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Interpretation and management of INR results: A case history based survey in 13 countries

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ABSTRACT

Introduction: Standardisation of treatment with vitamin K antagonists (VKAs) is still an issue after 60 years of use. The study aimed to explore aspects of VKA monitoring in primary and secondary care.
Methods: Two case histories were distributed to physicians in 13 countries. Case history A focused on a patient with atrial fibrillation on stable anticoagulation (latest INR 2.3). Physicians were asked about frequency of INR measurement, when to change the VKA dose, and the patient's annual risk of ischemic stroke and bleeding. Case history B focused on a patient with an unexpected INR of 4.8, asking for the patient's 48-hour bleeding risk, the immediate dose reduction and time until a repeat INR.
Results: Altogether, 3016 physicians responded (response rate 8 – 38%), of which 82% were from primary care and 18% from secondary care. Answers varied substantially within and between countries regardless of level of care and VKA used. Median number of weeks between INR measurements was 4 – 6 weeks. Median threshold INR for increasing or decreasing the VKA dose was 1.9 and 3.1, respectively. Risk of ischemic stroke and bleeding were overestimated 2 – 3 times. In case history B, the median dose reduction the two first days was 75% for GPs and 55% for specialists, irrespective of estimates of bleeding risk; with one week to a repeat INR.
Conclusion: Variation in VKA monitoring is substantial implying clinical consequences. Guidelines seem either unknown or may be considered impracticable. Further efforts towards standardisation of VKA management are needed.

Introduction

Treatment with vitamin K antagonists (VKAs) is monitored with INR, and there is a strong relation between time in therapeutic range (TTR) and the risk of bleeding and thromboembolic complications

Abbreviations: INR, (prothrombin time), international normalized ratio; VKA, vitamin K antagonists; TTR, time in therapeutic range; GP, general practitioner.

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[1]. Even so, TTR is found to be about 60 – 70% in anticoagulation clinics and clinical trials and about 55% in community practice [2–6], and seems to be especially low in certain countries [7].

The 2008 guidelines of the American College of Chest Physicians (ACCP) recommend three different ways of standardizing care that have been shown to increase TTR: use of anticoagulation clinics, computerized dose adjustments, or patient self-monitoring [8,9]. In addition, there is also emerging evidence that higher TTR is achieved when manual dosing algorithms are used [10,11]. The management of patients treated with VKAs is organized differently in different countries with respect to level of care and physician qualifications [6]. Computer dosing programmes are widely used in a few countries [6,12], but otherwise there is scarce knowledge both of how guidelines [8,9,13–16] are used in everyday practice, and also concerning the practical use of manual dosing algorithms for VKAs [10,11,17,18].

In two case history-based studies covering some aspects regarding INR monitoring of warfarin treatment; one distributed to Norwegian general practitioners (GPs) and another to participants in the external quality assessment scheme in the United Kingdom (UKNEQAS), large variation was found [12,19]. The results from the two studies apply mostly to Norway and the United Kingdom (UK), and the situation in other countries is not addressed. In addition, the study in Norway only addressed GPs, while the UK study did not distinguish between results from the different types of care providers involved in the study.

The aim of this study was to explore in detail important aspects of treatment with various VKAs performed by clinicians in both primary and secondary care in many countries, and to examine if INR monitoring followed guideline recommendations. The survey focused on follow-up of a patient on stable anticoagulation, and on handling a patient with an unexpected high INR result.

Materials and Methods

Method

A questionnaire with two case histories (Fig. 1) was sent to physicians in 13 countries in spring of 2010. The project was organized by NOKLUS (the Norwegian centre for Quality Improvement of Primary Care Laboratories), which had been responsible for similar studies [19,20], and the survey was carried out in collaboration with EFCC (European Federation of Clinical Chemistry and Laboratory Medicine) and EQALM (European Committee for External Quality Assurance Programmes in Laboratory Medicine).

The case histories were based on *patient A* with atrial fibrillation and *patient B* with pulmonary embolism (Fig. 1). Case history A focused on the frequency of INR measurements and at which INR value the VKA dose should be changed in a patient on stable anticoagulation treatment (latest INR 2.3). The physicians were also asked to state the patient's annual risk of ischemic stroke with and without VKA treatment, and his annual risk of a major bleeding with treatment. In addition, participants were asked to state their familiarity with the CHADS2 score or other equivalent clinical tools to determine the risk of stroke in patients with atrial fibrillation [21]. Case history B focused on how to handle an unexpected INR result of 4.8 in a patient treated for venous thromboembolism for four months. Participants were first asked to state the patient's 48-hour risk of a serious bleeding, the immediate dosing of VKA, and when to measure INR next. Then they were asked to suggest a new weekly dose when INR had returned to the therapeutic range, and the time to a repeat INR (Fig. 1). Finally, the participants were asked to state some personal and practice particulars, and if they based their dosing of VKA on clinical experience, manual algorithms, or computer dosing programs.

Case histories and the dosing schedule were given with the most prevalent VKA in each country (Table 1), except in the Netherlands where the physicians responded to schedules both for phenprocoumon (Netherlands (ph)) and acenocoumarol (Netherlands (ac)). The doses of the VKAs were comparable (Fig. 1) [22]. Warfarin and fluindione have quite similar half-lives, 36–42 hours and 31 hours, respectively, while acenocoumarol and phenprocoumon have half-lives of approximately 11 and 140 hours [22].

The questionnaire was sent to project coordinators in the different countries, and in addition to a small group of Norwegian GPs for comments. Only minor changes were made. The final version was translated by the project coordinators, if necessary. Coordinators were then asked to distribute the questionnaire to at least 300 physicians in their country, i.e. GPs or secondary care specialists routinely treating VKA patients. Recruitment was either through participation in External Quality Assessment Schemes (EQAS) (Austria, the UK, the Netherlands, Norway, Spain, Sweden), through affiliation to one or several clinical chemistry laboratories or laboratory networks (Australia, Belgium, Croatia, France, Hungary) or the questionnaire was sent to the GPs in certain counties (Denmark, Estonia). In addition, the questionnaire was sent to selected members of the Society of Thrombosis and Haemostasis in Hungary, and to physicians with interest in VKA treatment in one particular hospital in Croatia, Estonia, and France. In Norway, the questionnaire was sent to all the GPs in the country, since all participate in a nationwide EQAS.

The deadline for returning the questionnaire was 10 – 14 days, after which a reminder was sent except in Australia, Austria, Belgium and Denmark. The project coordinators entered the results into a custom-made web database provided by NOKLUS. All participants were offered a feedback report including recommendations for the treatment and follow-up of the patients in the case histories.

Critical difference

In case history A, the physicians were asked to state the change in INR (from 2.3) deemed necessary to increase or decrease the VKA dose (target INR 2.5). The calculated INR changes from INR 2.3 were used as critical differences (CDs) [23] in order to calculate the analytical variation (CV_a) implicated by the physicians, using the formula:

$CD = \text{bias} + z\ \text{value} \times \sqrt{2} \times \sqrt{CV_a^2 + CV_{ws}^2}$ [23], with a z-value for one-sided tests and 95% probability ($z = 1.64$), a CV_{ws} of 10% (within-subject biological variation in patients under stable oral anticoagulation) [24,25], assuming no bias between measurements. Further, using the formula and values described above and a CV_a of 3%, it was calculated that a change within ± 24% (decrease from INR 2.3 to 1.8 or increase to 2.9 in case history A) may be explained by analytical and biological variation only (95% probability).

Statistics

Data was analysed by simple cross tabulations and frequency distributions as well as by Mann–Whitney U test, Kruskall-Wallis test and Spearman's correlation (SPSS 17.0; SPSS Inc). In general, data for participants in each country are presented as medians with 10th and 90th percentiles, whereas summary data for several countries are presented as the median of country medians and the range of country medians. Respondents not stating type of practice ($n = 30$) and subgroups with less than 11 physicians were excluded ($n = 31$), leaving only subgroups with more than 40 physicians for analysis. Nurses and pharmacists were also excluded ($n = 86$, mostly from the UK), since the case histories were intended for doctors only, and because these groups do not have the clinical responsibility for patients.

Results

The median response rate was 25% and 3016 physicians were included. An overview of participants is given in Table 1. Most of the GPs and specialists used their clinical experience when dosing VKAs, and the use of computer programmes was prevalent only in the UK

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Part I: Case histories and questionnaire Practice ID no. : _____

Patient A is a 76-year-old man with permanent atrial fibrillation and hypertension who is treated with warfarin[†] and antihypertensives. The therapeutic interval for this patient is INR 2,0-3,0 (target INR 2,5). He is otherwise healthy and is feeling well at the moment. His INR results have been stable, and have varied between 2,0 and 2,8 during the last months.
His INR today is 2,3, and you decide not to change the warfarin dose.

- State the number of weeks until the next INR measurement: at least _____week(s), but no more than _____ week(s).
- If you were to increase his warfarin dose, how low must this next INR value be? _____.
- If you were to decrease his warfarin dose, how high must this next INR value be? _____.

In your opinion, what is this patient's probability (in percent) in the next year of having:

- an ischemic stroke if he is not treated with warfarin? _____% ( ) do not know
- an ischemic stroke while being treated with warfarin? _____% ( ) do not know
- a serious bleeding event with admission to hospital while treated with warfarin? _____% ( ) do not know

Are you familiar with clinical scores for deciding whether VKA or aspirin should be used in atrial fibrillation patients (e.g. CHADS2 score)? ❑ yes ❑ no

Patient B is a 62-year-old woman, who was hospitalized with pulmonary embolism four months ago. The embolism was idiopathic (no known precipitating factors). She is now treated with warfarin. The therapeutic interval for this patient is INR 2,0-3,0 (target INR 2,5). Her last INR results and warfarin doses have been:

Warfarin dose (mg) and day	Mon	Tue	Wed	Thurs	Fri	Sat	Sun	
INR 7 weeks ago: 2,4	10	12	12	12	10	12	12 mg	(80 mg per week)[††]
INR 3 weeks ago: 3,0	10	12	12	12	10	12	12 mg	(80 mg per week)

On a Monday, you receive a new INR result, which is 4,8 (measured twice). The patient feels well and has not yet taken her daily dose of warfarin. There seems to be no obvious reason for the INR increase.

- What do you think is her risk of having a serious bleeding episode, with admission to hospital, during the next two days?_____% ( ) do not know

Please, fill in the daily doses of warfarin (in mg) for the patient from Monday until the day when you would order the next INR.

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

Suppose that after your changes in the table above, **the next INR result is 2,9**.

- Please, estimate the new weekly dose of warfarin: _____mg ❑cannot estimate, need more INR results.
- After the INR result of 2,9 – when will you order another INR measurement? In approximately ____days.

[†]Warfarin was replaced by phenprocoumon (Austria, Belgium and The Netherlands ph), acenocoumarol (Hungary, Spain and The Netherlands ac) or fluindione (France).
[††]The dosing schedule was replaced by comparable doses of phenprocoumon (33 mg per week), acenocoumarol (40 mg per week) or fluindione (260 mg pr week) (22).

Fig. 1. The case histories (patient A and B) sent to the physicians.

(GPs 79% and specialists 58%) and the Netherlands (78%), whereas manual dosing algorithms were used by almost 50% of GPs in Denmark and Norway. In general, both within and between countries, the range of responses was substantial for all questions asked (Fig. 1).

Frequency of INR monitoring (based on patient A with atrial fibrillation)

The *median* minimum and maximum numbers of weeks until the next INR measurement, in a stable patient, were 4 (range 3 – 6) and 6 (range 4 – 10) weeks, respectively. The longest intervals were

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Table 1
Characteristics of study participants.

Country	Physicians invited, number	Responders, number (%)	Age, median	Male, %	Physicians in primary care, %	Physicians in secondary care, %	Vitamin K antagonist	GPs with POC instruments %
Australia	993	159 (16)	50	65	96	4	Warfarin	63
Austria	1099	274 (25)	53	77	61	39	Phenprocoumon	97
Belgium	400	135 (34)	52	76	100	0	Phenprocoumon	4
Croatia	559	119 (21)	48	47	51	49	Warfarin	2
Denmark	900	74 (8)	57	56	93	1[a]	Warfarin	48
Estonia	318	75 (24)	49	4	85	15	Warfarin	19
France	282	108 (38)	52	72	62	38	Fluindione	14
Hungary	939	267 (28)	52	54	78	22	Acenocoumarol	3
Norway	4338	1385 (32)	50	66	100	0	Warfarin	91
Spain	656	83 (13)	47	57	13	87	Acenocoumarol	55
Sweden	-[b]	94	52	57	99	1	Warfarin	76
the Netherlands (ac)	250	62 (25)	51	40	0	94[a]	Acenocoumarol	NA
the Netherlands (ph)	250	59 (24)	51	43	0	93[a]	Phenprocoumon	NA
the United Kingdom	3380	265 (8)	48	50	34	34[a]	Warfarin	96

[a] 29% (78), 6% (4) and 7% (4) of responders from the United Kingdom, Denmark and the Netherlands, respectively, were nurses or pharmacists, and were excluded from comparisons.
[b] The total number of GPs in the surgeries was unavailable. Invitations were sent to 180 surgeries of which 94 physicians from 57 surgeries answered the survey.
NA = not applicable.

suggested by the UK clinicians, with a minimum of 6 weeks and a maximum of 10 weeks suggested by the GPs, and a minimum of 4 weeks and a maximum of 8 weeks by specialists.

When to change the VKA dose (patient A)

Most GPs and specialists would change the dose of VKA if the INR result increased or decreased to a level at or right outside the therapeutic range (Fig. 2A and B). The median INR to increase or decrease the VKA dose was 1.9 (range of medians 1.8 – 2.0) and 3.1 (range 3.0 – 3.4), respectively. In Belgium and Hungary, 30 – 40% of the physicians would change the VKA dose *within* the therapeutic range, compared to10% or less in the other countries (Fig. 2A and B). Quite low and high INR values ($\leq$ 1.7 and $\geq$ 3.5, respectively) were tolerated by about 50% of GPs in Denmark before changing the VKA dose, while in the other countries, 5 – 25% increased the dose at INR $\leq$1.7 and 15 – 30% decreased the dose at INR $\geq$3.5 (Fig. 2A and B).

The CV_a values based on median INR changes could not be calculated for an increase in VKA dose, but ranged from 3.4% - 16.4% for a decrease (Supplemental Table 1A and B).

Risk estimates (patient A)

Specialists tended to estimate lower annual risk of *ischemic stroke* with and without VKA treatment, but similar risk of *bleeding* with treatment compared to the GPs (Table 2). The assumed median *absolute* risk reduction for ischemic stroke when treated with VKA varied from 3.5 – 40% for the GPs and 3.5 – 17% for the specialists in the different countries, whereas median risk estimates for bleeding were 3% for GPs and 2% for the specialists.

The percentage of physicians familiar with the CHADS2 score was higher among specialists (72%) compared to GPs (47%). The physicians familiar with the score estimated lower risk for ischemic stroke with VKA treatment (median 5% vs. 2.5% for GPs and 2.7% vs. 1.5% for specialists). Risk estimates for bleeding and ischemic stroke tended to be lower, and more correct (Table 2), for physicians dosing VKA at least once a week, and for respondents using manual algorithms or computer dosing programs.

Management of a supra-therapeutic INR (patient B: pulmonary embolism and INR 4.8)

The median risk for an acute serious bleeding was estimated to be 5% by GPs and 3% by specialists (Table 3). The median dose reduction the two first days was 75% for GPs and 55% for specialists, but much lower (27%) for specialists prescribing acenocoumarol in the Netherlands (Table 3). The percentages of physicians who would not omit VKA for at least one day were 54% for respondents prescribing the short-acting acenocoumarol, compared to about 20% for warfarin, fluindione or phenprocoumon. The median number of days before a new INR measurement was 7 days both for GPs and specialists independent of type of VKA used (Table 3), but shorter for GPs with POC instruments (median 4 days vs. 7 days). Both in primary and secondary care there was no correlation between the bleeding risk stated and the percent dose reduction during the first two days ($r = -0.07$), and no correlation between the bleeding risk and the number of days until a new INR measurement ($r = 0.06$). No differences were found comparing those seeing less than one VKA patient per week with those managing more patients. Further, there were no within-country differences between clinicians using algorithms vs. clinical experience regarding dose reduction and time to a new INR.

Reduction in weekly dose and repeat INR (patient B when INR had returned to 2.9)

The median reduction in weekly dose was about 15% for both GPs and specialists, but with large variations within the countries (Table 3). The dose was reduced less than 10% (median) by specialists in the Netherlands and Spain and by GPs in Norway (Table 3). The size of the dose change did not seem to be dependent on type of VKA (Table 3). The median time suggested to the next INR was 7 days, and was not related to level of care or number of VKA patients per week, the VKA used (Table 3), the size of the dose reduction, or the use of dosing algorithms.

Discussion

The main findings of the study were the considerable variability of answers both to questions regarding dosing regimes and assessment of the risk for stroke and serious bleeding. This was found within and between countries and in primary as well as secondary care, and will have clinical consequences for VKA patients. The response rate was low in most countries, but comparable to two other questionnaire based surveys with response rates of 7% – 43% [20] and 33% [26]. Response rates were especially low in Denmark, Spain, and the UK. In Denmark our co-workers were relatively unknown to participating GPs, and there was no reminder; the same kind of argument holds true for Spain. In the UK, GPs were used to providing answers on-line, and not on paper, and may also have been reluctant to enter imaginary patients into computer schemes. Clinicians interested in VKA treatment were probably more likely to respond to the

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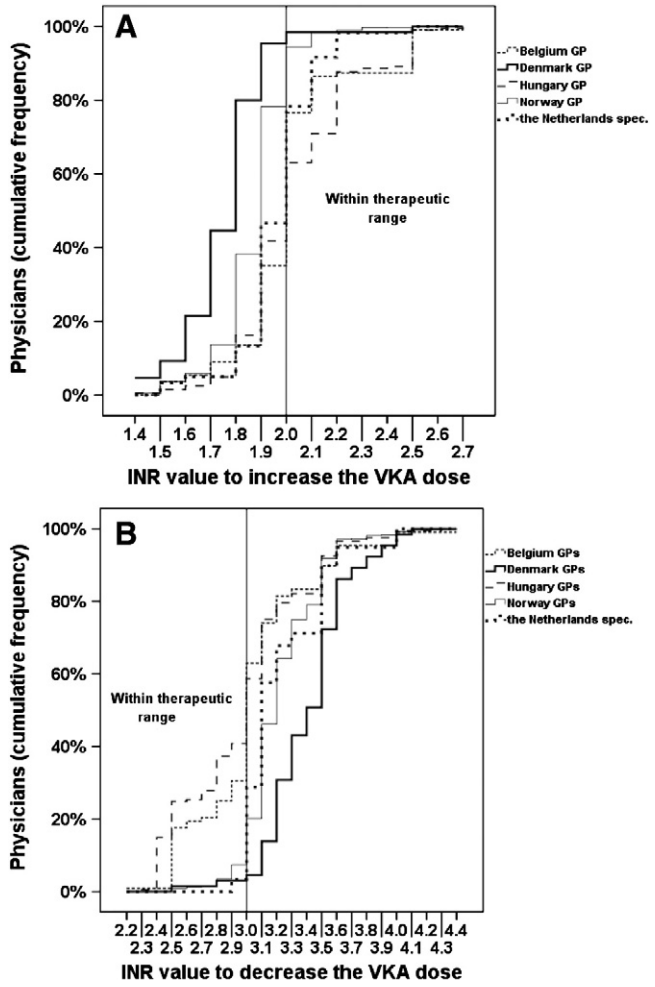

Fig. 2. A and B. Patient A with atrial fibrillation; Physicians increasing (A) or decreasing (B) the VKA dose at different INR values. The countries omitted from the figures would have been represented with lines inbetween these results. The vertical lines represent the lower (A) and upper (B) therapeutic limits. GP = general practitioners, spec. = specialists (secondary care).

questionnaire, which implies that we may have "best practice" data. Higher response rates might be achieved primarily by sending the questionnaires from organizations more familiar to physicians, but also by using more reminders and web-based responding.

Frequency of INR monitoring

Guidelines suggest that INR monitoring intervals of 4 – 6 weeks are appropriate for a stable patient [8,14–16,18,27], as suggested by respondents in all countries, except in the UK with longer intervals. This difference might be due to traditions in the UK [28], and that the British guideline from 1998 suggests a recall interval of as long as 12 weeks in stable patients [13]. But our results are not in accordance with results from a case-history based study from the UK, where the most frequent recall intervals suggested by users of computer programmes for a stable patient was shorter (3 or 4 weeks) [12]. The evidence for recommendations on INR testing intervals is weak [8,28], but recent evidence may justify longer than 4 weeks intervals in very stable patients [29–31]. VKA monitoring is probably based largely on habits rather than recommendations.

When to change the VKA dose

Guidelines in English do not specify the exact INR values for changing the dose for stable patients [8,13,32]. Still, different dosing algorithms recommend no change if the INR is within therapeutic range [10,11,16,18], and to change the VKA dose right above or below the limits [11,18], as was done by many respondents (Fig. 2A and B).

The reason for the high percentage of physicians in Hungary and Belgium increasing and decreasing the dose at INR values *within* the therapeutic interval may reflect an undue focus on the "target value of 2.5". The practice of acting on small INR changes demonstrates no considerations of the consequences of analytical and biological variation, i.e. very small changes may not represent real changes in the intensity of VKA treatment (see Methods).

The high proportion of physicians in Denmark accepting INRs ≤ 1.7 and ≥ 3.5 before changing the VKA dose is of concern because of the increasing risk of adverse effects this far outside of the therapeutic limits [1]. This practice is not in keeping with the Danish algorithm which recommends changing the dose when INR is ≤ 1.9 or ≥ 3.1 [18]. In general, the variation with regard to dose change was rather large within and between countries (Fig. 2A and B), signalling that dosing guidelines for stable patients are either unknown to the physicians or considered impractical or inappropriate.

Risk estimates

The annual stroke risk was grossly overestimated by many physicians, and so was the absolute risk reduction, and thus the effect of VKA treatment. The annual risk of a major bleeding was estimated somewhat more correctly overall, but with striking differences between physicians, even among specialists. Physicians managing more VKA patients, using algorithms when dosing, and who were aware of the CHADS2 score estimated risks more adequately, but still with substantial variation. This finding indicates that many clinicians are not able to discuss risks and benefits with the patients. If treatment effects were indeed discussed with patients, it would be reasonable to expect more accurate knowledge on the part of the doctor. There are few studies on how perceived risks affect decisions about VKA treatment, but one study has shown that the decision to use warfarin in atrial fibrillation was strongly affected by the physicians' perception of the risks of bleeding, but not so much of the perceived benefit from treatment [26].

Management of a supra-therapeutic INR

The relative risk of bleeding increases exponentially with INR values above 4.5 [33], but the absolute risk for a serious bleeding within 48 hours is only about 0.1 - 0.2% for INR 4.5 – 6.9 [1,34,35]. The risk was generally overestimated in our study, with no correlation between the estimate and the acute management. Thus physicians did not handle patients according to risk estimates, which is in line with findings in a previous study [19].

The large variation in acute dose reduction of the VKA could be explained by the high proportion of respondents relying only on clinical experience. However, guideline recommendations are scarce, relate mainly to warfarin and are mostly based on consensus. Thus guidelines may not be very useful, especially for managing patients treated with non-warfarin VKAs [8]. Most clinicians omitted the VKA dose for at least one day. The ACCP guideline recommends either to omit one VKA dose or only to reduce the weekly dose [8], whereas manual dosing algorithms suggest to omit the VKA from 0 – 2 days [10,11,16–18]. To stop the VKA treatment results in different INR changes for individual patients [36], which could explain difficulties in establishing recommendations on this issue. The short half-life of acenocoumarol may explain both less dose reduction and reluctance to omit a dose among specialists in the Netherlands, although such an effect was not seen in other countries using this VKA (Table 3).

The median number of days until a new INR measurement was seven, but varied considerably within each country, and was shorter

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Table 2
Patient A: Annual risk (%) of ischemic stroke and major bleeding assumed by physicians for a patient with atrial fibrillation on stable anticoagulation (medians with 10–90 percentiles).

Country	Risk of ischemic stroke *without* VKA[a]	Risk of ischemic stroke *with* VKA[b]	Risk of bleeding *with* VKA[c]
Primary care			
Australia	10 (4 – 30)	2 (1 – 10)	2 (1 – 10)
Austria	25 (5 – 70)	5 (1 – 15)	3 (0.5 – 10)
Belgium	20 (5 – 64)	5 (1 – 12)	3 (0.9 – 10)
Croatia	30 (7 – 84)	10 (0.3 – 20)	5 (0.5 – 26)
Denmark	10 (4 – 30)	3 (0.8 – 11)	2 (0.6 – 10)
Estonia	50 (5 – 80)	10 (1 – 30)	5 (0.4 – 17)
France	30 (5 – 70)	5 (1–14)	5 (1 – 17)
Hungary	40 (10 – 80)	8 (1.5 – 20)	5 (1 – 25)
Norway	10 (3 – 35)	2 (0.7 – 10)	1.5 (0.5 – 10)
Sweden	10 (4 – 50)	2 (0.6 – 18)	2 (0.5 – 10)
the United Kingdom	6 (3 – 30)	2.5 (1 – 10)	2 (0.5 – 11)
Secondary care			
Austria	6 (4 – 30)	2 (0.5 – 5)	1 (0.4 – 5)
Croatia	10 (4 – 65)	2 (1 – 15)	3 (1 – 10)
France	18 (5 – 50)	2.5 (0.8 – 10)	5 (0.9 – 21)
Hungary	21 (5 – 73)	4 (0.9 – 20)	2 (0.5 – 10)
Spain	5 (3.8 – 75)	1.5 (0.1 – 11.9)	2 (0.5 – 5)
the Netherlands (ac)	5 (2 – 13)	1.5 (1 – 5)	2 (0.5 – 5)
the Netherlands (ph)	6 (3 – 17)	1.4 (1 – 5)	1 (0.3 – 15.2)
the United Kingdom	5 (3 – 20)	1.5 (1 – 5)	1 (0.5 – 5)

[a] Annual risk of ischemic stroke without VKA is about 4% according to the CHADS2 score for patient A (hypertension and > 75 years old = 2 points) [21].
[b] Annual risk of ischemic stroke with VKA is reduced to about 1.3% in patient A (relative risk reduction of 62 - 67%) [40].
[c] Annual risk of bleeding is about 1.3 - 1.9% in atrial fibrillation patient treated with VKA [41].

for GPs with POC instruments who probably preferred to have a repeat INR before the week-end (Table 3). Recommendations vary from stating "more often" [8], to stating 7–14 days [10] and even only 1–2 days [37]. A recent study [38] found a mean of 6 to 18 days until a repeat test after INR ≥ 4.0, which is in keeping with our findings. Shorter follow-up intervals in the study were associated with higher TTR [38]. The median of seven days in our study therefore seems reasonable, but the variation found may have clinical consequences. It is unknown to which degree dosing algorithms were actively used while responding, e.g. by entering data into computer schemes, and this might have resulted in similar answers from doctors using algorithms vs. clinical experience.

Reduction in weekly dose and repeat INR

Weekly dose reduction varied greatly, and may reflect uncertainty with regard to whether the patient was stabilized or not after the acute dose changes. The ACCP guideline recommends the weekly dose reduction to be 5 – 20% [8], while other dosing algorithms suggest from 5 - 10% [10,16,18] to 33% [11] after an INR of 4.8. In this patient, as in most, probably small dose changes (not more than 10%) should be made to avoid over-adjusting the dose and a resulting see-saw effect with regard to INR-values [27]. The number of days until a repeat INR in our study (7 days (median)) is rather short and not very different from the time stated after the acute dose reduction. About two weeks may be more appropriate since the INR was within therapeutic range. Recommendations and algorithms have no specific advice on the frequency of INR measurements after the acute phase. Within-country differences were large, and in general the frequency of INR measurements will be of consequence for TTR [30,39], but also for the workload associated with VKA treatment.

Conclusions

The practice of VKA monitoring varies substantially both for stable patients and in the different ways a supra-therapeutic INR is handled. Most physicians failed to judge the magnitude of bleeding risks and treatment effects correctly. The large diversity of responses suggests variable quality of anticoagulation treatment both in primary and secondary care seemingly irrespective of dosing routines (experience vs algorithms), with potentially negative clinical consequences. Efforts to standardize VKA treatment and to develop practicable guidelines are still needed.

Conflict of interest statement

First author received honoraria from Nycomed Pharma AS, Norway for a lecture in 2008 and in 2009. The other authors state no conflict of interest.

Table 3
Patient B with pulmonary embolism: Risk of major bleeding, dose reduction in the next 48 h, and days until the next INR measurement in response to an INR of 4.8. Suggested weekly dose reduction and time to a repeat INR after INR had returned to 2.9. All numbers are given as median (10- and 90-percentiles).

Country (VKA)	48 h bleeding risk with INR 4.8 (%)	48 h dose reduction (%)	Days until next INR	Weekly dose reduction (%) when INR returned to 2.9	Days until next INR
Primary care					
Australia (w)	5 (1 – 10)	100 (50 – 100)	2 (1–7)	13 (4 – 30)	4 (2 – 7)
Austria (ph)	5 (1 – 50)	78 (33 – 100)	7 (2–14)	18 (9 – 61)	7 (4 – 14)
Belgium (ph)	6 (1 – 40)	96 (33 – 100)	7 (3–14)	18 (9 – 49)	7 (4 – 14)
Croatia (w)	30 (5 – 80)	63 (13 – 100)	7 (2–8)	22 (10 – 89)	7 (2 – 14)
Denmark (w)	5 (1 – 10)	67 (30 – 100)	7 (4–14)	13 (3 – 25)	9 (7 – 14)
Estonia (w)	15 (1 – 72)	75 (13 – 100)	7 (3–14)	22 (5 – 71)	7 (4 – 14)
France (fl)	10 (1 – 50)	53 (12 – 100)	5 (2–7)	19 (6 – 88)	7 (3 – 15)
Hungary (ac)	10 (2 – 50)	55 (9 – 100)	7 (4–14)	20 (6 – 89)	14 (6 – 30)
Norway (w)	2 (0 – 10)	100 (44 – 100)	4 (2–8)	6 (3 – 16)	7 (4 – 14)
Sweden (w)	5 (1 – 30)	78 (33 – 100)	3 (2–7)	13 (3 – 25)	7 (3 – 10)
the United Kingdom (w)	2 (0 – 20)	55 (9 – 100)	7 (2–7)	13 (4 – 34)	7 (4 – 14)
Secondary care					
Austria (ph)	4 (0 – 20)	100 (33 – 100)	7 (2–14)	18 (9 – 36)	7 (3 – 14)
Croatia (w)	10 (2 – 49)	94 (25 – 100)	7 (2–14)	48 (9 – 94)	7 (3 – 19)
France (fl)	5 (1 – 25)	53 (7 – 100)	4 (1–7)	19 (2 – 87)	7 (3 – 9)
Hungary (ac)	10 (1 – 50)	55 (9 – 82)	7 (2–14)	18 (8 – 90)	7 (3 – 20)
Spain (ac)	1 (0 – 4)	55 (9 – 81)	7 (7–14)	5 (3 – 13)	15 (7 – 28)
the Netherland (ac)	2 (0 – 5)	27 (9 – 55)	7 (4–14)	9 (5 – 23)	7 (7 – 14)
the Netherland (ph)	2.5 (0 – 10)	67 (32 – 100)	7 (7–14)	5 (3 – 23)	7 (7 – 14)
the United Kingdom (w)	1 (0 – 9)	55 (29 – 100)	7 (2–7)	13 (4 – 25)	7 (7 – 14)

w = warfarin, ph = phenprocoumon, fl = fluindione, ac = acenocoumarol.

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