The potential clinical and economic outcomes of pharmacogenetics-oriented management of warfarin therapy – a decision analysis

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Summary
Variant cytochrome P450 (CYP) 2C9 genotypes are associated with low maintenance dose requirement of warfarin therapy and increased risk of major bleeding events. The objective of the present study was to evaluate the potential clinical and economic outcomes of using CYP2C9 genotype data to guide the management of anticoagulation therapy and to identify influential factors affecting the cost-effectiveness of this treatment scheme. A decision tree was designed to simulate, over 12 months, the clinical and economic outcomes of patients newly started on warfarin associated with two alternatives: (1) no genotyping (non-genotyped group) and (2) CYP2C9 genotyping prior to initiation of warfarin therapy (genotyped group). Non-genotyped group patients would receive standard care of an anticoagulation clinic (AC). In the genotyped group, patients with at least one variant CYP2C9 allele would receive intensified anticoagulation service. Most of the clinical probabilities were derived from literature. The direct medical costs were estimated from the Diagnosis-Related Group charges and from literature. The total number of events and the direct medical cost per 100 patient-years in the genotyped and non-genotyped groups were 9.58 and USD 155,700, and, 10.48 and USD 150,500, respectively. The marginal cost per additional major bleeding averted in the genotyped group was USD 5,778. The model was sensitive to the variation of the cost and reduction of bleeding rate in the intensified anticoagulation service. In conclusion, the pharmacogenetics-oriented management of warfarin therapy is potentially more effective in preventing bleeding with a marginal cost. The cost-effectiveness of this treatment scheme depends on the relative cost and effectiveness of a pharmacogenetics-oriented intensified anticoagulation service comparing to the standard AC care.

Keywords
Warfarin, CYP2C9, cost-effectiveness

Introduction
Warfarin is the most commonly prescribed anticoagulant for prevention and treatment of thromboembolic events (1). The anticoagulation effect of warfarin, measured by the international normalized ratio (INR), is subject to wide inter- and intra-individual variability that possibly leads to hemorrhagic or thromboembolic events despite careful dosage titration. Successful warfarin therapy requires individualized dosage adjustment and therapeutic drug monitoring. A number of fac-
tors have been identified to influence the anticoagulation effect of warfarin therapy, including age, sex, body weight, comorbidity, concurrent medications, vitamin K intakes and patient compliance level (2, 3).

Warfarin is a racemic mixture of two enantiomers, S- and R-warfarin, with different pharmacodynamic and pharmacokinetic properties (4). S-warfarin is 3 to 5 times more potent than the R-warfarin (5). The metabolism of S-warfarin is primarily catalysed by cytochrome P450 (CYP) 2C9 while R-warfarin is catalysed by multiple hepatic microsomal enzymes, including CYP1A2, 2C18, 2C19 and 3A4 (5, 6). Genetic polymorphisms of CYP2C9 have a major effect on the clearance of the S-enantiomer of warfarin whereas genetic variation of CYP2C19 shows no significant effect on the clearance of warfarin enantiomers (7, 8). To date, 12 distinct polymorphisms of CYP2C9 have been registered with the Human Cytochrome P450 Allele Nomenclature Committee (9, 11). CYP2C9 polymorphism was associated with lower warfarin dosage requirement and with increased risk of major bleeding events during the induction phase of warfarin therapy, though its effect on bleeding during long-term warfarin therapy is yet to be determined (2, 12-16). A pharmacogenetic dosing algorithm for initiation of warfarin dosage may reduce the incidence of warfarin over-dose and it needs to be confirmed prospectively (16).

A priori knowledge of a patient's genotype can potentially guide a clinician to triage the patient to an intensified anticoagulation management strategy that includes CYP2C9 polymorphism as a risk factor to design the initial and maintenance doses and to determine the frequency of INR monitoring. The objectives of the present study were to evaluate the potential clinical and economic outcomes of using CYP2C9 genotype data to guide the management of anticoagulation therapy in patients newly started on warfarin therapy, and to identify factors affecting the cost-effectiveness of this treatment scheme.

**Materials and methods**

A decision tree was designed to simulate, using probabilistic cohort simulation over a period of 12 months, the outcomes of a hypothetical cohort of patients newly started on warfarin therapy associated with two alternatives: (1) no genotyping (non-genotyped group) and (2) CYP2C9 genotyping prior to initiation of warfarin therapy (genotyped group) (Fig. 1). Each alternative could lead to three possible outcomes: No event, major bleeding or major thromboembolic event. The definitions of major events were adopted from Fihn et al. (17). Major bleeding included gastrointestinal bleeding, gross hematuria, hemoptysis, bleeding that lead to cardiopulmonary arrest, to surgical or angiographic intervention, to irreversible sequelae such as myocardial infarction, neurologic deficit or massive hemothorax, to systolic hypotension (< 90 mmHg), to critical anemia (hematocrit of 0.20 or less) or to death. Major thromboembolic events were 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 was sought.

Patients in the non-genotyped group would receive the standard care of an anticoagulation clinic (AC) which was recommended as the cost-effective model of care for anticoagulation management (18). In the genotyped group, patients with at least one variant CYP2C9 allele would be triaged to an intensified anticoagulation service while wild-typed patients would receive

![Figure 1: Decision model.](image-url)
standard AC care. The intensified anticoagulation service would design the initial dose of warfarin by a pharmacogenetic model using demographic, clinical and pharmacogenetic (CYP2C9 genotypes) factors that were obtained at the time of warfarin initiation (16) and a more strict INR control would be targeted. The number of events and total direct medical cost for each study arm were simulated.

Clinical outcomes

The prevalence of CYP2C9 polymorphisms and the event rates during warfarin therapy were estimated from clinical trials reported in literature (Table 1). A literature search on MEDLINE during the period 1984 - 2003 was performed using keywords “warfarin”, “bleeding”, “thromboembolism” and “CYP2C9”. The selection criteria of clinical trials for event rates were: (1) reports were written in English; (2) patients involved in the trials were at least 18 years of age; (3) warfarin therapy was prescribed for at least 3 months; (4) the incidence of major events (bleeding or thromboembolic event) was reported. Data from a total of 23 reports were included (2, 8, 12-14, 17, 19-35). Thirteen studies reported the prevalence of CYP2C9 polymorphism in Caucasian populations (2, 8, 12-14, 19-26). The incidence of thromboembolic events among patients with wild-type CYP2C9 or with variant genotypes, was assessed from 10 trials (one randomized clinical trial, two prospective cohort studies and seven retrospective cohort studies) (17, 27-35). Thirteen studies reported the prevalence of CYP2C9 polymorphism in Caucasian populations (2, 8, 12-14, 19-26). The incidence of thromboembolic events among patients in AC, assumed to be same for patients with wild-type CYP2C9 or with variant genotypes, was assessed from 10 trials (one randomized clinical trial, two prospective cohort studies and seven retrospective cohort studies) (17, 27-35). The incidence of bleeding events in patients with wild-type CYP2C9 and in those with variant genotypes were estimated from a retrospective cohort trial conducted in an anticoagulation clinic (14). No clinical trial has reported the effectiveness of a pharmacogenetics-oriented intensified anticoagulation service in preventing bleeding complications. One clinical trial found about a 50% reduction in bleeding events from an intensified anticoagulation service (36). The hypothetical pharmacogenetic-oriented intensified anticoagulation service was therefore assumed conservatively to be 20% more effective than the standard AC service in preventing major bleeding events and has the same effect on the rate of thromboembolic events as the standard AC service. The assumption on the relative effectiveness of the intensified service in preventing bleeding by 20% was tested in the sensitivity analysis over a range of 0%-100%.

Cost data

Cost analysis was conducted from the perspective of healthcare providers. Cost of standard AC service and management of events were shown on Table 1. The cost of bleeding and thromboembolic events were estimated from the Diagnosis-Related Groups 2001 (DRG) total charges per discharge for gastrointestinal hemorrhage (with and without complication and co-morbidity) and thromboembolic events, respectively (37). The yearly cost of routine management in AC, including staff time, laboratory tests and administrative cost, was obtained from literature (38). The cost of the hypothetical intensified anticoagulation service was assumed to be 1.5-fold of the standard AC service cost. The cost of CYP2C9 genotyping was estimated from the cost of major consumables (blood and cell culture DNA kit, and intron-specific primers) used for genotyping as described by Higashi et al. (14).

Sensitivity analysis

Sensitivity analysis was performed by DATA 3.5 (TreeAge Software, Inc., Williamstown, MA, USA) to examine the robustness of the model. Sensitivity analysis was conducted with all the clinical variables and direct medical costs. The smallest and the largest values were used as the lower and upper limits of the range, respectively, for sensitivity analysis on: the rate of thromboembolic events in AC; cost of bleeding and thromboembolic events; and cost of standard AC service. The base-case value of the prevalence of CYP2C9 was derived from studies among Caucasian populations. As the prevalence varies in different ethnic groups, the sensitivity of the model was therefore tested on variation of the prevalence of CYP2C9 polymorphisms over a range from 2.3%-51% to include ethnic

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### Table 1: Yearly transition probabilities and economic inputs for the model.

<table>
<thead>
<tr>
<th>Prevalence of CYP2C9 polymorphisms</th>
<th>Yearly event rates under standard care in AC</th>
<th>Odds ratio of bleeding events in intensified anticoagulation service compared to standard AC service</th>
</tr>
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<tbody>
<tr>
<td>AC = anticoagulation clinic</td>
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<td>AC = anticoagulation clinic</td>
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<tr>
<td>Yearly event rates under standard care in AC</td>
<td>Odds ratio of bleeding events in intensified anticoagulation service compared to standard AC service</td>
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<tr>
<td>Major thromboembolic event</td>
<td>Major bleeding in patients with wild-type CYP2C9 genotype</td>
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<tr>
<td>Major bleeding in patients with variant CYP2C9 genotype</td>
<td>Major bleeding in patients with wild-type CYP2C9 genotype</td>
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<tr>
<td>Odds ratio of bleeding events in intensified anticoagulation service compared to standard AC service</td>
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<tr>
<td>Direct medical cost (USD)</td>
<td>Cost of genotyping</td>
<td>Cost of standard service at AC</td>
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<tr>
<td>Cost of standard service at AC</td>
<td>Cost of major bleeding</td>
<td>Cost of major thromboembolic event</td>
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<tr>
<td>Increment factor on cost of intensified anticoagulation service relative to standard AC care</td>
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</table>

- **Base-case value**
- **Range for sensitivity analysis**
- **References**

- **a**: AC = anticoagulation clinic
- **b**: Base-case values were derived from references 2,8,12-14,19-26. References 39-42 provided the lowest prevalence value of CYP2C9 polymorphisms
- **c**: Base-case values were derived from reference 14. Reference 17 provided the highest bleeding rate reported in AC settings
groups (African-American, Japanese, Chinese, Taiwanese and Korean) with low prevalence values of CYP2C9 polymorphism (39-42). The rates of bleeding in patients with CYP2C9 wild-type and patients with variant genotypes were examined over a range of 0 to 0.13 (the highest bleeding rate reported in AC settings) (17). The assumption on the effectiveness of the intensified anticoagulation service in reduction of bleeding rate comparing to the standard AC service were examined over an odds ratio of 0 to 1. Applying pharmacogenetic approach to design the initial dose of warfarin may result in fewer INR tests during the initial phase of therapy and subsequently decrease the cost of service. The cost of intensified anticoagulation service was therefore tested over a range of 0.5- to 2-fold of the cost of standard AC service, and the cost of genotyping was tested over a range of 0.5- to 2-fold of the base-case value.

**Results**

The results of the cost-effectiveness analysis were shown in Table 2. The base-case analysis showed that the total event rate per 100 patient-years of the genotyped group was lower than that of the non-genotyped group by 0.9 (8.6%). The cost per 100 patient-year in the genotyped group was USD5,200 more than the non-genotyped group. The marginal cost to prevent one additional bleeding event in the genotyped group equaled to:

\[
\frac{(\text{Cost}_{\text{genotyped}} - \text{Cost}_{\text{non-genotyped}})}{(\text{Event rate}_{\text{genotyped}} - \text{Event rate}_{\text{non-genotyped}})} = \text{USD 5,778 (USD 5,200/0.9)}
\]

One-way sensitivity analysis showed that the genotyped group remained to have a lower event rate than the non-genotyped group until the bleeding rate of the intensified service became the same as that of the standard AC care (odds ratio of bleedings in intensified service compared to standard AC care = 1). The economic outcome, however, was sensitive to variation of two variables: the odds ratio of bleeding in the intensified anticoagulation service and the cost of the intensified service relative to the standard AC service. When the bleeding rate in the intensified anticoagulation service was 30% lower than that in the standard AC (odds ratio = 0.7), the cost of the two groups became the same and the marginal cost per additional bleeding averted declined to zero (Fig. 2). The genotyped

<table>
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<th>Table 2: Results of cost-effectiveness analysis.</th>
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<tr>
<td>Cost per 100 patient-years (USD)</td>
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<tr>
<td>Non-genotyped group</td>
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<tr>
<td>Genotyped group</td>
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<tr>
<td>Marginal cost per 100 patient-years (USD)</td>
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<tr>
<td>150,500</td>
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<tr>
<td>155,700</td>
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<tr>
<td>Number of events per 100 patient-years</td>
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<tr>
<td>Major bleeding</td>
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<tr>
<td>8.08</td>
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<tr>
<td>Major thromboembolic events</td>
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<tr>
<td>2.40</td>
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<tr>
<td>Total Number of events per 100 patient-years</td>
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<tr>
<td>10.48</td>
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<tr>
<td>Marginal number of events per 100 patient-years</td>
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<td>0.90</td>
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![Figure 2: The change of marginal cost per additional bleeding averted against the odds ratio of bleeding in intensified service.](image-url)
group cost less than the non-genotyped group (marginal cost < zero) when the bleeding rate in the intensified anticoagulation service was lower than that in the standard AC by > 30% (odds ratio < 0.7). The marginal cost per additional bleeding averted of the genotyped group increased sharply as the difference in bleeding rates between the two services decreased to < 30% (odds ratio > 0.7).

The marginal cost of the gentoyped group was also sensitive to the variation of the cost of the intensified anticoagulation service that it increased with the increment factor on cost of intensified anticoagulation service relative to standard AC service (Fig. 3). The marginal cost became zero (the cost of two groups were the same) when the cost of the intensified service was 1.04-folds the cost of the standard AC service, and it was less than zero (genotyped group cost less than non-genotyped group) when the intensified service cost less than 1.04-folds.

A two-way sensitivity analysis was further conducted with the cost and the effectiveness of the intensified anticoagulation service (Fig. 4) to examine their effects on the model. The combinations of variables on the line (threshold line) indicated that the genotyped group had the same total cost and lower event rate than the non-genotyped group. The combinations of these two variables on the left side of the threshold line were associated with a lower total cost as well as a lower event rate in the genotyped group than the non-genotyped group. The area on the right side of the threshold line indicated the combinations of variables leading to a higher total cost and a lower event rate in the genotyped group.

**Discussion**

Studies have shown that variant CYP2C9 polymorphisms were associated with reduced dosage requirement of warfarin (12-16). Investigation on the effect of CYP2C9*3 allelic variant (Ile359Leu) showed that the frequency of CYP2C9*3 allele was the highest in patients on lower warfarin dosing (<3.1mg) and patients who were homozygote for Leu359 were at higher risk of bleeding during the first 3 months of warfarin therapy (15). Patients requiring a warfarin dose of 1.5 mg or less were six times more likely to be positive for one or more the CYP2C9
variant alleles, and a significantly higher number of major bleeding episodes occurred in patients with low dose requirements (12). Patients with at least one variant allele had an increased risk of exceeding the INR therapeutic range and also required more time to achieve stable dosing (with a median difference of 95 days) when compared with those who had wild-type CYP2C9. A dosing model estimating the maintenance warfarin dose from demographic, clinical and pharmacogenetic (CYP2C9 genotypes) factors that are obtained at the time of warfarin initiation may reduce the incidence of warfarin overdose significantly by 10%, yet it needs to be confirmed prospectively (16). It is anticipated to reduce bleeding risk by selecting initial warfarin dosage using a pharmacogenetic dosing model together with a more strict INR control after warfarin initiation.

Genotyping has been proposed as a proactive approach of therapeutic drug monitoring (TDM) (43). Drugs that are potential candidates for pharmacogenetic-oriented TDM should share similar characteristics with those drugs requiring traditional TDM: (1) Drugs with a narrow therapeutic index; (2) the polymorphic isoenzyme is responsible for the major pathway of metabolism of that drug; (3) drugs produce active metabolites in the major metabolic pathway and (4) variability in drug response is readily assessable. In current clinical practice, pharmacogenetic testing is only performed for a few drugs, such asmercaptopurine, thioguanine, azathioprine, trastuzumab and tacrine (44-46).

The feasibility of real-time genotyping is critical to the pharmacogenetics-oriented service. Rapid assays for CYP2C9 single nucleotide polymorphisms (including DNA extraction, amplification and sequencing) can be completed in a few days (47-48). Despite awaiting genotyping results can lead to a brief delay of warfarin therapy initiation and slightly increase the risk of stroke, the few strokes caused by delay in warfarin initiation would be counterbalanced by the complications prevented by a more accurate dosing of warfarin guided by the genotyping results.

The results of our base-case analysis showed that the genotyped group prevented one additional bleeding with an incremental cost of USD 5,778. The Panel on Cost-Effectiveness in Health and Medicine defined cost-effective as incremental cost-effectiveness ratio of less than USD 50,000 per quality-adjusted life-year (QALY) gained (49). The utility score for a major bleeding event ranged from 0 (patients who dies from the bleeding event) to 0.39 (patients with major gastrointestinal bleeding) (50-52). The number of QALY’s gained by preventing a major gastrointestinal bleeding in a patient who suffers for a month equals to (1-0.39) × (1/12 life-years) = 0.05 QALYs, and in a patient (with life expectation of one year) who dies from a bleeding event equals to (1-0) × 1 life-year = 1 QALY. The pharmacogenetic-oriented warfarin management scheme may therefore be cost-effective if it can gain >0.1 (5.778/50,000) additional QALYs and this hypothesis needs to be confirmed prospectively.

By varying the variables one at a time (one-way sensitivity analysis), it showed that the clinical outcome in the genotyped group (lower event rate) was robust to the variation of all the variables except when the effectiveness of the intensified anticoagulation service and the standard anticoagulation were the same. It is understood that the reduction of total event rate was a result of the reduction in bleeding events among the patient with variant CYP2C9 genotypes managed by the hypothetical intensified anticoagulation service. The effectiveness of the intensified anticoagulation service was also a critical factor affecting the total cost of the genotyped group. Another factor identified to be influential to the economic outcome of the models were the cost of the intensified anticoagulation service. By varying the relative cost and effectiveness of the intensified anticoagulation service to the standard AC care simultaneously in a 2-way sensitivity analysis, the combinations of these two variables associated with a lower total cost and a lower event rate in the genotyped group were identified. If the cost of the intensified service was same as the standard AC service, the intensified service should be at least 20% more effective than the standard AC service in preventing bleeding events in order for the genotype-guided scheme to be less costly and more effective. If the cost of the intensified service was 2-fold of the standard AC service, the breakpoint for the genotype-guided scheme to dominate the standard AC practice occurred when the intensified service prevented 40% more bleeding events than the standard AC service.

The acceptance of pharmacogenetics-oriented warfarin management by clinicians depends on clinical evidence. The effectiveness of the CYP2C9-guided anticoagulation service should be obtained by clinical trials. The present study is an example of decision analysis to undertake large-scale studies by simulating the magnitude of the clinical effectiveness and cost of an intensified anticoagulation service required for a CYP2C9 genotype-guided treatment scheme to translate into a cost-effective clinical strategy, before initiation of a trial to compare the genotyping scheme with the standard practice. The two-way sensitivity analysis provided the combinations of the two influential variables that should be targeted in a clinical trial for a less costly and more effective pharmacogenetics-oriented service. Our analysis also provides a framework for estimation of the required sample size of a clinical trial based upon the cost-effectiveness thresholds.

In our analysis, the decision tree was designed to simulate the outcomes of warfarin therapy over a period of 12 months. Beyond the first 12 months of warfarin therapy, most patients should reach stable maintenance dosage and the overall risk of bleeding beyond the initiation phase of warfarin therapy would be lower. Whether the variant genotypes continue to associate with an increased risk of bleeding after patients have achieved
the stable warfarin maintenance dose is yet to be determined. It is therefore uncertain how long should patients with variant genotypes be managed in the intensified anticoagulation service in order to achieve the optimal cost-effective outcomes. It was reported that the risk of bleeding was higher during the first 90 days after warfarin therapy initiated when compared with any time thereafter (15, 17). Future studies should analyze the cost-effectiveness of pharmacogenetics-oriented management of warfarin therapy during the initial phase of treatment as the impact of this strategy may be more prominent.

Our study was limited by the facts that the clinical probabilities were derived mainly from retrospective observational studies and limited data on the risk of bleeding associated with variant CYP2C9 genotypes were reported (one cohort study). Another limitation was that no clinical trial has reported the effectiveness of a pharmacogenetics-oriented intensified anticoagulation service in preventing bleeding complications. A hypothetical intensified service was assumed to be 20% more effective than the standard AC service. The limitations and assumptions of model inputs were examined in sensitivity analysis conducted over a broad range for all the clinical variables in order to test for the robustness of the model and to identify the threshold values of influential variables. The threshold values identified for critical variables, namely, relative cost and effectiveness of an intensified service to the standard AC care, provided information on the feasibility of cost-effective usage of CYP2C9 genotyping data in management of warfarin therapy.

In conclusion, the pharmacogenetics-oriented management of warfarin therapy is potentially more effective in preventing bleeding with a marginal cost. The cost-effectiveness of the CYP2C9 genotype-guided treatment scheme depends on the relative cost and effectiveness of an intensified anticoagulation service comparing to the standard AC care.

References


