. Atrial fibrillation accounts for what percentage of all cerebrovascular events?

☐ (a) 5% to 10%
☐ (b) 15% to 20%
☐ (c) 25% to 30%
☐ (d) 35% to 40%
☐ (e) none of the above

3. According to the $CHADS_2$ scoring system, a system that allocates points to patients based on their past and current medical conditions as criteria for future risk of stroke, patients with AF and a $CHADS_2$ score of ____ are at high risk of stroke.

☐ (a) ≥1
☐ (b) ≥2
☐ (c) ≥3
☐ (d) ≥4
☐ (e) The $CHADS_2$ scoring system does not evaluate stroke risk.

4. Which of the following statements is true regarding the quality of warfarin control in patients with AF:

☐ (a) Patients receive better anticoagulant care in the community setting.
☐ (b) Patients receive better anticoagulant care in the anticoagulation-clinic setting.
☐ (c) More than 50% of patients on warfarin achieve and maintain target blood levels.
☐ (d) Warfarin reduces the risk of stroke in patients with AF by 33%.
☐ (e) all of the above

5. Which of the following statements is true regarding anticoagulation therapy with rivaroxaban:

☐ (a) Rivaroxaban is an oral, reversible, direct factor Xa inhibitor.
☐ (b) Rivaroxaban has a rapid onset of action and high oral bioavailability.
☐ (c) Rivaroxaban has a half-life of 5 to 9 hours in patients aged 20 to 45 years and 11 to 13 hours in patients aged 75 years or older.
☐ (d) Rivaroxaban pharmacokinetics are dose proportional and generally unaffected by gender or body weight.
☐ (e) all of the above

6. Which of the following statements is *not* true regarding the anticoagulants apixaban and edoxaban:

☐ (a) Apixaban and edoxaban are selective, reversible, direct factor Xa inhibitors.
☐ (b) Apixaban has an onset of action of 8 hours.
☐ (c) Apixaban has a half-life of 12 hours.
☐ (d) Edoxaban has a half-life of 9 to 11 hours.
☐ (e) There are no dose-dependent increases in adverse events with edoxaban.

7. As the first alternative to warfarin approved by the US Food and Drug Administration, dabigatran...

☐ (a) inhibits thrombin-mediated activation of factors V, VIII, XI, and XIII.
☐ (b) inhibits thrombin-induced platelet aggregation.
☐ (c) is 80% renally cleared.
☐ (d) both a and c
☐ (e) a, b, and c

8. Which of the following statements is *not* true regarding dabigatran:

☐ (a) Dabigatran etexilate undergoes hepatic conversion to the active compound, dabigatran.
☐ (b) Dabigatran is a competitive, direct, and reversible inhibitor of thrombin.
☐ (c) The peak onset of action of dabigatran occurs within 1 hour.
☐ (d) Clinical steady state is achieved within 5 days of initiation of therapy with dabigatran.
☐ (e) The half-life of dabigatran is 12 to 17 hours.

9. Which of the following clinical trials/drugs demonstrated that a new oral anticoagulant was either superior or non-inferior to warfarin for the reduction of stroke or systemic embolism:

☐ (a) RE-LY/dabigatran
☐ (b) ROCKET-AF/rivaroxaban
☐ (c) ARISTOTLE/apixaban
☐ (d) AVERROES/dabigatran
☐ (e) a, b, and c

10. Which of the following is not considered a potential limitation of new oral anticoagulants:

☐ (a) unknown pharmacokinetic profiles
☐ (b) no clinically proven antidote
☐ (c) lack of validated tests to monitor anticoagulant effect
☐ (d) unknown long-term safety profile
☐ (e) unknown true cost-effectiveness

11. An integrated approach to health care by osteopathic physicians has the potential to improve anticoagulation therapy by which of the following processes:

☐ (a) improving patient adherence to recommended treatment
☐ (b) avoiding unnecessary hospitalizations, office visits, tests, and procedures
☐ (c) minimizing the use of expensive technology or treatments when less expensive options are equally effective
☐ (d) enhancing patient safety
☐ (e) all of the above