Dabigatran Appears to Be a Cost-Effective Alternative to Warfarin

Freeman J, Zhu R, Owens D, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med 2011;154:1–11.

Study Overview

Objective. To determine if anticoagulant therapy with the new direct thrombin inhibitor dabigatran is cost-effective compared with warfarin in elderly patients with atrial fibrillation.

Design. Markov design, cost-effectiveness model using data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial and other studies of anticoagulation for atrial fibrillation. Two doses of dabigatran (low dose, 110 mg twice daily; high dose, 150 mg twice daily) were compared with warfarin. Sensitivity analyses compared variations in costs of dabigatran, age, differential risk for ischemic stroke, intracranial hemorrhage, and myocardial infarction, and utility (quality of life estimates).

Setting and participants. Modeling conducted for patients 65 years and older with atrial fibrillation not caused by valvular disease and without contraindications to anticoagulation.

Main outcome measures. Quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios, which compare the cost per change in QALY compared with the standard treatment, which in this study was warfarin.

Main results. The estimated quality-adjusted life expectancy was 10.28 QALYs with warfarin, 10.70 QALYs with low-dose dabigatran, and 10.84 QALYs for high-dose dabigatran. The incremental cost-effectiveness (ICE) ratios of dabigatran versus warfarin were $51,229 per QALY for low-dose dabigatran and $45,372 per QALY for high-dose dabigatran. Sensitivity analyses demonstrated that the ICE ratio increased with rising estimated costs of dabigatran but the ICE ratio was relatively stable with varying other factors, such as age, utility, and risk of ischemic stroke, intracranial hemorrhage, or myocardial infarction. In sensitivity analyses simulations, comparing all variations of factors simultaneously, high-dose dabigatran was cost-effective in 53% of simulations and low-dose dabigatran in less than 30% of simulations, if the cost-effectiveness level was set at $50,000 per QALY. Either high-dose or low-dose dabigatran was favored over warfarin in 80% of cases for a cost-effectiveness level of $50,000 per QALY (high-dose favored in roughly 55% of cases, low-dose in roughly 25% of cases). When comparing preferred conditions for each of the therapies, warfarin was superior for patients with low risk for intracranial hemorrhage, low-dose dabigatran for patients at moderate to high risk for intracranial hemorrhage and low risk for ischemic stroke, and high-dose dabigatran for patients with moderate to high risk for intracranial hemorrhage and moderate to high risk for ischemic stroke.

Conclusion. Dabigatran is a cost-effective alternative to warfarin for elderly patients with atrial fibrillation, especially for those at moderate to high risk for ischemic stroke and intracranial hemorrhage.

Commentary

For decades, warfarin has been the mainstay of therapy to prevent ischemic strokes from atrial fibrillation. Warfarin

is safe and effective and reduces the risk of stroke by two-thirds [1]. Yet, because warfarin is sensitive to ingestion of vitamin K, its use is labor intensive, requiring frequent laboratory checks and dose adjustments. The search for an alternative has been long-standing. Ximelagatran is an oral direct thrombin inhibitor that held great promise as an anticoagulant and was found to have equivalent effectiveness to warfarin for prevention of stroke in atrial fibrillation and venous thromboembolism [2]. However, it was not approved for use in the United States because of associated hepatoxicity. Dabigatran is a newer oral direct thrombin inhibitor without associated hepatotoxicity that has been shown to be equally or more effective in preventing ischemic strokes, with fewer associated major bleeding episodes and intracranial hemorrhages than warfarin [3].

The primary trial showing the effectiveness of dabigatran was RE-LY, a randomized trial of over 18,000 patients who were at increased risk for stroke (CHADS2 score ≥ 1), with a mean age of 71 years, followed for a median of 2 years. This trial demonstrated a lower risk of ischemic stroke or systemic embolism in patients treated with high-dose dabigatran compared with warfarin (1.11% per year with dabigatran; 1.69% per year with warfarin) and lower risks of intracranial hemorrhage (0.10% per year with dabigatran; 0.38% per year with warfarin). Warfarin and low-dose dabigratran had similar risks for ischemic stroke or systemic embolism, but low-dose dabigatran also had a lower risk of intracranial hemorrhage. Based on the results of this study, the FDA approved high-dose dabigatran for use in the prevention of ischemic stroke and systemic embolism in atrial fibrillation, but they did not approve low-dose dabigatran.

This study by Freeman et al is a cost-effectiveness analysis based primarily on the RE-LY trial. The study found that both low-dose and high-dose dabigatran are generally cost-effective alternatives to warfarin. Warfarin appears to be a more cost-effective treatment for patients at relatively low risk for intracranial hemorrhage while high-dose dabigatran is more cost effective for patients at higher risk for intracranial hemorrhage. The study was well conducted with extensive attention to sensitivity analyses, altering the risks for stroke, hemorrhage, and myocardial infarction as well as the cost of dabigatran and the utility of each therapy.

The main limitations of the study are typical for cost-effectiveness modeling studies. Authors used primarily one 2-year study to provide 35-year estimates for risks and benefits associated with treatments. No study could provide adequate follow-up to overlap with the time period generally sought for simulation studies over the life course. Input data for comparisons of dabigatran to warfarin are particularly limited in this manner because dabigatran is quite new to the field. RE-LY was large, and estimates may well be proven to be stable across other studies; however, we will have to wait for additional data to emerge before we can be confident about RE-LY and the cost-effectiveness of dabigatran. For example, additional data may emerge that provide different estimates for both the efficacy and risk of dabigatran compared with warfarin. In a smaller study of venous thromboembolism treatment in 1274 subjects with a mean age of 54 to 55 years, warfarin and dabigatran had similar efficacy and major bleeding rates [4]. Dabigatran also appears to have somewhat higher risks of myocardial infarction than warfarin, and further data on this link will be critical to determining its safety. Further, dabigatran is so new to the market that authors do not know what its cost will be, and the costs of warfarin use and monitoring could decrease with improvements in home-based INR measurement. In this study, authors used only estimated costs for warfarin use and monitoring and for dabigatran, based on its present cost in the United Kingdom. The cost-effectiveness models were relatively sensitive to substantial increases over this estimated price.

Based on this study and RE-LY, dabigatran looks promising, especially for elderly patients at high risk for stroke and intracranial hemorrhage. Dabigatran may well be the preferred therapy and could save patients the hassle of repeated testing and dose adjustments. Time will determine whether initial data on safety holds up and whether it should become a mainstay of therapy. We cannot extrapolate these results to younger patients, who are most likely to be at low risk for ischemic stroke and intracranial hemorrhage.

Applications for Clinical Practice

Dabigatran appears to be a cost-effective alternative for the prevention of stroke and systemic embolism in elderly patients with atrial fibrillation, especially for patients at high risk for stroke and intracranial hemorrhage. Further developments on the cost of dabigatran and further data on safety and efficacy may allow dabigatran to replace warfarin at least in some patient groups.

—Review by Jason P. Block, MD, MPH

References

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