Postanalytical External Quality Assessment of Warfarin Monitoring in Primary Healthcare

Ann-Helen Kristoffersen,* Geir Thue,2 and Sverre Sandberg1,2

Background: An increasing number of patients are treated with warfarin worldwide, and many are monitored in general practice, often with office instruments. Bleeding or thromboembolic episodes may be consequences of inadequate treatment. We have therefore examined some important aspects of general practitioners’ (GPs’) knowledge of warfarin treatment.

Methods: A questionnaire including 2 case histories with familiar indications for warfarin treatment (mechanical heart valve prosthesis and pulmonary embolism) was circulated to 3781 GPs in Norway as a postanalytical quality assessment.

Results: A total of 1547 GPs (41%) responded. There were substantial variations among GPs concerning the frequency of international normalized ratio (INR) monitoring, stated therapeutic ranges for arterial (but not venous) indications for anticoagulation therapy, and handling of a moderately high INR result of 5.9. Most GPs estimated an unrealistically high risk of serious bleeding in the latter situation (median, 15%; 10th and 90th percentiles, 4% and 50%, respectively). The critical difference necessary to change the warfarin dose was highly dependent on perceived therapeutic intervals, and about half of the GPs suggested a critical difference of 0.8 INR, which is attainable with office instruments. Sex and age of the GPs, practice size, and availability of an INR instrument in the office laboratory did not influence the results to any substantial degree, as variations within subgroups were similar.

Conclusions: Gross variations in practice were found, especially for aspects of warfarin treatment that lacked uniform guidelines. Evidence-based and practicable recommendations for treatment and monitoring of these patients are still needed.

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The effectiveness of oral anticoagulant treatment with vitamin K antagonists (coumarin derivatives) has been demonstrated for several indications in the last decades, and the use of this treatment is increasing. The most important indications are atrial fibrillation, venous thromboembolism, and prevention of systemic embolism in patients with prosthetic heart valves. Several studies have also shown a marked decrease in mortality after myocardial infarction (1).

The drawbacks of vitamin K antagonist treatment are that regular laboratory control of prothrombin time international normalized ratio (INR)3 and individualized dose adjustment within narrow therapeutic intervals are necessary to avoid bleeding or thromboembolic complications (2). Every year, 1% of users experience a major bleeding episode, and fatal bleeding occurs in 0.25%–0.5% annually (3). The risk of thromboembolism increases with the use of low-intensity therapy (INR 1.5–1.9) compared with conventional-intensity therapy (INR 2.0–3.0), from 0.7 per 100 person-years to 1.9 per 100 person-years (4). Thus, good therapeutic control and time spent within the therapeutic interval have been associated with a decrease in bleeding and thromboembolic complications (5, 6).

In Norway, warfarin is the only vitamin K antagonist used, and the majority of patients are monitored by general practitioners (GPs). Instruments for point-of-care testing of INR are widespread in Norway and are currently used in ~60% of practices. Our study addressed GPs’ knowledge of aspects of warfarin treatment in 2 clinical situations in general practice, with special emphasis on whether this knowledge differed among the GPs with and without INR instruments in the office labora-

1 Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway.
2 Norwegian Centre for Quality Improvement of Primary Care Laboratories, Section for General Practice, Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway.
*Address correspondence to this author at: Laboratory of Clinical Biochemistry, Haukeland University Hospital, Helse Bergen HF, Postbox 1, 5021 Bergen, Norway. Fax 47-55973115; e-mail: ann.kristoffersen@helse-bergen.no.

Received April 3, 2006; accepted July 11, 2006.

Previously published online at DOI: 10.1373/clinchem.2006.071027

3 Nonstandard abbreviations: INR, (prothrombin time) international normalized ratio; NOKLUS, Norwegian Centre for Quality Improvement of Primary Care Laboratories; GP, general practitioner; CD, critical difference; CVa, analytical variation; CVws, within-subject variation.
tory. To our knowledge, postanalytical quality assessment of warfarin treatment in general practice, with standardized case histories, has not been studied.

**Materials and Methods**

A model for distributing case histories together with regular quality assessment material has been developed by the Norwegian Centre for Quality Improvement of Primary Care Laboratories (NOKLUS). The model is used systematically as an educational postanalytical tool (7, 8). Approximately 99% of all practices in Norway participate in the external quality assessment survey of NOKLUS. Two case histories with familiar indications for warfarin treatment and a short questionnaire (Fig. 1) were sent to all 1665 office laboratories in Norway that participated in the NOKLUS external quality assessment survey. Of these, 712 practices (1935 GPs) had instruments for INR analysis, whereas 953 practices (1846 GPs) did not have such equipment.

We chose case history A to focus on strict monitoring of warfarin treatment in a patient with a mechanical heart valve prosthesis and stable INR results, whereas case history B focused on INR measurement and warfarin dosage in a patient recovering from pulmonary embolism with INR above the therapeutic range. Both case histories were modeled after real patient encounters, and care was taken to present them in a form familiar to GPs. As is usual in the NOKLUS scheme of case histories, GPs had a responder limit of 10 days, and no reminders were used. NOKLUS had some information on practices, but not on individual GPs. We therefore collected background information on sex, age, and number of colleagues, and GPs also stated their initials so that they could receive individual feedback reports through practice staff, comparing their own response with results from the other participants. In addition, the feedback report included recommendations for the different issues posed in the questionnaire.

For their evaluation of the monitoring situation (patient A), doctors were asked to state the minimum changes in INR necessary to increase or decrease the warfarin dose. These changes were evaluated by use of the concept of critical difference (CD), also called reference change value. The CD is defined as the minimum difference needed between 2 consecutive test results to be certain (with a given degree of confidence) that results are truly different and not simply a reflection of usual analytical and biological variation (9):

\[
CD = \text{bias} + z \text{ value} \times \sqrt{\frac{2}{2} (CV_a^2 + CV_{ws}^2)}
\]

(10-12), with \(z\) values for 1-sided tests and the chosen probability. We used \(z\) values corresponding to probabilities of 80% (\(z = 0.84\)) and 95% (\(z = 1.64\)). Analytic variation (\(CV_a\)) is imprecision under reproducibility conditions and includes intermittent systematic variation such as batch-to-batch variation, and we therefore omitted the bias component in the calculations. Within-subject variation (\(CV_{ws}\)) is the mean coefficient of variation for INR in a patient on steady-state anticoagulation treatment with warfarin and is reported to be 9.6% (10, 13). With known CDs and \(CV_{ws}\) \(CV_a\) may be calculated by rearranging the following formula:

\[
CV_a = \sqrt{\frac{CD}{z \text{ value} \times \sqrt{2} (CV_a^2 + CV_{ws}^2)}}
\]

Differences between subgroups (age, sex, INR instrument available, and practice size) were explored with the Mann–Whitney U-test, Kruskal–Wallis test, and \(\chi^2\) test as appropriate, with a significance of 0.05. SPSS (ver. 13.0; SPSS Inc.) was used for statistical analysis.

**Results**

We received responses from 1547 (41%) of a total of 3781 GPs. The response rate was significantly higher among GPs analyzing INR in their office laboratory (45% vs 37%). Significantly more group practices performed INR analysis compared with solo practices, and solo practitioners were significantly older than responders in group practices. The 2 groups were otherwise comparable.

**FREQUENCY OF INR MONITORING AND THERAPEUTIC INTERVALS**

For patient A, the minimum number of weeks allowed until the next INR measurement was 4 (median), with 10th and 90th percentiles of 2 and 4 weeks, respectively, whereas the maximum number of weeks was 6 (10th and 90th percentiles of 4 and 8 weeks, respectively). GPs <35 years advocated a significantly shorter interval concerning the minimum number of weeks (median, 3 vs 4 weeks).

Several therapeutic ranges were stated by the GPs for arterial indications for anticoagulant therapy (Table 1, patient A). Of all the GPs, 29% stated the therapeutic interval to be 2.5–3.5 INR. In contrast, therapeutic ranges for venous indications (patient B) were much fewer and more homogenous, and 63% agreed on 2.0–3.0 INR. Approximately 16% of GPs stated a therapeutic interval where the difference between the high and low therapeutic limits was <1 INR unit in both case histories.

**CD AND ANALYTICAL QUALITY**

The range of CDs stated by the GPs for increasing or decreasing the warfarin dose from an INR result of 3.3 was substantial (Table 2, patient A), and CDs were significantly smaller when an increase in the INR result was considered. If the CDs were smaller than 0.8 and 0.4 INR units (95% and 80% confidence, respectively), \(CV_a\) could not be calculated (Table 2). Approximately 95% of the GPs would not change the warfarin dose if the INR results were within the therapeutic intervals stated by themselves (Fig. 2), 74% of the GPs would not increase the dose until the result was 0–0.3 INR units below their lower therapeutic limits (Fig.
**Questionnaire**

**Patient A** is a 72 year-old man, otherwise healthy, who had an operation two years earlier for aortic stenosis with a mechanical heart valve prosthesis. You have taken over his treatment with Marevan (warfarin). During the last months, his INR value have ranged from 3.0 to 3.5. The last result you received was 3.3 INR. His Marevan dosing has been unchanged during this time.

- Give the time in weeks until the next INR measurement: at least ____ week(s), but not more than ____ weeks.
- If you were to increase his Marevan dose, how low must this INR value be? ____.
- If you were to decrease his Marevan dose, how high must the INR value be? ____.
- In your opinion, what is the therapeutic range for this patient?: INR value between ____ and ____.

**Patient B** is a 56 year-old woman, who five months ago was found to have a pulmonary embolism. In addition, she has arthritis, which does not presently require treatment. No cause for the embolism has been found, and she is treated with Marevan. The last INR value and Marevan doses have been:

<table>
<thead>
<tr>
<th>Marevan dose (tablets(^1)) and day</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thurs</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 6 weeks ago: 3.3</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>INR 3 weeks ago: 4.2</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

On a Monday, you get a new INR value, which now is 5.9. The patient feels well and has taken her daily Marevan dose.

- Fill in the Marevan dose (tablets) from Tuesday and throughout the following week, or until the day when you would have ordered a new INR.

<table>
<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- What do you think is her risk of having a serious bleeding episode, with the need for hospital admission, during the next few days? ____ %

\(100\% - absolutely\, certain\, that\, she\, gets\, a\, serious\, bleeding\, episode;\) 
\(0\% - absolutely\, certain\, that\, she\, does\, not\)

In your opinion, what is the therapeutic range for this patient?: INR value between ____ and ____.

\(^1\) 1 tablet = 2.5 mg of warfarin

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Fig. 1. Case histories presented to the GPs.
2A), and 65% would not decrease the dose before the result was 0–0.3 INR units above their upper therapeutic limits (Fig. 2B). Approximately 25% reported that they would change the dose exactly on their upper or lower limit (Fig. 2).

Handling of a high INR result and estimation of the risk of serious bleeding
The median number of days until a new INR measurement was considered necessary, with a previous INR result of 5.9, was 7 days, with 10th and 90th percentiles of 3 and 8 days, respectively (patient B). Although GPs who had an INR instrument available in their practice, younger GPs, and GPs estimating a higher bleeding risk requested a new INR result much earlier than other subgroups, all subgroup medians were 7 days, and the range within subgroups was substantial.

The planned dose of warfarin for patient B for the first 2 days after receiving an INR result of 5.9, was 9 tablets (1 tablet = 2.5 mg). Approximately 95% of GPs suggested decreasing the warfarin dose after the high INR result, and the sum of tablets for the first 2 days was decreased to a median of 4 tablets, with 10th and 90th percentiles of 0 and 8 tablets, respectively.

Table 1. Therapeutic intervals suggested for patient A (mechanical heart valve prosthesis) and patient B (pulmonary embolism).

<table>
<thead>
<tr>
<th>Therapeutic intervals INR</th>
<th>Patient A, % of GPs (n = 1541)</th>
<th>Patient B, % of GPs (n = 1542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0–3.0</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td>2.0–3.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2.5–3.0</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>2.5–3.5</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>2.8–4.2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2.8–4.5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3.0–3.5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3.0–4.0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>3.0–4.5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other therapeutic intervals*</td>
<td>35</td>
<td>22</td>
</tr>
</tbody>
</table>

* Therapeutic intervals suggested by <3% of GPs.

GPs who stopped warfarin (0 tablets) for the first 2 days estimated a median risk of serious bleeding of 20%, which was significantly higher than the median bleeding risk of 10% estimated by the GPs prescribing 1–4 tablets or 5–8 tablets. Overall, the GPs estimated a median risk of bleeding during the next few days of 15%, with 10th and 90th percentiles of 4% and 50%, respectively, nearly irrespective of their dosage suggestions (Table 3). The GPs without instruments in their office laboratory estimated a higher bleeding risk than the GPs with instruments (20% vs 10%). Only 4.7% estimated a “small” bleeding risk of <2%.

Discussion
The GPs in Norway are used to responding to case histories from NOKLUS, and considering the short response time and no use of reminders, a response rate of 41% is satisfactory. Case histories are especially suitable for evaluating clinical judgments of INR results because information from other laboratory analyses or from clinical findings is seldom needed. The response rate was higher for GPs with instruments in their office laboratory, which could reflect more interest in and knowledge about warfarin treatment. However, all responders probably had more interest in and knowledge about warfarin treatment than the general GP population, although their age and sex distributions were very similar to that of the general GP population (14).

Frequency of INR monitoring and therapeutic intervals
It has been suggested that adequate INR monitoring can only be achieved if stable patients are reviewed at least every 3 or 4 weeks (5, 15, 16). Our findings of 3–5-week intervals are in line with these suggestions. However, studies do not agree on this issue (1, 17, 18), and thus agreement among GPs could not be expected.

Regarding therapeutic intervals stated by the GPs, the agreement was much higher for the venous indication (pulmonary embolism) compared with the arterial indication (mechanical heart valve prosthesis; Table 1). For venous indications, most of the guidelines agree on a therapeutic interval of 2.0–3.0 INR or a target value of 2.5 INR (1, 4–6, 19). However, the optimal intensity of anti-

Table 2. Calculated analytical imprecision (CVa) for INR based on critical differences from an INR value of 3.3 as stated by the GPs.

<table>
<thead>
<tr>
<th>INR value stated</th>
<th>Increase warfarin dose, percentiles of GPs</th>
<th>Decrease warfarin dose, percentiles of GPs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>CD, %</td>
<td>12.1</td>
<td>18.2</td>
</tr>
<tr>
<td>Calculated CVa, % (95% confidence)*</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Calculated CVa, % (80% confidence)*</td>
<td>3.5</td>
<td>11.9</td>
</tr>
</tbody>
</table>

* CVa = CD/2z/2CVws, z = 1.64 (95%).

* NC, not possible to calculate.

* CVa = CD/2z/2CVws, z = 0.84 (80%).
Fig. 2. Patient A is a patient with mechanical heart valve prosthesis and an INR value of 3.3. (A), the x axis shows the difference between the GP’s own lower therapeutic limit and the INR result stated by the same GP to increase the warfarin dose. A positive value means that the GP increased the warfarin dose when the INR result stated was below the GP’s own lower therapeutic limit, and a negative value means that the GP increased the warfarin dose when the INR value was within the therapeutic limits. The y axis represents the cumulative percentage of GPs increasing the warfarin dose. (B), the x axis shows the difference between the INR result stated by the GP to decrease the warfarin dose and the same GP’s higher therapeutic limit. A positive value means that the GP decreased the warfarin dose when the INR result stated was above the GP’s own higher therapeutic limit, and a negative value means that the GP decreased the warfarin dose when the INR value was within the therapeutic limits. The y axis represents the cumulative percentage of GPs decreasing the warfarin dose.
coagulation for patients with arterial indications has been a matter of debate, especially with regard to prosthetic valves, and consequently, several different therapeutic ranges have been suggested \cite{18,20-23}. This lack of consensus could be the explanation for disagreement among GPs regarding high-intensity anticoagulation.

**CD AND ANALYTICAL QUALITY**

Despite the substantial differences in CDs stated by the GPs for patient A, CDs were highly associated with the doctors’ perceived therapeutic limits (Fig. 2). This is in line with earlier studies showing that GPs preferentially react to changes in hemoglobin concentrations that are close to reference limits when they judge case histories \cite{24}. Seemingly, the GPs tolerated a larger decrease than increase in INR results before reacting, but this could be explained by the fact that 37% of the GPs stated their upper INR limit at 3.5, which is close to 3.3 stated in case history A (Table 1).

Instruments in hospital laboratories as well as the 2 most used INR instruments in Norwegian primary care (Thrombotrack\textsuperscript{TM},Axis-Shield, and CoaguChek\textsuperscript{®} S, Roche), have CV\textsubscript{a} values of 3%-5% in the therapeutic range (25, 26). Thus, for patients with stable INR results, an INR change of \pm 25% (or 0.8 INR units from 3.3) could be regarded as a real change (with 95% confidence, with a CV\textsubscript{a} of 5% and a CV\textsubscript{ws} of 9.6%). This is close to the median CD stated by the GPs (Table 2). However, because strict monitoring of patients with valve prosthesis is important, many GPs may intuitively react to smaller changes, and with 80% confidence, an INR change of \pm 13% (or 0.4 INR units from 3.3) thus may be considered “real.” Still, many GPs presuppose an analytical quality that cannot be achieved, probably because they are unaware of the effect of biological variation, or practice dose change at or near therapeutic limits irrespective of the previous INR result (Table 2). In a steady-state situation, changes in dose because of small changes in INR might lead to more frequent INR measurements and further dose changes, leading to unstable anticoagulant control. Furthermore, it has been shown that asymptomatic patients with mildly increased INR (0.3-0.4 above the upper therapeutic limit) could be maintained safely on unchanged warfarin dose \cite{27}. However, often the GPs have several INR measurements in the same patient and can evaluate trends toward higher or lower INR values, and not just compare one measurement with the next. For patient A, this could imply reacting on smaller changes.

Most of the publications on vitamin K antagonist treatment recommend a therapeutic interval where the difference between the high and low therapeutic limits is 1 INR unit \cite{1,5,19,20}. This goal implies that the GPs must react to rather small INR changes (Table 2), which might be difficult for reasons of biological and analytical variation. Consequently, some authors have recommended a target value instead of a range \cite{5,16,19} and predict more patients within therapeutic range with this strategy, because doctors will react to changes from a target value instead of reacting to small deviations from an upper or lower limit.

**HANDLING OF A HIGH INR RESULT AND ESTIMATION OF THE RISK OF SERIOUS BLEEDING**

In patient B, with a last INR result of 5.9, the GPs were asked to state the time until the next INR measurement. The range of suggestions was substantial in all subgroups, although concentrating on 4 days (until a Friday) and 7 days (until a Monday).

Norwegian guidelines suggest 2–4 days before measuring INR in such situations \cite{16,28}. On the basis of the half-lives of vitamin K-dependent coagulation factors, it takes 3–5 days for the anticoagulant effect to decrease to therapeutic levels after measurement of moderately high INR values \cite{29,30}. However, studies report a highly variable rate of INR decrease after omitting warfarin \cite{31,32}. The majority of GPs seemed to state a reasonable period, taking practical issues (an intervening weekend) into account. Still, many GPs probably are too reluctant to stop warfarin for a shorter period, and the variation in the warfarin doses suggested was substantial (Table 3).

The risk of hemorrhage increases exponentially with increasing INR values \cite{33,34}. Risk of serious bleeding complications per 48 h for a patient with INR between 4.5 and 6.9 has been estimated to be \pm 0.2% (3, 35), but estimates vary because of differences in cohorts studied and in what is considered “serious” \cite{36}. The GPs in our study tended to grossly overestimate the short-time bleeding risk. Beyth et al. studied bleeding risk in outpatients, and stated that “in clinical practice the ability of physicians to predict risk of bleeding in a cohort of patients was no better than could be achieved by chance” \cite{37}. In our study, the range of warfarin dose and the

<table>
<thead>
<tr>
<th>Bleeding risk estimate, %</th>
<th>0 tablet (n = 518)</th>
<th>1–4 tablets (n = 671)</th>
<th>5–8 tablets (n = 216)</th>
<th>( \geq 9 ) tablets (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>41.7</td>
<td>52.0</td>
<td>58.3</td>
<td>46.8</td>
</tr>
<tr>
<td>11–30</td>
<td>30.4</td>
<td>28.1</td>
<td>22.2</td>
<td>36.2</td>
</tr>
<tr>
<td>31–50</td>
<td>13.2</td>
<td>13.5</td>
<td>15.6</td>
<td>10.6</td>
</tr>
<tr>
<td>&gt;50</td>
<td>14.9</td>
<td>6.6</td>
<td>4.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>

* 1 tablet = 2.5 mg of warfarin.
range of days until a new INR measurement were wide, irrespective of the bleeding risk estimate. Thus, it seems that the bleeding risk estimate did not influence the handling of patient B, and GPs were seemingly unaccustomed to dealing with such estimates.

In conclusion, lack of guidelines seems to be associated with gross variations in practice, as was shown for suggestions concerning the frequency of INR monitoring, statement of arterial therapeutic range, and handling of a moderately high INR result. Most GPs were not aware of the “true” bleeding risk related to such results. Estimation of CD probably did not take account of the consequences of biological variation and was highly dependent on therapeutic intervals stated by the GPs themselves. Evidence-based and practicable recommendations for the treatment and monitoring of these patients are still needed.

We thank Lene G. Dalbak (Section for General Practice, University of Oslo, Oslo, Norway) for the first processing of raw data.

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