Stability of High-Quality Warfarin Anticoagulation in a Community-Based Atrial Fibrillation Cohort: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study

Liane O. Dallalzadeh, BS; Alan S. Go, MD; Yuchiao Chang, PhD; Leila H. Borowsky, MPH; Margaret C. Fang, MD, MPH; Daniel E. Singer, MD

**Background**—Warfarin reduces ischemic stroke risk in atrial fibrillation (AF) but increases bleeding risk. Novel anticoagulants challenge warfarin as stroke-preventive therapy for AF. They are available at fixed doses but are more costly. Warfarin anticoagulation at a time in therapeutic range (TTR) \( \geq 70\% \) is similarly as effective and safe as novel anticoagulants. It is unclear whether AF patients with TTR \( \geq 70\% \) will remain stably anticoagulated and avoid the need to switch to a novel anticoagulant. We assessed stability of warfarin anticoagulation in AF patients with an initial TTR \( \geq 70\% \).

**Methods and Results**—Within the community-based Anticoagulation and Risk Factors in AF (ATRIA) cohort followed from 1996 to 2003, we identified 2841 new warfarin users who continued warfarin over 9 months. We excluded months 1 to 3 to achieve a stable dose. For the 987 patients with TTR \( \geq 70\% \) in an initial 6-month period (TTR\(_1\); months 4–9), we described the distribution of TTR\(_2\) (months 10–15) and assessed multivariable correlates of persistent TTR \( \geq 70\% \). Of patients with TTR\(_1 \geq 70\% \), 57% persisted with TTR\(_2 \geq 70\% \) and 16% deteriorated to TTR\(_2 < 50\% \). Only initial TTR\(_1 \geq 90\% \) (adjusted odds ratio 1.47, 95% CI 1.07–2.01) independently predicted TTR\(_2 \geq 70\% \). Heart failure was moderately associated with marked deterioration (TTR\(_2 < 50\% \); adjusted odds ratio 1.45, 95% CI 1.00–2.10).

**Conclusions**—Nearly 60% of AF patients with high-quality TTR\(_1\) on warfarin maintained TTR \( \geq 70\% \) over the next 6 months. A minority deteriorated to very poor TTR. Patient features did not strongly predict TTR in the second 6-month period. Our analyses support watchful waiting for AF patients with initial high-quality warfarin anticoagulation before considering alternative anticoagulants. *(J Am Heart Assoc. 2016;5:e003482 doi: 10.1161/JAHA.116.003482)*

**Key Words:** anticoagulants • arrhythmia • embolism • prevention • risk factors

Atrial fibrillation (AF) is the most frequent significant cardiac arrhythmia and the strongest common risk factor for ischemic stroke.\(^1\) It increases stroke risk 5-fold and accounts for \( \approx 15\% \) of all strokes in the United States.\(^2,3\) Moreover, strokes caused by AF are more likely to prove fatal or severely disabling.\(^4,5\) High-quality anticoagulant therapy can largely prevent AF-associated thromboembolic events while minimizing bleeding risk.\(^6\) AF patients taking warfarin are at the lowest risk for both thromboembolism and intracranial hemorrhage at International Normalized Ratio (INR) levels of 1.8 to 3.5, a range that includes the guideline-recommended range of 2.0 to 3.0.\(^7,8\) Frequent INR monitoring with dose adjustment is generally needed to maintain INR levels in this target range of 2.0 to 3.0.\(^9\) Recently developed novel anticoagulants (ie, dabigatran, rivaroxaban, apixaban, and edoxaban) now compete with warfarin as the primary stroke-preventive therapy for AF patients. These agents offer fixed oral doses without the need for frequent INR monitoring and with a reduced risk of intracranial hemorrhage compared with average to poor warfarin anticoagulation control.\(^10\) These novel agents appear to be particularly attractive for AF patients starting anticoagulant therapy. What remains unclear is whether AF patients who are well anticoagulated on warfarin should switch to a novel agent.

Time in the therapeutic range (TTR) of INR 2.0 to 3.0 is the standard means of assessing quality of warfarin therapy.\(^11\) Secondary analyses of randomized trials indicate that warfarin...
at TTR ≥70% has efficacy and safety comparable to novel anticoagulants, suggesting that patients with TTR ≥70% would gain little clinical benefit from switching to a novel anticoagulant.\textsuperscript{12–14} This assumes, however, that such a high TTR is stable over time. Limited analyses have examined the stability of TTR in AF patients taking warfarin over a prolonged period.\textsuperscript{15–17} Our study aimed to address this knowledge gap by assessing the stability of high-quality anticoagulation over 12 months among patients initiating warfarin. Specifically, we used a large, real-world cohort of AF patients newly taking warfarin to determine the percentage of patients with an initial 6-month TTR (TTR\textsubscript{1}) ≥70% whose TTR persisted at ≥70% in the subsequent 6-month period (TTR\textsubscript{2}). We then assessed patient features potentially predicting continued high-quality TTR. Addressing these aims can provide guidance to patients and their providers when making the decision to continue warfarin or to switch to a novel agent.

### Methods

#### Cohort Assembly

The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) cohort consists of 13,559 adults diagnosed with nonvalvular AF who received care at Kaiser Permanente Northern California, a large integrated health care delivery system. Details of cohort identification have been described previously.\textsuperscript{18} Briefly, patients were identified between July 1, 1996, and December 31, 1997, by searching outpatient databases in which an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis of AF (427.31) was assigned and by searching electrocardiographic databases for diagnoses of AF. Those with at least 1 outpatient diagnosis of AF and an ECG diagnosis of AF were included in the cohort. Index date was defined as the date of first diagnosis of AF during cohort assembly. Patients were followed until September 30, 2003 (median 6.0 years; interquartile range 3.1–6.7 years), and censored at death or disenrollment from the health plan. Exclusion criteria included patients with diagnoses of mitral stenosis, valvular repair or replacement, transient postoperative AF, or concurrent hyperthyroidism to limit the cohort to those with nontransient, nonvalvular AF.

The study was approved by the institutional review boards of the collaborating institutions. Waiver of informed consent was obtained due to the nature of the study.

#### Study Variables

Our analysis focused exclusively on AF patients who were new and continuous users of warfarin. Warfarin status was assessed

![Figure 1](image-url). Selection of study cohort. Of the 13,559 patients in the ATRIA AF cohort, 4,460 met the criteria for new starts on warfarin during the study period. Of these, 2,928 had ≥9 months of continuous warfarin use, including our initial 3-month dose-finding period and our first period assessing TTR (months 4–9). There were 2,841 patients who had interpolatable INR values (ie, calculable TTR values) in period 1. From these, we identified the 1,156 patients newly started on warfarin and who had a TTR ≥70% in period 1 (TTR\textsubscript{1}, months 4–9). The primary analysis focused on the 987 patients who had TTR\textsubscript{1} ≥70% and had a calculable TTR in period 2 (TTR\textsubscript{2}, months 10–15). In a sensitivity analysis, we also included the 58 patients with TTR\textsubscript{1} ≥70% who discontinued warfarin in period 2. We did not include the following categories of patients in the analysis of TTR\textsubscript{2}: (1) died in period 2 (n=16), (2) discontinued warfarin in period 2 but restarted warfarin within 1 year (n=42), (3) period 2 follow-up was incomplete because the study ended (n=33), (4) no interpolatable INR values in period 2 (n=17), and (5) disenrolled in the health plan during period 2 (n=3). AF indicates atrial fibrillation; ATRIA, anticoagulation and risk factors in atrial fibrillation; INR, International Normalized Ratio; TTR, time in the therapeutic range.

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**Table 1. Features of ATRIA Cohort Patients Initiating Warfarin Therapy and Continuing to Take Warfarin Therapy for at Least 9 Months**

| Variable*          | All Patients, n (%) |  |
|--------------------|---------------------|------------------|
| All                | 2841 (100)          |  |
| Age                |                     |  |
| <75 y              | 1614 (56.8)         |  |
| ≥75 y              | 1227 (43.2)         |  |
| Sex                |                     |  |
| Men                | 1597 (56.2)         |  |
| Women              | 1244 (43.8)         |  |
| Race               |                     |  |
| White              | 2478 (87.2)         |  |
| Other              | 363 (12.8)          |  |
| Diabetes mellitus  | 466 (16.4)          |  |
| Hypertension       | 1575 (55.4)         |  |
| Coronary heart disease | 797 (28.1)    |  |
| Heart failure      | 752 (26.5)          |  |
| Peripheral artery disease | 71 (2.5)     |  |
| Renal impairment†  | 351 (12.4)          |  |
| Prior stroke       | 262 (9.2)           |  |
| Cancer             | 337 (11.9)          |  |
| Prior bleed        | 154 (5.4)           |  |
| Beta blockers      | 945 (33.3)          |  |
| Antiarrhythmics    | 469 (16.5)          |  |
| Calcium channel blockers | 744 (26.2)  |  |
| ATRIA stroke risk score at admission‡ |  |
| 0–5                | 1455 (51.2)         |  |
| 6                  | 404 (14.2)          |  |
| ≥7                 | 982 (34.6)          |  |
| CHA₂DS₂-VASc score at admission§ |  |
| 0                  | 161 (5.7)           |  |
| 1                  | 439 (15.5)          |  |
| ≥2                 | 2241 (78.9)         |  |

ATRIA indicates anticoagulation and risk factors in atrial fibrillation; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

*Variables assessed at the beginning of the 15-month follow-up period.
†eGFR <45 mL/min/1.73 m² or ESRD.
‡ATRIA risk score includes prior stroke, age, sex, diabetes mellitus, congestive heart failure, hypertension, proteinuria, and eGFR <45 mL/min/1.73 m² or ESRD.23
§CHA₂DS₂-VASc score includes congestive heart failure; hypertension; age; diabetes mellitus; stroke, transient ischemic attack, or thromboembolism; vascular disease; and sex.22

**Table 2. Distribution of TTR₁ (Months 4–9) for 2841 New Warfarin Users**

| TTR₁ Category | n (%)  |
|---------------|--------|
| ≥70%          | 1156 (40.7) |
| 65–69%        | 225 (7.9)  |
| 60–64%        | 213 (7.5)  |
| 50–59%        | 410 (14.4) |
| <50%          | 837 (29.5) |

TTR indicates time in the therapeutic range during the first 6-month period. *Months 4–9 are the first 6-month period after the initial 3-month period to establish a stable warfarin dose.

cohort assembly period who had no prior identified warfarin prescription and <2 outpatient INR measurements in the previous 12 months.19 Continuous warfarin exposure was defined as periods of <60 days between the end of the days supplied and the beginning of the subsequent prescription for any 2 consecutive filled prescriptions. For periods >60 days, continuous warfarin use was assumed if there were intervening INR measurements at least every 42 days. If neither requirement was met, the patient was considered to have discontinued warfarin from day 31 after the end date of the first prescription until the start date of the next prescription. The 30-day grace period was provided to account for reductions in dose or skipped doses.

TTR is the percentage of time an AF patient maintains an INR between 2.0 and 3.0. Using each patient’s INR data, we calculated individual patient TTRs via the standard Rosendaal interpolation method for both an initial 6-month period and the subsequent 6-month period.20 This method defines TTR as the number of person-days with an INR between 2.0 and 3.0 divided by total number of person-days for which INR could be interpolated. It assumes that changes between consecutive INR measurements are linear over time. We also provided a TTR for the INR range 1.8 to 3.5; there is empirical evidence that this is the full optimal INR range.7 Our 12-month study period excluded the first 3 months of warfarin use; this is a “break-in” period during which optimal warfarin dosing is sought. The initial period was defined as months 4 to 9 inclusive, providing our measures of TTR₁, and the subsequent period was defined as months 10 to 15 inclusive, providing TTR₂. We excluded the 8.1% of time on warfarin during which the inter-INR interval was >8 weeks.21 Characteristics of patients with and without 9 months of continuous warfarin use following initial prescription are shown for reference in Table S1.

Covariates included demographic features, risk factors for stroke in patients with AF, the CHA₂DS₂-VASc and ATRIA stroke risk scores, a current or past diagnosis of cancer (excluding nonmelanoma skin cancer), and common rate and rhythm control drugs used in AF. Covariates were identified using based on dispensed warfarin prescriptions and outpatient INR values in automated pharmacy and laboratory databases and was validated against warfarin status documented in medical records of potential outcome events.19 New users were defined as patients with a new prescription for warfarin during the
Table 3. Association of Patient Baseline Features With TTR \( \geq 70\% \) in Period 1

| Variable* | n    | Patients With TTR \( \geq 70\% \) in Months 4–9, n (%) | P Value§ |
|-----------|------|--------------------------------------------------------|---------|
| All       | 2841 | 1156 (40.7)                                            | 0.45    |
| Age       |      |                                                        |         |
| \(<75 \text{ y}) | 1614 | 647 (40.1)                                            |         |
| \(\geq 75 \text{ y}) | 1227 | 509 (41.5)                                            |         |
| Sex       |      |                                                        | 0.99    |
| Men       | 1597 | 650 (40.7)                                            |         |
| Women     | 1244 | 506 (40.7)                                            |         |
| Race      |      |                                                        | 0.44    |
| White     | 2478 | 1015 (41.0)                                            |         |
| Other     | 363  | 141 (38.8)                                             |         |
| Diabetes mellitus | 2375  | 977 (41.1) | 0.27 |
| No        | 1266 | 521 (41.2)                                            |         |
| Yes       | 1575 | 635 (40.3)                                            |         |
| Hypertension |      |                                                        | 0.65    |
| No        | 1266 | 521 (41.2)                                            |         |
| Yes       | 1575 | 635 (40.3)                                            |         |
| Coronary artery disease | 2044  | 841 (41.1) | 0.43 |
| No        | 2044 | 841 (41.1)                                            |         |
| Yes       | 797  | 315 (39.5)                                            |         |
| Heart failure | 2089  | 867 (41.5) | 0.14 |
| No        | 2089 | 867 (41.5)                                            |         |
| Yes       | 752  | 289 (38.4)                                            |         |
| Peripheral artery disease | 2770  | 1124 (40.6) | 0.45 |
| No        | 2770 | 1124 (40.6)                                            |         |
| Yes       | 71   | 32 (45.1)                                             |         |
| Renal impairment† | 2490  | 1034 (41.5) | 0.016 |
| No        | 2490 | 1034 (41.5)                                            |         |
| Yes       | 351  | 122 (34.8)                                            |         |
| Prior stroke | 2579  | 1049 (40.7) | 0.96 |
| No        | 2579 | 1049 (40.7)                                            |         |
| Yes       | 262  | 107 (40.8)                                            |         |
| Cancer    |      |                                                        | 0.35    |
| No        | 2504 | 1011 (40.4)                                            |         |
| Yes       | 337  | 145 (43.0)                                            |         |
| Prior bleed | 2687  | 1099 (40.9) | 0.34 |
| No        | 2687 | 1099 (40.9)                                            |         |
| Yes       | 154  | 57 (37.0)                                             |         |
| Beta blockers | 1896  | 748 (39.5) | 0.057 |
| No        | 1896 | 748 (39.5)                                            |         |
| Yes       | 945  | 408 (43.2)                                            |         |

Table 3. Continued

| Variable* | n    | Patients With TTR \( \geq 70\% \) in Months 4–9, n (%) | P Value§ |
|-----------|------|--------------------------------------------------------|---------|
| Antiarhythmics |      |                                                        | 0.82    |
| No        | 2372 | 963 (40.6)                                            |         |
| Yes       | 469  | 193 (41.2)                                            |         |
| Calcium channel blockers |      |                                                        | 0.15    |
| No        | 2097 | 870 (41.5)                                            |         |
| Yes       | 744  | 286 (38.4)                                            |         |
| ATRIA score at admission† | 1455  | 601 (41.3) | 0.76 |
| 0 to 5    | 404  | 164 (40.6)                                            |         |
| 6         | 982  | 391 (39.8)                                            |         |
| \(\geq 7\) | 2241 | 905 (40.4)                                            |         |
| CHA2DS2-VASc score at admissionk |      |                                                        | 0.79    |
| 0         | 161  | 66 (41.0)                                             |         |
| 1         | 439  | 185 (42.1)                                            |         |
| \(\geq 2\) | 2241 | 905 (40.4)                                            |         |

ATRIA indicates anticoagulation and risk factors in atrial fibrillation; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TTR, time in the therapeutic range.

* Variables assessed at the beginning of the 15-month follow-up period.

† P values from chi-square tests.

‡ eGFR <45 mL/min/1.73 m² or ESRD.

§ ATRIA risk score includes prior stroke, age, sex, diabetes mellitus, congestive heart failure, hypertension, proteinuria, and eGFR <45 mL/min/1.73 m² or ESRD.23

k CHA2DS2-VASc score includes congestive heart failure; hypertension; age; diabetes mellitus; stroke, transient ischemic attack, or thromboembolism; vascular disease; and sex.22

Clinical inpatient and ambulatory visit, administrative, and pharmacy databases for the 5 years before each patient’s cohort index date. Diabetes mellitus was identified using a validated diabetes registry.18 Ascertainment of individual stroke risk factors was validated against a review of samples of outpatient medical records; crude agreement was high (78–96%), and corresponding κ statistics ranged from 0.51 to 0.89.21

Statistical Analysis

TTR was first assessed as a continuous variable, summarized using mean with standard deviation and median with interquartile range (quartiles 1–3). We dichotomized TTR at 70%. We assessed patient features correlated with TTR1. Among those patients with an initial TTR \( \geq 70\% \), we recorded the distribution of TTR values in the second 6-month period (TTR2). We assessed the univariate and multivariable associations of clinical features with persistence of TTR \( \geq 70\% \) and with marked deterioration of TTR (ie, TTR <50%). In sensitivity analyses, we included patients with TTR1 \( \geq 70\% \) who discontinued warfarin in the second 6-month period as part of a
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(Figure 2). Expanding the definition of poor outcome to the composite of TTR <50% or discontinued warfarin, no patient features were significantly related to poor outcome in multivariable models. With this expanded definition of poor outcome, the adjusted odds ratio for heart failure was 1.24 (95% CI 0.89–1.73).

Results

Of the 13 559 patients in the ATRIA cohort, 4460 met the criteria for new starts on warfarin during the study period. Of these, 2928 had ≥9 months of continuous warfarin use, including our initial 3-month dose-finding period and our first period assessing TTR (months 4–9). There were 2841 patients who had interpolatable INR values (ie, calculable TTR values) in period 1 (Figure 1). Of those, 43% were aged ≥75 years at baseline, 56% were men, 87% were white, 16% had diabetes mellitus, 55% had hypertension, 28% had coronary artery disease, 27% had heart failure, and 12% had diminished renal function (estimated glomerular filtration rate <45 mL/min per 1.73 m²), among other features. Moreover, 79% had a CHA2DS2-VASc score ≥2, and 49% had an ATRIA stroke risk score ≥6 (Table 1).

For these 2841 new and continuous warfarin users, the mean TTR1 was 61.7% (SD 24.2%) and the median was 64.1% (interquartile range 45.7–80.1%). In total, 1156 (40.7%) patients had TTR1 ≥70% in the initial period, whereas 29.5% demonstrated poor control (TTR1 <50%) (Table 2). Most patient features were unrelated to initial TTR ≥70%, although patients with renal impairment had statistically significantly lower TTR1, and patients taking beta blockers had borderline significantly higher TTR1 (Table 3). In a multivariable logistic model, impaired renal function was the sole significant correlate of TTR1, with an adjusted odds ratio of 0.77 (95% CI 0.61–0.98) for TTR1 ≥70%.

Among the 987 patients who achieved TTR1 ≥70% and had interpolatable INR values through period 2 (months 10–15), 562 (56.9%) persisted as well-controlled warfarin users (TTR2 ≥70%). Most INR time that was out of range was below INR 2.0, and this pattern worsened in lower TTR categories (Figure 2). Expanding the definition of good-quality TTR to ≥65%, 650 (65.9%) persisted as good-quality warfarin users (TTR2 ≥65%). If the target INR range was expanded to include the full optimal INR range of 1.8 to 3.5 in the subsequent period, 891 (90.3%) achieved a TTR2 ≥70%.

In univariate analyses, TTR (using INR 2.0–3.0, the standard therapeutic range) in the initial period, absence of renal impairment, and absence of heart failure were significantly associated with high-quality TTR in the subsequent period (Table 4). In multivariable analysis, only TTR1 ≥65% remained a strong independent predictor of persistent high-quality warfarin therapy (adjusted odds ratio 1.47, 95% CI 1.07–2.01) (Table 4). Among patients with TTR1 ≥70%, 154 (15.6%) had the poor outcome of a TTR2 <50% (Figure 2). Only heart failure was significantly associated with deterioration to TTR <50% in the subsequent period (adjusted odds ratio 1.45, 95% CI 1.00–2.10) (Table 5). Of 1045 patients achieving a TTR ≥70% in months 4 to 9, 58 discontinued warfarin in months 10 to 15. If we broadened our definition of poor outcome to the composite of TTR <50% or discontinued warfarin, no patient features were significantly related to poor outcome in multivariable models. With this expanded definition of poor outcome, the adjusted odds ratio for heart failure was 1.24 (95% CI 0.89–1.73).

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Discussion

Using a large real-world community cohort of AF patients newly and continuously taking warfarin, we assessed how well
good control of anticoagulation persisted. We allowed an initial dose-finding period of months 1 to 3 and then calculated the TTR in study period 1 (months 4–9). We then focused on patients with high-quality anticoagulation (ie, TTR ≥70%) in period 1 and followed them over a subsequent 6-month period (months 10–15). We found that 41% of

### Table 5. Univariate and Multivariable Correlates of Markedly Deteriorated TTR (<50%) Among Those With TTR ≥70% in Months 4–9 (n=987)

| Variable* | n  | Patients With TTR <50% in Months 10–15, n (%) | Univariate P Value† | Multivariable Odds Ratio (95% CI)‡ |
|-----------|----|---------------------------------------------|---------------------|-----------------------------------|
| All       | 987| 154 (15.6)                                  | NA                  | NA                                |
| TTR in months 4–9 |      |                                           | 0.66                |                                   |
| 70–79%    | 375| 54 (14.4)                                   |                     |                                   |
| 80–89%    | 319| 54 (16.9)                                   |                     |                                   |
| ≥90%      | 293| 46 (15.7)                                   |                     |                                   |
| Age       |    |                                            | 0.63                |                                   |
| <75 y     | 511| 77 (15.1)                                   |                     |                                   |
| ≥75 y     | 476| 77 (16.2)                                   |                     |                                   |
| Sex       |    |                                            | 0.71                |                                   |
| Men       | 552| 84 (15.2)                                   |                     |                                   |
| Women     | 435| 70 (16.1)                                   |                     |                                   |
| Race      |    |                                            | 0.47                |                                   |
| White     | 874| 139 (15.9)                                  |                     |                                   |
| Other     | 113| 15 (13.3)                                   |                     |                                   |
| Diabetes mellitus | |                                       | 0.92                |                                   |
| No        | 823| 128 (15.6)                                  |                     |                                   |
| Yes       | 164| 26 (15.9)                                   |                     |                                   |
| Hypertension | |                                      | 0.83                |                                   |
| No        | 418| 64 (15.3)                                   |                     |                                   |
| Yes       | 569| 90 (15.8)                                   |                     |                                   |
| Coronary heart disease | |                                      | 0.34                |                                   |
| No        | 717| 107 (14.9)                                  |                     |                                   |
| Yes       | 270| 47 (17.4)                                   |                     |                                   |
| Heart failure | |                                      | 0.02                | 1.45 (1.00–2.10)                  |
| No        | 705| 98 (13.9)                                   |                     |                                   |
| Yes       | 282| 56 (19.9)                                   |                     |                                   |
| Peripheral artery disease | |                                      | 0.43                |                                   |
| No        | 958| 151 (15.8)                                  |                     |                                   |
| Yes       | 29 | 3 (10.3)                                    |                     |                                   |
| Renal impairment | |                                      | 0.18                | 1.25 (0.75–2.07)                  |
| No        | 871| 131 (15.0)                                  |                     |                                   |
| Yes       | 116| 23 (19.8)                                   |                     |                                   |
| Prior stroke | |                                       | 0.68                |                                   |
| No        | 895| 141 (15.8)                                  |                     |                                   |
| Yes       | 92 | 13 (14.1)                                   |                     |                                   |

### Table 5. Continued

| Variable* | n  | Patients With TTR <50% in Months 10–15, n (%) | Univariate P Value† | Multivariable Odds Ratio (95% CI)‡ |
|-----------|----|---------------------------------------------|---------------------|-----------------------------------|
| Cancer    |    |                                            | 0.43                |                                   |
| No        | 865| 132 (15.3)                                  |                     |                                   |
| Yes       | 122| 22 (18.0)                                   |                     |                                   |
| Prior bleed | |                                          | 0.29                |                                   |
| No        | 938| 149 (15.9)                                  |                     |                                   |
| Yes       | 49 | 5 (10.2)                                    |                     |                                   |
| Beta blockers | |                                       | 0.62                |                                   |
| No        | 658| 100 (15.2)                                  |                     |                                   |
| Yes       | 329| 54 (16.4)                                   |                     |                                   |
| Antiarrhythmics | |                                      | 0.064               | 0.52 (0.27–1.03)                  |
| No        | 881| 144 (16.3)                                  |                     |                                   |
| Yes       | 106| 10 (9.4)                                    |                     |                                   |
| Calcium channel blockers | |                                      | 0.12                | 0.72 (0.46–1.11)                  |
| No        | 753| 125 (16.6)                                  |                     |                                   |
| Yes       | 234| 29 (12.4)                                   |                     |                                   |
| ATRIA score at admission | |                                      | 0.33                |                                   |
| 0-5       | 472| 73 (15.5)                                   |                     |                                   |
| 6         | 136| 16 (11.8)                                   |                     |                                   |
| ≥7        | 379| 65 (17.2)                                   |                     |                                   |
| CHA2DS2-VASc score at admission | |                                      | 0.57                |                                   |
| 0         | 44 | 5 (11.4)                                    |                     |                                   |
| 1         | 138| 19 (13.8)                                   |                     |                                   |
| ≥2        | 805| 130 (16.1)                                  |                     |                                   |

ATRIA indicates anticoagulation and risk factors in atrial fibrillation; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NA, not available; TTR, time in the therapeutic range.

*Variables assessed at the start of month 10 of follow-up.
†Univariate P values from chi-square tests.
‡Variables entered into the multivariable logistic model were heart failure, renal impairment, antiarrhythmics, and calcium channel blockers at the start of month 10.
§eGFR <45 mL/min/1.73 m² or ESRD.
∥ATRIA risk score includes prior stroke, age, sex, diabetes mellitus, congestive heart failure, hypertension, proteinuria, and eGFR <45 mL/min/1.73 m² or ESRD.23
¶CHA2DS2-VASc score includes heart failure; hypertension; age; diabetes mellitus; stroke, transient ischemic attack, or thromboembolism; vascular disease; and sex.22
patients achieved TTR ≥70% in period 1. Of these, 57% persisted at TTR ≥70% in period 2. Another 8.9% maintained a TTR between 65% and 69%, a range still considered good quality and better than levels seen in recent randomized trials. With the target INR range in period 2 defined as 1.8 to 3.5, fully 90% maintained TTR ≥70%. Empirical evidence shows that the optimal INR range for AF is 1.8 to 3.5, not just 2.0 to 3.0. Only 16% deteriorated to a TTR <50% (using the standard target of INR 2.0–3.0). Although excellent TTR (ie, ≥90%) predicted continued high TTR levels, no other clinical feature was significantly associated with TTR ≥70% in the second period of warfarin anticoagulation. The presence of heart failure was the only significant predictor of marked deterioration (ie, TTR <50%) in the second follow-up period. When we expanded our definition of poor outcome in period 2 to include both TTR <50% or discontinuing warfarin, no clinical feature was significantly and independently associated with poor outcome. Our results indicate that most patients with well-controlled warfarin therapy continue to do well.

Because INR levels between 2.0 and 3.0 are associated with low rates of both ischemic stroke and major bleeding, linearly interpolated TTR has become a standard measure of quality of warfarin management. Several clinical trials have provided evidence of warfarin’s improved efficacy at high TTR levels, usually defined as approximately ≥70%. Multiple studies have aimed to identify predictors of TTR, including language, race, sex, age, and medical history, but such patient features account for only a small fraction of the variance of TTR. We found that only impaired renal function was significantly and inversely associated with TTR ≥70% in our first period of follow-up (months 4–9). Patients with impaired renal function were largely excluded from the trials of novel anticoagulants. These recently developed anticoagulants are not optimal replacements for warfarin in the face of renal insufficiency.

AF patients receiving warfarin now have the opportunity to switch to novel oral anticoagulants. These agents have comparable efficacy for reducing risk of stroke and do not require frequent INR monitoring. They have a clear advantage in reducing rates of intracranial hemorrhage compared with warfarin by approximately four per thousand per year. Although there is some inconsistency across trials, warfarin at TTR ≥70% appears to be equivalent to novel anticoagulants in terms of preventing stroke and systemic embolism, with increased risk of hemorrhagic stroke countered by reduced risk of ischemic stroke. There may still be a small benefit favoring novel agents in terms of nonstroke intracranial hemorrhage, partially balanced by an increased risk of gastrointestinal hemorrhage. Patients are likely to incur greater out-of-pocket costs with novel agents than with warfarin. Moreover, patients may prefer to continue taking warfarin. Our results are directly relevant to patients deciding whether to continue warfarin or to seek a substitute and for whom the convenience of novel agents is not an important factor. Our results support a watchful waiting approach for AF patients who have achieved a TTR ≥70% when taking warfarin because most of these patients will continue to do well. Providers should be particularly attentive to patients with heart failure because such patients are at modestly increased risk of substantial deterioration in TTR.

Our study represents the experience of AF patients in a community-based cohort within a large, well-resourced, integrated health care delivery system. Management of warfarin was coordinated predominantly through dedicated anticoagulation management services. Our results should apply broadly to patients whose anticoagulation was managed in a similar fashion. It is not clear whether our findings generalize to other, less formal systems of managing anticoagulation. High-quality warfarin anticoagulation depends on patients obtaining frequent INR tests. Patient- or system-level barriers to such a testing regimen will pose a challenge to maintaining TTR levels ≥70%. Our results strictly apply to AF patients at the 9-month mark after initiating warfarin therapy. Although we assume these results apply more broadly to all AF patients after a prolonged period (ie, 6 months) of high-quality warfarin treatment, validation of this assumption awaits further study.

Conclusion

Overall, 57% of AF patients with high-quality 6-month TTR after initiating warfarin (excluding an initial 3-month dose-finding period) maintained TTR ≥70% over the subsequent 6 months. A minority deteriorated to very poor TTR. Patient features do not strongly predict deterioration, although heart failure moderately increases this risk. Our analyses support watchful waiting for AF patients with initial high-quality warfarin anticoagulation before considering switching to a novel anticoagulant.

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SUPPLEMENTAL MATERIAL
Table S1. Characteristics of patients with and without 9 months of continuous warfarin use following initial prescription

| Variable* | Patients with at least 9 months of continuous warfarin use | Patients without 9 months of continuous warfarin use | P value† |
|-----------|----------------------------------------------------------|---------------------------------------------------|---------|
| All       | 2928 (100%)                                              | 1532 (100%)                                       |         |
| Age       |                                                          |                                                   | 0.60    |
| ≥75 years | 1264 (43.2%)                                             | 656 (42.8%)                                       |         |
| Sex       |                                                          |                                                   | 0.022   |
| Women     | 1272 (43.4%)                                             | 611 (39.9%)                                       |         |
| Race      |                                                          |                                                   | 0.002   |
| White     | 2555 (87.3%)                                             | 1291 (84.3%)                                      |         |
| Diabetes mellitus |                                                  |                                                   | 0.87    |
| Yes       | 480 (16.4%)                                              | 254 (16.6%)                                       |         |
| Hypertension |                                                  |                                                   | 0.089   |
| Yes       | 1611 (55.0%)                                             | 802 (52.3%)                                       |         |
| Coronary artery disease |                                                |                                                   | 0.60    |
| Yes       | 813 (27.8%)                                              | 414 (27.0%)                                       |         |
| Heart failure |                                                  |                                                   | 0.79    |
| Yes       | 779 (26.6%)                                              | 402 (26.2%)                                       |         |
| Peripheral artery disease |                                                |                                                   | 0.62    |
| Yes       | 74 (2.5%)                                                | 35 (2.3%)                                         |         |
| Renal impairment‡ |                                                |                                                   | 0.72    |
| Variable*                  | Patients with at least 9 months of continuous warfarin use | Patients without 9 months of continuous warfarin use | P value† |
|----------------------------|-------------------------------------------------------------|-----------------------------------------------------|----------|
| N (%)                      | N (%)                                                       |                                                     |          |
| Yes                        | 360 (12.3%)                                                 | 194 (12.7%)                                         |          |
| Prior stroke               | 0.020                                                       |                                                     |          |
| Yes                        | 279 (9.5%)                                                 | 114 (7.4%)                                          |          |
| Cancer                     | 0.012                                                       |                                                     |          |
| Yes                        | 342 (11.7%)                                                 | 219 (14.3%)                                         |          |
| Prior bleed                | 0.019                                                       |                                                     |          |
| Yes                        | 162 (5.5%)                                                 | 112 (7.3%)                                          |          |
| Beta blockers              | 0.79                                                        |                                                     |          |
| Yes                        | 969 (33.1%)                                                 | 513 (33.5%)                                         |          |
| Anti-arrhythmics           | 0.073                                                       |                                                     |          |
| Yes                        | 484 (16.5%)                                                 | 286 (18.7%)                                         |          |
| Calcium channel blockers   | 0.68                                                        |                                                     |          |
| Yes                        | 764 (26.1%)                                                 | 391 (25.5%)                                         |          |
| ATRIA score at admission§  | 0.18                                                        |                                                     |          |
| 0-5                        | 1500 (51.2%)                                                | 824 (53.8%)                                         |          |
| 6                          | 418 (14.3%)                                                 | 200 (13.1%)                                         |          |
| ≥7                         | 1010 (34.5%)                                                | 508 (33.2%)                                         |          |
| CHA₂DS₂-VASc score at admission‖ | 0.001                                                     |                                                     |          |
| 0                          | 168 (5.7%)                                                 | 134 (8.7%)                                          |          |
Patients with at least 9 months of continuous warfarin use

| Variable* | N (%)       | N (%)       | P value†  |
|-----------|-------------|-------------|-----------|
| 1         | 457 (15.6%) | 265 (17.3%) |           |
| ≥2        | 2303 (78.7%)| 1133 (74.0%)|           |

*Variables assessed at the beginning of the 15-month follow-up period.

†Univariate p values from chi-square tests.

‡Estimated glomerular filtration rate <45 ml/min/1.73m² or end stage renal disease.

§ATRIA risk score includes prior stroke, age, sex, diabetes, congestive heart failure, hypertension, proteinuria, and eGFR<45 or ESRD.36

‖CHA₂DS₂-VASc score includes congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA/thromboembolism, vascular disease, and sex.37