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Amanda R. Harrington, Edward P. Armstrong, Paul E. Nolan, Jr and Daniel C. Malone

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Cost-Effectiveness of Apixaban, Dabigatran, Rivaroxaban, and Warfarin for Stroke Prevention in Atrial Fibrillation

Amanda R. Harrington, MS; Edward P. Armstrong, PharmD; Paul E. Nolan Jr, PharmD; Daniel C. Malone, PhD

Background and Purpose—To estimate the cost-effectiveness of stroke prevention in patients with nonvalvular atrial fibrillation by using novel oral anticoagulants apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg compared with warfarin.

Methods—A Markov decision-analysis model was constructed using data from clinical trials to evaluate lifetime costs and quality-adjusted life-years of novel oral anticoagulants compared with warfarin. The modeled population was a hypothetical cohort of 70-year-old patients with nonvalvular atrial fibrillation, increased risk for stroke (CHADS2 ≥ 1), renal creatinine clearance ≥ 50 mL/min, and no previous contraindications to anticoagulation. The willingness-to-pay threshold was $50,000/quality-adjusted life-years gained.

Results—In the base case, warfarin had the lowest cost of $77,813 (SD, $2,223), followed by rivaroxaban 20 mg ($78,738±$18,52), dabigatran 150 mg ($82,719±$19,59), and apixaban 5 mg ($85,326±$15,12). Apixaban 5 mg had the highest quality-adjusted life-years estimate at 8.47 (SD, 0.06), followed by dabigatran 150 mg (8.41±0.07), rivaroxaban 20 mg (8.26±0.06), and warfarin (7.97±0.04). In a Monte Carlo probabilistic sensitivity analysis, apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were cost-effective in 45.1%, 40%, 14.9%, 0% of the simulations, respectively.

Conclusions—In patients with nonvalvular atrial fibrillation and an increased risk of stroke prophylaxis, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg were all cost-effective alternatives to warfarin. The cost-effectiveness of novel oral anticoagulants was dependent on therapy pricing in the United States and neurological events associated with rivaroxaban 20 mg. (Stroke. 2013;44:1676-1681.)

Key Words: anticoagulation ■ atrial fibrillation ■ cost-effectiveness ■ intracranial hemorrhage ■ Markov model ■ stroke

The rate of ischemic stroke in people with nonvalvular atrial fibrillation (NVAF) averages ≈5% per year, which is 2 to 7 times the rate of those people without NVAF. An estimated 7 million Americans ≥ 20 years of age have had a stroke. Projections estimate that by 2030, an additional 4 million people in the United States will have had a stroke, a 24% increase in prevalence from 2010. Each year, ≈ 795,000 people in the United States experience a new or recurrent stroke.

Stroke represents a substantial financial burden on the healthcare system, as well as on patients, family, and society. The lifetime cost of an ischemic stroke is estimated to be > $90,000 for an individual in 1990, whereas the American Heart Association estimated that in 2008, total national direct and indirect costs of stroke in the United States exceeded $34 billion. Nearly 75% of the patients who had stroke are Medicare beneficiaries, qualifying the national health insurance program as the most common payer of healthcare for patients who had stroke. The total aggregated costs for this population were $60,177 for subarachnoid hemorrhage, $50,015 for intracranial hemorrhage (ICH), and $49,996 for an ischemic stroke.

Warfarin is the current standard therapy used for prolonged stroke management; however, its use is limited because of the narrow therapeutic window required, interindividual variability in dose response, and numerous drug–drug and drug–food interactions. Novel oral anticoagulant (NOAC) alternatives to warfarin, apixaban, dabigatran, and rivaroxaban, have recently become accessible for patients with NVAF, and their clinical trial data have become available. To date, published economic studies have only focused on the cost-effectiveness comparison between 2 of the 4 therapies for stroke prevention in patients in the United States with atrial fibrillation. The primary objective of this study is to estimate the long-term cost-effectiveness of stroke prevention in patients with NVAF in the United States comparing NOACs with the standard treatment, warfarin. Furthermore, this study will provide a more comprehensive evaluation of the cost-effectiveness of available anticoagulation therapies to assist clinicians and other healthcare decision-makers to make a more informed choice regarding patient treatment.
Methods

Decision Model

Using a Markov model, 4 treatment strategies and their associated outcomes were assessed: apixaban 5 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, and adjusted-dose warfarin (target international normalized ratio [INR] between 2.0 and 3.0). The baseline patient population was a hypothetical cohort of 70-year-old patients with NVAF, an increased risk for stroke (CHADS2: Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or transient ischemic attack (doubled)) ≥1, or equivalent), a renal creatinine clearance of ≥50 mL/min, and no previous contraindications to anticoagulant therapy. Therapy adherence rates were assumed to be similar across all treatments, and the efficacy was assumed to remain constant over time for all NOACs and warfarin. Patient movement between health states was modeled using 1-month cycles for 30 years or until death.

The following health states were included in the base case: well, ischemic stroke (minor or major), ICH (minor or major), myocardial infarction (MI), and death (Figure 1). Quality-adjusted life expectancy, risk of adverse events, and net costs were quantified over a period of 30 years using a societal perspective. Cost-effective therapies were selected using a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY) gained.16 Model implementation, sensitivity analyses, and outcome calculations were performed using TreeAge Pro 2012 (Williamstown, MA).17

Probability and Severity of Adverse Events

The risks of adverse events for NOACs and warfarin were based on clinical trial data from Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) (apixaban 5 mg twice daily); Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) (dabigatran 150 mg twice...
daily); and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) (rivaroxaban 20 mg once daily).8–10,18 Probabilities of adverse events for warfarin were calculated from pooled clinical trial results.4–10,18

Ischemic stroke was classified into one of the following 4 categories: fatal, major, minor, or no residual neurological sequelae.12 The rate of stroke increased by a factor of 1.4 per decade of life (multiplicative adjustment).12,13 After an ischemic stroke or ICH, a patient’s risk of mortality increased by a factor of 3.7.20 Hemorrhage was classified as one of the following 4 categories: fatal, ICH, gastrointestinal, or non-fatal minor extracerebral.4–10,18 Using aggregated probabilities reported in a study by Kamel et al,19 an ICH event was further subcategorized as minor, major, or fatal (Table in the online-only Data Supplement). The risk of MI was increased by a factor of 1.3 each decade of the patient’s lifetime (multiplicative adjustment).12 Mortality rates after an MI event increased multiplicatively by a factor of 1.051.18 A relatively common side effect of using dabigatran 150 mg is dyspepsia. As reported in the RE-LY trial, 11.3% of patients receiving dabigatran 150 mg experienced a dyspepsia event.9 The associated cost and utility decrement with dyspepsia were included for patients with the side effect.22,23

Mortality rates for the baseline population were initially adjusted in the model for age (starting at 70 years).14 A patient’s mortality risk was adjusted for age and postevent mortality risks (MI, ischemic stroke, and ICH) throughout the course of the patient’s lifetime and disease progression.20,21,24

Utilities
The baseline patient utility value was adjusted for age, atrial fibrillation, and anticoagulation treatment.21,22 Subsequent disutilities for ischemic stroke, neurological events (ischemic stroke or ICH) with residual MI, gastrointestinal hemorrhage, minor hemorrhage (1 week after the event), and dyspepsia were estimated using pooled nationally representative Medical Expenditure Panel Survey data, as well as derived from published population-specific articles (Table in the online-only Data Supplement).25–29

Costs
One-time event costs for ischemic stroke, ICH, MI, GI hemorrhage, and dyspepsia were estimated from 2009 mean costs published online by the Agency for Healthcare Research and Quality from Healthcare Cost and Utilization Project data under relevant primary International Classification of Diseases Ninth Revision codes and diagnosis-related group codes for Medicare remuneration.22 Cost of a minor hemorrhage was based on payment for an expanded problem-focused physician visit for an established patient (Current Procedural Terminology code 99213).30 Costs of INR testing (Current Procedural Terminology code 85610) and physician visits (Current Procedural Terminology codes 99211 and 99212) were estimated using Medicare reimbursement values.30 Mean prescription drug costs for dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were estimated using wholesale acquisition costs listed in the Medi-Span drug database. The US Food and Drug Administration recently approved apixaban 5 mg for use in the United States; however, the cost is not yet available to include in this analysis. The listed price for apixaban 5 mg in the United Kingdom reported in the National Institutes for Health and Clinical Evidence costing statement was used (£3.43 per day) and converted to US dollars.31

Long-term costs were calculated using the study by Leibson et al13 who evaluated the use of acute care services 12 months after an ischemic stroke or ICH. A study conducted by Jonas et al13 eliciting patient time requirements for warfarin anticoagulation therapy was used to estimate the economic cost of patient time. An equivalent study has not been conducted for NOACs, and therefore, the estimate of clinic visits alone (excluding anticoagulation-related activities) was used for patients modeled to receive apixaban 5 mg, dabigatran 150 mg, or rivaroxaban 20 mg. The medical care component of the US Bureau of Labor Statistics’ Consumer Price Index was used for cost inflation. All costs were expressed in 2012 US dollars.

Results

One-Way Sensitivity Analyses
One-way sensitivity analyses were conducted for costs, utilities, probabilities, age, and the discount rate to determine influential variables with the most impact on the results of the model. A tornado diagram illustrating the cost variables in descending order of influence is shown in Figure 2. Costs with the most influence on total costs estimated from the model were costs of therapy for apixaban, dabigatran, and rivaroxaban, as well as cost of dyspepsia adverse event for patients receiving dabigatran 150 mg. Probabilities contributing the most leverage to model results were age-associated probabilities of ischemic stroke, ICH, and MI, as well as the probability of either an ICH or ischemic stroke for patients receiving rivaroxaban 20 mg. Varying all of these variables over plausible ranges simultaneously did not substantially influence the ICER values of the NOACs compared with warfarin from the base case, nor did the values exceed $50000 per QALY gained (Table).

Probabilistic Sensitivity Analyses
Mean costs and QALYs derived from the probabilistic sensitivity analysis are presented in the Table. Using a WTP threshold of $50000 per QALY gained, apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were cost-effective in 45.1%, 40%, 14.9%, 0% of the simulations, respectively (Figure 3). Increasing the WTP threshold to $100000 per QALY gained yielded a greater difference in the probability of cost-effectiveness among the anticoagulant therapies, where apixaban 5 mg was cost-effective in 60.7% of the iterations, dabigatran 150 mg in

Sensitivity Analyses
Multiple sensitivity analyses of the model variables were performed. First, a series of univariate sensitivity analyses were conducted to assess the relative impact of each model parameter as well as key model assumptions (Figure 2). Parameters and model assumptions were varied over plausible ranges to identify influential model variables (Table in the online-only Data Supplement). Second, a Monte Carlo probabilistic sensitivity analysis was performed incorporating first- and second-order uncertainty (intraindividual and parameter uncertainty, respectively). The gamma distribution was used for costs, whereas a beta distribution was used for transition probabilities and utilities.35
34.9%, rivaroxaban 20 mg in 4.4%, and warfarin was cost-effective in 0% of the iterations.

**Discussion**

This study used published clinical trial data to build a decision model, and results indicated that for patients ≥70 years of age with an increased risk for stroke (CHADS2 ≥1), normal renal functionality, and no previous contraindications to anticoagulant therapy, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg may be cost-effective substitutes for warfarin in the prevention of stroke prophylaxis. Apixaban 5 mg was the most cost-effective anticoagulant among the 3 NOACs in 45.1% of the iterations conducted in a probabilistic sensitivity analysis (WTP threshold was $50,000 per QALY gained).

Published economic literature to date has solely focused on the comparison of 2 treatments: warfarin compared with one of the NOACs. The results from this study may be interpreted in light of previous analyses conducted from a US perspective. In their original study, Freeman et al. reported a baseline ICER of $45,372 per QALY gained for dabigatran 150 mg compared with warfarin. Newly released information prompted the authors to repeat the analysis, incorporating the US cost of dabigatran 150 mg and follow-up RE-LY trial results, which yielded a reduced ICER value of $12,386 per QALY gained. In a similar study conducted by Kamel et al., the authors found the ICER between dabigatran 150 mg and warfarin was $25,000 per QALY gained. The adjusted ICER value reported by Freeman et al and study results from Kamel et al indicate dabigatran is a cost-effective alternative to warfarin, which is a similar finding to this study.

Alternatively, Shah and Gage’s model of dabigatran versus warfarin yielded an ICER estimate of $86,000 per QALY gained.
A notable limitation inherent in this study is the need to extract model parameter values from a variety of different sources. Treatment efficacy and adverse events for apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg were based on one large clinical trial for each therapy (ARISTOTLE, RE-LY, and ROCKET-AF, respectively). Differences among trial designs, outcome definitions, and patient populations spotlight the challenges with cross-trial comparisons. In addition, it should be kept in mind that use of therapies in actual practice may result in different outcomes from clinical trials because different dosing regimens, monitoring, comorbidities, and inclusion/exclusion criteria may be used in actual practice compared with published clinical trials.6–10,24 Real-world evaluations of therapy effectiveness should also assess therapy compliance, which was not reported in the clinical trials, to provide essential data for future economic evaluations to incorporate adherence as a model parameter. Furthermore, important information about different subgroups was not available for each drug, including CHADS, stroke risk score and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly) hemorrhage risk score. Conducting head-to-head studies in real-world community practices will also allow for an assessment of the effectiveness of NOACs compared with the already established warfarin. Other sources were used to collect values for costs, utilities, and other adverse events (ie, stroke severity and disability after stroke), which potentially introduce bias into the analysis. Although cost estimates did not directly incorporate discounts, a range of costs was assessed in the probabilistic sensitivity analysis.

### Conclusions

The NOACs evaluated in this study were more cost-effective compared with warfarin treatment for stroke prevention in patients with NVAF. Of the 3 NOACs, apixaban 5 mg was the preferred anticoagulant for this population because it was most likely to be the cost-effective treatment option at all WTP thresholds $>40,000 per QALY gained. As additional data emerge from studies evaluating the efficacy in subgroups, side effect profile, and generalizability of NOACs, future analyses will perform a more inclusive evaluation of the cost-effectiveness of NOACs. Important subgroups to integrate into future cost-effectiveness models include strata of CHADS, stroke risk score, HAS-BLED hemorrhage risk score, renal impairment, and age. Meanwhile, healthcare providers already encounter choices between NOACs and

### Table. Projected Costs, QALYs, and ICERs for Patients With Nonvalvular Atrial Fibrillation Receiving Anticoagulation Therapy

<table>
<thead>
<tr>
<th></th>
<th>Base Case</th>
<th>Probability Sensitivity Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Cost</td>
<td>QALY (SD)</td>
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<tr>
<td>Warfarin</td>
<td>$77,813</td>
<td>7.97</td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg</td>
<td>$78,738</td>
<td>8.26</td>
</tr>
<tr>
<td>Dabigatran, 150 mg</td>
<td>$82,719</td>
<td>8.41</td>
</tr>
<tr>
<td>Apixaban, 5 mg</td>
<td>$85,226</td>
<td>8.47</td>
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</table>

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; and SD, standard deviation.

*aWarfarin is the reference therapy for the ICER calculation.*
warfarin in clinical practice for this high-risk population. The findings provided from this study, in combination with results of previously conducted analyses, provide an estimation of the implications of clinician decisions. NOACs are adequate cost-effective alternatives to warfarin for the prevention of stroke prophyaxis in patients with NVAF.

Disclosures
None.

References
17. TreeAge Pro, Inc. (TreeAge Pro Suite) [Computer Program]. Williamstown, MA: TreeAge Pro, Inc; 2012.
ONLINE SUPPLEMENT

1. Supplemental Table S1
2. Supplemental References
## Supplementary Table S1. Decision model inputs: event probabilities, utilities, and costs.

<table>
<thead>
<tr>
<th>Annual event probabilities</th>
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</tr>
<tr>
<td><strong>IS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban, 5 mg</td>
<td>0.0088</td>
<td>(0.008 - 0.010)</td>
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</tr>
<tr>
<td>Dabigatran, 150 mg</td>
<td>0.0091</td>
<td>(0.008 - 0.010)</td>
<td>2,3</td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg</td>
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<td>(0.009 - 0.012)</td>
<td>4</td>
</tr>
<tr>
<td>Warfarin†</td>
<td>0.0110</td>
<td>(0.009 - 0.012)</td>
<td>1-4</td>
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<tr>
<td>Severity of IS, all therapies</td>
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<tr>
<td>Non-disabling</td>
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<tr>
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<tr>
<td>Major</td>
<td>0.392</td>
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<td>5</td>
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<tr>
<td>Fatal</td>
<td>0.102</td>
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<tr>
<td><strong>Hemorrhage</strong></td>
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<tr>
<td><strong>ICH</strong></td>
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<td>0.0029</td>
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<tr>
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<td>Warfarin†</td>
<td>0.0066</td>
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<tr>
<td>ICH severity, all therapies</td>
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<tr>
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<td>Major</td>
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<tr>
<td>Fatal (within 30 days)</td>
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<td><strong>GI hemorrhage</strong></td>
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<tr>
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<tr>
<td>Warfarin†</td>
<td>0.0089</td>
<td>(0.008 - 0.010)</td>
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<tr>
<td><strong>Minor hemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>(0.08 - 0.10)</td>
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<tr>
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<td>(0.12 - 0.15)</td>
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</tr>
<tr>
<td>Rivaroxaban, 20 mg</td>
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<td>(0.07 - 0.09)</td>
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<tr>
<td>Warfarin†</td>
<td>0.1118</td>
<td>(0.10 - 0.12)</td>
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<tr>
<td><strong>Fatal hemorrhage</strong></td>
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<td>(0.001 - 0.003)</td>
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<tr>
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<tr>
<td>Rivaroxaban, 20 mg</td>
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<td>(0.001 - 0.003)</td>
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<tr>
<td>Warfarin†</td>
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<td>(0.002 - 0.005)</td>
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<tr>
<td><strong>Myocardial Infarction</strong></td>
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<td>(0.004 - 0.006)</td>
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<td>Dabigatran, 150 mg</td>
<td>0.0080</td>
<td>(0.007 - 0.009)</td>
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<tr>
<td>Rivaroxaban, 20 mg</td>
<td>0.0071</td>
<td>(0.006 - 0.008)</td>
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<td>Warfarin†</td>
<td>0.0068</td>
<td>(0.006 - 0.008)</td>
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<table>
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<tr>
<th><strong>QALY estimates (utilities)</strong></th>
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<td>Atrial Fibrillation (ICD-9 427)</td>
<td>0.81</td>
<td>(0.70-0.90)</td>
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<tr>
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<td>-0.0003</td>
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<tr>
<td>Decrement for anticoagulation</td>
<td>-0.0105</td>
<td>(-0.011 - 0.009)</td>
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<tr>
<td>Decrement for ischemic stroke (CCC 109)</td>
<td>-0.1393</td>
<td>(-0.150 - 0.120)</td>
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<td>Neurological event (IS and ICH) with residua</td>
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<tr>
<td>Minor</td>
<td>-0.2916</td>
<td>(-0.30 - -0.28)</td>
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<tr>
<td>Major</td>
<td>-0.4455</td>
<td>(-0.46 - -0.43)</td>
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<tr>
<td>Decrement for MI (ICD-9 410)</td>
<td>-0.1351</td>
<td>(-0.145 - 0.120)</td>
<td>6</td>
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</table>
### Costs

#### One-time events costs
- **IS, no residua (ICD-9 434.91, DRG 66)**
  - $9,503.39 ($4,000 - $16,000)
- **Minor IS (ICD-9 434.91, DRG 65)**
  - $10,669.51 ($4,000 - $16,000)
- **Major IS (ICD-9 434.91, DRG 64)**
  - $13,337.50 ($10,000 - $25,000)
- **ICH (ICD-9 430-432)**
  - $20,790.34 ($15,000 - $65,000)
- **MI (ICD-9 410.71)**
  - $20,323.17 ($10,000 - $45,000)
- **GI hemorrhage (ICD-9 578.9)**
  - $10,201.12 ($5,000 - $15,000)
- **Dyspepsia**
  - $6,648.00 ($3,500 - $9,000)
- **Minor hemorrhage (CPT 99213)**
  - $83.94 ($0 - $200)
- **Death**
  - $10,000.00 ($0 - $20,000)

#### Long-term event costs, yearly
- **Minor ischemic stroke**
  - $20,880.24 ($12,000 - $48,000)
- **Major ischemic stroke**
  - $64,629.36 ($24,000 - $102,000)
- **ICH**
  - $96,926.04 ($24,000 - $120,000)
- **MI**
  - $3,638.40 ($1,568.28 - $7,267.68)

#### Therapy costs, yearly
- **Apixaban 5 mg**
  - $3,920.10 ($1,825 - $5,475)
- **Dabigatran 150 mg**
  - $2,664.50 ($1,460 - $3,650)
- **Rivaroxaban 20 mg**
  - $2,660.85 ($1,460 - $3,650)
- **Warfarin**
  - $164.25 ($109.90 - $730)

#### Warfarin associated costs, yearly
- **INR testing (monthly) (CPT 85610)**
  - $83.80 ($27.93 - $167.60)
- **Minimal established visits (monthly)**
  - $408.00 ($136 - $816)
- **Economic value of patient time for INR test**
  - $1,750.92 ($583.64 - $1,750.92)

#### Non-warfarin associated costs, yearly
- **Minimal established visit (every 3 months) (CPT 99211, 99212)**
  - $136.00 ($68 - $408)

#### Cost and utility discounting rate, %
- 3 (0 - 5)

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Supplementary Table S1 (continued). Decision model inputs: event probabilities, utilities, and costs.

<table>
<thead>
<tr>
<th>Decision model inputs</th>
<th>Value</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrement for GI hemorrhage</td>
<td>-0.0486</td>
<td>(-0.060 - 0.030)</td>
<td>10</td>
</tr>
<tr>
<td>Decrement for minor hemorrhage (1 week)</td>
<td>-0.0031</td>
<td>(-0.004 - 0.002)</td>
<td>11</td>
</tr>
<tr>
<td>Decrement for dyspepsia§</td>
<td>-0.0032</td>
<td>(-0.004 - 0.002)</td>
<td>10</td>
</tr>
</tbody>
</table>

CPT = Current Procedural Terminology; DRG = Diagnostic Related Group; ICH = intracranial hemorrhage; INR = International Normalized Ratio; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year

* Summed ischemic and unspecified strokes for rivaroxaban 20 mg, once daily.

† Warfarin event rates were pooled warfarin events from ARISTOTLE, RE-LY, and ROCKET-AF.

‡ Fatal hemorrhage was not reported in the dabigatran trial (RE-LY). A weighted average was calculated using ARISTOTLE (apixaban 5 mg) and ROCKET-AF (rivaroxaban 20 mg).

§ Dyspepsia events and costs only for patients receiving dabigatran 150 mg, twice daily.
Supplementary References


19. Jonas DE, Shilliday BB, Laundon WR, Pignone M. Patient time requirements for 
20. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the 