Patient-Specific Decision-Making for Warfarin Therapy in Nonvalvular Atrial Fibrillation
How Will Screening With Genetics and Imaging Help?

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Background and Purpose—Intracerebral hemorrhage (ICH) accounts for a majority of long-term morbidity and mortality associated with bleeding while on warfarin. Both ICH and warfarin-related ICH appear to have a genetic component. Furthermore, advanced neuroimaging using MRI can now identify individuals at increased risk of ICH. We explore whether screening strategies that include genetic profiling and neuroimaging might improve the safety of chronic anticoagulation for atrial fibrillation by identifying individuals from whom warfarin should be withheld.

Methods—We used a Markov state transition decision model. Effectiveness was measured in quality-adjusted life-years. Data sources included the English language literature using MEDLINE searches and bibliographies from selected articles along with empirical data from our institutions. The base case was a 69-year-old man with newly diagnosed nonvalvular atrial fibrillation.

Results—For patients at average risk for thromboembolic events and known to possess a hypothetical genetic profile increasing risk for warfarin ICH, anticoagulation remains the preferred strategy until the relative hazard of ICH exceeds 23.8. Genetic profiling would be favored for patients at low risk of thromboembolism (1.5% per year) if the hypothetical gene variant(s) conferred a relative risk of ICH >4.1. Screening strategies in which patients underwent genotyping and MRI before anticoagulation did not improve aggregate patient outcomes unless the predictive power of MRI exceeded current best guess estimates and patients were at low to moderate risk of thromboembolism.

Conclusion—Currently identified genetic markers of bleeding risk do not confer a risk of ICH sufficiently high to warrant routine genetic testing for patients at average risk of thromboembolism. Even if patients undergo screening with MRI as well as genotyping, currently available data on the role of MRI on risk of ICH and warfarin ICH do not support use of these tests for withholding anticoagulation in patients with atrial fibrillation. (Stroke. 2008;39:3308-3315.)

Key Words: atrial fibrillation ■ cerebral hemorrhage ■ decision support techniques ■ genetics ■ magnetic resonance imaging

Individualized risk stratification of patients for chronic anticoagulation is likely to achieve a remarkable level of precision in the coming decade. Although anticoagulating patients with atrial fibrillation (AF) with warfarin is an effective treatment for prevention of thromboembolic stroke,1 warfarin can cause catastrophic intracerebral hemorrhage (ICH), a complication that has quintupled in incidence over the past decade as warfarin use has become more widespread.2,3 With a case-fatality rate exceeding 50% and a substantial risk of long-term functional impairment,4 small increases in the risk of this complication can tip the balance in favor of withholding anticoagulation.

Although the average risk of warfarin-related ICH is small,5 subsets of patients with AF may be at substantially increased risk. Although predictors of warfarin-related ICH have been identified such as advancing age and history of prior stroke, these alone are not adequate for screening. Furthermore, fewer than one third of warfarin-related ICH occur in the setting of supratherapeutic intensities of anticoagulation,4 limiting the effectiveness of careful anticoagulant control in preventing ICH.

Novel genetic6 and radiographic risk factors for ICH on warfarin raise the possibility that screening may allow physicians to identify individuals at high risk before initiating therapy.6–11 Genetic variants that will affect risk for warfarin-related ICH, and hence influence the decision to anticoagulate, will likely fall into 2 categories: those that affect warfarin sensitivity and metabolism such as VKORC112,13 and

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CYP2C94,15 and those that affect the underlying diseases that predispose to ICH such as apolipoprotein E genotype (APOE),16–19 MRI-detectable manifestations of cerebral small vessel disease, which appear to underlie a high proportion of warfarin-related ICH,6,10,20 are present in populations of elderly stroke-free individuals.21–33 In particular, the widespread application of gradient-echo MRI (GE-MRI) has revealed that small asymptomatic microhemorrhages are common and predispose to risk of subsequent symptomatic ICH,24,28,32 and perhaps warfarin-related ICH.

Methods
We developed a series of incrementally more complex Markov state transition models23 using a standard computer program (DECISION MAKER)34 to analyze decision trees and to perform sensitivity analyses like in prior studies.36 First, we compared 3 strategies for initiating or withholding anticoagulant therapy with warfarin for a hypothetical 69-year-old man with newly diagnosed nonvalvular AF: anticoagulation with warfarin, aspirin, and withholding of antithrombotic therapy. We next explored whether testing for gene profiles associated with an increased risk of ICH improves patient outcomes. In this model, the risk of ICH is increased in patients with putative warfarin-related ICH genetic variants (Supplemental Figure I A, available online at http://stroke.ahajournals.org). If testing has been performed, and hence those individuals at higher risk for ICH are identified, warfarin is withheld in those patients and aspirin is instead prescribed. We assumed that genetic testing is perfect, yielding no false-positive or false-negative results.

Finally, we introduced GE-MRI for detection of cerebral microhemorrhage (CM) with genetic screening as an additional testing modality for increased ICH risk.24,32 In assessing a strategy in which GE-MRI imaging is performed only in patients found to possess the genetic risk profile, we assumed that anticoagulation therapy is withheld (or aspirin is used as an alternative treatment) in patients who have genetic risk markers for ICH and have GE-MRI evidence of CM.

The Markov model contains 28 states of health (see Supplemental Figure I A for the decision tree). During each monthly cycle, patients face the chance of thromboembolic and hemorrhagic events (ICH, subdural hematoma, and noncentral nervous system bleeds). All of these events may lead to death, severe or mild permanent morbidity, or resolution. Baseline values for parameters used in the decision analysis model are summarized in the Table.

Assumptions
We made several simplifying assumptions. First, a noncentral nervous system hemorrhagic event without permanent morbidity will lead to temporary (1 month) discontinuation of anticoagulant therapy. However, ICH or subdural hematoma will lead to permanent discontinuation of anticoagulation. In patients not receiving anticoagulant therapy, any embolic event will lead to the initiation of long-term anticoagulation (except in patients with recurrent ICH or a subdural hematoma).

Second, we assumed that events with permanent morbidity reduced quality of life (Q) to a fixed lower level, which stays constant until the patient dies. Rather than modeling improving neurological functioning each month after recurrent ICH, we assumed a fixed Q based on neurological functioning at 3 months. Although this may overestimate Q in the early months and slightly underestimate Q in the later months, it should provide a reasonable estimate across the patient’s lifetime. Quality adjustment factors for states of health after stroke were obtained from a study of usefulness assessments in patients with AF (Table).37

Lastly, we made no base case assumption for the relative hazard of ICH in patients with the genetic variant. Rather, we explored this in sensitivity analyses. We assumed a base case prevalence of 23% based on the frequency of the APOE ε2 and ε4 alleles, which represent prototypical genetic markers for future ICH.16,17,38,39 Crude estimates for allele frequencies are 3% to 20% for APOE ε2 and 20% to 40% for APOE ε4 depending on the racial and ethnic heritage of the population studied.40

Sensitivity analyses were performed to examine the effect of variations in the following parameters: (1) relative risk of thromboembolic stroke; (2) relative hazard of ICH conferred by putative risk-conferring alleles; and (3) relative hazard of ICH in patients whose MRIs reveal cerebral microbleeds.

Review of the Data
Risk of Intracerebral Hemorrhage in the General Population
For our base case 69-year-old man with AF, we assumed an incidence of 30 per 100 000 patients (see Table).38,41 Because most data apply to the >80% of ICH that are located in the lobar (frontal, parietal, temporal, or occipital) or deep hemispheric (thalamus or basal ganglia) regions,4 we considered these 2 locations as the site of ICH. Stratifying ICH by location and age yields incidence estimates of 15, 43, and 71 per 100 000 in patients age 55 to 74, 75 to 84, and ≥85, respectively, for lobar ICH; and 15, 64, and 125 per 100 000 patients in those same age ranges, respectively, for deep hemispheric ICH.42

Relative Hazard of Intracerebral Hemorrhage in Patients Receiving Anticoagulant Therapy
We assumed that anticoagulant therapy resulted in a 3.1-fold increased risk of ICH and varied this in sensitivity analyses. This estimate is derived from a univariate analysis of risk factors for all ICH in patients with stroke who were enrolled in a Greater Cincinnati/Northern Kentucky stroke registry because of its population-based sampling and prospective data collection.16 Other studies have found similar or greater increases in risk of ICH.38,39,41–44 We assumed that aspirin resulted in a 1.9-fold increased risk of ICH.45–48

Relative Hazard of Intracerebral Hemorrhage in Patients With Cerebral Microbleeds on MRI
GE-MRI can reveal evidence of CM, described as small, hypodense foci (usually <5 mm in size), caused by hemosiderin deposits in macrophages. Because hemosiderin may remain in macrophages for many years after hemorrhage, GE-MRI can assess for a history of cerebral microhemorrhage.27,50 Pathological studies have demonstrated that GE-MRI hypodensities correlate well with hemosiderin-laden macrophages in brain parenchyma.51 CM occurs in roughly 6% of healthy elderly North American and European individuals (mean age, 55 to 65 years).51,55,52 Prevalence increases markedly with age reflecting the strong age-related risk of cerebral small vessel diseases such as cerebral amyloid angiopathy.16,38,53

Data on ICH in patients with CM were drawn from published studies21,24,28,54 as well as our own prospective cohort.6,55 In previously reported analyses by coauthors of the current study, CM among 121 Chinese patients with prior ischemic stroke were associated with a hazard ratio for subsequent ICH of 4.21 Similarly, in a prospective cohort of 938 survivors of acute ischemic stroke who underwent GE-MRI at the time of incident stroke and were followed for a mean (±SD) 26.9 (±15.8) months,28 the relative hazard for subsequent ICH associated with CM was 12.8.

Realizing that subjects in these studies were receiving antiplatelet or anticoagulant therapy,21,55 and lacking evidence from long-term studies of incident ICH in patients with CM, we conservatively estimated a 2-fold increased risk for our base case. We assumed that GE-MRI evidence of CM would be associated with the same extent of increased risk for ICH in the presence or absence of anticoagulation.

Results
Genetic Screening
In a patient known to have a hypothetical warfarin ICH gene variant, the relative hazard of ICH conferred by this gene must exceed 23.8 before withholding anticoagulation is best
### Table. Data Required in the Analysis: Probabilities, Rates, and Quality of Life

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of Apo ε 2 or 4</td>
<td>0.23 (39)</td>
</tr>
<tr>
<td>Relative hazard of lobar ICH with Apo ε 2 or 4</td>
<td>2.3 (16)</td>
</tr>
<tr>
<td>Rate of thromboembolism (untreated)</td>
<td>0.045/yr (46, 63)</td>
</tr>
</tbody>
</table>

**Efficacy of treatment**

- With warfarin | 0.68 (46) |
- With aspirin | 0.21 (63) |

**Rate of thromboembolism (treated)** | 0.014/yr |

**Probable outcome from thromboembolic event**

- Death | 0.27 (46) |
- Permanent sequelae | 0.44 (46, 64) |
  - With severe disability | 0.29 (46, 65, 66) |
  - With mild disability | 0.71 (46, 65, 66) |
- Good recovery | 0.29 |

<table>
<thead>
<tr>
<th>Location of Hemorrhage</th>
<th>Lobar ICH</th>
<th>Deep ICH</th>
<th>Extracranial</th>
<th>Subdural Hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of bleeding (untreated)</td>
<td>0.00015/yr (42)</td>
<td>0.00015/yr (42)</td>
<td>0.006/yr (67)</td>
<td>0.00025/yr (43, 46)</td>
</tr>
<tr>
<td>Probable outcome from bleeding event (without warfarin)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.190</td>
<td>0.207</td>
<td>0.13</td>
<td>0.20 (68)</td>
</tr>
<tr>
<td>Severe long-term disability GOS = 3†</td>
<td>0.428</td>
<td>0.436</td>
<td>0.07‡</td>
<td></td>
</tr>
<tr>
<td>Mild long-term disability GOS = 4†</td>
<td>0.196</td>
<td>0.187</td>
<td>0.40‡</td>
<td></td>
</tr>
<tr>
<td>Good recovery GOS = 5†</td>
<td>0.185</td>
<td>0.170</td>
<td>0.17‡</td>
<td></td>
</tr>
<tr>
<td>Relative hazard of bleeding on anticoagulants</td>
<td>3.1 (16)</td>
<td>3.1 (16)</td>
<td>2.4</td>
<td>4.0 (43, 45)</td>
</tr>
<tr>
<td>Rate of bleeding on anticoagulants</td>
<td>0.0005/yr</td>
<td>0.0005/yr</td>
<td>0.014/yr (67)</td>
<td>0.001/yr (46)</td>
</tr>
<tr>
<td>Probable outcome from bleeding event (on warfarin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.379</td>
<td>0.405</td>
<td>0.15</td>
<td>0.20 (68)</td>
</tr>
<tr>
<td>Severe long-term disability GOS = 3†</td>
<td>0.429</td>
<td>0.420</td>
<td>0.09 (68)</td>
<td></td>
</tr>
<tr>
<td>Mild long-term disability GOS = 4†</td>
<td>0.111</td>
<td>0.103</td>
<td>0.50 (68)</td>
<td></td>
</tr>
<tr>
<td>Good recovery GOS = 5†</td>
<td>0.080</td>
<td>0.073</td>
<td>0.20 (68)</td>
<td></td>
</tr>
</tbody>
</table>

**Quality of Life**

| Long-term morbidities (Q values) | | | | |
| Well | 1.0 |
| Well while receiving anticoagulants | 0.99 (37) |
| Severe long-term disability | 0.11 (37) |
| Mild long-term disability | 0.76 (37) |
| Dead | 0.0 |

| Short-term morbidities in patients with resolution | | | | |
| Extracranial bleeding event§ | 0.84 |
| Intracerebral hemorrhage|| 0.79 |
| Thromboembolic event|| 0.79 |

### Age-Adjusted Annual Excess Mortality

- Intracerebral hemorrhage with long-term disability | 0.08 (69) |
- Ischemic stroke with long-term disability | 0.08 (69) |

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*Assume outcomes of bleeding events for aspirin-treated patients are the same as for untreated patients (Rosand et al, unpublished data).
†GOS indicates Glasgow Outcome 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 (diagnosis-related group [DRG] 174) = 4.9 days.
||LOS for specific cerebrovascular disorders except transient ischemic attack (DRG 14) = 6.4 days.
for a 69-year-old man at average risk for ischemic stroke due to AF. If we assume that the genetic risk profile equally affects the relative hazard of ICH in patients receiving aspirin, then aspirin is never preferred (Figure 1A). This might be the case for genetic factors related to underlying cerebrovascular disease. However, some variants may be warfarin-specific (eg, warfarin sensitivity genes) in which case the relative hazard of ICH in patients receiving aspirin would remain unchanged (Figure 1B). In this circumstance, aspirin would be favored beyond a relative hazard of 13.1 for warfarin-related ICH. When we instantiated testing for genetic variants of APOE as a concrete example of genetic profiling, anticoagulate without prior testing was preferred. This finding is consistent with published data suggesting that possession of either APOE e2 or e4 is a relatively minor predictor of ICH (relative hazard, 2.3). Because the risk of warfarin-related ICH also depends on the risk of bleeding related to warfarin, we performed 2-way sensitivity analyses on both of these hazards simultaneously. Testing for the genetic variant would be preferred at higher combinations of relative hazard of ICH for both the genetic profile and treatment with warfarin (Figure 2).

We also examined how an increased risk of ICH associated with advancing age would impact the screening decision. In the base case, we used an annual ICH incidence of 0.03%. However, older patients (75 to 84 years of age) have an increased annual incidence of 0.11%, whereas those ≥85 years have an annual incidence approaching 0.2%. Older patients may also face an increased risk of thromboembolism (8.1%/year) if they have one or more risk factors beyond advanced age. In elderly patients without additional risk factors between the ages of 75 and 84 years of age, or ≥85 years of age, genetic profiling would be preferred if the relative hazard of ICH were >4.7 or 2.6, respectively. Elderly patients (75 to 84 years of age) with risk factors for thromboembolism would never benefit from screening, whereas those ≥85 years of age might benefit if the hazard conferred by the gene profile exceeded 7.2.
Imaging Screening
Assuming a 2-fold increased risk of ICH for patients with GE-MRI evidence of CM, patients at average risk for thromboembolism (4.5%/year) do not benefit from neuroimaging even if the relative hazard is as large as 12.8, as suggested by data from our cohort study. The risk of ICH would need to increase by 16-fold before screening would be beneficial. However, in a patient at lower risk for thromboembolism (eg, 1.5%/year), MRI-GE screening would be beneficial if the risk conferred by neuroimaging evidence of CM was more than 3.2-fold.

Combined Genetic and Imaging Screening
We next analyzed the impact of changes in the relative hazard of ICH in patients with the warfarin ICH genetic profile and in patients with GE-MRI evidence of CM across a range of risks of thromboembolism. As shown in Figure 3, at low relative hazards for both genetic and imaging risk markers (bottom left of figure), anticoagulation is preferred. When the risk of ICH is high in patients with either genetic or imaging risk markers, screening for both is preferred. Complex screening strategies involving both genetic testing and GE-MRI (treat with aspirin if either is positive or without anticoagulant therapy if either is positive) were almost as effective, trailing by less than 1/10th of a quality-adjusted life-year (QALY). The GE-MRI alone screening strategies were a close third (treat with aspirin or no therapy if CMs present), whereas genetic screening alone yielded the lowest expected utility. Treating all patients empirically with aspirin was less effective than all of this, and finally not treating with anticoagulant or antiplatelet therapy was the least effective strategy. Using APOE as a genetic example, testing before initiating anticoagulation was never favored across a clinically plausible range of values.

Discussion
Accumulating data suggest that the majority of bleeding-related morbidity and mortality in anticoagulated patients with AF is related to nontraumatic ICH. Determining risk of ICH in candidates for chronic anticoagulation is therefore the most pressing concern for clinical decision-making. Furthermore, over two thirds of warfarin-related ICH occur while patients are in the therapeutic range, suggesting that individual patient characteristics, rather than the effect of anticoagulation itself, are responsible for the majority of warfarin-related ICH. Because risk of cerebral small vessel disease appears to be substantially determined by genetic factors, it is reasonable to expect that these factors as well as neuroimaging may come to play a role in screening patients for anticoagulation.

Our analysis suggests that the usefulness of screening depends on several factors, including the strength of the indication as determined by the balance of thromboembolic and hemorrhagic risk for the individual patient, and the degree of increased hemorrhage risk conferred by the marker in question. For the “average” patient with nonvalvular AF, not otherwise at increased risk for major hemorrhage, screening for APOE does not yield superior outcomes. We note that the impact of ICH risk factors on the decision of whether to anticoagulate is somewhat attenuated by the fact that they affect risk of nonwarfarin as well as warfarin ICH. This situation contrasts with risk factors specific to warfarin-related complications only such as genetic variants of CYP2C9 and VKORC1.
Although screening for future genetic factors could yield superior outcomes in patients whose risk of warfarin-related ICH was sufficiently high and/or whose risk of thromboembolism was low, our analysis suggests that the risk associated with these factors would have to be substantial to alter the decision to anticoagulate. In a patient known to possess a hypothetical warfarin ICH gene variant, our model suggests that anticoagulation would be superior unless the relative hazard of ICH conferred by this gene exceeded 13.0, at which point aspirin would be favored (Figure 1B). However, if one assumes that the relative hazard conferred by asymptomatic microhemorrhages is larger, then for patients at lower risk of thromboembolism, screening with GE-MRI would make clinical sense. The most powerful potential strategy would incorporate screening for both genetic and imaging risk markers, which could conceivably apply to patients with AF at low to average risk for thromboembolic stroke, even with current imaging and genetic testing. The importance of CMs in the context of clinical decision-making is rapidly growing, because recent population-based studies have found these lesions to be surprisingly prevalent among the neurologically asymptomatic elderly.\textsuperscript{58}

With the field of complex disease genetics still in its infancy, it is difficult to predict whether genetic variants with effect sizes of sufficient magnitude are likely to exist. If emerging results from genomewide association studies are to be a guide, it is likely we will discover that susceptibility to cerebral small vessel disease (and warfarin-related ICH) is mediated by multiple variants, each with a small effect, which, in combination, contribute to a marked elevation in an individual’s risk for ICH.

Screening for CM with GE-MRI also failed to improve outcomes in our base case. Using a conservative estimate of only a 2-fold increase in risk conferred by asymptomatic CM, anticoagulant therapy still would be preferred for a patient at average risk for thromboembolic stroke, although by a small margin. Treating such patients with aspirin would be slightly inferior to anticoagulation. However, if one assumes that the relative hazard conferred by asymptomatic microhemorrhages is larger, then for patients at lower risk of thromboembolism, screening with GE-MRI would make clinical sense. The most powerful potential strategy would incorporate screening for both genetic and imaging risk markers, which could conceivably apply to patients with AF at low to average risk for thromboembolic stroke, even with current imaging and genetic testing. The importance of CMs in the context of clinical decision-making is rapidly growing, because recent population-based studies have found these lesions to be surprisingly prevalent among the neurologically asymptomatic elderly.\textsuperscript{58}

Like with all decision analyses, the accuracy of our model depends on the validity of both the data on which it is based and on the assumptions we have made. Although ultimately, randomized, controlled trials provide far more robust guidance to clinicians, decision analyses offer guidance where there is a lack of data from clinical trials. We have presented sensitivity analyses to explore the wide ranges of risk for ICH on warfarin that may be conferred by genetic and imaging risk factors. However, prospective studies of patients with these risk factors will ultimately be necessary to provide accurate estimates of risk. Estimators of annual risk of
thromboembolism in patients with atrial fibrillation such as the CHADS2 scoring system currently exist, but any given CHADS2 score depicts a range of stroke risks. We therefore elected to incorporate precise estimates of annual event risk in our modeling. Like in all medical decision-making, considerations of cost also play a role. If genetic variants are discovered that do indeed have sufficiently high impact on risk of warfarin ICH that they alter the decision to anticoagulate, then a future step would be to undertake an analysis of the cost-effectiveness of genetic screening.

The investigation of the genetic determinants of bleeding on warfarin remains an area of intense research. Indeed, randomized trials are already underway to determine whether genetic screening for warfarin sensitivity variants such as CYP2C9 and VKORC1 improves outcomes in patients receiving warfarin. Given our aging population, and the concomitant rise in the number of individuals with AF, the need for individualized selection of patients for chronic anticoagulation will increase. Given the prodigious rate of growth in our understanding of genetic variation across the population and the increasing recognition of subclinical manifestations of cerebrovascular disease, one can envision a not-too-distant future when individualizing anticoagulant therapy decisions for patients with nonvalvular AF will incorporate some combination of genetic and imaging screening.

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Disclosures

None.

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