

# Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Atrial Fibrillation

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**Background:** Warfarin reduces the risk for ischemic stroke in patients with atrial fibrillation (AF) but increases the risk for hemorrhage. Dabigatran is a fixed-dose, oral direct thrombin inhibitor with similar or reduced rates of ischemic stroke and intracranial hemorrhage in patients with AF compared with those of warfarin.

**Objective:** To estimate the quality-adjusted survival, costs, and cost-effectiveness of dabigatran compared with adjusted-dose warfarin for preventing ischemic stroke in patients 65 years or older with nonvalvular AF.

**Design:** Markov decision model.

**Data Sources:** The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial and other published studies of anticoagulation. The cost of dabigatran was estimated on the basis of pricing in the United Kingdom.

**Target Population:** Patients aged 65 years or older with nonvalvular AF and risk factors for stroke (CHADS<sub>2</sub> score  $\geq$ 1 or equivalent) and no contraindications to anticoagulation.

**Time Horizon:** Lifetime.

**Perspective:** Societal.

**Intervention:** Warfarin anticoagulation (target international normalized ratio, 2.0 to 3.0); dabigatran, 110 mg twice daily (low dose); and dabigatran, 150 mg twice daily (high dose).

**Outcome Measures:** Quality-adjusted life-years (QALYs), costs (in 2008 U.S. dollars), and incremental cost-effectiveness ratios.

**Results of Base-Case Analysis:** The quality-adjusted life expectancy was 10.28 QALYs with warfarin, 10.70 QALYs with low-dose

dabigatran, and 10.84 QALYs with high-dose dabigatran. Total costs were \$143 193 for warfarin, \$164 576 for low-dose dabigatran, and \$168 398 for high-dose dabigatran. The incremental cost-effectiveness ratios compared with warfarin were \$51 229 per QALY for low-dose dabigatran and \$45 372 per QALY for high-dose dabigatran.

**Results of Sensitivity Analysis:** The model was sensitive to the cost of dabigatran but was relatively insensitive to other model inputs. The incremental cost-effectiveness ratio increased to \$50 000 per QALY at a cost of \$13.70 per day for high-dose dabigatran but remained less than \$85 000 per QALY over the full range of model inputs evaluated. The cost-effectiveness of high-dose dabigatran improved with increasing risk for stroke and intracranial hemorrhage.

**Limitation:** Event rates were largely derived from a single randomized clinical trial and extrapolated to a 35-year time frame from clinical trials with approximately 2-year follow-up.

**Conclusion:** In patients aged 65 years or older with nonvalvular AF at increased risk for stroke (CHADS<sub>2</sub> score  $\geq$ 1 or equivalent), dabigatran may be a cost-effective alternative to warfarin depending on pricing in the United States.

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Atrial fibrillation (AF) is the second most common cardiovascular condition in the United States, affecting at least 2.3 million Americans (1) and 10% of adults older than 80 years. The age-adjusted prevalence is increasing; by 2030, AF will affect an estimated 4 million Americans (2, 3). The morbidity and mortality of AF are largely due to the 5-fold increased risk for ischemic stroke. The annual incidence of stroke in patients with AF who are not receiving antithrombotic therapy is 4.5% (4, 5). Atrial fibrillation is responsible for 15% of the 700 000 strokes in the United States each year (6), resulting in \$57.9 billion in annual direct and indirect costs (7).

Randomized trials have shown that anticoagulation with warfarin and other vitamin K antagonists can reduce the relative risk for stroke by two thirds (8). However, warfarin has a narrow therapeutic window and may fail to prevent stroke if anticoagulation is inadequate. Overanticoagulation can lead to serious or fatal hemorrhage (9–11). As a result, warfarin therapy re-

quires frequent and long-term laboratory monitoring and dose adjustment.

Oral direct thrombin inhibitors can modulate the coagulation cascade with a predictable pharmacokinetic profile and do not require laboratory testing or dose adjustment (12). Ximelagatran was the first such drug evaluated for stroke prevention in AF and had similar effectiveness as warfarin (13), but it was not approved in the United States

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Conversion of graphics into slides

**Context**

Dabigatran is a direct thrombin inhibitor shown to be about as safe and effective as warfarin for preventing thromboembolism in patients aged 65 years or older with nonvalvular atrial fibrillation.

**Contribution**

This analysis suggests that dabigatran is generally cost-effective as an alternative to warfarin. Treatment seems to become less cost-effective when daily costs exceed \$9.36 for low-dose therapy and \$13.70 for high-dose therapy.

**Caution**

Much of the analysis relies on data from the single available manufacturer-sponsored study of dabigatran.

**Implication**

Depending on how it is priced, dabigatran could be a cost-effective alternative to warfarin for treating atrial fibrillation.

—The Editors

because of hepatotoxicity. Dabigatran etexilate is a newer direct thrombin inhibitor that does not cause liver dysfunction (14–16). The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial was an international, multicenter randomized noninferiority trial in which 18 113 patients with AF at increased risk for stroke (CHADS<sub>2</sub> score  $\geq 1$  or equivalent [Appendix Table 1, available at [annals.org](http://annals.org)] [17]) were randomly assigned to receive dabigatran, 110 mg twice daily (low dose); dabigatran, 150 mg twice daily (high dose); or adjusted-dose warfarin (18). After a median 2-year follow-up, the rates of stroke and systemic embolism were similar in the low-dose dabigatran and warfarin groups, but the low-dose dabigatran group had lower rates of intracranial hemorrhage (ICH) and major hemorrhage. Patients in the high-dose dabigatran group had lower rates of stroke, systemic embolism, and ICH compared with warfarin recipients, although rates of any major hemorrhage were similar. In October 2010, the U.S. Food and Drug Administration (19) approved high-dose dabigatran (150 mg twice daily) for prevention of stroke and systemic embolism in AF, with reduced dosing (75 mg twice daily) available for patients with severe renal impairment. Low-dose dabigatran (110 mg twice daily) was not approved.

In this study, we compared the quality-adjusted survival, costs, and cost-effectiveness of warfarin, low-dose dabigatran, and high-dose dabigatran in patients with nonvalvular AF.

**METHODS****Decision Model**

Using a Markov model (20), we performed a decision analysis comparing 3 treatment strategies for the prevention of stroke in patients with AF: adjusted-dose warfarin

with a target international normalized ratio (INR) of 2.0 to 3.0, twice-daily dabigatran at 110 mg (low dose), and twice-daily dabigatran at 150 mg (high dose). Our base case was a hypothetical cohort of patients 65 years or older with AF who were at increased risk for stroke (on the basis of a CHADS<sub>2</sub> score  $\geq 1$  or equivalent) and had no contraindications to anticoagulation. We expressed our results in quality-adjusted life expectancy, 2008 U.S. dollars, and incremental cost-effectiveness ratios (ICERs).

The health states in the model included healthy with AF, transient ischemic attack, ischemic stroke (fatal, moderate to severe, mild, or reversible), hemorrhage (fatal, moderate to severe intracranial, mild intracranial, major noncerebral, or minor noncerebral), myocardial infarction, recurrent or combined events, and death (Appendix Figure 1, available at [www.annals.org](http://www.annals.org)). Appendix Table 2 (available at [www.annals.org](http://www.annals.org)) provides definitions of ischemic stroke, ICH, and myocardial infarction (21, 22). We applied utilities and costs to each outcome over its expected duration in 2-week increments, and we discounted costs and benefits at 3% annually (23). The risks for the adverse events included in our model were generally derived from the event rates published in the RE-LY trial unless stated otherwise (18). We assumed that event rates for other conditions not included in our model were similar across all treatments. For all treatments, we quantified quality-adjusted life expectancy, risk for adverse events, and net cost over 35 years or until death (if that occurred earlier). Model creation and analyses were performed by using TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, Massachusetts) and Microsoft Excel 2007 (Microsoft, Redmond, Washington).

**Probability of Adverse Outcomes in the Decision Model**

Mortality rates were adjusted for age (beginning at age 65 years). The presence of AF and antithrombotic therapy are accounted for in our model by the clinical event rates derived from the RE-LY trial (8, 18, 24–29).

**Ischemic Stroke**

In the base case, the annual rates of ischemic stroke were 1.20% for warfarin, 1.34% for low-dose dabigatran, and 0.92% for high-dose dabigatran (Table 1) (18). The rate of stroke and transient ischemic attack increased by a factor of 1.4 per decade of life (multiplicative adjustment) (8). We defined the annual risk for ischemic stroke at 3.20% with aspirin. We assumed that 28% of ischemic neurologic events were transient ischemic attacks (34–37).

**Hemorrhage**

For the base case, the annual rate of ICH was estimated at 0.74% for warfarin, 0.23% for low-dose dabigatran, and 0.30% for high-dose dabigatran (Table 1) (18). The rate of ICH increased by a factor of 1.97 per decade of life (multiplicative adjustment) (63). The annual rate of major hemorrhage was estimated at 3.36% with warfarin,

**Table 1. Base-Case Values and Ranges Used in Sensitivity Analyses**

Variable	Base-Case Value (Range)	Reference
<b>Stroke</b>		
Annual rate of ischemic stroke, %		
Warfarin	1.2 (1.0–1.4)	18, 28
Dabigatran, 110 mg twice daily	1.34 (1.13–1.55)	18
Dabigatran, 150 mg twice daily	0.92 (0.75–1.09)	18
Aspirin	3.2 (2.0–5.0)	24, 30–32
Ischemic strokes with warfarin or dabigatran, %		
Fatal (within 30 d)	8.2 (5.5–10.9)	18, 28, 31, 33–41
Moderate to severe neurologic sequelae	40.2 (35.3–45.1)	18, 28, 31, 33–41
Mild neurologic sequelae	42.5 (37.6–47.4)	18, 28, 31, 33–41
No residual neurologic sequelae	9.1 (6.2–12.0)	18, 28, 31, 33–41
<b>Hemorrhage</b>		
Annual rate of ICH, %		
Warfarin	0.74 (0.59–0.89)	13, 18, 42, 43
Dabigatran, 110 mg twice daily	0.23 (0.14–0.32)	18
Dabigatran, 150 mg twice daily	0.3 (0.2–0.4)	18
Annual rate of major hemorrhage, %		
Warfarin	3.36 (3.04–3.68)	18, 43–47
Dabigatran, 110 mg twice daily	2.71 (2.42–3.0)	18
Dabigatran, 150 mg twice daily	3.11 (2.8–3.42)	18
Annual rate of minor hemorrhage, %		
Warfarin	16.4 (15.7–17.0)	13, 18, 43
Dabigatran, 110 mg twice daily	13.2 (12.6–13.8)	18
Dabigatran, 150 mg twice daily	14.8 (14.2–15.5)	18
<b>MI</b>		
Annual rate of MI, %		
Warfarin	0.53 (0.4–0.66)	18
Dabigatran, 110 mg twice daily	0.72 (0.57–0.87)	18
Dabigatran, 150 mg twice daily	0.74 (0.59–0.89)	18
<b>Death</b>		
Age at start of 35-y interval, y	65 (65–100)	Assumption
Relative risk for nonstroke, nonhemorrhage death		
NVAF	1.3 (1.0–1.5)	25, 26, 48
NVAF and prior stroke	2.3 (1.3–3.0)	27
<b>Quality-of-life estimates (utility)</b>		
Healthy		
Aspirin	0.998 (0.994–1.0)	49
Warfarin	0.987 (0.953–1.0)	49
Dabigatran	0.994 (0.975–1.0)	Estimate (28)
Neurologic event (stroke and ICH) with residual neurologic sequelae		
Mild	0.75 (0–1.0)	49
Moderate to severe	0.39 (0–1.0)	49
MI	0.84 (0–1.0)	50
Temporary states		
Major hemorrhage other than ICH (2 wk)	0.8 (0.5–0.99)	51, 52
Minor hemorrhage (2 d)	0.8 (0.5–0.99)	28
<b>Costs</b>		
Daily cost of medication, \$		
Aspirin	0.02 (0.005–0.20)	53
Warfarin (not including INR monitoring)	1.07 (0.80–2.00)	53
Dabigatran, 110 mg twice daily	9.50 (6–13)	Estimate (54)
Dabigatran, 150 mg twice daily	13.00 (8–19)	Estimate (54)
Cost of INR laboratory, \$	6 (4–10)	55
One-time cost of ischemic neurologic event, \$		
Moderate to severe	13 020 (10 000–25 000)	28, 56–59
Minor	8769 (4000–16 000)	28, 56–59
TIA	5780 (3000–12 000)	28, 56–59
Monthly cost of ischemic neurologic event, \$		
Moderate to severe	5120 (2000–8500)	28, 56–59
Minor	2350 (1000–4000)	28, 56–59
One-time cost of ICH, \$	36 680 (15 000–65 000)	28, 56–59
Monthly cost of ICH, \$	5410 (2000–9500)	28, 56–59
Monthly cost of ischemic neurologic event and ICH, \$	6860 (3000–13 000)	28, 56–59
One-time cost of MI, \$	17 930 (15 000–12 000)	60
Monthly cost of MI, \$	290 (125–580)	61, 62
Other 1-time costs, \$		
Major hemorrhage	5250 (2000–8000)	28, 59
Minor hemorrhage	45 (0–200)	28
Cost discounting rate, %	3 (1–5)	20

ICH = intracranial hemorrhage; INR = international normalized ratio; MI = myocardial infarction; NVAF = nonvalvular atrial fibrillation; TIA = transient ischemic attack.

2.71% with low-dose dabigatran, and 3.11% with high-dose dabigatran (18, 28). We assumed that a major hemorrhage (intracranial or major noncerebral) resulted in discontinuation of anticoagulation and replacement with aspirin. The relative risk for hemorrhage with aspirin compared with warfarin was estimated at 0.87 (30–32).

### **Stroke and Hemorrhage Severity**

We classified initial ischemic stroke into 4 categories: fatal, moderate to severe neurologic sequelae, mild neurologic sequelae, and no residual neurologic deficit (Table 1) (28, 31, 33–41). We assumed that a second mild ischemic stroke resulted in a moderate to severe ischemic stroke and that a second moderate to severe ischemic stroke resulted in death or a utility of 0. We classified hemorrhage into 6 categories: fatal, ICH with moderate to severe neurologic sequelae, ICH with mild neurologic sequelae, ICH with no residual neurologic deficit, nonfatal extracerebral major hemorrhage, and nonfatal extracerebral minor hemorrhage (Table 1) (13, 18, 32, 42–47). We assigned temporary decrements in quality of life (utility) for 2 days for nonfatal extracerebral minor hemorrhage and 2 weeks for nonfatal extracerebral major hemorrhage. We considered ICH either fatal or with a permanent decrement in utility due to neurologic sequelae.

### **Myocardial Infarction Risk**

For the base case, the annual risk for myocardial infarction was 0.53% for warfarin, 0.72% for low-dose dabigatran, and 0.74% for high-dose dabigatran (Table 1) (18). The risk for myocardial infarction increased by a factor of 1.3 per decade on the basis of Framingham risk score mortality estimates for a person with the average risk factor profile of the RE-LY trial population (64).

### **Quality-of-Life Estimates**

To calculate quality-adjusted survival, we multiplied the probabilities of adverse events by quality-of-life estimates (utilities) (49). We adjusted baseline quality of life by age to reflect the disutility associated with aging. We obtained the utility for warfarin without complications from published data on patients with AF that were based on patient ratings of their quality of life while receiving warfarin, including prothrombin time monitoring and changes in diet or lifestyle. The mean utility was 0.987 for warfarin (22, 65) and 0.998 for aspirin (22, 49) (Table 1).

To estimate the utility for dabigatran, we used published estimates of utility for ximelagatran, an older direct thrombin inhibitor with similar dosing and mechanism of action. We used a utility of 0.994 for both doses of dabigatran, which was the utility for ximelagatran estimated from a survey of anticoagulation physicians (28). This estimate was based on the disutility of taking a medication with potential adverse effects, such as bleeding, as well as the need for regular hepatic function testing required for ximelagatran. Although dabigatran does not require he-

patric function testing, it is a twice-daily medication and is associated with substantial rates of dyspepsia (approximately 11%).

### **Costs**

Costs, expressed in 2008 U.S. dollars, reflected the perspective of an ideal insurer that covered inpatient and outpatient medical care and prescription costs. This analysis excluded indirect costs. We projected costs over 35 years; future costs and life-years were discounted at 3% per year. We included age-adjusted average health care expenditures for each patient and then added the costs associated with each of the 3 treatment strategies.

### **Drug Treatment Costs**

For warfarin, we combined the annual medication cost with the cost for 14 INR tests and the Center for Medicare & Medicaid Services (CMS) reimbursement for 90-day anticoagulation management (Current Procedural Terminology [CPT] code 99363). In sensitivity analysis, we allowed patients initiating warfarin anticoagulation to have up to 8 additional INR tests and CMS reimbursement to be at the higher rate allowed for anticoagulation initiation for 90 days (CPT code 99364) (66, 67).

Pricing for dabigatran has not yet been established in the United States. Dabigatran is approved in the United Kingdom, Canada, and other countries for the prevention of venous thromboembolism. The price for low-dose dabigatran in the United Kingdom National Health Service is £4.20 per day (equal to \$6.35 in 2008 U.S. dollars at time of analysis) (54). On the basis of historical cost ratios for other on-patent cardiovascular medications, we projected that the retail price in the United States would be 1.5 times higher than that in the United Kingdom (53, 68–70). We estimated a price of \$9.50 per day for low-dose dabigatran and \$13.00 per day for high-dose dabigatran, on the basis of the dosing ratio (150:110 mg) (53, 70). We also included the costs of established care patient visits at 1 and 3 months, then every 3 months through the first year and every 4 months thereafter (18).

### **Complications and Adverse Events**

We estimated the 1-time costs of ischemic stroke, transient ischemic attack, ICH, and myocardial infarction on the basis of the costs of a hospitalization for the diagnosis-related group published by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (59). We estimated monthly costs of care for each complication on the basis of previously published cost estimates by using CMS reimbursement for the diagnosis-related group, adjusted to 2008 U.S. dollars, and the gross domestic product deflator (22, 56–62). Costs of a minor hemorrhage were based on reimbursement for an expanded problem-focused patient visit (71). We estimated the 1-time cost of a major extracranial hemorrhage on the

basis of the CMS payment for the diagnosis-related group associated with gastrointestinal hemorrhage (22).

### Sensitivity Analyses

We performed 1-way sensitivity analyses of all variables included in the decision model over their plausible ranges (Table 1). Ranges for clinical events were derived from CIs for event rates from the RE-LY trial and from the published literature (18). Medication costs for aspirin and warfarin included the range of discount and retail costs (53). For dabigatran, we evaluated a cost range from below the price of the medication in the United Kingdom to more than twice the cost in the United Kingdom. We derived nonmedication costs and utilities from the published literature. In 2-way sensitivity analysis, we calculated cost-effectiveness ratios of dabigatran over combinations of stroke and ICH risk.

We also conducted a sensitivity analysis in which we varied the baseline risk for stroke for all 3 treatment strategies by the same ratio to simulate the ICERs for patients with AF at lower stroke risk (CHADS<sub>2</sub> score, 1) and higher stroke risk (CHADS<sub>2</sub> score, 4). The risk ratios used were based on the published annual rate of stroke for patients with AF who were receiving warfarin with CHADS<sub>2</sub> scores of 1 (0.72%) and CHADS<sub>2</sub> scores of 4 (2.35%) relative to our base case, which was derived from the RE-LY trial with an annual stroke rate of 1.2%.

### Probabilistic Sensitivity Analysis

We performed first-order Monte Carlo simulations (72), randomly sampling (with replacement) a distribution of all variables 10 000 times and then simulating outcomes. For event rates, we generally used a normal distribution, except for the mutually exclusive subcategorization

of stroke, for which we used a Dirichlet distribution. We used a  $\beta$  distribution for utilities and  $\gamma$  and log-normal distributions for cost.

### Role of the Funding Source

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## RESULTS

### Base-Case Analysis

Under base-case conditions, the quality-adjusted life expectancy was 10.28 QALYs with warfarin, 10.70 QALYs with low-dose dabigatran, and 10.84 QALYs with high-dose dabigatran (Table 2). Total costs were \$143 193 for warfarin, \$164 576 for low-dose dabigatran, and \$168 398 for high-dose dabigatran. The ICERs compared with warfarin were \$51 229 per QALY for low-dose dabigatran and \$45 372 per QALY for high-dose dabigatran. Thus, at our base-case prices, high-dose dabigatran was more cost-effective than low-dose dabigatran (extended dominance).

In a hypothetical cohort of 10 000 patients with AF followed over their lifetime starting at age 65 years, low-dose dabigatran averted 1300 ICHs compared with warfarin but resulted in an additional 400 ischemic strokes (including reversible events) and 400 myocardial infarctions. High-dose dabigatran averted 1000 ICHs and 600 ischemic

**Table 2. Projected Costs and QALYs for Patients With Nonvalvular Atrial Fibrillation, by Varying Risk for Stroke and ICH\***

Annual Stroke and ICH Rate With Warfarin, %	Therapy	Cost, \$	QALYs	Marginal Cost per QALY, \$
Stroke: 0.72 (CHADS <sub>2</sub> score, 1); ICH: 0.74	Warfarin	129 749	10.72	Reference
	Dabigatran, 110 mg	148 935	11.20	40 355
	Dabigatran, 150 mg	155 769	11.23	171 984
Stroke: 1.2 (CHADS <sub>2</sub> score, 1–2); ICH: 0.74 (base case)	Warfarin	143 193	10.28	Reference
	Dabigatran, 110 mg	164 576	10.70	Dominated†
	Dabigatran, 150 mg	168 398	10.84	45 372
Stroke: 2.35 (CHADS <sub>2</sub> score, 4); ICH: 0.74	Warfarin	161 620	9.36	Reference
	Dabigatran, 110 mg	185 822	9.65	Dominated†
	Dabigatran, 150 mg	186 910	10.00	39 680
Stroke: 1.2 (CHADS <sub>2</sub> score, 1–2); ICH: 0.44	Warfarin	134 655	10.75	Reference
	Dabigatran, 110 mg	163 083	11.00	Dominated‡
	Dabigatran, 150 mg	166 652	11.21	69 574
Stroke: 1.2 (CHADS <sub>2</sub> score, 1–2); ICH: 1.48	Warfarin	158 912	9.39	Reference
	Dabigatran, 110 mg	169 482	10.05	16 147
	Dabigatran, 150 mg	173 721	10.06	263 543

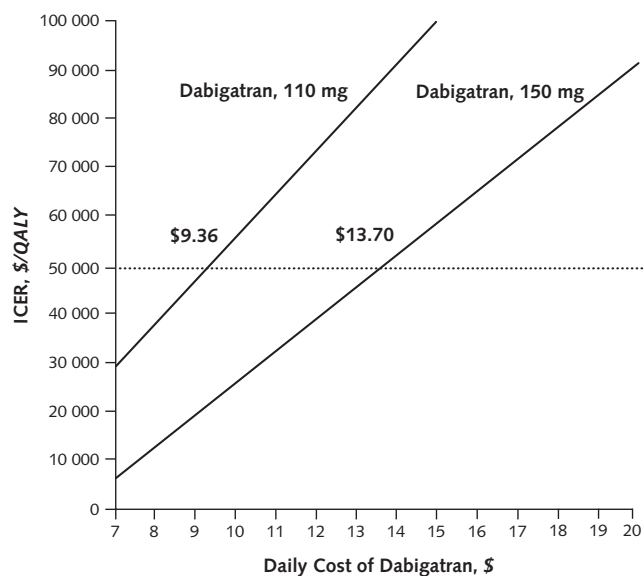
ICER = incremental cost-effectiveness ratio; ICH = intracranial hemorrhage; QALY = quality-adjusted life-year.

\* Risk for stroke defined by CHADS<sub>2</sub> score (range, 0 to 4). Costs are in 2008 U.S. dollars.

† Dabigatran, 110 mg, is dominated by extended dominance, meaning that it is less cost-effective than 150-mg dabigatran and the overall QALY results are lower than that of 150-mg dabigatran. For a stroke risk of 1.2%, the ICER of 110-mg dabigatran vs. warfarin was \$51 229. For a stroke risk of 2.35%, the ICER of 110-mg dabigatran vs. warfarin was \$82 746.

‡ Dabigatran, 110 mg, is dominated by extended dominance, meaning that its value in cost per QALY is less than that of 150-mg dabigatran and the overall QALY results are lower than that of 150-mg dabigatran. For an ICH risk of 0.44%, the ICER of 110-mg dabigatran vs. warfarin was \$115 129. For an ICH risk of 0.74%, the ICER of 110-mg dabigatran vs. warfarin was \$51 229.

**Figure 1. Cost-effectiveness of fixed-dose dabigatran, 110 mg (low dose) and 150 mg (high dose) twice daily, compared with adjusted-dose warfarin anticoagulation at varying daily costs of dabigatran.**



The slope of the cost-effectiveness line for high-dose dabigatran was lower than for low-dose dabigatran, so that at a pricing ratio  $\geq 1.66$  (\$9.50 per day for low-dose and \$15.73 per day for high-dose dabigatran), high-dose dabigatran no longer achieved extended dominance over low-dose dabigatran. The dotted line represents the cost-effectiveness threshold of \$50 000 per QALY. At a cost  $>$ \$9.36 for low-dose dabigatran, the ICER compared with warfarin exceeded \$50 000 per QALY, and at a cost  $>$ \$13.70 for high-dose dabigatran, the ICER compared with warfarin exceeded \$50 000 per QALY. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

strokes (including reversible events) compared with warfarin but resulted in 400 additional myocardial infarctions.

### Sensitivity Analyses

One-way sensitivity analyses showed that several key variables influenced the cost-effectiveness of dabigatran (Appendix Figure 2, available at [www.annals.org](http://www.annals.org)), including drug cost, stroke and ICH risk for dabigatran and warfarin, age, utility of dabigatran and warfarin, costs after ICH, and utility after myocardial infarction. When we varied other model variables across plausible ranges, the ICER for high-dose dabigatran versus warfarin varied by less than \$15 000 per QALY and remained less than \$85 000 per QALY.

### Costs

The cost of dabigatran had the greatest effect on its cost-effectiveness. At a cost greater than \$9.36 per day for low-dose dabigatran, the ICER compared with warfarin exceeded \$50 000 per QALY. At a cost greater than \$13.70 per day for high-dose dabigatran, the ICER compared with warfarin exceeded \$50 000 per QALY. When all 3 therapies were compared and the cost of high-dose dabigatran

was increased from the base-case estimate of \$13.00 to greater than \$15.73 per day (ratio of 1.66 compared with low-dose dabigatran at its base-case cost of \$9.50 per day), it no longer achieved extended dominance over low-dose dabigatran (Figure 1).

The model was also moderately sensitive to the monthly costs of medical care for patients after ICH (Appendix Figure 2). However, the ICER for high-dose dabigatran compared with warfarin for the full range of these costs evaluated was less than \$53 880 per QALY.

### Ischemic Stroke

The cost-effectiveness of high-dose dabigatran was moderately sensitive to changes in ischemic stroke rates. In a 1-way sensitivity analysis of the relative risk for stroke for high-dose dabigatran compared with warfarin, the ICER was less than \$64 455 per QALY over the full range of values tested (Appendix Figure 3, available at [www.annals.org](http://www.annals.org)).

In a secondary analysis, we performed sensitivity analyses varying the stroke rates for the 3 therapies to simulate patients with AF at low risk (CHADS<sub>2</sub> score, 1) or high risk (CHADS<sub>2</sub> score, 4) for ischemic stroke (0.72% to 2.35% per year with warfarin) (Table 2). We adjusted untreated baseline stroke rates for all interventions by the same factors and held ICH rates constant at the base-case rate (0.74% per year with warfarin). For the patients at low risk for stroke (0.72% per year with warfarin), low-dose dabigatran was more cost-effective than high-dose dabigatran and cost \$40 355 per QALY compared with warfarin. For patients at high risk for stroke (2.35% per year with warfarin), high-dose dabigatran was more cost-effective and cost \$39 680 per QALY compared with warfarin.

### Intracranial Hemorrhage

The ICER for high-dose dabigatran was moderately sensitive to changes in ICH rates in our analysis. High-dose dabigatran was more cost-effective than low-dose dabigatran over the range of ICH rates tested. In a 1-way sensitivity analysis for the relative risk for ICH for high-dose dabigatran compared with warfarin, the ICER was less than \$60 120 per QALY over the full range tested (Appendix Figure 3).

We also varied the ICH rates for the 3 therapies to simulate patients with AF at low risk to high risk for ICH (0.44% to 1.48% per year with warfarin) (Table 2). We adjusted the ICH rates for all interventions by the same factors and held stroke rates constant at the base-case rate (1.2% per year with warfarin). For patients at low risk for ICH (0.44% per year with warfarin), high-dose dabigatran was more cost-effective than low-dose dabigatran and cost \$69 574 per QALY compared with warfarin. For patients at high risk for ICH (1.48% per year with warfarin), low-dose dabigatran was more cost-effective than high-dose

dabigatran and cost \$16 147 per QALY compared with warfarin.

### Myocardial Infarction

In 1-way sensitivity analysis over the plausible range of myocardial infarction risk, the ICER for high-dose dabigatran versus warfarin varied by less than \$11 000 per QALY and remained less than \$51 000 per QALY over the entire range evaluated.

### Utility

We evaluated the sensitivity of our model to changes in the utility weights of included health states. The model was most sensitive to the utility for patients receiving warfarin and the utility for patients receiving dabigatran. The ICER for dabigatran compared with warfarin remained less than \$55 730 per QALY over the full range of utilities evaluated for warfarin and less than \$63 360 per QALY over the full range of utilities evaluated for dabigatran (0.975 to 1.0).

### Age

Using an 80-year-old patient for the base case, the quality-adjusted survival was 5.87 QALYs with warfarin, 6.24 QALYs with low-dose dabigatran, and 6.31 QALYs with high-dose dabigatran. The ICER was \$27 308 per QALY for low-dose dabigatran versus warfarin, \$31 168 per QALY for high-dose dabigatran versus warfarin, and \$52 613 per QALY for high-dose dabigatran versus low-dose dabigatran. The ICER decreased with age because older patients had higher rates of ischemic stroke and ICH and had a larger absolute risk reduction when dabigatran was used rather than warfarin.

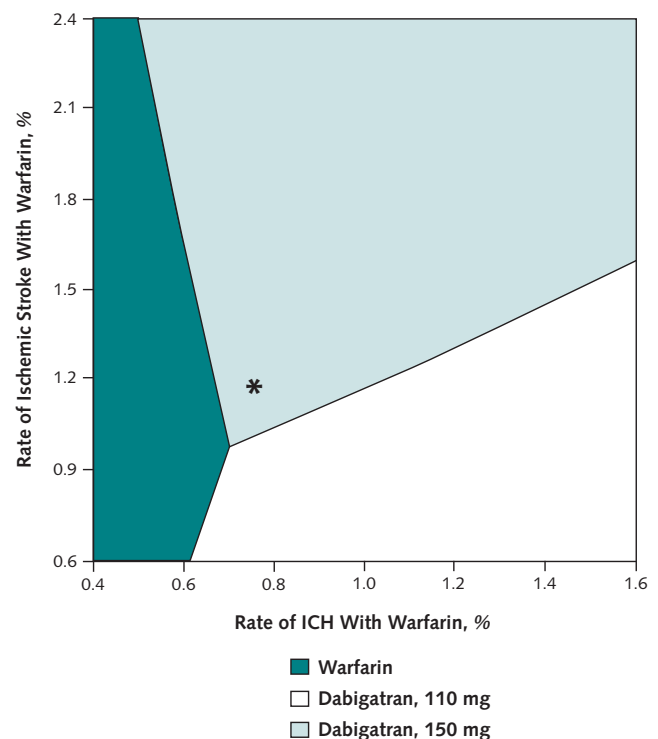
### Two-Way Sensitivity Analyses

We performed 2-way sensitivity analyses of key variables, including one demonstrating which therapy would be preferred for varying risks for ischemic stroke and ICH. We first performed this analysis without consideration of cost and demonstrated that purely on the basis of effectiveness, high-dose dabigatran was the preferred therapy for all combinations of risk except when a patient had a very low risk for stroke and a very high risk for ICH. Using a willingness-to-pay threshold of \$50 000 per QALY (Figure 2), high-dose dabigatran was favored for the base case and for patients with a higher risk for both ischemic stroke and ICH. For patients with a low absolute risk for ischemic stroke (for example, CHADS<sub>2</sub> score of 0 or 1), low-dose dabigatran was the preferred therapy, especially if the concurrent ICH risk was relatively high. For patients with a low absolute risk for ICH, warfarin was the preferred therapy.

### Probabilistic Sensitivity Analysis

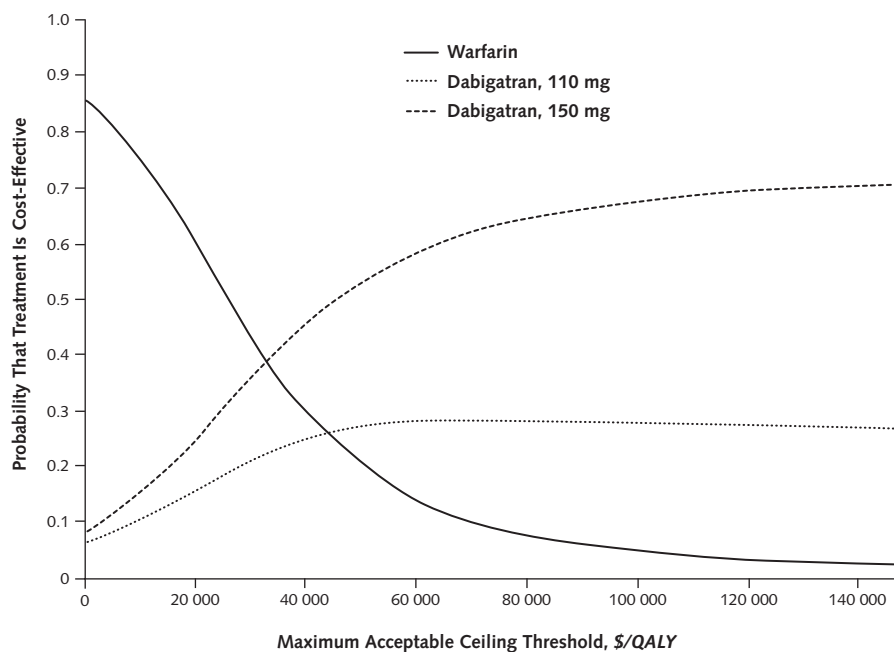
In the Monte Carlo simulation varying all variables simultaneously, high-dose dabigatran was cost-effective in 53% of the simulations using a willingness-to-pay threshold of \$50 000 per QALY and in 68% of the simulations using a willingness-to-pay threshold of \$100 000 per QALY. Although low-dose dabigatran was cost-effective in fewer than 30% of the simulations at any willingness-to-pay threshold, it had more QALYs than high-dose dabigatran in 26% of simulations. Either high-dose or low-dose dabigatran was preferred to warfarin in more than 80% of simulations using a willingness-to-pay threshold of \$50 000 per QALY and in more than 95% of simulations using a willingness-to-pay threshold of \$100 000 per QALY (Figure 3).

Figure 2. Two-way sensitivity analysis demonstrating which therapy would be preferred for varying risks for ischemic stroke and ICH, using a willingness-to-pay threshold of \$50 000 per quality-adjusted life-year.



The base-case rate of ischemic stroke and ICH for each therapy is multiplied by the same ratio, and the varying rate of events on warfarin is used as the reference. Dabigatran, 150 mg twice daily (high dose), was favored for the base case (*asterisk*) and for patients with a higher risk for both ischemic stroke and ICH. For patients with a low absolute risk for ischemic stroke, low-dose dabigatran was the preferred therapy, especially if the concurrent ICH risk was relatively high. For patients with a low absolute risk for ICH, warfarin was the preferred therapy. The annual rate of ischemic stroke for patients receiving warfarin with a CHADS<sub>2</sub> score of 1 is 0.72%, CHADS<sub>2</sub> score of 1–2 is 1.2%, and CHADS<sub>2</sub> score of 4 is 2.35%. ICH = intracranial hemorrhage.

**Figure 3. Cost-effectiveness acceptability curves representing the probability that each treatment strategy is cost-effective for a given maximum willingness-to-pay threshold per QALY gained.**



This graph is based on 10 000 Monte Carlo simulations of the model, drawing parameters for each input simultaneously from probability distributions. Warfarin is most likely to be cost-effective at a willingness-to-pay threshold  $\leq$  \$30 000 per QALY. At thresholds  $\geq$  \$35 000 per QALY, high-dose dabigatran is most likely to be cost-effective. High-dose dabigatran is 53%, 68%, and 70% likely to be cost-effective at willingness-to-pay thresholds of \$50 000, \$100 000, and \$150 000 per QALY, respectively. Either high-dose or low-dose dabigatran was preferred to warfarin in more than 80% of simulations using a willingness-to-pay threshold of \$50 000 per QALY. QALY = quality-adjusted life-year.

## DISCUSSION

We demonstrated that in patients aged 65 years or older with AF who are at increased risk for stroke (CHADS<sub>2</sub> score  $\geq$  1 or equivalent), dabigatran could be a cost-effective alternative to warfarin. Our base-case analysis estimated a cost of \$45 372 per QALY gained with high-dose dabigatran compared with warfarin, which was within a range generally considered to be cost-effective (73). High-dose dabigatran was also the most effective treatment option we evaluated, yielding an additional 0.56 QALY compared with warfarin. The cost-effectiveness of dabigatran was sensitive to drug costs and relative differences in cost between the high- and low-dose formulations, but it was relatively insensitive to other model inputs. In addition, for patients at higher risk for ischemic stroke or ICH, including those with CHADS<sub>2</sub> scores of 2 or greater, the ICER for high-dose dabigatran compared with warfarin improved.

Our analysis suggests that at a willingness-to-pay threshold of \$50 000 per QALY, low-dose dabigatran may be the preferred therapy for patients with a low absolute risk for ischemic stroke (for example, CHADS<sub>2</sub> score of 0 or 1), especially if their concurrent risk for ICH is high. For patients with low absolute risk for ICH, warfarin may be the preferred therapy. However, for some low-risk pa-

tients, antiplatelet therapy rather than anticoagulation may be a reasonable alternative, but further clinical study is needed to determine optimal treatment for patients who are at low risk for stroke and ICH.

Dabigatran is the first direct thrombin inhibitor to show similar safety and efficacy to warfarin for stroke prevention in AF. Warfarin is a generic medication and prescription costs are low, but the costs of laboratory monitoring and complications due to over- and underanticoagulation are substantial. Multiple strategies to reduce costs and improve effectiveness in warfarin-treated patients, including genotype-guided warfarin dosing and patient self-testing of INR, have been evaluated. Results to date suggest that these strategies are not cost-effective for the typical patient with nonvalvular AF (74–77). Therefore, cost-effective alternatives to current methods of delivering warfarin anticoagulation are needed.

Several caveats apply to our results. First, the therapeutic efficacies and adverse event rates used in our analysis were derived mostly from the open-label RE-LY randomized, controlled trial. Follow-up of this trial cohort is ongoing (ClinicalTrials.gov registration number: NCT00808067), and clinical event rates may change with longer term follow-up. Although additional phase 3 or 4 randomized trial results are desirable, we do not know that a replication trial to

confirm safety and efficacy will be performed. However, a randomized trial comparing high-dose dabigatran with adjusted-dose warfarin for the treatment of acute venous thromboembolism in 2539 patients had hemorrhage rates that were very similar to those in the RE-LY trial, demonstrating a consistent risk for adverse events (78). The results of our analysis would change if future effectiveness studies provide alternative estimates for bleeding risk and stroke reduction. Second, a treatment administered in clinical practice may not be as effective as one administered in randomized trials, which generally enroll healthier patients, achieve high levels of adherence, and monitor patients more intensively (79). Finally, although dabigatran in a reduced dose of 75 mg twice daily was approved by the U.S. Food and Drug Administration for patients with creatinine clearance of 15 to 30 mL/min (19), the RE-LY trial excluded patients with creatinine clearance less than 30 mL/min (18), so our results do not apply to that patient population.

In conclusion, we found that treatment with dabigatran could be a cost-effective alternative to adjusted-dose warfarin for stroke prevention in patients older than 65 years with nonvalvular AF at increased risk for stroke (CHADS<sub>2</sub> score  $\geq 1$  or equivalent). High-dose dabigatran was the most cost-effective and most effective therapy we evaluated, providing an additional 0.56 QALY over warfarin in our base-case analysis. For patients at higher risk for ischemic stroke and ICH, the ICER of dabigatran compared with warfarin improved. These results were robust over a wide range of model assumptions but were sensitive to dabigatran costs.

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**Reproducible Research Statement:** *Study protocol and statistical code:* Not available. *Data set:* Selected data elements are available to approved individuals with written agreement from Dr. Turakhia (e-mail, [mintu@stanford.edu](mailto:mintu@stanford.edu)).

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## References

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med.* 1995;155:469-73. [PMID: 7864703]
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation.* 2006;114:119-25. [PMID: 16818816]
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, 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;285:2370-5. [PMID: 11343485]
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22:983-8. [PMID: 1866765]
5. Hart RG. Warfarin in atrial fibrillation: underused in the elderly, often inappropriately used in the young [Editorial]. *Heart.* 1999;82:539-40. [PMID: 10525502]
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med.* 1987;147:1561-4. [PMID: 3632164]
7. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2006;113:e85-151. [PMID: 16407573]
8. 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;154:1449-57. [PMID: 8018000]
9. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med.* 1989;87:144-52. [PMID: 2787958]
10. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest.* 2001;119:108S-121S. [PMID: 11157645]
11. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med.* 2003;349:1019-26. [PMID: 12968085]
12. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost.* 2009;15 Suppl 1:9S-16S. [PMID: 19696042]
13. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, et al; SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA.* 2005;293:690-8. [PMID: 15701910]
14. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet.* 2008;47:285-95. [PMID: 18399711]
15. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol.* 2007;100:1419-26. [PMID: 17950801]
16. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al; RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet.* 2007;370:949-56. [PMID: 17869635]
17. Gage BF, Waterman AD, Shannon W, Boehler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* 2001;285:2864-70. [PMID: 11401607]

18. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-51. [PMID: 19717844]
19. Dabigatran: Approval history, letters, reviews, and related documents. Drugs@FDA. Accessed at [www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#apphist](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist) on 24 October 2010.
20. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13:322-38. [PMID: 8246705]
21. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634-53. [PMID: 17951284]
22. O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *JAMA*. 2005;293:699-706. [PMID: 15701911]
23. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA*. 1996;276:1253-8. [PMID: 8849754]
24. Antithrombotic Trialists' Collaboration. 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. [PMID: 11786451]
25. Yuan Z, Bowlin S, Einstadter D, Cebul RD, Conners AR Jr, Rimm AA. Atrial fibrillation as a risk factor for stroke: a retrospective cohort study of hospitalized Medicare beneficiaries. *Am J Public Health*. 1998;88:395-400. [PMID: 9518970]
26. Wyse DG, Love JC, Yao Q, Carlson MD, Cassidy P, Greene LH, et al. Atrial fibrillation: a risk factor for increased mortality—an AVID registry analysis. *J Interv Card Electrophysiol*. 2001;5:267-73. [PMID: 11500581]
27. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. 1993;24:796-800. [PMID: 8506550]
28. O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *JAMA*. 2005;293:699-706. [PMID: 15701911]
29. Arias E. United States life tables, 2004. *Natl Vital Stat Rep*. 2007;56:1-39. [PMID: 18274319]
30. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al; BAFTA investigators. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370:493-503. [PMID: 17693178]
31. Hellemons BS, Langenberg M, Lodder J, Vermeer F, Schouten HJ, Lemmens T, 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;319:958-64. [PMID: 10514159]
32. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288:2441-8. [PMID: 12435257]
33. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, 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;327:1406-12. [PMID: 1406859]
34. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. 1989;1:175-9. [PMID: 2563096]
35. Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, 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;158:1513-21. [PMID: 9679792]
36. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;343:687-91. [PMID: 7907677]
37. 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;348:633-8. [PMID: 8782752]
38. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet*. 1993;342:1255-62. [PMID: 7901582]
39. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*. 1991;18:349-55. [PMID: 1856403]
40. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019-26. [PMID: 12968085]
41. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation*. 1991;84:527-39. [PMID: 1860198]
42. Olsson SB; Executive Steering Committee of the SPORTIF III Investigators. 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;362:1691-8. [PMID: 14643116]
43. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med*. 2007;120:700-5. [PMID: 17679129]
44. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151:713-9. [PMID: 16504638]
45. Evans A, Kalra L. Are the results of randomized controlled trials on anticoagulation in patients with atrial fibrillation generalizable to clinical practice? *Arch Intern Med*. 2001;161:1443-7. [PMID: 11386894]
46. Copland M, Walker ID, Tait RC. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. *Arch Intern Med*. 2001;161:2125-8. [PMID: 11570942]
47. Bleeding during antithrombotic therapy in patients with atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. *Arch Intern Med*. 1996;156:409-16. [PMID: 8607726]
48. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Wacławski MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *Studies of Left Ventricular Dysfunction*. *J Am Coll Cardiol*. 1998;32:695-703. [PMID: 9741514]
49. 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;156:1829-36. [PMID: 8790077]
50. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. 2006;26:410-20. [PMID: 16855129]
51. Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. *Lancet*. 2000;355:956-62. [PMID: 10768433]
52. Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making*. 1993;13:89-102. [PMID: 8483408]
53. Red Book. Montvale, NJ; Thomson Reuters; 2009.
54. National Institute for Health and Clinical Excellence. Dabigatran Etxilate for the Prevention of Venous Thromboembolism After Hip or Knee Replacement Surgery in Adults. NICE technology appraisal guidance 157. London: National Institute for Health and Clinical Excellence; 2008.
55. Point-of-Care Testing Reimbursement FAQs. Indianapolis: Roche Diagnostics; 2009. Accessed at [www.poc.roche.com/coaguchek/rewrite/content/en\\_IE/70\\_2020/article/POC\\_general\\_article\\_08.htm](http://www.poc.roche.com/coaguchek/rewrite/content/en_IE/70_2020/article/POC_general_article_08.htm) on 22 January 2010.
56. Leibson CL, Hu T, Brown RD, Hass SL, O'Fallon WM, Whisnant JP. Utilization of acute care services in the year before and after first stroke: A population-based study. *Neurology*. 1996;46:861-9. [PMID: 8618713]
57. Holloway RG, Witter DM Jr, Lawton KB, Lipscomb J, Samsa G. Inpatient costs of specific cerebrovascular events at five academic medical centers. *Neurology*. 1996;46:854-60. [PMID: 8618712]
58. Matchar DB, Samsa GP. Secondary and Tertiary Prevention of Stroke: Patient Outcomes Research Team (PORT) Final Report—Phase 1. AHRQ publication no. 00-N001. Rockville, MD: Agency for Healthcare Research and Quality; 2000.
59. HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality; 2009. Accessed at <http://hcupnet.ahrq.gov/> on 15 November 2009.
60. Kauf TL, Velazquez EJ, Crosslin DR, Weaver WD, Diaz R, Granger CB,

- et al. The cost of acute myocardial infarction in the new millennium: evidence from a multinational registry. *Am Heart J*. 2006;151:206-12. [PMID: 16368320]
61. Mark DB, Knight JD, Cowper PA, Davidson-Ray L, Anstrom KJ. Long-term economic outcomes associated with intensive versus moderate lipid-lowering therapy in coronary artery disease: results from the Treating to New Targets (TNT) Trial. *Am Heart J*. 2008;156:698-705. [PMID: 18926150]
62. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *Am Heart J*. 2001;141:727-34. [PMID: 11320359]
63. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke*. 2003;34:2060-5. [PMID: 12843354]
64. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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;285:2486-97. [PMID: 11368702]
65. 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;156:1829-36. [PMID: 8790077]
66. CPT Code/Relative Value Search. American Medical Association. Accessed at [https://catalog.ama-assn.org/Catalog/cpt/cpt\\_search.jsp](https://catalog.ama-assn.org/Catalog/cpt/cpt_search.jsp) on 22 January 2010.
67. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. *Am J Med*. 2000;109:481-8. [PMID: 11042238]
68. Gross DJ, Purvis LG, Schondelmeyer SW. Trends in Manufacturer Prices of Brand-Name Prescription Drugs Used by Older Americans—2006 Year-End Update. Washington, DC: American Association of Retired Persons; 2007.
69. Prescription Cost Analysis England 2008. London: NHS Information Centre for Health and Social Care; 2009.
70. PharmacyChecker.com: Pricing & Ordering Comparisons. Accessed at [www.pharmacychecker.com/](http://www.pharmacychecker.com/) on 14 April 2010.
71. Centers for Medicare & Medicaid Services. 2009 Physician Fee Schedule. Baltimore: Centers for Medicare & Medicaid Services; 2008.
72. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making*. 1985;5:157-77. [PMID: 3831638]
73. Owens DK. Interpretation of cost-effectiveness analyses [Editorial]. *J Gen Intern Med*. 1998;13:716-7. [PMID: 9798822]
74. Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann Intern Med*. 2009;150:73-83. [PMID: 19153410]
75. Leey JA, McCabe S, Koch JA, Miles TP. Cost-effectiveness of genotype-guided warfarin therapy for anticoagulation in elderly patients with atrial fibrillation. *Am J Geriatr Pharmacother*. 2009;7:197-203. [PMID: 19766951]
76. Epstein RS, Moyer TP, Aubert RE, O Kane DJ, Xia F, Verbrugge RR, et al. Warfarin genotyping reduces hospitalization rates results from the MM-WES (Medco-Mayo Warfarin Effectiveness study). *J Am Coll Cardiol*. 2010;55:2804-12. [PMID: 20381283]
77. Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. *Health Technol Assess*. 2007;11:iii-iv, ix-66. [PMID: 17903392]
78. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342-52. [PMID: 19966341]
79. Waterman AD, Milligan PE, Bayer L, Banet GA, Gatchel SK, Gage BF. Effect of warfarin nonadherence on control of the International Normalized Ratio. *Am J Health Syst Pharm*. 2004;61:1258-64. [PMID: 15259756]

#### VITAL STATISTICS

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## Appendix Table 1. CHADS<sub>2</sub> Score Components

Diagnosed congestive heart failure, past or current (1 point)

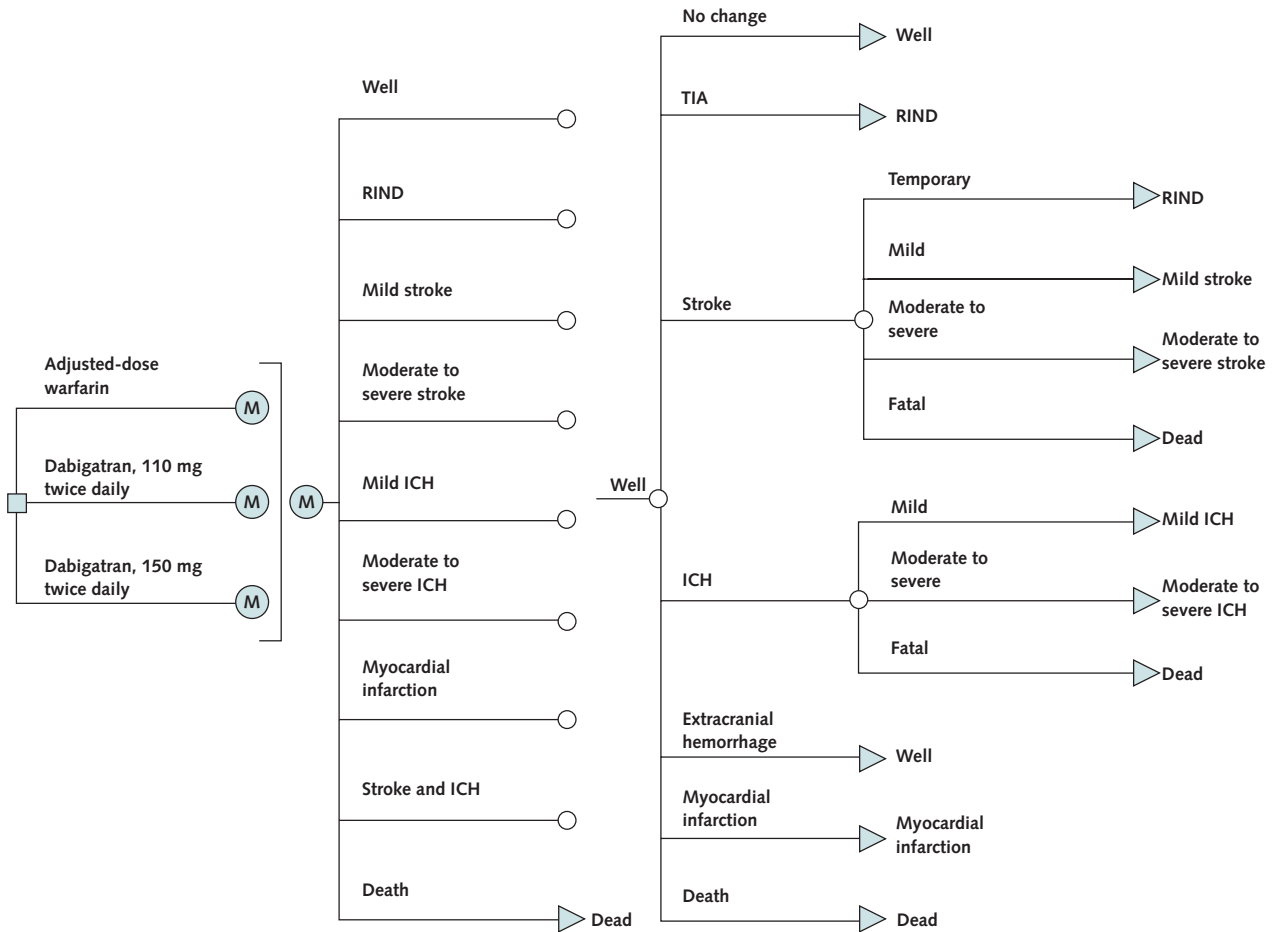
Hypertension, treated or untreated (1 point)

Age  $\geq 75$  y (1 point)

Diabetes mellitus (1 point)

Secondary prevention in patients with prior ischemic stroke, transient ischemic attack, or thromboembolism (2 points)

Appendix Figure 1. Decision model.



“M” represents a Markov process with 9 health states for each of the 3 treatment options. These potential health states are identical for each treatment option. All patients remain in the “Well” state until 1 of 6 events occurs: TIA, stroke, ICH, extracranial hemorrhage, myocardial infarction, or death. The probabilities of these events occurring depend on the prescribed therapy. Triangles indicate which health state the patient enters after an event. A “RIND” is the health state that patients enter after a TIA or stroke without residual neurologic deficit. “Mild” represents a neurologic event that results in neurologic deficit but no limitation in performing activities of daily living; “moderate to severe” represents a neurologic event that results in loss of independence for at least 1 activity of daily living. ICH = intracranial hemorrhage; RIND = reversible ischemic neurologic event; TIA = transient ischemic attack.

## Appendix Table 2. Definitions of Ischemic Stroke, Intracranial Hemorrhage, and Myocardial Infarction

### Ischemic stroke

Sudden onset of a focal neurologic deficit in a location consistent with a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation of ischemic stroke was not considered to be hemorrhagic stroke (22).

### Intracranial hemorrhage

Hemorrhagic stroke and subdural or subarachnoid hemorrhage (22).

### Myocardial infarction (any 1 of the following)

Detection of increase or decrease in cardiac biomarkers (preferably troponin) with  $\geq 1$  value above the 99th-percentile URL, with evidence of myocardial ischemia and  $\geq 1$  of the following:

Symptoms of ischemia;

ECG changes indicative of new ischemia (new ST-T changes or new LBBB);

Development of pathologic Q waves on ECG; or

Imaging evidence of new loss of viable myocardium or new regional wall-motion abnormality.

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST-segment elevation, new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, but death occurred before blood samples could be obtained or before the appearance of cardiac biomarkers in the blood.

For PCIs in patients with normal baseline troponin levels, elevations of cardiac biomarkers above the 99th-percentile URL indicate periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 3 times the 99th-percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.

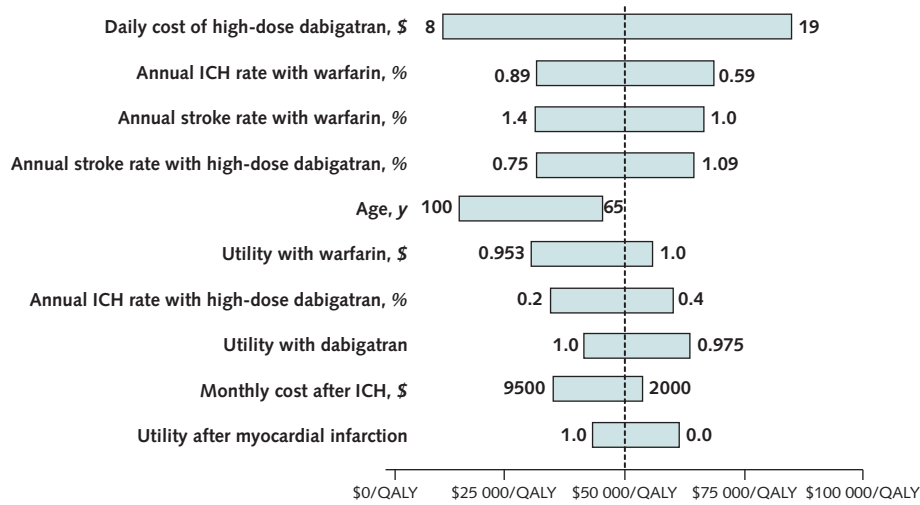
For CABG in patients with normal baseline troponin levels, elevations of cardiac biomarkers above the 99th-percentile URL indicate periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 5 times the 99th-percentile URL plus new pathologic Q waves, new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.

Pathology findings of acute myocardial infarction (21).

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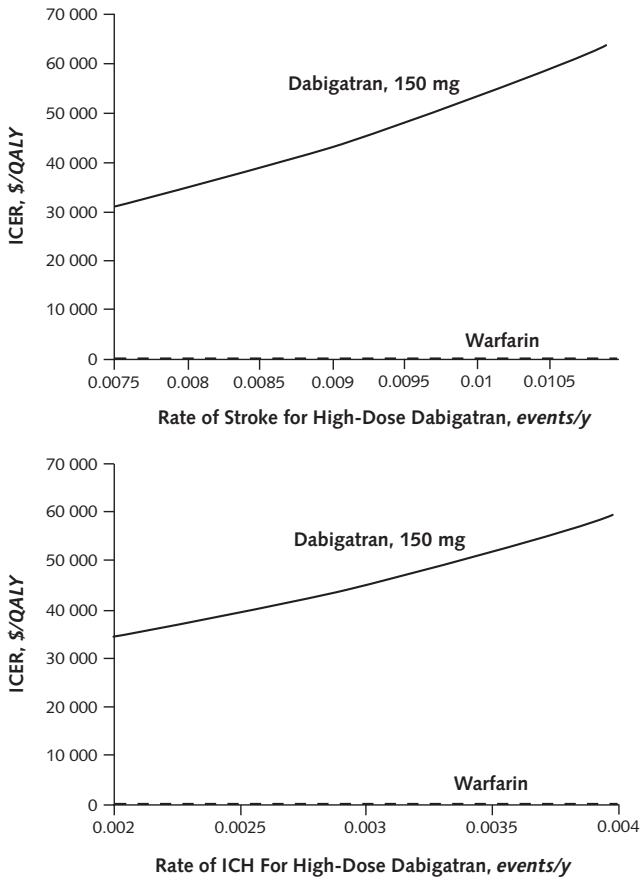
CABG = coronary artery bypass grafting; ECG = electrocardiography; LBBB = left bundle branch block; PCI = percutaneous coronary intervention; URL = upper reference limit.

**Appendix Figure 2. One-way sensitivity analyses on variables that most influenced the incremental cost-effectiveness of high-dose dabigatran compared with warfarin.**



Bars indicate the range of cost per additional QALY of dabigatran compared with warfarin as determined in 1-way sensitivity analyses over plausible ranges for variables. Upper and lower limits of values evaluated in sensitivity analysis are indicated next to the bars. One-way sensitivity analysis was performed on all model variables, and the cost-effectiveness of dabigatran relative to warfarin varied the most with the variables shown. The incremental cost-effectiveness ratio remained <\$85 000 per QALY over the full range of assumptions evaluated. The dotted line represents the cost-effectiveness threshold of \$50 000 per QALY. ICH = intracranial hemorrhage; QALY = quality-adjusted life-year.

**Appendix Figure 3. ICERs for high-dose dabigatran compared with warfarin with varying relative risk for ischemic stroke and ICH.**



The ICER for high-dose dabigatran compared with warfarin remained <\$64 455 per QALY for the full range of stroke rates tested and <\$60 120 per QALY for the full range of ICH rates tested. ICER = incremental cost-effectiveness ratio; ICH = intracranial hemorrhage; QALY = quality-adjusted life-year.