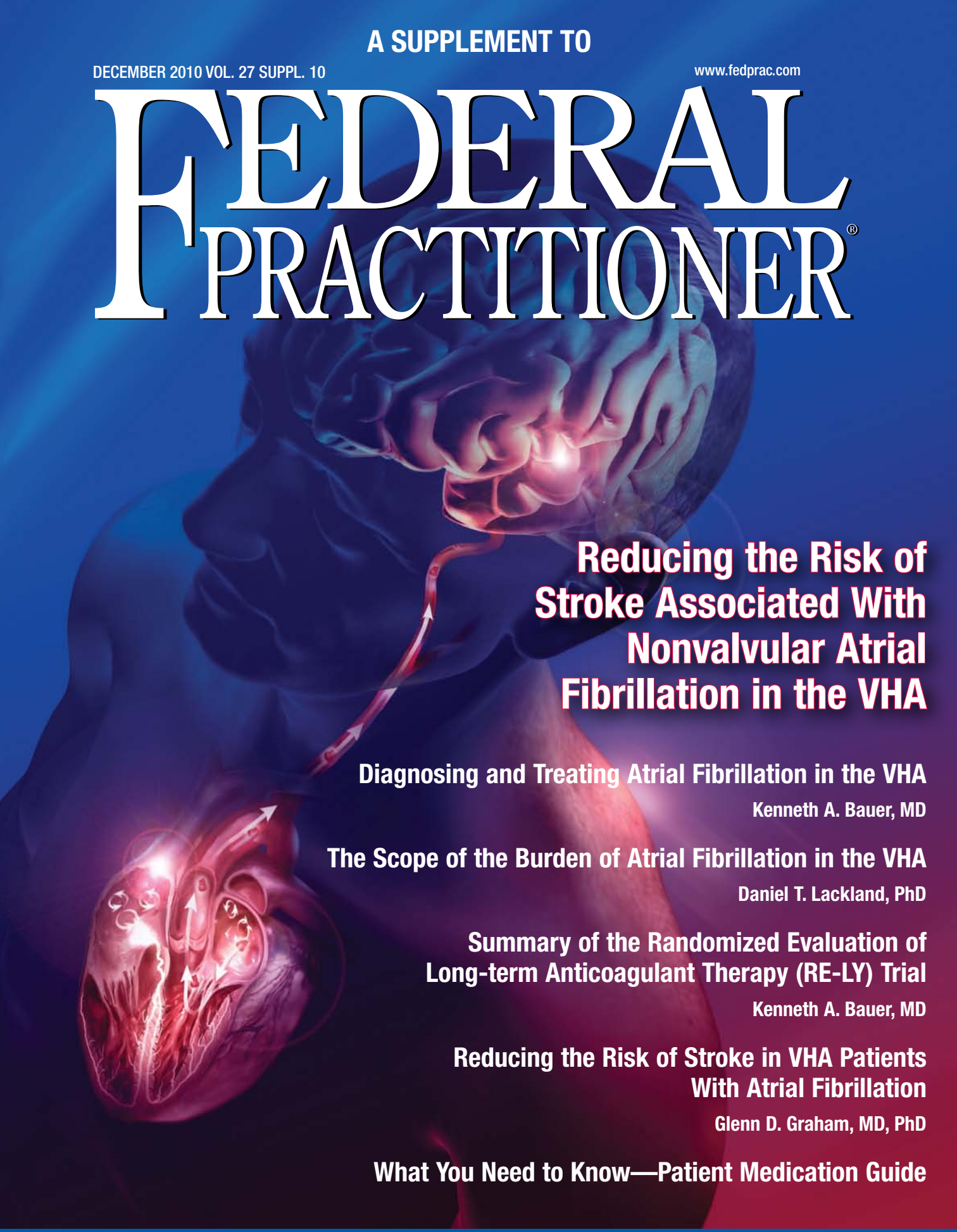
A SUPPLEMENT TO

DECEMBER 2010 VOL. 27 SUPPL. 10

www.fedprac.com

FEDERAL PRACTITIONER®



Reducing the Risk of Stroke Associated With Nonvalvular Atrial Fibrillation in the VHA

Support for this supplement was provided by Boehringer Ingelheim Pharmaceuticals, Inc.
PX78540PROF

The Scope of the Burden of Atrial Fibrillation in the VHA

Daniel T. Lackland, PhD

Hospitalizations due to stroke associated with atrial fibrillation represent a significant burden to the VHA, yet only half of patients with atrial fibrillation are prescribed an anticoagulant.

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia, with an estimated prevalence of approximately 2.7 million in the United States in 2010.[1] The prevalence of AF increases with age, from 0.1% in individuals younger than age 55 years to 9% among those aged 80 years or older, and is higher in men than in women.[1,2] Hospitalization for patients with AF has increased by 66% over the past 20 years, and prevalence is projected to rise further in the coming decades as the population ages.[1–3]

In the VHA patient population (3.4 million people), 92% are male, with an average age of 58 years.[4] Nearly 75% have at least 1 prevalent chronic disease or condition (such as hypertension, diabetes, AF, cardiovascular disease, cerebrovascular disease, or stroke), and 35% have 3 or more conditions.[4] Thus, AF presents a significant problem in the VHA population.

Although AF often is asymptomatic, it is an important independent risk factor for stroke, heart failure, and all-cause mortality in the general population.[5] In the Framingham study, patients with AF were almost 5 times more likely to experience a stroke than patients without AF over a 2-year period (Figure 1).[6] The percentage of strokes attributable to AF rose from 1.5% for participants aged 50 to 59 years to 23.5% for those aged 80 to 89 years.[6] On average, 20% of all strokes were attributable to AF.[6]

This article reviews information pertaining to the risk of stroke associated with AF in the general population and the VHA population. It also addresses the financial burden of events in VHA patients related to stroke as a result of AF.

RISK OF STROKE IN PATIENTS WITH AF

Stroke accounts for approximately 1 of every 18 deaths in the U.S. population.[7] Several risk factors are significant independent predictors of stroke in patients with AF, including increased age, previous transient ischemic attack or stroke, and comorbid conditions (such as diabetes, hypertension, and congestive heart failure) (Figure 2).[8] Between 15% and 30% of stroke survivors are left with significant severe disabilities.[3] Functional and mental impairments are associated with all levels of stroke severity.

In the VHA population, stroke is a major cause of morbidity and mortality, with at least 15,000 veteran patients hospitalized as a result of new strokes every year.[9] These characteristics are especially prevalent in the VHA population: mostly middle-aged males with significant comorbid conditions (it has been reported that 2.1% have cerebrovascular disease or previous stroke, 15.6% have diabetes, 36.8% have hypertension, and 4.7% have congestive heart failure).[4]

FINANCIAL BURDEN OF STROKE IN THE VHA

The burden that stroke imposes on the U.S. health care system is substantial. The estimated direct and indirect costs of stroke will reach $73.7 billion in 2010.[7]

In the VHA, the cost of stroke is approximately $111 million for inpatient care, $75 million for postacute inpatient care, and $88 million for follow-up care over the duration of 6 months poststroke.[9] Stroke patients represent more than 10% of the total patient population in the VHA, and the cost for treating each of these patients is more than 3 times higher than the overall average cost for VHA patients.[3]

ANTICOAGULATION FOR STROKE PREVENTION AND AF

Anticoagulation is an important treatment option for adults with AF.[2] Anticoagulation with a vitamin K antagonist, such as warfarin, is effective for reducing the risk of stroke in patients with AF. In a pooled analysis of 5 studies in the general population, warfarin reduced the risk of stroke by up to 68% compared with no treatment.[8]

Guidelines for antithrombotic therapy in AF, published in 2008 by

Dr. Lackland is a professor of epidemiology in the department of biometry and epidemiology at the Medical University of South Carolina, Charleston.

Please see Pradaxa® (dabigatran etexilate mesylate) capsules Important Safety Information on page 13 and full Prescribing Information on page 21.

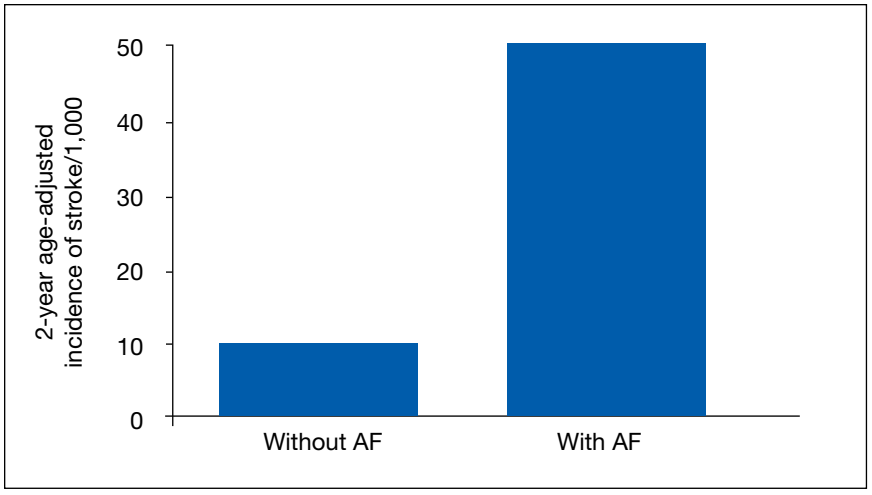


Figure 1. Incidence of stroke over 2 years according to the presence or absence of atrial fibrillation (AF). Adapted with permission from Wolf PA et al. *Stroke*. 1991;22(8):983–988.[6]

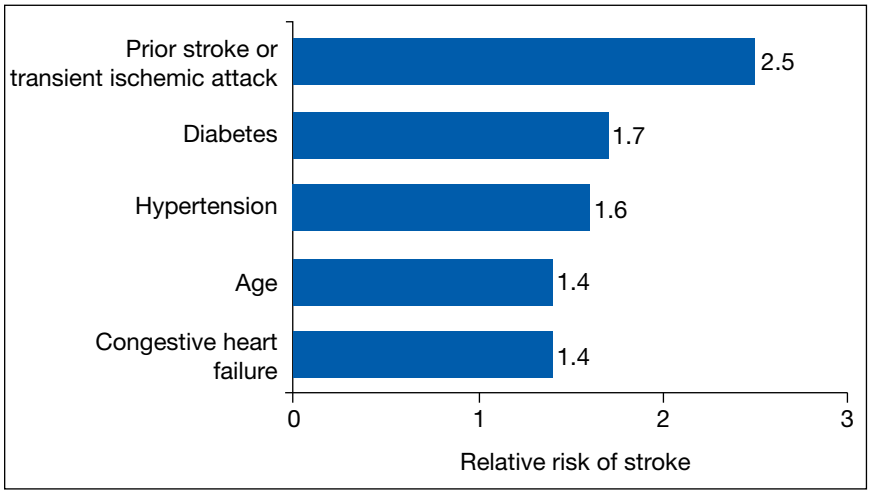


Figure 2. Relative risk of stroke associated with each condition in the setting of nonvalvular atrial fibrillation.[8]

the American College of Chest Physicians (ACCP), are based on the patient's level of stroke risk in the absence of therapy and reflect the hierarchy in therapeutic efficacy of the various agents available.[10] A vitamin K antagonist is recommended for high-risk patients with AF plus 2 or more risk factors, given their high risk of future stroke. Warfarin is generally targeted at an international normalized ratio (INR) of 2.5, with a range of 2 to 3.

Underuse of antithrombotic therapy

Despite guideline recommendations and extensive evidence from randomized clinical trials in favor of anticoagulation therapy for stroke prevention in patients with AF, anticoagulation is underused in the U.S. population. Data from a large U.S. health plan (n = 116,969) revealed that only 52% of patients with AF received anticoagulation with warfarin.[11] Similarly, among more than 17,000 Medicare beneficiaries hospitalized with AF, warfarin was prescribed or planned for only 49% of the overall patient group at discharge, and in less than two-thirds (65%) of those considered "ideal" candidates ($CHADS_2$ [congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack] score > 1 and low risk of bleeding).[12]

In a study of 405 elderly patients hospitalized with AF, factors associated with a real or perceived increase in bleeding risk were among the strongest negative predictors of warfarin use and included a history of hemorrhage, a previous fall, and cognitive impairment or dementia.[13] Age 75 years or older also was a significant deterrent to warfarin use, even though the 2008 ACCP guidelines emphasize that this age group has an increased risk of stroke.[10]

Warfarin use in the VHA shows similar patterns. For example, warfarin was prescribed for 504 of 998 patients (51%) with AF in a 2-year retrospective study at a VHA medical center.[14] In this study, warfarin was considered not indicated in 200 patients because they had transient (n = 192) or lone AF (n = 8). Of the remaining patients who were not prescribed warfarin, almost all (98%) had at least 1 risk factor for stroke, and 63% had 3 or more risk factors.

Several factors may partially explain the suboptimal use of warfarin in patients with AF, especially the fear of increased bleeding risk. In the VHA study cited above, 75% of patients had at least 1 contraindication to warfarin (including a history of major bleeding) and the authors suggested that the perceived risk of

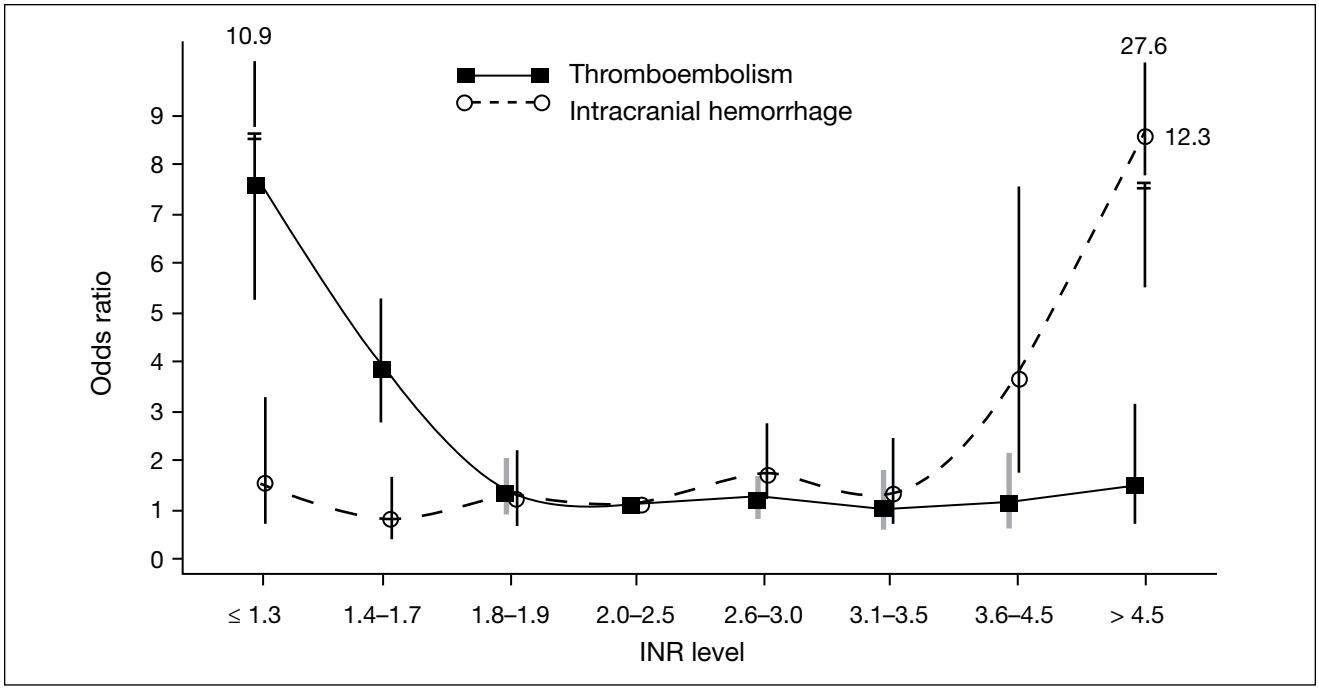


Figure 3. Risk of thromboembolism and intracranial hemorrhage according to international normalized ratio (INR) in adults with atrial fibrillation. Reprinted with permission from Singer DE et al. *Circ Cardiovasc Qual Outcomes*. 2009;2(4):297–304.[16]

bleeding may have outweighed the benefits of anticoagulation for many clinicians.[14] Other reasons for not prescribing warfarin included limited life expectancy, risk of falling, planned surgery, alcohol abuse, or dementia/poor adherence.[14]

The effect of age was even more remarkable in a study of 2,217 VHA patients with AF: The likelihood of anticoagulant use decreased by 14% for each decade of life, even after controlling for other risk variables.[15] Overall, only 34% of patients with AF in this study received a prescription for warfarin.

Warfarin therapeutic range

As suggested, warfarin should be maintained in the therapeutic range to derive the benefits of therapy.[16] More specifically, an INR between 2 and 3 maintains the optimal balance between reducing the risk of stroke and suppressing the risk of intracranial hemorrhage, as shown in a study of 9,217 patients with AF (Figure 3).[16] In general, INR levels less than 2 do not improve safety, and INR levels greater than 3 do not improve efficacy. Increasing the time a patient's INR remains within target therapeutic range has been associated with better stroke control, lower risk of bleeding, and reduced health care costs.[17] When measured as percentage of time in therapeutic range, however, warfarin therapy in patients with AF often is insufficient to achieve optimal stroke prevention.[17]

PROJECTED BENEFITS OF OPTIMAL WARFARIN THERAPY

Appropriate warfarin use and anticoagulation management can significantly affect clinical outcomes and associated health care costs. An economic model was constructed to examine the risks and benefits of different anticoagulation scenarios in patients with AF in the United States.[18] Approximately 1.3 million patients are untreated currently; but if half of these were treated with anticoagulation, more than 19,000 strokes would be prevented annually and $1.1 billion would be saved (Figure 4).[18] Fewer than 1,000 extra bleeding episodes due to warfarin would require treatment. Furthermore, if half of the patients currently taking warfarin received appropriate treatment, another 9,000 strokes might be prevented, 29,000 bleeding episodes might never occur, and $1.3 billion could be saved.

CONCLUSIONS

In the general population, AF is associated with a 5-fold increase in the risk of stroke, independent of other risk factors such as older age, prior

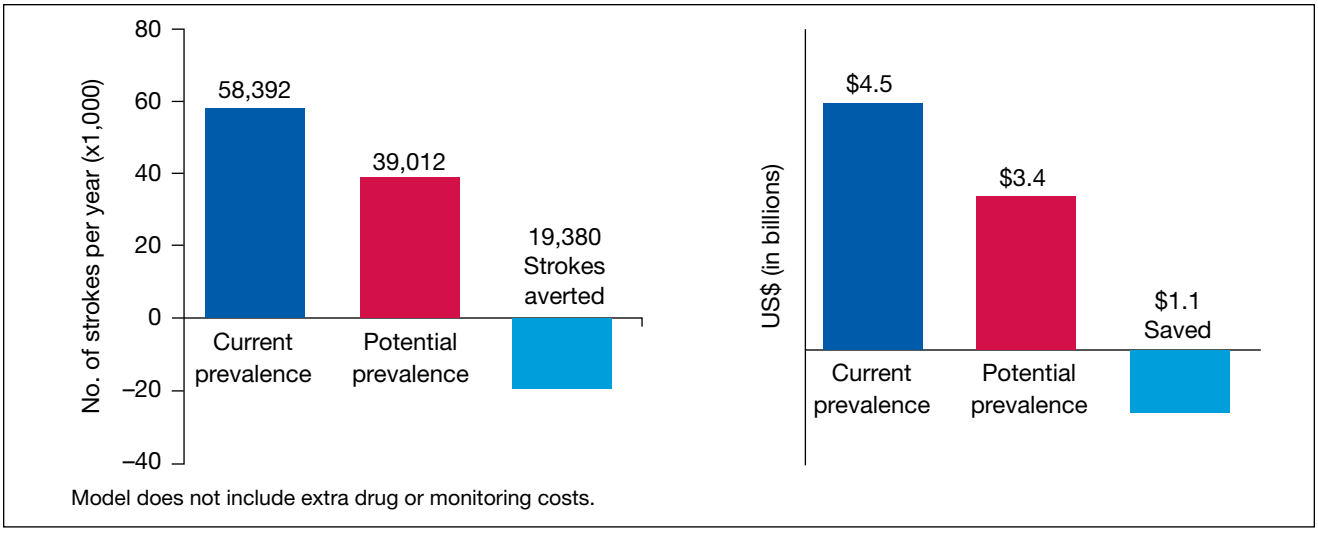


Figure 4. Estimated health and economic effects of increasing the prevalence of anticoagulation use in patients with nonvalvular atrial fibrillation.[18]

stroke, hypertension, or heart failure.[6] Anticoagulation therapy with warfarin, if INRs are maintained in therapeutic range, provides effective stroke prevention, but patients whose INRs are out of therapeutic range have an increased risk of stroke or hemorrhage.

Suboptimal use and management of warfarin in patients with AF may result in a considerable economic burden on the VHA.[3] Implementation of quality measures in the VHA should improve the prevalence and quality of anticoagulation for stroke prevention in patients with AF (see the last article in this supplement for more information on quality measures in the VHA).[19]

Author Disclosures

Dr. Lackland is a consultant for Boehringer Ingelheim Pharmaceuticals, Inc., and a member of the speakers bureau for sanofi-aventis U.S.

REFERENCES

1. 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.
2. Estes NA III, Halperin JL, Calkins H, et al. ACC/AHA/Physician Consortium 2008 clinical performance measures for adults with nonvalvular atrial fibrillation or atrial flutter: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and the Physician Consortium for Performance Improvement (Writing Committee to Develop Clinical Performance Measures for Atrial Fibrillation): Developed in collaboration with the Heart Rhythm Society. *Circulation.* 2008;117(8):1101–1120.
3. Williams LS; US Department of Veterans Affairs Quality Enhancement Research Initiative. Stroke Strategic Plan 2008. http://www.queri.research.va.gov/about/strategic_plans/str.pdf. Published December 2008. Accessed July 14, 2010.
4. VA Benefits & Health Care Utilization Pocket Guide. http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=2234. Published May 14, 2010. Accessed July 14, 2010.
5. Yu W, Ravelo A, Wagner TH, et al. Prevalence and costs of chronic conditions in the VA health care system. *Med Care Res Rev.* 2003;60(suppl 3):146S–167S.
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke.* 1991;22(8):983–988.
7. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: A report from the American Heart Association. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2010;121(7):e46–e215.
8. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154(13):1449–1457.
9. US Department of Veterans Affairs Quality Enhancement Research Initiative. Stroke Fact Sheet. http://www.queri.research.va.gov/about/factsheets/stroke_factsheet.pdf. Published June 2010. Accessed July 14, 2010.
10. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest.* 2008;133(suppl 6):546S–592S.
11. Walker AM, Bennett D. Epidemiology and outcomes in patients with atrial fibrillation in the United States. *Heart Rhythm.* 2008;5(10):1365–1372.
12. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke.* 2006;37(4):1070–1074.
13. Hylek EM, D'Antonio J, Evans-Molina C, Shea C, Henault LE, Regan S. Translating the results of randomized trials into clinical practice: The challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. *Stroke.* 2006;37(4):1075–1080.
14. Bradley BC, Perdue KS, Tisdel KA, Gilligan DM. Frequency of anticoagulation for atrial fibrillation and reasons for its non-use at a Veterans Affairs medical center. *Am J Cardiol.* 2000;85(5):568–572.
15. Brophy MT, Snyder KE, Gaehde S, Ives C, Gagnon D, Fiore LD. Anticoagulant use for atrial fibrillation in the elderly. *J Am Geriatr Soc.* 2004;52(7):1151–1156.
16. Singer DE, Chang Y, Fang MC, et al. Should patient characteristics influence target anticoagulation intensity for stroke prevention in nonvalvular atrial fibrillation? The ATRIA study. *Circ Cardiovasc Qual Outcomes.* 2009;2(4):297–304.
17. 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.
18. Caro JJ. An economic model of stroke in atrial fibrillation: The cost of suboptimal oral anticoagulation. *Am J Manag Care.* 2004;10(suppl 14):S451–S461.
19. US Department of Veterans Affairs; Veterans Health Administration. VHA Directive 2010-020: Anticoagulation Therapy Management. http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=2234. Published May 14, 2010. Accessed July 14, 2010.