Potential Clinical and Economic Outcomes of CYP2C9 and VKORC1 Genotype-Guided Dosing in Patients Starting Warfarin Therapy

JHS You¹, KKN Tsui¹, RSM Wong² and G Cheng²

Warfarin is the most commonly prescribed anticoagulant for the prevention and treatment of thromboembolic events.¹ The anticoagulation effect of warfarin, measured in terms of the international normalized ratio (INR), is subject to wide inter- and intraindividual variability that could possibly lead to hemorrhagic or thromboembolic events—even with careful dosage titration.²,³ A number of factors have been identified as influencing the anticoagulation effect of warfarin therapy; these include age, sex, body weight, comorbidities, concurrent medications, dietary intake, patient compliance level, and genetic factors.⁴,⁵

P450 enzyme (CYP2C9) is responsible for the metabolic clearance of the more pharmacologically potent (S)-warfarin enantiomer. Patients carrying the functionally defective *2 and *3 alleles of CYP2C9 are known to require significantly lower maintenance doses over longer periods of time to achieve stable dosing.⁶-⁸ Vitamin K epoxide reductase complex 1 (VKORC1) recycles reduced vitamin K and is essential for the post-translational ɣ-carboxylation of vitamin K–dependent clotting factors. The effect of VKORC1 variants on anticoagulant dose and response has also been examined.⁹-¹⁵ Patient clinical characteristics and genotypes of CYP2C9 and VKORC1 explain as much as 60% of the variability in warfarin dose requirement.¹⁶-¹⁸

The application of CYP2C9 and VKORC1 genotype data to the personalization of warfarin dosing was evaluated. Warfarin-dosing algorithms, using genetic (CYP2C9 and VKORC1), clinical, and demographic factors, were validated in observational studies against the maintenance-dose requirement.¹⁹-²³ Despite promising findings of improvement in dosing accuracy being reported in validation studies, the clinical benefits of genotype-guided dosing have not been clearly demonstrated in clinical trials. The Couma-Gen trial conducted by Anderson et al.—the only published randomized clinical trial comparing a CYP2C9 and VKORC1 genotype–based dosing algorithm with standard dosing—did not show significant differences in the primary study end point measured as INR control.²⁴ However, another randomized clinical trial...
trial comparing a validated dosing algorithm with a CYP2C9 genotype-adjusted dosing algorithm showed significant improvement in INR control. The US Food and Drug Administration, in August 2007, updated the label information for warfarin to encourage the use of genetic information in initiating warfarin therapy. Nevertheless, only interim treatment outcomes, such as INR control and time to reach stable dose, were examined in randomized clinical trials. The changes in the rates of major adverse events (bleeding and thromboembolism) and the economic impact of genotype-guided dosing are not well established. It is a challenge for practicing clinicians administering anticoagulation care to translate both findings on genotyping and the recommendations of the Food and Drug Administration into their practice. The objectives of the present study were therefore to evaluate the potential clinical and economic outcomes of the CYP2C9 and VKORC1 genotype-guided dosing algorithm in patients newly started on warfarin therapy and to identify factors affecting the cost-effectiveness of the dosing algorithm.

RESULTS

Base-case analysis

The results of the base-case analysis are shown in Table 1. They show that the genotype-guided dosing group accounted for a higher cost and gained a relatively modest improvement in quality-adjusted life-years (QALYs) and survival rate and a relatively modest drop in the rate of total adverse events. The incremental cost per unit outcome improved (ICER) was calculated using the equation:

\[
\text{ICER} = \frac{(\text{Cost}_{\text{genotype-guided dosing}} - \text{Cost}_{\text{standard dosing}})}{(\text{Outcome}_{\text{genotype-guided dosing}} - \text{Outcome}_{\text{standard dosing}})}
\]

The ICERs were $347,059 per QALY gained, $170,192 per event averted, and $1,106,250 per life saved.

### Table 1 Results of base-case analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Genotype-guided dosing</th>
<th>Standard dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per patient per year (US$)</td>
<td>1,367</td>
<td>1,190</td>
</tr>
<tr>
<td>Incremental cost$^a$</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>QALY gained per patient year</td>
<td>0.93130</td>
<td>0.93079</td>
</tr>
<tr>
<td>Incremental QALY</td>
<td>0.00051</td>
<td></td>
</tr>
<tr>
<td>Incremental cost per QALY gained (US$)</td>
<td>347,059</td>
<td></td>
</tr>
<tr>
<td>Adverse events per patient year$^b$</td>
<td>0.04013</td>
<td>0.04117</td>
</tr>
<tr>
<td>Adverse events averted per patient year$^c$</td>
<td>0.00104</td>
<td></td>
</tr>
<tr>
<td>Incremental cost per adverse event averted (US$)</td>
<td>170,192</td>
<td></td>
</tr>
<tr>
<td>Survival rate per year</td>
<td>0.99347</td>
<td>0.99331</td>
</tr>
<tr>
<td>Incremental survival rate</td>
<td>0.00016</td>
<td></td>
</tr>
<tr>
<td>Incremental cost per life saved (US$)$^d</td>
<td>1,106,250</td>
<td></td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life-year.

$^a$Incremental outcome (cost, QALY, survival rate) = Outcome$_{\text{genotype-guided dosing}}$ − Outcome$_{\text{standard dosing}}$.

$^b$Adverse events per patient year = Total adverse events (bleeding + thromboembolism) per patient year.

$^c$Adverse events per patient year averted = Total adverse events$_{\text{standard dosing}}$ − Total adverse events$_{\text{genotype-guided dosing}}$.

$^d$The incremental cost per unit outcome improved: (Cost$_{\text{genotype-guided dosing}}$ − Cost$_{\text{standard dosing}}$)/(Outcome$_{\text{genotype-guided dosing}}$ − Outcome$_{\text{standard dosing}}$).

### Figure 1

One-way sensitivity analysis of three influential variables on ICER per QALY gained by the genotype-guided dosing group. Horizontal lines: variation in incremental cost per QALY gained when the input value was varied over the range indicated. Dotted vertical line: incremental cost per QALY gained by genotype-guided dosing group in base-case analysis. (a) Cost of genotyping: when genotyping cost decreased from US$200 to $47, ICER was <$50,000. ICER became zero (genotype-guided dosing was less costly with higher QALYs) when genotyping cost further decreased to $22. (b) Relative percent reduction in out-of-range INRs in genotype-guided group. ICER was <$50,000 when the reduction in out-of-range INRs increased from 7.3% to 30%. ICER became zero (genotype-guided dosing was less costly with higher QALYs) when it further increased to 65%. (c) Per-patient average percentage of out-of-range INRs in standard dosing group (10%–92%): no threshold value identified for ICER <$50,000. ICER, incremental cost per unit outcome improved; QALY, quality-adjusted life-year.
A three-way sensitivity analysis incorporating the cost of genotyping, the relative percentage reduction in out-of-range INRs in the genotype-guided dosing group, and percentage of out-of-range INRs in standard dosing group on ICER per QALY gained by genotype-guided dosing group. The threshold line is the line dividing the gray zone from the white zone. Combinations of variables on the threshold line led to an ICER of US$50,000. Gray zone: combinations of variables led to ICERs <$50,000. White zone: combinations of variables led to ICERs >$50,000. Incremental cost per unit outcome improved; INR, international normalized ratio; QALY, quality-adjusted life-year.

**DISCUSSION**

Using genetic testing in the personalization of drug treatment is a potential trend in medical practice. This seems to be readily demonstrated in the management of warfarin therapy because the genetic issues relating to warfarin dosing have been extensively studied. A dosing algorithm using genetic (CYP2C9), clinical, and demographic factors was developed and predicted 42% of the maintenance dose of warfarin.\(^{19,20}\) The inclusion of the VKORC1 genotype in the regression model further increased the predictive power of the dosing algorithm to 79% (refs. 21–23).

The feasibility of CYP2C9-guided dosing was first demonstrated in a prospective, randomized pilot trial.\(^{28}\) A prospective, randomized clinical trial subsequently showed significant improvement in anticoagulation control by CYP2C9 genotype-guided dosing vs. standard dosing, in that patients in the genotyped group were within the therapeutic INR range for longer periods of time (80.4% vs. 63.4%, \(P < 0.001\)).\(^{25}\) Nevertheless, Anderson et al. reported that there was no significant difference in the percentage of out-of-range INRs in a comparison of CYP2C9 and VKORC1 genotype-guided dosing and standard dosing (33.1% vs. 30.7%, \(P = 0.47\)).\(^{24}\) The reasons for the failure to demonstrate a clear benefit of the genotype-guided
dosing seemed to be the high quality of anticoagulation control in standard AC care (66.9% INRs in-range) and the less-than-expected improvement in INR control in the study arm. Despite the established association between \textit{CYP2C9} and \textit{VKORC1} variants and warfarin dosage requirement, the relative effectiveness of genotype-guided dosing might be influenced by the baseline performance in INR control of standard anticoagulation care.

In our cost-effectiveness study, we assessed the effectiveness of genotype-guided warfarin dosing with respect to three clinical aspects that most concern clinicians as well as patients: adverse event rate, survival rate, and QALYs. In our base-case analysis, the ICER per adverse event averted ($170,192) was significantly higher than those reported in prior cost-effectiveness analyses (assessing bleeding rate as the primary clinical outcome) of genotype-guided management for warfarin by our team ($5,778 per bleeding episode averted) and Schalekamp \textit{et al.} ($4,233 per bleeding episode averted).\textsuperscript{29,30} Both studies, conducted before results of randomized clinical trials on genotype-guided dosing were available, assumed a large reduction in the bleeding rate and therefore projected a low ICER.

Our results on ICER per QALY gained ($347,059) are similar to the findings of the cost-effectiveness analysis recently reported by Eckman \textit{et al.} They assessed QALYs as the primary clinical outcome and reported an ICER ($170,000) that was also >$50,000.\textsuperscript{31} Although the ICER in our study was two-fold higher than that reported by Eckman \textit{et al.}, this could be explained by the differences in the model’s inputs with respect to the effectiveness of genotype-guided dosing (7.3% reduction in out-of-range INR vs. 32% reduction in major bleeding risk). The lower effectiveness attributed to genotype-guided dosing input in our model resulted in higher ICER, as indicated by the findings of sensitivity analysis.

The one-way sensitivity analysis showed the influence of key variables on ICER per QALY gained. Lowering the cost of genotyping seemed to balance the modest increment in QALYs when the ICER was lowered to <$50,000. Further lowering of the genotyping cost could render genotype-guided dosing cost saving. Similar results were demonstrated with the variation of the relative percentage reduction in out-of-range INRs by genotype-guided dosing, namely, that increase in the effectiveness of INR control could decrease the ICER to zero (when cost saving occurred). A three-way sensitivity analysis was conducted to analyze the interacting effects of effectiveness of genotype-guided dosing, genotyping cost, and the baseline INR control of an AC on the ICER of genotype-guided dosing. It showed that poor baseline INR control (high percentage of out-of-range INRs), a high relative reduction in out-of-range INRs by genotype-guided dosing, and low genotyping cost point to the desirability of lowering the ICER to <$50,000.

This study used decision analysis to evaluate the potential changes in clinical outcomes (QALYs gained, adverse event rates and survival rates) of genotype-guided dosing by simulating the risk of events from control of INRs, with inputs retrieved from the literature on warfarin anticoagulation control and treatment outcome. Our model provides a framework in which to examine the magnitude of improvement needed in the control

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig3.png}
\caption{Decision model of genotype-guided dosing vs. standard dosing for patients in whom warfarin therapy is to be initiated. Patients newly started on warfarin therapy could be managed by (i) standard dosing or (ii) genotype-guided dosing. Patients in both arms were followed up with standard anticoagulation care. The INR control could be within, below, or above the target range, and patients might consequently experience ICH, ECH, TE, or no adverse event. Four tiers of outcomes were simulated for each study arm: (i) total direct medical cost, (ii) major adverse event rate, (iii) survival rate, and (iv) QALYs gained. ECH, extracranial hemorrhage; ICH, intracranial hemorrhage; INR, international normalized ratio; QALY, quality-adjusted life-year; TE, thromboembolism.}
\end{figure}
of INR in order to translate inputs into a cost-effective gain in QALYs. Welte et al. described three factors that affect the generalizability of health-economic evaluation results across countries: method characteristics (e.g., study perspective, discount rates, and costing methods), health-care system characteristics (e.g., absolute and relative costs, practice variations, and technology availability) and population characteristics (e.g., disease incidence/prevalence, health-status preferences). On the basis of the checklist of Welte et al., our study results—which employed US clinical practice, cost structures, and population characteristics—would be more readily transferable to countries with health-care systems and populations similar to those of the United States (such as Canada and the United Kingdom), with minimal effort in checking for variations in these factors in those countries. The transferability of our results might be lower for countries in which the practices of ACs are less established and research on the effectiveness and complications associated with warfarin therapy is limited. It is anticipated that high-level effort would be required to ascertain these factors in countries such as China and India, given their different modes of clinical practice, cost structures, and populations. Our decision model and the influential factors identified could serve as a adaptable framework for the health-care systems in those countries to adopt.

Cost-effectiveness analysis of genotype-guided dosing for warfarin therapy has been limited by the fact that no published clinical trial was sufficiently powered to detect the changes in costs, adverse event rates or mortality rates. The modeling technique has been the only approach used to simulate long-term treatment outcomes of genotype-guided dosing using data from short-term trials. In our study, the effectiveness in INR control of genotype-guided dosing—a key model input, retrieved from a 3-month randomized clinical trial—was applied to project the outcomes at the end of 1 year. Without systematic review, the literature search for inputs for the model could potentially be influenced by publication bias, heterogeneity and robustness bias, and placebo effects, despite the fact that the literature selection process was conducted independently by two reviewers. The uncertainties caused by using efficacy data from a single 3-month trial for a 1-year model and by the literature selection process were examined using sensitivity analysis over a broad range for each input in the model, to test for robustness of the results.

A few factors that could affect the outcome estimation were not fully evaluated in this model. These were the turnaround time for genetic testing, racial differences in frequencies of allelic variants, and education and training of AC staff. The variation in turnaround time for genetic testing and differences in the frequencies of allelic variants were examined in previously published studies, and both factors seemed not to affect the robustness of the cost-effectiveness analysis. The effect of education and training of staff was indirectly examined in this study, in terms of the baseline performance in INR control by the AC. The study showed that this performance was associated with the cost-effectiveness of genotype-guided dosing. We used a standard cost-effectiveness threshold, $50,000, as the threshold of willingness to pay per QALY gained, and the influence of variation of willingness to pay was therefore not evaluated. Nevertheless, it is anticipated that lowering the willingness-to-pay threshold would further limit the acceptability of genotype-guided dosing.

Our findings are that the impact of genotype-guided dosing on clinical outcomes is one of the most crucial factors influencing its cost-effectiveness and acceptability for warfarin therapy. A multicenter clinical trial sponsored by the National Heart, Lung, and Blood Institute has been undertaken to evaluate the effectiveness and safety of genotype-guided dosing. Further cost-effectiveness analyses should be conducted on the basis of the findings of this trial. The baseline performance in INR control at the AC using standard initiation dosing is another important factor to be considered. Genotype-guided dosing appears to be a very costly option for achieving further improvements in clinical outcomes at practice sites where anticoagulation control is already of high quality. Further investigation of the cost-effectiveness of genotype-guided dosing is warranted for subgroups in which there are problems with respect to INR control. The cost of genotyping is the factor that has the most influence on the cost-effectiveness of genotype-guided dosing, and the development of genotyping technology should therefore focus on cost control and turnaround time. At present, the findings of our study contribute cost-effectiveness information to bridge the gap between interim outcomes (INR control) of genotype-guided dosing and clinical and economic outcomes (costs, adverse event rates, mortality rates, and QALYs) in order to aid decision making regarding application of pharmacogenetic information to warfarin therapy.

In conclusion, the potential cost of genotype-guided dosing for warfarin therapy is relatively high for modest improvements observed with respect to QALYs, adverse event rates and lives saved as compared with standard dosing. The estimated ICER per QALY gained by genotype-guided dosing exceeds the generally accepted threshold of $50,000. Lowering the genotyping cost, improving the effectiveness in INR control of the genotype-guided dosing algorithm, and applying the algorithm in practice sites with high out-of-range INRs would improve the cost-effectiveness of the dosing algorithm.

**METHODS**

A decision-tree model (Figure 3) was designed to simulate the outcomes of a hypothetical cohort of patients newly started on warfarin therapy. The model postulated two alternatives over a period of 12 months: (i) standard dosing and (ii) genotype-guided dosing. Patients in the standard dosing group would receive initiation dosing following the 10-mg warfarin nomogram, adopting the standard dosing employed by the Couma-Gen trial. In the genotype-guided dosing group, the starting dose of warfarin would be determined by a dosing algorithm, using demographic, clinical, and genetic (CYP2C9 and VKORC1 genotypes) data. Patients in both groups would be followed up with standard AC care, which is a cost-effective model of care for anticoagulation management. In both study arms, the INR control could be within, below, or above the target range. Patients might consequently experience bleeding, thromboembolism, or no event. Four tiers of outcomes were simulated for each study arm: (1) total direct medical cost, (2) major adverse event rate, (3) survival rate, and (4) QALYs gained.
The definitions of major adverse events were adopted from Fihn et al.37 Major bleeding was defined to include gastrointestinal bleeding; gross hematuria; hemoptysis; and bleeding leading to cardiopulmonary arrest, surgical or angiographic intervention, irreversible sequelae (e.g., myocardial infarction, neurologic deficit, or massive hemotherax), systolic hypotension (<90 mm Hg), critical anemia (hematocrit of ≤0.20), or death. Major thromboembolic events were defined as transient ischemic attacks, stroke, recurrent deep venous thrombosis, pulmonary embolism, and systemic embolism. Minor events (with no medical consequences) were not included, as no medical attention would be sought.

### Table 2 Inputs for the model

<table>
<thead>
<tr>
<th>Clinical inputs</th>
<th>Base-case value</th>
<th>Range for sensitivity analysis</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-patient average percentage of out-of-range INRs in nongenotyped group</td>
<td>33.1%</td>
<td>10–92%</td>
<td>24,25</td>
</tr>
<tr>
<td>Relative percentage reduction in out-of-range INRs in genotyped group</td>
<td>7.3%</td>
<td>0–100%</td>
<td>24</td>
</tr>
<tr>
<td>Proportion of below-range INRs among all out-of-ranges INRs</td>
<td>54%</td>
<td>0–100%</td>
<td>24</td>
</tr>
<tr>
<td>Rate of major bleeding in range INRs (per patient year)</td>
<td>1.4%</td>
<td>1.0–1.5%</td>
<td>38</td>
</tr>
<tr>
<td>Rate of major thromboembolism in range INRs (per patient year)</td>
<td>1.3%</td>
<td>0.5–1.6%</td>
<td>38</td>
</tr>
<tr>
<td>Odds ratio of major bleeding occurring at INRs above target range</td>
<td>3.21</td>
<td>1.24–8.28</td>
<td>38</td>
</tr>
<tr>
<td>Odds ratio of major bleeding occurring at INRs below target range</td>
<td>1</td>
<td>—</td>
<td>Assumption</td>
</tr>
<tr>
<td>Odds ratio of major thromboembolism occurring at INR above target range</td>
<td>1</td>
<td>—</td>
<td>Assumption</td>
</tr>
<tr>
<td>Odds ratio of major thromboembolism occurring at INR below target range</td>
<td>5.07</td>
<td>2.92–8.80</td>
<td>38</td>
</tr>
<tr>
<td>Proportion of intracranial hemorrhage among all major bleeding events</td>
<td>42%</td>
<td>34–50%</td>
<td>40</td>
</tr>
<tr>
<td>Mortality rate of intracranial hemorrhage</td>
<td>48.6%</td>
<td>36–61%</td>
<td>40,41</td>
</tr>
<tr>
<td>Mortality rate on account of extracranial hemorrhage</td>
<td>5.1%</td>
<td>0.1–10.1%</td>
<td>40</td>
</tr>
<tr>
<td>Mortality rate on account of major thromboembolism</td>
<td>10.3%</td>
<td>9.8–11.7%</td>
<td>39</td>
</tr>
<tr>
<td>Utility inputs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No event on warfarin therapy</td>
<td>0.95</td>
<td>0.9–1</td>
<td>42–44</td>
</tr>
<tr>
<td>Duration of warfarin therapy elapsed when an adverse event occurred (months)</td>
<td>1</td>
<td>1–12</td>
<td>Assumption</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.51</td>
<td>0.15–0.85</td>
<td>42–44</td>
</tr>
<tr>
<td>Extracranial hemorrhage</td>
<td>0.80</td>
<td>0.79–0.84</td>
<td>43,44</td>
</tr>
<tr>
<td>Major thromboembolism</td>
<td>0.39</td>
<td>0–0.95</td>
<td>42–44</td>
</tr>
<tr>
<td>Direct medical cost inputs (US$)</td>
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</tr>
<tr>
<td>Cost of genotyping</td>
<td>200</td>
<td>125–550</td>
<td>48,49</td>
</tr>
<tr>
<td>Annual cost of anticoagulation clinic care per patient</td>
<td>303</td>
<td>217–393</td>
<td>46,47</td>
</tr>
<tr>
<td>Cost of major bleeding events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>25,660</td>
<td>20,528–30,792</td>
<td>45</td>
</tr>
<tr>
<td>Extracranial hemorrhage</td>
<td>17,414</td>
<td>12,503–22,325</td>
<td>45</td>
</tr>
<tr>
<td>Cost of major thromboembolism events</td>
<td>22,079</td>
<td>15,392–25,660</td>
<td>45</td>
</tr>
</tbody>
</table>

INR, international normalized ratio.

- Base-case values were the inputs in the model, used for base-case analysis.
- Range for sensitivity analysis: for one-way sensitivity analysis, three-way sensitivity analysis, and probabilistic sensitivity analysis.
- Costs were adjusted to 2008 costs using a discount rate of 3%.

### Clinical inputs

The clinical inputs for the model were retrieved from the literature. A literature search on MEDLINE for the period January 1950–July 2008 was performed using the keywords “warfarin,” “bleeding,” “thromboembolism,” “QALY,” “INR,” “genotyping,” “VKORC1,” and “CYP2C9.” The selection criteria for clinical trials on warfarin treatment and related events were as follows: (i) the reports were in the English language; (ii) patients involved in the trials were at least 18 years of age; (iii) warfarin therapy was prescribed for at least 3 months; and (iv) control of INR and/or the incidence of major adverse events (bleeding or thromboembolic event) were reported.
All articles retrieved by this process were screened for relevance to our model. Case reports were excluded. Each retrieved manuscript was evaluated independently by two reviewers (J.H.S.Y. and G.C.) to determine whether the manuscripts had data pertaining to the inputs for the model. The preferred type of study was the meta-analysis. Where multiple randomized controlled trials were available for the same input, the pooled average was derived from the studies, weighted against the number of patients in each study, and used as the base-case input for the model. Where an input was reported in both randomized and nonrandomized trials, the pooled average from randomized trials was used as the base-case value, whereas the range for sensitivity analysis was derived from both randomized and nonrandomized trials. Where an input was not reported, either in meta-analyses or in randomized, controlled trials, it was estimated from the findings of nonrandomized controlled trials.

Clinical inputs of the model are shown in Table 2. To date, there have been no published randomized clinical trials on genotype-guided dosing with sufficient power to measure the change in adverse event rates as the primary outcome. Surrogate outcomes such as percentage of out-of-range INRs and percentage of patient-time spent within the therapeutic range were reported as the primary end points instead. The potential change in adverse event rates from using genotype-guided dosing has therefore been estimated from (i) the change in INR control values and (ii) the association between INR control and adverse event rate, as reported in the literature.

The model’s input on the effectiveness of genotype-guided warfarin dosing in INR control was derived from the Couma-Gem trial, because it was the only trial that compared the percentages of out-of-range INRs in patients in whom warfarin therapy was initiated, by CYP2C9 and VKORC1 genotype (CYP2C9*2, CYP2C9*3, and VKORC1 C1173T)–guided dosing vs. standard dosing.23 Out-of-range INR was defined as <1.8 or >3.2. Genotype-guided dosing was shown to reduce out-of-range INRs from 33.1 to 30.7% (relative percentage reduction of 7.3%; P = 0.47). The percentages of out-of-range INRs in patients in the control group (33.1%), relative percentage reduction of out-of-range INRs in the genotyped group (7.3%), and the percentage of subtherapeutic INRs (<1.8) among the out-of-range INRs (54%) reported in this trial were the inputs in the model.

The rates of major bleeding (intracranial and extracranial hemorrhage) and ischemic stroke in patients with normal anticoagulation (INR ≤ 3 and INR ≥ 2, respectively) and the odds ratios for stroke in patients with undercoagulation and for major bleeding in patients with overcoagulation were estimated in a meta-analysis.38 The risk of major bleeding in patients with undercoagulation and of major thromboembolic events in patients with overcoagulation were both assumed to be the same as in patients with in-range INRs. The proportion of intracranial hemorrhage among all major bleeding events and the mortality rates associated with intracranial hemorrhage, extracranial hemorrhage, and thromboembolism within 30 days of the relevant event were estimated from observational studies.39–41

Utility inputs. The QALYs gained in each study arm over the 1-year time horizon were estimated from the utilities scores of four statuses42–44 and the time spent in each status: (i) no event and on warfarin therapy, (ii) survived major thromboembolic event, and (iv) death. Warfarin dosage was usually adjusted during the first month of therapy, and the risk of adverse events was higher in this induction phase than during the maintenance phase.37 When any adverse event or death occurred, it was assumed to have taken place during the first month (ranging from month 1 to 12) of warfarin therapy.

Cost inputs. Cost analysis was conducted from the perspective of health-care providers. The cost of standard AC service and management of events is shown in Table 2. The costs associated with bleeding and thromboembolic events were estimated from the Diagnosis-Related Groups 2006 total charges per discharge for gastrointestinal hemorrhage (considered in the category of extracranial hemorrhage), intracranial hemorrhage, deep-vein thrombosis, pulmonary embolism, and stroke.45 The annual cost of routine management in AC—including staff time, laboratory tests, and administrative costs—was retrieved from two studies of economic analysis on anticoagulation care.46,47 The cost of CYP2C9 and VKORC1 genotyping was estimated from commercially available DNA testing data48 and from the literature,49 but none of the sources for genotyping costs included cost analysis, and the costs of major items such as reagents, labor, and equipment were not reported. The reported cost of genotyping ranged from $125 to $550. While the reagent cost per test is unlikely to change as a function of the number of samples, labor- and equipment-related costs tend to decrease with an increase in the number of samples. The genotype-guided dosing strategy would demand genotyping for all new patients in whom warfarin therapy is to be initiated, resulting in a high number of samples for genotyping. Lowering the cost of genotyping (to $200) was therefore assumed as a base-case input and examined over a range of $125–550. All costs were discounted to 2008 costs at a discount rate of 3%.

Sensitivity analysis. Sensitivity analysis was performed using TreeAge Pro 2008 (TreeAge Software, Williamstown, MA) and Microsoft Excel 2003 (Microsoft, Redmond, WA) to examine the robustness of the model results for variations in each of the parameters. Threshold values of influential factors were identified using one-way sensitivity analysis. All the parameters were examined over the high/low values, or the 95% CI when available. In order to evaluate the impact of the uncertainty in all variables simultaneously, a probabilistic sensitivity analysis was performed using Monte Carlo simulation. The cost, adverse event rate, mortality rate, and QALYs of each study arm were recalculated 10,000 times by randomly drawing each of the model’s inputs from a triangular probability distribution (base-case value and the upper and lower limits of the sensitivity range were the mode and the highest and lowest values, respectively) to determine the percentage of occasions in which each study arm would represent the most cost-effective strategy.

ACKNOWLEDGMENTS

This study was supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (project CUHK4519/06M). The funding source had no involvement in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit this article for publication.

CONFLICT OF INTEREST

The authors declared no conflict of interest.


