ORIGINAL ARTICLE

Should We Test for CYP2C9 Before Initiating Anticoagulant Therapy in Patients with Atrial Fibrillation?

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BACKGROUND: Genetic variants of the warfarin sensitivity gene *CYP2C9* have been associated with increased bleeding risk during warfarin initiation. Studies also suggest that such patients remain at risk throughout treatment.

OBJECTIVE: Would testing patients with non-valvular atrial fibrillation (AF) for *CYP2C9* before initiating warfarin improve outcomes?

DESIGN: Markov state transition decision model.

SETTING: Ambulatory or inpatient settings necessitating new initiation of anticoagulation.

PATIENTS: The base case was a 69-year-old man with newly diagnosed non-valvular AF. Interventions included: (1) warfarin, (2) aspirin, or (3) no antithrombotic therapy without genetic testing; and genetic testing followed by (4) aspirin or (5) no antithrombotic therapy in those with culprit *CYP2C9* alleles.

MEASURES: Quality-adjusted life years (QALYs).

RESULTS: In the base case, testing and treating patients with *CYP2C9*2* and/or *CYP2C9*3* with aspirin rather than warfarin was best (8.97 QALYs). However, warfarin without genetic testing was a close second (8.96 QALYs), a difference of roughly 5 days. Sensitivity analyses demonstrated that genetic testing followed by aspirin was best for patients at lower risk of embolic events. Warfarin without testing was preferred if the rate of embolic events was greater than 5% per year, or the risk of major bleeding while receiving warfarin was lower.

CONCLUSION: For patients at average risk for ischemic stroke due to AF and at average risk for major hemorrhage, treatment based on genetic testing offers no benefit compared to warfarin initiation without testing. The gain from testing may be larger in patients at lower risk of embolic events or at greater risk of bleeding.

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INTRODUCTION

While the effectiveness of anticoagulant therapy has been established clearly for patients with atrial fibrillation at average risk for thromboembolism, the decision to treat patients at low or moderate risk for ischemic stroke remains complex.[1–3] The balance between the risk of bleeding and the benefit appreciated by preventing stroke becomes particularly important in these lower risk patients. The identification of factors, be they clinical or genetic, that predict an increased risk of bleeding can inform this decision, and may affect the choice of antithrombotic therapy in patients at lower risk for ischemic stroke.

Genetic variation in warfarin metabolism and sensitivity genes recently has been associated with both a decreased warfarin dosing requirement and increased risk of bleeding.[4–7] Several studies have demonstrated that patients possessing certain variant alleles of vitamin K epoxide reductase, *VKORC1* and cytochrome P450 *CYP2C9* have greater instability in anticoagulation intensity[8], as measured by the international normalized ratio (INR), and increased bleeding risk during the initiation phase of anticoagulant therapy.[9–14] While the increased risk of bleeding attributable to *VKORC1* appears to be limited to the initiation phase of anticoagulant therapy, several studies have presented evidence suggesting that variant alleles of *CYP2C9* also are associated with a continued risk of bleeding during the maintenance phase of anticoagulant therapy.[4,11,15,16]

Therefore, we developed a decision analytic model to address the clinical question of whether testing for *CYP2C9* should be performed routinely before initiating anticoagulant therapy in patients with non-valvular atrial fibrillation. The Federal Drug Administration already has endorsed new labeling for Coumadin™/warfarin, suggesting that clinicians consider performing genetic testing before initiating warfarin to aid in initial dose selection, and indeed warfarin dose titration algorithms have been developed to incorporate the results of such testing.[17–20] Our intent is not to focus on this issue, but rather to examine whether testing for *CYP2C9* is useful in informing the decision of whether or not to treat with anticoagulant therapy.

METHODS

Review of Data

CYP2C9 Genotype and Bleeding Events. An association between the *CYP2C9* genotype and bleeding risk and anticoagulation status was first suggested by Ogg[21] and confirmed by Higashi et al.[11] Variation in the activity of this hepatic microsomal enzyme, which comprises the primary metabolic pathway for S-warfarin, leads to significant differences in patients' responses to warfarin. The *2 and *3 polymorphisms lead to decreased enzymatic activity of 30% and 80%, respectively; thus, patients with these genetic variants metabolize warfarin more slowly. In Higashi's study of 185 patients studied between 1990 and 2001, those with at least one culprit allele had a 1.4-fold increased risk of supratherapeutic INRs [95% confidence interval (CI), 1.03–1.90], and required a longer time to stable dosing. In addition, such patients had a significantly increased risk of serious or life-threatening bleeding, both during the initiation phase (1st 3 months) (HR, 3.94; 95% CI, 1.29–12.06) and during the entire follow-up period (HR, 2.39; 95% CI, 1.18–4.86).

Subsequently, a systematic review and meta-analysis has noted that patients with either *CYP2C9*2* or *CYP2C9*3* variant have lower mean daily warfarin dose requirements and a greater risk of bleeding [relative risk (RR), 2.26; 95% CI, 1.36–3.75].[4] Several studies have related the risk of bleeding in patients with culprit alleles to intensity of anticoagulation.[11] However, in separate studies by Margaglione[12] and Taube[13], such an association between higher risk of bleeding and elevated INRs was not seen. In a large Scandinavian study following 7,983 patients receiving either acenocoumarol or phenprocoumon, coumarins not commonly used in the United States, variant alleles of *CYP2C9* were not associated with an increased risk of bleeding events during the initiation phase of anticoagulation.[14] Furthermore, patients receiving phenprocoumon had no significantly increased risk of major bleeding during the entire study period. However, patients with the variant alleles who received acenocoumarol had an increased relative hazard of major bleeding events (HR, 1.83; 95% CI, 1.01–3.32), consistent with studies of warfarin.

Most recently, Limdi et al. reported on the association of genotype and bleeding risk in 446 patients taking warfarin with over 555 person-years of follow-up.[15] In Cox proportional hazards models adjusting for age, gender, race, BMI, *VKORC1* genotype, vitamin K and alcohol intake, warfarin dose, interacting drugs, significant comorbid illnesses, and INR at the time of hemorrhage, they calculated an overall hazard ratio of 3.0 (95% CI, 1.22–7.54). The availability of longitudinal data with 2-year follow-up allowed them to calculate relative hazards for major bleeding both before stabilization of therapy (HR, 5.3; 95% CI, 0.47–58.7) and the after first stabilization of therapy (HR, 2.2; 95% CI, 0.72–6.57), although these results were not statistically significant, and there was no significant increase in risk of minor hemorrhage (HR, 1.3; 95% CI, 0.8–2.1). These results are similar to those described in the earlier study by Higashi, although neither study recorded any intracranial hemorrhages among their major hemorrhages.[11]

Relative Hazard of Major Hemorrhage in Patients Receiving Anticoagulant Therapy. In a review of 16 trials examining the use of anticoagulant and antiplatelet agents for the prevention of stroke, the rate of major extracranial hemorrhage averaged 0.6% per year in patients not receiving anticoagulant therapy. The relative risk for major extracranial hemorrhage in patients receiving anticoagulant therapy was 2.4, resulting in an average rate of 1.4% per year for trial participants.[22,23] Higher rates of hemorrhage have been described in other populations.[24,25]

In a seminal multicenter study examining risk factors for complications of chronic anticoagulant therapy, Fihn et al. described a 1.9-fold (95% CI, 1.3–3.0) increased risk of serious bleeding during the first 3 months of treatment compared with the rest of the 1st year.[26] Fang et al. recently described the rates of intracranial hemorrhage in 13,559 AF patients in Kaiser Permanente's ATRIA cohort.[27] They noted a strong correlation between increasing age and risk of intracranial hemorrhage. Patients between 60 and 69 years of age had 0.07% (95% CI, 0.02%–0.27%) per year rate of intracranial hemorrhage off warfarin and a 0.40% (95% CI,.023%–0.68%) per year rate of intracranial hemorrhage on warfarin (relative hazard — 5.7). These results are consistent with those described in van Walraven's individual patient meta-analysis of six published randomized AF trials.[28] Other studies have found similar increases in risk of intracranial hemorrhage.[29–35] The risk of intracranial hemorrhage while receiving aspirin is roughly 0.6 that of patients receiving warfarin.[28,36–38]

Description of Decision Model. We developed a Markov state transition model [39] using a standard computer program (DECISION MAKER)[40] to analyze decision trees and to perform sensitivity analyses. We considered five strategies for a hypothetical 69-year-old man with newly diagnosed non-valvular atrial fibrillation at average risk for ischemic stroke (Fig. 1) (see online appendix for decision model and description).

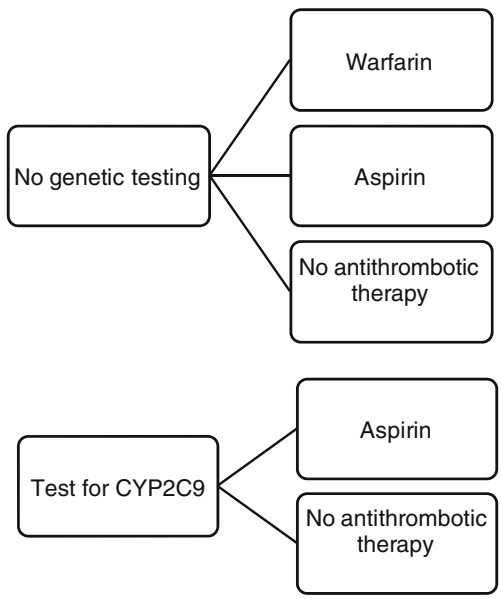

Figure 1. Strategies examined for prevention of thromboembolism in a 69-year-old man with newly diagnosed non-valvular atrial fibrillation. In the top panel treatment is initiated without knowledge of *CYP2C9* genotype. In the lower panel treatment is based on the results of *CYP2C9* genotyping. Those who are negative for the variant alleles receive warfarin, whereas in those who test positive, we examine treatment with either aspirin or no antithrombotic therapy.

Regardless of the strategy, patients may or may not possess a culprit allele of *CYP2C9*. Patients with the variants face approximately a four-fold increased risk of major bleeding versus those with the "wild-type" allele during warfarin initiation (the first 3 months) and a more than two-fold increased risk during the maintenance phase of treatment. We assumed that patients have a 1.9-fold increased risk of major bleeding during the initiation phase as described by Fihn and others. [24,26] Since the observed increased risk is a weighted average of higher risk in *CYP2C9* variants and lower risk in *CYP2C9* wild type, this resulted in a relative hazard of 4.7 for those with the culprit alleles and a lower relative hazard of 1.2 in those without the culprit alleles during the initiation phase versus the maintenance phase of warfarin therapy. In a similar manner, we calculated a lower relative hazard of major bleeds during the maintenance phase of therapy in those without the culprit alleles (0.65). We stratified major bleeding events into intracerebral hemorrhage, subdural hematoma, and extracranial bleeding. Intracerebral hemorrhage was further categorized into lobar and deep hemispheric locations, as previously described.[30,41]

The Markov model contains 28 states of health (Supplementary Figure 1. During each monthly cycle, patients face the chance of thromboembolic events, and the chance of hemorrhagic events (intracerebral hemorrhage, subdural hematoma, and non-CNS bleeds). All of these events may lead to death, severe or mild permanent morbidity, or resolution. These sequences of chance events filter patients in each cycle of the simulation from one state to the state they occupy in the next cycle. Baseline values for parameters used in the decision analytic model are summarized in Table 1.

RESULTS

In the base case (see Table 2, for a 69-year-old man at average risk for ischemic stroke due to AF and at average risk for major hemorrhage, testing and treating patients with *CYP2C9*2* and/or *CYP2C9*3* with aspirin rather than warfarin is best, yielding an expected utility of 8.97 quality-adjusted life years (QALYs). Anticoagulant therapy without prior testing for culprit alleles of *CYP2C9* is a close second, yielding 8.96 QALYs, a difference of roughly 5 days.

We performed sensitivity analyses to examine the impact of both uncertainty in parameter estimates and patient-to-patient variability in risk profiles for stroke and bleeding. While the average risk of stroke in patients with atrial fibrillation is 4.5% per year[35], there is a wide spectrum of risk depending upon other co-morbidities, such as diabetes mellitus, hypertension, congestive heart failure, etc.[42–44] Figure 2 examines the impact of changes in the risk of embolic events. The effectiveness of all strategies declines with increasing risk of embolic events. However, there are two thresholds of interest. Above an embolic rate of 5% per year ($CHADS_2$ score of approximately 3 or greater)[45], warfarin without prior testing is preferred; below a threshold of 1.3% per year no antithrombotic therapy is preferred. However, in the range between these two thresholds, testing followed by aspirin therapy in patients with culprit alleles is best. Thus, for the practicing physician who judges his or her patient to have an annual risk of thromboembolism between 1.3% per year and 5% per year, learning the results of *CYP2C9* genotyping could alter the decision to anticoagulate.

Patients may also vary in their underlying risk of major bleeding. In sensitivity analyses examining the risk of bleeding on warfarin, relative to the base hazards of intracerebral, subdural, and extracranial bleeding, testing is preferred unless the relative hazard of such events is less than 0.9, in which case anticoagulant therapy is best (Fig. 3. We also examined how an increased risk of intracranial hemorrhage associated with advancing age would impact the screening decision. In the base case we used an annual intracranial hemorrhage incidence of 0.07%.[27] However, older patients (75–84 years of age) have an increased annual incidence of 0.11%, while those 85 years or older have an annual incidence approaching 0.2%.[46] Older patients may also face an increased risk of thromboembolism (8.1%/year) if they have one or more risk factors beyond advanced age.[35] In elderly patients without additional risk factors for thromboembolism who are between the ages of 70 and 79 years of age, or 80 years of age or older, testing followed by aspirin in those with genetic variants yields increasing benefit compared with warfarin. For the more typical elderly patients (75–84 years of age) with risk factors for thromboembolism, warfarin is preferred unless the relative hazard of major bleeding exceeds 2.8 during the maintenance phase of anticoagulant therapy, in which case genetic testing would be best.

The evidence supporting an increased hazard of bleeding during the maintenance phase of warfarin therapy in patients with culprit alleles remains mixed. While testing was preferred at the base case relative hazard of 2.39, warfarin without prior testing would be preferred at lower relative hazards, less than 2.13. Figure 4 shows a two-way sensitivity analysis examining the effect of varying both the rate of embolic events and the relative hazard of major bleeding during the maintenance phase of anticoagulant therapy. Testing is favored in the region into which individuals fall if they are at lower risk of embolic events and, because of their possession of culprit variants of *CYP2C9*, at higher relative hazard of hemorrhage in the maintenance phase. While the base case falls within the region in which genetic testing is preferred, it is close to the threshold line. For patients at lower risk of thromboembolic events and at higher risk of bleeding, no antithrombotic therapy is favored.

The efficacy of screening is dependent upon the frequency of the variant alleles; hence, the benefit accrued by treating such patients with a potentially more appropriate therapy (such as aspirin) is diluted by the outcomes in the majority of patients who don't possess the culprit alleles. Therefore, we also examined outcomes of different treatments among patients known to have either the *CYP2C9 *2* or **3* alleles. In such patients, aspirin yielded the greatest expected utility, 8.60 QALYs, while warfarin and no antithrombotic therapy fared somewhat worse, yielding 8.53 and 8.47 QALYs, respectively. Thus, were a physician to already know that a patient possessed one or more of these culprit alleles, treatment with aspirin would be best.

Finally, we examined an alternative scenario in which a safer, novel antithrombotic therapy becomes available that is not affected by *CYP2C9*-related pathways, such as the direct thrombin inhibitors. We assumed the novel agent: (1) had an efficacy and overall bleeding risk similar to that of warfarin in patients who do not possess culprit *CYP2C9* alleles and (2) was not associated with an increased relative hazard of major bleeding during the initiation phase of treatment. This strategy yielded an expected utility of 9.04 QALYs, a gain of 0.09 QALYs vs. warfarin therapy.

Table 1. Data Required in the Analysis—Probabilities, Rates, Quality of Life

Parameter	Value	References						
Gene frequency of *CYP2C9*2* and/or *CYP2C9*3*	0.20	[4,11,54–56]						
Relative hazard of major bleed in variants versus "wild-type" CYP2C9 variants								
Initiation phase	3.94	[11,15]						
Maintenance phase	2.39	[11,15]						
Relative hazard of major bleed during initiation phase versus maintenance phase -								
General population	1.9	[26]						
CYP2C9 variants	4.7	Calculated						
CYP2C9 "wild-type"	1.2	Calculated						
Rate of thromboembolism - untreated (%/year)	0.045	[35,57]						
Efficacy of treatment								
With warfarin	0.68	[35]						
With aspirin	0.22	[23,57]						
Rate of thromboembolism - treated with warfarin (%/year)	0.014	Calculated						
Rate of thromboembolism - treated with aspirin (%/year)	0.04	Calculated						
Probable outcome from thromboembolic event								
Death	0.27	[35]						
Permanent sequelae	0.44	[35,58]						
With severe disability	0.29	[35,59,60]						
With mild disability	0.71	[35,59,60]						
Good recovery	0.29	[35,58]						
	Location of hemorrhage (value) (reference)							
	Lobar ICH		Deep ICH		Extra-cranial		Subdural hematoma	
Rate of bleeding —untreated (%/year)	0.00035	[46]	0.00035	[46]	0.006	[22]	0.00025	[29,35]
Probable outcome from bleeding event - without warfarin*								
Death	0.190	[41]	0.207	[41]	0.13		0.20	[61]
Severe long-term disability — GOS=3†	0.428	[41]	0.436	[41]			0.07‡	
Mild long-term disability — GOS=4†	0.196	[41]	0.187	[41]			0.40‡	
Good recovery - GOS=5†	0.185	[41]	0.170	[41]			0.17‡	
Relative hazard of bleeding on anticoagulants	5.7	[62]	5.7	[62]	2.4	[63]	4.0	[29,32]
Rate of bleeding on anticoagulants (%/year)	0.002	[46]	0.002	[46]	0.014		0.001	[35]
Probable outcome from bleeding event - on warfarin								
Death	0.379		0.405		0.15	[63]	0.20	[61]
Severe long-term disability - GOS=3†	0.429		0.420				0.09	[61]
Mild long-term disability — GOS=4†	0.111		0.103				0.50	[61]
Good recovery - GOS=5†	0.080		0.073				0.20	[61]
Variable	Quality of life							
	Value	Reference						
Long-term morbidities								
Well	1.0							
Well while receiving anticoagulants	0.99	[64]						
Severe long-term disability	0.11	[64]						
Mild long-term disability	0.76	[64]						
Dead	0.0							
Short-term morbidities in patients with resolution								
Extracranial bleeding event§	0.84							
Intracerebral hemorrhage‖	0.79							
Thromboembolic event‖	0.79							

*Assume outcomes of bleeding events for aspirin-treated patients are the same as for untreated patients
†GOS — Glascow Outcomes Score at 3 months
‡ Assume same distribution of neurological outcomes in survivors as in anticoagulated patients with subdural hematoma
§*Assume Q=0 for duration of hospitalization; length of stay (LOS) for gastrointestinal hemorrhage (DRG 174) =4.9 days*
‖*LOS for specific cerebrovascular disorders except transient ischemic attack (DRG 14) =6.4 days*

DISCUSSION

Our analysis suggests that the benefit of testing for culprit alleles of *CYP2C9* as an adjunct to decision making for antithrombotic therapy in patients with non-valvular atrial fibrillation depends upon several factors, particularly the risk of thromboembolic events for the individual patient. For the "average" patient with nonvalvular AF who would be assigned a $CHADS_2$ score of 2[47], not otherwise at increased risk for major hemorrhage, the strategy of choosing warfarin or aspirin based on the results of genetic testing for *CYP2C9* yields essentially equivalent outcomes compared to the strategy of initiating warfarin without genetic screening. For individuals at higher risk of thromboembolic stroke (i.e., $CHADS_2$ score 3–6), treatment selection in response to genetic testing would yield inferior outcomes. Testing followed by treatment with aspirin in those found to have the culprit alleles only becomes preferred for patients at low risk of thromboembolism (between 1.3% and 5% per year). Bleeding risk also influences the benefit of genetic testing, with the gain from testing increasing as the relative hazard of major hemorrhage increases.

Among the testing strategies, treatment with aspirin in those found to possess the genetic variant is always better than not treating unless the risk of embolic events is less than

Table 2. Results of Base Case Analysis

Strategy	Effectiveness (QALYs)
Testing for *CYP2C9* followed by aspirin if (+)	8.97
Anticoagulation without prior testing	8.96
Testing for *CYP2C9* followed by no antithrombotic therapy if (+)	8.95
Aspirin without prior testing	8.60
No antithrombotic therapy	8.47

roughly 1% per year, in which case no antithrombotic therapy is best. Although aspirin has a lower associated risk of major hemorrhage and is not impacted by the metabolic pathways governed by *CYP2C9*, it has only moderate efficacy (22%)[23] in preventing embolic events. However, should safer novel antithrombotic therapies that are not impacted by *CYP2C9*-related pathways, such as the direct thrombin inhibitors, become available, testing followed by treatment with these drugs might be a beneficial strategy, even for patients at average risk for embolic events. Alternatively, if increasing the frequency of INR measurements during initiation as well as maintenance of warfarin therapy were demonstrated to reduce the risk of hemorrhage conferred by high-risk *CYP2C9* alleles, then altering the INR monitoring strategy, rather than withholding warfarin altogether, might prove of benefit to affected individuals. Clearly, the adequacy of INR monitoring is an important determinant of the efficacy of warfarin for prevention of thromboembolism.[48] Future research is needed to determine what role more vigilant monitoring may play in pharmacogenetic dosing strategies.

This analysis did not examine a strategy of pharmacogenetic-based dosing, in which the dose of warfarin is adjusted in response to genetic information. Several prior decision analyses have examined this question with varying results.[49–51] In a separate study, we examined the cost-effectiveness of such a dosing strategy and found that for patients at average risk for

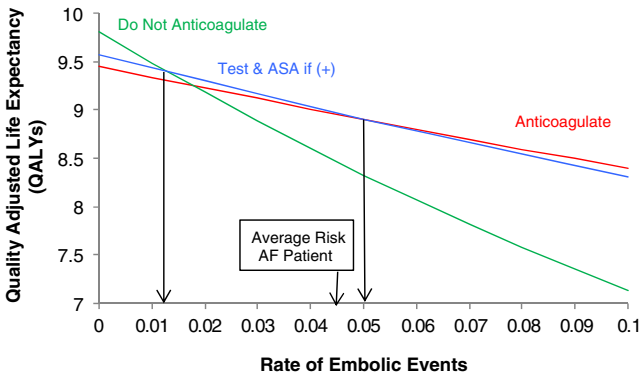

Figure 2. Quality-adjusted life expectancy (y-axis) predicted for three of the five strategies as a function of the estimated annual risk of thromboembolism (x-axis). At the base case value (4.5% annual rate of thromboembolism) for "average risk" patients with atrial fibrillation, testing and treating those found to possess the culprit alleles of *CYP29C* with aspirin is best. For patients having less than a 1.3% per year risk of embolic events, no antithrombotic therapy is best, while for those having greater than a 5% per year risk anticoagulation without prior testing is best. Thus, for individuals judged to have an annual risk of thromboembolism between 1.3% and 5% per year, testing and treating those found to possess culprit alleles of *CYP29C* with aspirin yields best outcomes, although by a very small margin.

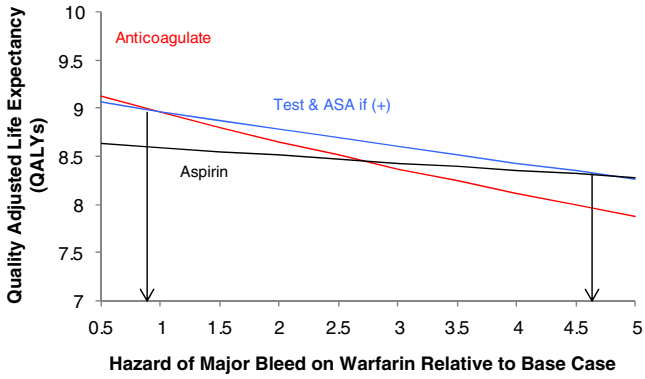

Figure 3. Quality-adjusted life expectancy (y-axis) predicted as a function of varying the hazard of major bleeding on warfarin (x-axis). Hazard of major bleeding on warfarin is relative to the baseline hazard estimate drawn from prior published reports. Thus, a hazard of 1.0 on the x-axis indicates relative hazards of 5.7, 4.0, and 2.4, respectively, for intracerebral, subdural, and extracranial bleeding while receiving warfarin. For patients in whom this hazard is judged to be less than 0.9, anticoagulation without prior testing yields superior outcomes. Aspirin without prior testing is best if the relative hazard exceeds 4.7, while genetic testing followed by aspirin for those possessing culprit alleles is favored in the range between these two values.

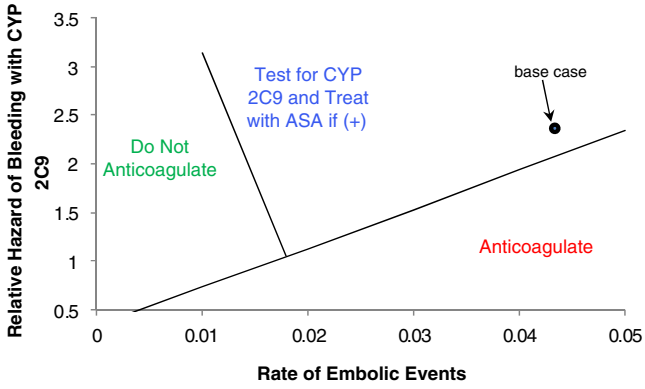

Figure 4. Two-way sensitivity analysis examining the effect of varying the annual risk of embolic events (x-axis) and the relative hazard of major bleeding associated with culprit alleles of *CYP2C9* during the maintenance phase of anticoagulant therapy (y-axis). Hypothetical patients can therefore be assigned risk estimates for each of these two parameters. The area on the graph where they fall then allows assignment of a strategy either of (1) "Do not anticoagulate," (2) genetic testing followed by aspirin for those individuals found to possess *CYP2C9*2* and/or *CYP2C9*3* culprit alleles, or (3) anticoagulation without genetic testing. Patients whose risk for thromboembolism is judged to be high are placed in the region to the right. For these patients, if the relative hazard for bleeding conferred by *CYP2C9* is low, anticoagulation without prior testing is favored. For patients in whom the rate of embolic events is judged to be low (but not less than 1% per year) and the relative hazard conferred by *CYP2C9* is high, genetic testing followed by aspirin in those found to possess the culprit genetic variants is best. For our base case 69-year-old man with nonvalvular AF, estimates for these two parameters place him just within the genetic testing region.

ischemic stroke due to AF and at average risk for major hemorrhage, genotype-guided dosing resulted in better outcomes, but at a high cost.[52] The marginal cost-effectiveness of testing versus standard induction was more than $170,000 per QALY. Further, we found there was only a 10% chance that genotype-guided dosing would likely be "cost-effective" (i.e., <$50,000 per QALY). We also identified several key parameters beyond the efficacy of pharmacogenetic-based dosing on bleeding risk that would influence the cost-effectiveness of this strategy, including the cost of genotyping and the delay in starting warfarin necessitated by waiting for testing results. Indeed, if future studies demonstrate efficacies above 32% in preventing major hemorrhages during warfarin initiation, then genotyping strategies that cost less than $200 and provide results quickly enough to avoid delays in initiating therapy could make genotype-guided dosing "cost-effective."

Like all decision analyses, ours is limited by the data that are available. We have incorporated published data on risk of hemorrhage in anticoagulated patients who have been genotyped. There is even less information on whether *CYP2C9* variants may influence risk of thromboembolism. Ongoing randomized trials are examining the efficacy of genotype-based dosing strategies for anticoagulation. Until these are completed, however, models such as ours can serve to guide bedside decision-making in an environment where genetic tests are widely available.

The discovery of genetic variants that influence the risk of bleeding during long-term anticoagulation holds the promise of improving the risk-benefit ratio of anticoagulation for the millions of individuals worldwide with atrial fibrillation and other conditions that increase risk for thromboembolism. It is important to recall, however, that the overwhelming majority of long-term morbidity and mortality related to bleeding on anticoagulants is due to intracranial hemorrhage[53] and that fully 2/3 of these hemorrhages occur in the absence of supratherapeutic anticoagulation.[41] Thus, if any genes are likely to play a major role in the decision to anticoagulate, they may well be unrelated to warfarin sensitivity or drug metabolism in general, but instead be discovered through their role in the underlying conditions that predispose to hemorrhage independent of the presence of anticoagulation.

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