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.

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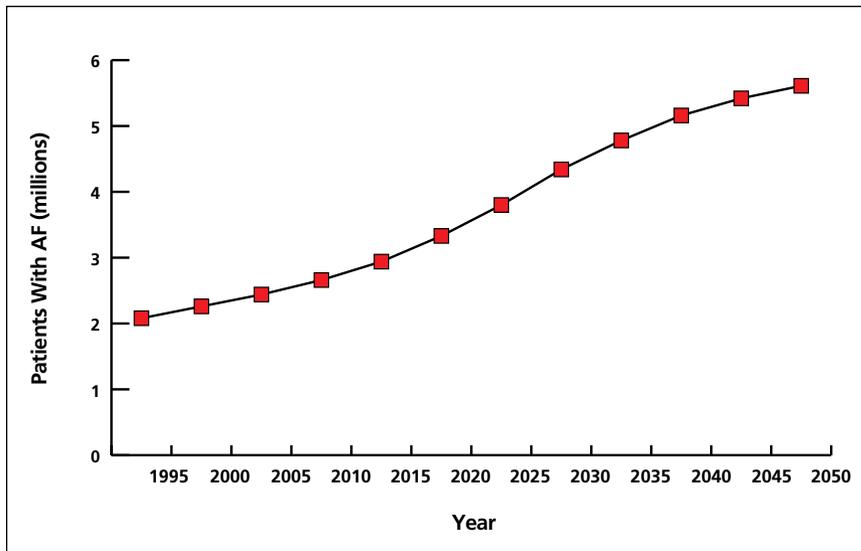
Figure 1. *Projected number of adults with atrial fibrillation (AF) in the United States between 1995 and 2050. An estimated 6 million Americans will be affected by AF by 2050. Adapted from Go et al.[6]*

er 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]

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 high-

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

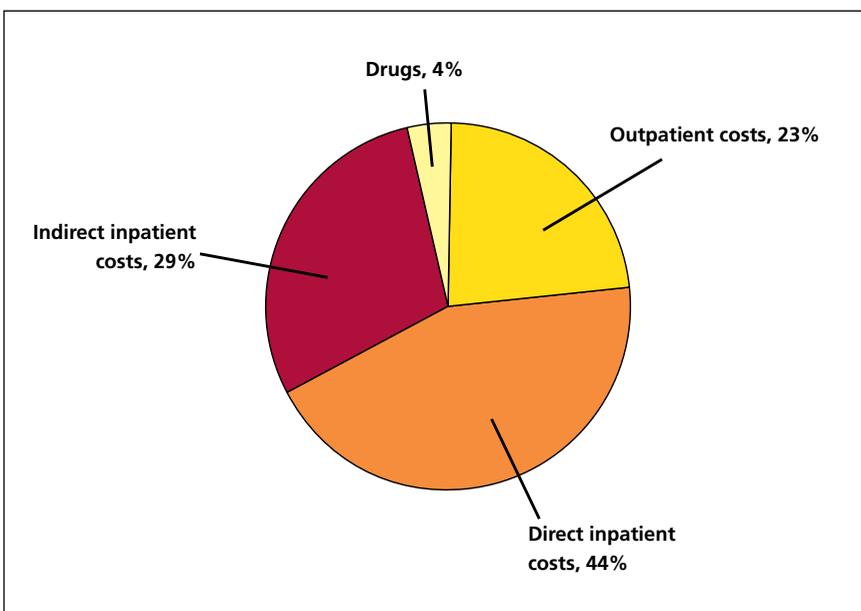Figure 2. *Distribution of direct and indirect costs for treating atrial fibrillation (AF). Total annual treatment costs for AF are approximately $6.65 billion, including $3 billion for hospitalizations directly attributable to an AF diagnosis, $1.95 billion for inpatient management of AF as a comorbid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

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]

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 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.

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.

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

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

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

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]

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-

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.

References

1. Atrial fibrillation fact sheet. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/docs/fs_atrial_fibrillation.pdf. February 2010. Accessed August 13, 2012.

2. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol*. 2009;104(11):1534-1539.

3. Roger VL, Go AS, Lloyd-Jones DM, et al; for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125(1):e2-e220.

4. Division of cardiovascular medicine strategic plan. National Heart, Lung, and Blood Institute Web site. http://www.nhlbi.nih.gov/about/dcvd/sp/dcvd-sp-goal-2.3b.htm. Accessed April 10, 2012.

5. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes*. 2011;4(3):313-320.

6. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study. *JAMA*. 2001;285(18):2370-2375.

7. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health*. 2006;9(5):348-356.

8. Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC. The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace*. 2011;13(10):1375-1385.

9. Rohrbacker NJ, Kleinman NL, White SA, March JL, Reynolds MR. The burden of atrial fibrillation and other cardiac arrhythmias in an employed population: associated costs, absences, and objective productivity loss. *J Occup Environ Med*. 2010;52(4):383-391.

10. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. *Neurology*. 1978;28(10):973-977.

11. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22(3):312-318.

12. Knuiman MW, Vu HT. Risk factors for stroke mortality in men and women: the Busselton Study. *J Cardiovasc Risk*. 1996;3(5):447-452.

13. Fisher CM. Reducing the risks of cerebral embolism. *Geriatrics*. 1979;34(2):59-61,65-66.

14. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke*. 2005;36(6):1115-1119.

15. Cardiogenic brain embolism: the second report of the Cerebral Embolism Task Force [published correction appears in *Arch Neurol*. 1989;46(10):1079]. *Arch Neurol*. 1989;46(7):727-743.

16. Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation: the Copenhagen Stroke Study. *Stroke*. 1996;27(10):1765-1769.

17. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline). *Circulation*. 2011;123(10):104-123.

18. Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. *Ann Intern Med*. 1999;131(9):688-695.

19. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288(19):2441-2448.

20. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes from predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864-2870.

21. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137(2):263-272.

22. Pisters R, Lane DA, Nieuwelaat R, et al. A novel, user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1100.

23. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367(9526):1903-1912.

24. McCormick D, Gurwitz JH, Goldberg RJ, et al. Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting. *Arch Intern Med*. 2001;161(20):2458-2463.

25. Fang MC, Stafford RS, Ruskin JN, Singer DE. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. *Arch Intern Med*. 2004;164(1):55-60.

26. Waldo AL, Becker RC, Tapson VF, Colgan KJ; NABOR Steering Committee. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol*. 2005;46(9):1729-1736.

27. Tapson VF, Hyers TM, Waldo AL, et al; NABOR (National Anticoagulation Benchmark and Outcomes Report) Steering Committee. Antithrombotic therapy practices in US hospitals in an era of practice guidelines. *Arch Intern Med*. 2005;165(13):1458-1464.

28. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123(7):638-645.

29. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm*. 2009;15(3):244-252.

30. Ahmad Y, Lip GYH. Stroke prevention in atrial fibrillation: where are we now? *Clin Med Insights Cardiol*. 2012;6:65-78.

31. McDonald KM, Sundaram V, Bravata DM, et al. Care coordination. In: *Agency for Healthcare Research and Quality. Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies*. Vol 7. Rockville, MD: US Dept of Health and Human Services; 2007. AHRQ Publication No. 04(07)-0051-7. http://www.ahrq.gov/downloads/pub/evidence/pdf/caregap/caregap.pdf. Accessed April 10, 2012.

32. Arepally G, Bauer KA, Bhatt DL, et al. The use of antithrombotic therapies in the prevention and treatment of arterial and venous thrombosis: a survey of current knowledge and practice supporting the need for clinical education. *Crit Pathw Cardiol*. 2010;9(1):41-48.

33. Connolly SJ, Ezekowitz MD, Yusuf S, et al; and RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation [published correction appears in *N Engl J Med*. 2010; 363(19):1875-1876]. *N Engl J Med*. 2009;361(12):1139-1151.

34. Patel MR, Mahaffey KW, Garg J, et al; and ROCK-ET AF Steering Committee for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

35. Granger CB, Alexander JH, McMurray JJ, et al; for ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

36. Rai R, Sprengeler PA, Elrod KC, Young WB. Perspectives on factor Xa inhibition. *Curr Med Chem*. 2001;8(2):101-119.

37. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther*. 2005;78(4):412-421.

38. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. December 2011.

39. He K, Luettgen JM, Zhang D, et al. Preclinical pharmacokinetics and pharmacodynamics of apixaban, a potent and selective factor Xa inhibitor [published online ahead of print April 2, 2011]. *Eur J Drug Metab Pharmacokinet*. 2011;36(3):129-139.

40. Samama MM, Gerotziafas GT. Newer anticoagulants in 2009. *J Thromb Thrombolysis*. 2010;29(1):92-104.

41. Furugohri T, Isobe K, Honda Y, et al. DU-176b, a potent and orally active factor Xa inhibitor: in vitro and in vivo pharmacological profiles. *J Thromb Haemost*. 2008;6(9):1542-1549.

42. Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. *N Engl J Med*. 2005;353(10):1028-1040.

43. Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2012.

44. Hankey GJ, Eikelboom JW. Dabigatran exilate: a new oral thrombin inhibitor. *Circulation*. 2011;123 (13):1436-1450.

45. Granger CB, Armaganijan LV. Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke and thromboembolism. *Circulation*. 2012;125(1):159-164.

46. Enthoven AC. Integrated delivery systems: the cure for fragmentation. *Am J Manag Care*. 2009;15 (suppl 10):S284-S290.

47. American Osteopathic Association, American Academy of Family Physicians, American Academy of Pediatrics, and American College of Physicians. Joint principles of the patient-centered medical home. March 2007. http://www.medicalhomeinfo.org/joint%20Statement.pdf. Accessed April 10, 2012.