Improving Quality Measurement for Anticoagulation
Adding International Normalized Ratio Variability to Percent Time in Therapeutic Range

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Background—Among patients receiving warfarin, percent time in therapeutic range (TTR) and international normalized ratio (INR) variability predict adverse events individually. Here, we examined what is added to the prediction of adverse events by using both measures together.

Methods and Results—We included 40404 patients anticoagulated for atrial fibrillation, aged 65+, within the Veterans Health Administration. TTR and log-transformed INR variability were calculated for each patient. Our study outcomes were ischemic stroke and major bleeding, defined using International Classification of Diseases-9 codes. We estimated the hazard ratios (HRs) for the study outcomes using 3 nested Cox regression models, including (1) TTR or log INR variability separately; (2) TTR and log INR variability together; and (3) both predictors together plus an interaction term. We divided TTR into 3 categories (high, >70%; moderate, 50% to 70%; low, <50%) and log INR variability into 2 categories (stable and unstable). The reference groups high TTR and stable anticoagulation each denote good control.

Higher log INR variability (ie, unstable control) predicted ischemic stroke (HR=1.45, P<0.001) and major bleeding (HR=1.57, P<0.001) independently, regardless of TTR levels. Our model with interaction terms showed that High log INR variability predicted a significantly higher risk for ischemic stroke and major bleeding compared with low log INR variability, at moderate TTR levels (HR= 1.27 and HR=1.29, respectively) and at high TTR levels (HR=1.55 and HR=1.56, respectively); but not at low TTR levels.

Conclusions—Unstable anticoagulation predicts warfarin adverse effects independent of TTR. Moreover, knowledge about anticoagulation stability further stratifies the risk for adverse events at given levels of TTR. (Circ Cardiovasc Qual Outcomes. 2014;7:00-00.)

Key Words: anticoagulants ■ healthcare quality ■ international normalized ratio ■ outcome ■ warfarin

One pillar in assessing quality of care is a reliable, measurable, intermediate outcome that serves as a surrogate for definitive outcomes, such as stroke, major bleeding, or death. Previous studies have shown that time in therapeutic range (TTR) strongly predicts both bleeding and thromboembolic events, leading to adoption of TTR as a widely used intermediate outcome measure. The most widely used method to calculate TTR is the Rosendaal method, which uses linear interpolation to assign an international normalized ratio (INR) value to each day between INR measurements over a prolonged interval.

Other measures of INR control, such as INR variability as calculated by Fihn’s method, have also been shown to predict definitive outcomes. Indeed, in a study, INR variability predicted events even more strongly than TTR. This measure is calculated as a time-weighted variance of the INR around the target INR and reflects the degree to which a patient-achieved INR deviates from his or her target INR or previous INR measurements.

TTR and INR variabilities measure different characteristics of anticoagulation control. TTR reflects the achievement of appropriate intensity, and not necessarily the stability, of the anticoagulation regimen. Conversely, INR variability measures stability, but not intensity, of anticoagulation. One approach to strengthen our prediction about warfarin adverse events would be to combine these measures. Whether the use of both measures jointly will improve risk stratification for ultimate outcomes of interest, such as thrombotic events, bleeding events, or mortality, requires further exploration.

Our study aimed to test whether using both measures will more accurately assign risk of warfarin therapy complications, such as ischemic strokes and major bleeding, among patients with atrial fibrillation. Improving intermediate outcome measures in anticoagulation will allow a more accurate reflection of the true quality of care received by patients.
WHAT IS KNOWN?

- Percent time in therapeutic range (TTR) and international normalized ratio (INR) variabilities measure different aspects of warfarin anticoagulation control. TTR is a measure of anticoagulation intensity, whereas INR variability is a measure of anticoagulation stability.
- TTR and INR variability have each been shown to predict warfarin-related adverse events, but little is known about whether using both measures would predict such events better than only 1 of them.

WHAT THE STUDY ADD?

- Patients with unstable anticoagulation (ie, high INR variability) had an increased hazard for warfarin-related adverse effects, despite similar levels of TTR.
- Achievement of high TTR may not protect patients unless stability of INR (ie, low INR variability) is also achieved.

Methods

Data Collection

The database for this study has been described elsewhere. The Veterans Affairs study to Improve Anticoagulation included all patients deemed to be receiving warfarin anticoagulation therapy from the Veterans Health Administration between October 1, 2006, and September 30, 2008. We used a merged Veterans Administration-Medicare database to maximize the likelihood of capturing all relevant events and complications related to warfarin therapy. The study was approved by the Institutional Review Board of the Bedford VA Medical Center.

Patients

We included all patients who have atrial fibrillation based on International Classification of Diseases-9 codes, aged ≥65, who did not enroll in Medicare Advantage plans. Patients with Medicare Advantage plans were excluded because they would not produce itemized claims data, leading to undercounting of events.

Laboratory Values and Calculation of Percent Time in Range and INR Variability

We included INR values within the VA system when patients were on warfarin, that is, when a patient was either (1) in possession of warfarin or (2) having INR tests at least every 42 days. We defined the period of warfarin possession as the duration of the most recent VA prescription for warfarin, plus 30 days. Because patients may be instructed to take half-doses of warfarin, we recognize that going >30 days beyond the end of prescription does not necessarily indicate that warfarin therapy has stopped. We therefore allowed a consistent pattern of INR measurements (ie, every 42 days or less) to indicate that a patient was still being managed.

We excluded INR tests measured while the patient was hospitalized within the VA system. Patients who are hospitalized may receive temporary parenteral anticoagulation (eg, with heparin) or no anticoagulation, and so out-of-range INR values while hospitalized may be intentional and do not necessarily reflect poor anticoagulation control.

We calculated TTR using Rosendaal’s method, which uses linear interpolation to assign an INR value to each day between successive observed INR values. Gaps of 56 days or more between INR values are not interpolated. After interpolation, we calculated the percentage of time during which the interpolated INR values lie between 2.0 and 3.0 (from 0% to 100%). We then divided patients into 3 groups: high TTR (>70%), moderate TTR (50%–70%), and low TTR (<50%). Such approach reflects the distribution of patients in our sample and balances the number of patients at each group, allowing sufficient examination of events at each category.

INR variability was calculated using Fihn’s method, which reflects the degree to which a patient’s INR deviates from the previous one. This formula does not take into account the intensity of warfarin therapy: a patient is most stable if his or her INRs are around the same level even if the INR is constantly above or below the limits of the target range. For example, a patient with log INR variability of −5.0 has a much more stable anticoagulation regimen compared with another patient with a log INR variability of −0.75. We log-transformed INR variability to reduce the leverage and undue influence of extreme observations on our estimates. We dichotomized log INR variability using a cut-off of −2.64 to define groups of high versus low anticoagulation stability, where lower values indicate a more stable regimen.

Primary Outcomes

The main outcomes for this study were ischemic stroke, major bleeding, and fatal bleeding, which is the subset of major bleeding where death occurred within 30 days. Death was assessed using the VA Vital Status Mini-File, which is known to be an accurate source for date of death.

We have previously described our methods for identifying major bleeding with this data set. Briefly, we began with all ICD-9 codes that might describe a hemorrhagic event and then retained the events that fulfilled 1 of 4 criteria: fatal hemorrhage, bleeding into a critical anatomic site, bleeding associated with transfusion, or bleeding which was identified as the main reason for a hospital stay. This is an adaptation of the definition of major bleeding of the International Society of Thrombosis and Haemostasis to a large, automated data set.

Ischemic strokes were also defined using ICD-9 codes. We used a restrictive set of codes to define our stroke outcome, emphasizing specificity over sensitivity. Namely, we used 433.x1 and 434.x1, “Oclusion of…artery…with cerebral infarction.” We only used inpatient codes for this outcome, according to our earlier work, but did allow codes in either the primary or secondary position to define a stroke.

Covariates

We adjusted for various clinical variables that are known to affect our outcome measures. For ischemic strokes, we adjusted for all of the variables included in the CHADS2 score (congestive heart failure, hypertension, age, diabetes mellitus, and previous stroke/Transient Ischemic Attack score). For major and fatal bleeding, we adjusted for many of the variables contained within the HAS-BLED bleeding risk score, hypertension, abnormal renal or liver function, previous stroke bleeding history or predisposition, labile international normalized ratios, elderly and concomitant drugs or alcohol excess, including age, hypertension, chronic kidney disease, liver disease, prior stroke, alcohol abuse, and drug abuse. However, we did not control for use of antiplatelet drugs or a history of bleeding, both of which are also in bleeding score, because our data set did not allow these variables to be assessed with confidence.

Statistical Analysis

TTR was categorized into low (<50%), moderate (50%–70%), and high (>70%), whereas log INR variability was divided into low (>−2.64) and high (≤−2.64). We chose this cutoff point (ie, −2.64) based on a Cox regression analysis that examined Log INR variability by deciles and rates of adverse events. We found that values beyond this point seemed to impart increased risk, with a dose–response relationship (ie, deciles 8–10), whereas values below this point did not seem to differ from other meaningful (ie, deciles 1–7; see Table 1).

To examine the benefit of adding INR variability to TTR, we fit 3 nested Cox regression models. All of our models to predict ischemic stroke controlled for variables from CHADS2, whereas our models to predict hemorrhage controlled for elements of HAS-BLED. Our nested models were specified as follows:

1. Model 1: We included only 1 measure, either TTR or log INR variability, in addition to covariates. We used high TTR and...
Results of Nested Cox Regression Models

Model 1

Both TTR and log INR variability were significant individual predictors estimating the risk for the study outcomes (Table 3). The reference categories were high TTR and low log INR variability, that is, best control in both cases. Low TTR was most strongly associated with adverse events, followed by high log INR variability. Moderate TTR had the weakest association with ischemic stroke, major bleeding, and fatal bleeding.

Model 2

The hazard ratios for low TTR, moderate TTR, and high log INR variability were 2.64 fatal hemorrhages. In contrast, the lowest percentage of events occurred at the best level of anticoagulation, at high levels of TTR, and at low levels of INR variability, that is, stable anticoagulation.

Model 3

There was a significant interaction between TTR and log INR variability, suggesting a nonadditive model can further predict higher risk of warfarin adverse effects beyond the independent effects that were shown in model 2 (Table 4).

Baseline Characteristics

Our database included 40404 patients aged ≥65, without Medicare Advantage, treated within VA for stroke prevention in atrial fibrillation. Our sample was predominately men, with a mean age of 76 years (Table 1). About 25% of patients were considered to have unstable INR regimens, with log INR variability ≥−2.64, 42.2% of patients had high TTR (≥70%); 34.4% had moderate TTR (50%−70%); and 23.2% had low TTR (<50%).

The Pearson correlation between our unadjusted TTR and log INR variability remained statistically significant, after including both anticoagulation measures in a single model, except that moderate TTR was no longer a significant predictor for fatal bleeding.

Adjusting TTR for log INR variability and vice versa illustrated that both TTR (low and moderate) and high log INR variability predicted outcomes independent of each other (Table 3). Similar to model 1, low TTR predicted the highest risk for all outcomes. High log INR variability was a much stronger predictor for fatal bleeding.

Results

Table 1. Log INR Variability Deciles Predicting Age-Adjusted Hazard Ratio for Ischemic Stroke and Major Bleeding, Including Fatal Bleeding

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>Age</th>
<th>TTR</th>
<th>Log INR Variability</th>
<th>Hazard Ratio Major Bleeding</th>
<th>Hazard Ratio Major Stroke</th>
<th>Hazard Ratio Fatal Bleeding</th>
<th>Hazard Ratio Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>40404</td>
<td>76.78</td>
<td>63.56</td>
<td>−3.41</td>
<td>0.86 (0.71−1.04)</td>
<td>0.57 (0.32−1.01)</td>
<td>0.86 (0.65−1.14)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile1</td>
<td>4040</td>
<td>76.93</td>
<td>73.43</td>
<td>−5.58</td>
<td>0.74 (0.56−1.00)</td>
<td>0.57 (0.32−1.01)</td>
<td>0.86 (0.65−1.14)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile2</td>
<td>4040</td>
<td>76.70</td>
<td>73.26</td>
<td>−4.70</td>
<td>0.86 (0.71−1.04)</td>
<td>0.57 (0.32−1.01)</td>
<td>0.86 (0.65−1.14)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile3</td>
<td>4041</td>
<td>76.73</td>
<td>70.52</td>
<td>−4.29</td>
<td>0.95 (0.79−1.15)</td>
<td>0.96 (0.69−1.67)</td>
<td>0.78 (0.59−0.94)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile4</td>
<td>4040</td>
<td>76.70</td>
<td>69.01</td>
<td>−3.97</td>
<td>0.94 (0.78−1.13)</td>
<td>0.87 (0.52−1.44)</td>
<td>1.00 (0.76−1.30)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile5</td>
<td>4041</td>
<td>76.80</td>
<td>65.88</td>
<td>−3.67</td>
<td>0.97 (0.81−1.17)</td>
<td>0.94 (0.58−1.55)</td>
<td>0.99 (0.76−1.30)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile6</td>
<td>4040</td>
<td>76.64</td>
<td>63.5</td>
<td>−3.37</td>
<td>1.16 (0.97−1.38)</td>
<td>0.89 (0.54−1.47)</td>
<td>1.16 (0.89−1.50)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile7</td>
<td>4041</td>
<td>76.78</td>
<td>61.02</td>
<td>−3.04</td>
<td>1.07 (0.90−1.29)</td>
<td>0.90 (0.55−1.48)</td>
<td>1.14 (0.88−1.48)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile8</td>
<td>4040</td>
<td>76.49</td>
<td>57.49</td>
<td>−2.64</td>
<td>1.25 (1.05−1.48)*</td>
<td>1.36 (0.86−2.15)</td>
<td>1.24 (0.96−1.61)</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile9</td>
<td>4041</td>
<td>76.87</td>
<td>54.1</td>
<td>−2.06</td>
<td>1.34 (1.12−1.59)*</td>
<td>1.62 (1.04−2.53)*</td>
<td>1.49 (1.16−1.91)*</td>
<td></td>
</tr>
<tr>
<td>Log INR variability decile10</td>
<td>4040</td>
<td>77.22</td>
<td>47.38</td>
<td>−0.75</td>
<td>1.60 (1.35−1.90)†</td>
<td>2.27 (1.48−3.46)†</td>
<td>1.75 (1.37−2.24)†</td>
<td></td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio; and TTR, time in therapeutic range.
Within fixed TTR levels, we found higher risk of ischemic strokes, major bleeding, and fatal bleeding at high levels of INR variability. For example, within moderate levels of TTR, patients with high INR variability had a higher risk of major bleeding, fatal bleeding, and ischemic stroke (HR=1.27, 1.29, and 1.70, respectively) compared with patients with low INR variability at the same level of TTR (ie, moderate TTR).

Our results further illustrate that the benefit of achieving higher levels of TTR is limited in the setting of high INR variability. For example, there was no statistical difference in the risk of ischemic stroke, major bleeding, or ischemic stroke (HR=1.27, 1.29, and 1.70, respectively) compared with patients with low INR variability at the same level of TTR (ie, moderate TTR).

## Results of the Proportional Hazard Analyses

We tested the assumption of proportional hazards violation for all models using Schoenfeld residuals method. Only the 3 models that examined fatal bleeding may have violated the proportional hazard assumption. However, in a sensitivity analysis, no further evidence of violation for this assumption was observed after removing the 2 covariates (hypertension and history of drug abuse) that seemed to be the culprit for this violation. In addition, the model parameter estimates were essentially unchanged. Therefore, we concluded that any minor violations of proportional hazards did not influence our estimates or conclusions.

### Discussion

In this study, we examined the added value of log INR variability (a measure of the stability of control) beyond that of TTR (a measure of anticoagulation intensity). Our results suggest that the 2 measures together provide more information about risk for adverse events than TTR alone. Unstable anticoagulation, measured by higher INR variability, is a significant independent predictor for warfarin adverse events, regardless of different TTR levels. In addition, adding INR variability to TTR further risk stratifies patients within the same TTR categories. Patients with unstable anticoagulation had an increased hazard for warfarin-related adverse effects, despite similar levels of TTR.

Moreover, our results suggest that reducing patients’ risk of adverse events by achieving higher levels of TTR may be contingent on achieving stability, as measured by INR variability. There was no difference in the risk of ischemic stroke, major bleeding, and fatal bleeding between moderate and high TTR levels of high INR variability. On the contrary, when TTR was poor (<50%), INR variability did not seem to have this effect, suggesting that when TTR is poor, INR variability may no longer matter in the same way.

Adopting the stability of INR regimen as a measure to assess anticoagulation control, in addition to percent time in therapeutic range, expands the definition of good or poor anticoagulation control by including measures of intensity and stability. Moreover, issues related to ceiling and floor effects of a single measure in predicting definite outcomes is less evident with the use of 2 measures together. Characterizing anticoagulation control by adding a new dimension will further classify care on a much more detailed level. Previous studies considered TTR levels >70% to be the standard for excellent care.21–23 However, in our study, even patients with high TTR levels experienced suboptimal levels of adverse events when they had unstable control, suggesting that a high degree of fluctuation in INR values within or adjacent to the therapeutic range might attenuate the protection from adverse events associated with it.
with high TTR. However, it is important to note that our results are limited in explaining the mechanism for this phenomenon.

Few studies have previously examined the relationship between these 2 measures of anticoagulation control. Log INR variability was superior to TTR in 1 study that examined ischemic strokes, major bleeding, and fatal bleeding in a population of patients with atrial fibrillation. That study showed no added benefits of combining TTR with INR variability measures, but it did not examine this effect within different levels of TTR. van Leeuwen et al, in a case–control study for patients with prosthetic heart valves, concluded that warfarin-associated complications increase with either high INR variability or low TTR, but that study did not demonstrate the differential effect of INR variability at different TTR levels, as we did here. Our results add to these previous studies and suggest in particular that INR variability can provide important information about risk of important outcomes when added to TTR.

From our results, using both measures together clearly has its advantage over the traditional use of TTR alone. However, there are other factors that might hinder adopting this approach. Currently, there is no agreed-upon method for calculating INR variability. We selected our method based on the conclusion of the superiority of this method in an earlier study. Likewise, there is no agreement on a cut-off value for INR variability that might be used to define stable and unstable anticoagulation. Previous studies used different thresholds for INR variability in identifying unstable anticoagulation measurements. In this study, we used a threshold value of −2.64. We chose this value because it seemed to have importance for event prediction in our data set. The reliability of this cut-off value, or any other cut-off value for INR variability, should be assessed in different data sets before it can be widely adopted.

Another possible limitation for the use of INR variability as a quality measure in daily clinical use may be its abstract meaning for providers. To demonstrate a way that this measure might be more easily understood, we depicted the INR values for 2 patients in Figure 1, one with stable anticoagulation and the other with unstable anticoagulation. Also, we calculated the degree of INR change between 2 successive measures for 3 instances of log INR variability from our sample: (1) −5.58, the mean of the most stable decile; (2) −0.75, the mean of the most unstable decile; and (3) −2.64, the cutoff to define stable and unstable anticoagulation. For instance, in a patient with 2 INR measurements, our selected cut-off value of log INR variability −2.64 corresponds to a difference of 0.53 over the course of 4 weeks or of 0.65 over the course of 6 weeks. However, TTR itself is also too complex to be “eyeballed.” To the extent that both measures are valuable in clinical practice, they will require computers to assist with their calculation.

There are several strengths and weaknesses in our present study. Our large data set with numerous definitive outcomes of warfarin-associated complications allowed us to examine the additive roles of our 2 summary measures at different levels of control. Also, our patient-level outcomes were detected using automated data and were not validated by chart review.

### Table 4. Hazard Ratios Comparing Outcomes (Ischemic Stroke, Major Bleeding, and Fatal Bleeding) at High vs Low INR Variability Levels Within Similar TTR Categories

<table>
<thead>
<tr>
<th>Time in Therapeutic Range</th>
<th>Ischemic stroke</th>
<th>Major Bleeding</th>
<th>Fatal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low TTR (&lt;50%)</td>
<td>HR=1.29 (1.06–1.56)</td>
<td>HR=1.04 (0.91–1.19)</td>
<td>HR=1.38 (0.98–1.97)</td>
</tr>
<tr>
<td>Moderate TTR (50% to 70%)</td>
<td>HR=1.27 (1.04–1.56)</td>
<td>HR=1.29 (1.12–1.48)</td>
<td>HR=1.70 (1.21–2.41)</td>
</tr>
<tr>
<td>High TTR (&gt;70%)</td>
<td>HR=1.55 (1.17–2.06)</td>
<td>HR=1.56 (1.29–1.89)</td>
<td>HR=1.93 (1.18–3.16)</td>
</tr>
</tbody>
</table>

Reference category is low INR variability. These results are estimated from model 3, which included both predictors (TTR and log INR variability) and interaction term. HR indicates hazard ratio; INR, international normalized ratio; and TTR, time in therapeutic range.
However, we used thoughtful approaches for using these automated data to maximize the accuracy of our findings.

Our study raises the possibility that interventions to help patients to improve their control with warfarin therapy may need to be customized depending on the lesion, whether it be unstable control, low time in range, or both. Previous studies have examined patient-level predictors of poor TTR,5,24 which may contribute to interventions to target and help such patients. In this study, we demonstrated the value of INR variability in addition to TTR. Future research should focus on patient-level factors and processes of care that are associated with INR variability. Identifying such elements will provide the opportunity to improve anticoagulation care through quality care initiatives that addresses INR stability regimens.

In conclusion, our study suggests that TTR is not the only important measure of quality in anticoagulation. Rather, the stability of the regimen, measured by log INR variability, adds important information on top of TTR, particularly within a single category of TTR. Incorporating both of these measures simultaneously might improve both quality measurement and clinical risk assessment.

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Disclosures
All authors state they have no conflict of interest.

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