Warfarin Discontinuation After Starting Warfarin for Atrial Fibrillation

Margaret C. Fang, MD, MPH; Alan S. Go, MD; Yuchiao Chang, PhD; Leila H. Borowsky, MPH; Niela K. Pomernacki, RD; Natalia Udaltsova, PhD; Daniel E. Singer, MD

Background—Although warfarin is widely recommended to prevent atrial fibrillation-related thromboembolism, many eligible patients do not take warfarin. The objective of this study was to describe factors associated with warfarin discontinuation in patients newly starting warfarin for atrial fibrillation.

Methods and Results—We identified 4188 subjects newly starting warfarin in the Anticoagulation and Risk Factors in Atrial Fibrillation Study and tracked longitudinal warfarin use through pharmacy and laboratory databases. Data on patient characteristics, international normalized ratio (INR) tests, and incident hospitalizations for hemorrhage were obtained from clinical and laboratory databases. Multivariable Cox regression analysis was used to identify independent predictors of prolonged warfarin discontinuation, defined as ≥180 consecutive days off warfarin. Within 1 year after warfarin initiation, 26.3% of subjects discontinued therapy despite few hospitalizations for hemorrhage (2.3% of patients). The risk of discontinuation was higher in patients aged <65 years (adjusted hazard ratio [HR], 1.33 [95% CI, 1.03 to 1.72] compared to those aged ≥85 years), patients with poorer anticoagulation control (HR, 1.46 [95% CI, 1.42 to 1.49] for every 10% decrease in time in therapeutic INR range), and patients with lower stroke risk (HR, 2.54 [95% CI, 1.86 to 3.47] for CHADS2 stroke risk index of 0 compared to 4 to 6).

Conclusions—More than 1 in 4 patients newly starting warfarin for atrial fibrillation discontinued therapy in the first year despite a low overall hemorrhage rate. Individuals deriving potentially less benefit from warfarin, including those with younger age, fewer stroke risk factors, and poorer INR control, were less likely to remain on warfarin. Maximizing the benefits of anticoagulation for atrial fibrillation depends on determining which patients are most appropriately initiated and maintained on therapy. (Circ Cardiovasc Qual Outcomes. 2010;3:624-631.)

Key Words: anticoagulants ■ atrial fibrillation ■ stroke ■ prevention ■ warfarin

Atrial fibrillation is an increasingly common condition among older adults and one that substantially increases the risk of ischemic stroke.1,2 Oral vitamin K antagonists, such as warfarin sodium, significantly reduce the risk of atrial fibrillation-associated thromboembolism and, consequently, are widely recommended for patients with atrial fibrillation who have additional risk factors for stroke.3 Despite the high efficacy of warfarin, however, multiple cross-sectional studies have shown that a substantial proportion of patients with atrial fibrillation do not take warfarin.4–6 It is unclear from such studies whether rates of warfarin nonuse were because of a lack of warfarin initiation at the time of atrial fibrillation diagnosis or patients starting warfarin and subsequently discontinuing therapy. To better delineate the pattern of warfarin discontinuation, we followed individuals in the large Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study who were newly started on warfarin for atrial fibrillation and described rates of warfarin discontinuation and clinical risk factors associated with discontinuation.

Methods

Cohort Assembly

The ATRIA Study followed 13,559 adults with nonvalvular atrial fibrillation who received care within Kaiser Permanente of Northern California, a large integrated healthcare delivery system.7 Patients receiving a diagnosis of atrial fibrillation between July 1, 1996, and December 31, 1997, were identified by searching automated inpatient, outpatient, and electrocardiographic databases for physician-assigned International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) code 427.31. The cohort was followed until September 30, 2003 (median, 6.0 years, interquartile range [IQR], 3.1 to 6.7 years). Patients with mitral stenosis, documented valvular repair or replacement, transient postoperative atrial fibrillation, or concurrent hyperthyroidism were excluded so as to focus on nontransient, nonvalvular atrial fibrillation. In a random sample of 115 cohort members with at least 3 available ECGs, 21% of patients had evidence of paroxysmal atrial fibrillation in that 2 ECGs showing atrial fibrillation were separated by at least 1 that did not demonstrate atrial fibrillation. We searched clinical inpatient and ambulatory (outpatient clinics and emergency department) databases during the 5 years before each subject’s index date to identify
previously diagnosed ischemic stroke, heart failure, coronary heart disease, and hypertension using relevant ICD-9 codes. A validated, comprehensive health plan diabetes registry was used to identify patients with diabetes mellitus. Risk factors for each patient also were used to calculate a CHADS score, stroke risk score, a risk index that assigns 1 point for a history of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points to a history of ischemic stroke or transient ischemic attack. Ascertainment of individual stroke risk factors was validated against a review of samples of outpatient medical records; the crude agreement between ICD-9 codes and medical record review for individual risk factors was high (78% to 96%), and the corresponding κ statistics ranged from 0.51 to 0.89. We did not assess for aspirin exposure because aspirin is available without prescription and, thus, not systematically captured in our database.

WHAT IS KNOWN
- Warfarin is widely recommended for the prevention of atrial fibrillation-related stroke.
- Cross-sectional studies show that many patients with atrial fibrillation are not on warfarin, but few describe which patients stop taking warfarin.

WHAT THIS STUDY ADDS
- More than 1 in 4 patients newly starting warfarin in this large, community-based cohort discontinued therapy within 1 year.
- Patients with fewer stroke risk factors and poorer warfarin control were more likely to discontinue therapy, suggesting that a portion of those who discontinue warfarin might be doing so because of limited benefits or excess risks.
- Stroke prevention efforts should address the appropriate persistence of warfarin therapy in patients with atrial fibrillation.

Identification of New Starts on Warfarin
We identified new starts on warfarin with at least 4 weeks of follow-up after warfarin initiation. New starts were defined as patients with a new prescription for warfarin during the study period who had been continuously enrolled in the health plan for at least 12 months and who had not prior identified warfarin prescription and fewer than 2 outpatient measurements of the international normalized ratio (INR) in the previous 12 months. Longitudinal warfarin exposure was assessed using a validated algorithm that was based on the number of days supplied per prescription as well as intervening INR measurements. Continuous warfarin exposure was assumed for periods where the second of any 2 consecutive filled prescriptions began within 60 days of the last day supplied by the previous prescription. For periods between consecutive warfarin prescriptions that were longer than 60 days, continuous warfarin therapy was assumed if there were intervening INR measurements at least every 42 days. If INR measurements were less frequently obtained, the subject was considered to be not taking warfarin from day 31 after the end date of the first prescription until the start date of the next prescription. This grace period of 30 days at the end of each warfarin prescription ended. For periods between consecutive warfarin prescriptions, such as is recommended for certain procedures.

Results
Magnitude and Pattern of Warfarin Discontinuation
We identified 4188 patients with atrial fibrillation in the ATRIA Study who were newly started on warfarin therapy and who had at least 4 weeks of follow-up in the cohort after initiation of warfarin. The median time of follow-up of these individuals was 4.6 years (IQR, 2.4 to 6.2), the mean age was 71.8 years, and 43% were aged ≥75 years. Most (70%) patients had at least 1 risk factor for atrial fibrillation-related ischemic stroke (heart failure, hypertension, diabetes mellitus, or prior stroke) in addition to age ≥75 years. Few had diagnosed risk factors for hemorrhage, such as mechanical fall diagnosed during a hospitalization or prior gastrointestinal hemorrhage (Table 1).
Kaplan–Meier estimates indicated that 26.3% (95% CI, 25.0% to 27.7%) of patients discontinued warfarin within the first year of therapy (Figure 1). However, patients who remained on warfarin throughout the first year of therapy were more likely to remain on therapy in subsequent years. By the end of the second year of follow-up, only an additional 8.0% of patients discontinued warfarin, whereas an additional 3.6% discontinued warfarin by the end of the third year.

Among the 1538 subjects who discontinued warfarin for at least 180 days, 25.2% (95% CI, 23.0% to 27.6%) had evidence of restarting warfarin (at least 1 filled warfarin prescription) during the 2 years after initial discontinuation. Because of this dynamic process of stopping and restarting warfarin, the overall proportion of cohort members taking warfarin at any given time remained relatively stable after the first year of therapy (at the end of year 1, 73.5%; at the end of year 2, 68.7%; at the end of year 5 of follow-up, 66.9%) (Figure 2).

**Univariate Predictors of Warfarin Discontinuation**

When stratified by age, the youngest patients (aged <65 years) were more likely than the older age groups to discontinue warfarin (Figure 3A), with 33.9% (95% CI, 30.9% to 37.1%) discontinuing warfarin within the first year of therapy. However, the older age subgroups did not differ significantly in terms of the proportion who discontinued therapy within the first year (patients aged ≥85 years, 23.8%; 95% CI, 19.4% to 29.1%; patients aged 75 to 84 years, 22.7%; 95% CI, 20.5% to 25.0%; patients aged 65 to 74 years, 25.4%; 95% CI, 23.2% to 27.8; P=0.49).

Other univariate predictors of warfarin discontinuation in the first year included male sex and no risk factors for ischemic stroke, such as prior stroke, diagnosed heart failure, hypertension, and diabetes mellitus (Table 2). As CHADS2 scores increased, indicating higher stroke risk, the likelihood of discontinuing warfarin decreased monotonically, where only 13.8% of patients with a CHADS2 score of 4 to 6 discontinued warfarin at 1 year (Figure 3B). Poorer INR control was associated with warfarin discontinuation as well; the median TTR in the overall cohort was 61% (IQR, 45% to 73%), and the likelihood of subsequent warfarin discontinuation increased by a hazard ratio of 1.44 (1.41 to 1.48) for every 10% absolute decrease in TTR.

We identified 263 patients with incident hospitalizations for hemorrhage after warfarin initiation in the study period. Hospitalization for hemorrhage was relatively uncommon overall, with only 2.3% (95% CI, 1.8% to 2.8%) of cohort members experiencing an event in the first year after warfarin initiation. However, hospitalizations for hemorrhages led to subsequent warfarin discontinuation in 65% (95% CI, 59% to 70%) of the patients.

**Multivariable Predictors of Warfarin Discontinuation**

Because the majority of patients experiencing a hemorrhage event discontinued warfarin and because we were interested in assessing other factors that contribute to discontinuation,
we performed a multivariable analysis of warfarin discontinuation, excluding the 263 patients who were hospitalized for hemorrhage. Table 3 presents the independent effects of baseline clinical features that were statistically significantly related to warfarin discontinuation or were components of the CHADS2 score. The presence of risk factors for stroke, assessed as individual risk factors and by the CHADS2 score, were associated with lower risk of warfarin discontinuation. Patients aged <65 years made up the age category most likely to discontinue warfarin, even after adjusting for other risk factors for stroke (Table 3).

**Discussion**

Maintaining appropriate patients with atrial fibrillation on warfarin therapy is vitally important because clinical outcomes strongly depend on remaining on anticoagulation therapy. Conversely, there may be patients at low stroke risk or with elevated risk from warfarin in whom discontinuation of therapy is appropriate. In our ATRIA cohort, >1 in 4 patients with atrial fibrillation newly started on warfarin discontinued therapy within the first year of treatment. Although there was a high rate of discontinuation in the first year, patients who remained on therapy at the end of the first year were then less likely to discontinue warfarin in subsequent years. In addition, sizable fractions of patients who discontinued warfarin eventually restarted therapy, leading to a relatively stable prevalence of warfarin use in the overall cohort over time.

It is challenging to determine what proportion of warfarin persistence versus discontinuation was clinically appropriate. Patients with low stroke risk may not derive much benefit from warfarin. We found that patients with the lowest predicted stroke risk were more likely to discontinue warfarin than those with additional stroke risk factors and higher CHADS2 scores, an observation noted in some prior studies of warfarin use. These results may reflect a rational assessment of the net benefit of anticoagulation by prescribing clinicians and their patients.

There also may be clinically appropriate reasons to discontinue therapy. Our study found that patients with lower proportions of time spent in the therapeutic INR range were more likely to discontinue warfarin. We were unable to determine the precise reasons for poorer INR control. Poor INR control may have been a marker for nonadherence to warfarin leading to subsequent discontinuation, or poor control may have led to concerns about the safety of continuing warfarin.

As expected, discontinuation of warfarin was high after hospitalizations for a hemorrhagic event, but because the overall rate of hospitalizations for hemorrhage in the cohort was low, such events could only account for a small fraction of discontinuations. It is possible that more minor, outpatient hemorrhagic events resulted in additional patients discontinuing therapy. The youngest patients were the most likely to discontinue warfarin therapy, a finding that has been observed in other analyses of warfarin adherence. Patients aged ≥85 years were not more likely to discontinue warfarin.
than those aged 65 to 84 years, despite the higher risk of hemorrhage among older adults.\textsuperscript{16}

Although warfarin discontinuation rates have varied across randomized clinical trial settings,\textsuperscript{17–19} it was notably high in the older patients enrolled in the recent Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial. After a mean follow-up period of 2.7 years, 33\% of elderly patients discontinued warfarin compared to a 24\% discontinuation rate on aspirin.\textsuperscript{20} Of note, a large number of potential subjects in the BAFTA trial were excluded because their physicians thought warfarin would be beneficial, which may have selected for less-suitable warfarin candidates. The BAFTA study also did not provide discontinuation rates stratified by age group, being a study of older patients. Observational studies have found that warfarin discontinuation frequently is due to concerns about bleeding complications or safe anticoagulation management as well as to issues of patient adherence and preference.\textsuperscript{12,21,22} One study of 651 patients who were prescribed oral anticoagulants after ischemic stroke observed a 22\% discontinuation rate after 1 year. Bleeding was the reason cited for 36.4\% of those stopping anticoagulants, and “patient request” or “hassle to visit anticoagulation clinic” were the reasons cited in another 31.5\%.\textsuperscript{22} Another study found that among 153 patients aged $\geq$80 years, 26\% discontinued warfarin within 1 year (excluding patients who died or who were in sinus rhythm), and the primary reason for discontinuation was concern about the safety of anticoagulation.\textsuperscript{21} There was a high bleeding complication rate observed in this study, which may have been related to a large proportion of patients who were recruited during an acute hospitalization. In addition, there was a 40\% rate of concomitant warfarin and aspirin use, which may have led to increased bleeding complications. Although the present study found low rates of hospitalizations for hemorrhage, it is possible that minor hemorrhages, such as epistaxis or superficial bruising that did not lead to hospitalization, could have contributed to warfarin discontinuation. A more in-depth investigation of the impact of minor bleeding while on anticoagulants would give a richer perspective to the reasons why patients discontinue warfarin.

Our results highlight the dynamic nature of adherence to anticoagulant therapy. Even after discontinuing warfarin for at least 180 days, a substantial proportion of patients restarted warfarin at some point over subsequent years. The balance of discontinuations and resumption of therapy resulted in a fairly stable prevalence of warfarin use after the first 2 years of warfarin anticoagulation. Nonetheless, the large fraction of patients who discontinue warfarin permanently has important implications for quality improvement programs. Programs that are primarily directed toward more widespread adoption of warfarin therapy in patients with atrial fibrillation must work to improve not only the initiation of therapy, but also the persistence of therapy in appropriate patients.\textsuperscript{23} The observation that patients with lower stroke risk and worse Figure 3. Kaplan–Meier graph of time to first warfarin discontinuation period of $\geq180$ days among 4188 patients with atrial fibrillation starting warfarin. A, Stratified by patient age. B, Stratified by CHADS$_2$ score.
INR control were more likely to come off therapy, whereas patients with additional risk factors for stroke were more likely to remain on warfarin, suggests that clinicians have a significant influence on whether patients continue to take warfarin. Quality measurements that rely on cross-sectional assessments of the proportion of patients taking warfarin will not be able to capture the dynamic process of warfarin initiation and discontinuation in individual patients.

There are several limitations to our study. The primary limitation is that we were unable to directly determine the specific reason for discontinuation. Some studies have found that concerns about safety and adherence are strongly associated with avoidance or discontinuation of warfarin. However, it is likely that such concerns influenced warfarin discontinuation in our study, we lacked direct assessments of individual decision-making.

Our study also was unable to capture outpatient hemorrhagic events that did not lead to hospitalization but may have led to concerns about the safety of continuing on warfarin. Our measure of warfarin use and discontinuation may be subject to some errors in timing because we relied on an algorithm based on the number of pills prescribed to determine the length of warfarin therapy along with interim INR testing. In addition, our assessments of clinical factors associated with stroke risk were obtained using computerized clinical databases, which may introduce some level of misclassification. Our analysis was not able to capture comprehensive aspirin use because aspirin is available without a prescription. Because our study period largely preceded the publication of the results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial in 2002, it is possible that some physicians discontinued warfarin in patients with long periods of sinus rhythm; our study was not able to determine which patients had only a single episode of atrial fibrillation followed by prolonged sinus rhythm.

**Table 2. Univariate Association of Clinical Characteristics With Warfarin Discontinuation at 1 Year Among 4188 Subjects With Atrial Fibrillation Newly Starting Warfarin**

<table>
<thead>
<tr>
<th>Patients Discontinuing Warfarin by the End of 1 y, % (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23.4 (21.4–25.5)</td>
</tr>
<tr>
<td>Male</td>
<td>28.5 (26.7–30.4)</td>
</tr>
<tr>
<td>Prior ischemic stroke</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15.1 (11.6–19.5)</td>
</tr>
<tr>
<td>No</td>
<td>27.4 (26.0–28.9)</td>
</tr>
<tr>
<td>Diagnosed heart failure</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21.0 (18.7–23.7)</td>
</tr>
<tr>
<td>No</td>
<td>28.3 (26.7–30.0)</td>
</tr>
<tr>
<td>Diagnosed hypertension</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24.2 (22.5–26.1)</td>
</tr>
<tr>
<td>No</td>
<td>29.0 (27.0–31.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23.0 (20.0–26.4)</td>
</tr>
<tr>
<td>No</td>
<td>27.1 (25.6–28.6)</td>
</tr>
<tr>
<td>CHADS2 score†</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34.7 (31.6–38.1)</td>
</tr>
<tr>
<td>1</td>
<td>28.1 (25.8–30.7)</td>
</tr>
<tr>
<td>2</td>
<td>23.7 (21.2–26.3)</td>
</tr>
<tr>
<td>3</td>
<td>21.9 (18.6–25.7)</td>
</tr>
<tr>
<td>4–6</td>
<td>13.8 (10.2–18.6)</td>
</tr>
<tr>
<td>History of gastrointestinal bleed</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28.2 (21.3–36.6)</td>
</tr>
<tr>
<td>No</td>
<td>26.4 (25.0–27.8)</td>
</tr>
<tr>
<td>Diagnosed dementia</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17.3 (10.9–26.8)</td>
</tr>
<tr>
<td>No</td>
<td>26.6 (25.3–28.1)</td>
</tr>
<tr>
<td>Mechanical fall diagnosis during prior hospitalization</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27.6 (20.9–35.8)</td>
</tr>
<tr>
<td>No</td>
<td>26.4 (25.0–27.8)</td>
</tr>
</tbody>
</table>

*P values calculated using log-rank tests comparing survival curves.
†CHADS2 indicates stroke risk score assigning 1 point for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points for stroke/transient ischemic attack.

Although it is likely that such concerns influenced warfarin discontinuation in our study, we lacked direct assessments of individual decision-making. Our study also was unable to capture outpatient hemorrhagic events that did not lead to hospitalization but may have led to concerns about the safety of continuing on warfarin. Our measure of warfarin use and discontinuation may be subject to some errors in timing because we relied on an algorithm based on the number of pills prescribed to determine the length of warfarin therapy along with interim INR testing. In addition, our assessments of clinical factors associated with stroke risk were obtained using computerized clinical databases, which may introduce some level of misclassification. Our analysis was not able to capture comprehensive aspirin use because aspirin is available without a prescription. Because our study period largely preceded the publication of the results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial in 2002, it is possible that some physicians discontinued warfarin in patients with long periods of sinus rhythm; our study was not able to determine which patients had only a single episode of atrial fibrillation followed by prolonged sinus rhythm.

Warfarin largely reverses the risk of stroke attributable to atrial fibrillation. Multiple guidelines recommend warfarin therapy in patients with atrial fibrillation with additional...
stroke risk factors, a clinical profile describing the majority of patients with atrial fibrillation. In this large, community-based cohort of patients newly starting warfarin for atrial fibrillation, more than 1 in 4 discontinued therapy within the first year. Although hemorrhage events leading to hospitalization greatly increased the risk of warfarin discontinuation, the rate of such hemorrhages was too low to account for more than a small fraction of all discontinuations. It is probable that difficult warfarin control and concern about bleeding risk led patients, clinicians, or both to stop warfarin. Quality indicators that rely simply on rates of warfarin use for atrial fibrillation will be unlikely to capture appropriate versus inappropriate discontinuation of anticoagulation. Stroke prevention programs should consider the net benefit of warfarin for individual patients with atrial fibrillation, weighing the risks and benefits, and be attentive toward maintaining anticoagulation in appropriate patients.

Sources of Funding
Funding for the study was provided by the National Institute on Aging (R01 AG15478 and K23 AG28978); the National Heart, Lung, and Blood Institute (U19 HL91179 and RC2 HL101589); and the Eliot B. and Edith C. Shoolman fund of the Massachusetts General Hospital (Boston, Mass). The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of this manuscript.

Disclosures
Dr Go has received a research grant from Johnson & Johnson, Inc. In the past 2 years, Dr Singer has received a research grant from Daiichi Sankyo, Inc, and consulted for Boehringer Ingelheim, Daiichi Sankyo, Inc, Johnson and Johnson, Inc, Merck and Co, and Sanofi Aventis, Inc, and Bayer Schering Pharma.

References


Warfarin Discontinuation After Starting Warfarin for Atrial Fibrillation
Margaret C. Fang, Alan S. Go, Yuchiao Chang, Leila H. Borowsky, Niela K. Pomernacki, Natalia Udaltsova and Daniel E. Singer

_Circ Cardiovasc Qual Outcomes._ 2010;3:624-631; originally published online October 19, 2010;
doi: 10.1161/CIRCOUTCOMES.110.937680
_Circulation: Cardiovascular Quality and Outcomes_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
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:
http://circoutcomes.ahajournals.org/content/3/6/624

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Quality and Outcomes_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Quality and Outcomes_ is online at:
http://circoutcomes.ahajournals.org/subscriptions/