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RESEARCH ARTICLE

Drug-Related Problems and Factors Involved in the Imbalance of Oral Anticoagulants in Lebanese Patients: A Cross-Sectional Study

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Abstract

The goal of this study was to identify drug-related problems (DRPs) and the factors involved in the imbalance of new oral anticoagulants (NOACs) and vitamin K antagonists in a Lebanese adult population with cardiovascular diseases. An imbalance in the hemostatic systems between procoagulant and anticoagulant factors in circulating blood produces either hemorrhagic or thrombotic conditions. A prospective cross-sectional study was conducted during 5 months in a teaching hospital. All patients at least 18 years of age taking oral anticoagulants were included in the study. A standardized questionnaire was used, and information was obtained from the patients' profiles and electronic medical records. DRPs were identified and categorized according to the Pharmaceutical Care Network Europe classification system. A total of 258 patients were included. The overall prevalence of DRPs was 87.2%; the highest prevalence was observed in patients taking acenocoumarol (96.0%), in contrast to 76.7% and 59.0% in patients taking dabigatran and rivaroxaban, respectively. Drug interaction was the most frequent DRP (83.3%), followed by inappropriate monitoring (42.6%) and excessive dose (26.7%). Having renal disease, and taking proton-pump inhibitors or nonsteroidal anti-inflammatory drugs were among the factors affecting the international normalized ratio (INR) range (adjusted odds ratio [OR_a] = 2.513, 95% confidence interval [CI] 1.238, 5.101; OR_a = 2.487, 95% CI 1.139, 5.430 and OR_a = 2.114, 95% CI 1.043, 4.286, respectively), whereas smoking and renal disease significantly affected activated partial thromboplastin time (aPTT) (OR_a = 8.325, 95% CI 1.577, 43.965 and OR_a = 6.922, 95% CI 1.471, 32.570, respectively). Patients taking NOACs had greater aPTT control and fewer DRPs, with a wide therapeutic index enabling administration of fixed doses.

Keywords Vitamin K antagonist · New oral anticoagulant · International normalized ratio · Activated partial thromboplastin time · Factors of imbalance · Drug-related problem

Abbreviations

ADEs	Adverse drug events
aPTT	Activated partial thromboplastin time
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CVD	Cardiovascular disease
DRPs	Drug-related problems
INR	International normalized ratio
NOACs	New oral anticoagulants
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCNE	Pharmaceutical Care Network Europe
PMH	Past medical history
PPI	Proton pump inhibitor
PT	Prothrombin time
SPSS	Statistical Program for Social Sciences
SrCr	Serum creatinine
VKA	Vitamin K antagonist
WRN	Warfarin-related nephropathy

1 Introduction

Cardiovascular disease (CVD) is the greatest contributor to morbidity and mortality worldwide. In 2015, the total number of CVD deaths represented 31% of global deaths,

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and an estimated 17.7 million people, mostly in low- and middle-income countries. Of these, 7.4 million and 6.7 million deaths were associated with coronary artery disease and stroke, respectively [1]. However, by 2030, the total number of CVD deaths is expected to exceed 23.6 million [2].

For many years, vitamin K antagonist (VKA) treatment was the only option and the gold standard oral anticoagulant worldwide for the management of patients with CVD [3]. The effects of VKA are influenced by several factors, including patient compliance, age, and sex, because older patients, particularly women, require a lower total weekly dose of warfarin, the most commonly used oral VKA [4]. Lifestyle, and a high-protein, high-vitamin K diet also appear to play roles in the stability of the VKA response, in addition to several pathological conditions and drug interactions [5].

The limitations associated with VKA, including a requirement for strict drug monitoring, a narrow therapeutic window, and significant inter/intraindividual variability, have prompted research on many new oral anticoagulants (NOACs) that can be administered in fixed doses without such constraints [6]. Generally, NOACs have fewer interactions with other concomitantly administered drugs. Nonetheless, specific considerations must be made for every patient, particularly when a combination of interfering factors is present (pharmacokinetic effects of accompanying drugs and co-morbidities). Food affects the bioavailability of rivaroxaban; therefore, this medication must be taken with meals. In addition, patient age (≥ 75 years), weight (≤ 60 kg), and renal function affect NOAC plasma levels [7]. Hence, the optimal use of NOACs in real life remains challenging for several reasons, particularly the use of multiple-dose regimens for various indications and specific populations (e.g., older patients, patients with renal insufficiency, or those taking interacting drugs); patient adherence; and international variations in approved indications, dosages, and dosage forms [8].

Medical therapy has improved patient care and enabled optimal treatments and outcomes. However, when drugs are misused, drug-related problems (DRPs) can arise. Pharmaceutical Care Network Europe (PCNE) defines a DRP as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes." Identifying, resolving, and preventing DRPs are cornerstones of pharmaceutical care and a major focus of pharmacists to ensure optimal drug use and minimize possible adverse drug events (ADEs) [9]. A previous study [10] has reported factors associated with VKA related ADEs. However, the factors involved in the imbalance of NOACs were not investigated. Thus, the goal of this study was to identify DRPs and the factors involved in the imbalance of NOACs (dabigatran and rivaroxaban) and a VKA (acenocoumarol) in a Lebanese adult inpatient population with CVD.

2 Materials and Methods

2.1 Study Design and Population

A prospective observational cross-sectional study was conducted in a tertiary care teaching hospital in Lebanon. All patients 18 years or older currently taking oral anticoagulants (dabigatran, rivaroxaban, or acenocoumarol) and admitted to the hospital between March 1, 2019 and July 31, 2019 were included. Pregnant women were excluded from the study.

2.2 Data Collection

The following data were extracted from electronic patient files: patients' characteristics (age, sex, weight, height, body mass index [BMI]), social history (marital status, smoking, and alcohol consumption), patient medical and medication history, prescribed drugs (indication, dose, frequency, and duration of administration), biochemical results (serum creatinine (SrCr), international normalized ratio (INR) or activated partial thromboplastin time (aPTT) or prothrombin time (PT), hemoglobin, and creatinine clearance (CrCl) calculated with the Cockcroft Gault formula).

Chronic kidney disease (CKD) is diagnosed when the glomerular filtration rate is less than 60 ml/min/1.73 m^2 for more than 3 months or when other signs of kidney damage are present (such as albuminuria, hematuria, or abnormal kidney ultrasound or kidney biopsy results) [11].

INR and aPTT/PT were measured to assess the safety and efficacy of acenocoumarol and NOACs, respectively. Both aPTT and PT provide a qualitative assessment of the presence of dabigatran and rivaroxaban, respectively. However, they are not sensitive to the quantitative assessment of NOACs [7]. Their values were compared with a reference target range [12–16], then classified as controlled or not controlled. The uncontrolled values were divided into two categories (more or less than the target value).

DRP identification was performed by a clinical pharmacist. DRPs were categorized according to PCNE [17] as follows: inappropriate drug according to guidelines (C1.1), inappropriate selection of the drug form (C2.1), inappropriate dispensing process or frequency (C3.3, C3.4), inappropriate duration of treatment (C4), inappropriate monitoring (C8.1), inappropriate combination of drugs (C1.4), and drug dose too high (C3.2) or too low (C3.1).

Assessment of the oral anticoagulants' dose, frequency, and duration conformity was based on the guidelines of

the European Society of Cardiology and American Heart Association for the management of atrial fibrillation [12, 13, 18] and the European Society of Cardiology guidelines and other guidance on the diagnosis and management of acute pulmonary embolism [14, 15, 19]. The appropriateness of drug dosage was assessed on the basis of patient CrCl, age, and concomitant drug use (possible drug-drug interactions encountered with these oral anticoagulants, such as antiarrhythmic activity, particularly for amiodarone, proton pump inhibitors (PPIs), and nonsteroidal anti-inflammatory drugs (NSAIDs) [5, 7, 20].

ADEs were assessed on the basis of the presence of bleeding, intracranial hemorrhage, gastrointestinal adverse effects, thrombocytopenia, dyspnea, blue/purple toes, warfarin-induced skin necrosis, or elevated liver enzymes/hepatitis [21]. Therefore, the potential pharmaceutical interventions were evaluated by switching the drug, adjusting the dose, monitoring the drug, or discontinuing use [17]. In addition, the presence of contraindications was evaluated on the basis of the presence of active/major bleeding, dialysis/severe renal impairment (CrCl < 15 ml/min), and hypersensitivity [22].

2.3 Statistical Analysis

Analysis of data was performed in Statistical Program for Social Sciences (SPSS) software for Mac, version 23. Descriptive statistics was used to determine the sociodemographic characteristics of the participants. The results are expressed as frequency (%) for qualitative variables and as mean (standard deviation) for quantitative variables.

Bivariate analysis was conducted to compare all variables according to the drug used and to examine any associations among all independent and dependent variables. Student's *t*-test (or Mann Whitney test as a non-parametric test) was used to compare two means, and ANOVA was used to compare three or more means for quantitative continuous variables. The χ^2 test (or Fisher's exact test as a non-parametric test) was used to compare two or more percentages in cases of qualitative variables. Only independent variables with a *P*-value < 0.2 in the bivariate analysis were included in the logistic regression analysis. In logistic regression, the omnibus test was used to verify that the new model (with the explanatory variables included) provided an improvement over the baseline model. It was based on χ^2 tests. Nagelkerke's R^2 test indicated the percentage of variance of the dependent variables explained by the model. The Hosmer and Lemeshow test, a statistical test for goodness of fit for logistic regression, was required to be non-significant. A value of $P \leq 0.05$ was considered statistically significant.

2.4 Sample Size Calculation

Sample size calculation was performed in Epi Info version 7.2.2.6. The prevalence of DRPs associated with NOACs in hospitalized patients was 8.4% [23] vs. 12.3% with VKA treatment [24]. Using these percentages as the expected frequencies, with a 95% confidence interval (CI) and 6% acceptable margin of error for NOACs and VKA, we determined that the minimum required sample size was 82 participants taking NOACs and 166 participants taking VKA. Therefore, the chosen sample size was 248 participants.

3 Results

3.1 Characteristics of the Study Population

In total, 258 patients taking one of the three oral anticoagulants were included in this study. Approximately 48.4% of patients were men, and 51.6% were women. This distribution did not significantly differ among groups. However, the distribution of age significantly differed among the three groups. The mean age of the included participants was 66.35 ± 13.16 years, and the mean BMI was 28.78 ± 5.51 kg/m^2. Most patients were nonsmokers (67.4%) and did not have renal disease (67.8%). Patients took oral anticoagulants mainly for stroke prevention in atrial fibrillation (48.8%). The percentage of patients with a controlled INR was 43.18%, whereas the percentage of patients with controlled aPTT was 84.2%. The baseline characteristics are summarized in Table 1.

3.2 Prevalence of Drug-Related Problems

A total of 225 DRPs were identified among the 258 patients with single oral anticoagulant use (Table 2). The overall prevalence of DRPs was 87.2%. The highest percentage of DRPs was found among patients who received acenocoumarol (96%), whereas the prevalence of DRPs was lower in the subgroup of patients who received dabigatran (76.7%) and rivaroxaban (59%). All types of DRPs were screened. According to the guidelines, no DRPs were associated with inappropriate drugs (C1.1), selection of the drug form (C2.1), dispensing process, or frequency (C3.3, C3.4) and duration of treatment (C4). Inappropriate monitoring (C8.1), inappropriate combination of drugs (C1.4), a drug dose either too high (C3.2) or too low (C3.1), and pharmaceutical intervention significantly differed among the three groups, with $P < 0.05$. Inappropriate monitoring was present primarily among acenocoumarol users (61.4%, compared with 5.1% of rivaroxaban users). The inappropriate combination of drugs in the acenocoumarol group was 93.8%, compared with 69.8% and 51.3%

Table 1 Baseline characteristics of the study population

Characteristics	All patients $N=258$	Acenocoumarol $N=176$	Dabigatran $N=43$	Rivaroxaban $N=39$	*P*-value
Sex					0.545
Male, *n* (%)	125 (48.4%)	86 (48.9%)	18 (41.9%)	21 (53.8%)	
Female, *n* (%)	133 (51.6%)	90 (51.1%)	25 (58.1%)	18 (46.2%)	
Age, years					0.001
> 75 years, *n* (%)	79 (30.6%)	43 (24.4%)	23 (53.5%)	13 (33.3%)	
< 75 years, *n* (%)	179 (69.4%)	133 (75.6%)	20 (46.5%)	26 (66.7%)	
Mean (SD)	66.35 ± 13.16	64.99 ± 13.09	72.16 ± 12.01	66.07 ± 13.22	0.006
Smoking status					0.468
Yes, *n* (%)	84 (32.6%)	55 (31.3%)	13 (30.2%)	16 (41.0%)	
No, *n* (%)	174 (67.4%)	121 (68.8%)	30 (68.8%)	23 (59.0%)	
BMI (kg/m^2)					0.285
Mean (SD)	28.78 ± 5.51	28.6342 ± 5.52	29.95 ± 6.13	28.18 ± 4.69	
Anemia					< 0.001
Yes, *n* (%)	131 (50.8%)	103 (58.5%)	18 (41.9%)	10 (25.6%)	
No, *n* (%)	127 (49.2%)	73 (41.5%)	25 (58.1%)	29 (74.4%)	
Renal disease					0.009
Yes, *n* (%)	83 (32.2%)	67 (38.1%)	10 (23.3%)	6 (15.4%)	
No, *n* (%)	175 (67.8%)	109 (61.9%)	33 (76.7%)	33 (84.6%)	
Indication					
Stroke prevention in AF, *n* (%)	126 (48.8%)	70 (55.6%)	27 (21.4%)	29 (23.0%)	
Thrombosis prophylaxis in valve replacement, *n* (%)	50 (19.4%)	50 (100%)	0 (0%)	0 (0%)	
Post MI, *n* (%)	47 (18.2%)	33 (70.2%)	12 (25.5%)	2 (4.3%)	
DVT/PE treatment and prophylaxis, *n* (%)	15 (5.8%)	7 (46.7%)	2 (13.3%)	6 (40%)	
Cardio-embolic stroke/TIA prevention, *n* (%)	14 (5.4%)	10 (71.4%)	2 (14.3%)	2 (14.3%)	
Others, *n* (%)	6 (2.4%)	6 (100%)	0 (0%)	0 (0%)	
INR controlled					
Yes, *n* (%)		76 (43.2%)			
Below target, *n* (%)		38 (21.6%)			
Above target, *n* (%)		62 (35.2%)			
aPTT controlled					
Yes, *n* (%)			37 (86.1%)	32 (82.1%)	
Above target, *n* (%)			6 (14.0%)	7 (18.0%)	

AF atrial fibrillation, *aPTT* activated partial thromboplastin time, *DVT/PE* deep vein thrombosis and pulmonary embolism, *INR* international normalized ratio, *MI* myocardial infarction, *SD* standard deviation, *TIA* transient ischemic attack

Table 2 Drug-related problems (DRPs) and pharmaceutical interventions among the oral anticoagulants used

Characteristics	Total $N=258$ (%)	Acenocoumarol $N=176$ (%)	Dabigatran $N=43$(%)	Rivaroxaban $N=14$ (%)	*P* value
Percentage of DRP	225 (87.2%)	169 (96%)	33 (76.7%)	23 (59.0%)	*< 0.001*
Inappropriate monitoring (C8.1)	110 (42.6%)	108 (61.4%)	0 (0.0%)	2 (5.1%)	*< 0.001*
Inappropriate combination of drugs (C1.4)	215 (83.3%)	165 (93.8%)	30 (69.8%)	20 (51.3%)	*< 0.001*
Drug dose too high (C3.2)	69 (26.7%)	62 (35.2%)	3 (7.0%)	4 (10.3%)	*< 0.001*
Drug dose too low (C3.1)	40 (15.5%)	39 (22.2%)	1 (2.3%)	0 (0.0%)	*< 0.001*
ADE (P2.1)	25 (9.7%)	23 (13.1%)	1 (2.3%)	1 (2.6%)	*0.029*
Potential pharmaceutical intervention	111 (43.0%)	98 (55.7%)	8 (18.6%)	5 (12.8%)	*< 0.001*

ADE adverse drug events

Table 3 Effects of past medical history (PMH) and home medication on international normalized ratio (INR) control

Characteristics, $n=176$	Uncontrolled INR $N=100$ (%)	Controlled INR $N=76$ (%)	P value
PMH			
Anemia	66 (64.1%)	37 (35.9%)	0.030
DL	39 (50%)	39 (50%)	0.126
Renal disease	49 (73.1%)	18 (26.9%)	0.001
Dialysis	15 (93.8%)	1 (6.3%)	0.002
Home medications			
PPI	32 (66.7%)	16 (33.3%)	0.125
Antidyslipidemic	43 (51.2%)	41 (48.8%)	0.172
NSAIDs	41 (66.1%)	21 (33.9%)	0.080

DL dyslipidemia, NSAIDS nonsteroidal anti-inflammatory drugs, *PPI* proton pump inhibitors

Table 4 Factors affecting uncontrolled international normalized ratio (INR)

Factors in imbalance of INR	Adjusted OR [95% CI]	P value
Renal disease	2.513 [1.238–5.101]	0.011
Proton pump inhibitors	2.487 [1.139–5.430]	0.022
Nonsteroidal anti-inflammatory drugs	2.114 [1.043–4.286]	0.038
Anemia	1.509 [0.768–2.966]	0.233

Omnibus test: $P<0.001$

Nagelkerke $R^2=0.176$

Hosmer–Lemeshow test: $P=0.378$

Overall predicted percentage = 64.2%

in the dabigatran and rivaroxaban groups, respectively. Approximately 35.2% of acenocoumarol users had an excessive drug dose, compared with only 7% and 10.3% of dabigatran and rivaroxaban users, respectively; 22.2% of acenocoumarol users had a drug dose that was too low, compared with only 2.3% of dabigatran users.

3.3 Predictors of VKA Imbalance

Anemia, renal disease, and dialysis in the past medical history (PMH) were significantly associated with uncontrolled INR ($P=0.03$, $P=0.001$ and $P=0.002$, respectively). A total of 66 patients with anemia (64.1%), 15 patients on dialysis (93.8%), and 49 patients (73.1%) with renal disease had uncontrolled INR. None of the home medications showed a statistically significant difference in INR control (Table 3). In the multivariate analysis, three main factors were found to affect the control of INR. Renal disease and the concomitant use of PPI increased the probability of having an uncontrolled INR by almost 2.5-fold (renal disease [$OR_a=2.513$, 95% CI 1.238, 5.101] and PPI [$OR_a=2.487$, 95% CI 1.139, 5.430]), and the concomitant use of NSAIDs increased this probability by almost two-fold ($OR_a=2.114$, 95% CI 1.043, 4.286) (Table 4).

3.4 Predictors of NOAC Imbalance

Among dabigatran and rivaroxaban users ($n=82$), most patients were non-smokers, and 49 (92.5%) of them had controlled aPTT ($P=0.01$). The number of pathologies was significantly associated with uncontrolled aPTT ($P=0.013$). Regarding the patients' PMH, anemia and renal disease were found to affect aPTT control, $P=0.052$ and $P<0.001$, respectively. Regarding patients' home medications, only the antiplatelet drugs showed a significant difference in aPTT control ($P=0.025$), and 29.6% of patients receiving antiplatelet therapy had uncontrolled aPTT (Table 5). In the multivariate model, two main factors affected the control of aPTT: smoking ($OR_a=8.325$, 95% CI 1.577, 43.965) and renal disease ($OR_a=6.922$, 95% CI 1.471, 32.570) (Table 6).

Table 5 Effects of sociodemographic characteristics, past medical history (PMH), and home medication on activated partial thromboplastin time (aPTT) control in patients taking new oral anticoagulants

Characteristics, $n=82$	Uncontrolled aPTT $N=69$ (%)	Controlled aPTT $N=13$ (%)	P value
Sociodemographic characteristics			
Smoker	9 (31%)	20 (69%)	0.010
Nonsmoker	4 (7.5%)	49 (92.5%)	
Number of pathologies in PMH	5.84 ± 2.40	4.21 ± 2.06	0.013
PMH			
Anemia	8 (28.6%)	20 (71.4%)	0.052
Renal disease	8 (50%)	8 (50%)	<0.001
Home medications			
Antiplatelets	8 (29.6%)	19 (70.4%)	0.025

Table 6 Factors affecting uncontrolled activated partial thromboplastin time (aPTT)

Factors in imbalance of aPTT	Adjusted OR [95% CI]	*P* value
Smoking	8.325 [1.577–43.965]	0.013
Renal disease	6.922 [1.471–32.570]	0.014
Antiplatelets	4.078 [0.874–19.036]	0.074
Anemia	3.790 [0.738–19.455]	0.110

Omnibus test: $P < 0.001$

Nagelkerke $R^2 = 0.463$

Hosmer–Lemeshow test: $P = 0.605$

Overall predicted percentage = 90.2%

4 Discussion

This study demonstrated that the overall prevalence of DRPs was highest among patients taking VKA. The most frequent inappropriate criteria were drug interaction, and inappropriate monitoring and oral anticoagulant dosage. Patients taking NOACs showed greater control of aPTT. Moreover, having renal disease, and taking PPIs or NSAIDs significantly affected the range of INR, whereas smoking and renal disease significantly affected aPTT values.

We observed a discrepancy in the use of AVK and NOACs, although the necessary number of patients was calculated beforehand. Most of the study population was taking acenocoumarol, in agreement with real-world clinical practice, given that AVK has been a cornerstone of the treatment of different CVDs and their complications for almost 70 years [25].

Indications for NOACs continue to increase. The combination of NOACs with antiplatelet therapy has been tested in several large randomized trials for recurrent ischemic events after acute coronary syndrome [26, 27]. Overall, current evidence suggests that the use of NOACs in addition to dual antiplatelet therapy after acute coronary syndrome decreases the rate of recurrent ischemic events, despite increasing the risk of major bleeding. In addition, NOACs may be associated with fewer bleeding complications than VKA [28, 29].

Several factors including anemia have been associated with increased risk of major bleeding [30]. Warfarin, which can cause renal damage, has also been recently detected [31]. Warfarin-related nephropathy (WRN) is a syndrome to which patients with CKD are particularly susceptible. It is defined as an acute increase in INR to > 3.0, followed by evidence of acute kidney injury within 1 week after the INR increase. An abnormally elevated INR alone is not sufficient to cause WRN. WRN may occur in the setting of undiagnosed CKD/glomerular injury coupled with over-anticoagulation, and leading to severe tubular obstruction by red blood cells [32]. Although the therapeutic effect of acenocoumarol is much more difficult to control, NOACs have recently been found to show significantly higher rates of kidney-associated adverse effects than acenocoumarol [33]. NOACs are preferred in the first three stages of CKD, but in stage 4 CKD, the choice between AVK and NOACs must consider the pharmacokinetics of the drugs and patient characteristics. However, AVK has remained the first-line treatment in end-stage renal disease [34]. In addition, NSAID use in combination with oral anticoagulant therapy is significantly associated with higher rates of major bleeding, stroke/systemic embolism, and hospitalization, probably because of their antiplatelet effects and a decrease in gastric mucosal protection [35]. PPIs were found to be significantly associated with uncontrolled INR. However, this result contradicts other findings wherein the INR ratios did not significantly differ before and after PPI initiation [36]. Although PPI co-therapy in patients taking warfarin concurrently with an antiplatelet agent or NSAID is beneficial in decreasing the risk of upper gastrointestinal bleeding, PPI co-therapy provides no benefit to patients taking warfarin exclusively [37].

For NOAC users, aPTT control was affected by cigarette smoking. This finding is in accordance with those from a study that has indicated an inverse correlation between the duration of smoking and PT and aPTT, and demonstrated that long-term chronic cigarette smoking can lead to hemostatic dysfunction in chronic smokers [38]. Anemia and renal disease also affected aPTT control, similarly to the findings of the Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study, which has shown that CKD with an estimated CrCl of < 30 ml/min and anemia are independent predictors of major hemorrhage [39].

The highest percentage of DRPs was found among patients who received acenocoumarol, in agreement with the results of another study in which AVK was the most prominently reported for medication errors involving oral anticoagulants (81.5%) [40]. This result has also been observed in a Palestinian study in which warfarin was among the drugs causing the most frequent DRPs [41]. For patients taking acenocoumarol, the high frequency of DRPs may be associated with inappropriate monitoring started at home, because the INR value on the day of admission was not within the therapeutic range. A study has confirmed the difficulty in maintaining AVK dose within the therapeutic range, as measured by the INR [42], because of its narrow therapeutic index, inter- and intra-individual variability, and environmental and genetic factors [43]. However, dose nonconformity among NOACs is mainly due to the presence of renal disease [12, 18]. Acenocoumarol requires monitoring of the INR, particularly in the presence of bridging and intake of other medications that lead to fluctuations in INR levels. Notably, as reported in the literature, the most drug–drug interactions were observed with PPIs, statins, antibiotics, and

parenteral anticoagulants [20]. In a previous study [44] evaluating the appropriateness of direct oral anticoagulants prescribed to adult patients, 32.4% of the total doses administered were considered inappropriate. In our study, the percentage of DRPs associated with doses either too high or too low was 26.7% and 15.5%, respectively.

Regarding the use of NOACs, few DRPs were seen in cases with no need for drug monitoring. A study has shown that all NOACs are at least noninferior (and in some cases superior) to warfarin. Beyond their high efficacy, NOACs have been reported to have a better safety profile and to provide the additional advantage of eliminating the requirement for regular coagulation monitoring [7]. Thus, a more appropriate combination of drugs was observed with NOACs, even though the main interactions were with amiodarone and verapamil, as confirmed by other studies [45]. Although this article is the first of its kind in Lebanon, this study has some limitations. First, this was a single-center study. Thus, our results cannot be generalized to the entire Lebanese population. Second, although the minimum sample size required was met, the statistical power was insufficient for subgroup analysis. Third, we did not follow up patients to assess ADEs, and DRPs were only described, but interventions were not performed. Finally, the evaluation of appropriateness might be a matter for further discussion, particularly in cases in which no international consensus exists.

5 Conclusion

NOAC use in CVD is a great step forward, because these drugs are associated with fewer DRPs and confer major advantages over acenocoumarol in improving clinical outcomes. However, whether acenocoumarol or one of its new alternatives should be prescribed remains a challenging decision for physicians. DRPs in general hospitals are frequent, serious, and predictable. Because a perfect anticoagulant does not exist, treatment decisions are based on the risks and benefits in each situation. Thus, decision-makers should consider regular, systematic medication reviews to maintain high quality treatment in older patients expected to benefit from avoiding DRPs in hospital admissions.

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Data Availability The data that support the findings of this study are available from the corresponding author, AAH, upon reasonable request.

Declarations

Conflicts of Interest The authors declare that there are no conflicts of interest.

Ethical Standard The study protocol was approved by the Clinical Research Department at the Lebanese University School of Pharmacy and was authorized by the Clinical Research Unit in the hospital.

Consent to Publication Not applicable.

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