FACTORS INVOLVED IN THE IMBALANCE OF VITAMIN K ANTAGONISTS: EVALUATION OF PATIENTS' KNOWLEDGE AND PRACTICES

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ABSTRACT

Background and purpose: Vitamin K antagonists (VKA) are considered to be one of the top five medications that are directly related to drug errors and to be one of the most common causes of emergency visits. This study aims to assess patients' knowledge and practices to VKA treatment and to determine the factors related to VKA imbalanced treatment. **Methods:** A hospital-based case-control study was conducted in Beirut between September 1^{rst} 2016 and June 30th 2017. Data were collected through a standardized questionnaire. Bivariate and multivariate analyses were done. **Results:** Patients with an INR within the therapeutic range were older (p<0.001) and had a lower educational level (p<0.001). They were also less knowledgeable about the name of the VKA medication (p<0.001), the dose (p<0.001), the indication (p<0.001), the action mechanism (p<0.001), the risk of over- and under-dose (p<0.001), the biological monitoring test (p<0.001), and the events accompanying taking aspirin along with VKA treatment (p=0.008). They were significantly more likely to forget to take their VKA treatment (P=0.023), double the VKA dose in case of

forgetfulness (p=0.037), never notify health professionals about the VKA treatment (p=0.006), not inform the dentist about the VKA treatment in case of tooth extraction (p<0.001), and to not measure INR in case of blue spots (bruises) appearance (p=0.039) than control patients. Logistic regression showed that patients having an increased knowledge in regard to the name of the VKA taken and to the risk of overdose and under-dose were 2 to 3 times more likely to have an INR within the therapeutic range (ORa=0.39, 95% CI [0.21–0.73], p=0.003; ORa=0.59, 95% CI [0.36–0.96], p=0.034; and ORa=0.4, 95% CI [0.24–0.68], p=0.001 respectively). Moreover, informing the dentist about the VKA treatment and taking the right precautions in case of tooth extraction significantly decrease the risk of having an INR outside the therapeutic range (ORa=0.02, 95% CI [0.001–0.81], p=0.039). Patient's therapeutic education on physical activity that may influence the VKA treatment has a significant association with reducing the risk of having an INR outside the therapeutic range among patients aged less than 65 years (ORa=0.36, 95% CI [0.15–0.88], p=0.026) than among patients aged 65 years or older. However, reading the instructions of usage available on the VKA box significantly reduce the risk of having an INR outside the therapeutic range among patients 65 years old or older (ORa=0.45, 95% CI [0.22–0.91], p=0.025). **Conclusion:** Patient education, physicians' involvement and anticoagulant monitoring are critical for a balanced VKA treatment. Every patient taking VKA treatment has to acquire certain level of knowledge in regards to his/her treatment and know how to adopt the ordinary dose in order to limit the iatrogenic risk related to this treatment.

KEYWORDS: Vitamin K antagonists, Knowledge, Practices, Imbalance, International Normalised Ratio.

1. INTRODUCTION

For many decades, Vitamin K Antagonists (VKA) have been the only oral form of therapeutic anticoagulation.[1] VKA use continues to increase worldwide by millions of patients due to the aging population and has been showing great effectiveness in many settings. It is highly effective in preventing thromboembolism, systematic embolism, acute myocardial infarction, and stroke.[2] However, VKA are considered to be among one of the top five medications that are directly related to adverse events.[3]

It is very challenging to manage VKA due to its narrow therapeutic range, drug and food interactions, and dosing problems.[2] Many factors contribute to high risks of iatrogenic complications when taking VKA treatment.[1,4,5] Different adverse effects may occur with

VKA treatment including, hemorrhagic risk, undesirable digestive effects, and hypersensibility.

The ENEIS study showed that VKA are responsible for more than 50% of serious adverse events.[6] In Lebanon, a study carried out at a tertiary teaching centre showed that VKA were responsible of 7.4% of Adverse Drug Events (ADE).[7]

Major hemorrhage of all patients treated with VKA is about 1.2 to 7% per year compared to 2 to 24% for minor hemorrhages.[8,9] A meta-analysis showed that the rate of major bleeding from VKA treatment for venous thromboembolism is about 8.9% per patient year in the first 3 months of therapy then decreases to reach 2.5% after 3 months.[10] In France, 17,000 hospitalizations occur per year for VKA-related bleeding events where half of these events are preventable.[11] In Grenoble-France, 38% of patients taking VKA treatment (older than 65 years) and admitted to Emergency department at CHU Grenoble presented Hemorrhagic ADE.[12] In the USA, around 2.5 million of adults and children are on VKA therapy with major hemorrhage occurring at an annual rate of 1.7-3.4%.[13] Life-threatening or fatal hemorrhagic complications increase with age with a relative risk, RR=4.5 for patients $\geq$ 80 years of age compared with patients $\leq$ 50 years of age.[8]

It is important to monitor the effect of VKA by measuring the International Normalised Ratio (INR).[9] Patients using VKA have to frequently monitor their INR especially when starting VKA treatment, changing the dose, or changing their diet or medications that are known to interact with VKA. For most conditions, the recommended therapeutic range is between 2.0 and 3.0.[9]

Patient education concerning VKA treatment is essential for a balanced and effective treatment as well as a reduced iatrogenic accidents.[1] Many studies have confirmed that insufficient understanding of the VKA treatment is an important risk factor for treatment instability and a predictor of nonadherence and patient risk.[9,14,15] A six months randomized controlled trial showed that major bleeding was more common in the group receiving usual care than in the group receiving education program as intervention (12% vs. 5.6%; p=0.0498).[16] Another randomised study also proved that insufficient patient education is usually associated with poorly controlled anticoagulation, and patients' therapeutic education is greatly effective in reducing the hemorrhagic risk death caused by thrombotic relapse, OR 0.25 (95% IC 0.1-0.7).[17]

Therefore, the objective of this study is two-folded: first, to assess patients' knowledge and practices to VKA treatment; second, to determine the factors related to VKA imbalanced treatment.

2. METHODS

2.1 Study Design

A hospital-based case-control study was conducted on hospitalized patients admitted to a Lebanese tertiary hospital for cardiology located in the Beirut between September 1ˢᵗ, 2016 and June 30ᵗʰ, 2017.

2.2 Inclusion and Exclusion Criteria

Patients were included if they were 18 years of age or older, admitted to the hospital, and taking VKA treatment regardless of the value of their INR on the day of admission. Patients with an INR higher or lower than the therapeutic range were considered as cases and patients with an INR within the therapeutic range were considered as controls.

Patients were excluded if they were non-Lebanese and under 18 years old, taking an anticoagulant treatment other than VKA prior to hospital admission, started their VKA treatment after admission to the hospital, presented psychiatric or comprehension disorders, or simply refused to participate in the study.

2.3 Sample Size

All patients admitted to the hospital during the period of collection and meeting the inclusion criteria were included in this study.

2.4 Data Collection

A well-structured and standardized questionnaire was used to address the study objective. Data were collected prospectively by interviewing patients. The items of the questionnaire were based on the booklet developed by the French Society of Cardiology for information and treatment follow-up for patients taking VKA treatment.[18] The questionnaire was written in French and translated into Arabic before collection. An oral consent form was obtained from each participant prior to the participation in the study.

Data concerning VKA name, indication, daily dosage, date of initiation of the treatment, and the value of the patient's INR on the day of admission to the hospital were collected from the patient's medical record at the hospital. Patient's INR was classified as "within the

therapeutic range" or "Outside the therapeutic range" according to the recommendations of the ANSM (Agence Nationale de Sécurité du Médicament).[19]

Tool

The questionnaire used for data collection was divided into four sections including

• The first section was related to patient's identification, socio-economic and demographic characteristics such as age, gender, education, social status, income, health insurance, and employment status. Moreover, it also included information about patient's medical habits: doctor's visits, medications, and medical condition as well as physical activities.

• The second section assessed patients' knowledge about the medication characteristics and its usage. It included questions regarding the name of the anticoagulant, dose, overdose and underdose risks, mechanism of action, biological monitoring test, and therapeutic range.

• The third section covered the different medical iatrogenic events that may occur during VKA treatment. This section included questions related to hemorrhagic signs (gingivorrhage, epistaxis, melena, hematoma, hematuria, etc.), frequency of measuring INR, dose modification, and backup plan in case of high INR. Additionally, this section involved questions related to patient's behavior in specific cases such as visiting a dentist, or taking other medications, etc. as well as whether reporting or not any concern about VKA treatment to any healthcare professional such as pharmacist, dentist, surgeon and anesthesiologist.

• The fourth section included questions about other factors that may interfere in the stability of VKA treatment other than patients' knowledge and practices such as the preparation of the anticoagulant if done by the patient or a primary caregiver, time of intake, interruption of treatment by the patient when feeling good, increasing the dosage when feeling down, stopping the medication when the patient feels well, adding the drug when not feeling well, the forgetfulness of the medication and the attitudes to adopt in case of forgetfulness, and the change of the food during the treatment. The therapeutic education of patients by health professionals about VKA treatment was evaluated; including the usage of this medication, precautions of use, drugs to avoid, adopted diet and food to avoid, activities and sports to proscribe, reading the instructions for use of the VKA box, and what to do in case of INR lower or higher than the target value.

2.5 Statistical Methods: Data were analyzed using SPSS version 23. Continuous variables were presented as means with standard deviation and categorical variables as percentages. Comparison between groups was done using the Chi-square 2x2 for categorical variables,

Student's *t* tests for continuous variables, and Fisher's Exact test when >20% of the cells have an expected size less than 5. A stepwise ascending logistic regression was done. The strength of association between the dependent variable and independent variables was expressed in odds ratio (OR) through 95% confidence interval. A correlation analysis was used to evaluate the collinearity between the independent variables. In case of significant collinearity between two variables (ie, r>0.7), only one of the two was chosen and reported in the analysis. P-value <0.05 determined statistical significance.

3. RESULTS

Overall, 408 patients were enrolled in this study between September 1ʳˢᵗ, 2016 and June 30ᵗʰ, 2017. Two hundred and four patients taking VKA treatment were admitted to the hospital with an INR within the therapeutic range and considered as controls, and 204 other patients taking VKA treatment were admitted with an INR outside the therapeutic range and considered as cases.

3.1 Socio-economic and Demographic Characteristics of Patients taking VKA Treatment: The cases were older than controls (older than 65 years of age) (P<0.001). In addition, patients in the control group had a higher educational level (P<0.001) (Table 1).

3.2 Evaluation of Patients Knowledge Concerning VKA Treatment: Patients with an INR within the therapeutic range significantly differed from those with an INR outside the therapeutic range concerning the VKA treatment duration (P<0.011). Controls were more knowledgeable about the name of the VKA medication (P<0.001), the dose (P<0.001), the indication (P<0.001), the action mechanism (P<0.001), the risk of over- and under-dose (P<0.001), the biological monitoring test (P<0.001), and the events accompanying taking aspirin along with VKA treatment (P=0.008) (Table 2).

3.3 Evaluation of Patients Practices that May Interfere in the Balance of VKA Treatment: Patients in the case group were significantly more likely to exercise less (P=0.012), never measure INR (P=0.008). They also self-prepare their VKA treatment less than the controls (P=0.012). They were significantly more likely to forget to take their AVK treatment (P=0.023), double the VKA dose in case of forgetfulness (P=0.037), never notify health professionals about the VKA treatment (P=0.006), not inform the dentist about the VKA treatment in case of tooth extraction (P<0.001), and to not measure INR in case of blue spots (bruises) appearance (P=0.039) than control patients (Table 3).

3.4 Evaluation of the Therapeutic Education of Patients by Health Professionals Concerning VKA Treatment: Controls differ significantly from the cases: They were more likely to read the instructions for usage available on the VKA box (P=0.01), be educated by the doctor and/or the pharmacist on the physical activities that can influence the VKA treatment (P=0.017), and name at least one correct answer about the physical activities that can unbalance the VKA treatment (P=0.034) than patients with an INR outside the therapeutic range (Table 4).

3.5 Multivariate Analysis: Relationship between the Different Potential Factors that can Influence the VKA Treatment and having an INR within or outside the Therapeutic Range Stepwise ascending logistic regression was performed by considering the potential of confounding. Variables with p < 0.2 in the bivariate analysis were considered in the regression. Results of logistic regression showed that patients having an increased knowledge in regard to the name of the VKA taken and to the risk of overdose and under-dose were 2 to 3 times more likely to have an INR within the therapeutic range (ORa=0.39, 95% CI [0.21–0.73], p=0.003; ORa=0.59, 95% CI [0.36–0.96], p=0.034; and ORa=0.4, 95% CI [0.24–0.68], p=0.001 respectively) (Table 5). Moreover, informing the dentist about the VKA treatment and taking the right precautions in case of tooth extraction significantly decrease the risk of having an INR outside the therapeutic range (ORa=0.02, 95% CI [0.001–0.81], p=0.039) (Table 6). However, patients' therapeutic education concerning VKA treatment did not reach the significance, although it was found to be related to patient's age (ORa=1.03, 95% CI [1.01-1.04], p=0.003) (Table 7).

3.6 Stratification by Age: In an investigation whether there is a relationship between patients' therapeutic education and having an INR outside the therapeutic range, being 65 and older is suspected of being a confounding factor.[20,21] The confounding effect of age can be eliminated by stratifying on this factor: patients aged < 65 years and patients aged ≥ 65 years.

Table 8 shows that patient's therapeutic education on physical activity that may influence the VKA treatment has a significant association with reducing the risk of having an INR outside the therapeutic range among patients aged less than 65 years (ORa=0.36, 95% CI [0.15–0.88], p=0.026) than among patients aged 65 years or older. However, reading the instructions of usage available on the VKA box significantly reduce the risk of having an INR outside the therapeutic range among patients 65 years old or older (ORa=0.45, 95% CI [0.22–0.91], p=0.025). We also conducted the Breslow-Day test of homogeneity in order to

test the hypothesis that the odds ratio between patient's therapeutic education on physical activity and having a reduced risk of an INR outside the therapeutic range may be the same at each level of age (Age < 65 years and age ≥ 65 years). The p value for Breslow-Day test was 0.039 indicating that we have to reject the hypothesis test.

Table 1: Socio-economic and demographic characteristics of cases and controls.

Variables	Cases N=204	Controls N=204	P value
Age (mean ± SD)	60.85 ± 14.1	54.80 ± 12.74	<0.001*
Age (≥ 65 years)	93 (45.6%)	55 (27.0)	<0.001*
Sex (male) N(%)	110 (53.9%)	116 (56.9%)	0.619
Marital status (married) N(%)	157 (77%)	175 (85.8%)	0.077
Education status (educated) N(%)	156 (76.5%)	183 (89.7%)	0.001*
Employment status (employed) N(%)	20 (9.8%)	34 (16.7%)	0.076
Medical insurance (insured) N(%)	113 (55.4%)	132 (64.7%)	0.069

*Statistically significant

Table 2: Comparison between cases and controls in regard to their knowledge concerning VKA treatment.

Variables	Cases N (%)	Controls N (%)	P value
Taking the VKA treatment for less than 3 months	26 (12.7)	9 (4.4)	0.011*
The patient knows			
The name of the VKA taken	133 (65.2%)	184 (90.2%)	<0.001*
The dose of VKA	162 (79.4%)	189 (92.6%)	<0.001*
The indication of the VKA	162 (79.4%)	189 (92.6%)	<0.001*
The action mechanism of the VKA	120 (58.8%)	152 (74.5%)	0.001*
The risk of over-dose	92 (45.1%)	148 (72.5%)	<0.001*
The risk of under-dose	64 (52.9%)	23 (19%)	<0.001*
The biological monitoring test	78 (38.2%)	140 (68.6%)	<0.001*
The therapeutic range	48 (23.5%)	43 (21.1%)	0.552
The signs of hemorrhage	87 (42.6%)	105 (51.5%)	0.074
The events accompanying taking aspirin along with VKA treatment	115 (56.4%)	141 (69.1%)	0.008*
The influence of diet on VKA treatment	48 (23.5%)	40 (19.6%)	0.336
The restriction of intramuscular injection with VKA treatment	110 (53.9%)	92 (45.1%)	0.164

*Statistically significant

Table 3: Comparison between cases and controls in regard to their practices with VKA treatment.

Variables	Cases N (%)	Controls N (%)	P value
Physical activity (active)	74 (36.6%)	99 (48.5%)	0.012*
Doctor's consultation			0.796
1 time / month	60 (29.4%)	54 (26.5%)	
< 1 time / month	99 (48.5%)	102 (50.0%)	
Frequency of INR measure			0.008
≥ 1 time / month	123 (60.3%)	143 (70.1%)	
< 1 time / month	49 (24.0%)	48 (23.5%)	
Self-preparation of the VKA treatment	169 (82.8%)	186 (91.2%)	0.012*
Random time of taking the VKA	114 (94.2%)	118 (97.5%)	0.196
Self-modification of treatment	12 (5.9%)	24 (11.8%)	0.863
Forget to take VKA	42 (20.6%)	25 (12.3%)	0.023*
In case of forgetfulness, double the dose	30 (14.7%)	17 (8.3%)	0.037*
Contact the doctor if INR=9	176 (86.3%)	179 (87.7%)	0.742
Notify health professionals about VKA	132 (60.3%)	149 (73%)	0.006*
In case of tooth extraction, inform the dentist about the VKA treatment or stop taking VKA few days ahead	123 (60.3%)	166 (81.4%)	<0.001*
In case of blue spots appearance, make an INR measurement	3 (1.5%)	9 (4.4%)	0.036*
Take non-steroidal anti-inflammatory drugs in case of pain	61 (29.9%)	57 (27.9%)	0.908

*Statistically significant

Table 4: Comparison between cases and controls in regard to patients therapeutic education about VKA treatment.

Variables	Cases N (%)	Controls N (%)	P value
Reading the instructions for usage available on the VKA box	78 (38.2%)	104 (51%)	0.01*
The doctor and/or the pharmacist has educated the patient on how to take VKA	191 (93.6%)	194 (95.1%)	0.52
The doctor and/or the pharmacist has educated the patient about the influence of diet on VKA treatment	46 (22.5%)	52 (25.5%)	0.487
The patient names at least one correct answer about foods that can unbalance VKA	169 (82.8%)	170 (83.3%)	0.361
The doctor and/or the pharmacist has educated the patient on the influence of some drugs on VKA treatment	32 (15.7%)	33 (16.2%)	0.892
The patient names at least one correct answer about drugs that can unbalance VKA	28 (13.7%)	24 (11.8%)	0.253
The doctor and/or the pharmacist has educated the patient on the physical activities that can influence the VKA treatment	12 (5.9%)	26 (12.7%)	0.017*
The patient names at least one correct answer about the physical activities that can unbalance the VKA treatment	10 (4.9%)	20 (9.9%)	0.034*
The doctor and/or the pharmacist has educated the patient on the actions to take if INR is outside the therapeutic zone	13 (6.4%)	24 (11.8%)	0.828
The patient decreases the dose of VKA if INR is greater than the therapeutic range	10 (4.9%)	12 (5.9%)	0.909
The patient increases the dose of VKA if INR is lower than the therapeutic range	6 (2.9%)	12 (5.9%)	0.339

*Statistically significant

Table 5: Stepwise ascending logistic regression: Assessment of the relationship between patients' knowledge and having an INR outside the therapeutic range.

Variables	p value	Adjusted OR$_a$ [95% CI]
Age	0.058	1.02 [0.99 – 1.04]
The patient knows the name of the VKA taken	0.003*	0.39 [0.21 – 0.73]
The patient knows the risk of overdose	0.034*	0.59 [0.36 – 0.96]
The patient knows the risk of under-dose	0.001*	0.4 [0.24 – 0.68]

OR$_a$, adjusted OR; *, statistically significant

This multivariate analysis included the following variables with $p < 0.2$ in the bivariate analysis: instauration date, age, education, and patient's knowledge (name of VKA, dose, indication, action mode, risk of overdose, risk of under-dose, biological monitoring test, hemorrhagic signs, taking aspirin, and intramuscular injection). The variables instauration date, age, and education have been controlled. The -2 Log likelihood was 477.984 and Nagelkerke R Square was 0.258.

Table 6: Stepwise ascending logistic regression: Assessment of the relationship between patients' practices with VKA treatment and having an INR outside the therapeutic range.

Variables	p value	Adjusted OR$_a$ [95% CI]
Age	0.736	1.01 [0.95 – 1.08]
Physical activity	0.296	2.5 (0.45 – 13.92]
Frequency of INR measure		
$\geq$ 1 time / month	0.450	2.62 (0.22 – 31.87]
< 1 time / month	0.990	0.98 [0.07 – 13.55]
In case of tooth extraction, inform the dentist about the AVK treatment or stop taking VKA few days ahead	0.039*	0.02 [0.001 – 0.81]

OR$_a$, adjusted OR; *, statistically significant

This multivariate analysis included the following variables with $p < 0.2$ in the bivariate analysis: instauration date, age, education, and patient's practices (physical activity, frequency of INR measure, VKA preparation, timing, forgetfulness, double dose, health professionals' notifications, tooth extraction, and blue spots). The variables instauration date, age, and education have been controlled. The -2 Log likelihood was 45.161 and Nagelkerke R Square was 0.650.

Table 7: Stepwise ascending logistic regression: Assessment of the relationship between patients' therapeutic education about VKA treatment and having an INR outside the therapeutic range.

Variables	p value	Adjusted OR$_a$ [95% CI]
Age	0.003*	1.03 [1.01 - 1.04]
Education status (educated)	0.069	0.57 [0.31 – 1.04]
Taking the VKA treatment for less than 3 months	0.069	0.72 [0.51 – 1.03]
Reading the instructions for usage available on the VKA box	0.22	0.77 [0.5 – 1.18]
The doctor and/or the pharmacist has educated the patient on the physical activities that can influence the VKA treatment	0.55	0.66 [0.17 – 2.53]
The patient names at least one correct answer about the physical activities that can unbalance the VKA treatment	0.99	-

OR$_a$, adjusted OR; *, statistically significant

This multivariate analysis included the following variables with $p < 0.2$ in the bivariate analysis: instauration date, age, education, reading the instructions for usage available on the VKA box, the doctor and/or the pharmacist has educated the patient on the physical activities that can influence the VKA treatment, and the patient names at least one correct answer about the physical activities that can unbalance the VKA treatment. The variables instauration date, age, and education have been controlled. The -2 Log likelihood was 510.245 and Nagelkerke R Square was 0.169.

Table 8: Adjusted Odds Ratios for patient's therapeutic education with having an INR outside the therapeutic range among patients < 65 years of age and patients ≥ 65 years of age.

Independent Variables	Age < 65 years		Age ≥ 65 years	
	OR adjusted	95% CI, P	OR adjusted	95% CI, p
Education status (educated)	0.14	0.03 – 0.66 0.013*	0.81	0.39 – 1.67 0.575
Taking the VKA treatment for less than 3 months	0.63	0.40 – 1.0 0.05	0.79	0.46 – 1.38 0.411
Reading the instructions for usage available on the VKA box	1.04	0.61 – 1.79 0.875	0.45	0.22 – 0.91 0.025*
The doctor and/or the pharmacist has educated the patient on the physical activities that can influence the VKA treatment	0.36	0.15 – 0.88 0.026*	3.19	0.35 – 28.93 0.301

OR, odds ratio; CI, confidence interval; *, statistically significant

This multivariate analysis included the following variables, instauration date, education, reading the instructions for usage available on the VKA box, the doctor and/or the pharmacist has educated the patient on the physical activities that can influence the VKA treatment, and

the patient names at least one correct answer about the physical activities that can unbalance the VKA treatment. The variables instauration date, and education have been controlled.

4. DISCUSSION

This study showed that having a controlled INR within the therapeutic range in Lebanon depends on patient's knowledge about the VKA treatment, practices, age, and therapeutic education. The VKA population in Lebanon was generally 60.85 years of age ($\pm$ 14.1 years). Similar results were found in a study conducted in Grenoble-France which stated that 73% of patients under VKA treatment were older than 65 years therefore, justifying the advanced age of this study's patients taking VKA.[12]

Men and women were almost equally represented in this case-control study (p=0.619). The influence of sex on the anticoagulant response is controversial. Indeed, some studies showed a higher frequency of bleeding in women with VKA treatment, while others showed no difference between men and women.[22]

The average number of medications prescribed for patients was 6.8 drugs. However, a survey done in USA gave an average of prescribed drugs at 5.8.[23] The average daily dose of VKA taken in this study was 2.2mg/day [1 mg/day-5mg/day] (less than one tablet/day). This is concordant with another retrospective study which aimed to analyze the data concerning the prescription of VKA at the Geneva University Hospital where the average dose was 1.71mg $\pm$0.95mg for a mean age of the population of 74.2$\pm$14.8 years.[24] The risk of bleeding with VKA increased when the dose of VKA is higher than the recommended dose.[25] Nevertheless, with this prescribed daily dose of VKA, 50% of patients admitted to the hospital had their INR outside the therapeutic range. These results are much higher than those of an epidemiological survey showing that only 28.8% of patients taking VKA treatment are outside the therapeutic range.[25] However, they are confirmed by a study conducted in Lebanon which stated that between the 386 patients taking VKA treatment, only 20% had their INR within the therapeutic range compared to 78% who had their INR outside it.[7]

The majority of the patients knew their VKA name, dose, indication, under- and overdose risks, and action mechanism. These results are similar to those of a study in which 70 to 80% of patients were known to know the name and indication of their VKA.[26] Another study pointed out that only 19% of patients treated by VKA know the risk of an overdose while 61% of patients know the role of the VKA. However, in this study, the majority of the

participants didn't know the signs of hemorrhage, nor the frequency of INR measurement: Only 42.6% of cases knew the first sign of hemorrhage compared to 51.5% of controls. This is in occurrence with another study showing that more than half of the patients surveyed do not know the warning signs of overdose.[24] The lack of knowledge of patients in regard to the hemorrhagic signs and the insufficient supervision of INR were identified as major risk factors for hemorrhage and that the increase in frequency of measurement of INR (≥1x/month) would reduce the risk of development of iatrogenic events.[25,27]

Many studies confirm that patient therapeutic education is a major step in improving the knowledge of patients. This strategy remains very relevant by the fact that it reduces the probability of hemorrhage occurrence and by then, reduces the cost of hospitalization due to iatrogenic events caused by medications. In respect to patients who were engaged in an education programme regarding their VKA treatment, the probability of having a hemorrhage caused by VKA is four times reduced than with uneducated patients.[17, 28] The majority of the participants in this study were responsible of preparing their medication and the majority used to take VKA treatment at a random time. Moreover, 148 (36.3%) of patients in this study were age advanced (≥ 65 years old) and the preparation of the VKA medication by themselves increases the risk of dosage errors especially that Sintrom tablet (VKA medication available in Lebanon) is quarter-scored and the majority of recommended doses are less than one tablet (¼, ½, ¾). However, reading the instruction for usage available on the VKA box was very beneficial among VKA patients. It was found to significantly reduce the risk of having an INR outside the therapeutic range among patients 65 years of age or older. Taking VKA in a random way increases the risk of haemorrhage.[1] A large number of studies showed that older people do not respect their treatment and that only 5% of this population took the right treatment at the right doses.[29] The results of this study found that advanced age increases the risk of having an INR outside the therapeutic range when it comes to patient's therapeutic education. Advanced age was found to be a risk factor for hemorrhage in many studies, which requires from physicians an increased knowledge of the phenomena of aging and the pharmacokinetics particularities of elderlies.[25,30]

Physician/patient relationship has a significant role on patients' practices in VKA treatment.[31] This study confirms these findings where patients' therapeutic education concerning the physical activities to avoid during VKA treatment has shown to significantly reduce the risk of having an INR outside the therapeutic range in the Lebanese population for

patients aged less than 65 years, although, only 9.3% of patients were educated about the physical activities to avoid during treatment. This highlights the need to increase patients' education for a balanced VKA treatment.

Although, therapeutic education has proved to enhance patients' knowledge and behaviors about VKA treatment and by then, provide patients with skills in treatment management.[32,33] In this study, patients did not have the ability of modifying their treatment. Similarly to what reported by a survey where 90% of patients do not change the dosage of their VKA treatment alone.[34] However, in this study, patients were knowledgeable enough to inform dentists about VKA treatment and take the right precautions before any dental operation which significantly reduced the risk of having an INR outside the therapeutic range.

Cases and controls were mainly educated by their physician or pharmacist on how to take the VKA treatment. However, almost 76% of patients were not aware of the necessity of changing their diet during VKA treatment. Although, therapeutic education concerning diet proved that around 71.5% of patients exposed to therapeutic education were aware of the dietary constraints caused by their VKA treatment.[35] Moreover, another lack of patients' therapeutic education among the VKA population is related to drugs. Only 16% of patients were educated about the drugs to avoid during VKA treatment, a faraway percentage than what was shown by a clinic anticoagulants study where 60% of patients taking VKA treatment know about prohibited drugs.[36] The difference between the two results may be explained by the fact that the patients in the anticoagulant clinic study received some education during the initiation of anticoagulant therapy. The initial period of treatment did not appear to be associated in this study with an increased risk of an INR outside the therapeutic zone (less than 3 months for 12.7% of cases and 4.4% of controls). However, many studies found an increased frequency of overdoses during the first 90 days of treatment initiation often related to the fact that the INR is less stable at the beginning of treatment mainly related to the determination of the right dosage which may be problematic in some patients.[37] The majority of studies suggests that the incidence of hemorrhage is greatest at the start of treatment (first month, or first three months) and with the prolongation of the duration of the treatment by the VKA.[38] However, in our study, the frequency of having an INR outside the therapeutic area was 73.5% beyond 1 year of treatment.

The intervention of the pharmacist appears absent in almost all patients in this study (present in 3.7% of patients). It is absent in 76% of iatrogenic hemorrhagic drug events.[25] The

pharmacist, being a dispenser of medicines, should not only provide pharmaceutical advice, validate the prescription, but also analyze and organize with the patient daily practices optimally integrating the taking of his medication.

An important strength to this study is the control of different bias that might be present in a case-control study. However, to minimise selection bias, controls were selected from the same hospital as cases in order to be representative of the same population. Adding to this, recall bias was limited by blinding patients to the study hypothesis, since this study depended largely on the ability of patients to recall their exposure experience. Moreover, observer bias was also minimised by using a standardised questionnaire to collect information about the exposure, having only one investigator collecting the information, and developing a protocol for collecting, measuring and interpreting information. A limitation of this study is the lack of data about patient/physician relationship which might have enhanced the findings of this study in regards to the lack of patients' therapeutic education.

Patients' therapeutic education is therefore a major step towards improving patients' compliance and knowledge: a patient who knows his treatment will be more inclined to respect the prescription. This strategy may be relevant because it reduces the likelihood of having an INR outside the therapeutic range and, as a result, reduces the cost of hospitalization for adverse drug events.

CONCLUSION
This study reinforces the importance of patient education, physicians' involvement and anticoagulant monitoring. Every patient taking VKA treatment has to acquire certain level of knowledge in regards to his treatment and know how to adopt the ordinary dose in order to limit the iatrogenic risk related to this treatment. Consequently, interventions to increase the contact and relationship between patients and physicians are highly recommended and may lead to optimal anticoagulation management. A great deal of time should be set in place to educate patients in order to get them involved in the management of their VKA therapy to optimise the efficacy of this treatment and guarantee a secured utilization.

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