Bleeding and asymptomatic overdose in patients under Vitamin K antagonist therapy: Frequency and risk factors

F. Ben Mbarka *, K. Ben Jeddou, E. Allouche, I. Boukhris, N. Khalfallah, H. Baccar, Z. Ouahchi

Charles Nicolle University Hospital, Boulevard 9 Avril 1938, Bab Saidaoun, 1007 Tunis, Tunisia

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ABSTRACT

Background: Vitamin K antagonists are widely used in the treatment and prevention of thromboembolic disease. However, these drugs can cause serious side effects, especially bleeding. This study aims to evaluate frequency and risk factors of both bleeding and asymptomatic overdose in North African patients undergoing Vitamin K antagonist therapy.

Methods: We performed a cross-sectional study in patients undergoing Vitamin K antagonist therapy. A statistical analysis has been conducted to identify overdose and bleeding risk factors by using chi-square test (p < .05).

Results: One hundred and eleven patients were included. We recorded 14 cases of bleeding and 26 cases of asymptomatic overdose. Advanced age, poor adherence, concomitant use of paracetamol and history of previous bleeding are significant risk factors of over-anticoagulation. An INR value over 6 at admission, a high therapeutic target range for INR, concomitant use of acetylsalicylic acid, lack of information on overdose signs and measures to be taken in case of bleeding were identified as risk factors for bleeding.

Conclusion: Most of the risk factors identified in our study seem to be related to patients lack of information and education. These results highlight the importance of creating a therapeutic patient education program.

1. Background

Vitamin K antagonists (VKA) (acenocoumarol, warfarin, fluindione) are widely prescribed for the prevention and treatment of thromboembolic complications of cardiovascular diseases. Bleeding is a frequent side effect of this treatment and it can limit its use substantially. A great number of studies have evaluated bleeding prevalence in patients under VKA therapy. In nationally representative emergency departments in the United States in 2002, 2004, and 2005, warfarin was identified as the drug most commonly associated with adverse events. In France, two national studies in 1998 and 2007 conducted by pharmacovigilance centers revealed that 13% of hospital admissions for adverse events are related to hemorrhage with VKA, with about 17,000 hospitalizations and 5000 deaths per year. In Tunisia, a study carried out in an university hospital in 2009 showed an incidence of hospitalization for severe hemorrhage under VKA of 0.8%. A number of studies have evaluated factors that are associated with bleeding such us advanced age, recent initiation of VKA therapy and intensity of anticoagulation with an International Normalized Ratio (INR) value > 4.5. In 15 to 30% of cases, VKA overdose is asymptomatic, an asymptomatic overdose is defined by an INR value outside of the therapeutic range without any clinical sign of hemorrhage. It is a risky situation that needs to be quickly managed to avoid bleeding complications. This study aims to evaluate the frequency and risk factors of both bleeding and asymptomatic overdose in a sample of North African patients undergoing VKA therapy.

2. Methods

We performed a cross-sectional study in a Tunisian university hospital. The study enrolled inpatients and outpatients followed up in cardiology and internal medicine departments for VKA therapy. The only exclusion criteria were the absence of patient’s consent and the presence of a cognitive impairment that affects the patient’s comprehension.
As a first step, patients’ medical records were reviewed for individual clinical characteristics including sex, age, indication of oral anticoagulant therapy, co-treatment and previous history of oral anticoagulant therapy-related bleeding.

Second, we collected detailed information on VKA therapy such as: dosage of acenocoumarol, age of oral anticoagulant therapy, INR value on admission and possible signs of bleeding. To evaluate bleeding risk, the HAS BLED score was calculated for all patients. Finally, interviews with patients allowed us to collect information on:

- Knowledge about VKA therapy and pathology using a 19-item survey; knowledge level was considered insufficient if the patient did not correctly answer at least one question among the 5 questions that were considered most relevant to the risk of over-anticoagulation (regular time of intake, drug interaction, action to be taken in case of a missing dose, INR monitoring and frequency).
- Medication adherence which was assessed with the “Compliance assessment test” developed by Girerd et al.
- Compliance to INR monitoring.
- Social background and level of education.
- Hand function disability or vision impairment.

Patients were divided into 3 groups:

- Group 1: Patients with a therapeutic INR value on admission and without any sign of bleeding.
- Group 2: Patients with overdose with or without bleeding signs. Overdose was defined by an INR value that is outside the therapeutic range (between 2 and 3 or 4.5, depending on the therapeutic indication).
- Group 3: Patients with bleeding signs on admission.

A statistical analysis has been conducted to identify overdose and bleeding risk factors. Statistical analyses were conducted using IBM SPSS version 19. The chi-square test was applied and a significance threshold of 0.05 was adopted in the statistical analysis.

3. Results

One hundred and eleven patients at an average age of 56.5 years (54 men and 57 women) were included. Atrial fibrillation was the most common indication for VKA therapy (47.7%). Most of the patients were under anticoagulant treatment for more than 5 years (37.8%). The clinical characteristics of the study population are indicated in Table 1.

During the study, we reported 14 cases of bleeding (12.6%) and 26 cases of asymptomatic overdose (23.4%). Bleeding complications were mainly minor: bleeding gums (4 patients), bruising (4 patients), epistaxis (3 patients) and hemoptysis (2 patients). A single case of thalamic hematoma with intraventricular hemorrhage was recorded.

The main INR value in the population was 4.5. Among the 14 patients having experienced bleeding complications, 10 (71.4%) had INR values over 6.0.

The comparison between patients in group 1 and group 2 shows, as described in Tables 2 and 3, that advanced age (p = .001), poor adherence to treatment (p = .003) and to INR monitoring (p = .028), history of previous bleeding (p = .014) and concomitant use of paracetamol (p = .033) are significant factors correlated with an increased risk of over-anticoagulation. Lack of knowledge about VKA therapy, the risk of drug interactions and precautions before invasive procedure, was also correlated with a higher risk of over-anticoagulation.

The comparison between group 1 and group 3 patients shows that concomitant use of acetylsalicylic acid (p = .034), lack of information on overdose signs (p = .002), an INR value over 6 at admission (p = .002) and a high therapeutic target range for INR (between 3 and 4.5) (p = .031) were correlated with an increased risk of bleeding (Tables 4 and 5).

4. Analysis and discussion

This study allowed us to evaluate the prevalence of bleeding complication and asymptomatic overdose under VKA therapy in a representative sample of North African patients. Among 111 random patients, the prevalence of bleeding was estimated at 12.6% and that of asymptomatic overdose at 23.4%. The bleedings observed were mainly minor such us bleeding gums, bruising, epistaxis and haemoptysis. Only one case of thalamic hematoma with intraventricular bleeding was reported. In a French case-control study conducted in 2009, authors estimated bleeding prevalence under VKA therapy at 31.5%, this rate seems to be higher than our findings but it can be explained by the fact that this study was conducted in the emergency department.9

In Dakar, in a study that included 154 patients, Khadidiatou Dia et al. reported 8.4% of asymptomatic overdose, but this cannot be compared to our findings since they only included patients with INR values upper than 5.10 Another study evaluating overdose frequency established that 1.19% of patients presented oral-anticoagulant-related over-anticoagulation but this rate cannot be compared to our result since they defined over-anticoagulation as an INR value greater than or ranging from 4 to 6 and complicated with bleeding.11 In a similar study, this rate was estimated at 9.7% of all included patients.12

In a prospective and observational study enrolling 1019 patients in New York, the rate of asymptomatic overdose (INR values greater than 3) was estimated at 29%.13 In our study population, we found that advanced age (over 65 years) was strongly associated with VKA-related overdose and bleeding (P = .001). Our finding is strongly supported by several studies that have shown that patients older than 65 years are the
most affected by hemorrhagic complications. In a Tunisian study, Jouini S et al. reported that VKA are responsible for 20% of elderly visits to emergencies. This could be explained by several factors including co-morbidities, poly-medication, psychosocial context, dementia and high frequency of falls. The problem is that little data are available on the efficacy and security of these medications on elderly subjects, since they were not included in clinical trials. The management of these patients remains highly controversial, as some views consider that advanced age should limit the prescription of VKA, while others think that, despite all the risk factors, old age should not constitute a limit for prescription especially when the thromboembolic risk is very important.

Lack of drug compliance was also identified as a major risk factor of over-anticoagulation. This result is consistent with literature where poor adherence was frequently found as a significant risk factor of bleeding. In 1997, Felix J et al. have shown in their study that drug compliance is an important factor of response variability to VKA therapy with an increased risk of over or under-dosage. Kumar S et al., established that poor drug compliance was the major cause of INR instability.

Another finding of our study is the correlation between compliance to INR monitoring, overdose (p = .028) and bleeding risk (p = .002). In theory, the safety and efficacy of VKA therapy are dependent on maintaining the INR within the target range since the indication and inappropriate management can lead to subtherapeutic or supratherapeutic INR values, increasing the risk of thromboembolic or bleeding events. This finding is supported in another study that has shown that inadequate INR monitoring increases the risk of bleeding complications. Nevertheless, the results of a controlled retrospective study including 7539 patients demonstrate that non-adherence to biological monitoring increases only the rate of subtherapeutic INR value and thromboembolic complications. The authors explained that by the fact that most patients who are not compliant to INR monitoring are generally not compliant to drug intake, which often results in a reduction in the prescribed dose.

Moreover, we observed that insufficient level of knowledge was associated with an increased risk of over-anticoagulation.

### Table 2
**Risk factors of overcoagulation.**

| Item                              | Group 1 (N = 71) | Group 2 (N = 40) | OR [IC 95%] | P    |
|-----------------------------------|------------------|------------------|-------------|------|
| Age > 65 years                    | 5                | 12               | 5.867 [1.88–18.25] | 0.001|
| Bad compliance                    | 5                | 11               | 5.186 [1.65–16.31] | 0.003|
| History of bleeding               | 6                | 10               | 3.736 [1.24–11.25] | 0.014|
| Insufficient biological monitoring| 7                | 10               | 3.153 [1.09–9.11]  | 0.028|
| Concomitant take of paracetamol    | 6                | 4                | 4.333 [1.03–18.10] | 0.033|
| VKA therapy duration              | 11               | 4                | 0.623 [0.18–2.11]  | 0.444|
| Treatment intensity (>1 pill)     | 7                | 4                | 1.045 [0.28–3.82]  | 0.947|

### Table 3
**Risk factors of overcoagulation: patients' knowledge.**

| Item                              | Group 1 (N = 71) | Group 2 (N = 40) | OR [IC 95%] | P    |
|-----------------------------------|------------------|------------------|-------------|------|
| Insufficient knowledge about treatment | 63               | 39               | NA          | 0.029|
| VKA role                          | 7                | 13               | 4.571 [1.64–12.75] | 0.002|
| Drug interactions                  | 20               | 21               | 2.975 [1.32–6.72]  | 0.008|
| Precautions before invasive procedure | 7                | 11               | 3.592 [1.26–10.23] | 0.013|

### Table 4
**Risk factors of bleeding.**

| Item                              | Group 1 (N = 71) | Group 3 (N = 14) | OR [IC 95%] | P    |
|-----------------------------------|------------------|------------------|-------------|------|
| History of bleeding               | 6                | 7                | 10.833 [2.835–41.393] | <0.001|
| Age > 65 years                    | 5                | 5                | 7.333 [1.769–30.395] | 0.002|
| Insufficient biological monitoring| 7                | 6                | 6.857 [1.841–25.541] | 0.002|
| Bad compliance                    | 5                | 5                | 7.333 [1.769–30.395] | 0.002|
| HAS BLED Score ≥ 3                | 0                | 2                | NA          | NA   |
| INR Value at admission ≥ 6        | 0                | 10               | NA          | NA   |
| Concomitant treatment             |                  |                  |             |      |
| Acetylsalicylic acid              | 9                | 5                | 3.827 [1.045–14.010] | 0.034|
| Paracetamol                       | 23               | 7                | 2.087 [0.655–6.654]  | 0.208|
| Amiodarone                        | 10               | 4                | 2.440 [0.640–9.305]  | 0.182|
| Statins                           | 10               | 3                | 1.664        | 0.485|
| Allopurinol                       | 3                | 2                | 3.778 [0.570–25.044] | 0.144|

### Table 5
**Risk factors of bleeding: patients' knowledge.**

| Item                              | Group 1 (N = 71) | Group 3 (N = 14) | OR [IC 95%] | P    |
|-----------------------------------|------------------|------------------|-------------|------|
| VKA role                          | 7                | 7                | 9.143 [2.476–33.756] | <0.001|
| Signs of overdose                 | 16               | 9                | 6.1875 [1.814–21.102] | 0.002|
| Actions to be taken in case of bleeding | 20               | 9                | 4.590 [1.370–15.383]  | 0.009|
| Drug interactions                 | 20               | 9                | 4.590 [1.370–15.383]  | 0.009|
| Precautions before invasive procedure | 7                | 5                | 5.079 [1.326–19.460] | 0.011|
The ISCOAT study showed that the relative risk of dose appears to be greater when initiating treatment with VKA was associated with a risk of overdose (p = .014). The risk was even greater in patients with bleeding events (p < .001). This correlation has been underlined by other studies which reported that previous bleeding history with VKA was a risk factor for overdose and bleeding.

As regards drug interaction, concomitant use of aspirin seems to increase bleeding risk (p = .034), according to our study. This interaction is related, on the one hand, to a pharmacodynamic mechanism by the anti-platelet aggregation and direct damage of the gastroduodenal mucosa by aspirin and, on the other hand, to a pharmacokinetic mechanism by the displacement of the oral anticoagulant from its site of binding to the plasma proteins thus causing a plasma overdose and a high bleeding risk. In addition, an association between concomitant use of paracetamol and the risk of overdose was found to be significant in our study (p = .033). Nevertheless, this association did not turn out to be significant for bleeding risk. Paracetamol has always been the first-line analgesic, as it has very few drug interactions. However, Hylek et al., in 1998, demonstrated a dose-dependent relationship between paracetamol intake and INR values greater than 6. The mechanism of this interaction remains unclearly elucidated. However, it has been proposed that a competition for CYP1A2 between paracetamol and warfarin causes a decreasing hepatic clearance which results in an increase warfarin blood level.

Moreover, we observed that an INR value over 6 was associated with an increased risk of bleeding (p = .002). The fact that higher intensity of anticoagulation is related to a greater risk of bleeding is already known from literature. Landefeld et al. found that for each 1.0 increase in the prothrombin time, the odds ratio for temporally related major bleeding increased by 80%. Likewise, Van der Meer showed that as the target INR range increases, so does the risk of bleeding.

According to the above studies, the risk of bleeding and overdose appears to be greater when initiating treatment with VKA. The ISCOAT study showed that the relative risk of bleeding is twice as high during the first 90 days of therapy. However, in our study, this factor was not significant since only 19 patients were undergoing VKA therapy for a short duration (less than 3 months). The difficulty in balancing the dose of medication at the beginning of the treatment and the poor understanding and adherence to the anticoagulant treatment may explain this risk. Some authors, such as Casais P et al., disagree with this observation, as they reported in a retrospective study involving 811 patients that the bleeding risk increases proportionally with the duration of the therapy, so that after 6 years of anticoagulant treatment, the risk of bleeding is much greater than during the first 4 months.

5. Conclusion

Although some overdose and bleeding risk factors identified are not modifiable such as advanced age, the prevalence of VKA associated adverse events may be reduced by attending to modifiable risk factors, that is, those related to patients lack of information and education (adherence, monitoring, etc.). These results are consistent with those reported in the literature and highlight the importance of creating a therapeutic patient education (TPE) program for all patients on oral anticoagulant treatment.

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Conflict of interest

None.

Author’s contributions

F. Ben Mbarka: Data collection and analysis of results.
K. Ben Jeddou: Analysis of results and Revision of the manuscript.
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References

1. Budnitz DS, Pollock DA, Mendelsohn AB, Weidenbach KN, McDonald AK, Annest JL. Emergency department visits for outpatient adverse drug events: demonstration for a national surveillance system. Ann Emerg Med. 2005;45(2):197–206.
2. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. AMIA. 2006;296(12):1858–1866.
3. Agence Nationale de Sécurité du Médicament et des produits de santé. Mise au point sur le bon usage des médicaments antivitamine K (AVK): principales informations concernant les indications et la surveillance du traitement pour les professionnels de santé. Paris: ANSM; 2009.
4. Ben Ameur Y, Chaabane O, Zairi I, Longo S, Battikh K, Slimane ML. Les accidents hémorragiques graves sous antivitamines K. Étude descriptive et pronostique. Tun Med. 2009;87:763–769.
5. Levine MN, Raskog G, Borthy RJ, Kearon C, Schulman S. Hemorrhagic complications of anticoagulant treatment: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004;126:2875–3105.
6. Berwaerts J, Webster J. Analysis of risk factors involved in oral-anticoagulant-related intracranial hemorrhages. Q J Med. 2000;93:513–521.
7. Hylek EM, Evans-Molina C, Shea C, Henaults LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007;115:2689–2696.
8. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004;141:747–752.
9. Al Hajje AH, Calop NJ, Bosson JL, Calop J, Allenet B. Quels facteurs associés à la survenue d'un événement iatrorgénique hémorragique chez les patients sous antivitamines K ?. Ann Pharm Fr. 2010;68(1):36–43.
10. Dia Khididiatou, Sarr Simon Antoine, Mboup Mohamed Cherif, Ba Djibril Marie, Fall Pape Diadie. Les surdosages aux antivitamines K à Dakar: aspects épidémiologiques, cliniques et éolutivités. Pan Afr Med J. 2016;24:186.
11. Cadiou G, Tire I, Levesque H et al. Facteurs de risque de surdosage en antivitamines K: une étude cas-témoins menée chez des patients non sélectionnés admis dans un service d’urgences. J Pharm Clin. 2009;28:73–81.
12. Marie I, Leprince P, Menard JF, Tharasse C, Levesque H. Risk factors of vitamin K antagonist overcoagulation. QJM. 2012;105(1):53–62.
13. Newman DH, Zhitomirsky I. The prevalence of nontherapeutic and dangerous international normalized ratios among patients receiving warfarin in the emergency department. Ann Emerg Med. 2006;48(2):182–189.
14. Borthy RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998;105:91–99.
15. Wehinger C, Stollberger C, Langer T, Schneider B, Finsterer J. Evaluation of risk factors for stroke/embolism and of complications due to anticoagulant therapy in atrial fibrillation. Stroke. 2001;32:2246–2252.
16. Jouini S, Djeibbi O, Souissi S, Bouhajja B. Part de la iatrogénie médicamenteuse dans le recours des personnes âgées aux urgences: Etude épidémiologique observationnelle prospective. Tun Med. 2013;91:200–204.

17. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Ann Intern Med. 1996;124:970–979.

18. Fihn SD, McDonell M, Martin D, et al. Risk factors for complications of chronic anticoagulation. A multicenter study. Warfarin Optimized Outpatient Follow-up Study Group. Ann Intern Med. 1993;118:511–520.

19. Van der Meer FJ, Briet E, Vandenbroucke JP, Sramek DI, Versluijs MH, Rosendaal FR. The role of compliance as a cause of instability in oral anticoagulant therapy. Br J Haematol. 1997;98:893–900.

20. Kumar S, Haigh JR, Rhodes LE, et al. Poor compliance is a major factor in unstable outpatient control of anticoagulant therapy. Thromb Haemost. 1989;62:729–732.

21. Witt DM, Delate T, Clark NP, et al. Nonadherence with INR monitoring and anticoagulant complications. Thromb Res. 2013;132(2):124–130.

22. Tang BD, Lai CS, Lee KK, Wong RS, Cheng G, Chan TV. Relationship between patients' warfarin knowledge and anticoagulation control. Ann Pharmacother. 2003;37:34–39.

23. Palareti G, Legnani C, Guazzaloca G, et al. Risks factors for highly unstable response to oral anticoagulation: a case-control study. Br J Haematol. 2005;129:72–78.

24. Barcelona D, Contu P, Marongiu F. Patient education and oral anticoagulant therapy. Haematologica. 2002;87:1081–1086.

25. Poli D, Antonucci E, Testa S, Tosetto A, Ageno W, Palareti G. Bleeding risk in very old patients on vitamin K antagonist treatment: results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. Circulation. 2011;124:824–829.

26. Chan TY. Adverse interactions between warfarin and nonsteroidal antiinflammatory drugs: mechanisms, clinical significance, and avoidance. Ann Pharmacother. 1995;29:1274–1283.

27. Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. JAMA. 1998;279:657–662.

28. Lehmann DF. Enzymatic shunting: resolving the acetaminophen-warfarin controversy. Pharmacotherapy. 2000;20:1465–1468.

29. Linkins LA. Bleeding risks associated with vitamin K antagonists. Blood Rev. 2013;27:111–118.

30. Optimal Oral Anticoagulant Therapy in Patients with Nonrheumatic Atrial Fibrillation and recent cerebral ischemia. N Engl J Med. 1995;333:5–10.

31. Hull R, Hirsh J, Jay R, et al. Different Intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med. 1982;307:1676–1681.

32. Landedfeld CS, Beyth RJ. Anticoagulant-related bleeding clinical epidemiology, prediction and prevention. Am J Med. 1993;95:315–328.

33. van der Meer FJM, Rosendaal FR, Vandenbroucke JP, Briet E. Assessment of a bleeding risk index in two cohorts of patients treated with oral anticoagulants. Thromb Haemost. 1996;76:12–16.

34. Palareti G, Leali N, Cochehi S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT), Italian Study on Complications of Oral Anticoagulant Therapy. Lancet. 1996;348:423–428.

35. Casais P, Sanchez Luceros A, Meschuggeser S, Fonddevila C, Santarelli MT, Lazzari MA. Bleeding risk factors in chronic oral anticoagulation with acenocoumarol. Am J Hematol. 2000;63:192–196.