Cost-Effectiveness of Genotype-Guided Warfarin Dosing for Patients With Atrial Fibrillation

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Background—CYP2C9 and VKORC1 genotyping has been advocated as a means of improving the accuracy of warfarin dosing. However, the effectiveness of genotyping in improving anticoagulation control and reducing major bleeding has not yet been compellingly demonstrated. Genotyping currently costs $400 to $550.

Methods and Results—We constructed a Markov model to evaluate whether and under what circumstances genetically-guided warfarin dosing could be cost-effective for newly diagnosed atrial fibrillation patients. Estimates of clinical event rates, treatment and adverse event costs, and utilities for health states were derived from the published literature. The cost-effectiveness of genetically-guided dosing was highly dependent on the assumed effectiveness of genotyping in increasing the amount of time patients spend appropriately anticoagulated. If genotyping increases the time spent in the target international normalized ratio range by <5 percentage points, its incremental cost-effectiveness ratio would be greater than $100 000 per quality-adjusted life year. The incremental cost-effectiveness ratio falls below $50 000 per quality-adjusted life year if genotyping increases the time spent in range by 9 percentage points. The results were also sensitive to assumptions about the rate of major bleeding events during treatment initiation and the cost of the test.

Conclusions—Our results suggest that genotyping before warfarin initiation will be cost-effective for patients with atrial fibrillation only if it reduces out-of-range international normalized ratio values by more than 5 to 9 percentage points compared with usual care. Given the current uncertainty surrounding genotyping efficacy, caution should be taken in advocating the widespread adoption of this strategy. (Circ Cardiovasc Qual Outcomes. 2009;2:429-436.)

Key Words: anticoagulants • genetics • cost-benefit analysis • arrhythmias, cardiac

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a prevalence of approximately 5% in people over age 65.1 Patients with nonvalvular AF face a 5-fold increased risk of thromboembolic stroke.2 Warfarin can reduce this risk substantially,2 but its narrow therapeutic index and marked interpatient variability in metabolism can cause substantial morbidity and mortality because of over- or underanticoagulation.3

Editorial see p 402

Genetic testing has been advocated as a means to improve the accuracy of warfarin dosing. Patients with 2 common variant alleles of the CYP2C9 gene, which codes for a hepatic enzyme required for warfarin metabolism, have lower warfarin requirements4,5 and are at increased risk of excess anticoagulation3-8 and bleeding.6,7 The vitamin K epoxide reductase complex subunit 1 (VKORC1) gene also plays a role in warfarin metabolism.5,8 A patient’s demographic and clinical characteristics and CYP2C9 and VKORC1 genotype together account for approximately 50% of the dose variability between individuals,8,9 whereas demographic and clinical factors alone account for only 20%.3 Under genotype-guided dosing, an algorithm is used to predict the starting dose for each patient, with patients carrying CYP2C9 *2 or *3 alleles or VKORC1 CT and TT variants receiving lower doses than CYP2C9*1 and VKORC1 CC patients.

Despite its theoretical appeal, the effectiveness of pharmacogenomically-guided dosing in improving clinical outcomes remains controversial. Only 2 published trials have compared genotype-guided and standard dosing for patients initiating warfarin.10 One study found that genotyping did not reduce the proportion of international normalized ratio (INR) values that were out-of-target range, but did predict stable warfarin doses more accurately and result in fewer and smaller dosing changes.10 A second study found that CYP2C9 genotyping increased the time patients spent with a therapeutic INR (80.4% versus 63.4%, P<0.001) and reduced minor bleeding events.11 No published trials have adequately evaluated the impact of genotype-guided dosing on rates of major bleeding or thrombotic events.

Nevertheless, the US Food and Drug Administration recently updated the warfarin label to include the potential
value of genetic testing for patients taking this drug. Several companies are developing genotyping assays for CYP2C9 and VKORC1. With test prices ranging from $400 to $550, the widespread implementation of genetic testing to guide warfarin dosing for the 7 to 10 million patients taking this drug in the United States would have significant economic consequences. It is therefore important to establish the plausible range of cost-effectiveness of pharmacogenetic testing for warfarin while trials are underway to define its clinical properties.

WHAT IS KNOWN

- CYP2C9 and VKORC1 genotyping has been advocated as a means of improving the accuracy of warfarin dosing.
- Genotyping currently costs $400 to $550, and its effectiveness in improving anticoagulation control and reducing major bleeding has not yet been compellingly demonstrated.

WHAT THE STUDY ADDS

- Our results suggest that genotyping before warfarin initiation will be cost-effective for patients with atrial fibrillation only if it reduces out-of-range international normalized ratio values by 5 to 9 percentage points compared with usual care.
- Given the current uncertainty surrounding genotyping efficacy, caution should be taken in advocating the widespread adoption of this strategy.

Methods

We constructed a state transition Markov model to evaluate under what circumstances CYP2C9 and VKORC1 genotyping before warfarin initiation could be cost-effective in a cohort of patients with AF. This model (Figure 1) simulates the progression of a hypothetical cohort of 70-year-old patients with newly-diagnosed AF who initiate warfarin as they move through a series of states describing treatment (on or off warfarin) and health status (healthy, post ischemic stroke with major residual deficit, postischemic stroke with minor residual deficit, postrinacranial hemorrhage [ICH] with major residual deficit, post-ICH with minor residual deficit, and dead). Movement between these states is governed by transition probabilities estimated from the clinical literature.

The model tracks the proportion of the cohort in each health state over time and produces estimates of life expectancy, costs, and quality-adjusted life years (QALYs). A metric that captures both mortality and morbidity, over a lifetime horizon. The model is run over time and produces estimates of life expectancy, costs, and quality-adjusted life years (QALYs), a metric that captures both mortality and morbidity, over a lifetime horizon.

Because of the conflicting data on the effectiveness of genotyping, our primary analysis was a threshold analysis to assess the test characteristics under which genetically-guided dosing would be cost-effective. Although there is no single accepted threshold below which interventions should necessarily be funded, one commonly cited level is $50 000/QALY. At the other extreme, few interventions with cost-effectiveness ratios greater than $100 000/QALY receive funding. Our analysis was conducted from a societal perspective such that all costs were included regardless of payer.

Future costs and life years were discounted at an annual rate of 3%. Analyses were performed with Data TreeAge Pro (TreeAge).

Model Inputs

Model inputs were derived from the published literature (Table). Relevant articles were identified through Medline searches, with the Cost-Effectiveness Analysis Registry serving as an additional resource for utility data. Where possible, data from meta-analyses were used. When only a single article provided sufficiently granular data for the population of interest, the generalizability of these data were assessed through a comparison to other available data.

Impact of Genetic Test on Anticoagulation Control

We estimated the distribution of patient-time spent in various INR ranges under usual care from a study of AF patients initiating warfarin. In this study, patients spent 57.7% of time in range (INR 2 to 3), 28.7% at an INR <2, 11.2% at an INR of 3 to 4, and 2.4% at an INR >4. Data from the anticoagulation clinic arm of a recent trial was used to further divide the INR <2 category into <1.5 versus 1.5 to 2. Assumptions about genetically-guided dosing would increase the percentage of time patients spent in the target INR range during the first 3 months after warfarin initiation but not subsequently, as sufficient time would have elapsed to adjust dosing in response to repeated INR measurements. This assumption is supported by data on time to stable dosing within the control arm of a recent trial of genetically-guided dosing. We modeled varying effectiveness of genotyping during the initial 3-month period from a 0% to 30% increase in the percentage of time spent in the target INR range, and used a value of 8.5% more time spent in range for 1-way sensitivity analyses of other variables (see below) as this was the midpoint of the results of the 2 published RCTs of genetically-guided dosing.

We assumed that genotyping would move patients from each out-of-range INR category (ie, sub- or supratherapeutic) into the target range, based on the contribution of that out-of-range category to total person-time.

INR-Specific Bleeding Rates

We classified major bleeding events as intracerebral hemorrhage (ICH), gastrointestinal, or other. All events were then subdivided into fatal or nonfatal, with nonfatal ICH further classified as resulting in major, minor, or no neurological deficit. During the first 3 months of therapy, patients were assumed to have major bleeding events at rates predicted by their INRs; INR-specific bleeding rates were obtained from a study of AF patients initiating warfarin. Because patients in this study were followed for up to a year and because INR-specific bleed rates are higher during the first 90 days of warfarin therapy than over the subsequent period, we incremented the reported rates by a factor of 1.95 to match the overall bleed rate (14.23/100 person-years) reported during the first 90 days of treatment. During subsequent periods patients taking warfarin were assumed to have bleeding events at a rate of 1.2% per year, based on data from a recent systematic review. Minor bleeding events were assumed to occur at a rate 6.25 times the major bleed rate based on data from the anticoagulation clinic arm of a recent RCT. Patients who have a bleeding event were assumed to discontinue warfarin therapy and to have bleeds at a rate 0.45 times that of warfarin-treated subjects, based on data from a recent meta-analysis. Because not all patients with warfarin-associated bleeding will discontinue treatment, we conducted a secondary analysis assuming that such patients would continue treatment.

INR-Specific Ischemic Stroke Rates

The incidence of ischemic stroke by INR during the first 3 months of treatment was determined from the published literature. During subsequent periods, we modeled stroke rates using a validated prediction rule (CHADS). In our primary analysis, we assigned patients an initial CHADS, score of 0, increasing the score when subjects turned 75 or had an ischemic stroke. Based on the trial literature, we modeled warfarin as reducing the rate of ischemic stroke by 65%.
We assumed monitoring would include 8 INR tests during the first month of treatment and 1 in each subsequent month. The costs of bleeding events and ischemic strokes were calculated by summing the costs associated with acute hospitalization, physician services, and postacute care (see supplementary materials). An estimate of the cost of deaths attributable to hemorrhagic strokes, nonevent deaths, or event-free survival at rates specific to that INR range. Hemorrhages are further classified as ICH, gastrointestinal (GI) bleed, or other, and both ICHs and ischemic strokes are classified based on resulting residual deficit. Based on their status at the end of the cycle, patients begin the next 3-month cycle in one of the health states depicted under “patient status in subsequent cycles.” The process continues until all patients are dead. *States that are further classified based on treatment status (on or off warfarin).

Mortality Rates
We used recent population-based studies to estimate the relative mortality rates for incident AF patients with and without prior stroke compared with the general US population. The mortality rate ratios matched for age and gender are 9.6 during the 1st 3 months, 4.3 during the following 3 months, and 1.7 for all subsequent periods. Patients with a prior stroke were assigned a background mortality rate 1.8 times higher. We validated survival curves generated from our model against survival curves from the literature. Warfarin treatment was assumed to confer a 26% reduction in all-cause mortality based on a recent meta-analysis of RCT data.

Costs
We estimated the cost of CYP2C9 and VKORC1 genotyping at $475, based on current pricing, and added $100 for phlebotomy and record-keeping. To assess the effect of reductions in cost attributable to technological advances, we considered a total cost of $200 in a sensitivity analysis. We used the RedBook average wholesale price to estimate the cost of warfarin at an average daily dose of 5 milligrams. We assumed monitoring would include 8 INR tests during the first month of treatment and 1 in each subsequent month. The costs of bleeding events and ischemic strokes were calculated by summing the costs associated with acute hospitalization, physician services, and postacute care (see supplemental materials). An estimate of the cost of deaths attributable to causes other than bleeding events and ischemic strokes was obtained from a published analysis of end-of-life costs in the Medicare Current Beneficiary Survey. In our primary analysis we excluded medical costs arising in added years of life; these were included in a sensitivity analysis.

All costs are expressed in 2007 US dollar values. Where necessary, older estimates were inflated using the Medical Care Component of the Consumer Price Index.

Quality-of-Life Adjustment (Utilities)
Patient preferences for the health states of being healthy with AF and alive with major or minor residual deficit after a stroke were estimated from published literature. Utilities for stroke states were obtained by multiplying published stroke utility values by the AF utility of 0.82.

Sensitivity Analyses
To assess the degree to which our results were sensitive to uncertainty surrounding parameter estimates and population heterogeneity, we performed 1-way analyses varying individual variables over the ranges presented in the Table, holding all other parameters at their expected values. We conducted multi-way analyses on parameters identified as influential in 1-way analyses. Lastly, we performed a probabilistic sensitivity analysis in which all parameters were varied simultaneously over specified probability distributions. In this analysis, the model was run using a value for each parameter drawn randomly from the distribution assigned to that parameter. The process is repeated 10,000 times. Distributions were assigned based on the data from which the parameter estimates were derived. Beta distributions were assigned to utilities and probabilities, which are constrained to fall between 0 and 1. Rates and rate-ratios were assumed to follow log-normal distributions, and adverse event-related costs were assumed to be gamma distributed. We assigned a uniform distribution to the cost of genotyping and its effectiveness in increasing the percentage of time spent appropriately anticoagulated.

Results
For a cohort of 70-year-old incident AF patients who initiate warfarin under usual care, we estimated a life expectancy of 11.42 life years, a discounted quality-adjusted life expectancy of 7.28 QALYs, and a discounted lifetime healthcare cost of $22,541 for expenditures related to AF sequelae and treatment.

The results of our primary analysis are presented in Figure 2. The cost-effectiveness of genetically-guided dosing was...
Table. Model Variables: Base Case Values and Ranges Used in Sensitivity Analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Expected Value</th>
<th>Range</th>
<th>Distribution for Probabilistic Sensitivity Analysis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution of time spent in INR ranges</td>
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<tr>
<td>Under usual care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Within range INR (2 to 3)</td>
<td>57.7%</td>
<td>52.6% to 62.9%</td>
<td>beta</td>
<td>21, 22</td>
</tr>
<tr>
<td>% Very low INR (&lt;1.5)</td>
<td>6.7%</td>
<td>2.5% to 10.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Low INR (1.5 to 2)</td>
<td>22.0%</td>
<td>16.5% to 27.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% High INR (3 to 4)</td>
<td>11.2%</td>
<td>7.9% to 14.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Very high INR (&gt;4)</td>
<td>2.4%</td>
<td>1.1% to 4.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute increase in % in range with genetically-guided dosing</td>
<td>8.5%</td>
<td>0% to 17%*</td>
<td>Uniform</td>
<td>10, 11</td>
</tr>
<tr>
<td>Event rates (per person-year)</td>
<td></td>
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<tr>
<td>Hemorrhagic events</td>
<td></td>
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<tr>
<td>Major bleeding rate as a function of INR</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>INR &lt;3</td>
<td>0.038</td>
<td>0.021 to 0.068</td>
<td>Log-normal</td>
<td>21</td>
</tr>
<tr>
<td>INR 3 to 4</td>
<td>0.158</td>
<td>0.071 to 0.351</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR &gt;4</td>
<td>0.993</td>
<td>0.496 to 1.985</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplier applied to event rates above to reflect increased risk during 1st 90 d of warfarin use</td>
<td>1.95</td>
<td>0.55 to 3.35</td>
<td>Triangle</td>
<td>21</td>
</tr>
<tr>
<td>Major bleeding rate in patients receiving warfarin after 90 d</td>
<td>0.0146</td>
<td>0.011 to 0.02</td>
<td>Log-normal</td>
<td>23</td>
</tr>
<tr>
<td>Relative rate of bleeding among untreated vs warfarin-treated patients</td>
<td>0.45</td>
<td>0.25 to 0.82</td>
<td>Log-normal</td>
<td>24</td>
</tr>
<tr>
<td>Percentage of all bleeds that are major (to calculate minor bleed rates)</td>
<td>13.8%</td>
<td>9% to 20%</td>
<td>beta</td>
<td>23</td>
</tr>
<tr>
<td>Ischemic strokes</td>
<td></td>
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<tr>
<td>Ischemic stroke rate as a function of INR</td>
<td></td>
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</tr>
<tr>
<td>INR &lt;1.5</td>
<td>0.077</td>
<td>0.057 to 0.104</td>
<td>Log-normal</td>
<td>25</td>
</tr>
<tr>
<td>INR 1.5 to 1.99</td>
<td>0.019</td>
<td>0.014 to 0.024</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR ≥2</td>
<td>0.006</td>
<td>0.005 to 0.008</td>
<td></td>
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</tr>
<tr>
<td>Ischemic stroke rate in untreated patients as a function of CHADS2 score after 1st 90 days</td>
<td>0.019–0.182</td>
<td>See Gage, 2001</td>
<td>Log-normal</td>
<td>26</td>
</tr>
<tr>
<td>Relative rate of stroke with warfarin vs no treatment</td>
<td>0.36</td>
<td>0.26 to 0.51</td>
<td>Log-normal</td>
<td>27</td>
</tr>
<tr>
<td>Mortality after acute events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of death after ICH in patients on warfarin</td>
<td>52%</td>
<td>42% to 61%</td>
<td>beta</td>
<td>28</td>
</tr>
<tr>
<td>ICH mortality rate ratio for warfarin users vs untreated</td>
<td>2.2</td>
<td>1.3 to 3.8</td>
<td>Log-normal</td>
<td></td>
</tr>
<tr>
<td>Probability of death after GI bleed</td>
<td>7.23%</td>
<td>4% to 10%</td>
<td>beta</td>
<td>29</td>
</tr>
<tr>
<td>Probability of death after other bleed</td>
<td>2.10%</td>
<td>0% to 4%</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Probability of death after ischemic stroke if INR &lt;2</td>
<td>16%</td>
<td>10% to 23%</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Probability of death after ischemic stroke if INR ≥2</td>
<td>6%</td>
<td>2% to 12%</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Distribution of adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability that major bleeding event is ICH</td>
<td>30%</td>
<td>24% to 37%</td>
<td>beta</td>
<td>2, 30</td>
</tr>
<tr>
<td>Probability of major deficit among nonfatal ICH</td>
<td>22.1%</td>
<td>14% to 32%</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Probability that major bleeding event is GI hemorrhage</td>
<td>60%</td>
<td>53% to 64%</td>
<td></td>
<td>2, 30</td>
</tr>
<tr>
<td>Probability of major deficit among nonfatal ischemic stroke with INR &lt;2</td>
<td>51%</td>
<td>45% to 64%</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Probability of major deficit among nonfatal ischemic stroke with INR ≥2</td>
<td>43%</td>
<td>32% to 54%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
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<tr>
<td>Warfarin, 3-mo supply</td>
<td>$71</td>
<td>$39 to $112</td>
<td>gamma</td>
<td>32</td>
</tr>
<tr>
<td>CYP2C9 and VKORC1 genotyping + blood sample collection</td>
<td>$575</td>
<td>$500 to $650</td>
<td>Uniform</td>
<td>13, 14</td>
</tr>
<tr>
<td>INR monitoring</td>
<td>$29</td>
<td>$15 to $46</td>
<td>gamma</td>
<td>33</td>
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</table>

(Continued)
highly dependent on the impact of genotyping on the additional amount of time that patients would spend within the therapeutic INR range of 2 to 3, compared with usual care. If genotyping increases time spent in range by 5 percentage points (eg, from 57.7% to 62.7%), its incremental cost-effectiveness ratio (ICER) would be $100 000 per QALY. The ICER would be $50 000 per QALY if genotyping increases time spent in range by 9 percentage points, and $8000 per QALY with a 30–percentage point increase.

These results were sensitive to several other parameters, as illustrated in Figure 3. Genotyping was more cost-effective in younger patients, with the ICER increasing from $29 000 per QALY in 50-year-old patients to $120 000 per QALY in 85-year-old patients. Test costs and assumptions about the rate of major bleeding during treatment initiation also influenced the results, because this parameter affected the number of bleeding events that could be averted through genotyping.

The results were also sensitive to the degree to which out-of-range patients were shifted into range from subtherapeutic versus supratherapeutic INRs. Because the difference in bleeding rates between ranges is larger than the difference in stroke rates, moving patients from supratherapeutic INR

Table. Continued

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Expected Value</th>
<th>Range</th>
<th>Distribution for Probabilistic Sensitivity Analysis Source</th>
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<tr>
<td>Acute events</td>
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<tr>
<td>ICH with major residual deficit</td>
<td>$33 218</td>
<td>$18 000 to 50 000</td>
<td>gamma</td>
<td>See text</td>
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<tr>
<td>ICH with minor residual deficit</td>
<td>$25 692</td>
<td>$14 000 to 41 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke with major residual deficit</td>
<td>$21 537</td>
<td>$12 000 to 34 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke with minor residual deficit</td>
<td>$15 499</td>
<td>$8000 to 24 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>$10 286</td>
<td>$7000 to 16 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other hemorrhage</td>
<td>$9601</td>
<td>$5000 to 15 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other death</td>
<td>$10 396</td>
<td>$5000 to 16 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor bleed</td>
<td>$183</td>
<td>$100 to 290</td>
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<td>Ongoing postacute care</td>
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<td></td>
<td>See text</td>
</tr>
<tr>
<td>ICH or ischemic stroke with major deficit</td>
<td>$3940</td>
<td>$2000 to 6000</td>
<td>gamma</td>
<td></td>
</tr>
<tr>
<td>ICH or ischemic stroke with minor deficit</td>
<td>$1266</td>
<td>$700 to 2000</td>
<td></td>
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<tr>
<td>Utilities</td>
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<tr>
<td>Atrial fibrillation</td>
<td>0.82</td>
<td>0.70 to 0.91</td>
<td>beta</td>
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<tr>
<td>Stroke with major residual deficit</td>
<td>0.36</td>
<td>0.11 to 0.66</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>Stroke with minor residual deficit</td>
<td>0.76</td>
<td>0.52 to 0.94</td>
<td></td>
<td>34</td>
</tr>
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</table>

*The effectiveness of genotyping in increasing time in the target anticoagulation range was varied up to 30% in 1-way sensitivity analyses.

Figure 2. Cost-effectiveness of genotyping as a function of its effectiveness on anticoagulation control. In the primary analysis, genotyping was assumed to cost $575 and the bleeding rate during the first 3 months of treatment under usual care set at 14.4 per 100 person-years. Under these assumptions, and assuming a willingness to pay of $50 000 per QALY, genetically-guided dosing would be cost-effective if it increased time in the target INR range by >8.5 percentage points (denoted by point A). Under a favorable scenario (test cost of $200, bleed rate of 24.7/100 person-years), genotyping was cost-effective if it increased time in range by more than 2 percentage points (point B) and became cost-saving if it increased time in range by more than 14 percentage points. Under an unfavorable scenario (test cost of $650, bleed rate of 4.1/100 person-years), genotyping was not cost-effective at a willingness to pay of $50 000 per QALY unless it increased time in range by more than 22 percentage points.
Genotype-guided dosing has received increasing attention as a potentially useful strategy to improve the efficacy and safety of warfarin. We constructed a model of genetically-guided warfarin dosing versus usual care in patients with new AF who initiate warfarin and found that the cost-effectiveness of genotype-guided warfarin dosing is highly dependent on the effectiveness of genotyping in reducing out-of-range INR values under our base case assumptions about cost. The approach would have an ICER < $100 000 per QALY if it increased the time spent in the target INR range during the first 3 months of treatment by 5 percentage points compared with usual care, and an ICER of <$50 000 per QALY if it increased time in range by 9 percentage points. This level of performance has not been consistently reported in the existing literature. These results were sensitive to assumptions about the test cost, the rate of major bleeding during this period, and the degree to which the strategy would eliminate supra-therapeutic INRs.

Two prior peer-reviewed economic evaluations of the potential value of genotype-guided warfarin dosing have yielded estimates of approximately $6000 per major bleed averted, although they do not provide estimates of cost per QALY gained, as is generally recommended. Further, these studies use lower test costs and more optimistic estimates of the effectiveness of pharmacogenomically-guided warfarin
dosing at reducing bleeding rates than used in our analy-
sis. A third publication reported estimates ranging from
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Details of Costing Methodology

We estimated the cost of CYP2C9 and VKORC1 genotyping at $475, based on current pricing\textsuperscript{23-25} and added $100 for phlebotomy and record-keeping.\textsuperscript{26} To assess the effect of reductions in cost due to future technological advances, we also considered a total cost of $200 in a sensitivity analysis. We used the RedBook average wholesale price to estimate the cost of warfarin at an average daily dose of 5 milligrams.\textsuperscript{45} We assumed monitoring would include 8 INR tests during the first month of treatment and 1 in each subsequent month.\textsuperscript{46} The costs of bleeding events and ischemic strokes were calculated by summing the costs associated with acute hospitalization, physician services, and post-acute care. Additional details are provided in the appendix. Inpatient hospitalization costs were calculated by applying cost-to-charge ratios to charges reported for the events of interest, identified by primary diagnosis codes in patients with atrial fibrillation coded as a comorbid condition in the Nationwide Inpatient Sample (NIS).\textsuperscript{47} Physician service costs were estimated from payment rates from the Medicare Physician Fee Schedule\textsuperscript{48} and NIS data on lengths of stay and procedures performed for specific diagnoses. Data on discharge placement were also obtained from the NIS data and augmented with data from the North Manhattan Stroke Study, stratified by neurological deficit.\textsuperscript{49} Costs for rehabilitation stays, home health care and long term care were obtained from published sources for each diagnosis and neurological status.\textsuperscript{50, 51} Informal care
costs were estimated by multiplying the average hourly wage of a home health aide, as a proxy for the monetary value of an hour of informal caregiving, by the number of hours of informal care use reported by stroke patients. An estimate of the cost of deaths due to causes other than bleeding events and ischemic strokes was obtained from a published analysis of end-of-life costs in the Medicare Current Beneficiary Survey. In our primary analysis we excluded medical costs arising in added years of life; these were included in a sensitivity analysis.

All costs are expressed in 2007 U.S. dollar values. Where necessary, older estimates were inflated to 2007 dollar values using the Medical Care Component of the Consumer Price Index.