Cost-Effectiveness of Genotype-Guided Warfarin Therapy for Anticoagulation in Elderly Patients With Atrial Fibrillation

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ABSTRACT

Background: In patients with atrial fibrillation (AF), anticoagulation with warfarin decreases the risk of embolic stroke by >50%. Identification of genetic polymorphisms in enzymes involved in the metabolism of warfarin can partially predict the maintenance dose and thus potentially decrease the incidence of bleeding episodes secondary to warfarin overdose.

Objectives: The objectives of this study were to evaluate the potential clinical and economic outcomes of genotype-guided warfarin therapy in elderly patients newly diagnosed with AF and to identify a threshold in bleeding risk at which such therapy may be cost-effective.

Methods: A decision tree was designed to represent the medical decision (pharmacogenetic testing or not) and the main clinical outcomes (embolic stroke, bleeding). Event rates of embolic stroke and bleeding complications were based on data from previously published clinical trials and an observational study, respectively; costs were from a third-party payer perspective; and utilities were from the patient perspective. It was assumed that use of pharmacogenetic testing would not lead the clinician to make any potentially harmful modifications to the regimen.

Results: This analysis found that any reduction in major bleeding as a result of pharmacogenetic testing would lead to improved utility. The higher costs of pharmacogenetic testing compared with no testing would be immediately offset by any reduction in major bleeding.

Conclusions: In this decision analysis, genotype-guided warfarin therapy for anticoagulation in elderly patients with AF was potentially cost-effective, and its benefits were closely related to efficacy in preventing bleeding events. Clinical trials testing the efficacy of genotype-guided warfarin therapy are warranted. (*Am J Geriatr Pharmacother.* 2009;7:197–203) © 2009 Excerpta Medica Inc.

Key words: decision analysis, cost-effectiveness, warfarin, pharmacogenetics, bleeding, stroke.

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INTRODUCTION

Atrial fibrillation (AF) affects 5% to 10% of the elderly population, substantially increasing the risk of embolic events such as stroke.[1] If untreated, AF can have a catastrophic outcome for the patient and result in an enormous cost of care. Anticoagulation with warfarin decreases the risk of embolic stroke by >50%; however, warfarin poses a risk for major hemorrhagic events such as intracranial hemorrhage and gastrointestinal bleeding.[2,3] Major and minor embolic strokes associated with AF are estimated to cost $1,758,548 and $19,352, respectively, per event, whereas severe lower gastrointestinal hemorrhages are estimated to cost $193,804 per event.[4]

Adjustment of the warfarin dose is cumbersome and depends on several factors, including demographic characteristics (age, sex, and race), nutrition (diet and vitamin K intake), medical history (heart disease, liver disease, and concomitant medications), anthropometric variables (weight, height, and body surface area), and genetic factors (cytochrome P450 [CYP] 2C9 and vitamin K epoxide reductase [VKORC1] genotypes).[5] CYP2C9 is the enzyme that metabolizes *S*-warfarin, the main enantiomer of warfarin. Carriers of some genetic polymorphisms of *CYP2C9* metabolize *S*-warfarin more slowly than do others, leading to elevated international normalized ratios (INRs) at common initial doses of warfarin.[6] VKORC1, which is inhibited by warfarin, is an enzyme that activates vitamin K, allowing the synthesis of several clotting factors. In carriers of some genetic polymorphisms of *VKORC1*, the enzyme has a greater affinity for warfarin, requiring a lower dose to appropriately inhibit coagulation. It is possible to have polymorphisms of both of these enzymes, inducing resistance to warfarin.[6]

Identification of these genetic polymorphisms through pharmacogenetic testing has been reported to have 50% to 60% accuracy in predicting the warfarin maintenance dose,[5] potentially decreasing the incidence of bleeding secondary to elevated INRs. Routine assessment of genetic polymorphisms related to warfarin metabolism has the potential to improve clinical management and decrease the likelihood of bleeding.[7] However, genetic testing would represent an additional cost in an already expensive process. The efficacy and economic outcomes of such genotype-guided therapy remain unknown.

Given the limited number of published clinical trials that have assessed the effectiveness of genotype-guided warfarin therapy,[8,9] this scenario represents an appropriate model for decision analysis. Decision analysis is a method used to help make the best decisions in the face of uncertainty. It is useful when a randomized trial is not feasible due to ethical considerations, economic constraints, time pressure, changing technology, or logistic impossibility. The decision-analysis method involves creating a model of the alternative decisions and their consequences based on the probabilities of the events or final states of health (ie, risk of embolic stroke, risk of major bleeding, risk of death or disability) and patient preferences for each of the final states.[10] Each final state is given a preference value, or *utility*. The utility value, which is assigned by patients, ranges from 0 to 1, representing the worst and best possible outcomes, respectively. These values are then weighted by the probability of the events actually occurring. The decision alternative with the highest expected value is the recommended choice. Given the inputs into the decision model and its structure, this method identifies the best long-term choice. Adding the cost of each outcome makes it possible to weigh the economic impact of decisions based on patients' preferences (utilities) and the probability of events.

The objectives of this study were to evaluate the potential clinical and economic outcomes of genotype-guided warfarin therapy in elderly patients newly diagnosed with AF and to identify a threshold in bleeding risk at which genotype-guided warfarin therapy may be cost-effective in these patients. One of the questions investigated was whether all patients who are candidates for warfarin therapy are likely to benefit from pharmacogenetic testing, even those with a low bleeding risk.

METHODS

A decision tree was created to simulate a common scenario in geriatric practice: a patient aged >65 years is newly diagnosed with nonvalvular AF, and the initiation of warfarin therapy is clinically indicated (**Figure 1**). There are 2 alternatives with respect to initiating this therapy: pharmacogenetic testing and no testing. Each option has 2 types of clinical outcome, the first related to the incidence of embolic stroke and the second related to complications of warfarin use. In clinical practice, patients with mild or moderate embolic stroke would most likely continue to take warfarin after recovery from the stroke; therefore, in the model, the warfarin complications outcome was added after the occurrence of embolic stroke. The warfarin complications included were major bleeding episodes sufficiently significant to prompt hospital admission and blood transfusion, that involve a critical site (intracranial, intraspinal, intraocular), or that are fatal.

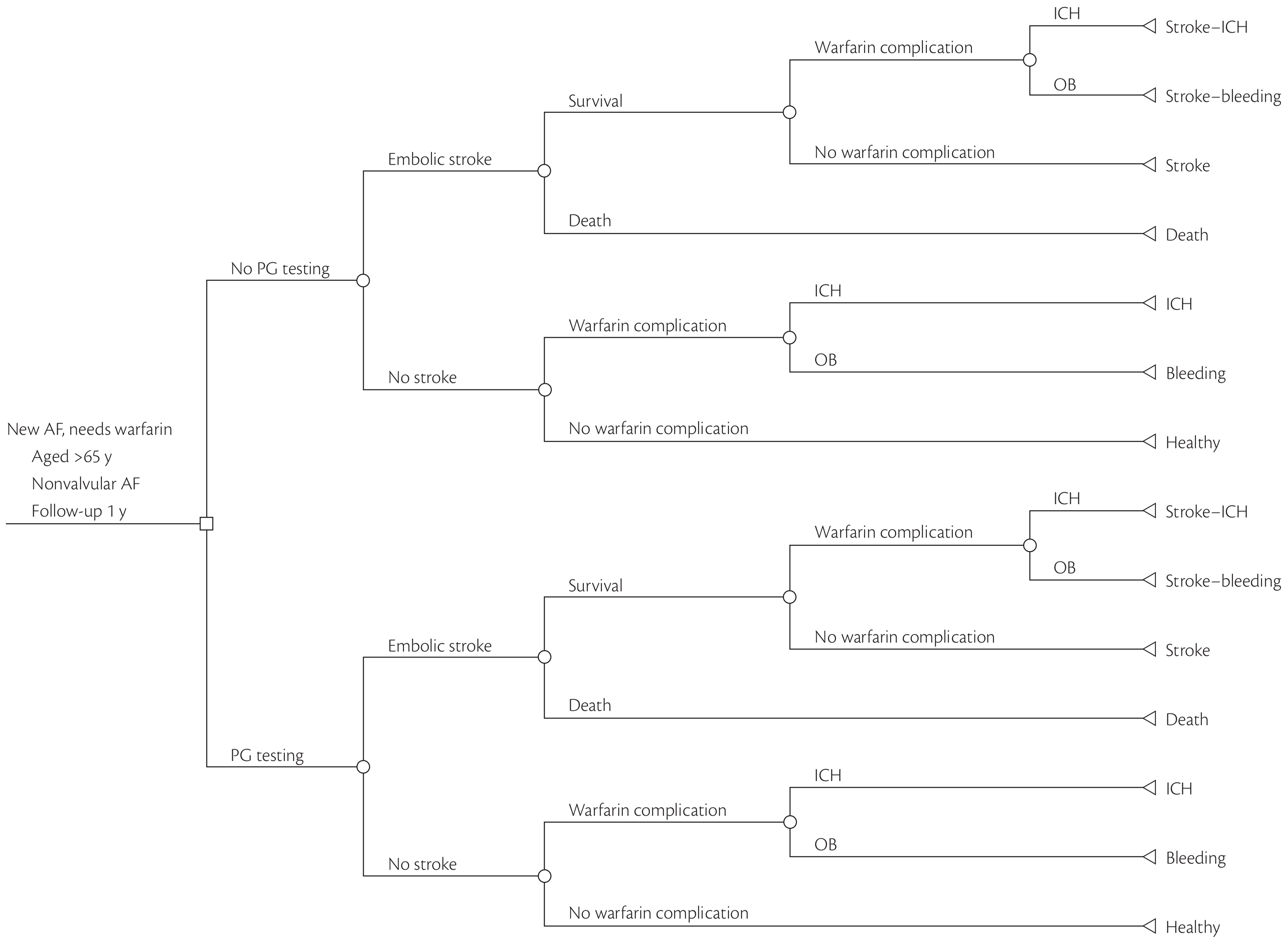

Figure 1. Decision tree model. The potential outcomes depicted are embolic stroke and warfarin complications (intracranial hemorrhage [ICH] or other bleeding [gastrointestinal or any other type of bleeding requiring hospitalization and blood transfusion]). AF = atrial fibrillation; PG = pharmacogenetic; OB = other bleeding.

Given that most adjustment of the warfarin dose and the majority of complications typically occur in the first year of therapy, the decision tree considered clinical outcomes over a period of 12 months. The results were expressed in terms of the cost of adverse events (eg, death, embolic stroke, warfarin complications) from the perspective of a third-party payer (in 2003 US dollars) and in terms of utility from the patient's perspective, a measure of the desirability of the outcome.

Probability, Cost, and Utility Values

The event rate of embolic stroke was based on the outcomes of published clinical trials,[11] and event rates of bleeding complications were based on outcomes from an observational study (**Table**).[12] Costs and utility values were taken from previous cost-effectiveness studies of anticoagulation.[4,11,13] The costs of intracranial hemorrhage, other severe bleeding, and stroke were estimated from 2003 diagnosis-related groups, as calculated and used in previous analyses.[4,11] The yearly cost of INR monitoring was approximated on the assumptions that a patient initiating warfarin therapy would require frequent INR monitoring during the first months and that the frequency of monitoring would be slightly lower in the setting of pharmacogenetic testing.[4] The cost of testing was approximated from the Medicare Reimbursement Estimate and rounded to $250, as in a previous analysis.[13]

It was assumed that pharmacogenetic testing would not lead the clinician to make potentially harmful dose adjustments, an assumption supported by data indicating no difference in time spent within the therapeutic INR range among patients with genotype-guided versus standard dosing of warfarin.[8]

Sensitivity Analysis

A sensitivity analysis was performed using a range of values for the risk of embolic stroke and the incidence of warfarin complications to examine the robustness of the model. Because the 2 main branches of the tree (pharmacogenetic testing and no testing) were assumed to have similar distribution but different values, the sensitivity analysis was based on 2 factors: the incidence of embolic stroke and the incidence of warfarin complications. It was reasoned that the higher the rate of embolic stroke, the more likely that pharmacogenetic testing would prevent this event; therefore, the rate of embolic stroke needed to be included in the sensitivity analysis. Pharmacogenetic-guided dosing of warfarin has been reported to predict the maintenance dose in 50% to 60% of patients,[5] particularly in 2 patient subgroups: those with increased susceptibility to warfarin intoxication and those who are resistant to warfarin compared with the general population. Because the degree of success in predicting the maintenance dose of warfarin would have an effect on complication rates, rates of warfarin complications also were included in the sensitivity analysis.

All analyses were performed using TreeAge Pro 2006 (TreeAge Software, Inc., Williamstown, Massachusetts).

Table. Probabilities, costs, and utility values used in the model.

Assumption	Value
Probabilities	
Embolic stroke[11]	0.023 per year (range, 0.01–0.1)
Major bleeding[12]	0.072 in first year (range, 0.01–0.1)
Intracranial hemorrhage	0.025 in first year
Other major bleeding	0.047 in first year
Costs, 2003 US $[4]	
Intracranial hemorrhage	112,302
Other major bleeding	193,804
Pharmacogenetic testing	250
Warfarin and INR monitoring (no pharmacogenetic testing)	884
Warfarin and INR monitoring (pharmacogenetic testing)	832
Embolic stroke (hospital and nursing home)	380,355
Utilities	
Atrial fibrillation, no stroke, no warfarin complications	0.98
Death	0.00
Embolic stroke (mild, moderate, and severe)	0.67
Intracranial hemorrhage	0.39
Other major bleeding*	0.80
Stroke + intracranial hemorrhage	0.12
Stroke + other major bleeding	0.39
Pharmacogenetic testing	0.99

INR = international normalized ratio.
*Other major bleeding = gastrointestinal bleeding and epistaxis.

RESULTS

Because embolic stroke is a relatively long-term outcome that is not likely to be affected by early improvement in adjustment of the warfarin dose as a result of pharmacogenetic testing, the main differences between the 2 options were the potentially reduced risk of bleeding associated with testing and the increased cost of testing. Analysis of the decision tree indicated that any reduction in major bleeding would be expected to result in an improvement in utility. The cost of pharmacogenetic testing would offset the savings associated with a reduction in the need for INR monitoring as a result of rapid dose adjustment, but any reduction in major bleeding would favor the use of pharmacogenetic testing.

The greater cost associated with pharmacogenetic testing would be immediately offset by any reduction in major bleeding. The present analysis found that if major bleeding were reduced by any percentage, the pharmacogenetic testing option would be less expensive and, as noted earlier, result in higher expected utility (**Figure 2**).

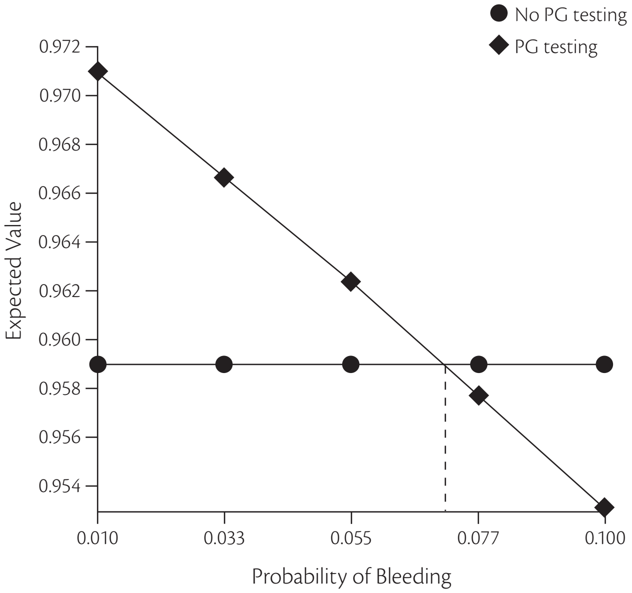

Figure 2. Sensitivity analysis of the probability of bleeding. The probability of bleeding associated with the use of pharmacogenetic (PG) testing would have to be less than the probability during the first year without PG testing to have greater utility, or expected value. In this analysis, the probability of bleeding was assumed to be 0.072 during the first year of warfarin therapy,[12] and the expected value was 0.959.

DISCUSSION

This analysis found that if pharmacogenetic testing resulted in less major bleeding in association with warfarin anticoagulation in elderly patients newly diagnosed with AF, this option would have a higher expected utility and, given a slight improvement in the risk of bleeding, less overall cost than no testing.

The decision tree considered clinical outcomes over a period of 12 months, since beyond the first year of warfarin therapy, most patients would be expected to have reached a stable maintenance dose, and the risk of bleeding associated with overdose would be lower. Because the use of pharmacogenetic testing would be expected to help achieve maintenance dosing rapidly, it made sense for the model to focus on bleeding events within the first 12 months after the initiation of therapy. Whether the use of genotype-guided warfarin dosing would have any effect on the incidence of stroke during the first weeks or months is not known. Considering stroke as a constant in the model ensured that the utility of pharmacogenetic testing was not overestimated.

The outcome of drug therapy is often unpredictable, ranging from a beneficial effect to a lack of efficacy to a serious adverse effect. Polymorphisms in single genes that code for enzymes involved in drug metabolism are a well-known cause of such unpredictability. The ability to identify genetic variations by pharmacogenetic testing has raised expectations concerning the ability to predict the appropriate maintenance dose and, therefore, the response. However, acceptance of pharmacogenetic-guided warfarin therapy will depend on clinical evidence, which has, thus far, been scarce.

In a randomized clinical trial involving 206 patients, Anderson et al[8] found that an algorithm based on pharmacogenetic and clinical factors improved the accuracy and efficiency of warfarin dosing, although the primary end point of reduction in out-of-range INRs was not achieved. In contrast, in a clinical trial in 283 patients, Caraco et al[9] found that patients who underwent *CYP2C9* genotyping spent more time within the therapeutic INR range. In a study by Klein et al,[14] a pharmacogenetic-based algorithm accurately identified greater proportions of patients requiring warfarin doses ≤21 or ≥49 mg per week to achieve the target INR compared with a clinical algorithm. Even if a clinical trial were to report a decrease in the proportion of out-of-range INRs, this end point would not necessarily correspond to a reduction in embolic stroke, particularly if the incidence of stroke was relatively low. The present analysis found that lowering the incidence of warfarin complications by as little as 0.1% (from 7.2% to 7.1%) would be associated with a cost benefit.

Two decision-analysis models of pharmacogenetic-oriented warfarin dosing have been published that were also sensitive to reductions in the rate of bleeding.[15,16] Both analyses found that this practice may be cost-effective in patients who are at high risk for hemorrhage. As in the study by You et al,[15] the present study focused on the 12 months after initiation of warfarin therapy, as most bleeding episodes occur during the first months of therapy. The model indicated that patients at high risk of bleeding would benefit from pharmacogenetic testing. HEMORR2HAGES,[17] a clinical score used to identify patients at risk for bleeding, may be useful for stratifying bleeding risk.

The prevalence of *CYP2C9* and *VKORC1* variants associated with slow warfarin metabolism and, therefore, a high risk of bleeding would be likely to affect the present model. Schwarz et al[18] found that the frequency of A/A polymorphism for the *VKORC1* gene was 11% and 0% in the white and black populations, respectively. In a population with a very low prevalence of these polymorphisms, use of pharmacogenetic testing would have no benefit, whereas the ability to titrate the warfarin dose appropriately would be improved in those with a higher prevalence of these polymorphisms.

A study by the International Warfarin Pharmacogenetics Consortium is currently under way to determine the dosing effectiveness, efficiency, and tolerability of genotype-based dosing of warfarin. The results are expected in late 2011.

The decision tree used in this analysis had several limitations. First, for clarity of the model, the utility values for mild, moderate, and severe stroke were merged into a single category. The costs of bleeding episodes were similarly merged into a single category (mild, moderate, severe, and death), as were the costs of stroke. Second, the incidence of stroke was considered a constant in both groups in the model, although it is possible that the incidence of stroke might be slightly lower in the pharmacogenetic-testing group if testing led to a decrease in out-of-range INR values due to underdosing of warfarin in patients who were carriers of a polymorphism for warfarin resistance. Finally, costs were for a 12-month period only, whereas the sequelae of stroke and intracranial hemorrhage may require more extended care and, therefore, be more expensive. Because the efficacy of pharmacogenetic testing in preventing bleeding has not yet been determined, there is a need for clinical trials or detailed cohort studies in which bleeding rates are compared in patients whose anticoagulation is and is not guided by such testing.

CONCLUSIONS

In this decision analysis, genotype-guided warfarin therapy for anticoagulation in elderly patients with AF was potentially favorable in those at high risk for bleeding. The benefits of this strategy would be closely related to its efficacy in preventing bleeding events. Further clinical studies are needed to fully assess the impact of using pharmacogenetic testing to help prevent bleeding complications of warfarin therapy in elderly patients with AF.

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