
THE AMERICAN JOURNAL OF MANAGED CARE®

SUPPLEMENT

Reassessing the Stroke Prevention Paradigm: Evolving Strategies for Managed Care of Patients With Atrial Fibrillation

Highlights

- An Overview of Stroke and the Impact of Atrial Fibrillation
- Finding a Balance in Long-Term Anticoagulation Therapy
- A Pharmacoeconomic Perspective on Stroke Prevention in Atrial Fibrillation
- New Options for Stroke Prevention in Atrial Fibrillation
- CME/CPE Posttest



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University of Michigan Medical School
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Reassessing the Stroke Prevention Paradigm: Evolving Strategies for Managed Care of Patients With Atrial Fibrillation

Method of Participation

This is a self-study activity; completion involves reading the monograph, which includes charts/graphs, and completing the online posttest and evaluation form. There is no fee to participate in this activity.

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Estimated time to complete activity: 1 hour

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Intended Audience

This activity is accredited for directors of managed care, primary care physicians, and other healthcare professionals who treat patients with atrial fibrillation (AF).

Statement of Educational Need

Although there has been considerable recent progress in the prevention of stroke, the new 2020 Impact Goals of the American Heart Association encourage continued improvement, calling for a 20% reduction in deaths due to stroke by the year 2020. While clinicians generally recognize the importance of AF in raising a patient's risk of stroke, a tendency to overestimate the risks of anticoagulant therapy and underestimate its efficacy can lead to missed opportunities for preventing stroke in AF.

Educational Objectives

After completing this activity, the participant should be better able to:

- Utilize a risk-versus-benefit evaluation within clinical practice that will help clinicians to better identify and treat patients with AF who are at high risk of stroke, and implement a safe, effective treatment strategy for all qualified patients.
- Develop treatment strategies for patients, taking into consideration managed care implications for physicians and hospital systems.
- Evaluate emerging agents for stroke prevention in AF, and determine how newly approved agents may be incorporated into clinical practice, including effective methods of converting patients from older therapies to newer agents.
- Employ long-term strategies for stroke prevention that take into account patient preferences and pharmacoeconomic realities.

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Reassessing the Stroke Prevention Paradigm: Evolving Strategies for Managed Care of Patients With Atrial Fibrillation

This supplement to *The American Journal of Managed Care* expands on the presentations by 3 nationally recognized experts in cardiology and managed care from the educational podcast *Reassessing the Stroke Prevention Paradigm: Evolving Strategies for Managed Care of Patients With Atrial Fibrillation* (available at www.ajmc.com). The 4 papers in this supplement will provide clinicians with expert insight on the stratification of stroke risk, and the risks, benefits, and pharmacoeconomic considerations associated with anticoagulation therapy for stroke prevention.

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Introduction

A. Mark Fendrick, MD

Atrial fibrillation (AF) is presently estimated to occur in at least 5 million Americans, and this number is projected to increase to about 12.1 million by 2050, assuming no further increase in age-adjusted incidence.¹ AF carries a 5-fold risk of stroke, which is the third-leading cause of death in the United States. About 1 in 5 strokes are attributable to AF.^{2,3} Ischemic strokes associated with AF are often fatal, and survivors of these strokes are typically more disabled and more likely to have recurrent stroke, consequently increasing the cost of care 1.5-fold.² Treatment aims to reduce AF symptoms, but also to prevent the severe complications of AF, such as stroke. Prevention of AF-related stroke relies on antithrombotic therapy, control of ventricular rate, and adequate therapy for concomitant cardiac diseases. Several risk factors for stroke are responsive to prophylactic measures, including AF, hypertension, high blood cholesterol, and smoking; the overall risk of stroke can be significantly lowered by controlling each of these factors.³ It is currently the goal of the American Heart Association to reach a 20% reduction in deaths from cardiovascular diseases and stroke by 2020.⁴ The risk of AF-associated stroke can be lowered through long-term anticoagulation therapy. Warfarin therapy, maintained at an international normalized ratio (INR) of 2.0 to 3.0, has long been the best available option, reducing the risk of stroke by approximately 68%.⁵

All patients with AF who use warfarin therapy face the long-term challenge of avoiding stroke and other embolic events without acquiring an unacceptably high bleeding risk. Anticoagulation therapy is recommended for patients with AF according to their level of risk,⁵ but surveys indicate that anticoagulation recommendations are not routinely followed in more than half of these patients.⁶ It is likely that concern about bleeding is an important contributor to this underuse. Further, another survey revealed a tendency on the part of clinicians to overestimate the risks of warfarin by more than 10-fold.⁷ Widespread underuse of anticoagulation in AF can be improved by providing clinicians with a more accurate picture of the comparison between a patient's risk of stroke without anticoagulation therapy versus the risk of bleeding events with anticoagulation therapy. Bleeding risk can be substantially reduced through consistent INR monitoring, strictly controlled dosing, and consistency on the part of the patient regarding medication use and dietary restrictions.

There is also growing interest in the development of new oral antithrombotic agents that have comparable efficacy to warfarin, but a lower bleeding risk. The stage is now set to extend the use of anticoagulation in patients with AF and take a step toward the 20% goal for reducing deaths due to stroke.⁴ This supplement discusses advances in the stratification of stroke risk, bleeding risk, and recent changes in recommendations for anticoagulation therapy. It also provides an update on the development of new agents that move us closer to the goal of inhibiting thrombus formation while avoiding adverse bleeding events.

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An Overview of Stroke and the Impact of Atrial Fibrillation

Christopher P. Cannon, MD

Stroke is a very significant but preventable health problem that is estimated to account for 45.1 deaths in every 100,000 people in the United States.¹ According to the most recent statistical update from the American Heart Association (AHA), approximately 795,000 people in the United States experience a new or recurrent stroke each year, and 87% of these are ischemic in nature.² Additionally, about 610,000 of these strokes are first events, while the remaining 185,000 are recurrent attacks. The overall burden of stroke is quite large in terms of life-years lost and diminished quality of life, as well as the direct and indirect medical costs associated with providing care for stroke victims.² Despite considerable evidence that supports preventative measures to improve outcomes among patients at risk of stroke, many of these patients do not receive the recommended interventions. Stroke prevention can be significantly improved through greater, more effectively targeted implementation of proven risk reduction measures.

Preventative Measures Have a Positive Effect

A recent analysis from the Centers for Disease Control and Prevention using data from 2007 shows that, despite a continuing, long-term downward trend among the top 3 causes of death in the United States, stroke continues to rank third, trailing behind only heart disease and cancer.³ This downward trend is evident in an encouraging report on the recent progress toward meeting the 2010 Impact Goals for reduction of stroke, coronary heart disease (CHD), and cardiovascular risk.⁴ As set forth in 2000, the stated 2010 Impact Goals were to achieve: (1) a 25% reduction in deaths due to stroke and CHD, and (2) a 25% reduction in risk factors, including the prevalence of smoking, uncontrolled hypertension, high blood cholesterol, and physical inactivity. The 2010 Impact Goals also included the ambitious target of zero growth in obesity and diabetes by 2010. By 2008, the estimated reductions included a 29.2% decrease in deaths due to stroke and a 30.7% decrease in deaths due to CHD. Similarly, reductions in risk factors included a 29.4% decrease in uncontrolled hypertension, a 24.5% decrease in high blood cholesterol, and a 15.8% decrease in smoking. Unfortunately, the reported prevalence of obesity and diabetes in 2008 increased rather than meeting the stated goal of zero growth.

Abstract

As the third-leading cause of death in the United States, stroke has a very significant impact on patients and the total healthcare burden. Many factors that increase the risk of stroke are modifiable, and changes in these factors can provide effective avenues toward significantly reducing the incidence of stroke. Atrial fibrillation (AF) is one such risk factor; it is strongly associated with an elevation of stroke risk that can be greatly diminished using antithrombotic therapy. However, currently recommended prevention measures, particularly oral vitamin K antagonists, are underused due to difficulties associated with their use. There is an evident need for oral anticoagulant drugs with a wide therapeutic range, which do not require international normalized ratio monitoring and have a safe bleeding profile. By targeting patients with AF for stroke prevention treatment through greater use of long-term anticoagulation therapy, the burden of stroke can be substantially reduced.

(Am J Manag Care. 2010;16:S273-S277)

For author information and disclosures, see end of text.

Stroke Prevention Can Be Improved

On the heels of this recent progress, the AHA established a new set of Impact Goals for 2020, which have been broadened to address morbidity and mortality due to all manifestations of stroke and cardiovascular disease (CVD).⁴ Current efforts are aimed at improving the cardiovascular health of all Americans by 20%, while achieving a 20% reduction in deaths from CVD and stroke by 2020. The AHA notes that reaching this ambitious goal will depend on improved acute care processes and therapies, as well as greater efforts toward advocating, promoting, and implementing population-level programs to reduce nonfatal and fatal CVD and stroke. With respect to the latter statement, there are some populations that should receive more emphasis in such programs; characteristics like sex, age, and race should be considered, as well as cardiovascular risk factors like hypertension, hypercholesterolemia, and atrial fibrillation (AF).²

Attention to Gender Differences May Be an Important Avenue Toward Improving Stroke Prevention

Data derived from the Framingham Heart Study cohort demonstrate some important characteristics regarding the impact of age and sex on stroke incidence (Figure 1).⁵ At the first occurrence of a stroke, women were significantly older than men (average age, 75.1 years vs 71.1 years, respectively; $P < .001$). Furthermore, stroke incidence was higher in women than men older than 85 years of age, but lower in women of all other age groups. Overall, women had a higher lifetime risk of stroke than men. One very interesting observation from the Framingham cohort was that women who reached menopause before the age of 42 years had twice the stroke risk of all other women across different age groups.⁶ No differences in stroke subtype, stroke severity, or case fatality rates were observed between sexes.⁵

Differences between sexes were also observed following a stroke. Three to 6 months after a stroke, women reported significantly greater disability ($P < .01$) and were 3.5 times more likely to be institutionalized ($P < .01$).⁵ An examination of specific activities of daily living revealed disparities in impairment among women and men: being able to dress themselves (59% vs 37%, respectively), grooming (57% vs 34%), and moving from the bed to a chair (59% vs 35%).

In addition to disabilities, sex-related differences have been observed in stroke mortality. In 2006, the overall rate of death due to stroke was 43.6 per 100,000 people; however, examination of specific populations showed that death rates due to stroke were 41.7 for white males, 67.1 for black

males, 41.1 for white females, and 57.0 for black females.² In contrast, death rates due to stroke among other races were 35.9 for Hispanic or Latino males and 32.3 for females, 39.8 for Asian or Pacific Islander males and 34.9 for females, and 25.8 for American Indian/Alaska native males and 30.9 for females. These data suggest that racial background and sex should be considered in the development of more targeted stroke prevention strategies.

Racial Disparities in the Risk of Stroke and Mortality Should Have a Role in Improved Prevention Strategies

The risk of a first stroke in black patients is almost twice that of white patients²; however, compared with other stroke risk factors (eg, hypertension or type 2 diabetes), AF is not likely to have an important role in this disparity of risk, given that it has a lower prevalence in black patients compared with white patients.⁷ AF is consistently found more often in white patients than in black patients across all age groups in those older than 50 years of age. The Anticoagulation and Risk factors In Atrial fibrillation (ATRIA) study found rates of 1.8% white versus 1.3% black ($P = .001$) among patients aged 60 to 69 years; 5.2% white versus 4.4% black ($P = .003$) for patients aged 70 to 79 years; and 9.9% white versus 7.7% black ($P = .001$) for patients 80 years and older. Overall, black patients appeared to be less likely than white patients to have AF, but those black patients who do have AF are likely to have a higher risk of stroke, given the higher rate of hypertension among blacks.⁸ The risk of a first stroke is also elevated in Hispanics relative to whites.² In a comparison of racial backgrounds using pooled data from multiple studies by the National Heart, Lung, and Blood Institute, the age-adjusted incidence of a first ischemic stroke per 100,000 people was 88 in white patients, 191 in black patients, and 149 in Hispanic patients. This racial disparity in stroke incidence has not changed over time, and community socioeconomic status appears to explain 39% of the excess stroke risk in black patients. Racial differences have also been documented in stroke recurrence. In people aged 40 to 69 years, 5-year stroke recurrence was reported in 15% of white men and 17% of white women compared with 10% of black men and 27% of black women. Further examination of older patients (aged ≥ 70 years) found stroke recurrence in 23% of white men and 27% of white women compared with 16% of black men and 32% of black women. Therefore, age, sex, and race should alert clinicians to particular patients who have a greater need for evaluation of risk of first stroke or recurrent stroke, and may require prophylactic measures.

AF Is a Powerful but Modifiable Risk Factor for Stroke

As demonstrated in **Figure 2**, data from the Framingham Heart Study cohort point to AF as a significant factor in determining the risk of stroke.⁹ AF increases the risk of stroke, independent of other cardiovascular abnormalities that are often associated with elevated risk of stroke.

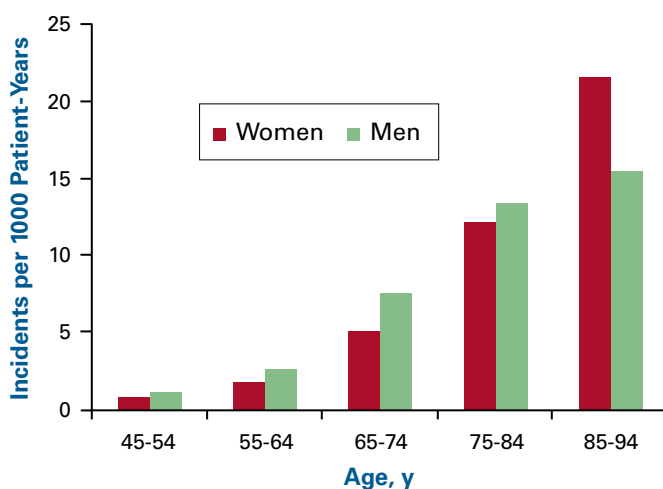
Across all age groups, AF independently increases risk of stroke by approximately 5-fold. AF is responsible for 15% to 20% of all strokes, and it is projected that AF will affect up to 12 million Americans by 2050.¹⁰ The risk of stroke in AF increases with age. In people older than 80 years of age, AF is the direct cause of 1 in every 4 strokes.¹¹ Recurrent strokes are common among AF patients and recurrent strokes are often more severe than the first occurrence.¹² Greater stroke severity predicts longer hospital stays, a higher degree of disability, and admission to nursing homes. The cost of care for severe strokes can run twice as high as that associated with mild strokes. Therefore, targeted prevention of stroke due to AF could significantly lower the total economic burden of healthcare in the United States.

The mortality rate from AF, either as the primary or underlying cause of death, has increased over the past 20 years.^{10,13} In addition to advancing age, risk factors for AF include high blood pressure, heart failure, diabetes, hyperthyroidism, and heart disease.¹⁰ In a community-based study, AF was diagnosed in 18% of patients who were undergoing treatment for acute stroke.¹⁴ In this population, AF increased sharply with age: from 2% in patients less than 50 years old, to 15% in patients who were in their 70s, to 28% in those in their 80s, and up to 40% in patients at least 90 years of age. Compared with those without AF, patients with AF had a higher mortality rate (odds ratio, 1.7; 95% confidence interval [CI], 1.2-2.5). Among stroke survivors, the average hospital stay for patients with AF was 50 days, compared with 40 days for patients without AF ($P < .001$). Patients with AF in this study population also had worse neurological and functional outcomes.

How Does AF Affect the Risk of Stroke?

AF is commonly encountered in daily practice. It is characterized by rapid, irregular impulses, and no regular contraction of the atria. The left atrial appendage is particularly affected in many patients with AF. However, the mechanism underlying thrombogenesis in AF is multifactorial and is not only related to abnormalities in flow stasis in the poorly contracting left atrium.¹⁵ There is also evidence for abnormal

■ Figure 1. Stroke Incidence by Gender and Age (in 10-Year Intervals) Over 56 Years of Follow-Up⁵



Adapted from Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. *Stroke*. 2009;40:1032-1037.

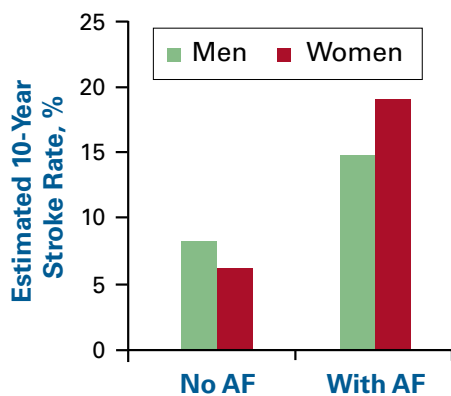
changes in vessel walls, such as endothelial damage and dysfunction, as well as abnormalities in blood constituents leading to coagulation cascade activation, inflammation, and growth factor changes. Some patients with AF experience palpitations, sensing the irregularity of the heart rhythm, but they may also experience shortness of breath, dizziness, or fatigue. Other patients may experience no symptoms.

More recently, the REduction of Atherothrombosis for Continued Health (REACH) Registry has followed stroke incidence in a cohort of patients who either had or did not have AF, but who also had established atherothrombosis or ≥ 3 atherothrombotic risk factors.¹⁶ Among the patients with AF, 6.7% experienced cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke within a year. The annual incidence of nonfatal stroke was higher in AF than in non-AF patients, with rates of 2.4% and 1.6%, respectively ($P < .0001$). After adjustment for age, sex, smoking, diabetes, hypertension, and hypercholesterolemia, the presence of AF at baseline was associated with higher rates of adverse cardiovascular outcomes (combined cardiovascular death/MI/stroke) at a 1-year follow-up. Mortality rates were substantially higher in patients with AF. All-cause mortality was 4.3% in AF and 2.3% in non-AF subjects, while cardiovascular mortality was 3.2% in AF and 1.4% in non-AF subjects ($P < .0001$).

Equivalent Influences of Paroxysmal and Permanent AF on Stroke Risk

A comparison of patients having either paroxysmal

Figure 2. Estimated 10-Year Stroke Risk Increases Substantially With Atrial Fibrillation⁹



Risk was estimated for a 55-year-old adult who smokes, has diabetes, and has a blood pressure measurement between 138 and 148 mm Hg. Adapted from Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. *Stroke*. 1991;22:312-318.

(n = 855) or permanent (n = 1126) AF recently tracked the incidence of stroke over 3.6 years and found a similar frequency of ischemic stroke associated with each group of patients with AF, specifically 26 events/1000 patient-years for paroxysmal AF versus 29 events/1000 patient-years for permanent AF.¹⁷ The multivariable-adjusted hazard ratio for risk of ischemic stroke in paroxysmal versus permanent AF was 1.07 (95% CI, 0.71-1.61). These findings are similar to those of a previous meta-analysis that examined 5 randomized studies of stroke prevention in patients with AF.¹⁸ Of the 3706 patients in that analysis, 462 had paroxysmal AF at the time of randomization, and the analysis showed no discernible effect on the stroke rate by the type of AF, either constant or paroxysmal, or the length of time the patient was in AF, supporting the findings of previous studies. Some drawbacks associated with this analysis include the fact that the number of patients with paroxysmal AF who subsequently reverted to constant AF was not known, and the definition of paroxysmal AF was changed in the Stroke Prevention in Atrial Fibrillation (SPAF) study from documented normal sinus rhythm within 12 months to documented normal sinus rhythm within 2 months. Despite the uncertainty in the underlying evidence, it seems reasonable to treat patients with paroxysmal AF in a manner similar to those with persistent AF, basing use of anticoagulants on the presence of risk factors for stroke. However, this approach is not being taken as

demonstrated in the recent study by Friberg et al, which observed that patients with paroxysmal AF did not receive protective anticoagulant treatment as often as patients with permanent AF.¹⁷ This observation represents another important area for improving implementation of stroke prevention measures.

Since AF is associated with a higher risk of stroke, it seems a reasonable prediction that restoring normal sinus rhythm should diminish the risk of stroke; however, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial compared rate- versus rhythm-control strategies in patients with persistent or paroxysmal AF and found no difference in mortality or stroke rate.¹⁹ Long-term oral anticoagulation therefore seems appropriate for most patients with AF who have risk factors for thromboembolism, regardless of treatment strategy and whether AF is documented at any given time.²⁰

Conclusion

AF is a modifiable risk factor for stroke. Appropriate prophylactic measures can substantially reduce the incidence or recurrence of stroke. The AHA recommends aggressive treatment of AF, which includes reducing stroke risk with anticoagulant and antiplatelet medications. Stroke risk is further reduced by controlling hypertension and diabetes and treating patients with statins to reduce levels of low-density lipoprotein cholesterol.^{21,22} Many patients with AF are not currently receiving stroke prophylaxis. Implementation of guideline recommendations, in conjunction with concomitant improvements in other modifiable risk factors, can have a major impact on reaching the goal of improving the cardiovascular health of all Americans by 20% in 2020, while achieving a 20% reduction in deaths from CVD and stroke.

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Finding a Balance in Long-Term Anticoagulation Therapy

Eric C. Stecker, MD, MPH

Abstract

The treatment of atrial fibrillation (AF) takes a 2-pronged approach that addresses (1) symptoms caused by the arrhythmia and (2) safety, which is largely focused on reduction of the risk of stroke due to the effects of AF on blood flow. Treatment of AF includes rate-control and rhythm-control strategies. However, achieving control of AF symptoms will generally not protect a patient against the risk of stroke. Currently available antithrombotic agents effectively reduce the risk of stroke in patients with AF, and guidelines have been established for selecting the appropriate agent. Recommendations currently center on a choice between aspirin or warfarin (target international normalized ratio of 2.0-3.0) and are based on an assessment of the level of risk for the individual patient. The choice between aspirin or warfarin comes down to a choice between lower anticoagulant efficacy coupled with a lower bleeding risk versus higher anticoagulant efficacy coupled with a higher bleeding risk. Minimizing the risks of antithrombotic treatment in AF patients involves finding the appropriate balance between the risk for each individual of having a stroke while using less effective anticoagulation versus the risk of having a major bleeding event while using more effective anticoagulation.

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For author information and disclosures, see end of text.

The 2 main concerns in the treatment of atrial fibrillation (AF) are to achieve control of AF symptoms and lower the risk of stroke with antithrombotic therapy. From a safety standpoint, there is no distinction to be made between paroxysmal AF, persistent AF, and permanent AF; they are all associated with equivalent elevations in the risk of stroke, and appropriate preventative measures should be taken for each.^{1,2} Likewise, appropriate stroke prophylaxis should be implemented regardless of whether antiarrhythmic medications are believed to be successfully suppressing AF or not. However, this particular caveat may change as more rigorous methods for detecting silent arrhythmias, such as implantable devices, become more widely available.³

Symptomatic Treatment in AF

Treatment of AF relies on a rate-control strategy or a rhythm-control strategy.⁴ A rate-control strategy does not stop AF, but does act to maintain control of the ventricular rate while the atria are fibrillating. Rate control using pharmacologic agents is recommended for patients with paroxysmal, persistent, or permanent AF. The recommended agents include β -blockers, nondihydropyridine calcium channel antagonists, digitalis, or a combination thereof.⁵ A combination of a β -blocker and digitalis may be beneficial in patients with heart failure; digoxin and digitoxin are effective for rate control at rest, but not during exercise.

Some proven agents recommended for rhythm control in AF include amiodarone, dofetilide, flecainide, propafenone, sotalol, and a newly released medication called dronedarone.⁴ Recommended dosages, routes of administration, and safety considerations are specific to each agent. It is important to be familiar with the specific toxicities of the various rhythm control agents. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study compared rate control against rhythm control in elderly patients with AF and found no difference in outcomes between the 2 strategies.⁶

Catheter ablation of paroxysmal AF achieves effective rhythm control in approximately 75% of patients, but sometimes requires repetition or continued use of an antiarrhythmic agent.⁷ Patients should understand that the goal of ablation is not to gain independence from anticoagulation therapy. Ablation has not yet

Table 1. Efficacy of Antithrombotic Therapy for Primary Stroke Prevention in Patients With Atrial Fibrillation: A Meta-Analysis of Pooled Data From Randomized Trials¹⁵

Treatment Comparisons	Relative Risk Reduction, % ^a	95% Confidence Interval
Adjusted-dose Oral Anticoagulant Versus No Antithrombotic Therapy	68	50-79
Aspirin Versus No Antithrombotic Therapy	21	0-38
Adjusted-dose Oral Anticoagulant Versus Aspirin	52	37-63

^aOutcome is ischemic stroke. Note that the trials are not identical in all 3 analyses.
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been shown to prevent stroke and there is a periprocedural stroke risk. There is a large ongoing study sponsored by the National Institutes of Health called the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial that will evaluate whether percutaneous, left atrial catheter ablation is superior to pharmacologic rate or rhythm control for the reduction of mortality and stroke in AF patients.⁸ CABANA will randomize 3000 patients who have documented AF into 6 months of either catheter ablation or pharmacologic therapy with rate- or rhythm-control drugs. Patients will be at least 65 years of age or less than 65 years of age and with more than 1 risk factor for stroke, and they will be eligible for both catheter ablation and at least 2 rhythm-control agents or at least 3 rate-control drugs. Regardless of whether the rate-control or rhythm-control strategy is used for symptom treatment, antithrombotic therapy should always be used concomitantly.

Improving Safety in Patients Who Are at Elevated Risk of Stroke Due to AF

Anticoagulation therapy lowers the elevated risk of clot formation that is associated with AF and reduces the incidence of both mild and severe ischemic strokes and systemic embolism.^{2,4} The efficacy of anticoagulation as a stroke prevention measure is shown in Table 1. Using pooled data from 5 primary prevention trials in AF, the overall annual rate of stroke was 4.5% in the control group compared with 1.4% in the warfarin group.² As shown in Table 1, the total risk reduction for ischemic stroke attributable to warfarin therapy was 68%. Warfarin efficacy was consistent across all the studies and subgroups of patients. These benefits were balanced against minimal changes in the annual rate of major hemorrhage, which was defined as intracranial bleeding or a bleed requiring hospitalization or 2 units of blood. This pooled analysis reported annual rates of major bleeding of 1.0% in the control group and 1.3% in warfarin-treated patients. These bleeding events included an annual rate of

intracranial hemorrhage of 0.1% in the control group versus 0.3% in the warfarin group. In contrast, the efficacy of aspirin for stroke prevention in AF was less consistent. The Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy (AFASAK 2) study showed a nonsignificant 18% decrease in risk of stroke with 75-mg aspirin, while the Stroke Prevention in Atrial Fibrillation (SPAF) study found a significant decrease of 44% associated with 325-mg aspirin.² The investigators found identical rates of major bleeding in the control group (1.0%) and in the aspirin group (1.0%). A later meta-analysis of aspirin therapy versus placebo (or no treatment) for both primary and secondary prevention found a 19% reduction in the overall incidence of stroke, with no evidence favoring one dose of aspirin over another.⁹

These primary prevention trials included patients with persistent or permanent AF, as well as paroxysmal or intermittent AF.¹⁰⁻¹⁴ It was common for AF to have been present for many months or years. Anticoagulation was found to reduce all-cause mortality by 33% (95% confidence interval [CI], 9%-51%) and a combined outcome of stroke, systemic embolism, and death by 48% (95% CI, 34%-60%).¹⁵ Overall, evidence for the efficacy of anticoagulation in AF is strong, consistent, and based on high-quality studies.

Anticoagulation Guidelines for Stroke Prophylaxis in Patients With AF

Because the purpose of anticoagulation therapy is to inhibit clot formation, it can have both beneficial and adverse effects. Anticoagulation therapy blocks thromboembolism leading to stroke, but it also blocks appropriate clot formation, which could lead to a major bleeding event.¹⁶ Thus, the clinician must find a balance between the benefits and inherent risks of the therapy. The American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) 2006 guidelines for antithrombotic therapy are shown in Table 2.⁴ The guidelines represent a systematic approach to finding a balance

Table 2. ACC/AHA/ESC 2006 Guidelines: Antithrombotic Therapy for Patients With Atrial Fibrillation⁴

Risk Category	Recommended Therapy
No Risk Factors	Aspirin 81-325 mg once daily
1 Moderate Risk Factor ^a	Aspirin 81-325 mg once daily or Warfarin, INR 2.0-3.0 (target 2.5)
Any High Risk Factor ^b or More Than 1 Moderate Risk Factor ^a	Warfarin, INR 2.0-3.0 (target 2.5) ^c

ACC indicates American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; INR, international normalized ratio.
^aModerate risk: age ≥75 years, hypertension, heart failure, diabetes, left ventricular ejection fraction ≤35%.
^bHigh risk: prior stroke, transient ischemic attack or embolism, mitral stenosis, prosthetic heart valve.
^cIf mechanical heart valve, target INR >2.5.
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between the risk of thromboembolism and the risk of major bleeding events. Aspirin is recommended for patients with a lower risk of stroke (ie, those with no risk factors other than AF). Warfarin (target international normalized ratio [INR] of 2.5) is recommended for patients with a high risk of stroke (ie, those with a high risk factor or ≥1 moderate risk factor). For patients with 1 moderate risk factor, clinicians must decide between aspirin or warfarin.

These guidelines stand in contrast to the recently revised guidelines of the ESC, especially with respect to patients whose stroke risk is at the lower end of the spectrum.⁵ The ESC has recently implemented a revised, 9-point scoring system, called CHA₂DS₂VASc, for estimating the risk of stroke in patients with AF.¹⁷ This scoring system stratifies the contribution of age to stroke risk by assigning 2 points (A₂) to patients who are aged at least 75 years, and 1 point (A) to patients aged 65 to 74 years. The new system also takes into account the contributions of vascular disease (V) and sex category (Sc), assigning 1 point for each. Based on the risk of stroke determined by this method, the ESC now recommends choosing between aspirin or no treatment for patients with a CHA₂DS₂VASc score of 0, noting that the preferred choice is no treatment.⁵ The recommendation for a CHA₂DS₂VASc score of 1 is now a choice between warfarin or aspirin, where warfarin is designated as the preferred choice.

Antithrombotic Therapy Is Underused in Patients With AF

A commonly used, validated method of quantitating the risk of stroke is to score a patient's risk factor using 1 point each for congestive heart failure, hypertension, age greater than 75 years, and diabetes.¹⁸ Finally, 2 points are added for a history of prior stroke. The scoring system is

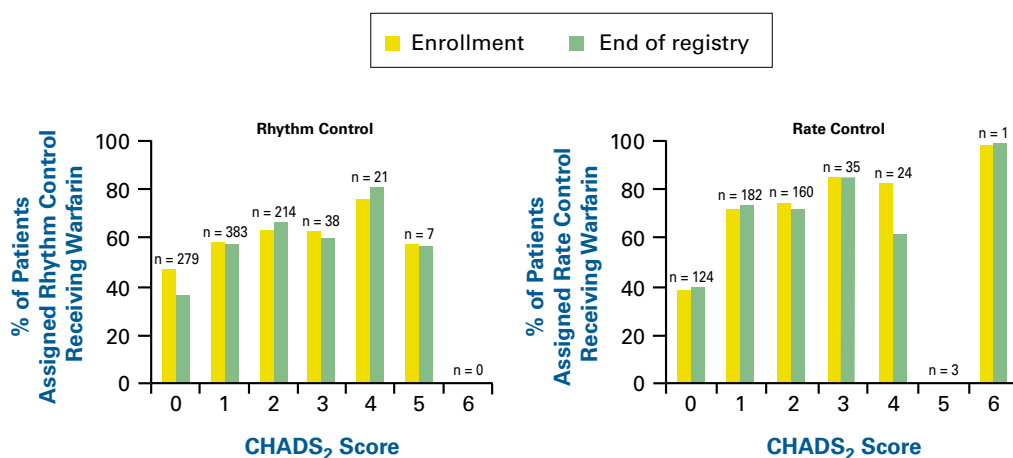
abbreviated using the acronym, CHADS₂. A recent study from the Atrial Fibrillation: Focus on Effective Clinical Treatment Strategies (AFFECTS) Registry provides an example of using the CHADS₂ score to gauge stroke risk in patients with AF.¹⁹ This study found that appropriate antithrombotic therapy is not being implemented in many patients with AF who are at elevated risk of stroke. The results are shown in the [Figure](#). Anticoagulant use was high among participating cardiologists,

but still did not match guidelines and evidence-based recommendations for patients with AF. Among patients with AF and a CHADS₂ score of at least 2, 73% were receiving warfarin concomitantly with rate-control treatment, and 66% were receiving both warfarin and rhythm-control treatment. The AFFECTS Registry did not report the reasons why physicians did not use anticoagulation therapy.

An elevated risk of bleeding events is sometimes the underlying reason for underuse of anticoagulation therapy in patients who would otherwise benefit. Despite the availability of relevant and validated tools, as well as regularly updated guidelines, anticoagulants continue to be underused in clinical practice.²⁰ [Table 3](#) shows recent data from the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) study that further illustrates the relative hazards of bleeding risk compared with stroke risk.²¹ In this analysis, the risk of death attributable to thromboembolic events was greater than the risk of death due to major bleeding events, which suggests that although the bleeding risk is a valid concern, avoiding the risk of death due to stroke is the greater concern in treating many patients with AF. Furthermore, only the major bleeding events that were considered severe were associated with increased mortality, further supporting the priority of stroke prevention.

The outpatient bleeding risk index (OBRI) is used to evaluate bleeding risk in a patient prior to initiating long-term oral anticoagulation therapy.¹⁶ The OBRI is scored on the basis of (1) history of stroke; (2) age older than 65 years; (3) history of gastrointestinal bleeding; and (4) presence of at least 1 comorbid condition, including recent myocardial infarction, renal insufficiency, severe anemia, or diabetes. On the OBRI scale, a score of 0 is a low risk, while scores of

■ **Figure.** AFFECTS Registry: Warfarin Use in Patients With Atrial Fibrillation¹⁹



Percentage of patients at enrollment and at end of registry who received warfarin according to CHADS₂ score. AFFECTS indicates Atrial Fibrillation: Focus on Effective Clinical Treatment Strategies; CHADS₂, congestive heart failure, hypertension, age (older than 75 years), diabetes, stroke. Reprinted with permission from Kowey PR, Reiffel JA, Myerburg R, et al. *Am J Cardiol.* 2010;105:1130-1134.

1 to 2 reflect a moderate risk of bleeding, and scores of 3 to 4 indicate a high bleeding risk. In the original report, cumulative rates at 2 years for major bleeding according to the OBRI risk score ranged from 3% to 53%.²²

The persistent disparity between real-world stroke prevention practices and published stroke prevention guidelines was examined recently in studies involving patients with AF.²³ Undertreatment was defined as treatment of less than 70% of high-risk patients. In this analysis, of 54 studies examined, the majority demonstrated underuse of oral anticoagulants in high-risk patients. Furthermore, 25 of 29 studies examining patients with prior stroke or transient ischemic attack (TIA) reported undertreatment, with 21 of 29 studies reporting oral anticoagulation treatment levels below 60% (range 19%-81.3%). The case study below provides an example of a patient who has both high stroke risk and high bleeding risk for whom there is no clear-cut “right” answer.

Case Study Discussion: William H.

The patient is a 91-year-old man who was diagnosed 1 year ago with persistent AF. Because he has not shown clear improvement, a rate-control strategy was chosen to address the symptoms of AF. His clinician must now choose an appropriate treatment to address the safety aspect of his treatment plan. An examination of his medical history shows some risk factors that will help estimate his level of stroke risk. Regarding his CHADS₂ score, he is well over 75 years of age and has borderline hypertension (ie, blood pres-

sure is typically 152/82 mm Hg), but does not have diabetes, or any history of congestive heart failure, stroke, or TIA. The fact that he has AF raises his risk of stroke considerably; furthermore, a transthoracic echocardiogram showed mild left ventricular hypertrophy and moderate left atrial enlargement, but a normal ejection fraction. A subsequent transesophageal echocardiogram (TEE) in AF revealed that he may have a thrombus in the left atrial appendage.

Another important consideration is the fact that William uses a walker and had a traumatic fall within the past year. It is likely that he has had a few less serious falls or close calls that he is reluctant to tell you about. Given his high risk of stroke, aspirin alone may not provide adequate protection. Given his instability, however, a fall while using anticoagulation could result in a serious hematoma. William represents the typical patient in whom the risk of stroke (due to inadequate anticoagulation) must be balanced against the risk of bleeding with anticoagulation therapy. Because the imaging data indicate that he has a likely left atrial thrombus that could potentially reach the brain, causing a catastrophic stroke or death, the recommended treatment for William is warfarin therapy with the goal of maintaining an INR between 2.0 and 3.0. Even without the possible clot on the TEE, warfarin is likely the safest overall approach at this time, despite the bleeding risk associated with warfarin.

Conclusion

Anticoagulation therapy has been shown to effectively

Table 3. Risk of Subsequent Mortality After Nonfatal Vascular and Bleeding Events^{21,a}

Event Type	Hazard Ratio	95% Confidence Interval	P
Nonfatal Stroke	5.58	3.84-8.10	<.0001
Ischemic Stroke ^b	5.29	3.53-7.93	<.0001
Hemorrhagic Stroke ^b	7.38	2.74-19.9	<.0001
Disabling Stroke ^c (Rankin Score ≥3)	9.54	6.42-14.2	<.0001
Severe Bleeding ^d	3.35	2.12-5.27	<.0001

^aPatients with atrial fibrillation were receiving antithrombotic therapy that utilized either warfarin or clopidogrel + aspirin.

^bTransient ischemic attacks did not increase mortality.

^cNondisabling strokes did not increase mortality.

^dMajor bleeding that was not severe did not increase mortality.

lower the incidence of stroke in high-risk populations, including patients who are at risk of stroke due to AF. Unfortunately, anticoagulation therapy in AF is underused. Underuse is more prevalent in cases of paroxysmal AF than in cases of permanent AF, despite the fact that the risk of stroke is essentially the same for both. When considering the choices for anticoagulation therapy, treatment decisions made by clinicians often lean toward taking the risk of inadequate anticoagulation versus the risk of major bleeding. As a consequence, many studies now demonstrate underuse of anticoagulation in populations who are at risk of stroke, including patients with AF. However, it can be argued that a shift in opinion would only result in more studies that show increased incidence of major bleeding events. The underuse of anticoagulants may simply translate to fewer deaths due to intracranial hemorrhage. Thus, clinicians now anxiously await a new generation of anticoagulant agents that promise to offer more protection against thromboembolism with lower bleeding risk and simpler dosing and monitoring. These emerging agents, direct thrombin inhibitors and factor Xa inhibitors, promise to diminish the risks that currently must be considered with anticoagulation therapy.^{24,25}

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Authorship Information: Concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content; administrative, technical, or logistical support; and supervision.

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A Pharmacoeconomic Perspective on Stroke Prevention in Atrial Fibrillation

A. Mark Fendrick, MD

Abstract

Atrial fibrillation (AF) is predictive of higher costs for stroke care, in part due to the influence of AF on stroke severity. Costs associated with severe strokes, which are more likely in patients with AF, are about twice those of mild strokes. Thus, adequately weighing the costs associated with stroke care is important when making prevention and treatment recommendations for patients diagnosed with AF. Costs associated with AF are estimated at \$6.65 billion annually, which breaks down to 44% for hospitalizations, 29% for the incremental inpatient costs of AF as a comorbid diagnosis, 23% for outpatient treatment of AF, and 4% for medications. A diagnosis of AF should be followed by careful consideration of the treatment plan. Clinicians who tend to underuse warfarin should consider whether the patient has valid contraindications to warfarin or if the risk of stroke would be unacceptably high using the alternative—low-dose aspirin. Optimal use of anticoagulation in patients with AF is projected to result in substantial savings in direct costs. Optimization of anticoagulation therapy in only half of the suboptimally anticoagulated patients with AF would save approximately \$1.3 billion annually. New and emerging oral alternatives to warfarin promise to combine the advantages of oral dosing and effective anticoagulation with improvements in safety, leading to reduced monitoring and dose adjustment. As these agents become available, treatment decisions will likely incorporate economic considerations, such as the costs of medication, patient monitoring, and treatment of bleeding events.

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Although several risk factors for stroke are responsive to preventative measures, and overall risk of stroke can be significantly lowered by controlling factors like smoking, body weight, blood pressure, and blood glucose, stroke continues to be the third-leading cause of death in the United States.¹ The burden of stroke, from the perspective of life-years lost, diminished quality of life, and direct and indirect medical costs, is quite large. The direct and indirect costs of stroke care are estimated to be \$73.7 billion (2010 US dollars), and the mean lifetime cost of ischemic stroke per patient is estimated at \$140,048 (which includes inpatient care, rehabilitation, and any follow-up care needed to cope with lasting deficits). Race and economic status also play a significant role in the economics of stroke care. According to 1 study, socioeconomic status may underlie 39% of the excess risk of stroke reported in African Americans.² African Americans are also estimated to have the highest per capita cost for stroke care (\$25,782), followed by Hispanics (\$17,201) and non-Hispanic whites (\$15,597).¹ Costs must be considered when making recommendations for stroke prevention and treatment in patients with AF. Comorbidities like AF and ischemic heart disease predict higher costs for stroke care. Furthermore, the costs of severe strokes are typically twice those of mild strokes. Thus, the costs of stroke care versus stroke risk reduction should be understood and considered throughout the course of AF management.

Anticoagulation Therapy Is Underused in Patients With AF Who Are at Risk of Stroke

There is a consistent and systematic underuse of anticoagulation despite evidence supporting its use for stroke prevention in patients with AF.³ Randomized trials have demonstrated that a relatively low intensity of anticoagulant therapy can largely eliminate the risk of stroke attributable to AF. **Figure 1** illustrates the risk reduction achieved using monitored warfarin treatment in patients with AF.⁴

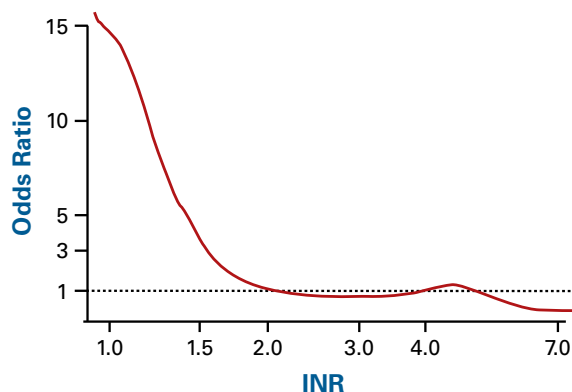
The reasons for underuse of anticoagulation are still emerging, but in many cases there is an underlying concern that the benefits of prescribing antithrombotic therapy shown in clinical trials may not translate into everyday practice, namely that the risk of hemorrhage associated with anticoagulants may be higher in certain patient populations, particularly the elderly. Many randomized trials exclude the majority of potential participants, more than 90% in

some cases, because of advanced age or relative contraindications to anticoagulation. Thus, the efficacy of anticoagulation is often demonstrated under ideal circumstances (ie, patients enrolled in the 5 studies examined in a landmark meta-analysis were at low risk of bleeding and the intensity of their anticoagulation was carefully regulated, which is frequently not the case in patients with AF).⁵ For many other patients, anticoagulation therapy is used inappropriately. As shown in **Table 1**, a survey of hospital pharmacy representatives reveals some of the reasons for inappropriate use of specific anticoagulant agents.⁶ Inappropriate dosing (53.7%) and monitoring (36.6%) were especially important factors in relation to warfarin use, while 50% of respondents indicated that direct thrombin inhibitors were used for inappropriate indications.

Overall, several studies report that typical implementation of anticoagulation therapy is approximately 60% in patients with AF. In 1 study, underuse of antithrombotic therapy in patients with nonvalvular AF was specifically associated with advanced age, female gender, and rural residency.⁷ Compared with younger patients, the odds of receiving antithrombotic therapy were 1.7 times lower (95% confidence interval [CI], 1.2-2.5) for patients older than 75 years of age ($P < .01$). For females, the odds of receiving antithrombotic therapy were 1.5 times lower (95% CI, 1.0-2.1) than that in male patients ($P = .05$), and patients discharged from a rural healthcare setting were 1.7 times less likely (95% CI, 1.2-2.5) to receive anticoagulation than patients discharged from urban hospitals ($P < .05$). In 195 ideal anticoagulation candidates (ie, those who had nonvalvular AF, no contraindication to anticoagulation, and ≥ 1 stroke risk factor), 46% received warfarin and 23% received aspirin, while 31% received no antithrombotic therapy. In 111 ideal anticoagulation candidates older than 75 years of age, only 41% received warfarin, while 22% used aspirin.

Many clinicians interpret the results of large clinical trials with caution when considering the individual needs

■ **Figure 1.** Odds Ratios for Stroke According to INR Value in Patients With Atrial Fibrillation⁴



Unadjusted odds ratios were calculated by dividing the estimated density of patients who had a stroke at a given international normalized ratio (INR) by the estimated density of control patients with the same INR. The resulting ratio was then divided by the ratio at an INR of 2.0. Reprinted with permission from Hylek EM, Skates SJ, Sheehan MA, Singer DE. *N Engl J Med.* 1996;335:540-546. Copyright ©1996 Massachusetts Medical Society. All rights reserved.

and characteristics of their patients with AF. However, this approach often develops into an overall trend of systematic underuse of anticoagulation. To avoid this, clinicians must decide whether their patients who are not receiving anticoagulation truly have a strong contraindication to warfarin, because the alternatives are aspirin (which may not offer adequate protection against stroke) or no treatment (ie, no protection against stroke).

Real-World Compliance With Recommendations

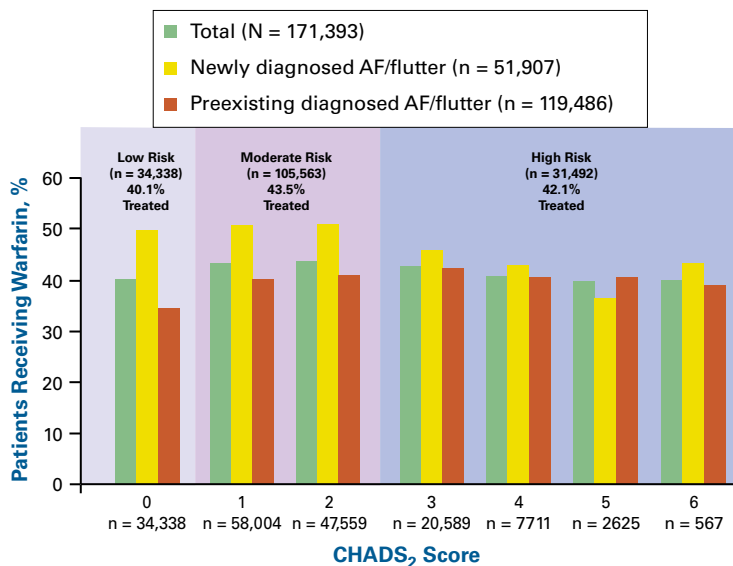
A recent examination of clinician compliance with anticoagulation guidelines in patients with AF found that warfarin was used in only 42.6% of the overall study population.⁸ Compliance was slightly higher in patients with newly diagnosed AF or atrial flutter (49.6%) compared with those with

■ **Table 1.** Perceived Reasons for Inappropriate Anticoagulant Use⁶

Anticoagulant	Inappropriate Dose, %	Inappropriate Indication, %	Inadequate Monitoring, %	Failure to Comply With Guidelines, %
Unfractionated Heparin (n = 12)	41.7	41.7	8.3	8.3
Warfarin (n = 27)	53.7	2.4	36.6	7.3
Low Molecular Weight Heparin (n = 26)	75.0	22.2	0	2.8
Direct Thrombin Inhibitor (n = 6)	33.3	50.0	0	16.7
Factor Xa Inhibitor (n = 4)	71.4	28.6	0	0

Adapted from Vats V, Nutescu EA, Theobald JC, Wojtynek JE, Schumock GT. *Am J Health Syst Pharm.* 2007;64:1203-1208.

Figure 2. Underutilization of Anticoagulation in Patients With AF⁸



Warfarin use within 30 days of the first atrial fibrillation (AF) diagnosis assessed according to stroke risk, estimated by CHADS₂ (congestive heart failure, hypertension, age [older than 75 years], diabetes, stroke) score. Reprinted with permission from Zimetbaum PJ, Thosani A, Yu HT, et al. *Am J Med.* 2010;123:446-453.

preexisting AF or atrial flutter (39.5%). Anticoagulation use was less than 50% across all groupings of congestive heart failure, hypertension, age at least 75 years, diabetes mellitus, and stroke (CHADS₂) scores, specifically 42.1% of high-risk patients (CHADS₂ score 3-6), 43.5% of moderate-risk patients, and 40.1% of low-risk patients (Figure 2).

Despite guideline recommendations that anticoagulation should be provided in accordance with a patient's risk of stroke, some patients who would benefit most from anticoagulation, due to a high risk of stroke, did not receive treatment.⁹ In contrast, recent results from the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) study show that low-risk patients derive a benefit from anticoagulation beyond that obtained from dual antiplatelet therapy.¹⁰ As shown in Table 2, even with a CHADS₂ score equal to 1, there was a significant benefit with warfarin compared with aspirin plus clopidogrel. Given these results, the European Society of Cardiology now recommends an oral anticoagulant over aspirin, even in low-risk patients with AF and CHADS₂ equal to 1.¹¹

Treatment of AF Represents a Significant Healthcare Burden

The use of healthcare resources and other costs attributable to AF has been examined in terms of hospital inpatient stays, physician office visits, emergency department visits, and hospital outpatient department visits.¹² Figure 3 shows the findings from case-control analyses conducted to estimate the annual incremental costs of AF. Regression models assessed the impact of AF on hospitalization costs (estimated in 2005 US dollars). The total annual

Table 2. ACTIVE-W: Stroke Rates After Treatment With Warfarin Versus Clopidogrel + Aspirin¹⁰

CHADS ₂ Score	Stroke Rate W/Aspirin (/100 pt-y) ^a	Number (%) of Patients in ACTIVE-W ^b	Stroke Rate W/Clopidogrel + Aspirin (/100 pt-y)	Stroke Rate W/Warfarin (/100 pt-y)	Relative Risk (Clopidogrel + Aspirin Vs Warfarin) ^c
0	0.8	178 (3)	1.90	0.80	3.02
1	2.2	2436 (36)	1.21	0.40	3.11
2	4.5	2286 (34)	1.93	1.86	1.04
3	8.6	1107 (17)	2.79	1.72	1.62
4	10.9	490 (7)	6.73	3.25	2.07
5	12.3	183 (3)	11.65	2.69	7.01
6	13.7	26 (0.4)	0	0	N/A

AF indicates atrial fibrillation; ACTIVE-W, Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; CHADS₂, congestive heart failure, hypertension, age (older than 75 years), diabetes, stroke; RR, relative risk.

^aAnnual rate of stroke among 2580 aspirin-treated patients with AF.

^bPatients had evidence of peripheral vascular disease or coronary artery disease and were aged >55 years.

^cInfluence of baseline CHADS₂ score on RR (P trend = .29).

Reprinted with permission from Healey JS, Hart RG, Pogue J, et al. *Stroke.* 2008;39:1482-1486.

costs for AF were estimated at \$6.65 billion: \$2.93 billion (44%) for hospitalizations (principal discharge diagnosis was AF), \$1.95 billion (29%) for the incremental inpatient cost of AF as a comorbid diagnosis, \$1.53 billion (23%) for outpatient treatment of AF, and \$235 million (4%) for medications. Overall, the treatment of AF represents a significant healthcare burden, and the costs of treating AF in the inpatient setting outweigh the costs of treating AF in the office, emergency department, or hospital outpatient settings.

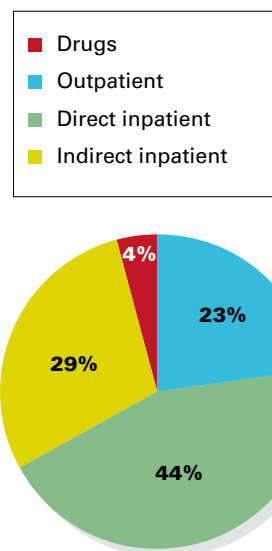
Cost Considerations in AF Symptom Control

Using a rate-control strategy for symptomatic treatment of AF has been shown to be more cost-effective than using a rhythm-control strategy in patients with AF. The analysis by Marshall et al¹³ combined data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study and unit cost estimates from various US databases in patients who were similar to those in the AFFIRM population. Patients in the rate-control group used fewer resources, including hospital days, pacemaker procedures, cardioversions, short-stay visits, and emergency department visits. The overall cost of rate-control therapy was less than that of rhythm control by a difference of \$5077 per person. In addition to being more costly, rhythm control was less effective than rate control over a wide range of assumptions. For a case-base scenario, the probability that rhythm control was cost-effective relative to rate control was less than 0.01, even when analyzed at a value of \$100,000 per life-year gained.

Optimal Use of Anticoagulation Can Reduce the Costs of AF Care

Beyond the anticipated benefits to patients in terms of mortality and quality of life, it has been projected that optimal use of anticoagulation in patients with AF would lead to substantial savings in direct costs.¹⁴ This cost analysis is illustrated in Figure 4. The model estimated that 2.3 million patients in the United States have AF. An estimated 1.3 million of those patients are not receiving oral anticoagulants and about half of that group are assumed to be using aspirin. Moreover, about 70% of the patients who are using anticoagulation receive it in a routine medical care setting without special support, while only 30% of patients using anticoagulation therapy receive it in an anticoagulation clinic. As shown in Figure 4, during the first year of AF care, 58,392 strokes were estimated to occur in the patients not using anticoagulants, while 38,468 were estimated in the patients with AF who were receiving anticoagulation therapy.

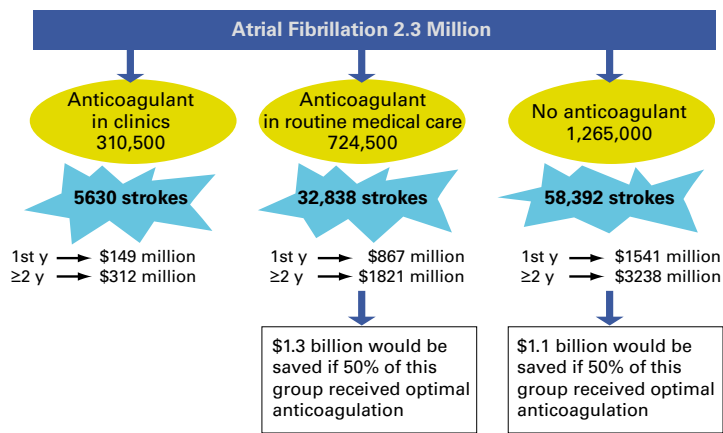
Figure 3. Distribution of Inpatient and Selected Outpatient Costs Associated With AF¹²



The treatment of atrial fibrillation (AF) represents a significant cost burden in healthcare. A combined total of \$6.65 billion (US dollars) was spent in 2005 for AF treatment in the inpatient, emergency department, and hospital outpatient settings. Reprinted with permission from Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. *Value Health*. 2006;9:348-356.

The total direct costs associated with these AF-related strokes are estimated at approximately \$8 billion.¹⁴ Many factors that follow a stroke must be taken into account for such an analysis. For instance, about 50% of stroke survivors can be anticipated to return home after discharge, 25% will require special skilled nursing care, and another 20% will go to rehabilitation centers; the remainder will require services from a skilled nursing facility. Among patients who return home, only about half of those have no need for further care (other than follow-up physician visits). The remainder of those who return home will need home healthcare (25%), day care (10%), or will go through a rehabilitation program (15%). The initial estimate of \$8 billion for AF-related strokes includes \$2.6 billion during the first year and another \$5.4 billion in Medicare-covered costs thereafter. At the individual level, the total financial cost of a stroke is about \$3435 per patient annually. The estimated cost savings of anticoagulation, projected at the individual patient level, are also illustrated in Figure 4. For patients using an anticoagulation clinic, the cost of a stroke was estimated at \$1485, compared with \$3710 for patients receiving anticoagulation as part of routine medi-

Figure 4. Improvements in Anticoagulant Utilization Could Yield Both Clinical and Economic Gains¹⁴



Projected costs for patients in the 3 main treatment groups reflect the varying stroke rates in those groups. Adapted from Caro JJ. *Am J Manag Care.* 2004;10:S451-S461.

care. The estimate for patients not using anticoagulants was \$3778. The surprisingly small cost difference between anticoagulation in routine medical care compared with no anticoagulation therapy stems from the costs associated with treating complications of anticoagulation therapy, like gastrointestinal bleeding.

However, these savings estimates do not consider the costs associated with a dedicated anticoagulation clinic capable of delivering such a level of stroke reduction. As shown in Figure 4, a second analysis from this study found that approximately \$1.3 billion would be saved if only half of the patients receiving anticoagulation through routine medical care were given optimal anticoagulation therapy.¹⁴ Much of this cost reduction would be anticipated to arise from decreases in the expenses associated with the treatment of warfarin-related bleeding, which can often entail surgery, intensive care unit stays, or blood transfusions. These savings should be weighed against the costs of maintaining an anticoagulation clinic.

Over the long term, an anticoagulation management clinic can be anticipated to cost less and provide greater efficacy compared with the costs of managing warfarin therapy in a routine-care setting. Community-based studies have reported significant variation in the effectiveness of anticoagulation depending on the management approach used. By some estimates, the average patient receiving warfarin maintains an international normalized ratio (INR) within the target therapeutic range for less than half of the time. Sullivan et al¹⁵ compared estimated lifetime costs and health benefits of stroke prevention with warfarin managed through

usual care versus anticoagulation management services with dedicated anticoagulation professionals (eg, a physician or pharmacist). Patients were elderly (mean age, 70 years) and had AF and high risk of stroke. This analysis found that using an anticoagulation management service improved effectiveness by 0.057 quality-adjusted life-year—a significant enhancement in the cost-effectiveness of warfarin therapy. Compared with routine care, an anticoagulation management service reduced costs by \$2100 (2004 US dollars). This improvement supports the notion that it is preferable to use warfarin therapy within the context of an anticoagulation management service and that greater consideration toward therapies that do not require monitoring may be appropriate when anticoagulation management services are not accessible. Improved stroke prophylaxis in a rapidly growing population of older, high-risk patients is achievable through the addition of patient-monitoring technology strategies, like a formally organized anticoagulation monitoring program.

No Monitoring Costs Associated With New and Emerging Anticoagulant Agents

New classes of anticoagulant agents may soon serve as alternatives to warfarin. They offer oral dosing and good efficacy, coupled with the advantage of a lower bleeding risk, which eliminates much of the expense of monitoring, potentially reducing the total cost of anticoagulation therapy.¹⁶ Apixaban, rivaroxaban, and edoxaban, factor Xa inhibitors, as well as dabigatran, a direct thrombin inhibitor, offer several important advantages over warfarin.¹⁶⁻¹⁸ None of these agents require the close laboratory monitoring that is required with warfarin therapy. They also have more predictable pharmacodynamics than warfarin, which should simplify dosing.¹⁷ These agents could emerge as alternatives to warfarin in patients with AF. Pharmacoeconomic considerations, in addition to efficacy and safety issues, need to be assessed when these new anticoagulants are evaluated for use in the management of AF.¹⁶

Conclusion

The high risk of stroke associated with AF leads to significantly higher morbidity and mortality in patients with AF and negatively impacts the quality of life for many patients in this population. There is a strong connection between advancing age and onset of AF; it is anticipated

that any increase in average life span will be accompanied by increases in the personal and financial impact of AF, particularly with regard to the risk of stroke and the long-term consequences for stroke survivors. Fortunately, using evidence-based antithrombotic therapy can greatly diminish the incidence of stroke in patients with AF. Making an individualized comparison between risks and benefits associated with antithrombotic therapy lies at the heart of every decision to use it and the choice of antithrombotic agent. The risk of stroke in patients with AF is easily estimated using the CHADS₂ scoring system. Evidence-based US guidelines currently recommend warfarin for patients who are determined to be at high or intermediate risk; however, the use of warfarin is complicated by a continuous need for laboratory monitoring due to the narrow therapeutic window and an association with bleeding events. Aspirin, an alternative agent, is less effective than warfarin for primary prevention of stroke in patients with AF, and it is currently only recommended in the United States for patients at low or intermediate risk of stroke. The European Society for Cardiology (ESC) now recommends using a newly developed 9-point scoring system called the CHA₂DS₂VASc score to estimate the risk of stroke in AF patients.^{11,19} The CHA₂DS₂VASc system stratifies the contribution of age to stroke risk by assigning 2 points (A₂) to patients aged at least 75 years, but only 1 point (A) to patients aged 65 to 74 years. It includes the contributions of vascular disease (V) and sex category (Sc) to stroke risk as well, assigning 1 point for each. The CHA₂DS₂VASc score also assigns 2 points for a previous stroke (S₂) and 1 point each for congestive heart failure (C), hypertension (H), or diabetes (D).¹⁹ This scoring system takes the influence of clinically relevant nonmajor risk factors into account when estimating individual risk of stroke. Using the CHA₂DS₂VASc score, the ESC now states that warfarin is the preferred therapy for patients with AF who have a risk score as low as 1 point.¹¹

Warfarin is currently underused, and opportunities to achieve additional reduction in the total burden of stroke in the United States are lost in many patients with AF. There are a number of reasons for underuse of warfarin, most having to do with the need for INR monitoring and associated risks of major bleeding events or inadequate anticoagulation. New and emerging antithrombotic agents that combine antithrombotic efficacy with improved safety and less stringent monitoring requirements are likely to shift treatment decisions toward the costs of treatment. As more patients are diagnosed with AF, subsequent treatment decisions will focus more on the anticipated course of care for an entire episode,

looking not only to the silo of drug and monitoring costs, but also to the billions of dollars that are estimated to go into the treatment of stroke victims.

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Authorship Information: Concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and supervision.

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New Options for Stroke Prevention in Atrial Fibrillation

Christopher P. Cannon, MD; and Eric C. Stecker, MD, MPH

Historically, the options primarily recommended for antithrombotic therapy in patients with atrial fibrillation (AF) have been aspirin and warfarin, a vitamin K antagonist.¹ In 5 prospective, randomized, controlled clinical trials conducted in patients with nonrheumatic AF, warfarin was shown to significantly reduce the risk of thromboembolism by 48% to 72%.² However, warfarin also has complex pharmacokinetics and pharmacodynamics, including interactions with many medications and foods.³ Moreover, the use of warfarin is complicated by a narrow therapeutic window and a need for continual laboratory monitoring to avoid both the risk of major bleeding events and the risk of inadequate anticoagulation. Aspirin, although somewhat effective in preventing stroke in AF, is inferior to warfarin and is primarily used in low-risk patients.¹ These issues, as well as the 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, thus reducing the number of potential unwanted drug effects.^{3,4}

Any anticoagulant, like unfractionated heparin, low molecular weight heparins (LMWH), and warfarin, affects multiple components of the coagulation cascade. Vitamin K antagonists, including warfarin, disrupt the production of multiple functional vitamin K-dependent clotting factors (II, VII, IX, and X), as well as the anticoagulant proteins C and S (Figure 1).³ Argatroban, lepirudin, and bivalirudin are direct thrombin inhibitors that do not require thrombin for their anticoagulant effect. Newer agents have been developed that directly target and inhibit specific coagulation proteins.

Direct thrombin inhibitors (eg, argatroban, lepirudin, bivalirudin), LMWHs, and the factor Xa inhibitor fondaparinux overcome some of the disadvantages of unfractionated heparin, but require intravenous or subcutaneous administration, are contraindicated or difficult to use in patients with hepatic or renal dysfunction, and have not proved useful for long-term antithrombotic prophylaxis in patients with AF.³ For example, in a study of long-term anticoagulation in patients with AF that compared the once-weekly LMWH idraparinux and warfarin, idraparinux was associated with a significantly higher risk of bleeding.⁵ New oral agents could be used in a variety of settings, and some are currently in clinical trials to investigate their efficacy in AF and the possible advantages over current choices.⁶⁻⁹ It is anticipated that these new agents will eventually

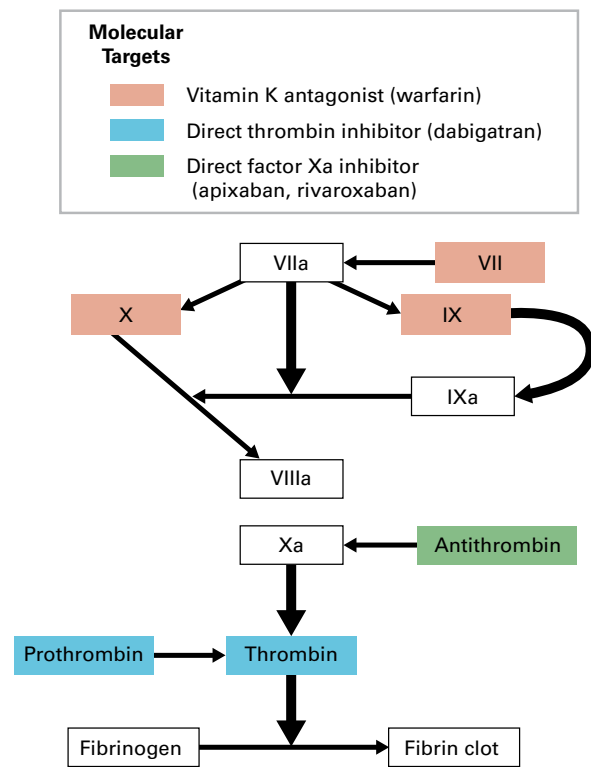
Abstract

Randomized trials have demonstrated that warfarin is effective for stroke prevention in patients with atrial fibrillation (AF), yielding relative risk reductions for ischemic stroke of nearly 70%. However, successful use of warfarin requires frequent monitoring and dose adjustment to maintain an international normalized ratio (INR) within the range of 2.0 to 3.0. Many clinicians and patients have been reluctant to use warfarin therapy in AF, with underuse generally attributed to the inconvenience of INR monitoring, complexities of drug and dietary interactions associated with warfarin, and perceived bleeding risk. The ensuing search for safe, effective alternatives with a lower associated risk of bleeding and no need for monitoring and dose adjustment has focused attention on more specific inhibitors of the clotting cascade, such as factor Xa inhibitors or direct thrombin inhibitors. The direct thrombin inhibitor dabigatran has recently been approved by the US Food and Drug Administration for the prevention of stroke in patients with AF. New factor Xa inhibitors apixaban, rivaroxaban, and edoxaban are also currently being studied in stroke prevention trials in patients with AF to determine their comparability with warfarin. It is anticipated that fixed-dose administration of these new oral agents will provide effective anticoagulation without the need for frequent monitoring and with a lower risk of bleeding events.

(*Am J Manag Care.* 2010;16:S291-S297)

For author information and disclosures, see end of text.

Figure 1. Oral Antithrombotic Agents Used for the Treatment of Atrial Fibrillation Act on Different Molecular Targets in the Coagulation Cascade³



Warfarin affects clotting factors II, VII, IX, and X as well as the anticoagulant proteins C and S. Direct thrombin inhibitors act directly and specifically on thrombin activity, whereas factor Xa inhibitors specifically target factor Xa in the coagulation cascade. Adapted from Trujillo TC. *Am J Health Syst Pharm.* 2010;67(suppl 6):S17-S25.

replace warfarin in prophylactic and therapeutic regimens in many patients, including those with AF.

Direct Thrombin Inhibitors: Dabigatran

The efficacy of dabigatran and warfarin (adjusted to an international normalized ratio [INR] of 2.0-3.0 according to monthly measurements) in stroke prevention has been assessed in high-risk patients with AF. The stable pharmacodynamics and pharmacokinetics of dabigatran permitted fixed dosing (110 mg or 150 mg twice daily) with no need for monitoring.^{10,11} In addition to AF, these high-risk subjects also had at least 1 of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74

years plus diabetes mellitus, hypertension, or coronary artery disease. This study excluded patients who have a severe heart valve disorder, had a stroke within 14 days or a severe stroke within 6 months before screening, have conditions known to raise the risk of hemorrhage, have a creatinine clearance less than 30 mL/min, have active liver disease, or are pregnant.

Over a median follow-up period of 2 years, the study followed 18,113 patients for incidence of primary (ie, stroke or systemic embolism) or secondary (ie, stroke, systemic embolism, or death) outcome.^{10,11} The primary safety outcome was major hemorrhage. This noninferiority trial made an open-label comparison between warfarin and dabigatran 110 mg or 150 mg twice daily. The 2 dabigatran regimens were assigned in a blinded fashion. In comparison with warfarin, both dabigatran regimens met noninferiority criteria in their primary outcomes, and the higher dose of dabigatran was superior in efficacy to warfarin, as summarized in Table 1. The individual rates of stroke and systemic embolism were 1.69% per year for warfarin; 1.53% per year for dabigatran 110 mg, with a relative risk (RR) of 0.91 (95% confidence interval [CI], 0.74-1.11; *P* <.001 vs warfarin); and 1.11% per year for dabigatran 150 mg with an RR of 0.66 (95% CI, 0.53-0.82; *P* <.001) (Table 1 and Figure 2).

The incidence of major bleeding was 3.36% per year in the warfarin group, 2.71% per year for the dabigatran 110-mg regimen (RR = 0.80; 95% CI, 0.69-0.93; *P* = .003 vs warfarin), and 3.11% per year for the dabigatran 150-mg regimen (RR = 0.93; 95% CI, 0.81-1.07; *P* = .31).¹⁰ Rates of hemorrhagic stroke were 0.38% per year with warfarin, 0.12% per year with dabigatran 110 mg (*P* <.001 vs warfarin), and 0.10% per year with dabigatran 150 mg (*P* <.001) (Table 1 and Figure 3). By selectively inhibiting only thrombin, dabigatran may block clot formation with a greater specificity than warfarin and it does not affect other aspects of the coagulation cascade, thus potentially mitigating the risk of bleeding. Alternatively, a lower degree of variability in the anticoagulant effect of dabigatran may underlie its association with a reduced risk of bleeding. Life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin (*P* <.05 for all comparisons of dabigatran with warfarin) (Table 1 and Figure 3). Major gastrointestinal bleeding was significantly higher with dabigatran 150 mg than warfarin.

The length of time spent within the optimal therapeutic range for warfarin (ie, INR of 2.0-3.0) determines its efficacy and safety, and is a gauge of the quality of the warfarin regimen. To reveal whether the quality of warfarin therapy played a role in the results of the Randomized Evaluation of

Table 1. RE-LY Outcomes, Stroke, and Bleeding Events in Patients With Atrial Fibrillation¹⁰

Outcome	Dabigatran 110 mg Daily vs Warfarin ^a			Dabigatran 150 mg Daily vs Warfarin ^a		
	RR	95% CI	P ^a	RR	95% CI	P ^a
Stroke or Systemic Embolism	0.91	0.74-1.11	.34 ^b	0.66	0.53-0.82	<.001 ^b
Stroke	0.92	0.74-1.13	.41	0.64	0.51-0.81	<.001
Hemorrhagic	0.31	0.17-0.56	<.001	0.26	0.14-0.49	<.001
Ischemic or Unspecified	1.11	0.89-1.4	.35	0.76	0.60-0.98	.03
Nondisabling Stroke	0.86	0.61-1.22	.40	0.62	0.43-0.91	.01
Disabling or Fatal Stroke	0.94	0.73-1.22	.65	0.66	0.50-0.88	.005
Bleeding Events						
Major Bleeding	0.80	0.69-0.93	.003	0.93	0.81-1.07	.31
Gastrointestinal Bleeding ^c	1.10	0.86-1.41	.43	1.50	1.19-1.89	<.001
Minor Bleeding	0.79	0.74-0.84	<.001	0.91	0.85-0.97	.005
Life-Threatening Bleeding	0.68	0.55-0.83	<.001	0.81	0.66-0.99	.04
Intracranial Bleeding	0.31	0.20-0.47	<.001	0.40	0.27-0.60	<.001

CI indicates confidence interval; RE-LY, Randomized Evaluation of Long-term anticoagulation Therapy; RR, relative risk.

^aDose-adjusted warfarin, international normalized ratio 2.0-3.0.

^bRespective P values for noninferiority were P <.001 (dabigatran 110 mg) and P <.001 (dabigatran 150 mg).

^cGastrointestinal bleeding could be life threatening or non-life threatening.

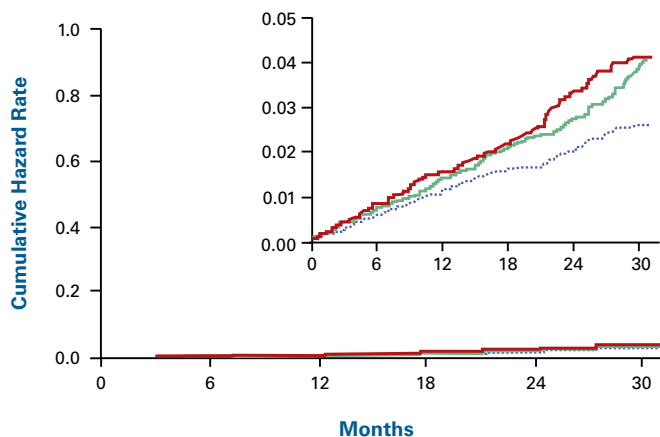
Adapted from Connolly SJ, Ezekowitz MD, Yusuf S, et al. *N Engl J Med.* 2009;361:1139-1151.

Long-term anticoagulation Therapy (RE-LY) study, a post hoc analysis compared primary and secondary outcomes for both dabigatran regimens with respective warfarin outcomes, relative to the time patients given warfarin spent within the therapeutic range (TTR).¹¹ Regression analysis revealed no significant interactions between TTR and prevention of the primary outcome (ie, stroke or systemic embolism) for either dabigatran regimen. The P values for interaction were P = .89 (dabigatran 110 mg) and P = .20 (dabigatran 150 mg) versus warfarin. There were reductions in the rates of stroke and intracranial bleeding with dabigatran 150 mg and similar reductions in stroke and major and intracranial bleeding with dabigatran 110 mg, irrespective of INR control. The benefits of dabigatran 150 mg in reducing stroke, dabigatran 110 mg in reducing bleeding, and both regimens in reducing intracranial bleeding compared with warfarin were shown to be consistent regardless of the quality of INR at individual study centers.

Factor Xa Inhibitors

Recent results from the Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial that compared apixaban, a novel selective direct factor Xa inhibitor, with

Figure 2. Primary Outcome in Patients With Atrial Fibrillation at High Risk of Stroke¹⁰

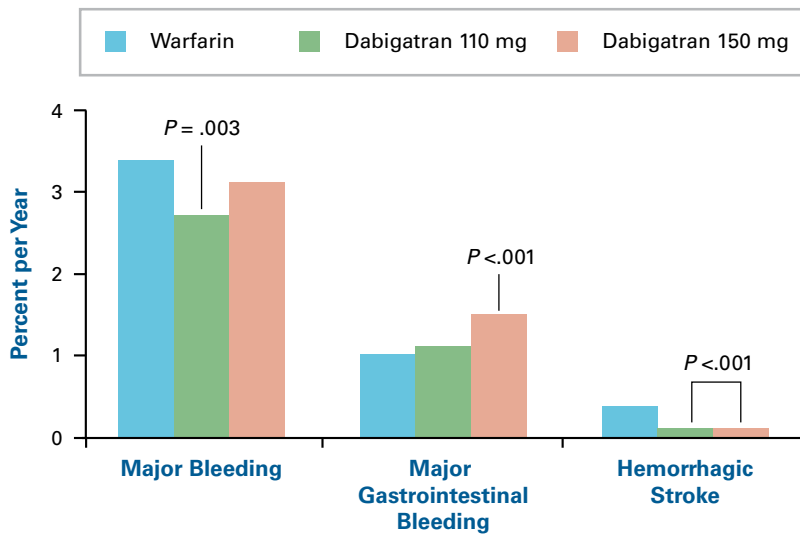


Rates of stroke and systemic embolism for warfarin therapy (red solid line) versus dabigatran 110 mg twice daily (blue solid line) or 150 mg twice daily (blue dotted line). Warfarin versus dabigatran 110 mg: relative risk (RR) = 0.91 (95% confidence interval [CI], 0.74-1.11; P <.001); 150 mg: RR = 0.66 (95% CI, 0.53-0.82; P <.001). Reprinted with permission from Connolly SJ, Ezekowitz MD, Yusuf S, et al. *N Engl J Med.* 2009;361:1139-1151.

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aspirin for primary stroke prevention in AF, have been published.⁶ The trial was stopped early after a first analysis showed a clear advantage with apixaban. Subjects who had AF and 1 or more risk factors for stroke were interviewed to identify any factors that would make them unsuitable

■ **Figure 3. Bleeding Events With Dabigatran Versus Warfarin (International Normalized Ratio 2.0-3.0)**¹⁰



Dabigatran 110-mg regimen: relative risk (RR) for major bleeding = 0.80 (95% confidence interval [CI], 0.69-0.93; $P = .003$). Dabigatran 150-mg regimen: RR = 0.93 (95% CI, 0.81-1.07; $P = .31$). Adapted from Connolly SJ, Ezekowitz MD, Yusuf S, et al. *N Engl J Med*. 2009;361:1139-1151.

for warfarin therapy, such as alcoholism, a history of canceling healthcare visits, an unwillingness to participate in consistent INR testing, and potential for drug interactions.⁷ Because aspirin (81-324 mg daily) is the usual care for patients who are not good candidates for warfarin therapy, the patients received aspirin or apixaban (5 mg twice daily).

After a median follow-up of 1 year, the primary endpoints (ie, stroke or systemic embolic event) were 1.6% in the apixaban group versus 3.6% in the aspirin group, a reduction of more than 50% by apixaban relative to aspirin.⁶ Relative risk reductions for the primary endpoint and various others are shown in **Table 2**. There was a significant increase in minor bleeding with apixaban (5.2% vs 4.1%; $P = .04$), but these events generally did not require intervention or result in discontinuation. Apixaban was well tolerated, as evidenced by the absence of liver toxicity.

Rivaroxaban is another factor Xa inhibitor that is currently under investigation in moderate-to-high-risk patients with AF; the Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study will determine the efficacy and safety of rivaroxaban compared with warfarin for the prevention of thromboembolism.⁸ During studies of venous thromboembolism prevention in orthopedic surgery patients, rivaroxaban demonstrated no food-drug interactions, and it has shown

little tendency toward drug-drug interactions, including interactions with digoxin, aspirin, or nonsteroidal anti-inflammatory drugs, suggesting little need for monitoring with this agent.^{12,13}

The selective, direct factor Xa inhibitor edoxaban is also currently being studied in comparison with warfarin for the prevention of stroke and systemic embolism in AF patients. The Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation – Thrombolysis in Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) is a large, phase 3, randomized, double-blind, double-dummy, multinational, noninferiority trial being conducted in patients with electrical documentation of AF lasting less than 12 months and a CHADS₂ (congestive heart failure, hypertension, age at least 75 years, diabetes mellitus, stroke) score of at least 2.⁹ The safety of 4 fixed-dose regimens

of edoxaban was previously compared with dose-adjusted warfarin therapy (INR 2.0-3.0) in patients with nonvalvular AF over a 3-month period.¹⁴ At the end of that study, the safety profiles of edoxaban 30 mg and 60 mg once daily were similar to warfarin. Major plus clinically relevant bleeding occurred in 3.2% of patients randomized to warfarin, 3.8% of patients using edoxaban 60 mg once daily, and 3.0% of patients using edoxaban 30 mg once daily. There were no significant differences in hepatic enzyme elevations or bilirubin values among the groups.

Warfarin Therapy Versus New and Emerging Agents: Role of INR Control

It is anticipated that the low bleeding risk associated with dabigatran and emerging factor Xa inhibitors will bring greater attention to the role of consistency in INR monitoring and dose adjustment for patients with AF currently using warfarin. Consistency in maintaining an INR between 2.0 and 3.0 will be a key consideration in determining whether a patient with AF may benefit from using a newer agent with a lower bleeding risk. The post hoc analysis mentioned above that examined INR control at individual RE-LY study sites found that dabigatran 150 mg was associated with significantly fewer major bleeding events than warfarin at the study sites having the poorest INR control. At study sites having better INR control, the

■ **Table 2.** AVERROES Outcomes: Stroke and Bleeding Events in Patients With Atrial Fibrillation⁶

Outcome	Apixaban Versus Aspirin ^a		
	RR	95% CI	P
Stroke or Systemic Embolic Event (SEE)	0.46	0.33-0.64	<.001
Stroke	0.48	0.34-0.68	<.001
Ischemic	0.38	0.26-0.56	<.001
Hemorrhagic	1.01	0.38-2.68	.99
Type Not Determined	1.99	0.60-6.62	.26
SEE	0.15	0.03-0.69	.01
Bleeding Events			
Major Bleeding	1.14	0.74-1.75	.56
Clinically Relevant, Nonmajor Bleeding	1.18	0.88-1.58	.28
Minor Bleeding	1.27	1.01-1.61	.04
Fatal Bleeding Event	0.84	0.26-2.75	.77
Intracranial Bleeding	1.09	0.50-2.39	.83

AVERROES indicates Apixaban versus Acetylsalicylic Acid to Prevent Strokes; CI, confidence interval; RR, relative risk.
^aApixaban 5 mg twice daily; aspirin 81-324 mg daily.
 Adapted from Connolly S. European Society of Cardiology 2010; August 28-September 1, 2010; Stockholm, Sweden.

incidence of major bleeding events was similar between dabigatran 150 mg and warfarin.¹¹ The rates of major bleeding associated with dabigatran 110 mg were significantly lower than those with warfarin, irrespective of TTR. In contrast to the primary and secondary outcomes of the study, examination of other outcomes including cardiovascular events and total mortality revealed significant interactions with the TTR. For vascular events, hemorrhagic events, and mortality, the advantages of dabigatran were greater at sites with poor INR control compared with those with good INR control. For this reason, local standards of care can be expected to determine the degree of benefit derived from newer anticoagulant agents compared with warfarin therapy.

The Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, currently under way, will provide a comparison of apixaban and warfarin in stroke prevention in AF.¹⁵ Similarly, the ROCKET-AF study will compare rivaroxaban with warfarin in patients with AF who are at high risk of stroke.⁸ Overall, local standards of care are expected to significantly affect the benefits of using new treatment alternatives.

Case Study Discussion: Lucia A.

Lucia A. is a 76-year-old Hispanic woman who was recently diagnosed with AF. She is a Medicare patient. Her medical history includes treatment for hypertension (fixed-

dose combination antihypertensive, hydrochlorothiazide/lisinopril 12.5 mg/20 mg once daily). Her blood pressure is 143/84 mm Hg. Lucia lives alone, but she is visited daily by her daughter or granddaughter (who both live nearby). AF raises Lucia's risk of stroke by up to 5-fold. Lucia's CHADS₂ score adds up to at least 2 (ie, age of 76 years = 1 point, plus hypertension = 1 point), and this score carries an expected annual stroke rate of 2.54 events per 100 person-years.¹⁶ Given her level of risk for stroke, she should clearly consider anticoagulation therapy. For an AF patient with a CHADS₂ score of 2, warfarin is expected to substantially reduce the projected annual rate of thromboembolism from 2.54 to 1.26 events per 100 person-years.¹⁶ Aspirin therapy is not expected to provide adequate stroke protection in a patient with a CHADS₂ score of 2 and is not recommended for her level of risk. Lucia has no definite contraindications for warfarin therapy.¹⁷ Lucia and her clinician must consider the anticipated benefit against the risks of warfarin therapy. Lucia's ability to take warfarin safely depends on her ability to have regular INR checks and to accurately follow instructions to make changes to warfarin doses when instructed by her anticoagulation clinic. Although Lucia lives alone, she is in close daily contact with her family; their commitment and level of involvement in her care should be ascertained before making a decision to use warfarin. One important consideration is Lucia's risk and her history of falling. Does she have limited mobility? Finally, depending on future availability and affordability, she may

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want to consider a direct thrombin inhibitor or a factor Xa inhibitor if she is reluctant to begin warfarin therapy. For example, the US Food and Drug Administration (FDA) has recently approved dabigatran for stroke prevention in patients with AF.¹⁸

Conclusion

Warfarin is clearly effective in preventing strokes in patients with AF who are at high risk, but it can also provide significant protection in patients with a low risk of stroke. A recent comparison of warfarin therapy with a regimen of clopidogrel plus aspirin reported treatment-specific rates of stroke and major bleeding for patients with AF and a CHADS₂ score of 1 and compared the results in patients with a CHADS₂ score greater than 1.¹⁹ The study found that even patients with a low risk of stroke (ie, CHADS₂ = 1) derived a modest (<1% per year) but significant absolute reduction in stroke accompanied by low rates of major hemorrhage with warfarin. The European Society of Cardiology has recently begun to recommend warfarin use in patients with AF and CHADS₂ scores as low as 1, in contrast to the prior recommendation of equivalent consideration of aspirin.¹⁷ However, a number of factors, including significant variability in dose-response, drug and dietary interactions, and a narrow therapeutic window, have influenced some clinicians to underuse warfarin in this patient population.²⁰ Underuse has subsequently driven a search for alternative orally administered antithrombotic agents that couple efficacy with a lower risk of major bleeding. Several new and emerging anticoagulant agents, such as the factor Xa inhibitors apixaban and rivaroxaban, are in the late stages of development. The direct thrombin inhibitor dabigatran has recently been approved by the FDA for stroke prophylaxis in AF.¹⁸ Results from clinical trials suggest that dabigatran may provide a safe, effective alternative to warfarin in AF. Apixaban was superior to aspirin for stroke prevention in AF⁶; whether it is a viable alternative to warfarin in patients with AF remains to be seen. Trials designed to make clinical comparisons between warfarin and rivaroxaban in AF are under way.⁸ The possibility of eliminating the need for continual INR testing is expected to offset a substantial portion of the cost of these new agents.

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Authorship Information: Concept and design (CPC, ECS); drafting of the manuscript (ECS); critical revision of the manuscript for important intellectual content (CPC, ECS); administrative, technical, or logistical support (ECS); and supervision (CPC, ECS).

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