Moving the Tipping Point
The Decision to Anticoagulate Patients With Atrial Fibrillation

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Background—The rate of ischemic stroke associated with traditional risk factors for patients with atrial fibrillation has declined over the past 2 decades. Furthermore, new and potentially safer anticoagulants are on the horizon. Thus, the balance between risk factors for stroke and benefit of anticoagulation may be shifting.

Methods and Results—The Markov state transition decision model was used to analyze the CHADS2 score, above which anticoagulation is preferred, first using the stroke rate predicted for the CHADS2 derivation cohort, and then using the stroke rate from the more contemporary AnTicoagulation and Risk Factors In Atrial Fibrillation cohort for any CHADS2 score. The base case was a 69-year-old man with atrial fibrillation. Interventions included oral anticoagulant therapy with warfarin or a hypothetical “new and safer” anticoagulant (based on dabigatran), no antithrombotic therapy, or aspirin. Warfarin is preferred above a stroke rate of 1.7% per year, whereas aspirin is preferred at lower rates of stroke. Anticoagulation with warfarin is preferred even for a score of 0 using the higher rates of the older CHADS2 derivation cohort. Using more contemporary and lower estimates of stroke risk raises the threshold for use of warfarin to a CHADS2 score ≥2. However, anticoagulation with a “new, safer” agent, modeled on the results of the Randomized Evaluation of Long-Term Anticoagulation Therapy trial of dabigatran, leads to a lowering of the threshold for anticoagulation to a stroke rate of 0.9% per year.

Conclusions—Use of a more contemporary estimate of stroke risk shifts the “tipping point,” such that anticoagulation is preferred at a higher CHADS2 score, reducing the number of patients for whom anticoagulation is recommended. The introduction of “new, safer” agents, however, would shift the tipping point in the opposite direction. (Circ Cardiovasc Qual Outcomes. 2011;4:14-21.)

Key Words: anticoagulants ■ atrial fibrillation ■ health services research ■ stroke prevention ■ decision analysis

The increased use of warfarin anticoagulation for prevention of thromboembolic stroke in patients with atrial fibrillation (AF) has produced substantial benefits, but has also resulted in an estimated quintupling of the incidence of warfarin-associated intracerebral hemorrhage (ICH).¹ Warfarin-associated ICH now comprises roughly 20% of all ICH. Furthermore, among patients with ICH, warfarin is associated with a doubling in the case fatality rate at 3 months and an increase in poor neurological outcomes.² There is suggestive evidence that the risk-adjusted incidence of ischemic stroke in patients with AF has declined over the past 2 decades, perhaps in response to more aggressive treatment of underlying risk factors, such as hypertension and hyperlipidemia.³⁻¹⁰ As a result, the balance between the risk and benefit of anticoagulation therapy in patients with nonvalvular AF may be shifting.

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The most recent guidelines from the American College of Chest Physicians on antithrombotic therapy focus on stroke risk (Appendix Table 1).⁹ Using the CHADS2 criteria¹¹ for stroke risk stratification, these guidelines recommend oral anticoagulant therapy for patients with a CHADS2 score ≥2 and consideration of either warfarin or aspirin for those with a CHADS2 score of 1. Bleeding risk is not explicitly considered, although these recommendations assume that the patient is not at high risk for bleeding, and that good control of anticoagulation will occur. Guidelines from the American College of Cardiology/American Heart Association/European Society of Cardiology are essentially the same.¹² Adding the consideration of bleeding risk, which may vary from patient to patient,¹³ the spectrum of decision-making for anticoagulant therapy in patients with AF can be schematized, as shown in Appendix Figure 1. Patients at lower risk of stroke and at high risk of bleeding should not receive oral anticoagulant therapy; patients at higher risk of stroke and at low risk of bleeding should receive anticoagulant therapy. The more difficult decisions lie in the middle where the risks of stroke

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and bleeding are more closely balanced. Here lies the so-called “tipping point.”

Our goal was to revisit the tipping point in light of more contemporary data suggesting a declining stroke risk for any of the typically defined risk factors, by constructing a decision analytic model examining strategies of oral anticoagulant therapy with warfarin, no antithrombotic therapy, and aspirin across a range of values for risk of ischemic stroke. We also wished to explore how the future availability in the United States of new, potentially safer anticoagulants, such as the direct thrombin inhibitor dabigatran, or the multiple direct factor Xa inhibitors in advanced development would impact the “tipping point” for anticoagulant therapy.

WHAT IS KNOWN
- The rate of stroke in patients with atrial fibrillation has declined over the past 2 decades.
- New and potentially safer anticoagulant medications are on the horizon.
- Thus, the balance between risk factors for stroke and benefit of anticoagulation may be shifting.

WHAT THE STUDY ADDS
- Tools in use to predict stroke risk may overestimate this risk, and thus result in recommendations for blood thinning therapy for some patients who may not require such treatment. The CHADS2 score is one such tool.
- Using more recent estimates of stroke risk shifts the “tipping point,” such that anticoagulation is preferred at a higher CHADS2 score (ie, higher stroke risk), reducing the number of patients for whom anticoagulation is recommended.
- The introduction of “new, safer” agents, however, would shift the tipping point in the opposite direction.

Methods

Review of Data

Risk of Ischemic Stroke
There are a number of risk stratification schemes that have been developed to predict ischemic stroke risk in AF patients.11,14–17 One of the more widely used is CHADS2,11 which assigns 1 point for each of the following risk factors for patients with AF: congestive heart failure, hypertension, age ≥75 years, and diabetes. Two points are assigned for a history of stroke or transient ischemic attack. A CHADS2 score of 2 (or 4% per year risk of stroke) roughly corresponds to the “average” patient not taking warfarin in the pooled analyses of AF trials.16 In a more contemporary study of 13,559 adults with nonvalvular AF receiving care within the Kaiser Permanente system of Northern California, rates of stroke among patients not taking warfarin were significantly lower.5 Although the derivation cohort for CHADS2 reported stroke rates ranging from 1.9% to 18.2% per year for scores between 0 and 6, stroke rates ranged between 0.36% and 6.10% per year in the Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) cohort for patients not receiving warfarin (Appendix Table 2).

Major Bleeding Events in Patients Receiving Anticoagulant Therapy
We stratified major bleeding events into intracranial hemorrhage, subdural hematoma, and extracranial bleeding. In a study of the ATRIA cohort, examining the net benefit of warfarin in AF, patients between 65 and 74 years of age had a 0.12% per year rate of intracranial hemorrhage off warfarin and a 0.44% per year rate on warfarin.3 Approximately 47% of these patients had intracerebral hemorrhages. Furthermore, roughly 50% of these patients were taking aspirin.19 After correcting for these factors, the annual rate of intracerebral hemorrhage in patients not receiving warfarin was 0.65%, and 0.21% in those receiving warfarin (relative hazard, 4.07). These were used for the base case values. Neurological outcomes (Table 1) were obtained from a study of 435 patients with warfarin intracerebral hemorrhage.2 A meta-analysis evaluating the effects of antiplatelet therapy in patients at high risk for vascular events, the Antithrombotic Trials’ Collaboration, reported an odds ratio of 1.22 (95% confidence interval [CI], 1.03 to 1.44) for fatal or nonfatal hemorrhagic stroke in patients receiving aspirin.19 This estimate is consistent with other summary analyses indicating that the incremental risk of hemorrhagic stroke in patients taking aspirin is small.40

In the ATRIA study noted above, 34% of patients with intracranial hemorrhages had subdural hematomas. Correcting for aspirin use, subdural hematomas occurred at an annual rate of 0.027% in patients not receiving warfarin and 0.0015% in those receiving warfarin.5 This is consistent with rates of subdural hematomas on warfarin described in other studies.16,21,22 The mortality associated with anticoagulant-related subdural hematoma is roughly 27%,23

In 16 trials examining the use of anticoagulant and antiplatelet agents for the prevention of stroke, 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 taking warfarin.5,14 In a large cohort study of 13,559 adults with AF, major extracranial hemorrhages were fatal in 5.1% of patients receiving warfarin.5 A meta-analysis of 4,052 patients with AF receiving either warfarin or aspirin reported a hazard ratio of 2.15 for lethal bleeding among patients receiving warfarin versus aspirin.26 In the absence of more specific data for mortality of extracranial bleeding among patients receiving aspirin, we calculated a mortality rate of 2.4%.

New, “Safer” Anticoagulants
We used data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial of the direct thrombin inhibitor dabigatran to describe base case values for both efficacy and bleeding risk for potentially safer and more efficacious novel anticoagulants. In sensitivity analyses, we explored how changes in either the efficacy or safety of such new agents would affect the “tipping point.” In RE-LY, the 150 mg dose of dabigatran was found to be more effective than warfarin in preventing ischemic stroke (relative risk, 0.76; 95% CI, 0.60 to 0.98).27 In addition, the relative risk of intracranial bleeding was 0.40 (95% CI, 0.27 to 0.60) compared with warfarin. The risk of extracranial bleeding was 1.07 (95% CI, 0.92 to 1.25). Of note, the absolute event rate for intracranial bleeding in patients receiving warfarin in this study was quite high, 0.74% per year, almost double the rate seen in other studies.5,18,28 Therefore, as a more conservative estimate for the relative risk of intracranial bleeding in patients receiving the new “safer” oral anticoagulant compared with warfarin, we hypothesized that the bleeding risk should be similar to that of an “ideal” agent, such as warfarin that was never out of the therapeutic range. In a study describing the odds of intracranial hemorrhage as a function of INR, 22% of bleeds occurred in patients with an INR ≥3.6, meaning that 78% of such bleeds occurred when patients were within the therapeutic range.29 Therefore, in our model we calculated the risk of intracranial hemorrhage associated with the new “safer” agent to be 0.78 times the intracranial hemorrhage risk of warfarin. In addition, a high proportion of patients (11.3%) had significant gastrointestinal side effects. We attempted to capture some of these issues by assigning a slightly lower quality of life to the hypothetical new, “safer” agent of 0.99.

Decision Analytic Model
We developed a 28-state Markov transition decision model to explore outcomes of the 4 strategies: (1) anticoagulate with warfarin;
(2) anticoagulate with a new, “safer” agent, using dabigatran as the model; (3) treat with aspirin; and (4) no antithrombotic therapy. We used a standard computer program (Decision Maker, Boston, Mass) to build the model, analyze results, and perform sensitivity analyses. Our base case involved a hypothetical 69-year-old man with nonvalvular AF who had no contraindications to warfarin therapy. During each monthly cycle, patients face a chance of stroke and hemorrhage, either of which may lead to death, significant neurological sequelae, or symptom resolution. The simulation is run for the entire life expectancy of the hypothetical cohort of similar patients. Base case values for model parameters are summarized in Table 1 and the decision tree Figure and modeling details provided in appendix Figure 2 and accompanying text.

Results

Results of the base case analysis for a 69-year-old man with nonvalvular AF with a CHADS<sub>2</sub> score of 2, corresponding to
an annual ischemic stroke risk of 2.5% in the ATRIA cohort are shown in Table 2. Antithrombotic therapy with warfarin provides a modest gain in quality-adjusted life expectancy compared with either no antithrombotic therapy or aspirin. However, anticoagulation with a new, “safer” agent results in the greatest gain in quality-adjusted life-years.

The question of the “tipping point” is addressed in the following 1-way sensitivity analyses examining outcomes for the strategies in quality-adjusted life-years as a function of the annual rate of ischemic stroke. Figure 1 examines the 3 historically available strategies in the United States: (1) anticoagulation with warfarin; (2) aspirin; and (3) no antithrombotic therapy. Superimposed as a second and third horizontal axis are the CHADS2 risk scores. The top axis shows the association between the CHADS2 scores and the annual stroke rate in the CHADS2 derivation cohort. The bottom-most axis shows annual stroke risk associated with CHADS2 scores in the more contemporary ATRIA cohort. The threshold lines form 3 regions. To the left, at lowest rates of stroke (<0.2% per year), no anticoagulant therapy is preferred. To the far right, at stroke rates greater than 1.7% per year, anticoagulation with warfarin is best. In the small region between 0.2% and 1.7% per year, aspirin is preferred. With reference to the scores in the CHADS2 derivation cohort, anticoagulation with warfarin is reasonable for patients with a score ≥0. Using a more contemporary estimate of stroke risk for any CHADS2 score (lower horizontal axis of Figure 1), our results suggest that patients with a score of zero or 1 should receive aspirin, whereas those with scores of 2 or greater should receive anticoagulation with warfarin. It should be noted that the magnitude of the differences in expected utility between the 3 strategies at low stroke rates (below 1.7% per year) is quite small. Therefore, patient-to-patient variability in either bleeding risk or preferences for outcomes could alter the optimal therapy in this region. The overall impact of the declining risk of ischemic stroke for any CHADS2 score was to shift the “tipping” point so that a higher CHADS2 score is needed to “justify” anticoagulant therapy.

We next examined how the use of a new, “safer” anticoagulant would affect the tipping point at which anticoagulant therapy is preferred over no anticoagulant therapy. As shown in Figure 2, the threshold for ischemic stroke risk above which anticoagulant therapy with a hypothetical new, “safer” agent is preferred over aspirin is lower (<0.9% per year). In fact, this threshold is near a CHADS2 score of 1, given the more contemporary assignment of stroke risk (ie, the bottommost axis).

Figure 3 depicts a 3-way sensitivity analysis examining the relative hazard of intracerebral hemorrhage (new, “safer”

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<td>Strategy</td>
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<td>Hypothetical “new and safer” oral anticoagulant, modeled on dabigatran</td>
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Base case was a 69-year-old man with AF (stroke risk, 2.3% per year), corresponding to CHADS2 of 2 in contemporary ATRIA cohort.
anticoagulant versus warfarin) on the horizontal axis, and the relative hazard of ischemic stroke (new, “safer” anticoagulant versus warfarin) on the vertical axis, for 3 different values of quality of life while taking the new anticoagulant (0.98, 0.99, and 1.0). The base case values are shown as an ellipse, demarked by the 95% CIs (from the RE-LY study) around the 2 relative hazards on the $x$ and $y$ axes. For a patient with a CHADS$_2$ score of 2, the base case ellipse falls within the region in which anticoagulation with the new, “safer” agent is preferred, even if the quality of life on this drug is 0.99 (eg, the same as the quality of life while taking warfarin). If the quality of life on this new agent is lower, for example, 0.98, the outer edge of the ellipse falls within the region in which warfarin is best. Should other hypothetical new oral anticoagulants be developed with greater efficacy and lower hemorrhage risk (toward the bottom left of the Figure), the gain in quality-adjusted life-years would become even greater.

**Discussion**

Our analysis suggests that the “tipping point,” the threshold of ischemic stroke risk below which anticoagulant therapy should be withheld and above which anticoagulant therapy...
should be prescribed, has changed. The risk of ischemic stroke in nonvalvular AF appears to have declined, perhaps as a result of more aggressive control of blood pressure and lipid levels.\(^3\)--\(^7\) Indeed, our analysis using a more contemporary cohort of patients with AF from the ATRIA study suggests that the threshold has shifted such that the balance of risk and benefit afforded by anticoagulation tips in favor of warfarin at a higher CHADS\(_2\) score than in the past. Specifically, anticoagulation with warfarin is preferred for patients with a CHADS\(_2\) score of 2 or more. Aspirin is preferred among patients with CHADS\(_2\) scores of zero or 1. No antithrombotic therapy is only preferable among those at close to no risk of ischemic stroke. However, the magnitude of gain between aspirin and either no antithrombotic therapy or warfarin at low CHADS\(_2\) scores is small. Therefore, patient-specific differences in bleeding risk or preferences for health outcomes, along with statistical uncertainty in parameter estimates, may affect the strength of this result. Furthermore, the magnitude of gain from warfarin increases as the annual rate of ischemic stroke increases above the threshold. Current American College of Chest Physicians and American College of Cardiology/American Heart Association/European Heart Society guidelines suggest either warfarin (grade 1A) or aspirin (grade 1B) for patients with a CHADS\(_2\) score of 1 and warfarin for patients with scores of 2 or more (grade 1A).\(^9\)

Although results of our decision analysis suggest that warfarin may have been preferred above a CHADS\(_2\) score of zero, based on older estimates of ischemic stroke risk, this is not congruent with older guidelines. Perhaps older guidelines were a bit too conservative about warfarin use, given data available at the time, but our analysis would suggest that current guidelines are now appropriate given the decreasing risk of ischemic stroke.

It also is important to note that whereas the CHADS\(_2\) score is categorical (a patient cannot have a score of 1.5, for instance), risk progresses in a continuous fashion. Therefore, it is difficult to interpret thresholds that fall between CHADS\(_2\) scores. Furthermore, the annual rate of stroke associated with each CHADS\(_2\) score has associated uncertainty (see Appendix Table 2).

A modification of CHADS\(_2\) has recently been proposed to incorporate additional stroke risk factors. This CHA\(_2\)DS\(_2\)-VASc scheme has been incorporated into the European Society of Cardiology guidelines, although there is no formal evidence that it is superior to CHADS\(_2\).\(^3\) Appendix Figure 3 demonstrates the addition of the CHA\(_2\)DS\(_2\)-VASc to the threshold analysis. Indeed, the limited precision of available risk prediction tools remains a major barrier to patient-specific decision-making for stroke prevention in nonvalvular AF. Although we have used the CHADS\(_2\) algorithm to highlight the secular change in ischemic stroke risk associated with patient-specific risk factors, the overall quality of prediction rules for ischemic stroke is mediocre.\(^8\) An assessment of 5 of the major stroke risk stratification schemes for patients with AF (CHADS\(_2\), Atrial Fibrillation Investigators, Stroke Prevention in AF, and Framingham indices, and the 7th American College of Chest Physicians guidelines) demonstrated receiver operating characteristic areas between 0.56 to 0.62, indicating poor discrimination.\(^3\)\(^1\) Similarly, assessment of the CHA\(_2\)DS\(_2\)-VASc in a verification cohort (Euro Heart Survey patients) yielded a c-statistic of 0.61, highlighting the need for better stroke prediction models.\(^3\)\(^0\) In particular, our analysis demonstrates the importance of being able to identify patients at very low risk of ischemic stroke who in fact might be best served by no antithrombotic therapy. Furthermore, there are no formal models estimating risk of ICH, although a variety of determinants of such risk has been identified.\(^1\)\(^8\)--\(^4\)\(^2\) To make better, patient-tailored decisions and recommendations regarding anticoagulant therapy for AF patients, new and more robust prediction tools will need to be developed for both ischemic stroke and ICH risk. A goal of these improved risk prediction tools would be to accurately move predicted risks away from threshold values, allowing more confident decisions.

The introduction of novel anticoagulants, such as dabigatran, which appear to be more efficacious while leading to lower risks of intracranial hemorrhage, expands the number of individuals for whom anticoagulation can be recommended compared with warfarin. Indeed, use of a more effective and safer anticoagulant also shifts the tipping point, such that anticoagulation with such an agent may be preferred over either warfarin or aspirin for patients with a CHADS\(_2\) score of 1. We have used data from RE-LY describing the efficacy, safety, and side-effect profile of dabigatran to characterize a prototypical new and safer anticoagulant. However, the very positive findings from the RE-LY trial may deteriorate in real world use.

Our decision analytic framework also can be used to model other new or novel therapies. For instance, for patients in whom vitamin K antagonists may not be suitable (poor anticipated compliance with INR measurement or dosage adjustment), the addition of clopidogrel to aspirin was examined in the ACTIVE-A trial.\(^4\)\(^3\) They found the combination of the 2 drugs had a relative hazard of 0.72 (95% CI, 0.62 to 0.83) for stroke and 1.57 (95% CI, 1.29 to 1.92) for major hemorrhage compared with aspirin alone. Examining these 2 strategies in our model, the combination antiplatelet regimen would be preferred for patients with a stroke risk greater than 0.4% per year, and the magnitude of the gain would increase as the patient-specific stroke risk increased. However, if a new and “safier” oral anticoagulant were also available, how might it compare with the combination antiplatelet regimen? Using the same base case assumptions from our previous analysis, we found that the new, “safier” oral anticoagulant would be preferred above a stroke risk of 1.3% per year, aspirin would be preferred for stroke risk below 0.4% per year, whereas combination antiplatelet therapy would be preferred for stroke risks in between these 2 thresholds. Nonpharmacological interventions for appropriate patients, such as catheter ablation or the Maze procedure, also could be examined using this analytic framework.

In summary, secular trends in the risk of ischemic stroke as reflected in ATRIA appear to have shifted the “tipping point” in favor of withholding anticoagulant therapy from patients who might have received it in the past based on their CHADS\(_2\) scores. However, as new, safer anticoagulants become available, the “tipping point” will shift again in the opposite direction. With the proliferation of new anticoagulant...
lants and antithrombotic therapies, along with nonpharmacological interventions for AF, and the improbability of clinical trials performing head-to-head comparisons of these treatments, a decision analytic framework can be used to examine new treatments as data become available. Finally, it is clear that the biggest barrier to personalized decision-making for patients with AF remains the limited discriminating ability of available tools for predicting risk of thromboembolic stroke and hemorrhage.

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