Risk factors of vitamin K antagonist overcoagulation

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Summary

Objectives: The aims of this prospective study were to identify, in vitamin K antagonist (VKA)-treated patients, factors associated with 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.

Methods: During a 6-month period, 3090 consecutive patients were referred to our Department of Internal Medicine, including 412 VKA-treated patients. At admission, the medical records of VKA-treated patients were reviewed for type, duration and indication of VKA therapy, previous medical history of VKA-related hemorrhage, comorbidities and concomitant medications.

Results: Forty of the 412 VKA-treated patients (9.7%) exhibited oral anticoagulant related overcoagulation. VKA overcoagulation was associated with high morbidity, leading to major bleeding in 27.5% of cases; moreover, 12.5% of these patients died, death being mainly due to major bleeding. Under multivariate analysis, significant factors for VKA-related overcoagulation were as follows: previous medical history of VKA therapy-related hemorrhage ($P = 0.00001$) and INR levels over therapeutic range ($P = 0.0006$), chronic liver disease ($P = 0.03$), therapy with amiodarone ($P = 0.009$); in contrast, statin therapy was found to be a protective factor of VKA overcoagulation ($P = 0.008$).

Conclusion: The knowledge of predictive factors of VKA-related overcoagulation seems of utmost importance to improve patients’ management. Our study underlines the fact that the potential of drug interaction should be taken into account when choosing amiodarone for patients receiving VKAs. Interestingly, long-term (>6 month) statin therapy may be a protective factor of VKA overcoagulation. Our findings, therefore, suggest that there may be no need to switch long-term users of VKA and statin to a safer alternative therapy.

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 is fraught with complications, in particular, the risk of hemorrhage. Unfortunately, warfarin-induced bleeding is not rare.¹⁻⁹ In a series of 6814 VKA-treated patients, the incidence of overall bleeding complications was 16.5 per 100 treatment years.⁸

More recently, only a few studies have investigated the possible risk factors of any type of bleeding during VKA therapy.¹²,⁷,⁸,¹⁰⁻²⁸ Advanced age was found to increase the risk of major warfarin-related bleeding from 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 3.0–7.9 for international normalized ratio (INR) > 4.5] and recent initiation of oral anticoagulant therapy (<3 months; relative risk: 1.9–5.9).⁴,¹⁰,¹⁸,³⁰ Finally, other clinical
features have also been related to VKA-induced bleeding, including hypertension, diabetes mellitus or malignancy.\textsuperscript{1,7,10–19,21–28,31–33} Nevertheless, to date, much of our knowledge regarding VKA-associated risk factors of bleeding is based on clinical trials, where acutely diseased patients are more often excluded; therefore, information on causes of high INR levels in usual clinical practice still remains scarce.

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

Patients and methods

Patients and methods

From January to June 2009, 3090 patients >18 years of age were referred to the Department of Internal Medicine of the Rouen University Hospital. The total number of acute admissions to our Department of Internal Medicine was obtained from the University Hospital information database. Of these 3090 patients, 412 received VKA therapy at admission. VKA-related overcoagulation was, in fact, observed in 40 of these 412 latter patients; the

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Statistical analyses

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We compared the characteristics between patients with and without VKA-related overcoagulation.

Statistical analyses were conducted using SAS version 8.02 (SAS Institute Inc.; Cary, NC). For group comparison involving binary data, we used either the chi-square test or Fisher’s exact test, depending on the sample size ($n > 5$ and $n < 5$, respectively). Comparisons involving continuous data were made using the Mann–Whitney test. The results were regarded as significant when the $P$-value was <0.05. With regard to variables with $P$-value <0.1, we further proceeded with multiple logistic regression to calculate multivariate odds ratio (OR) [95% confidence interval (CI)]; the used level of significance was $P < 0.05$ in all performed tests.

Results

Results

From January to June 2009, 3090 consecutive patients were referred to the Department of Internal Medicine of Rouen University Hospital. Of these 3090 patients, 412 patients received VKA therapy at admission. VKA-related overcoagulation was, in fact, observed in 40 of these 412 latter patients; the
prevalence of VKA overcoagulation was, therefore, 9.7% in overall patients receiving oral anticoagulant therapy.

The 412 VKA-treated patients consisted of 186 men and 226 women with a median age of 79 years (range: 18–92 years). These patients received the following VKA therapy: fluindione (85.9%), warfarin (9%) and acenocoumarol (5.1%). The main conditions prompting oral anticoagulation were as follows: atrial fibrillation (56%), heart valves (8.7%), myocardial infarction (3.2%), pulmonary embolism (12.1%) and deep venous thrombosis (13.6%).

**General characteristics of VKA-treated patients with and without VKA overcoagulation**

Patients with VKA-related overcoagulation were older than those without (79.7 vs. 75.7 years; \( P = 0.02 \)). As shown in Table 1, we observed a higher prevalence of women in the group of patients with VKA-related overcoagulation (\( P = 0.127 \)) (Table 1).

At admission, we have found that the median INR value was 10 (4–35) and 2.4 (1–5.8) in patients with and without VKA-related overcoagulation, respectively (\( P < 10^{-6} \)).

Among the 40 patients with VKA overcoagulation, 35 had INR values greater than 6.0 as follows: INR results ranging from 6.0 to 9.0 (\( n = 11 \)), and INR values over 9.0 (\( n = 24 \)). The five other patients exhibited both INR values ranging from 4.0 to 6.0 and concomitant bleeding.

With regard to the type of oral anticoagulant therapy, patients with VKA overcoagulation more commonly received warfarin therapy (17.5% vs. 8.1%; \( P = 0.04 \)) (Table 1). The median daily doses of fluindione, warfarin or acenocoumarol were not different in patients with or without VKA-related overcoagulation.

As shown in Table 1, the conditions prompting oral anticoagulation were not similar in patients with or without VKA overcoagulation. We have, in fact, observed that patients with VKA overcoagulation less commonly exhibited both cardiovascular and cerebrovascular diseases (54.3% vs. 71.8%; \( P = 0.02 \)).

**Anticoagulation history of patients with and without VKA overcoagulation**

We observed that the median duration of VKA therapy tended to be shorter in patients with VKA-related overcoagulation; VKA therapy duration <1 year was more frequently found in this latter group of patients (28.1% vs. 15.4%; \( P = 0.08 \)).

Patients with VKA-related overcoagulation, compared with those without, more frequently exhibited: (i) previous medical history of VKA therapy-related hemorrhage of all causes (32.5% vs. 4%; \( P < 10^{-7} \)); and (ii) previous history of gastrointestinal bleeding (15% vs. 2.4%; \( P = 0.0006 \)) (Table 2).

**Concomitant medications between patients with and without VKA overcoagulation**

The median number of concomitant daily drugs tended to be higher patients with VKA-related overcoagulation [8(0–18) vs. 7(0–18); \( P = 0.06 \)]; in addition, patients with VKA overcoagulation more

### Table 1  Comparison of general characteristics between VKA-treated patients with and without overcoagulation

<table>
<thead>
<tr>
<th></th>
<th>Patients with overcoagulation (( n = 40 ))</th>
<th>Patients without overcoagulation (( n = 372 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>32.5% males/67.5% females</td>
<td>46.5% males/53.5% females</td>
<td>0.127</td>
</tr>
<tr>
<td>Age (median, years) (range)</td>
<td>79.7 (28–92)</td>
<td>75.7 (18–90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pattern of VKA therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluindione (%)</td>
<td>77.5</td>
<td>86.8</td>
<td>0.107</td>
</tr>
<tr>
<td>Acenocoumarol (%)</td>
<td>5</td>
<td>5.1</td>
<td>0.976</td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>17.5</td>
<td>8.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Indication of VKA therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases (%)</td>
<td>54.3</td>
<td>71.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Venous thromboembolism (%)</td>
<td>45.7</td>
<td>28.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean INR value (range)</td>
<td>10 (4.01–35)</td>
<td>2.4 (1–5.8)</td>
<td>( &lt;10^{-6} )</td>
</tr>
<tr>
<td>Duration of VKA therapy at admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months (%)</td>
<td>12.5</td>
<td>11.9</td>
<td>1</td>
</tr>
<tr>
<td>3–12 months (%)</td>
<td>28.1</td>
<td>15.4</td>
<td>0.08</td>
</tr>
<tr>
<td>13–36 months (%)</td>
<td>9.4</td>
<td>25.3</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;36 months (%)</td>
<td>50</td>
<td>47.4</td>
<td>0.85</td>
</tr>
</tbody>
</table>
commonly received more than 3 drugs/day at admission (23.1% vs. 9.1%; \(P=0.01\)).

With regard to concomitant long-term therapy (drugs >6-month duration), patients with VKA overcoagulation, compared with those without, less commonly received: statins (12.5% vs. 34.1%; \(P=0.004\)). On the other hand, this group of patients with VKA overcoagulation more frequently received amiodarone (27.5% vs. 10.8%; \(P=0.005\)). As shown in Table 3, other medications were not different between the two groups of patients.

A recent history (<1-month duration) of drug institution was similarly found in patients with or without VKA overcoagulation, including antibiotics (10% vs. 11.6%; \(P=0.768\)) and antifungal agents (2.5% vs. 0.5%; \(P=0.185\)).

### Concurrent diseases between patients with and without VKA overcoagulation

Results are shown in Table 4. No statistically significant difference was found between patients with and without VKA overcoagulation regarding acute disorders, i.e. infection (25% vs. 23.4%; \(P=0.819\)), fever (15% vs. 16.4%; \(P=0.820\)) or diarrhea (7.5% vs. 3%; \(P=0.131\)).

With regard to chronic conditions, patients with VKA overcoagulation, compared with those without, more frequently exhibited liver diseases (15% vs. 4%; \(P=0.002\)) (Table 4).

### Results of multiple logistic regression analysis to identify risk factors of VKA-associated overcoagulation

Under multivariate analysis, significant factors for VKA-related overcoagulation were previous medical history of VKA therapy-related hemorrhage of all causes (\(P=0.00001\)), previous medical history of INR levels over therapeutic range (\(P=0.0006\)), amiodarone therapy (\(P=0.009\)) and chronic liver diseases (\(P=0.03\)); on the other hand, long-term statin therapy was, in fact, found to be a protective factor of VKA-related overcoagulation (\(P=0.008\)).

### Morbidity in patients related to INR exceeding therapeutic range

At admission, 19 patients with VKA-related overcoagulation exhibited bleeding complications as follows: (i) major bleeding: melena (\(n=1\)), rectal hemorrhage (\(n=4\)), intracranial bleeding (\(n=3\)) and hematuria (\(n=3\)); and (ii) minor bleeding: epistaxis (\(n=5\)) and ecchymosis (\(n=3\)).

In addition, 5 of the 40 patients with overcoagulation (12.5%) died. Death was due to intracranial bleeding (\(n=3\)), cardiac failure (\(n=1\)) and metastatic malignancy (\(n=1\)).

### Discussion

Much of our knowledge with regard to 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 trials provide limited information relevant to routine clinical cases. In contrast, observational studies in routinely anticoagulated patients may provide more useful data regarding day-to-day practice. In the present study, 412 consecutive VKA-treated patients were referred to our Department of Internal Medicine during a 6-month period. Nevertheless, our study design has limitations as: (i) it does not provide indication on both the absolute risk and incidence of VKA overcoagulation in the general population and (ii) it may lead to selection bias. Indeed, the current study design

### Table 2

Comparison of anticoagulation history between VKA-treated patients with and without overcoagulation

<table>
<thead>
<tr>
<th></th>
<th>Patients with overcoagulation (n=40)</th>
<th>Patients without overcoagulation (n=372)</th>
<th>OR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous medical history of VKA therapy-related hemorrhage (%)</td>
<td>32.5</td>
<td>4</td>
<td>11.3 (4.47–28.6)</td>
<td>&lt;10(^{-7})</td>
</tr>
<tr>
<td>Previous medical history of VKA therapy-related gastrointestinal hemorrhage (%)</td>
<td>15</td>
<td>2.4</td>
<td>5.72 (1.42–20.28)</td>
<td>0.006</td>
</tr>
<tr>
<td>Previous medical history of INR levels over therapeutic range (%)</td>
<td>22.5</td>
<td>3.5</td>
<td>7.93 (2.77–22)</td>
<td>&lt;10(^{-5})</td>
</tr>
</tbody>
</table>
has not permitted us to include all cases of VKA-associated complications during the study period; therefore, our study strategy has likely missed cases of severe VKA-related overcoagulation (e.g. gastrointestinal, retroperitoneal or spinal bleeds) in patients who were admitted in the Emergency Department and Intensive Care Unit of our hospital.

Nevertheless, our study interestingly permitted us to evaluate the prevalence of patients presenting with INR values >6 as well as INR levels >4 (with severe bleeding) in our Department of Internal Medicine; among 3090 consecutive unselected patients, both INR values >6 and >4 (with severe bleeding) have been observed in as high as 1.3% of patients. Our series was performed during a 6-month period; this prevalence of VKA-related overcoagulation was similar from the first to the sixth month of study. Thus, our series underlines that INR values more than 6 and more than 4 with major bleeding were frequently encountered in unselected patients who were referred to our

<table>
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<th>Table 3</th>
<th>Comparison of concomitant medications between VKA-treated patients with and without overcoagulation</th>
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<tr>
<td></td>
<td>Patients with overcoagulation (n = 40)</td>
</tr>
<tr>
<td>Acetaminophen (%)</td>
<td>25</td>
</tr>
<tr>
<td>Amiodarone (%)</td>
<td>27.5</td>
</tr>
<tr>
<td>Antibiotics (%)</td>
<td>10</td>
</tr>
<tr>
<td>Anti-arrhythmic agents (other than amiodarone) (%)</td>
<td>6</td>
</tr>
<tr>
<td>Antifungal agents (%)</td>
<td>2.5</td>
</tr>
<tr>
<td>Antipsychotics (%)</td>
<td>0</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>42.5</td>
</tr>
<tr>
<td>Calcium channel antagonists (%)</td>
<td>22.5</td>
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<tr>
<td>Diuretics (%)</td>
<td>47.5</td>
</tr>
<tr>
<td>Histamine-2 receptors (%)</td>
<td>5</td>
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<tr>
<td>Inhibitors of platelet function (%)</td>
<td>2.5</td>
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<tr>
<td>Leukotriene antagonist agents (%)</td>
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<tr>
<td>Non-steroidal anti-inflammatory agents (%)</td>
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<tr>
<td>Proton pump inhibitors (%)</td>
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<tr>
<td>Serotonin re-uptake inhibitors (%)</td>
<td>4</td>
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<tr>
<td>Statins (%)</td>
<td>12.5</td>
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<td>Steroids (%)</td>
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<th>Table 4</th>
<th>Comparison of comorbid illnesses between VKA-treated patients with and without overcoagulation</th>
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<tbody>
<tr>
<td></td>
<td>Patients with overcoagulation (n = 40)</td>
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<tr>
<td>Acute conditions</td>
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<tr>
<td>Fever (%)</td>
<td>15</td>
</tr>
<tr>
<td>Infection (%)</td>
<td>25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.5</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>5</td>
</tr>
<tr>
<td>Acute congestive heart failure (%)</td>
<td>17.5</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>20</td>
</tr>
<tr>
<td>Chronic disorders</td>
<td></td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>25</td>
</tr>
<tr>
<td>Malignancy (%)</td>
<td>10</td>
</tr>
<tr>
<td>Liver disorder (%)</td>
<td>15</td>
</tr>
<tr>
<td>Chronic renal failure (%)</td>
<td>22.5</td>
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</tbody>
</table>
Department of Internal medicine, resulting in (i) high morbidity due to VKA-associated hemorrhage and/or concomitant organ failure and (ii) patients’ hospitalization.

Another finding in the present series was that VKA overcoagulation tended to occur more often in women. Among our patients with VKA-related overcoagulation, we also observed that the median level of INR tended to be higher in women than in men (6.8 vs. 5.4) at admission. Therefore, we suggest that female gender may be a risk factor for VKA overcoagulation, which may have important implications for patient safety and anticoagulation control. Few studies have also 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 a factor of major bleeding [relative hazard: 1.7 (95% CI: 1.3–2.1)]. Furthermore, the warfarin dose has been shown to be associated with gender. In warfarin-treated patients, 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); these investigators have postulated that women probably require lower daily doses of warfarin. We suggest that women, independently of age, more commonly develop VKA overcoagulation because of differences in mean body size, hepatic fat; reports of sex-associated differences in liver clearance by cytochrome P450 enzymes have also been described.17 Additionally, we suggest that women adherence with VKA regimen may also be higher, leading to increased risk of VKA-related overcoagulation. In a retrospective study of 47 680 statin-treated patients, Vinker et al.45 found women to have better adherence with statin therapy than men. Interestingly, overdosage to warfarin therapy (using monitoring with electronic medication bottle caps) has also been associated with a significant increase in overcoagulation onset.36

Moreover, we observed that patients with VKA-related overcoagulation were older than those without. Our findings confirm previously reported data.7,19,30,37–39 Thus, although many older reports indicate that older patients do not have an increased risk for bleeding, more recent reports have described such an association;15,40,41 the discrepancy may be explained partly by the wide range in the mean age of the patients enrolled in the various studies as well as the relative lack of representation in most series of patients >80 years of age. A recent meta-analysis of six trials with more than 1900 patients with atrial fibrillation found a rate of major hemorrhage of 1.8 per 100 patient-years in those <75 years of age, rising to 3.2 per 100 patient-years in those ≥75 years of age.32 In VKA-treated patients, Torn et al.43 further found an increase of major hemorrhage with age, rising from 1.5 per 100 patient-years in those <60 years to 4.2 per 100 patient-years in those >80 years of age. Finally, in a series of 433 patients, major bleeding more often occurred in elderly patients >75 years of age than in younger subjects (5.1%/year vs. 1%/year); the cumulative incidence of major bleeding in patients >75 years of age (10.8%; 95% CI, 1.8–19.8) was significantly higher than in younger subjects (2.8%; 95% CI, 0.3–5.3, P=0.006).44 Taken together, these data identify elderly patients as a high-risk group of developing VKA-related overcoagulation; thus, elderly patients should be monitored carefully in order to reduce the number of bleeding complications.

From a practical point of view, the knowledge of predictive factors of VKA overcoagulation appears of utmost importance in order to improve patient management. In randomized trials, variables of VKA-related overcoagulation have been reported. In our experience, shorter duration of VKA therapy (<1 year) was associated with VKA overcoagulation. Previous investigators found that frequency of major bleeding decreased from 3%/month the first month of warfarin therapy to 0.8%/month during the rest of the first year of therapy and to 0.3%/months thereafter.2 In another trial, a higher rate of bleeding was found during the first 90 days for warfarin therapy as later compared [11 per 100 patient-years vs. 6.3 per 100 patient-years; RR: 1.75 (95% CI: 1.27–2.44)].24

Furthermore, the risk of bleeding complications has been reported to be dependent on the type of oral anticoagulant.8 Penning-van Beest et al.45 have shown that the use of VKA with longer half-life resulted in fewer bleeds; other investigators have also reported that the use of acenocoumarol led to fewer bleeds (46% less regarding major bleeding) than use of phenprocoumon.8 In our series, we have interestingly observed that the use of warfarin resulted in more bleeds than use of fluindione; we have, therefore, found that the group of patients with VKA overcoagulation more commonly received warfarin (17.5% vs. 8.1%).

In the present series, we found that previous medical history of VKA therapy-related hemorrhage (of all causes) and INR levels over therapeutic ranges were strongly associated with VKA-related overcoagulation and/or bleeding (P=0.01). Previous investigators have also observed that the patient factor most consistently predictive of major bleeding is a history of bleeding (especially gastrointestinal bleeding);7,14,37,46,47 thus, White et al.28 have reported a history of gastrointestinal bleeding during the previous 18 months to be a risk factor of VKA-related
bleeding (relative risk: 2.6; 95% CI: 1.6–4.1). Additionally, only limited studies have evaluated the influence of concomitant drug intake on the complication rate of VKA therapy. The use of numerous medications has been identified as a risk factor for bleeding complications.\textsuperscript{4,27,31,33,48–50} In a previous series, bleeding complications more often occurred in patients receiving more than four drugs per day (24.4% vs. 4.3%).\textsuperscript{27} In another trial, patients receiving more than seven concomitant medications per day had 5.1 severe bleeding per 1000 patient-months, vs. 1.8 in the patients receiving less than or equal to seven concomitant medications per day [OR: 6.4 (95% CI: 1.2–42.4)].\textsuperscript{48} In the present study, we have also found a correlation between increased overcoagulation and drug intake more than seven medications per day. Taken together, our findings indicate that a higher number of daily medications may be a predictive factor of VKA overcoagulation onset.

Another main finding in our study is that long-term use (>6-month duration) of amiodarone was strongly associated with VKA overcoagulation. The relative risk of having an INR of more than 5 has previously been found to be higher in patients receiving combined therapy with amiodarone and warfarin compared with warfarin (alone)-treated patients.\textsuperscript{46–52} Other investigators have also shown that amiodarone use is associated with a reduction of 7.3 mg/week in warfarin maintenance dose.\textsuperscript{16} Additionally, in a series of 30 patients, potentiation of the anticoagulant effect of warfarin by amiodarone has been reported; thus, the authors found a 35–65% reduction in the required daily dose of warfarin in patients receiving amiodarone therapy.\textsuperscript{53}

Recently, Edwin et al.\textsuperscript{54} have further assessed whether simultaneous initiation of warfarin and amiodarone leads to alteration in the INR response to warfarin; total and average daily doses were found to be lower in the amiodarone-treated patients. Warfarin is available as a racemate mixture of the S- and R-enantiomers, the S-enantiomer being five times more potent as an anticoagulant;\textsuperscript{51} both S- and R-enantiomers are metabolized by hepatic cytochrome P450 isoenzymes: CYP 2C9 and CYP 1A2, respectively. Indeed, the enhanced anticoagulant effect observed when amiodarone and warfarin are co-administered is attributable to inhibition of CYP 2C9 by amiodarone, this isoenzyme of P450 being primarily responsible for the conversion of S-warfarin to its major metabolite S-7 hydroxywarfarin.\textsuperscript{48,51,55,56} Taken together, warfarin dosing guidelines may be developed; by incorporating these guidelines into clinical practice, both initiation and maintenance of therapeutic warfarin therapy could be facilitated in patients receiving amiodarone therapy, and adverse sequelae of this significant interaction might be minimized.

Furthermore, ~30% of warfarin users are co-prescribed an antihyperlipidemic agent.\textsuperscript{57} In a population-based, nested case-control study, long-term (>1 year) statin use was associated with a lower risk of any bleeding.\textsuperscript{58} Recently, Schelleman et al.\textsuperscript{57} evaluated whether initiation of statins increases the risk of gastrointestinal bleeding in warfarin-treated patients. These authors have, in fact, found a decreased overall risk of gastrointestinal bleeding in patients receiving: atorvastatin (OR: 0.77; 95% CI: 0.70–0.84) and pravastatin (OR: 0.65; 95% CI: 0.54–0.78). Moreover, the ORs for the primary time period (1–30 days) expected for a warfarin–statin interaction was 1.96 for atorvastatin (95% CI: 1.04–1.61), 0.46 for pravastatin (95% CI: 0.47–1.75) and 1.33 for simvastatin (95% CI: 1.1–1.78).\textsuperscript{53} During the 31–60 days period of statin therapy, all ORs were attenuated, i.e. 0.96 for atorvastatin (95% CI: 0.68–1.35), 0.88 for pravastatin (95% CI: 0.45–1.71) and 1.26 for simvastatin (95% CI: 0.83–1.61).\textsuperscript{57} Finally, only atorvastatin and pravastatin initiators had a statistically significantly decreased OR of gastrointestinal bleeding after 61 days therapy: 0.62 for atorvastatin (95% CI: 0.46–0.85) and 0.54 for pravastatin (95% CI: 0.29–1.01).\textsuperscript{57} In our experience, long-term statin therapy (>6-month duration) was markedly associated with a decreased risk of VKA overcoagulation [OR: 0.276 (95% CI: 0.082–0.732); \( P = 0.004 \)]; interestingly, we observed that these patients mainly received atorvastatin (85%) and pravastatin (10.5%), whereas only 4.5% received simvastatin. Therefore, we suggest that atorvastatin/pravastatin may be protective factors of overcoagulation onset in patients receiving oral anticoagulant therapy. Our findings may be explained, in part, by the fact that (i) pravastatin is classified as a non-interacting statin, as it is not metabolized by CYP 450 isoenzymes;\textsuperscript{59} and (ii) atorvastatin has also been classified as an agent that does not interact with warfarin.\textsuperscript{60} Taken together, we suggest that there may be no need to switch long-term users of both VKA and atorvastatin/pravastatin to safer alternative; moreover, VKA-treated patients receiving atorvastatin/pravastatin may not require enhanced INR monitoring.

On the other hand, we failed to find a correlation between other long-term therapy and VKA overcoagulation onset. Other drugs have been reported to be associated with VKA-associated overcoagulation, i.e.:

- inhibitors of platelet function.\textsuperscript{4,33,61} In a series that compared warfarin plus aspirin (80 mg/d) to aspirin (160 mg/d), major bleeding was more common in
the warfarin-associated aspirin group than in the aspirin group (1.28 events vs. 0.72 events/100 person-years).62
- serotonin re-uptake inhibitors (citalopram, fluoxetine, paroxetine and sertraline);3,33
- acetaminophen.4,17,35,63 However, Levine et al.4 have reported that the weight of evidence indicate that any 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.

Finally, comorbid chronic conditions have also been associated with the onset of VKA-associated overcoagulation, such as hypertension, heart disease, diabetes mellitus, prior stroke, chronic renal disorder or extensive malignancy.1,3,7,18–21,25–28,62 In the present study, we have shown that chronic liver disease was associated with the onset of VKA overcoagulation (OR: 4.2; 95% CI: 1.25–12.35; P = 0.002). In White et al.’s series,26 hepatic disease also increased the risk of bleeding (OR: 2.6; 95% CI: 1.4–4.82).

In conclusion, our study underlines that the knowledge of predictive factors of VKA-related overcoagulation is of utmost importance to improve patients’ management. Interestingly, we have found that the potential of drug interaction should be taken into account when choosing amiodarone for patients receiving a concomitant medication such as warfarin with a narrow therapeutic index. Another main finding of the present study is that long-term atorvastatin/pravastatin therapy might be a protective factor of VKA overcoagulation; taken together, our findings suggest that there may be no need to switch long-term users of VKA and atorvastatin/pravastatin to a safer alternative therapy.

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