

Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Patients With Atrial Fibrillation and Prior Stroke or Transient Ischemic Attack

Hooman Kamel, MD; S. Claiborne Johnston, MD, PhD;
J. Donald Easton, MD; Anthony S. Kim, MD, MAS

Background and Purpose—The cost-effectiveness of dabigatran for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack has not been directly assessed.

Methods—A Markov decision model was constructed using data from the Randomized Evaluation of Long-Term Therapy (RE-LY) trial, other trials of warfarin therapy for atrial fibrillation, and the published cost of dabigatran. We compared the cost and quality-adjusted life expectancy associated with 150 mg dabigatran twice daily versus warfarin therapy targeted to an international normalized ratio of 2 to 3. The target population was a cohort of patients aged ≥ 70 years with nonvalvular atrial fibrillation, prior stroke or transient ischemic attack, and no contraindication to anticoagulation.

Results—In the base case, dabigatran was associated with 4.27 quality-adjusted life-years compared with 3.91 quality-adjusted life-years with warfarin. Dabigatran provided 0.36 additional quality-adjusted life-years at a cost of \$9000, yielding an incremental cost-effectiveness ratio of \$25 000. In sensitivity analyses, the cost-effectiveness of dabigatran was inversely related to the quality of international normalized ratio control achieved with warfarin therapy. In Monte Carlo analysis, dabigatran was cost-effective in 57% of simulations using a threshold of \$50 000 per quality-adjusted life-year and 78% of simulations using a threshold of \$100 000 per quality-adjusted life-year.

Conclusions—Dabigatran appears to be cost-effective relative to warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. Our analysis is limited by its reliance on data from a substudy of a single randomized trial, and our results may not apply in settings with uncommonly good international normalized ratio control using warfarin. (*Stroke*. 2012;43:881-883.)

Key Words: anticoagulation ■ atrial fibrillation ■ cost-effectiveness ■ embolic stroke

Warfarin is superior to antiplatelet agents for secondary stroke prevention in patients with atrial fibrillation (AF).¹ However, warfarin has significant limitations, and only two thirds of eligible patients with AF receive warfarin when indicated.²

Dabigatran is the first warfarin alternative approved for thromboembolism prevention in patients with AF, but its promise is tempered by concerns about cost (\$6.75 per day³). However, although warfarin tablets are inexpensive, warfarin therapy entails costs associated with monitoring and complications.⁴ Two analyses of dabigatran versus warfarin in patients with AF regardless of prior stroke or transient ischemic attack (TIA) provided different estimates of dabigatran's incremental cost-effectiveness.^{5,6} Furthermore, dabigatran's cost-effectiveness in patients with stroke or TIA may differ from these estimates because such patients have different characteristics. Although clinicians will increasingly need

to choose between warfarin or dabigatran for secondary stroke prevention, specific cost-effectiveness data in this population do not yet exist. We therefore conducted a cost-effectiveness analysis of dabigatran compared with warfarin in patients with AF and a history of stroke or TIA.

Methods

Decision Model

Using a Markov model,⁷ we compared 2 strategies: adjusted-dose warfarin with an international normalized ratio target of 2 to 3 versus 150 mg dabigatran twice daily. Our base case was a hypothetical cohort of 70-year-old patients with nonvalvular AF, prior stroke or TIA, and no contraindications to anticoagulation.

We included the following health states in our base case: no disability, ischemic stroke, intracerebral hemorrhage, recurrent or combined stroke and/or intracerebral hemorrhage, and death (online-only Supplemental Figure, <http://stroke.ahajournals.org>). A temporary (1-month) cost and decrement in the quality of life (utility) was assumed for patients with TIA, nondisabling stroke, myocardial

Received October 6, 2011; final revision received October 26, 2011; accepted October 27, 2011.

From the Department of Neurology and Neuroscience (H.K.), Weill Cornell Medical College, New York, NY; and the Departments of Neurology (S.C.J., J.D.E., A.S.K.) and Epidemiology and Biostatistics (S.C.J.), University of California, San Francisco, CA.

The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.641027/-/DC1>.

Correspondence to Hooman Kamel, MD, 525 East 68th Street, F610, New York, NY 10065. E-mail hok9010@med.cornell.edu

© 2012 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.111.641027

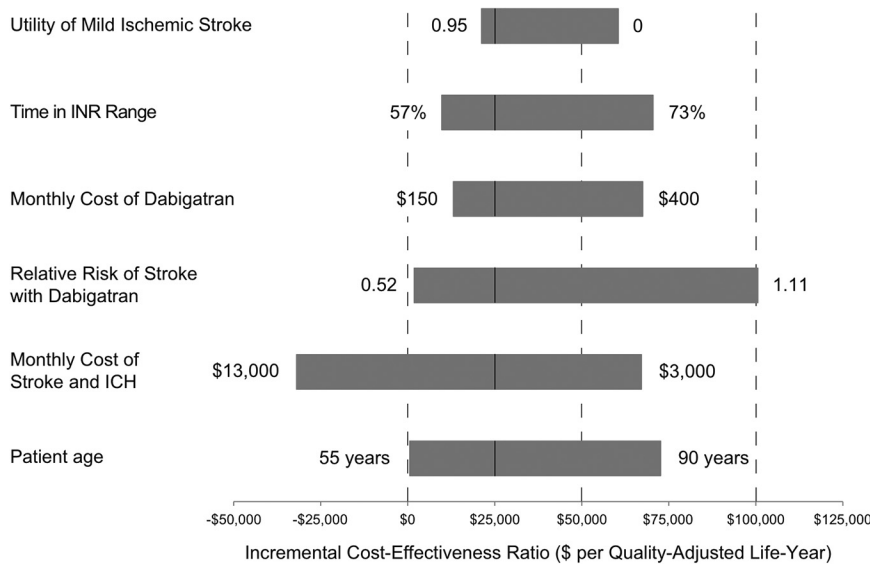


Figure. Results of sensitivity analyses of variables with significant impact on the incremental cost-effectiveness of dabigatran compared with warfarin in patients with atrial fibrillation and prior stroke or transient ischemic attack.

infarction, or major extracranial hemorrhage. We quantified quality-adjusted life expectancy, risks of adverse events, and net costs over a period of 20 years or until death. Costs and life-years were discounted at 3% per year. For both treatments, we report our results in quality-adjusted life-years (QALYs) and 2010 US dollars (rounded to the nearest \$1000). All analyses were performed using TreeAge Pro Suite 2011 (TreeAge Software, Williamstown, MA). Our methods and the reporting of our results are consistent with guidelines for cost-effectiveness analyses.⁸ Full details of our decision model, input variables, and sources can be found in the online-only Supplemental Methods (<http://stroke.ahajournals.org>).

Probability of Adverse Events

The risks of adverse events were based on data from the Randomized Evaluation of Long-Term Therapy (RE-LY) secondary stroke prevention substudy and other trials of warfarin therapy for AF (online-only Supplemental Table). Mortality rates were adjusted for age (beginning at age 70 years), presence of AF and prior stroke or TIA, and type of antithrombotic therapy. We assumed that patients who developed intracerebral hemorrhage stopped anticoagulation and began lifelong aspirin therapy, whereas patients with a major extracranial hemorrhage resumed anticoagulation after 1 month.

Quality-of-Life Estimates

To obtain estimates of quality-adjusted life expectancy, we multiplied the probability of adverse events in our model by their expected utilities. Because no direct data exist regarding the utility of dabigatran, we chose to maintain consistency with prior analyses by assigning it the same utility as ximelagatran, an older direct thrombin inhibitor.⁹

Costs

Our model adopted a societal perspective. The cost of dabigatran therapy was based on its wholesale price and regular office visits for monitoring (Current Procedural Terminology code 99211). The cost of warfarin therapy included Medicare reimbursement for 90 days of anticoagulation management (Current Procedural Terminology code 99363) and 14 international normalized ratio tests. The costs of hospitalization for adverse events were estimated from costs published by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project under the relevant diagnosis-related group. Ongoing costs of care related to adverse events were estimated from the median value of published studies and Medicare reimbursement rates.

Sensitivity Analyses

We performed 1-way sensitivity analyses of all model inputs by varying them over plausible ranges, which were based on the

confidence intervals of inputs derived from the RE-LY substudy or the differences in values reported in published studies. In addition, we performed a probabilistic sensitivity analysis using a first-order Monte Carlo simulation over 10 000 iterations.

Results

Base Case

In our base case, quality-adjusted life expectancy was 4.27 QALYs with dabigatran compared with 3.91 QALYs with warfarin. Dabigatran provided 0.36 additional QALYs at a cost of \$9000, yielding an incremental cost-effectiveness ratio of \$25 000.

Sensitivity Analyses

The most influential variables in our model were the monthly cost of combined or recurrent stroke and/or intracerebral hemorrhage, the starting age of the cohort, the relative risk of stroke with dabigatran compared with warfarin, the cost of dabigatran, the average time in a therapeutic international normalized ratio range for patients receiving warfarin, and the utility of mild ischemic stroke (Figure). Varying other inputs across plausible ranges did not increase the incremental cost-effectiveness ratio associated with dabigatran above \$50 000 per QALY. For a full discussion of the results of our sensitivity analyses, see the online-only Supplemental Results.

Probabilistic Sensitivity Analysis

Using a willingness-to-pay threshold of \$50 000 per QALY, dabigatran was cost-effective in 57% of Monte Carlo simulations. This proportion increased to 78% at a threshold of \$100 000 per QALY.

Discussion

In an analysis using data from a randomized trial, we have found that dabigatran is a cost-effective alternative to warfarin in patients with AF and prior stroke or TIA. The cost-effectiveness of dabigatran appears to depend on the adequacy of warfarin management with a greater advantage for dabigatran in centers with poor international normalized

ratio control in warfarin-treated patients (see online-only Supplemental Discussion).

Our results should be interpreted in light of 2 prior cost-effectiveness analyses of dabigatran in the overall population of patients with AF.^{5,6} Freeman et al estimated an incremental cost-effectiveness ratio of approximately \$12 000 per QALY.⁶ Shah et al used slightly different methodology and found that in patients at high risk of stroke, dabigatran's incremental cost-effectiveness ratio is <\$50 000 per QALY.⁵ We used broadly similar inputs to ensure comparability of our results but made several assumptions that more specifically reflect the natural history of patients with prior stroke and TIA. Combined with these prior studies, our findings confirm that dabigatran appears cost-effective for secondary stroke prevention in patients with AF.

In sensitivity analyses, dabigatran was not cost-effective if its relative risk of stroke compared with warfarin exceeded 0.92, a number within the 95% CI of the RE-LY secondary stroke prevention substudy.¹⁰ This highlights the main limitation of our study, which is the reliance on data from a single trial. As more data emerge from studies of dabigatran and warfarin in patients with stroke or TIA, future analyses will be able to better define the cost-effectiveness of dabigatran. In the meantime, clinicians already face choices between dabigatran and warfarin in this important population, and our findings provide a first approximation of the economic implications of such choices.

Conclusions

Dabigatran is likely to be a cost-effective alternative to warfarin for stroke prevention in typical patients with AF who have had a stroke or TIA. Our results may not apply in

settings with excellent international normalized ratio control using warfarin.

Disclosures

J.D.E. serves on the Steering and Executive Committees of Apixaban for Reduction In Stroke and Other Thromboembolic Events in atrial fibrillation (ARISTOTLE) and on the Data Safety Monitoring Board of Global Study to Assess the Safety and Effectiveness of DU-176b vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48).

References

1. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, 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;367:1903–1912.
2. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke*. 2006;37:1070–1074.
3. Pradaxa prescribing information. US FDA web site. October 19, 2010. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2010/022512s000lbl.pdf. Accessed April 8, 2011.
4. O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *JAMA*. 2005;293:699–706.
5. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation*. 2011;123:2562–2570.
6. Freeman JV, Turakhia MP. Dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011;154:570–571.
7. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13:322–338.
8. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996;276:1339–1341.
9. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA*. 1995;274:1839–1845.
10. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol*. 2010;9:1157–1163.

Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Patients With Atrial Fibrillation and Prior Stroke or Transient Ischemic Attack

Hooman Kamel, S. Claiborne Johnston, J. Donald Easton and Anthony S. Kim

Stroke. 2012;43:881-883; originally published online February 3, 2012;
doi: 10.1161/STROKEAHA.111.641027

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://stroke.ahajournals.org/content/43/3/881>

Data Supplement (unedited) at:

<http://stroke.ahajournals.org/content/suppl/2012/02/21/STROKEAHA.111.641027.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>

ONLINE SUPPLEMENTARY APPENDIX

Kamel et al, Dabigatran Cost-Effectiveness

1. Supplementary Results
2. Supplementary Discussion
3. Supplementary Table
4. Supplementary Figure
5. Supplementary References

Supplementary Results (Sensitivity Analyses)

Costs

The cost-effectiveness of dabigatran improved as the monthly cost of combined or recurrent stroke and/or ICH increased. As the monthly cost of caring for these patients increased above \$5,000, dabigatran's incremental cost-effectiveness ratio (ICER) dropped below \$50,000 per QALY; above a monthly cost of \$10,000, dabigatran was dominant and cost-saving. Our model was moderately sensitive to the cost of dabigatran. In our base case, the overall monthly cost of dabigatran was \$210; its ICER increased above \$50,000 per QALY once its monthly cost exceeded \$320, while dabigatran would be cost-saving at a monthly cost below \$100.

Time in Therapeutic Range

The incremental cost-effectiveness of dabigatran was also sensitive to the time in the therapeutic INR range (TTR) for patients receiving warfarin. In centers with uncommonly good INR control (TTR > 73%, which is well above the average TTR reported in previous studies¹), dabigatran was not cost-effective at a threshold of \$50,000 per QALY, while the ICER dropped to \$16,000 in centers with poor INR control (TTR < 57%).

Utility

In our model, patients with mild disability after their initial, qualifying stroke were more likely to remain in this state without suffering recurrent stroke or ICH if they received dabigatran rather than warfarin. Therefore, an isolated reduction in the utility of this state reduced the cost-effectiveness of dabigatran. Dabigatran's ICER exceeded \$50,000 per QALY if the utility of mild ischemic stroke was less than 0.10, well below our baseline value of 0.75. Our model was not sensitive to variations in the values of other quality-of-life measures in our model, including that of dabigatran.

Age

Dabigatran remained cost-effective at a threshold of \$50,000 per QALY as long as the starting age of patients was 81 years or less. Above this age, the competing risk from background mortality prevented dabigatran's greater effectiveness from justifying its greater fixed costs.

Stroke

Predictably, dabigatran's ICER was proportional to its associated stroke risk, and inversely related to the stroke risk associated with warfarin. Dabigatran's ICER exceeded \$50,000 per QALY if the relative risk of stroke with dabigatran compared with warfarin exceeded 0.92.

Supplementary Discussion

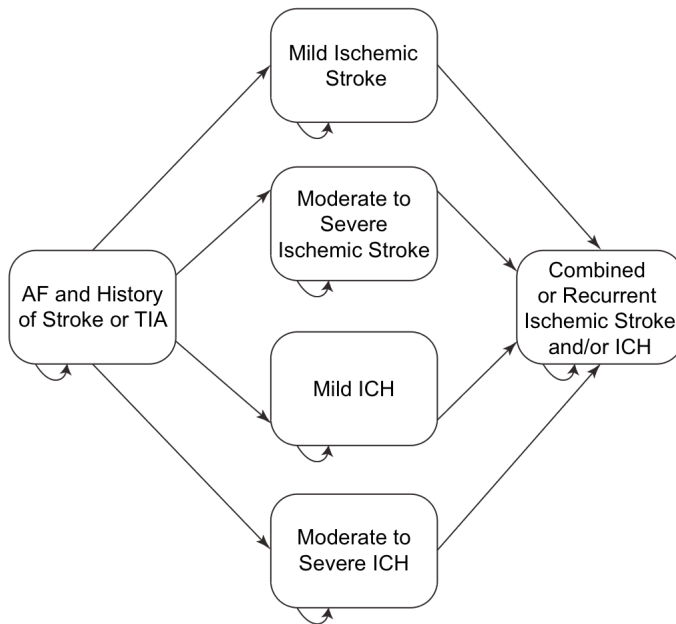
Based on data from the RE-LY trial, our model assumed a 64% time in the therapeutic INR range (TTR) for patients receiving warfarin. However, it is important to emphasize that many anticoagulation clinics have reported TTR > 80% with warfarin.^{2,3} In these settings, dabigatran would not be cost-effective at a threshold of \$50,000 per QALY. Therefore, clinicians should carefully consider their own institution's quality of warfarin management, as well as each individual patient's historical TTR if applicable, when deciding between dabigatran and warfarin for stroke prevention from AF.

In addition, many patients with AF and stroke or transient ischemic attack (TIA) lack ready access to anticoagulation clinics,⁴ and in these patients dabigatran may be an appealing alternative to warfarin therapy managed by a less experienced provider.

Supplementary Table. Decision Model Inputs: Base Case Values and Ranges Used in Sensitivity Analyses		
Variable	Base Case (Range)	References
Probabilities of adverse events		
Ischemic stroke		
Distribution of ischemic events, %		
Stroke	72	5-7
Transient ischemic attack (TIA)	28	5-7
Rate of ischemic stroke, % per year		
Warfarin	1.75 (1.25-2.25)	8-11
Dabigatran	1.75 (1.25-2.25)	8, 12
Aspirin	6.3 (4-10)	11, 13
Relative risk of ischemic stroke per decade of age	1.4 (1-2)	14
Severity of ischemic strokes, %		
Fatal (within 30 days)	10.2 (7.5-12.9)	5-8, 10, 11, 15-21
Major (nonfatal)	39.2 (34.3-44.1)	5-8, 10, 11, 15-21
Minor	41.5 (36.6-47.4)	5-8, 10, 11, 15-21
Non-disabling	9.1 (6.2-12.0)	5-8, 10, 11, 15-21
Intracranial hemorrhage (ICH)		
Rate of ICH, % per year		
Warfarin	1.28 (0.7-2.1)	8, 11, 22-24
Dabigatran	0.53 (0.2-1.1)	8, 12
Aspirin	0.3 (0.2-0.4)	9, 11, 13
Relative risk of ICH per decade of age	1.97 (1.5-2.5)	25
Severity of ICH, %		
Fatal (within 30 days)	42 (35-60)	26-29
Major (nonfatal)	41 (30-45)	26-29
Minor	17 (10-25)	26-29
Myocardial infarction		
Rate of myocardial infarction, % per year		
Warfarin	0.64 (0.4-1.0)	8, 12
Dabigatran	1.02 (0.7-1.5)	8, 12
Aspirin	0.47 (0.4-0.6)	30
Relative risk of MI per decade of age	1.3 (1-2)	31
Short-term mortality of MI, %	7.8 (5-10)	32
Mortality		
Age at start of 20-year interval, years	70	8
Male, %	50	Assumption
Relative risk of nonvascular death		
Atrial fibrillation (AF) and TIA	1.7 (1.3-2.3)	33
AF and prior stroke	2.3 (1.3-3)	34
Relative risk of all-cause mortality		
Aspirin v. anticoagulation	1.24 (1-1.5)	14, 22, 23, 35, 36
Quality of life estimates (utility)		
No disability		
Warfarin	0.987 (0.953-1)	37
Dabigatran	0.994 (0.975-1)	10, 38 (estimate)
Aspirin	0.998 (0.994-1)	37
Stroke or ICH with residual disability		
Mild	0.75 (0-0.95)	37
Moderate to severe	0.39 (0-0.75)	37
Recurrent	0.12 (0-0.39)	37
Myocardial infarction	0.84 (0-1)	39
Temporary states		39
TIA	0.95 (0.8-1)	40
Major extracranial hemorrhage (2 weeks)	0.8 (0.5-1)	41, 42

Initiation of warfarin therapy (1 month)	0.98 (0.9-1)	10
Drug effects and costs		
Drug costs		
Warfarin tablets, \$ per day	1.14 (0.8-2)	43, 44
Cost of INR laboratory test, \$	5.9 (5-10)	45
Overall monthly cost of warfarin, \$ per month	55 (30-100)	43-45
Dabigatran tablets, \$ per day	6.75 (5-30)	43, 46
Overall cost of dabigatran, \$ per month	210 (150-900)	43, 46
Aspirin tablets, \$ per day	0.02 (0.01-0.1)	44
Time in therapeutic range with warfarin, %	64 (57-73)	47
One-time cost of ischemic stroke, \$		
TIA	6,200 (3,000-12,000)	48-50
Mild	9,400 (4,000-16,000)	48-50
Moderate to severe	13,900 (10,000-25,000)	48-50
Monthly cost of ischemic stroke, \$		
Mild	2,500 (1,000-4,000)	48-50
Moderate to severe	5,500 (2,000-8,500)	48-50
One-time cost of ICH, \$	39,100 (15,000-65,000)	48-50
Monthly cost of ICH, \$	5,800 (2,000-9,500)	48-50
Monthly cost of ICH with ischemic stroke, \$	7,300 (3,000-13,000)	48-50
Other costs, \$		
One-time cost of myocardial infarction	19,100 (15,000-25,000)	51
One-time cost of major extracranial hemorrhage	5,600 (2,000-8,000)	10
One-time cost of nonvascular death	10,000 (1,000-20,000)	52

Supplementary Figure. Representation of the Markov decision model. Patients begin with atrial fibrillation (AF) and a history of stroke or transient ischemic attack (TIA). They cycle between health states in 30-day periods for 20 years or until death. Possible health states are equivalent for both dabigatran and warfarin, but the probability of transitions differ.



Supplementary References

1. Reynolds MW, Fahrbach K, Hauch O, et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. *Chest*. 2004;126:1938-1945.
2. Baker JW, Pierce KL, Ryals CA. INR goal attainment and oral anticoagulation knowledge of patients enrolled in an anticoagulation clinic in a Veterans Affairs medical center. *J Manag Care Pharm*. 2011;17:133-142.
3. Garton L, Crosby JF. A retrospective assessment comparing pharmacist-managed anticoagulation clinic with physician management using international normalized ratio stability. *J Thromb Thrombolysis*. 2011;32:426-430.
4. Burkiewicz JS. Effect of access to anticoagulation management services on warfarin use in patients with atrial fibrillation. *Pharmacotherapy*. 2005;25:1062-1067.
5. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;343:687-691.
6. Gullov AL, Koefoed BG, Petersen P, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med*. 1998;158:1513-1521.
7. Petersen P, Boysen G, Godtfredsen J, et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. 1989;1:175-179.
8. Diener HC, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol*. 2010;9:1157-1163.
9. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288:2441-2448.
10. O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *JAMA*. 2005;293:699-706.
11. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet*. 1993;342:1255-1262.
12. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-1151.
13. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066-2078.
14. 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;154:1449-1457.
15. Jorgensen HS, Nakayama H, Reith J, et al. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. *Neurology*. 1997;48:891-895.

16. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*. 1992;327:1406-1412.
17. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019-1026.
18. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med*. 1990;323:1505-1511.
19. Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*. 1991;18:349-355.
20. Hellemons BS, Langenberg M, Lodder J, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ*. 1999;319:958-964.
21. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*. 1996;348:633-638.
22. Albers GW, Diener HC, Frison L, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293:690-698.
23. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362:1691-1698.
24. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med*. 2007;120:700-705.
25. Ariesen MJ, Claus SP, Rinkel GJ, et al. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke*. 2003;34:2060-2065.
26. Bamford J, Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 1990;53:16-22.
27. Clarke JL, Johnston SC, Farrant M, et al. External validation of the ICH score. *Neurocrit Care*. 2004;1:53-60.
28. Hemphill JC, 3rd, Bonovich DC, Besmertis L, et al. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897.
29. Hemphill JC, 3rd, Farrant M, Neill TA, Jr. Prospective validation of the ICH Score for 12-month functional outcome. *Neurology*. 2009;73:1088-1094.
30. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med*. 2002;347:969-974.
31. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.

32. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155-2165.
33. van Wijk I, Kappelle LJ, van Gijn J, et al. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. *Lancet*. 2005;365:2098-2104.
34. Dennis MS, Burn JP, Sandercock PA, et al. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. 1993;24:796-800.
35. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003;290:2685-2692.
36. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71-86.
37. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med*. 1996;156:1829-1836.
38. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011;154:1-11.
39. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. 2006;26:410-420.
40. Young KC, Benesch CG, Jahromi BS. Cost-effectiveness of multimodal CT for evaluating acute stroke. *Neurology*. 2010;75:1678-1685.
41. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making*. 1993;13:89-102.
42. Thomson R, Parkin D, Eccles M, et al. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. *Lancet*. 2000;355:956-962.
43. CPT Code Search. American Medical Association. <https://commerce.ama-assn.org/store/>. Accessed April 8, 2011.
44. *Red Book*. Montvale, NJ: Thomson Healthcare; 2009.
45. Point-of-care reimbursement FAQs. http://www.poc.roche.com/en_US/pdf/44156_Coag2009Handbook_FINAL_APPROVED.pdf. Accessed April 8, 2011.
46. Pradaxa prescribing information. Boehringer Ingelheim Pharmaceuticals. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022512s000lbl.pdf. Accessed April 8, 2011.
47. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 376:975-983.
48. Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality. <http://hcupnet.ahrq.gov>. Accessed April 8, 2011.
49. Holloway RG, Witter DM, Jr., Lawton KB, et al. Inpatient costs of specific cerebrovascular events at five academic medical centers. *Neurology*. 1996;46:854-860.

50. Leibson CL, Hu T, Brown RD, et al. Utilization of acute care services in the year before and after first stroke: A population-based study. *Neurology*. 1996;46:861-869.
51. Kauf TL, Velazquez EJ, Crosslin DR, et al. The cost of acute myocardial infarction in the new millennium: evidence from a multinational registry. *Am Heart J*. 2006;151:206-212.
52. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation*. 2011;123:2562-2570.