Risk factors of vitamin K antagonist overcoagulation

A case-control study in unselected patients referred to an emergency department

Gwenaëlle Cadiou¹, Rémi Varin¹, Hervé Levesque², Vanessa Grassi³, Jacques Benichou¹, Isabelle Tiret¹, Bernard Dieu¹, Véronique Lecam-Duchez¹, Jeanne-Yvonne Borg¹, Jean-Michel Muller³, Ygal Benhamou³, Isabelle Marie³

¹Department of Pharmacy, Rouen University Hospital, Rouen Cedex, France; ²Department of Internal Medicine, Rouen University Hospital, Rouen Cedex, France; ³Department of Biostatistics, Rouen University Hospital, Rouen Cedex, France; ⁴Laboratory of Hematology, Rouen University Hospital, Rouen Cedex, France; ⁵Emergency Department, Rouen University Hospital, Rouen Cedex, France

Summary

The aims of this case-control study were to identify in vitamin K antagonist (VKA)-treated unselected patients, factors associated with international normalised ratio (INR) values: (i) greater than 6.0; and (ii) ranging from 4.0 to 6.0 complicated with bleeding. We also assessed VKA-related morbidity in these patients. During a two-month period, 4,188 consecutive and unselected patients were referred to our Emergency Department. At admission, the medical records of each patient and two age- and sex-matched controls were reviewed for: both duration and indication of VKA therapy, previous medical history of VKA-related haemorrhage, underlying co-morbidities, concomitant medications other than VKA, duration of hospitalization and deaths’ causes. Of these 4,188 subjects, 50 case-patients (1.19%) were identified; both case-patients and controls did not differ as regards indications and patterns of VKA therapy. Interestingly, two-thirds of case-patients were women, suggesting that female gender may be a risk factor of VKA over-coagulation onset. We identified the following risk factors of VKA over-coagulation: previous medical history of INR levels over therapeutic range, therapy with antibiotics, amiodarone and proton pump inhibitors, as well as fever. A total of 88% of case-patients were hospitalized; mean duration of patients’ hospitalization was seven days [range: 1–56 days]; no patient died from major bleeding. Our study underscores that it is of utmost importance to consider the strength of indication before starting VKA therapy, as this therapy has been responsible for as high as 1.19% of admissions in unselected subjects referred to an Emergency Department. Our data therefore suggest that internists should be aware of VKA-related high morbidity, particularly in situations at risk of VKA over-coagulation.

Keywords

Vitamin K antagonist, haemorrhage, risk factors, proton pump inhibitors, gender, outcome, morbidity, mortality

Introduction

Oral anticoagulants are one of the most commonly prescribed classes of drugs to treat or prevent arterial and/or venous thrombosis. Despite its usefulness, vitamin K antagonist (VKA) therapy (e.g. with warfarin) is fraught with complications, including principally the risk of haemorrhage. Unfortunately, warfarin-induced bleeding is not rare (1–9). In fact, in a series of 6814 VKA-treated patients, the incidence of overall bleeding complications and major bleeds was: 16.5 per 100 treatment-years (8).

More recently, few studies have investigated the possible risk factors of any type of bleeding during VKA therapy (1, 2, 7, 8, 10–28). Advanced age was found to increase the risk of major warfarin-related bleeding 1.8 to 3.2 (4, 10, 14–17, 29). Additional factors have also been reported to be associated with warfarin-induced bleeding, such as intensity of oral anticoagulant (relative risk [RR] 3.0–7.9 for international normalised ratio [INR] > 4.5) and recent initiation of oral anticoagulant therapy (< 3 months; RR: 1.9–5.9) (4, 10, 18, 30). Finally, other clinical parameters have also been related to VKA-induced bleeding, including: hypertension, comorbid diseases as well as drug-drug interaction (1, 7, 10, 17–19, 21–28, 31–33). Nevertheless, to date, much of our knowledge on VKA-associated risk factors of bleeding is based on clinical trials, where very diseased patients
are more often excluded; in essence, information on causes of high INR levels in usual clinical practice still remains scarce.

These data prompted us to conduct the present case-control study, in VKA-treated subjects, to: 1) identify factors associated with INR values: (i) greater than 6.0. We focused on INR values > 6.0, because these values are considered to increase the risk of major haemorrhage, and are unlikely to result from intra-individual fluctuation in VKA response; and (ii) ranging from 4.0 to 6.0 complicated by bleeding; and 2) assess VKA-related morbidity in these patients.

**Patients and methods**

From March 27 to June 7, 2006, 4,188 patients > 18 years of age were referred to the Emergency Department of Rouen University Hospital, France. The total number of acute admissions to the Emergency Department was obtained from the Rouen University Hospital information database.

During this two-month study period, 50 consecutive VKA-treated case-patients were included in the study. At admission, these case-patients exhibited: (i) INR results greater than 6.0; or (ii) INR values ranging from 4.0 to 6.0, concomitantly associated with major bleeding.

One hundred control subjects were concomitantly included in the study; these VKA-treated controls were age- and sex-matched with case-patients. They were admitted to the Emergency Department for reasons unconnected with VKA therapy; these controls had INR values in the therapeutic range and exhibited no minor/major bleeding. A member of the Laboratory of Hematology was responsible for identifying controls. In essence, as the first case-patient was identified, two controls matched for sex and age were selected. This procedure was repeated until all case-patients and both age- and sex-matched controls were identified during the two-month period.

First, the medical records of all case-patients and controls were reviewed for clinical characteristics at admission, i.e.:

- indication of oral anticoagulant therapy, including: cardiovascular disorders (atrial fibrillation, ischemic heart disease or congestive heart failure, tissue and mechanical heart valves), cerebrovascular diseases, as well as venous thromboembolism;
- previous medical history of oral anticoagulant therapy-related haemorrhage, particularly gastrointestinal bleeding and cerebral haemorrhage;
- presence of underlying comorbid illness, i.e.: liver disease, renal failure (renal insufficiency was considered if creatinine clearance value was lower than 60 ml/min), malignancy, diabetes mellitus, stroke;
- recent history of infection.

Second, the medical records of all case-patients and controls were reviewed for the following treatment characteristics at admission:

- pattern of oral anticoagulant therapy, e.g.: warfarin, fluindione and acenocoumarol;
- duration of oral anticoagulant therapy, classified as: therapy of more or less than three-month duration;
- characteristics of VKA-related bleedings, e.g.: epistaxis, gastrointestinal haemorrhage, or intracranial bleeding.

In all case-patients and controls, we also investigated the presence of concomitant medications other than oral VKA therapy, that might have interfered with VKA metabolism such as: anti-arrhythmic agents, antibiotics, antifungal agents, histamine-2 receptor antagonists, proton-pump inhibitors, leukotriene antagonist agents, antipsychotics, cholesterol-lowering agents. Particular attention was further paid to the use of: aspirin, clopidogrel, non-steroidal anti-inflammatory agents and acetaminophen. In addition, the number of concomitant medications was also recorded in all case-patients and controls, i.e.: 1) long-term therapy (> 6-month); and 2) recently instituted therapy (< 1-month).

Finally, data regarding case-patient outcome were reviewed for the following: significant disability and life-threatening manifestations, increased duration of hospital incharge (i.e. for care during patient stay in hospital). Deaths for all causes were recorded in all case-patients; case-patient deaths have been coded as follows: 1) death caused by bleeding; 2) death due to an underlying or other disease, which was not considered a thrombotic event; and 3) death due to a thrombotic event.

**Statistical analyses**

We compared the characteristics between each case-patient and both sex- and age-matched control patients.

The effect of the various risk factors (e.g.: timing of the event from the beginning of VKA therapy, previous history of VKA-related bleeding, underlying comorbidities, other concomitant therapy…) was assessed using conditional logistic regression. We computed matched odds ratios (OR) and 95% confidence interval (95% CI) in all analyses; a p-value lower than 0.05 was considered significant.

As regards variables with p-values <0.1, we further proceeded with multiple conditional logistic regression to calculate multivariate OR (95% CI); the used level of significance was p <0.05.
Results

From March 27 to June 7, 2006, 4,188 consecutive patients were referred to the Emergency Department of Rouen University Hospital. Of these 4,188 patients, we identified 50 consecutive case-patients. In the total population of unselected patients referred to our Emergency Department, the prevalence of patients, exhibiting either INR levels > 6.0 or INR values ranging from 4.0 to 6.0 (with major bleeding), was as high as 1.19%.

General characteristics of case-patients and controls

The general characteristics of both case-patients and age- and sex-matched controls are summarized in Table 1. Approximately, two-thirds of case-patients were females (Table 1). Moreover, at admission, we have found that the mean INR value was 6.2 [4.01–37.9] and 2.48 [2–3.50] in case-patients and controls, respectively (p=0.0001).

Among the 50 case-patients, 31 had INR values greater than 6.0 as follows: INR results ranging from 6.0 to 9.0: n=24, and INR values over 9.0: n=7. The 19 other case-patients exhibited both INR values ranging from 4.0 to 6.0 and concomitant bleeding.

Furthermore, case-patients received the following VKA therapy: fluindione (94%) and acenocoumarol (6%); 0% of case-patients and 6% of controls were given warfarin therapy (OR: 0.14 [95%CI: 0.008–2.61]; p=0.18) (Table 1). We observed that the mean daily dose of fluindione and acenocoumarol was similar in both case-patients and controls.

As shown in Table 1, the conditions prompting oral anticoagulation did not differ between case-patients and controls; atrial fibrillation was the major indication in both groups (70% vs. 61%). There was no significant difference between both groups as regards other conditions prompting anticoagulation, i.e.: heart valves (8% vs. 9%), myocardial infarction (2% vs. 1%), pulmonary embolism (10% vs. 11%) and deep venous thrombosis (10% vs. 14%).

Anticoagulation history of case-patients and controls

As shown in Table 2, we observed that the median duration of VKA therapy tended to be shorter in case-patients than in controls, although not significantly so. Indeed, VKA therapy duration less than three months tended to be more commonly found in patients than in controls (18% vs. 8%; OR: 2.394 [0.883–6.448].

Table 2: Anticoagulation history of both case-patients and age- and sex-matched controls.

<table>
<thead>
<tr>
<th>Duration of VKA* therapy at admission &lt;3 months (%)</th>
<th>Case-patients (n=50)</th>
<th>Controls (n=100)</th>
<th>OR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous medical history of VKA* therapy-related haemorrhage (%)</td>
<td>12</td>
<td>4</td>
<td>3.00 [0.847–10.631]</td>
<td>0.089</td>
</tr>
<tr>
<td>Previous medical history of VKA* therapy-related gastrointestinal haemorrhage (%)</td>
<td>12</td>
<td>7</td>
<td>1.804 [0.572–5.689]</td>
<td>0.314</td>
</tr>
<tr>
<td>Previous medical history of INR levels over therapeutic range (%)</td>
<td>22</td>
<td>11</td>
<td>2.288 [0.901–5.81]</td>
<td>0.082</td>
</tr>
</tbody>
</table>

*VKA: vitamin K antagonist, INR: international normalised ratio, OR: odds ratio, 95% CI: 95% confidence interval.

Previous medical history of VKA therapy-related haemorrhage of all causes (12% vs. 4%; OR: 3.00; p=0.089) and INR levels over therapeutic range (22% vs. 11%; OR: 2.288; p=0.082) tended to be more frequent in case-patients than in controls, although not significantly so. Previous history of gastrointestinal bleeding also tended to be more commonly encountered in case-patients than in controls (12% vs. 7%; p=0.314); we observed the following causes of gastrointestinal bleeding in case-patients: gastric/duodenal ulcer (n=4), diverticulosis (n=2).

Concomitant medications of patients and controls

The median number of concomitant daily drugs was higher in controls than in case-patients (5 [0–15] vs. 4 [0–10]; p=0.042); we observed a similar prevalence of case-patients and control patients who concomitantly received > 7 drugs at admission (24% vs. 23%; p> 0.05).

As regards long-term therapy (drugs >6-month duration), we interestingly found that case-patients more commonly received, as compared with controls, the following drugs: amiodarone (24% vs. 11%; p=0.042) and proton pump inhibitors (34% vs. 15%; p=0.016). As shown in Table 3, other medications were not different between the two groups.

As regards acute disorders, we observed that fever more frequently found in case-patients than in controls (p=0.0001). Among these recently initiated medications, only antibiotics were more commonly found in case-patients than in controls (12% vs. 1%; p=0.021) (Table 3); these seven case-patients received the following antibiotics: penicillin (n=2), macro-lide (n=2) and sulfamide (n=3).

Concurrent illnesses of case-patients and controls

Results are shown in Table 4. We observed that the median number of investigated concomitant risk factors of INR exceeding therapeutic values did not differ between case-patients and control patients (5 vs. 4; p>0.05).

As regards acute disorders, we observed that fever was more often encountered in case-patients than in controls (24% vs. 9%; p=0.018). Moreover, infection tended to be more frequent in case-patients than in controls (28% vs. 14%; p=0.065) (Table 4). As shown in Table 4, we failed to find differences between case-patients and controls regarding other acute diseases.

As regards chronic conditions, case-patients more frequently exhibited liver diseases (28% vs. 14%; p=0.038) than controls.
In contrast, we failed to find any differences between case-patients and controls for: chronic renal failure (36% vs. 40%), malignancy (24% vs. 24%), left ventricular dysfunction (46% vs. 45%), alcoholism (14% vs. 16%) as well as diabetes mellitus (30% vs. 28%) (Table 4).

Results of multiple conditional logistic regression analysis to identify risk factors of VKA-associated over-coagulation
Conditional logistic regression models were constructed to predict the occurrence of VKA-related over-coagulation on the basis of the following identified variables with p-values < 0.1.

Table 3: Comparison of concomitant medications between case-patients and age- and sex-matched controls.

<table>
<thead>
<tr>
<th>Acetaminophen (%)</th>
<th>8</th>
<th>9</th>
<th>0.88 [0.259–2.993]</th>
<th>0.838</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone (%)</td>
<td>24</td>
<td>11</td>
<td>2.705 [1.039–7.045]</td>
<td>0.042</td>
</tr>
<tr>
<td>Antibiotics (%)</td>
<td>12</td>
<td>1</td>
<td>12.00 [1.445–99.673]</td>
<td>0.021</td>
</tr>
<tr>
<td>Anti-arrhythmic agents (other than amiodarone %)</td>
<td>6</td>
<td>7</td>
<td>0.843 [0.204–3.491]</td>
<td>0.814</td>
</tr>
<tr>
<td>Antifungal agents (%)</td>
<td>2</td>
<td>1</td>
<td>2.00 [0.125–31.974]</td>
<td>0.624</td>
</tr>
<tr>
<td>Antipsychotics (%)</td>
<td>0</td>
<td>2</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>28</td>
<td>36</td>
<td>0.712 [0.351–1.446]</td>
<td>0.347</td>
</tr>
<tr>
<td>Calcium channel antagonists (%)</td>
<td>22</td>
<td>24</td>
<td>0.89 [0.39–2.031]</td>
<td>0.782</td>
</tr>
<tr>
<td>Digitalin (%)</td>
<td>26</td>
<td>25</td>
<td>1.05 [0.499–2.08]</td>
<td>0.899</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>38</td>
<td>51</td>
<td>0.602 [0.304–1.189]</td>
<td>0.144</td>
</tr>
<tr>
<td>Histamine-2 receptors (%)</td>
<td>0</td>
<td>9</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Inhibitors of platelet function (%)</td>
<td>6</td>
<td>8</td>
<td>0.73 [0.183–2.914]</td>
<td>0.656</td>
</tr>
<tr>
<td>Leukotriene antagonist agents (%)</td>
<td>0</td>
<td>2</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory agents (%)</td>
<td>2</td>
<td>0</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Proton pump inhibitors (%)</td>
<td>34</td>
<td>15</td>
<td>2.52 [1.19–5.336]</td>
<td>0.016</td>
</tr>
<tr>
<td>Serotonin re-uptake inhibitors (%)</td>
<td>4</td>
<td>6</td>
<td>0.633 [0.116–3.435]</td>
<td>0.596</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>26</td>
<td>26</td>
<td>1.00 [0.449–2.226]</td>
<td>1</td>
</tr>
<tr>
<td>Steroids (%)</td>
<td>6</td>
<td>3</td>
<td>2.00 [0.404–9.909]</td>
<td>0.396</td>
</tr>
</tbody>
</table>

OR: odds ratio; 95% CI: 95% confidence interval. * Not applicable because there were no exposed subjects whether in case-patients or in controls.

Table 4: Risk factors of VKA* over-coagulation in both case-patients and age- and sex-matched controls.

<table>
<thead>
<tr>
<th>Acute conditions</th>
<th>Case-patients (n=50)</th>
<th>Controls (n=100)</th>
<th>OR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>– fever (%)</td>
<td>24</td>
<td>9</td>
<td>3.347 [1.233–9.085]</td>
<td>0.018</td>
</tr>
<tr>
<td>– infection (%)</td>
<td>26</td>
<td>14</td>
<td>2.38 [0.949–5.969]</td>
<td>0.065</td>
</tr>
<tr>
<td>– myocardial infarction (%)</td>
<td>8</td>
<td>13</td>
<td>0.542 [0.157–1.869]</td>
<td>0.312</td>
</tr>
<tr>
<td>– acute congestive heart failure (%)</td>
<td>10</td>
<td>14</td>
<td>0.674 [0.225–2.022]</td>
<td>0.482</td>
</tr>
<tr>
<td>– stroke (%)</td>
<td>22</td>
<td>27</td>
<td>0.752 [0.331–1.711]</td>
<td>0.497</td>
</tr>
<tr>
<td>Recent history of gastrointestinal haemorrhage (%)</td>
<td>12</td>
<td>4</td>
<td>3.00 [0.847–10.631]</td>
<td>0.089</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic disorders</th>
<th>Case-patients (n=50)</th>
<th>Controls (n=100)</th>
<th>OR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>– diabetes mellitus (%)</td>
<td>30</td>
<td>28</td>
<td>1.117 [0.505–2.47]</td>
<td>0.786</td>
</tr>
<tr>
<td>– malignancy (%)</td>
<td>24</td>
<td>24</td>
<td>1.00 [0.442–2.260]</td>
<td>1</td>
</tr>
<tr>
<td>– liver disorder (%)</td>
<td>28</td>
<td>14</td>
<td>2.559 [1.042–6.283]</td>
<td>0.04</td>
</tr>
<tr>
<td>– alcoholism (%)</td>
<td>14</td>
<td>16</td>
<td>0.852 [0.323–2.249]</td>
<td>0.746</td>
</tr>
<tr>
<td>– chronic renal failure (%)</td>
<td>36</td>
<td>40</td>
<td>0.841 [0.412–1.714]</td>
<td>0.633</td>
</tr>
<tr>
<td>– left ventricular dysfunction (%)</td>
<td>46</td>
<td>45</td>
<td>1.053 [0.487–2.277]</td>
<td>0.895</td>
</tr>
</tbody>
</table>

* VKA: vitamin K antagonist; OR: odds ratio; 95% CI: 95% confidence interval.
The results of multivariate analyses are shown in Table 5. Under multivariate analysis, significant risk factors for VKA-related over-coagulation were: 1) previous medical history of INR levels over therapeutic range (OR: 4.345; p=0.02); 2) fever (OR: 6.018; p=0.007); 3) amiodarone therapy (OR: 3.575; p=0.022); and 4) recent initiation of antibiotics (OR: 12.932; p=0.03).

Morbidity in patients related to INR exceeding therapeutic range
At admission, case-patients exhibited the following VKA-related bleedings: 1) major bleeding: melena (n=5), haematemesis (n=1), rectal haemorrhage (n=4), small bowel haematoma (n=1), intracranial bleeding (n=3) and haematuria (n=6); and 2) minor bleeding: epistaxis (n=2), ecchymosis (n=4).

In our series, 88% of case-patients had to be hospitalized related to INR exceeding therapeutic range. Mean duration of patients' hospitalization after admission in the Emergency Department was seven days [range: 1–56 days].

Among the 50 case-patients, 36 underwent therapy, i.e.: 1) drugs for reversal of oral anticoagulation therapy, as follows: oral (n=15) or intravenous (n=3) vitamin K therapy, prothrombin complex concentrates (n=6); and 2) transfusion of packed red blood cells (n=12).

Finally, four of the case-patients (8%) died. Death was not directly due to haemorrhage; it was due to: 1) other organ failure, i.e.: septicemia (n=1), acute renal failure (n=1); and 2) metastatic malignancy: lymphoma (n=1), adrenal gland carcinoma (n=1).

Discussion
Much of our knowledge as regards the relationship between bleeding risk and VKA therapy is based on randomized clinical trials, where acutely diseased patients are often excluded (34). However, these previously reported studies provide limited information relevant to routine clinical cases. In contrast, case-control studies in routinely anticoagulated patients may provide more useful data regarding day-to-day practice. Nevertheless, the case-control design has limitations as: 1) it does not provide evidence on both the absolute risk and incidence of VKA over-coagulation in the general population; and 2) it may lead to selection and ascertainment bias. In our case-control study, both case-patients and controls were not followed-up at an anticoagulant clinic; in fact, all case-patients and controls were unselected and referred to our Emergency Department. In this instance, patients and controls characteristics were therefore not biased. Furthermore, because a member of the Laboratory of Hematology was responsible for identifying all patients exhibiting INR values > 4 during the two-month period of the study, this strategy has permitted us to include all cases of VKA-associated complications during the study period; therefore, our strategy did not miss cases of VKA-related over-coagulation in patients who were admitted in our Emergency Department.

Interestingly, our study permitted us to evaluate the prevalence of patients presenting with INR values > 6 as well as INR levels > 4 (with severe bleeding) in our Emergency Department; among 4,188 consecutive unselected patients, both INR values > 6 and > 4 (with severe bleeding) have been observed in as high as 1.19% of patients. Our series was performed during a two-month period, this prevalence of INR values > 6 or > 4 (with severe bleeding) was similar during both the 1st and 2nd month of study. Interestingly, our series underlines that INR values > 6 and > 4 with major bleeding are frequently encountered in unselected patients who were referred to our Emergency Department, resulting in: 1) high morbidity related to VKA-associated haemorrhage and/or concomitant organ failure; and 2) patients hospitalization (88% of cases).

The second main finding in the present series was that two-thirds of our case-patients were women (sex ratio: 2:1). Interestingly, we observed that only 56.5% of these 4,188 unselected patients, who were referred to our Emergency Department, were women. Among our case-patients, we further observed that the median level of INR tended to be higher in women than in men (6.25 vs. 5.5). Therefore, we suggest that female gender may be a risk factor of VKA over-coagulation, which may have important implications for patient safety and anticoagulation control. Few studies have previously noted an increased frequency of bleeding among women treated with warfarin (15, 28); in White et al.'s series (28), female gender was a risk factor of major bleeding (relative hazard: 1.7 [95% CI: 1.3–2.1]). Additionally, the warfarin dose has been shown to be associated with gender. In warfarin-treated patients (> 70 years of age), Garcia et al. (17) found the often-suggested initiation dose of 5 mg/day will be excessive for 82% of women and 65% of men (p < 0.05); the authors concluded that women probably require lower warfarin doses. Our study and other series’ observations that women, independently of age, more frequently develop VKA over-coagulation may be explained, in part, by differences in mean body size, hepatic fat, as well as intrinsic differences in warfarin metabolism. Reports of sex-associated differences in liver clearance by cytochrome P450 enzymes warrant additional investigations, although previous experiments, using animal models, have indicated that the expression of at least some cytochrome P450 enzymes may be regulated by sex steroids (17). Furthermore, we suggest that women adherence with VKA regimen may also be higher, resulting in increased risk of both VKA-related over-coagulation. In a retrospective study of 47,680 statin-treated patients, Vinker et al. (35), in fact, found women to have better adherence with statin therapy than men. Interestingly, over-adherence to warfarin therapy (using monitoring with electronic medication bottle caps) has also been associated with a significant increase in over-coagulation onset (36).

<table>
<thead>
<tr>
<th>Table 5: Variables found to be independently associated with VKA over-coagulation using multiple conditional logistic regression.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Previous medical history of VKA* therapy-related gastrointestinal haemorrhage</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Fever</td>
</tr>
</tbody>
</table>

*VKA: vitamin K antagonist; OR: odds ratio; 95% CI: 95% confidence interval.
From a practical point of view, the knowledge of predictive factors of VKA over-coagulation appears essential in order to improve patient management. In randomized trials, previous investigators have reported variables of VKA over-coagulation.

In our experience, shorter duration of VKA therapy (< 3 months) tended to be associated with VKA over-coagulation. Previously reported data found a higher rate of bleeding during the first 90 days of treatment as later compared (11 per 100 patient-years vs. 6.3 per 100 patient-years; RR: 1.75; 95% CI: 1.27–2.44) (7). In another study, the frequency of major bleeding decreased from 3%/month the 1st month of warfarin therapy to 0.8%/month during the rest of the 1st year of therapy, to 0.3%/months thereafter (2).

Furthermore, the risk of bleeding complications has been reported to be dependent on the type of coumarin derivative (8). Penning-van Beest et al. (37) have previously demonstrated that the use of VKA with longer half-life resulted in fewer bleeds; other authors have reported that the use of acenocoumarol resulted in fewer bleeds (46% less regarding major bleeding) than use of phenprocoumon (8). In our series, VKA therapy did not differ between case-patients and controls; most of case-patients and controls received fluididone (which is more commonly used in France).

In the present series, we observed that previous medical history of INR levels over therapeutic ranges was associated with VKA-related over-coagulation and/or bleeding (OR: 4.345; p=0.02). White et al. (28) have previously reported hospitalization with gastrointestinal bleeding during the previous 18 months to be a risk factor of VKA-related bleeding (RR: 2.6; 95% CI: 1.6–4.1).

Furthermore, only limited studies have evaluated the influence of concomitant drug intake on the complication rate of VKA therapy. The use of multiple medications has indeed been identified as a risk factor for bleeding complications (4, 27, 31, 33, 38, 39). In a previous series, patients receiving more than seven concomitant medications had 5.1 severe bleeding per 1000 patient-months, versus 1.8 in the patients receiving seven or fewer concomitant medications (OR: 6.4 [95% CI: 1.2–42.4]) (38). Nevertheless, previous series did not mention whether these concomitant drugs were recently initiated or not. In the present study, we failed to find a correlation between increased over-coagulation and drug intake >7 medications/day. Our findings suggest that a higher number of long-term medications may not be a predictive factor of VKA over-coagulation onset. In contrast, we observed that a recent history of drug institution (< 1-month) was associated with VKA over-coagulation onset. In our experience, combined use of VKA and antibiotics drugs (penicillin, macrolide, sulfamethoxazole-trimethoprim) was indeed strongly associated with over-coagulation (OR: 12.932; p=0.03). Interestingly, we also observed that patients exhibiting fever/infections more often developed VKA over-coagulation (OR: 6.018; p=0.007). Our data do not allow us to definitely conclude whether over-coagulation is related to antibacterial drugs or fever/infection itself. In a study of acenocoumarol/phenprocoumon-treated patients, sulfamethoxazole-trimethoprim has been reported to increase the risk of over-coagulation with an adjusted RR of 20.1 (39).

Another main finding in our study is that other long-term therapy (>6-month duration) was associated with VKA over-coagulation, i.e.: amiodarone. We observed that, in comparison, case-patients, received amiodarone more commonly than controls (OR: 3.575; p=0.022). The RR of having an INR of > 5 has been found to be higher in patients receiving combined therapy with amiodarone and warfarin compared with warfarin (alone)-treated patients (40–42). Previous authors have further mentioned that amiodarone use was associated with a reduction of 7.3 mg/week in warfarin maintenance dose (16). The enhanced anticoagulant effect observed when amiodarone and warfarin are coadministered is attributable to inhibition of P 450 2C9, the isoenzyme of P450 primarily responsible for the conversion of S-warfarin to its major metabolite S-7 hydroxywarfarin (40, 43, 44). Nevertheless, interaction between amiodarone and warfarin is difficult to manage, because of the slow onset of action of warfarin and its long half-life (20 to 100 days) (44).

proton-pump inhibitors. Proton-pump inhibitor therapy tended to be associated with VKA over-coagulation/haemorrhage onset. Only few studies have previously evaluated the interaction of proton-pump inhibitors on the pharmacokinetics and pharmacodynamics of warfarin in both healthy subjects and anticoagulated patients receiving omeprazole regimen (45–48). Clinically observed warfarin-omeprazole interaction has been suggested to be associated with the inhibition of R-warfarin hydroxylation by omeprazole (46, 47). In a series of 28 warfarin-treated patients, Unge et al. (47) found that the mean plasma concentration of R-warfarin increased by 9.5% during omeprazole therapy (20 mg/day) compared with placebo, although the coagulation time was not significantly changed (106 sec during omeprazole vs. 98 seconds during placebo). In Zhou et al.’s series (48), omeprazole has also been shown to inhibit the formation of the following warfarin enantiomers: R-6, R-7 and S-7 hydroxywarfarin. The inhibition of the in-vitro biotransformation of warfarin enantiomers by omeprazole has been attributed to its inhibitory effect on the activities of cytochrome P450 isoenzymes (CYP 1A2, CYP 3A4, CYP 2C9 and CYP 2C19) (48, 49). In addition, proton-pump inhibitors may also increase the risk for bleeding when combined with VKA therapy through intrinsic platelet properties (without elevated prothrombin INR levels). Nevertheless, no definite conclusion can be drawn from our data; in fact, additional studies are warranted to investigate the putative association between proton-pump inhibitor use and bleeding risk in warfarin users. However, we suggest that co-administration of omeprazole and warfarin, which is common in daily practice, should be closely monitored in these patients.

In this instance, we failed to find a correlation between other long-term therapy and VKA over-coagulation onset. However, additional drugs have been reported to be associated with VKA-associated over-coagulation, i.e.: inhibitors of platelet function (4, 33, 50). In a series that compared warfarin plus aspirin (80 mg/d) to aspirin (160 mg/d), major bleeding was more common in the warfarin-as-
pirin group than in the aspirin group (1.28 events vs. 0.72 events/100 person-years) (51);
- serotonin re-uptake inhibitors (citalopram, fluoxetine, paroxetine, sertraline) (4, 33);
- acetaminophen (4, 17, 35). Parra et al. (52) have observed that acetaminophen-treated patients had higher mean INRs compared with subjects receiving placebo. Levine et al. (4) have, in fact, postulated that the weight of evidence indicate that any important INR rise in acetaminophen-treated patients is likely a result of concurrent illness necessitating the intake of this medication, and there is little evidence that paracetamol increases bleeding due to VKAs;
- statins. In a population-based, nested case-control study, long-term (> 1 year) statin use was associated with a lower risk for any bleeding; however, the authors underlined the role of potential confounders and the lack of biological plausibility (53).

Finally, comorbid chronic conditions have also been associated with the onset of VKA-associated bleeding. These include treated hypertension, serious heart disease, diabetes mellitus, prior stroke or transient ischemic attack as well as extensive malignancy (1, 3, 7, 18–21, 25–28, 51). In White et al.’s series (28), chronic renal disease increased the risk of bleeding (relative hazard: 2.4; 95% CI: 1.4–4.2). In this instance, these disorders did not influence the VKA-related complication rate. Our data may be explained by the fact that our patients and control subjects were age- and sex-matched; in our series, bias related to polymorbidity of elderly patients may, in part, be excluded.

In conclusion, our study confirms that it is of utmost importance to consider the strength of indication before starting VKA therapy. This type of therapy has been responsible for 1.19% of admissions in unselected subjects referred to our Emergency Department; VKA therapy over-coagulation was further responsible for a high morbidity rate and life-threatening complications. Moreover, our case-control study underlines that patients with fever and/or previous history of INR levels over therapeutic range, as well as those receiving antibiotics, have an increased over-coagulation risk and therefore require particularly careful monitoring of VKA therapy. Our study also suggests that the potential of drug interaction should be taken into account when choosing amiodarone or proton-pump inhibitor therapy for patients receiving a concomitant medication such as warfarin with a narrow therapeutic index. Finally, high-risk patients should be identified and may be considered for alternative therapies to oral anticoagulation.

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What is known about this topic?
- To date, much of our knowledge on vitamin K antagonist (VKA)-associated risk factors of bleeding is based on clinical trials, where very diseased patients are more often excluded.
- In essence, information on causes of high international normalised ratio (INR) levels in usual clinical practice still remains scarce.

What does this paper add?
- Our case-control study underscores that it is of utmost importance to consider the strength of indication before starting VKA therapy, as this therapy has been responsible for as high as 1.19% of admissions in unselected subjects referred to an Emergency Department.
- Interestingly, two-thirds of case-patients were women, suggesting that female gender may be a risk factor of VKA overcoagulation onset.
- We identified the following risk factors of VKA overcoagulation: previous medical history of INR levels over therapeutic range, therapy with antibiotics, amiodarone and proton pump inhibitors, as well as fever.

References
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