Variation in Warfarin Dose Adjustment Practice Is Responsible for Differences in the Quality of Anticoagulation Control Between Centers and Countries : An Analysis of Patients Receiving Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial

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Variation in Warfarin Dose Adjustment Practice Is Responsible for Differences in the Quality of Anticoagulation Control Between Centers and Countries

An Analysis of Patients Receiving Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial

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Background—The outcome of atrial fibrillation patients on warfarin partially depends on maintaining adequate time in therapeutic International Normalized Ratio range (TTR). Large differences in TTR have been reported between centers and countries. The association between warfarin dosing practice, TTR, and clinical outcomes was evaluated in Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial patients receiving warfarin.

Methods and Results—RE-LY provided an algorithm for warfarin dosing, recommending no change for in-range, and 10% to 15% weekly dose changes for out-of-range International Normalized Ratio values. We determined whether dose adjustments were consistent with algorithm recommendations but could not verify whether providers used the algorithm. Using multilevel regression models to adjust for patient, center, and country characteristics, we assessed whether algorithm-consistent warfarin dosing could predict patient TTR and the composite outcome of stroke, systemic embolism, or major hemorrhage. We included 6022 nonvalvular atrial fibrillation patients from 912 centers in 44 countries. We found a strong association between the proportion of algorithm-consistent warfarin doses and mean country TTR (R^2=0.65). The degree of algorithm-consistency accounted for 87% of the between-center and 55% of the between-country TTR variation. Each 10% increase in center algorithm-consistent dosing independently predicted a 6.12% increase in TTR (95% confidence interval, 5.65–6.59) and an 8% decrease in rate of the composite clinical outcome (hazard ratio, 0.92; 95% confidence interval, 0.85–1.00).

Conclusions—Adherence, intentional or not, to a simple warfarin dosing algorithm predicts improved TTR and accounts for considerable TTR variation between centers and countries. Systems facilitating algorithm-based warfarin dosing could optimize anticoagulation quality and improve clinical outcomes in atrial fibrillation on a global scale.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00262600.

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Key Words: atrial fibrillation ■ outcomes assessment ■ quality improvement ■ warfarin

Atrial fibrillation confers a 5-fold increased risk of stroke and systemic embolism, and vitamin K antagonists such as warfarin remain the most common anticoagulants used to reduce the risk of stroke. Warfarin has marked variability of pharmacokinetics and requires monitoring to maintain the plasma International Normalized Ratio (INR) within the therapeutic range, between 2.0 to 3.0.[1] A high time in therapeutic range (TTR) is associated with a lower risk of thromboembolic events and bleeding.[2,3] Several trials have reported large differences in TTR between centers and countries.[3–5] Reasons for this variation could include differences in patient characteristics or country socioeconomic and healthcare standards. Although anticoagulation clinics, patient self-management, and computerized warfarin management systems have been reported to improve TTR, and are recommended by the American College of Chest Physicians 2008 guidelines, most physicians continue to perform warfarin dose adjustment without such assistance.[6–8] Little attention has been paid to the clinical skill of the healthcare practitioner making warfarin dose adjustments in response to

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changes in the INR. The impact of dosing decisions on TTR is not understood and could explain the large variations in TTR.

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Clinical Perspective on p 2316

The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) multinational clinical trial provided an opportunity to study the impact of clinical skill in warfarin dosing on TTR. In RE-LY, 6022 patients receiving warfarin in 44 countries were followed for 2 years, with careful documentation of all INR results and concurrent warfarin dosing decisions. The purpose of our study was to establish the determinants of between-country and between-center variation in TTR and to evaluate the importance of warfarin dosing practice in predicting TTR and clinical outcomes in patients.

Methods

Evaluation of Warfarin Dosing Practice and TTR

This study used data on patients receiving dose-adjusted warfarin in the RE-LY trial who had nonvalvular atrial fibrillation and risk factors for stroke.[9] The RE-LY trial was approved by an institutional review committee, and informed consent was obtained from all patients. The trial protocol specified that investigators manage warfarin according to local practice with the following provisions: the target INR was 2.0 to 3.0 (except in Japan, where it was 2.0–2.5), and the maximum interval between INR tests was 4 weeks. A warfarin dosing algorithm was provided to investigators and its use was encouraged, although not mandated; the goal of the algorithm was to optimize warfarin dosing decisions, particularly in countries in which vitamin K antagonists other than warfarin were typically used. The algorithm recommended an increase, decrease, or no change in the weekly warfarin dose based only on the current INR. The algorithm recommended that the dose be calculated on a weekly, rather than daily, basis because the recommended dose changes were small and difficult to achieve with daily dosing. For example, a patient with a weekly dose of 30 mg would take 5 mg on 5 of 7 days of the week and 2.5 mg on 2 days. A 10% dose increase would raise the weekly dose to 33 mg, which would lead to a dose instruction of 5 mg per day on 6 of 7 days of the week, with 2.5 mg on 1 day. The algorithm dose recommendations were as follows: no change for INR 2.00 to 3.00; +15% change for INR ≤1.50, +10% for INR 1.51 to 1.99, −10% for INR 3.01 to 4.00. For INR 4.00 to 4.99, the recommendation was to hold the dose for 1 day and then reduce it by 10%. For INR 5.00 to 8.99, the dose was to be held until the INR was therapeutic and then decreased by 15% per week. Weekly INR monitoring was recommended for out-of-range INR values. Centers received regular feedback about the TTR in their RE-LY warfarin patients.

This analysis assessed the warfarin dose modification documented in response to each INR result to determine whether it was algorithm-consistent, defined as within 5% of the dose recommended by the algorithm. Algorithm consistency was expressed as the percentage (%) of total dose instructions consistent with the algorithm in each patient. The analysis did not distinguish between whether physicians actually used the dosing algorithm or not, but whether their dose adjustments were algorithm-consistent or not. TTR was determined using the method of linear interpolation between consecutive INR values in each patient,[10] excluding values during discontinuation of warfarin or within 7 days of warfarin initiation or recommencement.

Weighted Linear Regression

Mean country algorithm-consistent dosing and TTR were calculated by averaging the values obtained from patients in each country, and reported with standard deviations (SD). A linear regression model, weighted by the number of patients per country, was developed with mean country algorithm-consistency as a predictor and mean country TTR as the outcome. A coefficient of determination (R^2) was calculated using the least squares method.

Multilevel Linear Regression

To avoid false inferences from single-level models that ignore the correlation of outcomes within centers and countries,[11–14] a multilevel, multivariable linear regression model, with patients (1st level) nested in centers (2nd level), and centers nested in countries (3rd level), was developed for the outcome of patient TTR. Patient-level characteristics included age (years); weight (kg); sex (male versus female); race (white versus other); current smoking status (yes versus no); past history of heart failure (yes versus no), hypertension (yes versus no), diabetes mellitus (yes versus no), or stroke (yes versus no); previous warfarin use (yes versus no); current amiodarone use (yes versus no); and current insulin use (yes versus no).

Center-level characteristics included specialty (anticoagulation clinic versus other), setting (secondary/tertiary hospital versus primary), and mean algorithm-consistent warfarin dosing (%). Algorithm-consistency was analyzed as a center-level variable because although warfarin dosing was tracked in individual patients, dosing was performed by healthcare professionals at centers.

Country-level characteristics included the 2006 country Gross Domestic Product (high versus medium/low), Disability Adjusted Life Expectancy (years), and Health System Performance Index. The latter 2 are measures used by the World Health Organization to quantify the performance of health systems.[15] The Health System Performance Index, a measure of health system efficiency, is the ratio between actual gains in Disability Adjusted Life Expectancy and the maximum potential gains in Disability Adjusted Life Expectancy achievable with per capita health expenditure.

Sensitivity Analysis

To better understand the way in which deviations from the algorithm were occurring, we created separate multilevel linear regression models for in-range and out-of-range INRs. Intercept and risk estimates, along with P values, were determined using the χ^2 test in MLwiN [v 2.0] (University of London, London, UK).

Analysis of Proportion of Variance Explained

A 3-level null model (ie, without predictor variables) was developed with patient at the 1st level, center at the 2nd, and country at the 3rd; this was done to partition the total TTR variance in the study population into a between-patient, between-center, and between-country variance. Residual, between-center, and between-country TTR variances were estimated using the Iterated Generalized Least Squares method in MLwiN [v 2.0] (University of London, London, UK). Variables were sequentially added to the model to determine their contribution to TTR variance in the following order: center mean algorithm-consistent dosing (%), all patient variables, the remaining center variables, and all country variables. The proportional change in TTR variance (PCV) across centers and countries was calculated for each set of variables using the formula $PCV=(V_0-V_1)/V_0$, where V_0 is the null variance at the country or center level and V_1 is the country or center level residual variance after adjusting for each variable set.[12] Variances were presented with standard errors and P values based on the χ^2 test. The country and center intracluster correlation coefficients were calculated using the formula V/(V+residual variance) where $V=V_0$ or V_1.[11] The intracluster correlation coefficient is a measure of clustering or within-group correlation and ranges from 0 to 1; it is a ratio of the between-group variance to the within-group+between-group variance. A high intracluster correlation coefficient implies high within-group correlation.[16]

Multilevel Cox Proportional Hazards Model for Clinical Outcomes

Previously reported definitions for stroke, systemic embolism, and major hemorrhage were used.[9] A 2-level Cox proportional hazards model was fitted for the composite outcome of stroke, systemic embolism, or major hemorrhage. In this model, patients (1st level) were nested in centers (2nd level), and adjustments were made for the within-country correlation in time to composite clinical outcome. Individual hazard ratios (HRs) with 95% confidence intervals (CI)

were obtained from the β-coefficient (standard error) in the fixed part of the model. In addition to the patient-, center-, and country-level variables used in the linear regression model, 4 additional patient-level variables were added to the Cox proportional hazards model on the basis of clinical relevance to the outcome: baseline use of aspirin (yes versus no), β-blockers (yes versus no), ace-inhibitors (yes versus no), or statins (yes versus no). For patients who experienced stroke, systemic embolism, or major hemorrhage, % algorithm-consistent dosing was calculated using warfarin prescriptions before the outcome; for other patients, it was calculated using all warfarin prescriptions during the study. Mean % algorithm-consistency was then calculated for each center and analyzed as a center-level variable. TTR was not included as a covariate because it is believed to be on the causal pathway between warfarin dosing and clinical outcomes.[17,18]

The multilevel Cox proportional hazards analysis was refitted among RE-LY patients on dabigatran to assess whether algorithm consistency at centers could independently predict outcomes among nonwarfarin patients. This was to explore whether algorithm consistent dosing at centers was a marker of generalized high quality care, independent of its influence on warfarin control.

Analysis of Optimal Warfarin Dosing Strategy

Recent guidelines for anticoagulation recommend against adjusting warfarin doses when INR values are slightly out of range.[19] To establish whether there is clinical utility in altering the warfarin dose rather than leaving it unchanged for slightly out-of-range INR values, we performed sensitivity analyses of varying warfarin dose regimens. Using the multilevel regression models described above, we examined TTR and the composite outcome of stroke, systemic embolism, or major hemorrhage when warfarin doses were held steady for the following INR ranges: 1.9 to 3.1, 1.8 to 3.2, 1.7 to 3.3, and 1.6 to 3.4.

Multilevel linear regression was performed using MLwiN [v 2.0]. Other analyses were performed using SAS [v 9.1] (Carey, North Carolina).

Results

Our primary analysis included 6022 atrial fibrillation patients randomized to warfarin from 912 centers and 44 countries. Patient, center, and country characteristics are shown in Table 1. Patients were predominantly (77%) managed at primary care centers, with a minority (15%) managed at anticoagulation clinics. 55% of patients were treated in high–Gross Domestic Product countries, and 39% in countries with a Health Systems Performance Index of >0.8.

The mean (SD) duration of patient follow-up was 715 (214) days, and the median (interquartile range) was 729 (305) days. Mean (SD) monthly frequency of INR measurements was 1.6 (1.3), and mean (SD) TTR was 64 (20)%. Mean (SD) time below and above therapeutic INR range was 22 (19%) and 13 (13)%, respectively. There was considerable regional variation in both TTR and the % of algorithm-consistent warfarin dosing decisions (Table 2). The mean (SD) TTR ranged from a low of 54 (21)% in East Asia to 73 (15)% in North Europe. Mean (SD) percentage of algorithm-consistent warfarin dose changes ranged from a low of 55 (21)% in East Asia to 68 (17)% in North Europe. Deviations from algorithm-consistent dosing were not limited to changing the dose by >5% of the algorithm recommendation when the INR was out of range; they also included altering the warfarin dose when the INR was in range. There was a strong positive association (R^2=0.65) between the % of algorithm-consistent warfarin dose adjustments and TTR at the country level (Figure).

TTR Variation

The 3-level null model partitioned the total population TTR variance into between-patient, between-center, and between-country variances. The country intracluster correlation coefficient of 11.9% in the null model indicated the within-country TTR variation far exceeded the between-country TTR variation. When center mean algorithm-consistent warfarin dosing was added to the model, the between-center and between-country TTR variance decreased by 87% and 55%, respectively (Table 3), indicating that warfarin dosing practice explained 87% of the between-center and 55% of the between-country TTR variation. Collectively, patient-level variables explained an additional 1% of the between-center and 20% of the between-country TTR variance. Our model explained a total of 89% of the between-center and 86% of the between-country TTR variance. A small, significant between-center (P=0.02) and between-country (P=0.01) variance remained after all variables were adjusted for, reflecting persistent, unexplained differences in TTR between centers and countries.

Predictors of TTR

After adjusting for patient, center, and country characteristics in the multilevel model, algorithm-consistent dosing was a strong predictor of TTR. Each 10% increase in algorithm-consistent dosing at the center level predicted a 6.12% increase in TTR (95% CI, 5.65–6.59; P<0.001). Independent patient-level predictors of TTR were male sex (1.37% increase in TTR; 95% CI, 0.30–2.45; P=0.01), white race (2.27% increase in TTR; 95% CI, 0.72–3.82; P=0.004), age (0.07% decrease in TTR per year increase in age; 95% CI, −0.13–0.00; P=0.03), smoking (3.70% decrease in TTR; 95% CI, −5.57 to −1.82%; P<0.001), heart failure (2.70% decrease in TTR; 95% CI, −3.81 to −1.60%; P<0.001), previous warfarin use (3.63% increase in TTR; 95% CI, 2.63–4.62%; P<0.001), and current amiodarone use (2.11% decrease in TTR; 95% CI, −3.66 to −0.56; P=0.008; Table 4). Center algorithm-consistent dosing was a strong independent predictor of TTR (P<0.001), irrespective of whether INR was in range (where the algorithm recommends no change) or out of range (where a 10%–15% dose change is recommended). Other center-level variables, including center specialty (anticoagulation clinic versus other), did not independently predict TTR. Country-level variables did not independently predict TTR.

Predictors of the Composite Clinical Outcome

In the multi-level multivariable Cox proportional hazards model, algorithm-consistent dosing was an independent predictor of the composite outcome of stroke, systemic embolism, or major hemorrhage. A 10% increase in algorithm-consistent dosing at the center-level was associated with an 8% lower annual rate of the composite outcome (HR, 0.92; 95% CI, 0.82–1.00; P=0.05). Patient factors that predicted an increased annual rate of the combined clinical end point included increasing age (HR, 1.04 per year; 95% CI, 1.02–1.05; P<0.001), a history of smoking (HR, 1.48; 95% CI, 1.06–2.07; P=0.02), previous stroke (HR, 1.34; 95% CI, 1.02–1.75; P=0.03), insulin use (HR, 1.75; 95% CI, 1.19–2.58; P=0.005), and baseline use of aspirin (HR, 1.28; 95% CI, 1.04–1.56; P=0.02). Patient factors that independently predicted a lower annual rate of combined clinical end points

Table 1. Baseline Characteristics of Patients, Centers, and Countries

Characteristics	No. of Patients in RE-LY (%) n=18 113	No. of Patients in Substudy (%) n=6022	No. of Centers in Substudy (%) n=912	No. of Countries in Substudy (%) n=44
Patient-level				
Sex				
Male	11 514 (63.6)	3809 (63.2)	. . .	. . .
Female	6599 (36.4)	2213 (36.8)	. . .	. . .
Age				
≥75 y	7238 (40.0)	2423 (40.2)	. . .	. . .
<75 y	10 875 (60.0)	3599 (59.8)	. . .	. . .
Weight				
≥85 kg	7410 (40.9)	2475 (41.1)	. . .	. . .
<85 kg	10 703 (59.1)	3547 (58.9)	. . .	. . .
Race				
White	12 679 (70.0)	4203 (69.8)	. . .	. . .
Other	5434 (30.0)	1819 (30.2)	. . .	. . .
Current smoking				
Yes	1335 (7.4)	448 (7.4)	. . .	. . .
No	16 778 (92.6)	5574 (92.6)	. . .	. . .
Heart Failure				
Yes	5793 (32.0)	1922 (31.9)	. . .	. . .
No	12 320 (68.0)	4100 (68.1)	. . .	. . .
Hypertension				
Yes	14 283 (78.9)	4750 (78.9)	. . .	. . .
No	3830 (21.1)	1272 (21.1)	. . .	. . .
Diabetes mellitus				
Yes	4221 (23.3)	1410 (23.4)	. . .	. . .
No	13 892 (76.7)	4612 (76.6)	. . .	. . .
Previous stroke				
Yes	2273 (12.5)	756 (12.5)	. . .	. . .
No	15 840 (87.5)	5266 (87.5)	. . .	. . .
Previous warfarin use				
Yes	8984 (49.6)	2929 (46.9)	. . .	. . .
No	9129 (50.4)	3093 (53.1)	. . .	. . .
Current amiodarone use				
Yes	1933 (10.7)	657 (10.9)	. . .	. . .
No	16 180 (89.3)	5365 (89.1)	. . .	. . .
Current insulin use				
Yes	802 (4.4)	271 (4.5)	. . .	. . .
No	17 311 (95.6)	5751 (95.5)	. . .	. . .
Center-level				
Hospital type				
Secondary/tertiary	4203 (23.2)	1399 (23.2)	195 (21.4)	. . .
Primary	13 910 (76.8)	4623 (76.8)	717 (78.6)	. . .
Anticoagulation clinic				
Yes	2694 (14.9)	901 (15.0)	139 (15.2)	. . .
No	15 419 (85.1)	5121 (85.0)	773 (84.8)	. . .
Country-level				
Gross Domestic Product				
High	9996 (55.2)	3323 (55.2)	. . .	14 (31.8)
Medium/Low	8117 (44.8)	2699 (44.8)	. . .	30 (68.2)

(*Continued*)

Table 1. Continued

Characteristics	No. of Patients in RE-LY (%) n=18 113	No. of Patients in Substudy (%) n=6022	No. of Centers in Substudy (%) n=912	No. of Countries in Substudy (%) n=44
Disability Adjusted Life Expectancy*				
≥70	11 689 (64.5)	3888 (64.6)	. . .	16 (36.4)
<70	5590 (30.9)	1857 (30.8)	. . .	22 (50.0)
Health Systems Performance Index*				
≥0.8	7023 (38.8)	2339 (38.8)	. . .	18 (40.9)
<0.8	10 256 (56.6)	3406 (56.6)	. . .	20 (45.4)

*Data unavailable for 6 of 44 countries.

included weight (HR, 0.99 per kg; 95% CI, 0.99–1.00; $P=0.02$) and white race (HR, 0.73; 95% CI, 0.58–0.91; $P=0.006$). Country-level characteristics did not predict clinical outcomes.

Because the influence of warfarin dosing on clinical outcomes is likely mediated through INR control, TTR was not included as a covariate in the Cox proportional hazards model analysis of clinical outcomes.[17,18] However, the association between TTR and clinical outcomes was confirmed in a separate multi-level multivariable model that included all previous variables except center algorithm-consistence; in this model, a 10% increase in TTR independently predicted a 20% lower rate ($P<0.001$) of the composite clinical outcome among patients on warfarin. To assess whether algorithm consistency in centers was a marker of generalized higher quality care, we explored the relationship between center-level algorithm consistent warfarin dosing and rate of composite stroke, systemic embolism, or major hemorrhage in patients on dabigatran (n=8014) and found no association (HR, 1.00; 95% CI, 0.99–1.01; $P=0.76$).

Analysis of Optimal Warfarin Dosing Strategy

Algorithm-consistent dosing remained an independent predictor of TTR when warfarin doses were unchanged for slightly out-of-range INRs ($P<0.0001$). However, the strength of association between algorithm consistency and TTR decreased progressively as the acceptable INR range for no dose change widened. Adherence to algorithms that did not change the warfarin dose for INRs 1.9 to 3.1, 1.8 to 3.2, 1.7 to 3.3, and 1.6 to 3.4, predicted a 6.05% (95% CI, 5.53–6.57), 5.98% (95% CI, 5.42–6.54), 5.82% (95% CI, 5.23–6.40), and 5.25% (95% CI, 4.63–5.87) increase in TTR, respectively (per 10% increase in algorithm-consistent dosing). Algorithm-consistent dosing did not independently predict the composite clinical outcome when the algorithm specified no dose change for slightly out-of-range INR values ($P\geq0.6$ for INR ranges 1.9–3.1, 1.8–3.2, 1.7–3.3, and 1.6–3.4).

Discussion

The major finding of this study is that clinical skill in warfarin dosing decisions is an important determinant of TTR, accounting for most of the variation between countries and centers. Clinical skill was measured by the extent to which warfarin dosing was consistent with a simple algorithm, which specified no dose change if the INR was in range and small (10%–15%) dose changes if the INR was out of range. Algorithm consistency had a large impact on TTR. Both not changing the dose when the INR was in range and changing by small amounts when the INR was out of range independently predicted improved TTR.

In RE-LY and the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) study,[4] many centers and countries achieved a TTR that was below the accepted standard of at least 65% time in range.[20] The present study indicates that, to a considerable extent, this is a result of suboptimal warfarin dose adjustment decisions. The degree of algorithm-consistent warfarin dosing explained

Table 2. Algorithm-Consistent Warfarin Dosing and Time in Therapeutic Range (TTR) by Region

Sub-Continent (No. of Countries, Centers)	No. of Patients (% Total)	Mean (SD) Frequency of INR Checks per Month	Mean (SD) % Algorithm-Consistence	Mean (SD) TTR	Mean (SD) % Time INR<2	Mean (SD) % Time INR>3
North America (2, 401)	2167 (36.0)	1.7 (1.2)	64.31 (17.2)	66.9 (17.0)	19.2 (15.1)	13.9 (11.2)
Central/South America (5, 42)	316 (5.2)	1.5 (1.6)	64.83 (21.8)	61.3 (22.6)	23.8 (21.9)	14.8 (15.7)
Northern Europe (5, 57)	417 (6.9)	1.5 (0.7)	68.09 (17.3)	73.5 (14.6)	13.2 (11.3)	13.3 (11.5)
Western Europe (6, 105)	899 (14.9)	1.8 (1.7)	61.57 (20.2)	68.0 (19.0)	15.7 (16.1)	16.3 (15.7)
Southern Europe (4, 45)	236 (3.9)	1.7 (2.2)	57.79 (22.0)	63.9 (21.6)	23.7 (21.7)	12.3 (11.9)
Eastern Europe (8, 82)	699 (11.6)	1.3 (1.3)	59.89 (21.6)	61.3 (21.9)	26.2 (21.4)	12.5 (13.5)
Africa (1, 9)	55 (0.9)	1.4 (0.6)	57.74 (17.4)	58.0 (19.5)	23.9 17.2)	18.1 (15.3)
Western Asia (2, 32)	236 (3.9)	2.0 (1.7)	54.9 (19.6)	62.6 (18.5)	24.6 (17.7)	12.8 (10.9)
South East Asia (5, 39)	375 (6.2)	1.4 (0.7)	56.5 (21.9)	54.6 (22.0)	32.4 (21.7)	13.0 (11.5)
Eastern Asia (5, 90)	551 (9.1)	1.2 (0.6)	55.5 (21.2)	54.3 (21.8)	37.5 (22.7)	8.2 (9.2)
Australia (1, 10)	71 (1.2)	1.8 (0.5)	69.5 (17.5)	74.0 (15.9)	15.8 (15.5)	10.2 (8.0)
Total (44, 912)	6022 (100.0)	1.6 (1.3)	61.8 (19.8)	64.4 (19.8)	22.2 (19.1)	13.4 (12.6)

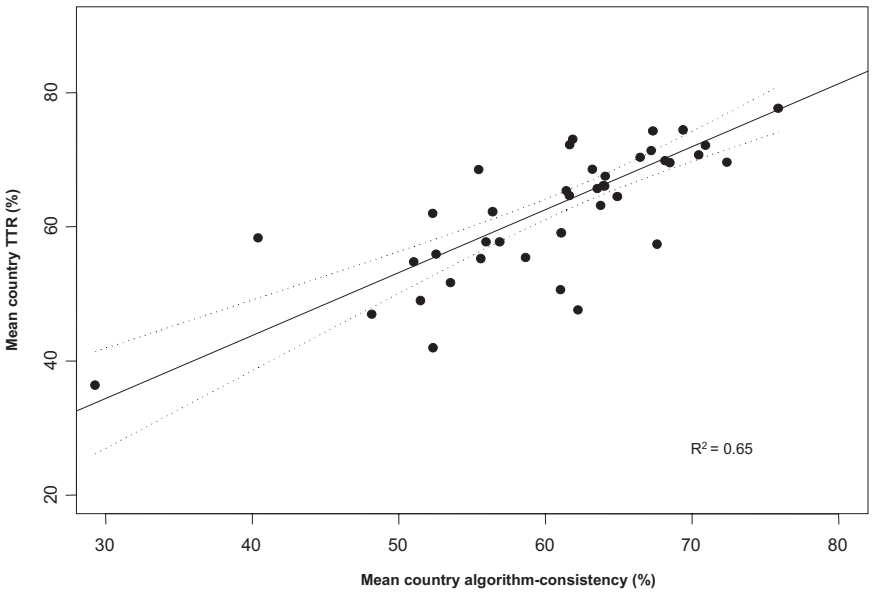

Figure. Weighted linear regression of the association between mean country algorithm-consistency and mean country time in therapeutic range (TTR). Mean country algorithm-consistent dosing and TTR were calculated by averaging the values obtained from patients in each country. The regression model was weighted by the number of patients per country. Each data point represents a single country. R^2 is the coefficient of determination.

58% of the between-country and 87% of the between-center TTR variation, and algorithm consistent dosing independently predicted improvements in patient TTR.

We also observed that skill in warfarin dosing, as measured by algorithm-consistency, was an independent predictor of the composite clinical outcome of stroke, systemic embolism, and major bleeding among patients on warfarin. Although it would have been ideal to separate the outcomes related to the efficacy of warfarin from those related to its safety (in particular, intracerebral hemorrhage), our study was underpowered to do so.

The relationship between algorithm-consistency and clinical outcomes suggests a possible causal relationship but could also be a result of an association between improved anticoagulation control and better overall medical care. However, we did not observe an association between algorithm-consistent warfarin dosing and clinical outcomes in patients treated with dabigatran at the same centers. This supports the idea that algorithm-consistency is not merely a marker for overall improved health care delivery.

This study did not separate out how the algorithm consistency was achieved, and many methods are possible. Dosing recommendations similar to those in the RELY algorithm are commonly made in clinical practice, guided by physician experience, computerized warfarin management systems, or other algorithms and nomograms.[6–8,21] There may be other algorithms for warfarin dose adjustment that give better INR control than the one used in RE-LY. Current guidelines suggest that for INR values slightly out of range, the warfarin dose should not be altered but merely reassessed within 1 to 2 weeks, because this may be more effective than adjusting the dose.[19] We found that the strength of association between

Table 3. Multi-Level Analysis of TTR Variance at the Center and Country Level

3-Level Models	Adjusted Variables	Between-Center Variance (SE, *P* Value)	% Between-Center Variance Explained	Within-Center ICC*	Between-Country Variance (SE, *P* Value)	% Between-Country Variance Explained	Within-Country ICC*
Model 1	Null model (no variables)	49.6 (5.6, <0.001)	Ref	0.143	46.8 (13.1, <0.001)	Ref	0.119
Model 2	Center algorithm-consistency (%)	6.3 (2.5, 0.01)	87%	0.021	21.1 (6.1, <0.001)	55%	0.066
Model 3	Center algorithm-consistency+Patient† variables	6.0 (2.4, 0.01)	88%	0.020	11.8 (3.8, 0.002)	75%	0.039
Model 4	All patient†+center‡ variables	5.8 (2.4, 0.02)	88%	0.020	11.9 (3.8, 0.002)	75%	0.039
Model 5	Patient†+center‡+country§ variables	5.7 (2.4, 0.02)	89%	0.020	6.7 (2.5, 0.008)	86%	0.023

The 3-level model comprised patient, center, and country levels. The 3 null model (Model 1) partitioned the total population TTR variance into between-patient, between-center, and between-country components. Variables were sequentially added to the null model to determine their contribution to TTR variance in the following order: center mean algorithm-consistent dosing (Model 2), all patient variables (Model 3), the remaining center variables (Model 4), and all country variables (Model 5).

*ICC indicates intra-cluster correlation coefficient.

†Patient variables included age, weight, sex, smoking status, heart failure, hypertension, diabetes mellitus, stroke, previous warfarin use, amiodarone use, and insulin use.

‡Center variables included algorithm-consistency of warfarin dosing, level of expertise, and specialty of clinic.

§Country variables included Gross Domestic Product, Disability Adjusted Life Expectancy, and Health System Performance Index.

Table 4. Multi-Level Multivariable Linear Regression Model for the Outcome of Patient TTR in Patients With AF on Warfarin

Characteristics	Adjusted Change in Mean TTR	95% Confidence Intervals	*P* Value
Patient-level			
Age (per year)	−0.07	−0.13, 0.00	0.0317
Weight (per kg)	0.03	0.00, 0.06	0.0987
Male (yes vs no)	1.37	0.30, 2.45	0.0121
White	2.27	0.72, 3.82	0.0041
Current smoker	−3.70	−5.57, −1.82	0.0001
History of heart failure	−2.70	−3.81, −1.60	<0.0001
History of hypertension	−0.39	−1.60, 0.81	0.5250
History of diabetes mellitus	−1.74	−2.97, −0.50	0.0058
Previous stroke	−1.11	−2.60, 0.38	0.1442
Previous warfarin use	3.63	2.63, 4.62	<0.0001
Current amiodarone use	−2.11	−3.66, −0.56	0.0077
Current insulin use	−2.36	−4.83, 0.12	0.0626
Center-level			
Algorithm-consistent dosing (per 10%)	6.12	5.65, 6.59	<0.0001
Secondary/tertiary hospital	0.65	−0.84, 2.15	0.3916
Anticoagulation clinic	1.02	−0.48, 2.52	0.1829
Country-level			
High GDP	1.22	−1.56, 4.00	0.3897
Disability Adjusted Life Expectancy	0.39	−0.05, 0.83	0.7506
Health System Performance Index	−3.36	−24.09, 17.38	0.0820

algorithm-consistency and TTR decreased progressively as the acceptable INR range for no warfarin dose change widened. Furthermore, there was no significant association between algorithm-consistent dosing and clinical outcomes when the warfarin dose was unchanged for slightly out-of-range INR values. These findings suggest that it may be preferable to adjust warfarin dose when INR values are slightly out of range. However, our study did not have an optimal design to establish the most effective warfarin-dosing algorithm for INR control, and further research is required to determine the best dosing strategy for slightly out-of-range INR values. This does not diminish the findings of our primary analyses, which show that adherence to a simple algorithm like the one used in RE-LY is associated with improved INR control and appears to be an easy, reliable, and cost-effective way to achieve good INR control.

Country-level characteristics accounted for only 11% of intercountry TTR variation in the unadjusted model, and neither predicted TTR nor the composite clinical outcome in the adjusted models. These findings are compatible with studies in coronary artery disease that demonstrate that international variations in clinical outcomes in myocardial infarction are not explained by country characteristics.[12]

Some countries typically use vitamin K antagonists other than warfarin, and we found a modest time-delay in achieving good INR control in these countries; for example, Argentina, Netherlands, Germany, and Belgium lagged several months in INR control, with lower initial TTR values than later in the study. However, these countries had better than average TTRs by the end of the study, with values of 69.5, 70.2, 67.8, and 65.5 for Argentina, Netherlands, Germany and Belgium, respectively. Comparable western countries that exclusively used warfarin such as Canada, United States, Sweden, and United Kingdom had similar INR control (70.9, 66.0, 77.0, and 71.7 TTR, respectively). There was no systematic difference in warfarin-experienced and warfarin-naïve countries at study completion.

The sum of all variables in our model accounted for 87% of the between-country and 89% of the between-center variance in TTR, leaving only a relatively small amount of unexplained variation. These data suggest that differences in patient characteristics not measured in this study have only a modest impact on between-country and between-center TTR variation. Support systems that facilitate algorithm-based warfarin dosing may have greater value in minimizing regional variations in anticoagulation quality than dosing approaches guided by individual patient characteristics.

Limitations

Our multi-level model did not account for the contribution of individual healthcare providers to between-center and between-country TTR variation. Whereas warfarin dosing decisions were made by healthcare providers, centers sometimes had multiple providers who shared the care of patients. We were unable to analyze algorithm-consistence at the level of the individual provider because data were captured at the level of the patient. Because the data for this analysis were collected as part of a clinical trial, it is likely that our results underestimate not only the variation in TTR that exists between centers and countries but also the association between algorithm-consistent warfarin dosing and clinical outcomes.

Summary

Warfarin dose adjustment practice that does not change the dose when the INR is in range, and that makes relatively small (10%–15%) weekly dose adjustments for the majority of INRs out of range, is a simple concept that is associated with improved TTR and clinical outcomes. Systems that implement algorithm-based dosing for patients with atrial fibrillation on warfarin could potentially improve outcomes, especially in centers and countries with suboptimal INR control.

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CLINICAL PERSPECTIVE

The outcome of atrial fibrillation patients on warfarin partially depends on maintaining adequate time in therapeutic International Normalized Ratio (INR) range (TTR). Large differences in TTR have been reported between centers and countries, but the reasons are unclear. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, a warfarin dosing algorithm provided to participating centers recommended no change for in-range and 10% to 15% weekly dose changes for out-of-range INR values. We determined whether algorithm-consistent warfarin dosing could predict patient TTR and the composite outcome of stroke, systemic embolism, or major hemorrhage. Among 6022 nonvalvular atrial fibrillation patients from 44 countries, we found a strong association between the proportion of algorithm-consistent warfarin doses and mean country TTR (R^2=0.65). The degree of algorithm-consistent warfarin dosing accounted for a majority of the TTR variation between centers and countries. Each 10% increase in center algorithm-consistent dosing independently predicted a 6.12% increase in TTR (95% confidence interval, 5.65–6.59), and an 8% decrease in rate of the composite clinical outcome (hazard ratio, 0.92; 95% confidence interval, 0.85–1.00). In summary, warfarin dosing practice that does not change the dose when the INR is in range, and that makes relatively small (10%–15%) weekly dose adjustments when the INR is out of range, is associated with improved TTR and clinical outcomes. Systems that implement algorithm-based dosing for patients with atrial fibrillation on warfarin could potentially improve outcomes on a global scale, especially in centers and countries with suboptimal INR control.