

Community pharmacists' knowledge of direct oral anticoagulants and warfarin in the North of Jordan: a cross sectional study

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Abstract. – OBJECTIVE: The aim of this cross-sectional study is to assess community pharmacists' knowledge of the therapeutic aspects of direct oral anticoagulants and warfarin. Another objective was to study the effect of different demographic factors and relevant characteristics on community pharmacists' knowledge of warfarin and direct oral anticoagulants.

MATERIALS AND METHODS: The study was conducted prospectively at community pharmacies in the north of Jordan. Community pharmacists were interviewed using a validated questionnaire consisting of three sections. The first section included demographics and other relevant characteristics. The second and third sections included questions about direct oral anticoagulants and warfarin respectively.

RESULTS: A total of 251 participants completed the questionnaire. Two-thirds of participants knew that direct oral anticoagulants are available in Jordan (67.3%). Of the pharmacists who were able to state at least one direct oral anticoagulant, 60.9% knew at least one main indication. More than half of participating pharmacists had insufficient knowledge (57.8%). Almost half of participants (48.6%) were able to state the most important monitoring parameter of warfarin, and 30.7% were able to state one medication that interacts with warfarin. More than half of participating pharmacists had insufficient knowledge (64.9%). In addition, the results showed that degree of pharmacy, years of experience, university from which pharmacy degree was obtained, and year of graduation were significantly associated with warfarin knowledge.

CONCLUSIONS: Most participating pharmacists had insufficient knowledge with regards to direct oral anticoagulants and warfarin. Doctor of Pharmacy degree were more knowledgeable with regards to warfarin compared to participants with a bachelor's degree in Pharmacy. Continuing educational programs are required to keep community pharmacists up to date with new developments in the pharmaceutical field.

Key Words:

Community pharmacists, Direct oral anticoagulants, Jordan, Knowledge, Warfarin.

Introduction

Oral anticoagulants are widely used for the prevention and treatment of various types of thromboembolic diseases¹. Oral anticoagulants include warfarin and the new direct oral anticoagulants (DOACs)². DOACs include direct thrombin inhibitors, such as dabigatran, and factor Xa inhibitors, such as apixaban, rivaroxaban, and edoxaban³.

Numerous studies were conducted to compare between DOACs and warfarin in different clinical indications⁴⁻⁸. Warfarin has a number of important practical limitations such as slow onset of action, unpredictable pharmacokinetics and pharmacodynamics, numerous food and drug interactions, a narrow therapeutic window, and frequent monitoring. In comparison, DOACs lack many of these limitations³⁻⁹. Nevertheless, DOACs have major drug-drug interactions and special dosing considerations in patients with renal insufficiency¹⁰.

While DOACs are becoming more common in clinical practices, knowledge among physicians, pharmacists, and patients is suboptimal and inadequate¹¹⁻¹⁴. Healthcare providers in general and pharmacists specifically need to become familiar with the mechanism of action, dosing, administration, and other clinical aspects of the new DOACs in order to provide patients with the best pharmaceutical care.

In Jordan, warfarin has been the most commonly used anticoagulant. Recently, dabigatran, rivaroxaban, and apixaban have become available in Jordan¹⁵. Community pharmacists are the

most accessible healthcare providers in Jordan; they play an important role in counselling patients about their prescribed oral anticoagulants to ensure safety and efficacy. To the best of the researchers' knowledge, no previous studies have been conducted in Jordan to investigate the knowledge of community pharmacists with regards to warfarin and DOACs.

The objectives of the current study were to assess the knowledge of community pharmacists regarding DOACs side effects and other related aspects in addition to assessing the knowledge of community pharmacists regarding warfarin drug and food interactions, monitoring parameters, and other related aspects. Another objective was to study the effect of different demographic factors and relevant characteristics of participating pharmacists including the universities where they obtained their pharmacy qualification, year of graduation, and years of experience on the level of their knowledge of DOACs and warfarin.

Materials and Methods

This was a cross-sectional questionnaire-based observational study. The study protocol was approved by the Jordan University of Science and Technology Institutional Review Board (Research Number 28/124/2019) on May 21, 2019. Written informed consent was obtained from all individual participants included in the study.

The study was conducted prospectively at convenience sample of community pharmacies in the north of Jordan (Irbid, Jarash, Al-Ramtha, Ajloun, and Al-Mafraq). Community pharmacists during their working shifts were invited to participate in the study. Those who agreed to participate had the research goals and methods explained to them. The inclusion criteria were community pharmacists working in the north of Jordan and agreeing to participate in the study. The study excluded pharmacy support staff.

An anticoagulation knowledge tool (AKT) that was developed and validated by Obamiro et al¹⁶ was used to interview participating pharmacists after taking permission from the authors. The tool was checked for face validity in its original language (English) by specialists (four clinical pharmacists and two physicians), and minor modifications were made. To improve clarity and limit response bias, the questionnaire was piloted on a small sample ($n = 10$) after which necessary minor modifications were made. Examples of mod-

ifications included adding a question about the availability of DOACs in Jordan and what conditions or drugs are considered contraindications to DOACs use. In addition, a question about the most important monitoring parameters of warfarin was added. The results of the pilot study were included in the final analysis.

The tool consisted of three sections with open-ended and close-ended questions. The first section included demographic questions and other relevant characteristics such as years of experience, place of work, and university of graduation. The second section consisted of 21 items assessing the anticoagulation knowledge for available DOACs in Jordan, for example, their indications, mechanism of action, contraindications, and side effects. The term new oral anticoagulants was used in the questionnaire to refer to DOACs. The third section consisted of eight questions specific to warfarin therapy, for example, warfarin monitoring, target INR, and drug and food interactions.

One mark was allocated for each correct answer and zero for each wrong answer. Exceptions in the second section were for the question naming DOACs, where one mark was allocated for each answer of the three available DOACs in Jordan. Of note, scientific or brand names of DOACs were considered correct answers. In addition, for the two questions concerning the signs of side effects and approaches used to reduce the risk of bleeding, one mark was allocated for each correct sign of side effects (three signs were required) and each correct approach to reduce the risk of bleeding (three approaches were required). Exceptions in the third sections concerned drug and food interactions of warfarin. For example, one mark was allocated for each correct medication that interacts with warfarin (three correct medications were required) and one mark was allocated for each correct food substance (three correct food substances were required). Half a mark was allocated for less specific or general correct answers for all answers in the second and third sections.

The total score for a correct answered questionnaire was 27 marks for the second section and 13 marks for the third section. For the second section, a score equal or less than 13.5 means that the participants have insufficient knowledge. For the third section, a score equal or less than 6.5 means that the participants have insufficient knowledge.

A clinical pharmacy master student, with a Doctor of Pharmacy background, who was trained to conduct interviews and administer

questionnaires, conducted face-to-face structured interviews.

The Statistical Package for Social Sciences (SPSS, version 25.0) software was used to analyze the data. Descriptive statistics were computed to describe all the items of the questionnaire; mean and standard deviation were used for continuous variables while frequency and percent were used for categorical ones. The total score for each question about knowledge was the dependent (outcome) variables in the study. A multiple linear regression model was used to assess the association of various predictor variables. A one way ANOVA analysis model was used to determine whether there were any statistically significant differences between the means of three or more independent (unrelated) groups. A p -value < 0.05 (two-sided) was considered as statistically significant.

Results

A total of 251 participants were recruited with a response rate of 97.6%. Data collection took place from January to February 2020. Each interview duration was about fifteen minutes. The mean age of participants was 33.12 ± 11.73 years. The majority of pharmacists held a bachelor's degree in Pharmacy (75.7%) and about one quarter held a Doctor of Pharmacy degree (22.3%) while 5 participants (2%) held graduate degrees in pharmacy. Forty-six participants (18.3%) were with experience less than or equal one year and twenty-six participants (10.6%) were with experience equal to 42 years or more. Thirty-six participants (14.3%) graduated before 2000, forty participants (16%) graduated between 2001 and 2010 and about two-thirds (68.5%) graduated after 2011.

With regards to knowledge about DOACs, two-thirds of participants knew that DOACs are available in Jordan (67.3%). When participants were asked the names of DOACs available in Jordan, 37.8% did not know any DOACs and 15.9%, 8.4%, and 1.2% knew one agent, two agents, or three agents, respectively. Wrong answers included clopidogrel, warfarin, heparin, aspirin, enoxaparin, ticagrelor, tinzaparin, nitrate, prasugrel, dipyridamole, valproic acid, and escitalopram. A total of 64 out of 251 (25.5 %) knew at least one correct agent of DOACs. Of note, participants who failed to state at least one DOACs or named incorrect agents as DOACs were excluded from the rest of the questions pertaining to DOACs.

Table I lists participants' knowledge of indications, mechanisms of action, and administration related issues of DOACs. Of the 64 pharmacists who knew at least one DOACs, 39 pharmacists (60.9%) knew at least one main indication of DOACs. Main indications include venous thromboembolism treatment, prevention of stroke, and systemic embolism related to atrial fibrillation. Fifteen participants (23.4%) gave other less specific answers such as myocardial infarction (MI), coronary artery bypass grafting (CABG), prevention of clot formation, and anticoagulant in case of percutaneous coronary intervention (PCI) with stenting. Four pharmacists (6.3%) stated incorrect indications of DOACs. Incorrect answers of DOACs indications included hypertension, aspirin allergy, damage, destruction or lysis of thrombosis, and heart failure.

With regards to participants' knowledge of the mechanism of action of DOACs, nine pharmacists (14.1%) stated specific and correct answers, for example, direct thrombin inhibitors or FXa inhibitors. In contrast, twenty-three pharmacists (35.9%) had less specific correct answers which included preventing clotting, inhibiting coagulation factor, and anticoagulant. However, six pharmacists (9.4%) stated incorrect answers such as dissolving thrombosis, antiplatelet, and clot lysis.

Twenty-three pharmacists (35.9%) stated that if DOACs were not taken as prescribed by the doctor, they would increase the risk of bleeding and thrombosis, which was considered as a specific correct answer. On the other hand, a quarter of participants (25%) stated that DOACs should be taken as prescribed by physicians because they are dangerous drugs, have safety and efficacy issues, and have drug or food interactions which were all considered as general correct answers. However, 12.5% of participants believed that the main reasons to take DOACs as prescribed by doctors might be related to monitoring, dose adjustment, adjustment of the INR, half-life of the drug, and avoiding abortion. About a quarter of participants (26.6%) did not know the main reason why DOACs should be taken exactly as prescribed by the doctor.

Table II shows participants' knowledge of drug interactions, contraindications, precautions, adverse effects, and other related issues of DOACs. Twenty-four pharmacists (37.5%) stated that bleeding was the most important contraindication of DOACs. Moreover, fourteen pharmacists (21.9%) stated that they did not know the contraindications of DOACs.

Table I. Participants' knowledge of indications, mechanisms of action, and administration related issues of direct oral anticoagulants (N = 64).

Question	N (%)
What are the indications for these medications?	
Main indication(s)	39 (60.9)
Other less specific indication(s)	15 (23.4)
Incorrect answer(s)	4 (6.3)
Correct and incorrect answers	3 (4.7)
Do not know	3 (4.7)
How do these medications work in the body?	
Accurate correct answer(s)	9 (14.1)
Other less specific correct answer(s)	23 (35.9)
Incorrect answer(s)	6 (9.4)
Do not know	26 (40.6)
How many times a day they should be administered?	
Accurate correct answer	19 (29.7)
General correct answer	42 (65.6)
Incorrect answer	1 (1.6)
Do not know	2 (3.1)
For how long they should be taken (for example, 3 months, and 6 months, lifelong)?	
Accurate correct answer	18 (28.1)
General correct answer	42 (65.6)
Incorrect answer	1 (1.6)
Do not know	3 (4.7)
Why is it important to take these medications exactly as prescribed by the doctor?	
Main correct reasons	23 (35.9)
Other less specific correct reasons	16 (25)
Incorrect answer(s)	8 (12.5)
Do not know	17 (26.6)
Is it acceptable to take these medications at different times as long as they are taken on the required day?	
Yes	2 (3.1)
No	61 (95.3)
Do not know	1 (1.6)
Is it acceptable to double the next dose of these medications were missed?	
Yes	9 (14.1)
No	52 (81.3)
Do not know	3 (4.7)
Is it possible that skipping one dose of these medications could worsen patient's condition?	
Yes	43 (67.2)
No	18 (28.1)
Do not know	3 (4.7)
Is it appropriate to stop taking these medications once the patients feel better?	
Yes	2 (3.1)
No	60 (93.8)
Do not know	2 (3.1)
Is it safe to take anti-inflammatory medicines like ibuprofen while patients are taking these medications?	
Yes	19 (29.7)
No	36 (56.3)
Do not know	9 (14.1)

DOAGs = Direct oral anticoagulants.

With regards to the scores of completed questionnaires related to DOAC knowledge, the re-

sults showed that the mean score for participants was 12.76 ± 3.84 out of 27 points. More than half

of participating pharmacists (57.8%) had insufficient knowledge.

Table III shows the knowledge of community pharmacists about warfarin. When participants were asked about the most important monitoring parameter of warfarin, almost half of participants

(n = 122, 48.6%) answered correctly. In contrast, thirty-five pharmacists (13.9%) stated kidney function, lipid profile, warfarin level, vitamin K level, blood pressure, complete blood count, and potassium level were the most important monitoring parameters of warfarin.

Table II. Participants' knowledge of drug interactions, contraindications, precautions, adverse effects and other related issues of direct oral anticoagulants (N = 64).

Question	N (%)
Is safe to take vitamins supplements and herbal medicines with these medications?	
Yes	22 (34.4)
No	27 (42.2)
Do not know	15 (23.4)
Mention a contraindication (conditions or drugs) for these medications?	
Bleeding	24 (37.5)
Other correct contraindications	25 (39.1)
Incorrect answer	1 (1.6)
Do not know	14 (21.9)
Will drinking too much alcohol increase the risk of side effects with these medications?	
Yes	55 (85.9)
No	1 (1.6)
Do not know	8 (15.5)
Is it necessary to inform a surgeon, dentist, or other health professional that patients are taking these medications before undergoing surgery or a procedure?	
Yes	60 (93.8)
No	0 (0.0)
Do not know	4 (6.3)
Is it important that all the health care practitioners know that a patient is taking these medications?	
Yes	60 (93.8)
No	0 (0.0)
Do not know	4 (6.3)
What is the most important side effect of these medications?	
Hemorrhage	42 (65.6)
Incorrect answers	12 (18.8)
Do not know	10 (15.6)
Three signs of side effects that patients should watch out while taking this medication?	
One correct sign of side effect	18 (28.1)
Two correct signs of side effects	11 (17.2)
Three correct signs of side effects	6 (9.4)
Incorrect answer	21 (32.8)
Do not know	8 (12.5)
Three things patients can do to reduce risk of side effects?	
One correct approach to reduce side effects	23 (35.9)
Two correct approaches to reduce side effects	4 (6.3)
Three correct approaches to reduce side effects	1 (1.6)
Incorrect answer	11 (17.2)
Do not know	25 (39.1)
What is the best step to take if a patient accidentally took too much of these medications?	
Refer to doctor or emergency department	43 (67.2)
Incorrect answer	18 (28.1)
Do not know	3 (4.7)

DOAGs = Direct oral anticoagulants.

Most community pharmacists stated that diet could affect warfarin therapy (74.9%). However, more than a quarter of participants (27.1%) did not know what type of diet could affect warfarin therapy and 9% stated incorrect types of food such as red meat, dairy products, legumes, fatty food, and carrots.

The results showed that ninety-two pharmacists (36.7%) knew that vitamin K can significantly affect anticoagulant therapy. Moreover, fifty-one (20.3%) participants stated wrong answers. Examples of wrong answers included vitamin E,

vitamin C, vitamin D, vitamin B12 injection, vitamin B-complex, and lipid soluble vitamins. Of the 20.3%, some participants considered some supplements such as green tea, garlic, ginseng, calcium, and magnesium as vitamins that can significantly affect warfarin therapy.

With regards to the scores of completed questionnaires related to warfarin knowledge, the results showed that the mean score for participants was 4.70 ± 3.26 out of 13. More than half of participating pharmacists (64.9%) had insufficient knowledge.

Table III. Community pharmacists' knowledge about warfarin (N = 251).

Question	N (%)
Q1: Mention the most important monitoring parameter for warfarin?	
INR	122 (48.6)
Other monitoring parameter	12 (4.8)
Incorrect answer	35 (13.9)
Do not know	72 (28.7)
Missing	10 (3.9)
Q2: What is the target INR range?	
Most common target INR (2-3) or 2.5	36 (14.3)
Other correct answer	62 (24.7)
Incorrect answer	48 (19.1)
Do not know	105 (41.8)
Q5: Is it possible for INR values below the target range to be bad for health?	
Yes	150 (59.8)
No	14 (5.6)
Do not know	87 (34.7)
Q6: List three medications that interact with warfarin in your pharmacy?	
One medication	77 (30.7)
Two medications	25 (10.0)
Three medications	21 (8.4)
Wrong answer	10 (4.0)
Do not know	118 (47.0)
Q7a: Is it possible for diet to affect warfarin therapy?	
Yes	188 (74.9)
No	16 (6.4)
Do not know	47 (18.7)
Q7b: If you answered "Yes" above, list three foods that can affect anticoagulant therapy (n = 188)	
One type of food	86 (45.7)
Two types of food	8 (4.3)
Three types of food	23 (12.2)
Incorrect answer	17 (9.0)
Right and wrong answers	3 (1.6)
Do not know	51 (27.1)
Q8: List one vitamin that can significantly affect anticoagulant therapy in your pharmacy?	
Vitamin K	92 (36.7)
Wrong answer	51 (20.3)
Right and wrong answers	2 (0.8)
Do not know	106 (42.2)

INR: International normalized ratio; PT: Prothrombin time.

The results of the multiple linear regression models showed no statistically significant association was found between other variables and knowledge of DOACs. However, degree of pharmacy, years of experience, university from which pharmacy degree was obtained, and year of graduation were significantly associated with warfarin knowledge (p -value < 0.05). For example, the results showed that participants who held a Doctor of Pharmacy degree were more knowledgeable compared to participants with a bachelor's degree in Pharmacy (p -value < 0.05). Also, the results showed that participants with experience less than or equal one year and participants with experience equal to 42 years or more did not have sufficient knowledge compared to other groups (p -value < 0.05). Additionally, the results showed that participants graduating after 2011 were more knowledgeable than those graduating before the year 2000 (p -value < 0.05).

Discussion

The current study showed that a significant proportion of the respondents did not know about the availability of DOACs in the Jordanian market. Moreover, the knowledge of respondents who were aware of the availability of DOACs in the Jordanian market was inadequate. This finding is of major significance based on the fact that DOACs are relatively new in clinical practice and community pharmacists are considered a main source of drug information especially since community pharmacists in Jordan are easily accessible and can provide free patient education services. Moreover, the study found an inadequate knowledge level with regards to warfarin. Warfarin is a narrow therapeutic index medication with numerous drug and food interactions³. The inadequate knowledge of pharmacists with regards to warfarin could have a detrimental effect on patients who rely on pharmacists as their source of drug information. To the best of the researchers' knowledge, this study was the first study to assess the knowledge among community pharmacists about warfarin and DOACs in Jordan.

The results of the current study were in concordance with previously published studies¹⁷⁻¹⁹. In Canada, an online questionnaire was distributed to different healthcare providers including pharmacists to assess their knowledge of DOACs. Fifteen pharmacists (35.7%) correctly stated all indications of oral anticoagulants¹⁷. In comparison,

39 pharmacists (60.9%) in the current study knew at least one main indication of DOACs. Incorrect indications for DOACs stated by healthcare providers in the Canadian study included heparin-induced thrombocytopenia, cerebral sinus venous thrombosis, or mechanical prosthetic valves¹⁷. In contrast, incorrect indications stated by community pharmacists in the current study included hypertension, aspirin allergy, damage, destruction or lysis of thrombosis, and heart failure.

In Qatar, a cross-sectional study¹⁸ was conducted to assess hospital and community pharmacists' knowledge of DOACs using an online questionnaire. The percentage awareness score was highest for awareness on counselling and lowest for awareness on efficacy. Interestingly, the age of participants and years of experience did not affect their percentage awareness score¹⁸. This was consistent with the results of our study where participants' age and years of experience did not significantly affect their knowledge. Another study was conducted in Scotland to assess the awareness of DOAC safety issues. The participants included pharmacist independent prescribers among other health care providers. The results of the aforementioned study showed rivaroxaban was the most identified DOAC (88%) by participants followed by dabigatran (80%) and apixaban (50%)¹⁹. In comparison, 67.3% of participants in the current study knew that DOACs are available in the market and of these only 1.2% were able to identify the three agents. This difference can be attributed to the different settings where Olaiya et al¹⁹ included both primary and secondary care settings and included other healthcare providers including medical and surgical specialists.

With regards to warfarin, the results of the current study presented that pharmacists had insufficient knowledge with regards to the anticoagulant warfarin. A number of studies were conducted to assess healthcare providers' knowledge of warfarin and warfarin therapy related aspects²⁰⁻²². In Saudi Arabia, a survey-based cross-sectional study was conducted to evaluate both community and hospital pharmacists' knowledge of warfarin. The results of the Saudi study showed that 41.1% of community pharmacists answered the target INR question correctly compared to the current study in which 14.3% of participants identified the most common target of INR and 24.7% stated other less commonly used INR targets²⁰. Another study was conducted in Saudi Arabia by Al-Arifi et al²¹ to investigate the knowledge of different healthcare providers including physicians, nurs-

es, and pharmacists with regards to warfarin and herbal interactions. The results found that 83.9% of pharmacists who participated in the study stated the correct answer concerning the interaction between aspirin and warfarin. In addition, 22.6% of participating pharmacists stated the correct answer with regards to multivitamin supplements interaction with warfarin²¹. In comparison with the current study, almost half of participants (47.0%) were not able to identify a medication that interacts with warfarin and less than one third (30.7%) were able to state one medication that interacts with warfarin. The differences in results between the two studies can be attributed to the fact that in the current study open ended questions were used compared to closed ended questions used in the Al-Arifi et al²¹ study. In addition, a hospital setting was investigated by Al-Arifi et al²¹ compared to a community setting in the current study.

Interestingly, the results of the current study showed that participants who held a Doctor of Pharmacy degree were more knowledgeable with regards to warfarin compared to participants with a bachelor's degree in Pharmacy. This indicates that practical and clinical courses provided through the Doctor of Pharmacy curriculum resulted in pharmacists being more knowledgeable in aspects related to patient counseling and providing drug information services to patients. In addition, the results showed that participants graduating after 2011 were more knowledgeable than those graduating before the year 2000; this highlights the need for continuing education programs. Such programs can be provided by the Jordanian Pharmacists Association in collaboration with colleges of pharmacy in different Jordanian universities. Continuing education programs and courses are expected to keep community pharmacists up to date with new developments in the pharmaceutical field and revise and refresh drug information they already have. Furthermore, license renewal should be conditional upon receiving continuing education; such a step would motivate community pharmacists to be involved in continuing education programs.

The current study has a number of limitations. For example, it was conducted in the north of Jordan, thus the results might not be generalizable to other areas. In addition, participants' responses may have been subjected to social desirability bias. Moreover, the environment of some community pharmacies restricted the interviewing time between the researcher and participants, thus limiting the information exchange process. Some of

the participating pharmacists did not understand what was meant by some questions in English which led to their translation into the Arabic language.

Conclusions

Most participating pharmacists had insufficient knowledge with regards to DOACs and warfarin. Insufficient knowledge areas concerning DOACs included agents' names, their mechanism of action, and main contraindications. Examples of insufficient knowledge areas concerning warfarin were target INR level and the ability to state more than one example of drug and food interactions with warfarin. This is an alarming finding that could reduce the chance of patients receiving proper counseling which could increase the risk of side effects and complications and decrease efficacy. Therefore, it is recommended to implement continuing education programs for community pharmacists.

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Conflicts of Interest

The authors declare no conflicts of interest.

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