Individual approach towards optimal oral anticoagulation
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Chapter 4

Minor Bleeds Alert for Subsequent Major Bleeding in Patients Using Vitamin K Antagonists

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Submitted
SUMMARY

Background: The majority of bleeding complications in patients on vitamin K antagonists (VKA) are clinically mild. These minor bleeds might be due to over-anticoagulation or a pre-existing mild bleeding disorder, which is enhanced by VKA.

Objective: We investigated whether minor bleeds were associated with an increased risk of major bleeding, whereas possible intensified monitoring of VKA therapy after a minor bleed would improve quality of anticoagulation, thereby modifying the risk of major bleeding.

Methods: In an inception cohort of 6758 consecutive patients followed at a specialist anticoagulation clinic, this dual hypothesis was retrospectively studied. The risk of major bleeding was estimated using a multivariable Cox proportional hazards regression model with including a time-varying exposure for occurring minor bleeds. The achieved individual time within INR target range (ITTR) was specifically addressed.

Results: In patients without a minor bleed (N=5410) the incidence rate of major bleeding was 1.6 per 100 person-years (95%CI 1.3-2.1) and in patients with a minor bleed 2.1 per 100 person-years (95% CI 1.5-2.9) (N=1348). Patients with a minor bleed had a 3.6-fold higher risk of subsequent major bleeding (95%CI 2.0-6.6, P<0.001). ITTR was also independently associated with major bleeding, with a 2.8-fold increased risk in patients with an ITTR<25% of the total treatment time (95% confidence interval (CI) 1.7-4.5, P<0.001). Comparing patients with and without a minor bleed, there was no difference in ITTR (43% vs. 42% respectively).

Conclusion: Minor bleeds alert for subsequent major bleeding, independent of the achieved quality of anticoagulation.
INTRODUCTION

Vitamin K antagonists (VKA) are widely used in primary and secondary prevention of thromboembolism. Although these drugs have shown to be effective, the associated risk of bleeding is an important limitation [1]. Both effectiveness and risk of bleeding are related to the actual level of anticoagulation, expressed by the international normalized ratio (INR) [1,2]. The intensity of anticoagulation widely varies within and between patients, due to environmental and genetic factors [3-9], as well as patient’s compliance [10,11]. In this respect, the individual time within INR target range (ITTR) can be used to identify patients on VKA who are at high risk of (recurrent) thromboembolism and bleeding [2,12].

In most of the research on the risk of bleeding while using VKA, the primary focus was on major bleeding [1]. The risk of major bleeding is strongly associated with the level of anticoagulation. Furthermore, a history of major bleeding is also identified as a risk factor for subsequent major bleeding, although not consistently in all studies [13-17]. However, the majority of bleeding complications in patients on VKA are clinically mild. Incidence rates of major bleeding range from 1.4 to 3.3 per 100 person-years, whereas for minor bleeding incidence rates up to 30 per 100 person-years are reported [1,4,18-20]. Minor bleeding might be due to over-anticoagulation or a pre-existing mild bleeding disorder, which is enhanced by VKA. In either case, as with a history of major bleeding, the occurrence of a minor bleed during VKA therapy could be associated with an increased risk of major bleeding.

In this study, we hypothesized that patients with a minor bleeding are at increased risk for subsequent major bleeding, similar to a history of major bleeding. In this, minor bleeds alert for subsequent major bleeding. On the other hand, minor bleeds occurring during VKA therapy could lead to intensified monitoring of VKA therapy to maximize the quality of anticoagulation and thereby reducing the risk of major bleeding.

METHODS

Patients and study design
A total of 6758 patients were retrospectively studied over a 3-year period. Patients already on VKA at the start of the study period were excluded (inception cohort). The
patients originated from two cohorts of consecutive patients referred to a large Dutch community based anticoagulation clinic for management of their VKA therapy from 1 January 1995 to 1 February 1998. Both cohorts were described in greater detail previously [2,12]. One cohort consisted of patients with deep vein thrombosis (n=1599) and patients with pulmonary embolism (n=705), and the other cohort of patients with atrial fibrillation (n=2614), patients with a myocardial infarction (n=1012) and patients with a prosthetic heart valve (n=828).

All patients were followed from the first INR measurement by the anticoagulation clinic until the end of treatment or the end of the study.

In the Netherlands, a unique nationwide network of 61 specialized anticoagulation clinics is responsible for the VKA management of all outpatients. In these specialized clinics, experienced physicians and dosing assistants are involved in optimizing VKA therapy, using computerized dosing programs and protocols for dose adjustments in case of under- and over-anticoagulation. In addition, patient education and awareness regarding factors influencing the quality of VKA therapy and signs of over-anticoagulation, i.e. minor bleeding, are specifically addressed.

Data collection

Patients' characteristics

Patients' characteristics were collected from the records on file at the anticoagulation clinic. Baseline data included age, sex, co-morbidity, concomitant drugs and indication for VKA therapy.

Anticoagulation data

INR target range, as recommended by the Dutch Federation of Anticoagulation Clinics, was 2.5 to 3.5 in patients with venous thromboembolism or atrial fibrillation, and 3.0 to 4.0 in patients with myocardial infarction. In patients with a prosthetic heart valve, up to January 1st 1997 the target range was INR 3.5 to 4.8. From January 1st 1997 onwards, it was lowered to INR 3.0 to 4.0. In all patients, VKA dosing was performed using a nomogram based automated system, with control by experienced physicians. INR was measured once every 3 to 4 weeks or more frequently when appropriate. In the initial phase, INR was checked more frequently, i.e. every 3 to 5 days. The dose was increased with predefined dose steps at INR values below the target range, and tapered at INR values exceeding the target range but less than 6.4.
Treatment was interrupted for one day at INR values above 6.4 and vitamin K was additionally given in case of INR > 10.0. The next measurement of INR was then performed within 3 days. The VKA of first choice was acenocoumarol. All data regarding anticoagulant therapy were stored in a computerized registration system. INR values, dates of measurements and dosage schedules were extracted from this system.

Adverse events
The physicians of the anticoagulation clinic registered all major bleeds, as a mandatory part of their quality system. Within the unique setting of VKA management in the Netherlands, patient education and awareness regarding the risks of VKA therapy also included reporting the occurrence of minor bleeds to the treating physicians. If treatment was interrupted due to a minor bleed, this was also included. For this study, all information about major and minor bleeds, hospital admissions, treatment interruptions or cessation, and death during the treatment period was collected. To minimize misclassification, all events were adjudicated by an experienced haematologist, who was not informed about the level of anticoagulation to assure a blinded classification.

Clinical outcome
Endpoints of clinical outcome were major and minor bleeds. Major bleeding was defined as a clinically overt bleed leading to transfusion, hospitalization and/or death, as well as a retroperitoneal, intracranial or intra-ocular bleed [21]. An overt bleed not classified as major was considered minor. When a minor bleed required any medical intervention, it was classified as clinically relevant minor bleed.

Statistical analysis
Based on actual INR values, the day-to-day INR values were calculated by linear estimation, as proposed by Rosendaal et al. with an adjustment of estimated values towards the next actual INR value [2,22]. Linear estimation was not performed when time between two assessments was more than 8 weeks, since the assumption of linearity was no longer judged as valid [23]. From the estimated day-to-day INR values, the percentage of time within the predefined target range was calculated for each individual patient (ITTR). Post-event data were not included in the calculation of
ITTR. Stability of anticoagulation was expressed as mean absolute difference (SD) in daily INR values.

Absolute risks (incidence rates per 100 person years) of minor and major bleeding were assessed. Ninety-five percent confidence intervals (95%CI) around the incidence rates were calculated under the Poisson distribution assumption. In these calculations, the post-event follow-up time was not included.

Table 1 Characteristics of patients at baseline and anticoagulation data.

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Total</th>
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<tbody>
<tr>
<td>Age, years †</td>
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<td>Male, %</td>
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<tr>
<td>Diabetes mellitus, %</td>
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<tr>
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<td>Concomitant drugs, %</td>
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<tr>
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<tr>
<td>lipid lowering drugs</td>
<td>8</td>
</tr>
<tr>
<td>oral contraceptives/HRT †</td>
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</tr>
<tr>
<td>NSAIDs</td>
<td>14</td>
</tr>
</tbody>
</table>

| Anticoagulation data *           |       |
| Follow-up time (months)          | 11.9 ± 11.4 |
| Number of INRs                   | 28 ± 25   |
| Time between INRs (days)         | 13 ± 8    |
| INR‡                             | 3.3 ± 0.7 |
| ITTR (%) §                       | 42 ± 22   |
| Time with INR > 5.0 (%)          | 7 ± 12    |
| INR stability¶                   | 0.1 ± 0.1 |

* mean ± SD; † hormone replacement therapy; ‡ International Normalized Ratio;
§ Individual Time within Target Range; ¶ INR stability is expressed as absolute daily INR change.
The effect of ITTR and minor bleeding on the risk of major bleeding was assessed by multivariable Cox proportional hazard regression analysis. Minor bleeding was incorporated in the analysis using a time-varying exposure approach, with a change in the exposure pattern at the time of the minor bleed up to 30 days thereafter, a priori defined. In the multivariable analyses, sex, age, co-morbidity, concomitant drugs, INR target range and indication for VKA therapy were included as potential confounders. As a sensitivity analysis on the a priori chosen exposure pattern, we repeated our time-varying exposure analysis using an exposure duration of 60 days.

Reported P-values are two-sided and a P-value < 0.05 was considered statistically significant. For all analyses, commercially available computer software (Statistical Analysis System version 9.1, SAS Institute, Cary, NC) was used.

RESULTS

A total of 6758 consecutive patients were included in our study. Their characteristics and anticoagulation data are summarized in Table 1. Cumulative treatment time was 6681 patients-years, during which 189762 INR measurements were performed. Acenocoumarol was the predominantly used VKA (96.7%). The remaining patients used phenprocoumon (2.3%) or switched during their treatment period (1%). VKA was combined with low dose aspirin in 3.5% of patients. Mean individual treatment time was 11.9 months (SD, 11.4), during which 28 (SD, 25) INR measurements were performed. Mean INR was 3.3 (SD, 0.7), mean ITTR was 42% (SD, 22) and stability of anticoagulation, i.e. mean absolute change in daily INR values was 0.1 (SD, 0.1).

Clinical outcome

Minor bleeding
A total of 2349 minor bleeds had occurred in 1348 patients (20%), 857 patients had a single minor bleed (64%), 272 patients two minor bleeds (20%), and 219 patients multiple recurrent minor bleeds (19%). INR at the time of the minor bleed was on average 3.7 (95% CI 3.6-3.8). The absolute risk, expressed as the incidence rate per 100 person-years was 25.1 (95%CI, 23.8-26.5). Haematoma (39%), nose bleeds (28%), conjunctiva bleeds (11%) and haematuria (9%) were the most frequently observed minor bleeds. In women, menorrhagia accounted for 3% of all reported minor bleeds. The most apparent difference between women and men was the occurrence of
haematoma, with 46% in women vs. 30% in men, leading to a significantly higher risk of minor bleeding in women than men (incidence rates 31.7, 95%CI, 29.5-34.0 in women vs. 19.8, 95%CI, 18.2-21.4 in men).

A medical intervention, including temporary interruption, was required for 111 minor bleeds in 99 patients. These minor bleeds were classified as clinically relevant.

**Major bleeding**

Major bleeding had occurred in 119 patients (1.8%), with an incidence rate of 1.8 per 100 person-years (95% CI, 1.5-2.2), of which 18 were fatal (0.3%). In 22 patients (18%) major bleeding had occurred within 30 days, and in 31 patients (26%) within 60 days. At the time of the major bleed, the INR was on average 4.4 (95% CI 3.8-5.1). The type of major bleeding is presented in Table 2.

When stratifying patients by minor bleeding, in patients without a minor bleed the incidence rate of major bleeding was 1.6 per 100 person-years (95% CI, 1.3-2.1), whereas in patients with a minor bleed the incidence rate was 2.1 per 100 person-years (95% CI, 1.5-2.9). The relative risk associated with minor bleeding was estimated using a multivariable time-varying exposure Cox regression model in which the exposure duration of the minor bleeds was set to 30 days. Using this exposure pattern, after a minor bleed patients were at a 3.6-fold increased risk of major bleeding up to 30 days after a minor bleed (HR=3.6, 95% CI, 2.0-6.6, P < 0.001).

Changing the exposure duration to 60 days, as a sensitivity analysis on the exposure duration, results were comparable (HR=3.6, 95% CI 2.2-5.9, P < 0.001), indicated a robustness of our finding of an increased risk after a minor bleed also over a substantial amount of time.

The composite of major bleeding and clinically relevant minor bleeding had occurred in 3.2% of patients (n=216) with an incidence rate of 3.3 (95% CI, 2.9-3.8). Also for the composite endpoint, patients with minor bleeding were at higher risk. The incidence rate in these patients was 7.0 per 100 person-years (95% CI, 5.9-8.3), whereas in patients without minor bleeding the incidence rate was 1.6 (95% CI, 1.3-2.1). Using the time-varying exposure model for this composite endpoint, the hazard ratio of minor bleeding (with the 30-day exposure duration pattern) was 4.7, 95% CI, 3.1-7.1, P < 0.001). Expanding the exposure duration to 60 days resulted in a HR of 3.9 (95% CI 2.7-5.7, P < 0.001).
Table 2  Major bleeding and clinically relevant minor bleeding.

| TYPE OF EVENT * | Minor bleeding | | Total |
|-----------------|----------------|-----------------|
|                 | Yes            | No              | n=6758 |
| Minor bleeding  | 1348           | 5410            | |
| Major bleeding  | 44 (3.3)       | 75 (1.4)        | 119 (1.8) |
| non-fatal gastrointestinal | 11 | 19 | 30 |
| fatal gastrointestinal | 3 | 6 | 9 |
| non-fatal intracranial | 4 | 4 | 8 |
| fatal intracranial | 2 | 7 | 9 |
| intra-ocular | 1 | 4 | 5 |
| other major bleeding | 23 | 35 | 58 |
| incidence rate (95% CI) per 100 patient-years | 2.1 (1.5-2.9) | 1.6 (1.3-2.1) | 1.8 (1.5-2.2) |
| Composite of major or clinically relevant minor bleeding n (%)† | 141 (10.5) | 75 (1.4) | 216 (3.2) |
| non-fatal gastrointestinal | 23 | 19 | 42 |
| fatal gastrointestinal | 3 | 6 | 9 |
| non-fatal intracranial | 4 | 4 | 8 |
| fatal intracranial | 2 | 7 | 9 |
| intra-ocular | 1 | 4 | 5 |
| other major or clinically relevant bleeding | 108 | 35 | 143 |
| incidence rate (95% CI) per 100 patient-years | 7.0 (5.9-8.3) | 1.6 (1.3-2.1) | 3.3 (2.9-3.8) |

* The number of patients with at least one event is presented. In case of multiple bleeding, only the first event was counted;
† Minor bleeding requiring any medical intervention was classified as clinically relevant minor bleeding.

Achieved level of anticoagulation

Overall, the mean individual time within INR target range (ITTR) was 42%. In one-fifth of all patients, ITTR was < 25%. Of all time spend outside the target range on average 27% was above the target range. Based on the 0.5 INR wider therapeutic range, as this was applied by the Dutch anticoagulation clinics in the day-to-day monitoring, the percentage of time spend within the therapeutic range was 60%. The percentage of time spend above INR 5.0 was 7%.

There was no difference between the patients with a minor bleed (ITTR = 43%) and the patients without a minor bleed (ITTR = 42%). Also the percentage of
time spend above the target range was similar, 28% and 26% respectively. In addition, the percentage of time spend above INR 5.0 was 7% in patients with as well as in patients without a minor bleed. Figure 1 shows the highly comparable day-to-day level of anticoagulation during the course of VKA therapy in patients without a minor bleed or before the occurrence of a minor bleed, and in the patients after the occurrence of a minor bleed.

Figure 1 Achieved day-to-day level of anticoagulation, expressed as the daily percentage of patients below (dark grey), within (light grey) and above (black) the therapeutic range during the course of VKA therapy. The number of patients on treatment are shown between brackets.

From the multivariable Cox regression analysis, ITTR was identified as an independent risk indicator for major bleeding, irrespective of the presence of a minor bleed. Patients with an ITTR less than 25% (lowest quintile) were at 2.8-fold increased risk of major bleeding (HR=2.8, 95%CI, 1.7-4.5, P<0.001). For the composite of major and clinically relevant minor bleeding, this was 2.9-fold increased. (HR=2.9, 95%CI, 2.1-4.2, P<0.001).

Figure 2 shows all risk independent risk indicators for major bleeding, as these were identified by multivariable Cox regression analysis. In addition to minor bleeding and ITTR < 25%, these were age (55-70 years and especially above 70 years), sex (male), malignancy, indication for VKA therapy and use of NSAIDs.
DISCUSSION

To our knowledge, this study is the first to report on minor bleeding as potential risk indicator for major bleeding. We showed that the occurrence of a minor bleeding was associated with a 3.6-fold increased risk of major bleeding during the subsequent month. The potential of minor bleeding as risk indicator was further corroborated by the similar risk when the duration of the exposure pattern was extended to 2 months.

When including clinically relevant minor bleeding as a composite endpoint with major bleeding, minor bleeding remained a strong risk indicator for subsequent adverse clinical outcome.

The absolute risk of major bleeding in our study was 1.8 per 100 person-years. Taking into consideration that our cohort consisted of unselected patients in whom VKA therapy was managed by a specialized anticoagulation clinic, this absolute risk is in line with those reported previously [24,25]. Our rate of minor bleeding of 25.1 per 100 person-years is more difficult to compare, however in a recent large clinical trial in AF patients the rate of minor bleeding was 18.2 [26]. Two other large trials reported...
higher incidence rates for combined major and minor bleeding, ranging from 30 to 47 per 100 person-years [27,28].

Our finding regarding the quality of anticoagulation as risk indicator is consistent with previous studies, where an association between ITTR and major bleeding also was observed [29,30]. Although quality of anticoagulation, i.e. the ITTR was an important risk indicator for major bleeding, the ITTR was comparable in patients with a minor bleed vs. patients without a minor bleed (43% vs. 42%). Time spend above the target range was also similar, 28% and 26% respectively, and no apparent differences were observed in the achieved quality of anticoagulation before and after the occurrences of minor bleeds. In this respect, our hypothesis of risk modification after the occurrence of a minor bleed by increasing quality of anticoagulation was not confirmed.

Our study has some limitations to consider. Unfortunately, due to the retrospective design of our study, we did not have data on genetic factors related to the individual sensitivity to VKA [31,32]. Another limitation is the potential underreporting of bleeding complications in a study with a retrospective design. However, we included new patients only (inception cohort, excluding patients already on VKA) and had access to detailed information regarding all bleeding complications, including minor bleeds. These were assessed by the experienced staff of the anticoagulation clinic responsible for monitoring the VKA therapy and/or reported spontaneously by the patients themselves. Therefore, in our opinion underreporting was very limited, which is also indicated by the observed bleeding risk that is consistent with previous reports [1,18,19,24-28,33-35].

The intensity of anticoagulation used in the Netherlands might limit the generalizability of our findings. To avoid, particularly, under-anticoagulation, the Dutch anticoagulation clinic used a therapeutic range, next to the target range, which was 0.5 INR wider towards a higher intensity, than the conventionally employed target ranges in other countries (e.g. INR 2.0-3.5 vs. INR 2.0-3.0). The target ranges that were used were 0.5 INR higher (e.g. INR 2.5-3.5 vs. INR 2.0-3.0). Due to this strategy, the ITTRs as observed in our study were at the lower end of those reported in previous studies [4,36]. When considering the therapeutic range, the percentage within range was 60%, with only 13% of time spend below the range, confirming the strategy of avoiding under-anticoagulation. With an absolute risk of major bleeding of
1.8 per 100 person-years, in the setting of a specialized anticoagulation clinic this strategy did not lead to excessive major bleeding.

Regarding the type of VKA, acenocoumarol was predominately used. This short-acting VKA is associated with less stable anticoagulation [36]. Although acenocoumarol may have reduced the ITTR, minor bleeding was identified as a risk indicator of major bleeding, also independent of the ITTR.

In conclusion, minor bleeding is associated with subsequent major bleeding. The occurrence of a minor bleed should increase the awareness towards a potentially high-risk situation. In this, the achieved level of anticoagulation should also be considered, not just the INR at the time of the minor bleed, but especially the ITTR of the preceding treatment period.

In line with this awareness, a renewed risk-benefit assessment should be performed. Whether a lower intensity of anticoagulation might be more suitable for these high-risk patients, without compromising the efficacy of VKA therapy to prevent thromboembolic complications is speculative. In this, also VKA as the anticoagulant drug of choice could be reconsidered. For some patients, no anticoagulant agent, aspirin, or – in the near future – an oral II or Xa inhibitor might be a more suitable option.
Minor Bleeds Alert for Major Bleeding

References


