Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder. Roughly 15% of all strokes in the United States are attributable to AF. With the aging of the US population, the prevalence of AF will increase substantially to >3 million by the year 2020.1 Numerous randomized trials have established that anticoagulation is effective and can reduce significantly the stroke risk posed by AF. However, studies also have documented widespread underutilization of oral anticoagulants in patients at low risk of stroke and at increased risk of bleeding.2-5 Our own data on the use of anticoagulation therapy in patients with atrial fibrillation are based on stroke risk as calculated by either the CHADS2 or the CHA2DS2VASc scores and do not integrate bleeding risk in an explicit, quantitative manner. Our objective was to quantify the net clinical benefit resulting from improved decision making about antithrombotic therapy.

Methods and Results—This study is a retrospective cohort study of 1876 adults with nonvalvular atrial fibrillation or flutter seen in primary care settings of an integrated healthcare delivery system between December 2012 and January 2014. Projections for quality-adjusted life expectancy reported as quality-adjusted life-years were calculated by a decision analytic model that integrates patient-specific risk factors for stroke and hemorrhage and examines strategies of no antithrombotic therapy, aspirin, or oral anticoagulation with warfarin. Net clinical benefit was defined by the gain or loss in quality-adjusted life expectancy between current treatment and treatment recommended by an Atrial Fibrillation Decision Support Tool. Current treatment was discordant from treatment recommended by the Atrial Fibrillation Decision Support Tool in 931 patients. A clinically significant gain in quality-adjusted life expectancy (defined as ≥0.1 quality-adjusted life-years) was projected in 832 patients. Subgroups were examined. For example, oral anticoagulant therapy was recommended for 188 who currently were receiving no antithrombotic therapy. For the entire cohort, a total of 736 quality-adjusted life-years could be gained were treatment changed to that recommended by the Atrial Fibrillation Decision Support Tool.

Conclusions—Use of a decision support tool that integrates patient-specific stroke and bleeding risk could result in significant gains in quality-adjusted life expectancy for a primary care population of patients with atrial fibrillation.


Key Words: atrial fibrillation ■ decision support techniques ■ medical informatics
WHAT IS KNOWN

- Roughly 15% of all strokes in the United States are attributable to atrial fibrillation.
- There is widespread underutilization of anticoagulant therapy in patients at higher risk of stroke and simultaneous inappropriate use of oral anticoagulants in patients at low risk of stroke and at increased risk of bleeding.
- Practice guidelines generate recommendations based only on stroke risk and do not integrate bleeding risk in a formal, quantitative manner.

WHAT THE STUDY ADDS

- The Atrial Fibrillation Decision Support tool used in this study integrates both stroke risk and bleeding risk along with the longer term sequelae of these events in a formal, quantitative manner by using a decision model as the analytic engine.
- At a population level, for a cohort of >1800 patients in our primary care network, >700 quality-adjusted life years could be gained by improving antithrombotic therapy.

Methods

Study Population

We used our health system’s clinical data store to identify 9270 patients with an International Classification of Diseases, Ninth Revision, Clinical Modification, diagnosis of AF (427.31) or atrial flutter (427.32) who did not have diagnoses of mitral valve disease (394.x), aortic valve disease (395.x), heart valve transplant (V42.2), or heart valve replacement (V42.3). Of these, 4021 had a visit within the 12-month period from January 1, 2013 to December 30, 2013, and 1876 were seen in the primary care network. The number of patients with AF in any single practice ranged between 4 and 366. The institutional review board at the University of Cincinnati approved this study.

Patient Characteristics

Information needed to calculate stroke risk (CHA2DS2VASC), major hemorrhage (HAS-BLED), and intracerebral hemorrhage (ICH) and to analyze the patient-specific decision model was extracted from the clinical data store using the active problem list and a combination of laboratory values and clinical measurements. Time in therapeutic range, needed to calculate the HAS-BLED score, was determined by interpolating International Normalized Ratio values through time during the past 1 year, similar to the method by Rosendaal et al. Current antithrombotic therapy was retrieved from the active medication list. Data were stored on a secure server at our Center for Health Informatics as Microsoft Excel spreadsheets or in Oracle or Microsoft SQL as appropriate. SAS data files were created as necessary for statistical analyses using unique coded patient identifiers.

Atrial Fibrillation Decision Support Tool

We used structured query language to generate a batch file containing values for clinical and demographic parameters needed to analyze the patient-specific decision model. We used a standard computer program (Decision Maker, Boston, MA) to build the decision analytic model and analyze results. Data required in the analysis (e.g., probabilities, rates, and quality of life) are detailed in Table I in the Data Supplement. Once the annual stroke and major hemorrhage rates were calculated, we used Decision Maker’s remote control function to run a script file containing the required information for each patient through a decision analytic model that estimates the quality-adjusted life expectancy (QALE) with each of 3 strategies: (1) no antithrombotic therapy, (2) aspirin, and (3) oral anticoagulant therapy (warfarin in the base case) for each individual patient. Results for the batch file run were stored to a text file which was then loaded into a structured query language database. The strategy recommended by the decision support tool is the one resulting in the largest expected utility in quality-adjusted life-years (QALYs). QALYs have been used as a metric for decision making in a variety of clinical contexts including individual patient-level decision making, particularly when a model considers outcomes with different implications and impacts quality of life. A strategy is not considered to be better if it results in a gain of <0.1 QALYs. The choice of a 0.1 gain in QALYs as our threshold for a minimum clinically significant difference was empirical. There is no clear definition of how large a gain constitutes a clinically significant gain. When the gain is too small to matter clinically, the decision is considered a toss-up. Theoretically, if all factors have been considered in a decision analysis, any gain in QALYs would be sufficient to identify the optimal strategy. However, a model never captures all elements of a decision problem and parameter values have associated uncertainty. Thus, the Atrial Fibrillation Decision Support Tool (AFDST) will not recommend one treatment over another unless the gain exceeds a threshold of 0.1 QALYs. Using a decision analytic model allows us to incorporate patient values (utilities) into the decision-making process. Life spent in less-than-perfect states of health, such as a nonfatal stroke, can be valued through multiattribute metrics, such as QALE, to facilitate explicit trade-offs between the risks and benefits of therapies. Population-based average utilities were used for the health states considered in the model for this analysis. Details of the 29-state Markov decision analytic models are described in the Data Supplement (see Figures I and II in the Data Supplement).

Results

Risk Factors for Stroke and Bleeding

Figure 1 shows distributions of CHADS2, CHA2DS2VASC, and HAS-BLED scores, along with annual predicted rate of ICH. Sixty-three percent of the cohort had a CHADS2 score ≥2, 85% had a CHA2DS2VASC score ≥2, and 67% had an HAS-BLED score ≥2. We tested the calibration of our decision model by simulating an observational study of future events in our cohort (first-order Monte Carlo), comparing event rates for ischemic stroke and ICH across strata of stroke risk using CHADS2 scores to those reported in a contemporary AF cohort, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, during a similar period of time. Stroke and ICH risk at all CHADS2 scores were not significantly different, indicating good calibration (see Data Supplement).
Projections of QALE

QALE was calculated for each of the 1876 patients with AF in the primary care network. An example of one such calculation is shown in Figure 2. Across the cohort of 1876 patients with AF, the AFDST recommended no antithrombotic therapy for 158 (8%) patients, aspirin for 89 (5%) patients, and oral anticoagulant therapy for 1629 (87%) patients. Table 1 describes results in patients for whom AFDST-recommended treatment and current treatment were discordant. There were 931 (50%) such patients, 832 (44%) of whom were projected to gain >0.1 QALYs were treatment discordant with decision model recommendations. For instance, oral anticoagulant therapy was recommended for 188 who currently were receiving no antithrombotic therapy. Of these 188 patients, 179 would be expected to achieve a clinically significant gain of >0.1 QALYs. Were their treatment to be changed to oral anticoagulant therapy, the projected aggregate gain in expected utility for this group of patients would be 209.4 QALYs, while the average gain per patient in this group would be 1.17 QALYs. To put this in context, the average projected QALE for the entire cohort was 12.82 QALYs for no treatment, 13.16 QALYs for aspirin, and 13.74 QALYs for oral anticoagulant therapy. Of particular interest, our analysis suggested that we have the potential to gain roughly 736 QALYs among the 931 patients with AF in our system’s primary care network whose current treatment is discordant with the recommendations of the AFDST if we improve our practice patterns for prescribing antithrombotic therapy.

We also determined the potential gain in QALE across our AF cohort were patients to be treated in accordance with the recently released 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines. This is the first US guideline to use the CHA2DS2VASc scoring algorithm. As shown in Table 2, of 1605 patients with a CHA2DS2VASc score ≥2, 887 (55%) were receiving guideline-concordant treatment with oral anticoagulant therapy. Five hundred fifty-three patients who were receiving aspirin could gain an average of 0.78 QALYs each, for an aggregate gain of 433 QALYs for the group, were they to receive oral anticoagulant therapy. One hundred sixty-five patients who were receiving no antithrombotic therapy could gain an average of 1.04 QALYs each, for an aggregate gain of 171 QALYs, were they to receive guideline-concordant treatment. The guideline recommends that any treatment is reasonable for patients with a CHA2DS2VASc score of 1; therefore, no patients in this group had treatment that was discordant from the guideline. Finally, a total of 78 patients had a CHA2DS2VASc score of 0. A total of 23 QALYs could be gained were patients in this group who were receiving either oral anticoagulant therapy or aspirin not to receive antithrombotic therapy in concordance with the guideline. In Table 3, we compare the CHA2DS2VASc-based treatment recommendations of the AHA/ACC/HRS guideline with the AFDST. Although there is a high level of agreement between the guideline and the decision support tool, there are some patients with a CHA2DS2VASc score ≥2 for whom either aspirin (41) or no antithrombotic therapy (65) is recommended. This discrepancy is attributable to the incorporation of bleeding risk into the projections made by the AFDST. Although the AHA/ACC/HRS guideline makes no specific recommendation for patients with a CHA2DS2VASc score of 1, the AFDST specifies oral anticoagulant therapy, aspirin, or no antithrombotic therapy for 54, 80, and 55 patients, respectively.

Discussion

Our analysis comparing current antithrombotic therapy with that recommended by an AFDST suggests that significant improvement in clinical outcomes can be achieved by improving treatment decisions. At a population level, for a cohort of >1800 patients in our primary care network, >700 QALYs
could be gained by improving antithrombotic therapy. This finding should not be surprising. At a national level, we still find significant underutilization of anticoagulant therapy for patients with AF. A recently published systematic review comparing current treatment practices with guidelines showed underuse of oral anticoagulants in high-risk patients in the

### Table 1. Projected Gains in Quality-Adjusted Life Expectancy Among Patient Groups for Whom AFDST-Recommended Treatment Is Discordant With Current Treatment

<table>
<thead>
<tr>
<th>Recommended Treatment</th>
<th>Current Treatment</th>
<th>No. of Patients (n)</th>
<th>No. of Patients With a Gain &gt;0.1* QALYs (n)</th>
<th>Average Gain per Patient (QALYs)</th>
<th>Total Gain for Group With &gt;0.1 Gain (QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulant therapy</td>
<td>None</td>
<td>188</td>
<td>179</td>
<td>1.17</td>
<td>209.38</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>575</td>
<td>547</td>
<td>0.83</td>
<td>455.21</td>
</tr>
<tr>
<td>Aspirin</td>
<td>None</td>
<td>19</td>
<td>17</td>
<td>0.60</td>
<td>10.22</td>
</tr>
<tr>
<td></td>
<td>Oral anticoagulant therapy†</td>
<td>41</td>
<td>31</td>
<td>0.60</td>
<td>18.73</td>
</tr>
<tr>
<td>None</td>
<td>Aspirin</td>
<td>59</td>
<td>30</td>
<td>0.21</td>
<td>6.15</td>
</tr>
<tr>
<td></td>
<td>Oral anticoagulant therapy†</td>
<td>49</td>
<td>28</td>
<td>1.31</td>
<td>36.55</td>
</tr>
<tr>
<td>Total for primary care network population</td>
<td>931</td>
<td>832</td>
<td></td>
<td></td>
<td>736.24</td>
</tr>
</tbody>
</table>

AFDST indicates Atrial Fibrillation Decision Support Tool; and QALYs, quality-adjusted life-years.

*Current treatment not considered discordant from recommended treatment for a given patient unless projected gain is >0.1 QALYs.
†Current treatment with oral anticoagulant therapy includes warfarin, dabigatran, rivaroxaban, and apixaban.
Table 2. Projected Gains in Quality-Adjusted Life Expectancy Among Patient Groups for Whom Current Treatment Is Discordant With AHA/ACC/HRS 2014 Guideline-Recommended Treatment

<table>
<thead>
<tr>
<th>Treatment Recommended by AHA/ACC/HRS Guideline</th>
<th>Current Treatment</th>
<th>No. of Patients (n)</th>
<th>Average Gain per Patient (QALYs)</th>
<th>Total Gain for Group (QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAT*</td>
<td>OAT</td>
<td>887</td>
<td>0.78</td>
<td>433.42</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>553</td>
<td>1.04</td>
<td>171.22</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antithrombotic Tx, aspirin, or OAT†</td>
<td>OAT</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None‡</td>
<td>OAT</td>
<td>12</td>
<td>1.51</td>
<td>18.07</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>30</td>
<td>0.17</td>
<td>5.22</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total for primary care network population</td>
<td></td>
<td></td>
<td></td>
<td>627.93</td>
</tr>
</tbody>
</table>

AHA/ACC/HRS indicates American Heart Association/American College of Cardiology/Heart Rhythm Society; OAT, oral anticoagulant therapy; Tx, therapy; and QALYs, quality-adjusted life-years.

*CHA2DS2VASC score ≥2.
†CHA2DS2VASC score =1.
‡CHA2DS2VASC score =0.

The majority of 54 published articles. More concerning, among patients in 29 studies with a history of prior stroke or transient ischemic attack, treatment with anticoagulant therapy averaged <60%. Among high-risk patients with a CHADS2 score ≥2, treatment levels averaged <70%. Finally, risk factors profiles for stroke or bleeding are dynamic, changing over time. A decision about anticoagulant therapy made several years ago may not remain the best option today. Therefore, it is reasonable to revisit the anticoagulant decision, particularly when new and significant diagnoses are made.

Current guidelines for anticoagulant therapy are based on stroke risk as calculated by either the CHADS2 (American College of Chest Physicians)22 or the CHA2DS2VASC scores (European Society of Cardiology and more recently American Heart Association/American College of Cardiology).Although mentioning that bleeding risk is a consideration, these guidelines do not integrate bleeding risk in a formal, quantitative manner. If one makes decisions based on overall event rates for bleeding and stroke, choosing to treat with anticoagulants only if the stroke risk in untreated patients exceeds the risk of major hemorrhage in treated patients, there is an implicit assumption that outcomes following both stroke and bleeding events are equivalent. However, most bleeds are extracranial and have less significant long-term consequences than strokes. Furthermore, ICH while receiving anticoagulant therapy generally results in worse clinical outcomes than ischemic stroke.24 Singer et al29 dealt with this later issue by differentially weighting ischemic stroke and ICH in their calculations of net clinical benefit of warfarin anticoagulation, using an impact weight of 1.5 for the latter. Using a similar weighting scheme for ICH, Friberg et al25 studied a large Swedish AF cohort of 182,678 patients. They found that in almost all patients, the risk of ischemic stroke without anticoagulant therapy was higher than the risk of ICH and concluded in their analysis of net clinical benefit that more patients may benefit from anticoagulant treatment and should be offered this treatment.26 The AFDST used in this study is able to integrate both stroke risk and bleeding risk along with their longer term sequelae in a formal, quantitative manner by using a decision model as the analytic engine. The projections of QALE generated by the AFDST for each individual patient and therapeutic alternative capture both the differential clinical outcomes following these events and their impact on patients’ quality of life. For quality assurance or performance improvement purposes, estimates of potential aggregate gains in QALE over a population of patients in a healthcare system may provide a more informative picture than the proportion of high-risk patients (eg, with a CHA2DS2VASC score ≥2) not receiving anticoagulant therapy.

The AFDST has several limitations. Most significantly, the tool assumes that the information extracted from the electronic health record is accurate and complete. One obvious concern is the under-reporting of over-the-counter medications such as aspirin or nonsteroidal anti-inflammatory drugs. Therefore, when we communicate AFDST recommendations to clinicians as part of our system’s performance improvement project, we have them first verify the accuracy of the clinical data on which recommendations are based. Furthermore, there may be extenuating circumstances not captured by the AFDST and our focused data extraction that affect the decision to use antithrombotic therapy. Current risk prediction models for major hemorrhage, such as HEMORR2HAGES and HAS-BLED, do not incorporate psychosocial and sociodemographic information that may bear on the risk of bleeding with anticoagulant therapy.26-27 Therefore, the recommendations of the AFDST cannot be interpreted as a mandate that replaces clinical judgment. Rather, they must be interpreted holistically within the broader clinical context of the whole patient. We must make sure to appropriately communicate these limitations to clinicians using such decision support tools.

During the past 2 years, several novel anticoagulants have come on the scene. Three, dabigatran, rivaroxaban, and apixaban,
have received Food and Drug Administration approval for use in patients with AF. At this time, knowledge about the use of these agents outside of selected populations within randomized trials is limited. Decisions among the various oral anticoagulants are nuanced and complex, and the benefits and circumstances in which one agent may be better than another for an individual patient remain unclear. Furthermore, the most recent guidelines from the both the ACCP and the AHA/ACC/HRS focus on the decision to use anticoagulant therapy rather than specifying a particular anticoagulant. Therefore, the AF DST does not address choices among competing anticoagulants. In this manner, we have biased the recommendations for anticoagulation to be conservative; thus, if a recommendation is made for warfarin, as in the ACCP or AHA/ACC/HRS guideline, the use of any of the novel agents would also be reasonable.

Finally, the AF DST uses population-based average utilities for health states and clinical outcomes such as stroke and major hemorrhage. Ideally, in the future, individuals will be able to assign their own values to different treatments and potential disease states or outcomes.

Given the increasing availability of real-time clinical information from electronic health records and clinical data warehouses, tools such as the AF DST can be used by healthcare systems for both retrospective reviews of the quality of care around anticoagulant therapy for patients with AF and prospectively to improve performance about decision making for these patients. Our next steps are to provide practices and clinicians in our system, patient and practice-level reports (see sample report, Figure 2) when current antithrombotic therapy and that recommended by the AF DST are significantly discordant. Performance improvement processes will be developed, using concepts of the patient-centered medical home to support revisiting the anticoagulation decision for these patients.

Acknowledgments
We thank Daniel P. Schauer, MD, MSc, Division of General Internal Medicine, University of Cincinnati for his helpful insights and suggestions regarding methodological approaches to decision model calibration.

Sources of Funding
Support for this study came from the Pfizer Educational Group, the Informed Medical Decisions Foundation, and National Institutes of Health/National Center for Advancing Translational Sciences grant 8UL1 TR000077-05. The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosures
Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, and Sanofi Aventis. Dr Flaherty has served as a consultant to Boehringer Ingelheim and has served on an advisory board for, as a consultant to, and on a speaker’s program for CSL Behring. The other authors report no conflicts.

References


Integrating Real-Time Clinical Information to Provide Estimates of Net Clinical Benefit of Antithrombotic Therapy for Patients With Atrial Fibrillation


_Circ Cardiovasc Qual Outcomes_. 2014;7:680-686; originally published online September 9, 2014;
doi: 10.1161/CIRCOUOUTCOMES.114.001163

_Circulation: Cardiovascular Quality and Outcomes_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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