

## Haemorrhagic Accidents Linked to Antivitamins K in Emergencies

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### Abstract

Hemorrhagic accidents under vitamin K antagonists (VKA) are the leading cause of iatrogenic hospitalizations Hemorrhagic stroke associated with vitamin K antagonists in emergencies.

The clinical relevance of vitamin K antagonists (VKA) has been demonstrated in many pathological situations thromboembolic their prescription is increasing. The occurrence of bleeding is the most feared complication of VKA and prevention remains a key concern in the des patients monitoring under VKA. The purpose of this study is to highlight the epidemiological, clinical and evolutive characteristics of patients with hemorrhagic stroke in VKA and put the focus on support. We conducted a retrospective study during the period of January 2018-December 2019 of 9 patients, performed service emergency of the military hospital Avicenna.

The average age of our patients is 54.5 with a sex ratio of 1.25. We note in our series multi-calibrated field VKA patients with more history involved.

Valve replacement was the main indication identified. The majority of our patients did not have a good biological monitoring based on international normalized ratio (INR). Externalized bleeding was the most common. Conduct was different depending on the case based on the judgment of VKA, administration saw K, transfusion of red blood cells and fresh frozen plasma and surgical homeostasis. 1 patient admitted died. The index Landefeld has proved useful, it allows to classify patients according to the predictive risk of bleeding (high medium or low), which was consistent with the results of our study. Its importance is all the more it is easy to measure simply based on data cliniques applicable by the physician -patient and to define patients requiring increased surveillance. Polypharmacy, advanced age and associated defects were identified as risk factor for bleeding under VKA. Preventing the occurrence of these accidents is based on the assumption, hence the importance of information and education of stakeholders in this iatrogenic potentially lethal complication.

**Keywords:** hemorrhagic accidents-VKA-iatrogenic complication-emergency

### INTRODUCTION

The use of VKA is more common with an average age of 68 years. The treatments are generally initiated by specialists, in 90% of cases, and followed by general practitioners, in 95% of cases. The main indications for long-term anti-coagulation are atrial fibrillation (58%), treatment of deep vein thrombosis and prevention of their recurrence (16%), treatment of pulmonary

embolism and prevention of its recurrence (9%), mechanical valves (8%), and mitral valve disease mainly (2%) [1]. However, these treatments are responsible for bleeding complications causing approximately 17,000 hospitalizations per year [2]. This is the leading cause of iatrogenic hospitalization in France. There are 1.2 to 5.5% of severe hemorrhages and 0.25% of fatal hemorrhages per year, i.e. nearly 5,000 deaths per year as a result of hemorrhagic accidents of VKA, which represents 0.6% of the treated population [3]. Bleeding events during treatment with VKA represent a growing public health problem due to the aging of the population. The aim of this work is to identify the risk factors in patients with hemorrhagic accidents under VKA, to assess the modalities of the therapeutic management of this frequent and potentially serious iatrogenic complication. Finally, emphasis will be placed on the prevention of these accidents which involve the functional and sometimes vital prognosis.

### **MATERIELS ET METHODES**

The objective of this work is to assess the management of hemorrhagic accidents under VKA in the emergency department of the Avicenna military hospital of Marrakesh, to identify errors in relation to the new recommendations of HAS, and try to identify areas for improvement.

This is a descriptive retrospective study carried out in the emergency services of the Avicenne military hospital in Marrakesh during the period January 2018-December 2019.

For each patient, a data collection sheet was used. It included anthropometric data, the patient's history, the indication and dose of VKA, the length of time he was prescribed and the associated treatments. The laboratory parameters identified were mainly INR (before and at the time of the accident), prothrombin time, hemoglobin level and platelet count. The sheet also included data on the bleeding complication as well as the evolution of the patients.

The aim of this study is to measure the impact of a multidisciplinary approach and morbidity and mortality reviews on the quality of the management of serious bleeding accidents under treatment with Antivitamin K in the emergency room.

Patients under VKA admitted to the SAMU Emergency Department for hemorrhagic accidents.

Inclusion criteria:

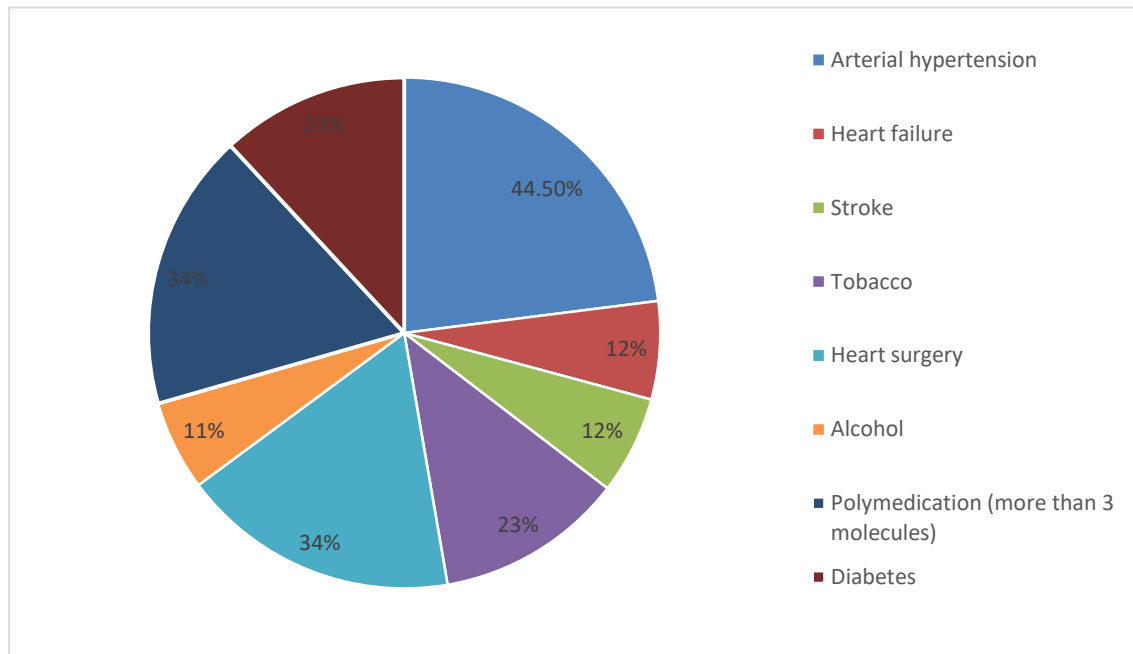
- Haemorrhagic accidents with heparins associated with VKA.

Exclusion criteria:

- INR beyond the therapeutic range without hemorrhagic manifestations

### **RESULTATS**

During this period, 09 cases of hemorrhagic accidents under VKA admitted, including 05 women and 04 men, with a sex ratio of 1.25. The average age is 54.5 (range: 33-76). The main antecedents were distributed as follows:



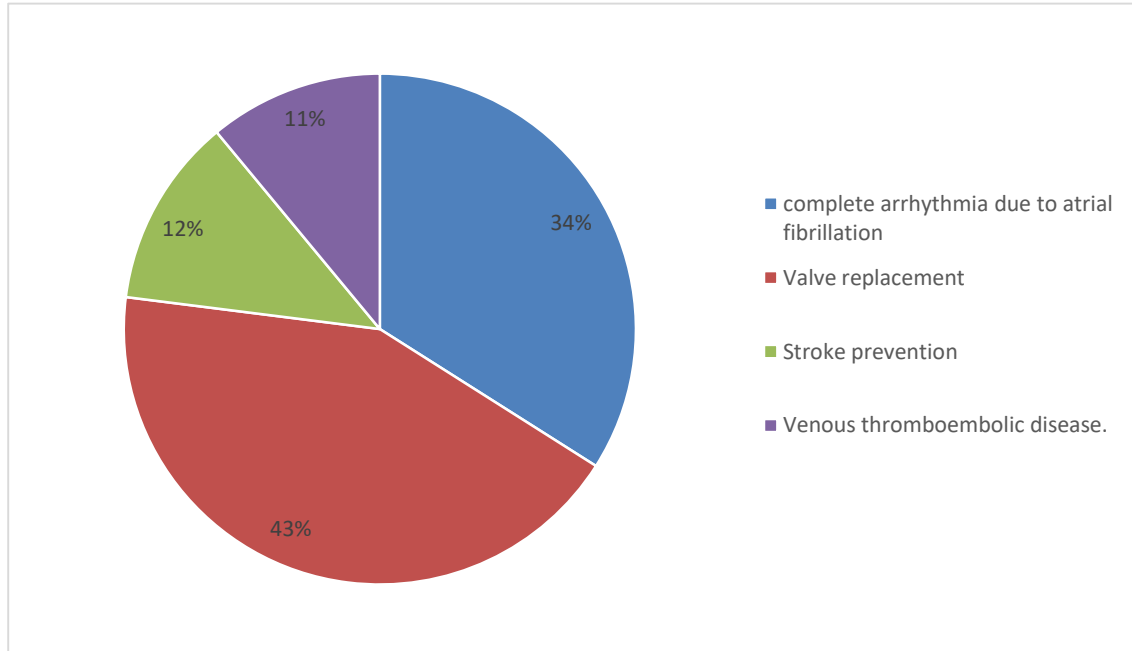
**Figure I: Notable patient history**

The associated treatments are grouped together in the table below.

Drugs associated	Pourcentage
Anti-platelet agents	34%
Diuretic	22.5%
ARA II	-
ICE	-
Cordarone	22.5%
Statin	22.5%
NSAIDs	11.5%
Calicium inhibitor	34%
B- blocking	-
Digital	-
Insulin	11.5%
Oral antidiabetic drugs	11.5%

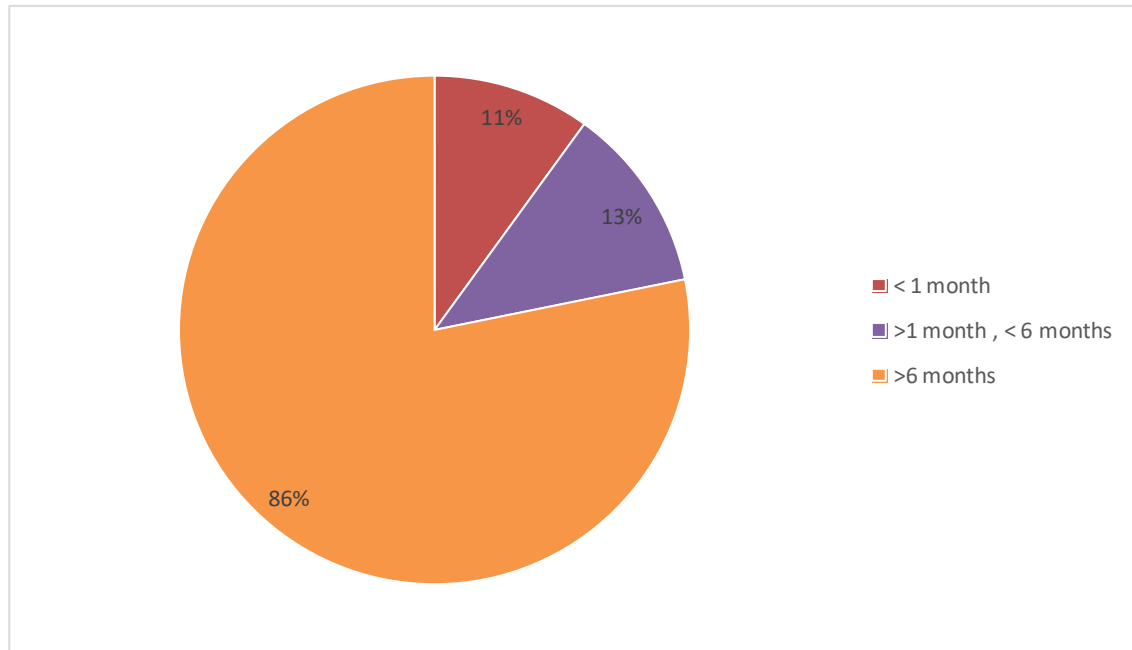
**Table I: Associated treatments to VKA**

The indications for taking antivitamin K were broken down as follows:



**Figure II: The indications of VKA**

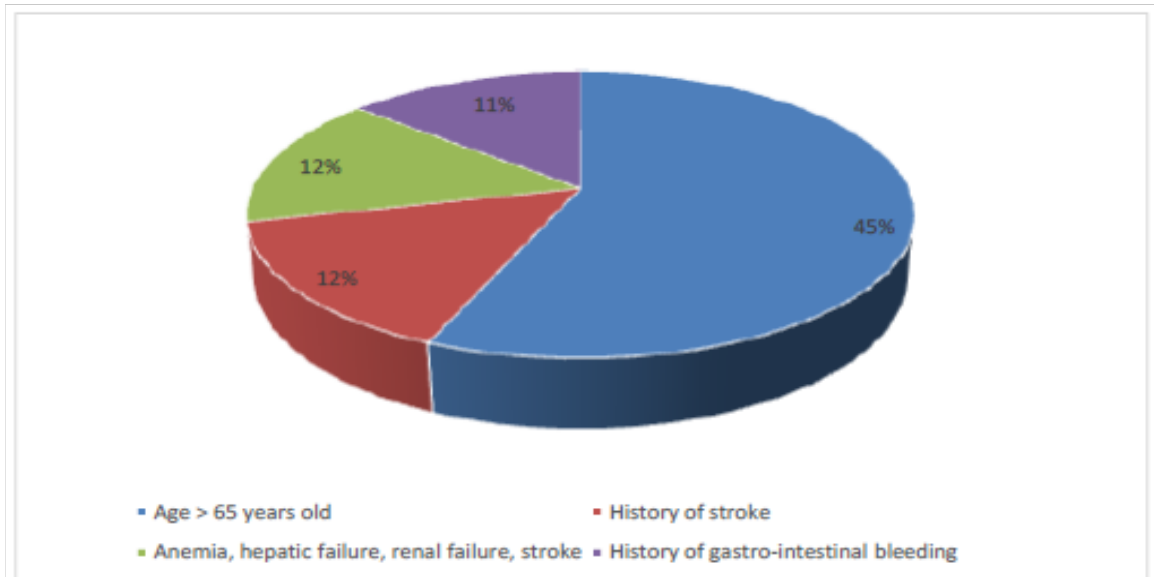
The average dose of acenocoumarol was 2.33 mg per day.



**Figure III: Duration of treatment with VKA**

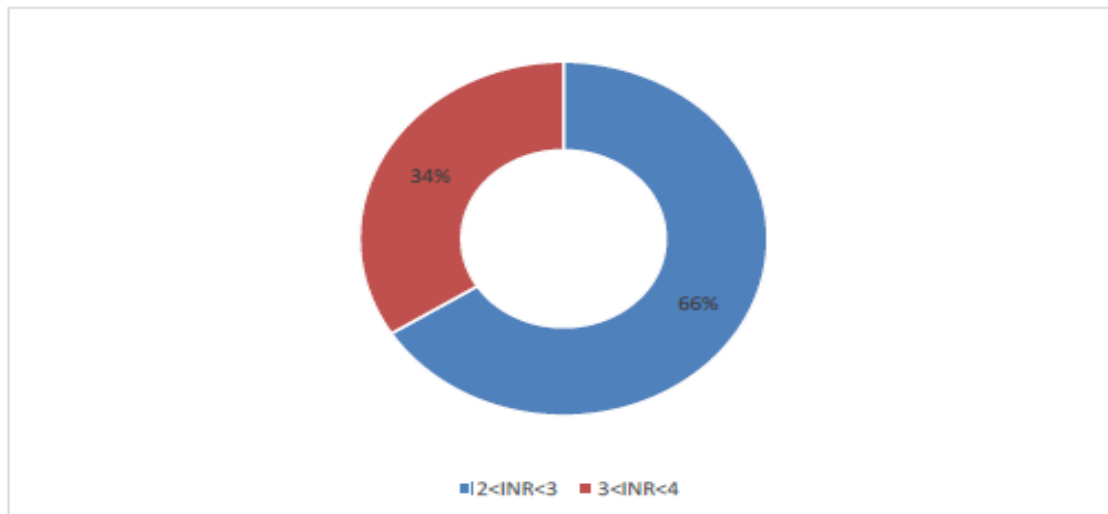
The mean duration of treatment was 27 months.

The bleeding risk was assessed using the Landefeld index in depending on certain risk factors such as: age > 65 years old, history stroke, gastrointestinal bleeding, heart attack myocardium, anemia, renal failure and hepatic failure.



**Figure IV: Risk factor for hemorrhagic complication under VKA**

The therapeutic zone is for most indications between 2 and 3 (target INR of 2.5); it may be higher in some patients with mechanical prostheses (up to 4).



**Figure V: the INR target value**

6 patients (66%) were admitted for externalized bleeding (melena, rectal bleeding, hematemesis, gingivorrhagia, epistaxis, hematuria). 1 patient (6.6%) for hemorrhagic stroke (neurological deficit, altered state of consciousness), 1 patient for calf hematoma and 1 patient (6.6%) admitted for anemia. More than half of the patients (60%) did not have a recent INR measurement and did not benefit from regular monitoring. Of the INRs recorded before the occurrence of the accident, the average was 2.27 (range: 1.4-3.15). As for the average INR at the time of the accident, it was 4.52 (range: 4-12.02). All patients were treated in a hospital setting. They all stopped the VKA. Almost a quarter of the patients were transfused with red blood cells, and 4 patients (or 44%) received units of fresh frozen plasma, only 5 patients (or 55.55%) received vitamin K. The mean duration stay is 6.4 days (range: 1-16). Anticoagulant therapy with heparin is resumed within an average of 36 hours after the bleeding event. Overlap with acenocoumarol after an average of 6 days. The course was marked by the occurrence of death following intracranial hemorrhage, the other patients progressed favorably.

### **DISCUSSION:**

Antivitamins K occupy an increasing place in drug prescriptions. They are the standard treatment for many pathological situations. Despite the standardization of monitoring by the INR and the better definition of therapeutic objectives, VKA treatments are still burdened by a too high percentage of hemorrhagic accidents.

Long-term oral anticoagulation with VKA is the standard treatment for thrombotic pathologies. It prevents the formation or spread of thrombosis or embolism.

According to AFSSAPS, the indications for long-term anticoagulation, validated by clinical studies or professional consensus, are as follows [2]

- Embologenic heart disease: prevention of thrombo-embolic complications related to certain atrial fibrillations, certain mitral valve diseases, valve prostheses.
- Venous thromboembolic disease: curative treatment (as a substitute for heparin) and prevention of recurrence of deep vein thrombosis and pulmonary embolism, prevention (hip surgery).
- Myocardial infarction:
  - o prevention of thromboembolic complications of complicated infarcts (mural thrombus, severe left ventricular dysfunction, embologenic dyskinesia ...) in relay of heparin;
  - o prevention of recurrence of myocardial infarction, in cases of aspirin intolerance.

The frequent prescription of VKA is accompanied by an increase in iatrogenic accidents associated with this type of treatment. Hemorrhagic accidents are the most serious and the most feared complications.

Little is known about their incidence and severity, however, in particular severe bleeding admitted to the emergency room. Several factors must be taken into account in a diagnostic approach of an overdose of VKA such whether or not the presence of bleeding, its minor or major nature, the medico-surgical and social context, the circumstances of occurrence.

Therapeutically, several options are possible, ranging from simple therapeutic abstention with clinical and biological monitoring, at a emergency surgery, through the administration of vitamin k and/or PPSB. These therapeutic modalities can be combined, which complicates support.

Although this is codified and is the subject of specific recommendations issued by the Haute Autorité de Santé in July 2019, a large variability of practices is observed [4]. Poor knowledge and/or application of these recommendations exposes a risk of error, abstention or delay therapy responsible for a functional or vital prognosis.

Close monitoring of treatment with VKA by the Index Normalized Ratio (INR) is necessary due to the risk of bleeding. The first check-up is carried out 24 to 72 hours after the first intake of VKA and then every 2 to 4 days until 2 consecutive INR is obtained in the objectives (between 2 and 3 except for valvular heart disease and mechanical valves between 3 and 4.5), then a Gradual spacing is possible up to a maximum interval of one month [2]. Despite this monitoring, the occurrence of hemorrhagic complications is noted. According to a survey carried out in 1998 by the network of regional pharmacovigilance centers, on a representative sample of medical services and medical specialties of public hospitals, hemorrhagic accidents of VKA rank first among iatrogenic accidents, with 17,300 hospitalizations patient per year [2]. Anti-vitamin K are the leading cause of hospitalization for adverse drug reactions in France [5]. This represents 13% of hospitalizations for adverse drug reactions [6]. These iatrogenic complications are potentially serious with 5,000 deaths per year, i.e. 0.6% of the population on anti-vitamin k with fatal hemorrhage, 8% of neurosurgery hospitalizations for central nervous system hemorrhages [5]. Intracerebral hemorrhage under VKA is a poor prognosis with a mortality rate greater than 50%.

In fact, risk factors for a hemorrhagic complication have been identified [17]: INR > 4, duration of treatment <3 months or > 3 years, comorbidities (> 70 years, renal and hepatic failure, hypertension, diabetes, history of ischemic stroke), drug interactions (mainly with antibiotics, antifungals, amiodarone, NSAIDs, and antiplatelet agents), quality of information and Landefeld's index.

The latter makes it possible to determine a risk of major bleeding at 3 and 12 months by adding the following risk factors: age greater than 65 years, history of stroke, history of gastrointestinal bleeding, comorbidities (anemia, renal or hepatic insufficiency, myocardial infarction). Each of these items, if present, is associated with a point. The total of points (from 0 to 4) makes it possible to determine a low (0 point), medium (1 to 2 points) or high (3 to 4 points) risk correlated with an estimated risk of major bleeding at 3 and 12 months [ 8]. (Table 1).

In this study, patients with a high predictive risk of bleeding (i.e., Landefeld's index score 3-4) had significantly more major bleeding complications compared to patients with a moderate predictive risk. (i.e. Landefeld's index score 1-2). This index appears to be important to consider, because it is simple to apply to patients; it can be easily measured on an outpatient basis by the attending physician and makes it possible to define, from the start of treatment with VKA, the patients requiring increased monitoring. However, this is a non-fixed progressive index, which

can change during patient follow-up [9]. In this study, overdoses with high INR levels were observed, but upon data collection, treatment adherence, patients' cognitive status and life conditions could not be collected.

However, for several authors, the existence of an impairment of cognitive functions in the elderly is strongly linked to the risk of hemorrhagic complications under VKA [12].

In addition, there are professional recommendations (HAS July 2019) for the management of hemorrhagic accidents.

Risk of major bleeding	Low risk (0point)	Medium risk (1 to 2 points)	High risk (3 to 4 points)
At 3 months	2%	5%	23%
At 12 months	3%	12%	48%

**Table 2: Landefeld index**

On the other hand, compliance is reduced in the event of polypharmacy, 33.33% of our patients were on more than 3 drugs at a time for various pathologies. The increase in life expectancy and the aging of the population, on the one hand, the prevalence of cardiovascular pathologies and the risk of thrombosis in elderly patients, on the other hand, explain why VKA treatments are increasingly popular. more prescribed in the elderly [12]. Two other factors appeared to be statically significant correlated with the hemorrhagic risk under VKA.

Biological overdose of INR and history of digestive bleeding. Authors have defined the percentage of major bleeding under VKA to be 30% at 3 years for patients with a history of gastrointestinal bleeding, while it was 5% for those with no history of digestive tract [10]. In this study, among the 4 patients who presented with bleeding from the digestive tract, 2 patients already had gastrointestinal bleeding at least once.

There is an interaction between the ingestion of certain vegetables rich in vitamin K and the treatment with VKA. This effect has been demonstrated for cabbage, spinach, lettuce, broccoli and other vegetables which decrease the effectiveness of VKA through an antagonistic effect. This type of interaction does not cause a stroke, but sometimes a lack efficiency or balancing difficulties. In practice, it makes sense to maintain a diversified and balanced diet avoiding too great differences. This is only in case unexplained instability of the INR that strict control of vitamin k intakes (40g / kg / d) is advised [16].

The basis of drug treatment is Vitamin K sometimes associated with PPSB (Prothrombin Proconvertin Stuart B), and can be supplemented by hemostasis (arteriography with embolization, hemostasis surgery).



HAS recommendations in April 2008 relate to three major situations: asymptomatic overdoses, the occurrence of spontaneous or traumatic hemorrhage, whether or not associated with an overdose, and management during surgery or an invasive procedure [14]. Vit K is complex concentrates

Prothrombin drugs (CCP) or proconvertin prothrombin Stuart B (PPSB) are the most appropriate means rather than PFCs whenever possible. The two specialties marketed in France are Kaskadil and Octapex. It is recommended to stop VKA; urgently administer a concentrate of prothrombin complexes: 35 IU / Kg if the initial INR is between 2-3, 40 U / Kg if it is between 3-3.5, 50 IU / Kg if it is greater than 3.5 and urgently administer Vit K: 10 mg intravenously or 5 mg orally) [15].

### **CONCLUSION**

Antivitamin K is currently the gold standard of long-term anticoagulant therapy.

The prescriber should never forget that complications with VKA are frequent and potentially dangerous. A trivial accident can have dramatic consequences. The prevention of these accidents by providing information intended for both the doctor and the patient is imperative. The value of an information and follow-up booklet for treatment under VKA seems essential, as well as regular monitoring of the INR.

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