INR targets and site-level anticoagulation control: results from the Veterans Affairs Study to Improve Anticoagulation (VARIA)


*Center for Health Quality, Outcomes and Economic Research, Bedford VA Medical Center, Bedford, MA; †Department of Medicine, Section of General Internal Medicine, Boston University School of Medicine, Boston, MA; ‡Department of Health Policy and Management, Boston University School of Public Health, Boston, MA; §Biostatistics Section, Boston Children’s Hospital, Boston, MA; and ††Department of Quantitative Health Sciences, Division of Biostatistics and Health Services Research, University of Massachusetts School of Medicine, Worcester, MA, USA

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Summary. Background: Not all clinicians target the same International Normalized Ratio (INR) for patients with a guideline-recommended target range of 2–3. A patient’s mean INR value suggests the INR that was actually targeted. We hypothesized that sites would vary by mean INR, and that sites of care with mean values nearest to 2.5 would achieve better anticoagulation control, as measured by per cent time in therapeutic range (TTR). Objectives: To examine variations among sites in mean INR and the relationship with anticoagulation control in an integrated system of care. Patients/Methods: We studied 103,897 patients receiving oral anticoagulation with an expected INR target between 2 and 3 at 100 Veterans Health Administration (VA) sites from 1 October 2006 to 30 September 2008. Key site-level variables were: proportion near 2.5 (that is, percentage of patients with mean INR between 2.3 and 2.7) and mean risk-adjusted TTR. Results: Site mean INR ranged from 2.22 to 2.89; proportion near 2.5, from 30 to 64%. Sites’ proportions of patients near 2.5, below 2.3 and above 2.7 were consistent from year to year. A 10 percentage point increase in the proportion near 2.5 predicted a 3.8 percentage point increase in risk-adjusted TTR (P < 0.001). Conclusions: Proportion of patients with mean INR near 2.5 is a site-level ‘signature’ of care and an implicit measure of targeted INR. This proportion varies by site and is strongly associated with site-level TTR. Our study suggests that sites wishing to improve TTR, and thereby improve patient outcomes, should avoid the explicit or implicit pursuit of non-standard INR targets.

Keywords: ambulatory care, anticoagulants, medication therapy management, quality of healthcare, warfarin.

Millions of patients receive warfarin each year to prevent or treat thromboembolic disease. Better anticoagulation control (i.e. a greater percentage of time in therapeutic range [TTR]), can reduce the occurrence of adverse events [1–4]. Therefore, to improve patient outcomes, sites of care should develop systems to measure and improve TTR [5–7]. Ideally, we should measure not only intermediate outcomes (such as TTR), but also processes of care, because process deficiencies provide a prescription for remediation. Because the most useful process measures are ‘tightly linked’ to outcomes [8], it would be ideal to demonstrate which processes of care are associated with better anticoagulation control.

We have profiled 100 sites of care in an integrated healthcare system (the Veterans Health Administration, or VA) on TTR [9]. Having profiled sites on anticoagulation control (an intermediate outcome of care), we sought to determine which processes of care predict this outcome [8]. Several site-level processes of care are related to TTR, most notably follow-up intervals after out-of-range International Normalized Ratio (INR) values [10]. Another process measure likely to affect anticoagulation control is pursuit of a target INR range of 2–3 for most patients. Several high-quality randomized trials have demonstrated that aiming for a lower INR target range (such as 1.5–2) produces inferior protection from thromboembolism with no reduction in rates of major hemorrhage [11–16]. Despite the established value of the standard target range of 2–3 for patients with atrial fibrillation (AF) or venous thromboembolism (VTE) [5,17,18], some clinicians may continue to implicitly or explicitly aim for non-standard target ranges. Although these clinicians may believe that they can successfully keep patients within a very narrow target range such as 2–2.5, target ranges narrower than a full INR unit do not reduce the variability of INR [19].
One prominent study includes use of a standard target range of 2–3 for patients with AF among its quality measures [20]. However, in most large automated databases, we do not have direct access to the target range, complicating efforts to use this as a quality measure. In this study, we propose a new process of care measure for oral anticoagulation: the proportion of patients at a site, anticoagulated for AF or VTE, who achieve a mean INR of 2.3–2.7. We assert that this does not merely measure differences in INR variability among sites of care, but actually measures site-level propensity to target non-standard target ranges, because even patients with highly variable INR values will still tend to achieve a mean INR very close to what is being sought. We used a large database from the VA to address three main questions. (i) At which level of mean INR do patients record the highest TTR? (ii) Do sites of care vary in their propensity to aim for non-standard target ranges? (iii) Are these differences associated with site-level anticoagulation control? Demonstration of variability of process and a relationship with an intermediate outcome of care would provide strong support for measuring, and intervening to optimize, this new process measure.

Methods

Data

The database for this study has also been described elsewhere [9]. The Veterans Affairs Study to Improve Anticoagulation (VARIA) included all patients deemed to be receiving oral anticoagulation therapy from the VA between 1 October 2006 and 30 September 2008, based on the criteria described below. The study was approved by the Institutional Review Board of the Bedford VA Medical Center.

Patients

We included all patients who received warfarin from the VA during the 2-year study period (i.e. at least 30 days’ worth dispensed by the pharmacy). We excluded patients whose primary indication to receive warfarin was valvular heart disease. Many such patients have a target INR range of 2.5–3.5 rather than the more standard 2–3, but it is not possible to determine with certainty which patients have the higher target range. Without specific knowledge of the target range, we cannot calculate TTR. For this study, we also excluded the inception period, or the first 6 months of warfarin therapy, a period when many patients may have erratic INR control and may spend much time below the target range.

Laboratory values and calculation of per cent time in range (TTR)

We included INR values within the VA system during times when a patient was ‘on warfarin’: that is, when a patient was either (i) in possession of warfarin or (ii) 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 more than 30 days beyond the end of a prescription does not necessarily indicate that warfarin therapy has stopped. We therefore also allowed a consistent pattern of INR measurements (i.e. every 42 days or less) to indicate that a patient was still being managed.

We excluded INR tests measured while the patient was hospitalized. Patients who are hospitalized may receive temporary parenteral anticoagulation or no anticoagulation, so low INR values while hospitalized may be intentional. We calculated TTR using Rosendaal’s method [21], 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, the percentage of time during which the interpolated INR values lie between 2.0 and 3.0 (from 0 to 100%) is calculated [21].

Sites of care

We included 100 VA sites of care, each of which includes a hospital, an outpatient care center and several outlying community-based clinics. Each site has a specialized anticoagulation clinic, which is usually run by clinical pharmacists under the supervision of a medical director[22]. Therefore, essentially all patients whose anticoagulation is managed in the VA are managed by specialized anticoagulation clinics. Most patients only visited one site of care, and their INR data were assigned to that site. If a patient visited more than one site (3% of patients), we partitioned their data by site.

While most INR values in the VA are processed via an automated laboratory, a few VA sites mostly or exclusively rely upon point-of-care (POC) testing. Our data do not specify which INR tests were obtained via POC. Home testing with POC devices is not covered by the VA, and therefore is extremely uncommon.

Risk adjustment model

We have previously described our risk adjustment model for TTR [9]. We considered many potential variables for inclusion in the model which were likely to impact TTR, including demographics, area-level poverty, driving distance to care, physical health conditions, mental health conditions, number of medications, and number of hospitalizations. Most variables were retained within the model, with the exception of several co-morbid conditions with small effect sizes. The model was derived and validated according to customary procedures, which included considerations of maximizing predictive ability, clinical credibility, and ease of use and understanding. This patient-level risk adjustment model for TTR has an $R^2$ of 13.3% when used with this dataset [9]. Table 1 contains all the variables in the model.
As explained above, we included all INR values that occurred when a patient was ‘on warfarin’ according to our definition, and that were within 56 days of another INR (a ‘valid interval’). We limited this study to patients who had at least four valid intervals for calculating per cent time in therapeutic range (TTR) [21]. For this purpose, a valid interval consists of two INR values separated by 56 days or less, without an intervening hospitalization. In this way, we ensured that patients had sufficient INR values to reliably indicate their target INR. For each patient, we calculated his or her mean INR value over the 2-year study period. We also calculated separate mean INR values in years 1 and 2 of the study for patients who had at least four valid intervals in one year. We computed, for each site, the overall mean INR value, as well as the proportions of patients with a mean INR value < 2.3, 2.3–2.7 and > 2.7.

INR values may be measured several times in rapid succession when the INR is low or high. We were concerned that this phenomenon might impact our assessment of patient- or site-level mean INR values. We therefore computed an alternative version of our independent variable, omitting all INR values obtained within 7 days after the previous value. The results of our analyses were essentially unchanged.

### Statistical analyses

We examined the baseline characteristics of patients in our database. We calculated unadjusted and risk-adjusted TTR for each patient and for each site of care. We characterized each patient’s mean INR value, each site’s mean INR value, and the proportion of patients at each site with a mean INR of 2.3–2.7. We examined the ability of patient-level mean INR value to predict unadjusted and adjusted TTR using ANOVA, linear regression, and cubic smoothing splines [23]. We examined the relationship between site-level proportion of patients with mean INR 2.3–2.7 and site-level anticoagulation control using linear regression. All analyses were conducted using SAS, version 9.1 (SAS Corporation, Cary, NC, USA).

### Results

#### Patients

Our database contained 103 897 patients who were experienced users of warfarin for indications ordinarily requiring a target INR range of 2–3 (i.e. not mechanical heart valves). Patient characteristics are shown in Table 1. The sample was mostly male (98%) and had a median age of 72 years (IQR 62–79). More than half of the patients were anticoagulated for AF (64%), with many of the others anticoagulated for VTE (27%). Patients had a substantial burden of chronic disease: 40% had diabetes, 32% had heart failure, 29% had chronic lung disease, and 14% had chronic kidney disease. Patients also had a substantial burden of mental health disorders: for example, 22% had major depression, and 9% carried a diagnosis of alcohol abuse. As might be expected with this burden of morbidity, patients received many medications (a median of eight) and 26% were hospitalized at least once during the study.
Overall anticoagulation control was fair for this population of experienced users of warfarin (mean TTR = 61.6%).

**Mean INR values – patient level**

Patients varied widely in their mean INR values. The mean of all INR values in the database was 2.42, but 10% of patients were below 2.00 and 10% were above 2.83, so extreme deviations were not uncommon. The maximum predicted TTR occurred at a mean INR value of 2.43. At this value, patients had a predicted TTR of 71%; for each deviation of 0.1 from this value, the predicted TTR was 3.9% lower ($P < 0.001$). However, this relationship was not symmetric, with greater decrements in TTR occurring below a mean INR of 2.43 than above it (Table 2). An ANOVA test, comparing deciles of patients with regard to mean INR values, demonstrated a similar phenomenon (Table 2). Anticoagulation control was generally excellent among patients with a mean INR between 2.3 and 2.7, but quite poor outside of this range.

**Mean INR values – site level**

There were 100 sites of care in the database. The number of patients per site ranged from 74 to 4371 (mean 1039 per site). Site TTR varied from a low of 43% to a high of 72%+, and site risk-adjusted TTR varied from 18% below to 12% above predicted. Site mean INR varied widely, from 2.22 to 2.89. The median site had 34% of patients with a mean INR < 2.3, 48% of patients with a mean INR 2.3–2.7, and 16% of patients with a mean INR > 2.7. However, there was considerable variation in this regard; sites ranged from 30 to 64% of patients with a mean INR of 2.3–2.7 (Fig. 1). In a regression analysis, for every 10% of patients at a site with a mean INR of 2.3–2.7, site-unadjusted TTR was 4.4% higher, and site risk-adjusted TTR was 3.8% higher ($P < 0.001$ for both findings).

The proportion of patients at each site with a mean INR 2.3–2.7 was consistent between years: comparing FY07 with FY08, the coefficient of correlation was 0.78 ($P < 0.001$). Sites were also somewhat consistent regarding whether their patients achieved mean INR values above or below this desirable range. For example, regarding the proportion of patients with a mean INR below 2.3, sites varied from 19% to 62%. The coefficient of correlation between FY07 and FY08 regarding the proportion with mean INR below 2.3 was 0.45 ($P < 0.001$). Several sites had a consistent pattern of having many patients with low mean INR. For example, sites KM and GD had among the very highest proportion of patients with a low mean INR in both years (KM, 56% and 65%; GD, 55% and 60%). The correlation between years for the proportion with a high mean INR was also appreciable ($r = 0.35, P < 0.001$), but not as strong a relationship.

**Discussion**

We examined mean INR values at the patient level and the site of care level. We had three main findings: (i) site mean INR varied widely; (ii) proportion of patients near 2.5 varied widely by site, and proportions low, high and near 2.5 were stable across years; and (iii) a higher proportion near 2.5 was strongly associated with higher site-level TTR. Several related points remain speculation: (i) intentional pursuit of non-standard INR target ranges is the principal cause of variation in site-level mean INR; (ii) actively discouraging clinicians from adopting non-standard targets will increase TTR and reduce adverse events; (iii) it will be possible to induce clinicians to change their practise regarding INR target ranges; and (iv) discouraging non-standard targets will not harm certain classes of patients, such as the oldest old (age 80+).

We will soon launch an initiative to improve mean TTR in the VA from its current 58% to 70% [9], an improvement that could prevent thousands of adverse events [24]. In light of the present study, one strategy will be to discourage sites from pursuing non-standard target INR ranges. We hypothesize that decreased use of non-standard target ranges will increase the proportion of patients with a mean INR of 2.3–2.7, and that sites that change this parameter the most will increase TTR the most. In addition, by directly measuring outcomes among important subgroups of patients (e.g. the oldest old), we hope to provide reassurance that avoiding non-standard target ranges benefits them as well, or at least does not harm them. This forthcoming study will therefore address whether the proportion of patients whose mean INR is near 2.5 can serve as a useful process measure in anticoagulation care.

The finding that extremes of mean INR are associated with poor anticoagulation control at the patient level is not surprising. However, the finding that sites of care vary more

### Table 2

<table>
<thead>
<tr>
<th>Mean INR group</th>
<th>Lowest</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Highest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range of mean INR</td>
<td>&lt; 2.00</td>
<td>2.00–2.16</td>
<td>2.16–2.25</td>
<td>2.25–2.33</td>
<td>2.33–2.40</td>
<td>2.40–2.48</td>
<td>2.48–2.56</td>
<td>2.56–2.66</td>
<td>2.66–2.83</td>
<td>&gt; 2.83</td>
</tr>
<tr>
<td>Observed TTR</td>
<td>30.6%</td>
<td>57.4%</td>
<td>65.9%</td>
<td>68.8%</td>
<td>70.6%</td>
<td>70.9%</td>
<td>70.8%</td>
<td>69.1%</td>
<td>64.7%</td>
<td>46.8%</td>
</tr>
<tr>
<td>Adjusted TTR</td>
<td>-28.4%</td>
<td>-3.7%</td>
<td>+4.1%</td>
<td>+6.6%</td>
<td>+8.2%</td>
<td>+8.5%</td>
<td>+8.4%</td>
<td>+6.9%</td>
<td>+2.9%</td>
<td>-13.4%</td>
</tr>
</tbody>
</table>

Observed TTR is between 0 and 100%. Adjusted TTR measures the difference between observed and expected TTR. Expected TTR is calculated for each patient based on his or her demographics and co-morbid conditions. Positive values for adjusted TTR indicate that a patient’s observed TTR exceeded the expected TTR. ANOVA tests are significant for comparisons of observed TTR and adjusted TTR ($P < 0.001$ for both). Groups designated by a common letter are not significantly different from one another by Tukey’s post hoc test.
than 3-fold regarding the proportion of patients with a mean INR below 2.3 suggests real differences in site-level practice. Our findings suggest that some sites routinely choose a guideline-concordant target range of 2–3 while others are likely to attempt to ‘shade’ patients below this range. This might take the form of an explicit designation of a non-standard target range (for example, 2–2.5) or an implicit tendency to aim for the lower end of a nominal target range of 2–3.

As discussed above, considerable work is needed to extend the results of this study and to clarify their implications. For now, however, we recommend that clinicians aim for standard target ranges, as are already recommended by prominent guidelines such as ACCP [5]. We are not advocating a target range of 2.3–2.7, or any other narrow range [19]. Clinicians should be equally satisfied with an INR of 2.1 or 2.9, provided the patient is under stable control. Rather, we recommend eliminating target ranges other than 2–3 and 2.5–3.5 [5,17,18,25,26].

Our study has important strengths, particularly the size and clinical detail of the database. However, we also acknowledge limitations. First, as stated above, we cannot know for sure why sites achieved such disparate mean INR values. While we suspect that it is a reflection of different styles of practise at each site, our observational database study is not equipped to confirm this suspicion. Second, we examined the impact of mean INR values on anticoagulation control, but did not examine the impact of mean INR values on adverse events. However, multiple studies have already linked TTR to adverse events [1–4], demonstrating the importance of pursuing a higher TTR both for populations and for individuals. In addition, multiple studies have also linked the pursuit of ‘low’ target INR ranges to inferior patient outcomes [11–15], as discussed above. Nevertheless, this study could have provided even more compelling evidence by directly linking site-level target ranges to site-level rates of adverse events. Unfortunately, we lack the data to directly examine adverse events with this dataset. In the future, we hope to examine this link more directly. Third, VA patients are mostly male and have higher rates of co-morbid illness, mental illness, substance abuse disorders and socioeconomic disadvantages than the general US population. This may have contributed to INR target range choices; for example, clinicians may justifiably fear hemorrhage in an alcoholic patient and therefore target a low INR value. However, these issues are unlikely to impact the underlying relationships we demonstrated between site-level mean INR values and site-level TTR. In addition, our risk-adjustment model should have accounted for the impact of these patient characteristics upon TTR, at least within the VA system [9].

In conclusion, 100 sites of care in the nation’s largest integrated healthcare system varied considerably in their mean INR values and in the proportion of patients with a mean INR of 2.3–2.7. Our results suggest that pursuing standard INR target ranges (2–3 for most patients) could improve anticoagulation control, as measured by TTR. In a forthcoming intervention study, we plan to test this proposition by actively promoting the use of standard INR targets and observing the effects on TTR and patient outcomes.

Disclaimer
The opinions expressed in this manuscript do not necessarily represent the official views of the Department of Veterans Affairs.

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Disclosure of Conflict of Interests
E. M. Hylek has received honoraria from Bayer and Bristol Myers Squibb, and has served on advisory boards for Boehringer-Ingelheim, Bristol Myers Squibb, Merck and Sanofi Aventis. None of the other authors report any potential conflict of interests.

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