

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

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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

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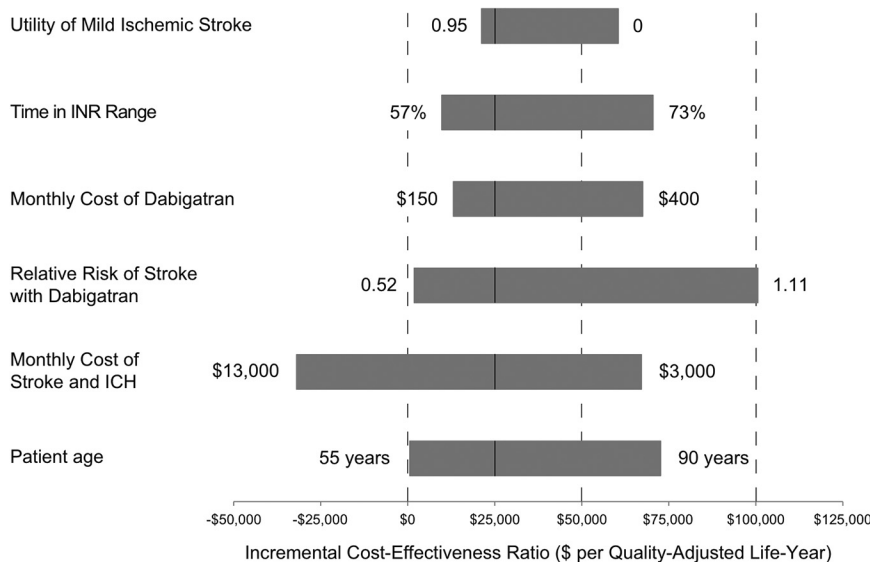


Figure. Results of sensitivity analyses of variables with significant impact on the incremental cost-effectiveness of dabigatran compared with warfarin in patients with atrial fibrillation and prior stroke or transient ischemic attack.

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).

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