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Major Haemorrhage during Vitamin K Antagonist Treatment: The Influence of Thyroid Hormone Levels

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Key Words
Free thyroxine · Vitamin K antagonists · Coagulation · Haemorrhage · Epidemiology

Abstract
Background: Annually, approximately 1–3% of patients treated with vitamin K antagonists (VKA) suffer from major haemorrhage. Since high levels of free thyroxine (fT_4) are associated with increased thrombosis risk, the aim was to assess whether low levels of fT_4 contribute to major haemorrhage in patients under VKA treatment. ***Methods:*** The FACTORS (Factors in Oral Anticoagulant Safety) study is a case-control study on patients receiving VKA treatment, including 110 cases with major haemorrhage. Controls were 220 matched participants treated with VKA without major haemorrhage. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association of fT_4 levels with major haemorrhage were calculated for different fT_4 cutoffs by conditional logistic regression. ***Results:*** In patients with an fT_4 level below 13 pmol/l, the risk of major haemorrhage was 5-fold increased (OR = 5.1; 95% CI: 0.9–28.6) compared with patients with an fT_4 level above 13 pmol/l. At a cutoff of 14 pmol/l, the risk was 3-fold increased (OR = 2.9; 95% CI: 1.0–8.5). High levels of fT_4 did not affect bleeding risk. No clear effect of thyroid-stimulating hormone and thyroid peroxidase antibodies was seen on the risk of major haemorrhage. ***Conclusions:*** These results indicate that fT_4 levels below 14 pmol/l play a role in the aetiology of major haemorrhage in VKA users.

Introduction

Vitamin K antagonist (VKA) treatment is used for several indications where anticoagulation is needed, such as the treatment and prevention of venous thrombosis or the prevention of cerebrovascular accidents in patients with atrial fibrillation. Haemorrhage is an important complication of anticoagulant treatment. Annually, 7–10% of patients treated with VKA suffer from haemorrhage, and 1–3% from major haemorrhage [1, 2]. Several risk factors for a bleeding tendency have been identified, such as comorbidities, older age and use of comedication [1, 2].

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Recently the relation between thyroid hormone and the coagulation system has gained interest as a focus of research [3–7]. High levels of free thyroxine (fT_4) are associated with high levels of factor VIII (FVIII), von Willebrand factor (vWF), fibrinogen and factor IX [6, 8, 9], and are a risk factor for venous thrombosis [10–12]. On the other side of the spectrum, low levels of FVIII, vWF and fibrinogen have been described in hypothyroidism, resulting in a protective effect on the risk of venous thrombosis [6]. It has also been reported that low levels of fT_4 may lead to acquired von Willebrand syndrome [5]. Low levels of FVIII and vWF are a risk factor for major haemorrhage [13]. Since FVIII and vWF are influenced by fT_4, low fT_4 levels may also influence bleeding risk in patients under VKA treatment.

FT_4 can exert its effect on the coagulation system also in yet another way. It is known that fT_4 has an effect on the pharmacodynamics of VKA, with different levels of fT_4 resulting in different INR values [14, 15]. Importantly, the VKA dosage is continuously adapted by the anticoagulation clinics to ensure therapeutic INR ranges. This prevents a clinical effect of fT_4 on INR levels in this study. The aim of the present study was to assess whether the level of fT_4 plays a role in the aetiology of major bleeding complications in patients under VKA treatment.

Materials and Methods

Patients and Data Collection

The study design of the FACTORS (Factors in Oral Anticoagulant Safety) case-control study has been described in a previous paper [16]. In short, in the registries of 2 anticoagulation clinics (Leiden and Amsterdam, The Netherlands) all patients with bleeding complications between 1999 and 2001 were identified, and these complications were classified as minor or major. Patients with major haemorrhage under VKA treatment were included as cases. Major haemorrhage was defined as: haemorrhage leading to death or hospitalization; a haemoglobin decrease >1.25 mmol/l; and intracranial, intramuscular, joint or intraocular haemorrhage. In total, 110 cases were included in the study. Two control subjects (i.e. patients under VKA treatment without haemorrhage) per case were selected from the same registries and matched for age (10-year age strata), sex, indication of VKA therapy, anticoagulation clinic, type of VKA, and whether individuals were still on active treatment at the time of data collection. If, for example, a case on VKA treatment for atrial fibrillation was included, 2 controls on VKA treatment for atrial fibrillation were included. A total of 220 controls were included. The study protocol was approved by both the ethics committee of the Leiden University Medical Centre and that of the Amsterdam Medical Centre.

Patients and controls were visited at home by a trained research nurse, a median of 14 months after the bleeding event. The patients completed a questionnaire, and citrated blood was drawn from the antecubital veins, kept at 4°C and centrifuged for 20 min at 2,250 *g* within 2 h from collection, and stored at –80°C.

Information on medication use was collected. Ten cases and 15 controls were treated with amiodarone, 0 cases and 9 controls received levothyroxine treatment, and 2 controls were on thyreostatics. Bearing in mind the 1:2 ratio at which the cases and controls were recruited, amiodarone use was evenly distributed in cases and controls, while levothyroxine treatment was only present in controls.

Laboratory Measurements

Levels of fT_4, thyroid-stimulating hormone (TSH) and thyroid peroxidase antibodies (anti-TPO) were measured in the available citrated plasma samples (103 cases and 213 controls; TSH in 103 cases and 208 controls) using commercially available assays (ADVIA Centaur® Immunoassay System; Siemens Healthcare Diagnostics, Marburg, Germany). As these tests have not been validated by the manufacturer for use with citrated plasma, studies comparing TSH and fT_4 in plasma and serum have been performed [10]. Only small systematic differences were detected, and linear regression analysis showed a strong association between levels of fT_4, TSH and anti-TPO measured in serum and plasma (regression coefficients: $\beta \geq 0.92$). The laboratories' reference range in plasma was 10–24 pmol/l for fT_4 and 0.32–4.32 mU/l for TSH.

Statistical Analysis

The fT_4 results were returned by the routine laboratory in round numbers. Actual reported values for fT_4 were used as cutoff points (fT_4 <13, <14, <15, <16, >21, >22, >23 and >24 pmol/l). Categorizing fT_4 based on percentiles was not possible due to the rounded number used to report fT_4. TSH and anti-TPO results were returned with 2 and 1 decimals, respectively, and cutoff values for the 2.5th, 5th, 10th, 20th, 80th, 90th, 95th and 97.5th percentiles were calculated for the control population. To study the effect on bleeding risk by high levels of fT_4, TSH or anti-TPO, we contrasted individuals with levels above the cutoff with those with levels below the cutoff, and vice versa, for the analysis of an effect of low levels. These analyses were repeated for the various cutoff levels. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated by conditional logistic regression to take the matched design into account. As density sampling for the controls was performed, the OR is identical to the rate ratio [17]. The analyses were stratified for men and women. In our analysis, we tried to disentangle pathways through which fT_4 might influence bleeding risk. An effect of fT_4 via VKA metabolism was considered unlikely, as changing INR levels are continuously adapted to and kept in a tight range. To assess whether fT_4 levels exert an effect on bleeding risk mediated by vWF and FVIII levels, we ran two logistic models: one including vWF and FVIII, and a model without these two variables. If the effect of fT_4 were mediated by vWF and FVIII, the adjusted model would be likely to show an attenuated effect (i.e. an OR towards 1.0), compared with the unadjusted model.

The INR used was the last known INR before the event for the cases, and the last known INR before blood sampling for the controls. All statistical analyses were performed by R version 2.12.1 [18] (packages: foreign_0.8-41 [19] and survival_2.36-5 [20]; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

The study population consisted of 110 cases and 220 controls (table 1). The median age of the cases was 66.5 years (2.5th–97.5th percentile: 32.6–84.4 years) and that of the controls 70.9 years (2.5th–97.5th percentile: 38.3–85.1 years). Of both cases and controls, 60% were men; 44% of the cases and 38% of the controls used phenprocoumon, the others used acenocoumarol.

Effect of fT_4 on Bleeding Risk

Patients with an fT_4 level <13 pmol/l had a 5-fold increased risk (OR = 5.1; 95% CI: 0.9–28.6) of major bleeding compared with patients with fT_4 levels ≥13 pmol/l (table 2). At a cutoff level of 14 pmol/l, the risk was 3-fold increased (OR = 2.9; 95% CI: 1.0–8.5). No clear attenuation of the effect was seen after adjusting for INR, vWF or FVIII, meaning that it is unlikely that the effect of fT_4 on bleeding risk is mediated by these factors. No clearly increased or decreased risk could be shown for high levels of fT_4, i.e. an OR of 0.6 (95% CI: 0.2–2.3) was found for a cutoff of 23 pmol/l, and an OR of 1.2 (95% CI: 0.3–5.0) for a cutoff of 24 pmol/l. Stratified analysis by sex revealed OR for women ranging from 5.1 (95% CI: 0.9–28.6) at an fT_4 level of 13 pmol/l to 0.8 (95% CI: 0.2–4.4) at 24 pmol/l. In men, the OR ranged from 2.9 (95% CI: 0.5–17.6) at 13 pmol/l to 0.3 (95% CI: 0.0–3.5) at 23 pmol/l (table 3).

At the 97.5th percentile, no association between TSH and bleeding risk was shown (OR = 1.1; 95% CI: 0.3–4.6; table 4a). At lower levels of TSH, an increased risk of major haemorrhage was observed, gradually rising to an OR of 3.6 (95% CI: 1.0–13.3) at the 2.5th percentile. Analysis of anti-TPO showed no effect of these antibodies on the risk of major haemorrhage under VKA treatment (table 4b).

Table 1. Patient characteristics

	Cases (n = 110)	Controls (n = 220)
Male, n	66 (60%)	131 (60%)
Median age at baseline, years	66.5 (32.6–84.4)	70.9 (38.3–85.1)
Phenprocoumon, n	48 (44%)	82 (38%)
Indication, n		
Atrial fibrillation	27	62
Cardioversion	1	11
Venous thrombosis	3	6
Mechanical heart valve	18	38
Recurrent venous thrombosis	8	14
Peripheral atherosclerosis	16	29
Ischaemic heart disease	19	33
Prophylactic	7	14
Stroke	5	5
Other	6	8
Type of haemorrhage, n		
Gastro-oesophageal bleeding	50	–
Epistaxis	8	–
Muscle bleeding	27	–
Intracranial bleeding	5	–
Retinal bleeding	9	–
Haematuria	9	–
Other bleeding	2	–
Thyroid function		
Median fT_4 level, pmol/l	17.7 (12.2–23.2)	17.7 (13.3–24.1)
Median TSH level, mU/l	1.09 (0.03–7.17)	1.17 (0.15–6.46)
Median anti-TPO level, U/dl	16.6 (16.6–1,444.4)	16.6 (16.6–1,444.4)
Subclinical hypothyroidism, n	6	10
Hypothyroidism, n	0	0
Subclinical hyperthyroidism, n	10	8
Hyperthyroidism, n	1	2
Coagulation		
Median FVIII level, IU/dl	118.5 (75.9–190.1)	115.0 (79.4–172.3)
Median vWF antigen level, IU/dl	160.0 (66.4–323.4)	148.0 (79.0–250.7)

Values in parentheses denote 2.5th–97.5th percentiles.

Discussion

In this case-control study we assessed the association between fT_4 and the occurrence of major haemorrhage in patients under VKA treatment. We found a 5-fold increased risk of major haemorrhage in patients with low levels of fT_4 (<13 pmol/l) relative to patients with higher fT_4 levels. Notably, this effect was found within the normal range of fT_4 levels. In this study, a pathway via INR, but not a pathway via vWF and FVIII, could be found as an explanation for the association between fT_4 levels and bleeding risk.

Unexpectedly, an association with bleeding risk was observed for lower TSH levels. This, however, is not in accordance with the increased risk at lower levels of fT_4, bearing in mind the negative feedback connecting TSH and fT_4. An explanation for the increased risk with both low TSH and low fT_4 levels could be the presence of non-thyroidal illness (NTI, i.e. the sick euthyroid syndrome). As we only found 1 case in our population with both fT_4 and TSH levels below the 5th percentile, indicating pos-

Table 2. Risk of major bleeding in VKA users with different levels of fT_4

fT_4 cutoff, pmol/l	Cases, n	Controls, n	OR[1]	OR[2]	OR[3]	OR[4]
<13.3	4/99	2/211	5.1 (0.9–28.6)	3.5 (0.4–31.2)	5.3 (0.9–30.8)	3.8 (0.3–40.7)
<14.4	9/94	8/205	2.9 (1.0–8.5)	5.1 (0.7–35.6)	2.5 (0.8–7.8)	7.1 (0.9–56.1)
<15.6	14/89	29/184	1.0 (0.5–2.1)	2.8 (0.9–8.8)	1.1 (0.5–2.2)	3.6 (1.0–12.8)
<16.7	20/83	58/155	0.6 (0.3–1.1)	0.9 (0.3–2.3)	0.7 (0.4–1.3)	1.3 (0.5–3.8)
>21.1	14/89	29/184	1.2 (0.5–2.4)	0.6 (0.2–1.9)	1.0 (0.5–2.1)	0.6 (0.2–1.7)
>22.2	6/97	20/193	0.6 (0.2–1.7)	0.4 (0.1–2.0)	0.6 (0.2–1.7)	0.4 (0.1–2.0)
>23.3	3/100	11/202	0.6 (0.2–2.3)	0.3 (0.0–2.8)	0.5 (0.1–2.1)	0.2 (0.0–2.4)
>24.4	3/100	6/207	1.2 (0.3–5.0)	0.7 (0.1–6.7)	1.1 (0.3–4.7)	0.7 (0.1–7.5)

Values in parentheses denote 95% CI. The reference group is the group above the cutoff value for the lower-than cutoffs, and the group below the cutoff value for the higher-than cutoffs.

[1] Crude OR.

[2] OR adjusted for last-measured INR.

[3] OR adjusted for factor VIII and vWF.

[4] OR adjusted for last-measured INR, factor VIII and vWF.

Table 3. Risk of major bleeding in VKA users with different levels of fT_4, in men and women

fT_4 cutoff, pmol/l	$Cases_{male}$, n	$Controls_{male}$, n	OR_{male}	$Cases_{female}$, n	$Controls_{female}$, n	OR_{female}
<13.3	0/61	0/126	n.a.	4/38	2/85	5.1 (0.9–28.6)
<14.4	3/58	2/124	2.9 (0.5–17.6)	6/36	6/81	2.9 (0.8–11.0)
<15.6	7/54	16/110	0.9 (0.4–2.4)	7/35	13/74	1.2 (0.4–3.3)
<16.7	10/51	29/97	0.6 (0.3–1.5)	10/32	29/58	0.6 (0.3–1.5)
>21.1	7/54	20/106	0.7 (0.3–1.9)	7/35	9/78	2.6 (0.7–9.0)
>22.2	3/58	13/113	0.5 (0.1–1.7)	3/39	7/80	1.0 (0.2–4.7)
>23.3	1/60	6/120	0.3 (0.0–3.5)	2/40	5/82	0.8 (0.2–4.4)
>24.4	1/60	1/125	3.5 (0.2–55.8)	2/40	5/82	0.8 (0.2–4.4)

Values in parentheses denote 95% CI. The reference group is the group above the cutoff value for the lower-than cutoffs, and the group below the cutoff value for the higher-than cutoffs. n.a. = Not applicable.

Table 4. Risk of major bleeding in VKA users

a With different levels of TSH

Percentile	TSH, mU/l	Cases, n	Controls, n	OR
<2.5th	0.12	6/97	5/203	3.6 (1.0–13.3)
<5th	0.29	10/93	10/198	2.5 (1.0–6.3)
<10th	0.45	17/86	20/188	2.2 (1.0–4.8)
<20th	0.72	27/76	41/167	1.8 (1.0–3.3)
>80th	2.14	21/82	41/167	1.0 (0.6–1.9)
>90th	2.74	14/89	22/188	1.5 (0.7–3.3)
>95th	4.47	6/97	10/198	1.2 (0.4–3.2)
>97.5th	6.60	3/100	5/203	1.1 (0.3–4.6)

b With different levels of anti-TPO

Percentile	Anti-TPO, U/dl	Cases, n	Controls, n	OR
>80th	22.4	19/84	42/171	0.9 (0.5–1.6)
>90th	155.1	12/91	21/192	1.3 (0.6–2.7)
>95th	585.2	7/96	10/203	1.5 (0.5–4.3)
>97.5th	1,444.4	5/98	9/204	1.3 (0.4–4.1)

Values in parentheses denote 95% CI. The reference group is the group above the cutoff value for the lower-than cutoffs, and below the cutoff value for the higher-than cutoffs.

sible NTI, NTI as an explanation for the found effect is unlikely; fT_4 is associated with change in coagulation factors, whereas TSH is not [8, 9]. Therefore, a direct effect of TSH seems to be biologically less plausible. Alternatively, because levels of TSH are related to many cardiovascular parameters and diseases (blood pressure, coronary heart disease, glomerular filtration rate and serum lipid concentrations) [21–26], it is possible that low TSH is a marker for other factors associated with haemorrhage. TSH also tends to increase over time, whereas fT_4 levels remain stable [27], potentially making that measured TSH levels do not accurately reflect TSH levels at the time of the event.

There are several limitations to this case-control study. By design, patients were included after the occurrence of a major haemorrhage and blood was drawn after the event. Therefore, the measured fT_4 levels in our study might not reflect the fT_4 levels at the time of the event. It has, however, been shown that fT_4 levels are very stable over time [27, 28], making it likely that the fT_4 levels after the event are a good reflection of the fT_4 levels at the time of the event. Blood was sampled after the acute phase of the disease, making it more likely for the coagulation parameters to reflect the levels before the event. Because of the study size, the confidence intervals presented were relatively wide and subanalyses were not possible. Lastly, the storage time of the blood samples may theoretically have caused changes in the parameters measurable in the samples. If this had been the case, these changes would have resulted in random misclassification, also resulting in an underestimation of the true effect. Altogether, none of the abovementioned limitations can explain the increased OR found in our study.

Since this is the first study to show an increased risk of major bleeding with lower levels of fT_4, it is too premature to draw conclusions regarding possible clinical implications. To speculate, a more strict regulation of thyroid function in patients on VKA might be indicated, aiming at fT_4 levels >15 pmol/l; also, in patients with spontaneous bleeding on VKA, thyroid status could be checked and, if necessary, corrected to prevent more bleeding episodes. At any rate, more research is needed to confirm our findings in larger studies and to study clinical implications. In conclusion, our findings indicate that VKA users with lower levels of fT_4 have an increased risk of major bleeding.

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Disclosure Statement

None.

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