Epidemiology of Subtherapeutic Anticoagulation in the United States

Adam J. Rose, MD, MSc; Al Ozonoff, PhD; Richard W. Grant, MD, MPH; Lori E. Henault, MPH; Elaine M. Hylek, MD, MPH

Background—Low international normalized ratio (INR; ≤1.5) increases risk for thromboembolism. However, little is known about the epidemiology of low INR.

Methods and Results—We prospectively collected data from 47 community-based clinics located throughout the United States from 2000 to 2002. We examined risk factors for low INR (≤1.5), reasons given in the medical record for low INR, and proportion of thromboembolic events that occurred during periods of low INR. Of the 4489 patients in our database, 1540 (34%) had at least 1 low INR. Compared with men, women had an increased incidence of low INR (adjusted incidence rate ratio, 1.44; P < 0.001). Compared with patients anticoagulated for atrial fibrillation, patients anticoagulated for venous thromboembolism had an increased incidence of low INR (adjusted incidence rate ratio, 1.48; P < 0.001). The 5 most common reasons for low INR were nonadherence (17%), interruptions for procedures (16%), recent dose reductions (15%), no reason apparent after questioning (15%), and second or greater consecutive low INR (13%). A total of 21.8% of thromboembolic events (95% CI, 12.2 to 35.4%) occurred during periods of low INR; 58% of these events were related to an interruption of warfarin therapy.

Conclusions—In this cohort of patients receiving warfarin, more than 1 in 5 thromboembolic events occurred during a period of low INR. Women and patients anticoagulated for venous thromboembolism were particularly likely to experience low INR. Improving adherence, minimizing interruptions of therapy, and addressing low INR more promptly could reduce the risk of low INR. (Circ Cardiovasc Qual Outcomes. 2009;2:591-597.)

Key Words: warfarin • thromboembolism • anticoagulants • quality of health care • medication therapy management

Warfarin is a highly effective therapy to prevent thromboembolic complications of venous thromboembolism (VTE), atrial fibrillation (AF), and valvular heart disease. However, warfarin is an extremely challenging therapy in clinical practice; a recent meta-analysis found that patients spend an average of only 66% of time in the therapeutic range when managed in specialized anticoagulation clinics, and only 57% of time when managed in usual care. The large amount of time spent outside the target range has important clinical consequences: patients with better control have fewer hemorrhagic and thromboembolic events. Many studies have focused on the risk factors for and effects of high international normalized ratio (INR), and therefore, we know a considerable amount about these topics. For example, Hylek et al showed that risk factors for INR >6.0 included high-dose acetaminophen, new medications known to potentiate warfarin, advanced malignancy, diarrhea, decreased oral intake, and taking more warfarin than prescribed. However, there has been considerably less research regarding low INR. Some studies have demonstrated that low INR is associated with attenuation of the protective effects of anticoagulation therapy, as would be expected. Although we know that low INR increases the risk of thromboembolism, relatively little is known about the epidemiology of low INR.

We therefore used data from a large nationally representative anticoagulation cohort to describe the epidemiology of low INR. We examined patient-level risk factors for INR ≤1.5, the threshold below which the risk of thromboembolism rises most acutely. We report clinician-documented explanations for low INR, recorded at the time the INR result was obtained. We examine predictors of time until the next INR and the next in-range INR. Finally, we estimate the proportion of thromboembolic events attributable to low INR. Low INR has been an understudied topic, and our study can serve as the beginning of an effort to understand, address, and reduce this phenomenon.
WHAT IS KNOWN

- Low international normalized ratio (INR; $\leq 1.5$) is a risk factor for thromboembolism in patients receiving warfarin. Reducing its occurrence in clinical practice could improve patient outcomes.
- However, little is known about the epidemiology of low INR, especially which patients are more likely to experience it and what factors may contribute to it.

WHAT THE STUDY ADDS

- In our study, the 5 most common reasons for low INR were nonadherence (17%), interruptions for procedures (16%), recent dose reductions (15%), no reason apparent after questioning (15%), and second or greater consecutive low INR (13%).
- Low INR was more common among women and patients anticoagulated for venous thromboembolism, even after controlling for covariates. These novel findings require confirmation and further investigation.
- Our study identifies groups of patients who may be at higher risk for low INR and factors that seem to cause it. This can serve as the beginning of a concerted effort to reduce the incidence of low INR in clinical practice.

Methods

Study Enrollment

Data collection for the Anticoagulation Consortium to Improve Outcomes Nationally (ACTION) study has been described elsewhere.18,25–29 Physician practices that were registered users of CoumaCare software (Bristol-Myers Squibb) were invited to participate. CoumaCare was a freely available software package which provided a rudimentary electronic medical record for anticoagulation management. The software assisted with record keeping and patient tracking, but did not provide advanced functions such as dosing guidance. The uniformity of data structure provided by the software package allowed us to collect data from diverse community-based sites at a time when few such sites had any sort of electronic medical record.

In total, 174 practices registered online to participate, and 101 sites had the technological capability and the review board approval necessary to proceed. One of the functions of CoumaCare is to allow providers to input a note regarding each INR value and how it was taken. This can serve as the beginning of a concerted effort to reduce the incidence of low INR in clinical practice.

Investigators developed 10 categories to encompass the reasons for low INR, and then assigned a reason to each value using chart review. One of these 10 categories, “initiation phase,” was defined as all consecutive low INR values before the first in-range or high INR was recorded. Another category, “continuing low,” was used for all successive low INRs, regardless of the reason for the first in the series, until the next in-range or high INR value.

We characterized all patients regarding age, gender, race, indication for anticoagulation, and comorbid conditions. In addition, we recorded instances when warfarin was intentionally interrupted (a “hold”) by reviewing all 84 915 anticoagulation notes. The great majority of these holds were for minor procedures such as biopsies or colonoscopies, whereas relatively few were for major surgery. For the purpose of this analysis, however, all holds were considered the same. We confirmed all thromboembolic events (ischemic stroke, systemic embolus, deep venous thrombosis, and pulmonary embolus) through chart review.

Statistical Analyses

We tabulated demographics (age, gender, and race) and comorbid conditions (hypertension, diabetes, prior stroke, coronary artery disease, congestive heart failure) and performed bivariate comparisons between patients with at least 1 low INR versus those without. Because of correlated data within sites of care, we computed probability values for bivariate comparisons using 10 000 Monte Carlo permutations (stratified on clinical site) of the indicator for at least 1 low INR value. We modeled the rate of low INR per person-year using patient-level risk factors as independent predictors. Covariates included demographics, indication for therapy, comorbid conditions, and warfarin holds. For indication for therapy, the reference category was atrial fibrillation without prior stroke, chosen because it was the most numerous. Patients with valvular heart disease comprised another category of indication for therapy; most such patients had mechanical replacement valves (90%), but some had other conditions (such as mitral stenosis). We further divided patients with valvular heart disease into those with target ranges of 2 to 3 versus 2.5 to 3.5, with the hypothesis that those with a high target range would be protected from low INR. We used a Poisson regression model, fit with generalized estimating equations (SAS PROC GENMOD, SAS version 9.1, SAS Institute, Inc.), to account for intraclass correlation by site of care. For this analysis, we excluded low INR values attributable to the inception phase of warfarin therapy, when low INR is to be expected.

Among patients who had at least 1 low INR, we computed the relative frequencies of the 10 reasons for low INR, which had been assigned through chart review (see “Variables” above). We then used Cox regression to model the effect of these reasons on the time until the next INR and the next in-range INR, corresponding to the target range stated in the clinical record. The reference category for these analyses was low INR because of a previous dose reduction. Such patients might be expected to have a relatively uniform risk for future INR instability, and to receive relatively uniform management. Our Cox models assumed separate baseline hazards by site of care, and our standard errors accounted for the fact that some patients contributed multiple low INR values (SAS PROC PHREG).

We used linear interpolation30 to divide all patient-time into 3 categories: days when the INR was $\leq 1.5$, days when the INR was 1.5 to 2.0, and days when the INR was $\geq 2.0$. For several patients, interpolation was not possible because the final INR determination occurred before a thromboembolic event; in such cases, we carried the last known INR value forward. We compared rates of thromboembolic events among these 3 categories of patient-time, using 1000 bootstrap resamples of the major event INR values to calculate 95% CIs. Finally, we calculated the proportion of thromboembolic events occurring during periods of low INR. Analyses were performed using the R statistical package version 2.8 (R Foundation) and SAS version 9.1. The authors had full access to the data and take.
Results

Risk Factors for Low INR

Of the 4489 patients, 1540 (34%) had at least 1 low INR (Table 1). Most demographic and clinical parameters were similar between patients with and without low INR, with the exception of gender and holds. We examined risk factors for low INR using multivariable Poisson regression (Table 2).

Women had an increased incidence of low INR (incidence rate ratio [IRR], 1.44; P<0.001). Compared with the reference category (AF without prior stroke), patients anticoagulated for valvular heart disease with a high INR target had less low INR (IRR, 0.59; P<0.001). Patients anticoagulated for VTE, in contrast, had more low INR than the reference category (IRR, 1.48; P<0.001), as did patients with valvular heart disease and a normal INR target (IRR, 1.37; P<0.05). Warfarin holds independently predicted low INR (IRR, 1.47 per hold; P<0.001).

Reasons for Low INR

Clinicians managing anticoagulation gave 10 reasons to explain the 3456 low INR values (Table 3). Five reasons...
Dose reduced in reaction to high INR or bleeding 20
Continuing low value 22
No reason apparent after questioning 15
Dose reduced in reaction to high INR or bleeding 15
Continuing low value (ie, second or third consecutive low INR) 13
Initiation of therapy 8
Dietary intake of vitamin K 6
Interaction with other medications 4
All other reasons 3
No data/unknown 2

Table 4. Reason for the Low INR Value Immediately Preceding a “Continuing Low” Value (n=442)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing low value</td>
<td>22</td>
</tr>
<tr>
<td>Dose reduced due to high INR or bleeding</td>
<td>20</td>
</tr>
<tr>
<td>Holds for procedures</td>
<td>20</td>
</tr>
<tr>
<td>No reason apparent after questioning</td>
<td>12</td>
</tr>
<tr>
<td>Adherence issues</td>
<td>9</td>
</tr>
<tr>
<td>Interaction with other medications</td>
<td>5</td>
</tr>
<tr>
<td>Dietary intake of vitamin K</td>
<td>6</td>
</tr>
<tr>
<td>All other reasons</td>
<td>3</td>
</tr>
<tr>
<td>No data/unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

Care Provided to Address Low INR
After a low INR, the median time until the next INR was 8 days (interquartile range, 7 to 14); the median time until the next in-range INR was 16 days (interquartile range, 8 to 30). The next INR occurred sooner (Table 5) when the patient

Table 5. Hazard Ratios for Time to Next INR Value Among 3337 Low INR Values and for Time to Next In-Range INR Value Among 3165 Low INR Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time to Next INR Test, HR (95% CI)</th>
<th>Time to Next In-Range INR, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for anticoagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1.05 (0.94, 1.16)</td>
<td>0.95 (0.85, 1.05)</td>
</tr>
<tr>
<td>Valvular heart disease/prosthetic valve</td>
<td>1.64 (1.45, 1.84)†</td>
<td>1.02 (0.90, 1.15)</td>
</tr>
<tr>
<td>Prior stroke/embolus</td>
<td>1.03 (0.91, 1.17)</td>
<td>1.10 (0.96, 1.25)</td>
</tr>
<tr>
<td>All others</td>
<td>0.98 (0.86, 1.12)</td>
<td>0.90 (0.78, 1.03)</td>
</tr>
</tbody>
</table>

Stated reason for low value

<table>
<thead>
<tr>
<th>Reason</th>
<th>Time to Next INR Test, HR (95% CI)</th>
<th>Time to Next In-Range INR, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose reduced due to high INR or bleeding</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Adherence issues</td>
<td>0.78 (0.69, 0.89)†</td>
<td>0.98 (0.86, 1.11)</td>
</tr>
<tr>
<td>Continuing low value</td>
<td>1.16 (1.02, 1.33)*</td>
<td>0.97 (0.84, 1.11)</td>
</tr>
<tr>
<td>Dietary intake of vitamin K</td>
<td>0.77 (0.65, 0.91)†</td>
<td>0.87 (0.73, 1.03)</td>
</tr>
<tr>
<td>Holds for procedures</td>
<td>0.90 (0.80, 1.03)</td>
<td>1.13 (0.99, 1.29)</td>
</tr>
<tr>
<td>Initiation of therapy</td>
<td>1.93 (1.64, 2.26)†</td>
<td>1.33 (1.13, 1.56)†</td>
</tr>
<tr>
<td>Interaction with other medications</td>
<td>0.97 (0.80, 1.17)</td>
<td>1.07 (0.88, 1.29)</td>
</tr>
<tr>
<td>All other reasons</td>
<td>0.99 (0.80, 1.22)</td>
<td>1.01 (0.81, 1.26)</td>
</tr>
<tr>
<td>No reason apparent after questioning</td>
<td>0.80 (0.70, 0.91)†</td>
<td>1.00 (0.87, 1.14)</td>
</tr>
<tr>
<td>No data/unknown</td>
<td>0.70 (0.51, 0.96)*</td>
<td>0.77 (0.55, 1.07)</td>
</tr>
</tbody>
</table>

A hazard ratio above 1.0 indicates reduced time until the event. These analyses control for demographics (age, gender, and race). Our Cox models assumed separate baseline hazards by site of care, and our standard errors accounted for the fact that some patients contributed multiple low INR values.

Table 3. Relative Frequencies of 10 Reasons Given by Clinicians for INR ≤1.5 (n=3456 INR Values)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence issues</td>
<td>17</td>
</tr>
<tr>
<td>Holds for procedures</td>
<td>16</td>
</tr>
<tr>
<td>No reason apparent after questioning</td>
<td>15</td>
</tr>
<tr>
<td>Dose reduced due to high INR or bleeding</td>
<td>15</td>
</tr>
<tr>
<td>Continuing low value</td>
<td>13</td>
</tr>
<tr>
<td>Initiation of therapy</td>
<td>8</td>
</tr>
<tr>
<td>Dietary intake of vitamin K</td>
<td>6</td>
</tr>
<tr>
<td>Interaction with other medications</td>
<td>4</td>
</tr>
<tr>
<td>All other reasons</td>
<td>3</td>
</tr>
<tr>
<td>No data/unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

Impact of Low INR on Thromboembolic Events
There were 55 major thromboembolic events during the study (Table 6), 12 of which occurred when the INR was ≤1.5, 9 of which when the INR was 1.5 to 2.0, and 34 when the INR was ≥ 2.0. Of the 12 events that occurred when the INR was ≤1.5,
Table 6. Rates of Thromboembolic Events in Different INR Ranges

<table>
<thead>
<tr>
<th>INR Value</th>
<th>Thromboembolic Events</th>
<th>Patient-Time, y</th>
<th>Rate, Events/100 Patient-y (95% CI)</th>
<th>Unadjusted IRR (95% CI)</th>
<th>Fraction of Events, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.5</td>
<td>12</td>
<td>70.8</td>
<td>16.95 (8.5–26.8)</td>
<td>16.3 (8.1–25.7)</td>
<td>21.8 (12.2–35.4)</td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>9</td>
<td>545.1</td>
<td>1.65 (0.73–2.75)</td>
<td>1.59 (0.70–2.64)</td>
<td>16.4 (8.2–29.3)</td>
</tr>
<tr>
<td>≥2.0</td>
<td>34</td>
<td>3262.3</td>
<td>1.04 (0.83–1.26)</td>
<td>1.0 (reference)</td>
<td>61.8 (47.7–74.3)</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>3878.2</td>
<td>1.42 (1.11–1.95)</td>
<td>...</td>
<td>100</td>
</tr>
</tbody>
</table>

INR values determined by linear interpolation.

7 were associated with a hold (58%). The crude IRR for the lowest INR category, compared with INR ≥2.0, was 16.3 (95% CI, 8.1 to 25.7), whereas the IRR for mildly low INR was only 1.59 (95% CI, 0.70 to 2.64). The fraction of thromboembolic events occurring with an INR value ≤1.5 was 12/55, or 21.8% (95% CI, 12.2% to 35.4%). However, an additional 7 events occurred within 30 days of an INR ≤1.5, so the true fraction could be as high as 19/55, or 34.5% (95% CI, 22.6% to 48.7%).

Although the absolute rate of thromboembolism during periods of low INR was high, the absolute rate of thromboembolism per episode of low INR was quite low. There were a total of 3375 separate episodes of INR ≤1.5 in our database, considering continuing low values as part of a single episode. A thromboembolic event occurred during or within 30 days after the end of only 19 of these episodes (0.6%; 95% CI, 0.3 to 0.9%), whereas the majority of episodes (99.4%) did not result in a thromboembolic event.

Discussion

We examined patient-level risk factors for low INR (≤1.5) using a large nationally-representative database of anticoagulation care. Low INR was not a rare event, occurring among 34% of our study population and accounting for 4.1% of INR values and 1.8% of patient-time. Low INR also had important consequences: there was an approximately 16-fold increase in the rate of thromboembolism during periods of low INR. We found that the fraction of thromboembolic events occurring during periods of low INR was at least 21.8%, considerably higher than the estimate by van Walraven et al (11%). Our results suggest that reducing or eliminating low INR could improve patient outcomes considerably.

Despite the impressive relative risk of a thromboembolic event during periods of low INR, the absolute risk of thromboembolism related to an episode of low INR was small (0.6%). Therefore, careful consideration should be given to balancing expected risks and benefits of interventions such as “bridging” with low-molecular-weight heparin, which is associated with a significant risk of bleeding complications. Ongoing clinical trials may settle the issue of whether, and for which patients, the benefits of bridging outweigh the risks.

Until the results of such trials become available, our estimate of the absolute risk of thromboembolism related to an episode of low INR may help to guide clinical decision-making.

Regarding risk factors for low INR, warfarin holds predicted more low INR values, whereas a high-target INR range predicted fewer. More novel and unexpected findings included increased incidence of low INR among patients anticoagulated for VTE and among women. These findings, which persisted after controlling for age, comorbid conditions, and holds, are potentially important, but require confirmation and further investigation. One possible explanation might have been a difference in target INR ranges between groups; however, we compared target ranges by gender and by indication and did not find differences that could have explained our findings. If confirmed, our findings may be attributable to different physiological responses to warfarin in different groups of patients, or may reflect disparities in anticoagulation management. For example, it is possible that clinicians fear the consequences of high INR more in female patients, which may affect dosing decisions.

We also examined reasons given to explain low INR values in the clinical record. Although no single reason predominated, the 4 most common reasons bear comment. Nonadherence was the most commonly cited reason for low INR. The impact of adherence on anticoagulation control has been described by Kimmel et al. In that study, 36% of patients missed more than 20% of bottle openings as measured by electronic bottle caps (“MEMS caps”); these patients had an odds ratio of 2.10 for INR below the target range. In our study, 17% of INR values ≤1.5 (a more serious deviation than merely below the target range) were attributed to adherence. We note that 15% of low INR values in our cohort could not be explained—it is possible that at least some of these were also attributable to inadequate adherence, which the patient did not recall or did not declare.

The next most common reason for low INR was intentional interruptions of warfarin for procedures (“holds”). Our group has previously demonstrated that holds are associated with the relatively poor anticoagulation control experienced by cancer patients. Although some holds may be necessary, our results suggest that avoiding holds whenever possible will reduce low INR. As an example of a situation in which a hold may be avoided, dental procedures can often be performed without holds, but this may be inconsistently applied in clinical practice.

The third most common reason for low INR was a recent dose reduction, most often in response to a previously recorded high INR value. This seesaw effect, where patients bounce between excessive and insufficient anticoagulation, may be partly attributed to the well-known fact that warfarin is a difficult drug to manage in clinical practice. However, at least part of this erratic control may be associated with excessive “tinkering” with warfarin doses when the INR is close to the target range.

In another analysis of this database, our group has already shown that INR control could be improved by reserving dose changes for patients whose
INR deviates from the target range by 0.3 or more in either direction.27

The fourth most common reason for low INR was a “continuing low.” Recall that we defined “low INR” as ≤1.5—a level of underanticoagulation clearly associated with patient harm.22–24 Nevertheless, we found that the median time until a next INR test was 8 days, and the median time until a next in-range INR value was 16 days. These values themselves are not alarming, but the 75th percentile for each (14 and 30 days) indicate that for a considerable proportion of patients in our dataset, low INR was addressed without a particular sense of urgency. Indeed, we found that the most common reason for the INR preceding a continuing low was another continuing low.

Current guidelines may reinforce a lack of urgency in addressing low INR values, because they contain limited guidance about how to address low INR. For example, the 2008 ACCP guidelines5 contain detailed instructions about how to deal with elevated INR, but limited information regarding how to address low INR, beyond the recommendation that “bridging” with low-molecular-weight heparin is not necessary for most patients. Although we agree that low-molecular-weight heparin is not warranted by the relative low daily risk of thromboembolism in most patients,35 it would be prudent to measure the INR weekly among patients with changes in clinical status or anticipated dose instability, to prevent prolonged or extreme deviations from the target INR range. We recognize, however, that some patients may not readily accept the burden of such frequent testing.

Our study has important strengths. This is the first systematic investigation of low INR in community practice. We used a large, nationally-representative database of community-based anticoagulation care in the United States, ensuring that our results are broadly generalizable. Finally, manual review of all 84,915 notes provided a level of clinical detail missing from many previous studies, which have used predominantly automated data. However, our study also has limitations. We were only able to ascertain the reason for low INR as stated by clinicians in the notes, but were unable to test the veracity of such claims. In addition, the reason for 15% of low values could not be determined by the clinician at the time of the visit, despite questioning the patient.

In conclusion, we used a nationally-representative database of community-based anticoagulation care to describe the epidemiology of low INR. In our study, low INR was associated with a 16-fold increase in the rate of thromboembolism. Despite this impressive relative risk, the absolute risk of thromboembolism per episode of low INR was only 0.6% per episode. Women and patients anticoagulated for VTE were at elevated risk for low INR. Nonadherence, interruptions for procedures, and insufficient urgency in addressing low INR all contribute to the incidence of low INR. The incidence of low INR could be reduced by interventions to improve adherence, minimize unnecessary interruptions of therapy, and encourage clinicians to address low INR with an appropriate (but not excessive) sense of urgency.

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Disclosures
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References


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