

Assessment of community pharmacists' knowledge about utilization, safety, and interactions of commonly prescribed anticoagulants: A report from North West of Iran

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Abstract:

Anticoagulants are used to treat different thrombotic conditions, and patients should be educated on administration, safety, and adverse reactions associated with their medication to achieve the optimum therapeutic effect. Pharmacists are an essential part of providing pharmaceutical care and a reliable source of information for patients; therefore, their knowledge of medications must be up-to-date. This study aimed to assess Urmia's community pharmacists' knowledge about the utilization, safety, and interactions of commonly prescribed anticoagulants.

This questionnaire-based cross-sectional study was conducted from September 1st, 2020, to February 31st, 2021, in Urmia, Iran. A 35-item questionnaire was designed based on previous studies and researchers' experience. The questionnaire was validated, and its final version was presented to randomly selected community pharmacists in Urmia. Filled-out forms were collected and analyzed in the context of three main areas of safety, adverse reactions, and administration.

Ninety-five participants filled out the questionnaire, for whom a mean score of 16.53 ± 4.56 was calculated. Out of 95 pharmacists, only 30 scored $\geq 50\%$ correct answers. No significant correlation was observed between age, years of employment, and pharmacists' competency in correctly answering the questions (p -value > 0.05). The participants' overall knowledge was more reliable for warfarin than for enoxaparin and DOACs, with a p -value < 0.001 .

The results of this study suggest a lack of sufficient knowledge among Urmia's community pharmacists concerning commonly prescribed anticoagulants. This puts patients at risk for therapy complications and should be addressed accordingly.

Keywords: Anticoagulant; community pharmacist; knowledge; safety; utilization; questionnaire.

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1. Introduction

Anticoagulants are the mainstay for treating thromboembolic conditions such as deep vein thrombosis (DVT), pulmonary embolism (PE), and preventing clot formation caused by atrial fibrillation or arrhythmia [1]. Warfarin and enoxaparin have been

Iran's most commonly prescribed anticoagulants for many years. However, newer agents such as rivaroxaban and apixaban - direct oral anticoagulants (DOACs)- seem to be taking warfarin's place in prescriptions in recent years [2, 3].

Failure in achieving optimum anticoagulation leads to serious complications due to blood clot expansion and

embolism. On the other hand, over-anticoagulation may result in bleeding. Both deviations from optimum therapy increase morbidity and mortality [4]. Considering the many factors that affect the dose and efficacy of these medications (such as drug, food, and vitamins interactions), patients should be educated by pharmacists and/or physicians on how to use these medications properly. [5, 6]. Compared with sole physician management, pharmacist collaboration in anticoagulation management has been associated with reduced adverse outcomes (such as thrombosis or bleeding), improved patient satisfaction and quality of life, and decreased healthcare costs [7]. In light of this observation, specialty pharmacist-led anticoagulation clinics have been established in some countries, such as Iran [8-10]. Since pharmacists are highly trained about the pharmacological properties of medications, they play a crucial role in providing advice on anticoagulant administration [11].

The present study aimed to assess the community pharmacists' knowledge about the utilization, safety, and interactions of enoxaparin, warfarin, rivaroxaban, and apixaban, in Urmia, Iran, as well as to re-evaluate local data about pharmacy practice, which is necessary for implementing and renewing educational policy and further conductors.

2. Materials & Methods

This cross-sectional study was carried out from September 1st, 2020, to February 31st, 2021 (6 months) on the practicing community pharmacists in Urmia, West Azerbaijan, Iran. The Ethics Committee for Human Research at Urmia University of Medical Sciences approved the study with the registration number of IR.UMSU.REC.1399.126.

1.1. Study protocol and measured outcomes

In this study, we aimed to evaluate knowledge of pharmacists about the pharmaceutical properties of anticoagulants that are prescribed mostly for outpatients.

Two pharmacotherapy specialists prepared a questionnaire that contained 35 questions based on drug monographs [12, 13], ACCP¹'s guideline on "antithrombotic therapy for venous thromboembolism" [4], "guide on the use of non-vitamin K antagonist oral" from EHRA² [5], "previous studies", and "researchers' clinical experience".

The questions covered three domains: medication safety, administration, and food or drug-drug interaction (question numbers 26, 3, and 6, respectively). The questions were about the available and most commonly prescribed anticoagulants for outpatients, including warfarin, rivaroxaban, apixaban, and enoxaparin.

The content validity and reliability of the questionnaire were evaluated by seven experts (two internal medicine specialists, one cardiologist, and four pharmacotherapy specialists). The content validity index (CVI) of each question was equal to or more than 85.71% indicating good content validity of the questionnaire. Therefore, all questions were necessary to be included in the survey context. The approved version of the questionnaire was filled out by 30 pharmacists chosen randomly to examine internal consistency; Cronbach's alpha for all domains of the questionnaire was 0.76, which shows a good and acceptable internal consistency [14].

To calculate each participant's score, 1 point was assigned to each correct answer and zero to incorrect or "I don't know the correct answer", with a total score of 35. The correct answer percentage for each participant was calculated using the following equation and was considered the participant's competency marker.

$$(Total\ number\ of\ correct\ answer/35) * 100$$

2.2. Study design and population

The randomization method in the current study was a m age and duration of practice in sampling. In the first stage, the drugstores were listed in five districts of Urmia. In the second stage based on the number of stores in each region, 95 pharmacies were randomly selected.

Attending to the selected pharmacies, a well-trained pharmacist of the study team interviewed the participants face-to-face, explained the study's purpose, and asked the participants to fill in the questionnaire. In addition, demographic data, duration of practicing as a pharmacist, and the pharmacy school from which the participants had graduated were all recorded. Incompletely filled questionnaires were excluded.

2.3. Sample size calculation and statistical analysis

The sample size was estimated using an online calculator [15] yielding a sample size of 90 participants (assuming a 50% response rate, 10% dropout, study power of 80%, and 10% significance). The total count of active pharmacies in Urmia city was 145 in August 2020. A cluster sampling technique was used to randomly select 95 out of the 145 pharmacies in five city districts.

The SPSS software version 21 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Kolmogorov-Smirnov test was used to assess the normality of data. Continuous and categorical values were reported as mean \pm SD and frequency (percentage) and or median (interquartile range), respectively. ANOVA and independent t-test were used to compare quantitative data between different anticoagulants. The correlation of nonparametric and parametric data was shown by Spearman and Pearson, which was used to check for the effect of age, sex, and duration of practice on correct response and for total score. A p-value ≤ 0.05 was considered to be statistically significant.

1. American College of Chest Physicians
2. European Heart Rhythm Association

3. Results and Discussion

A total of 95 pharmacists (65.3% male) participated in this study. All the participants worked in community pharmacies. Median (min-max) age and duration of practice as a pharmacist were 39 (30-56) years and 14 (5-25) years, respectively. The demographic data of participants is shown in Table-1.

The correct response rate was 16.53 ± 4.56 out of 35 questions, and only 30 pharmacists (31.58%) responded correctly to at least half of the questions. The lowest and highest scores were 17% (3 subjects) and 77% (1 participant) out of 35, respectively. The participants' total score by anticoagulant and their responses to survey items can be found in Table-2 and Table-3, respectively.

There was no significant correlation between age, sex and duration of practice, and total questionnaire score (p-value: 0.23, 0.34, 0.17; r: -0.08, 0.08, 0.09, respectively). There was no significant difference in the knowledge domain's score between participants with more than ten years of practice experience and less than ten years experience, despite a great gap in the mean duration of practice between the two groups. A significant difference in knowledge of warfarin, enoxaparin, and DOACs was observed between-groups (p-value:0.001). No difference was observed between apixaban and rivaroxaban (p-value:0.23).

Pharmacists play an essential role in the health care system, providing medication counseling at the pharmacy counter. *Pharmaceutical care* is defined as "a direct, responsible provision of medication-related care to achieve definite outcomes that improve a patient's quality of life" [16]. As the last link in the medical care chain, the pharmacist is easily available and is frequently sought to give medical advice especially about medications [17]. Patient education is highly valued as a means to prevent treatment harm or failure and hence, a

face-to-face interaction with patients can be an ideal method if the community or hospital pharmacist is effectively incorporated into the process. [18, 19].

Anticoagulants are well-known for their potential of causing serious adverse reactions in patients; hence, the need for effective patient education and close follow-up [18, 19]. The present study evaluated the community pharmacist's knowledge and attitude about more commonly prescribed anticoagulants for outpatients.

In our study, we observed a significantly low level of knowledge about anticoagulants, especially the newer ones (DOACs). Only one-third of our study population correctly answered at least half the questions.

Although a long time has passed since enoxaparin was introduced to Iran's pharmaceutical market, it is mostly prescribed for the inpatient population, so pharmacists practicing in community pharmacies have little practical experience with this medication. This was confirmed in our study, as participants' scores were higher in warfarin-related questions ($60.23\% \pm 16.41\%$) compared with DOACs and enoxaparin questions (rivaroxaban $43.51\% \pm 15.02\%$, apixaban $38.13\% \pm 18.88\%$, enoxaparin $39.85\% \pm 19.31\%$, $p=0.001$).

El-bardisi et al. reported a similar result in Qatar with the average awareness score of pharmacists being $41.6\% \pm 26.0\%$, with only 59 out of 211 participants (28%) being satisfied with their level of knowledge [20]. To our surprise, no correlation was observed between age and duration of practice with participants' knowledge scores. This means neither somewhat freshly out of school pharmacists, nor the experienced ones were satisfactorily qualified to counsel patients on anticoagulants. This result was again similar to what El-bardisi et al. have reported, as they also, did not detect a relation between age, practice duration and participants' scores [20].

Table 1: Demographic and professional characteristics of participants (n=95)

| | All participants | Practice years $\leq 10^\dagger$ | Practice years $>10^\dagger$ | p-value* |
|---|-----------------------|----------------------------------|------------------------------|----------|
| Sex (F/M) | 33/62 | 20/23 | 13/39 | |
| Age (years) median (min-max) | 39 (30-56) | 30 (24-49) | 55 (36-78) | 0.01 |
| Duration of practice (years) median (min-max) | 14 (5-25) | 4 (1-10) | 24.5 (12-45) | 0.00 |
| Correct-answer score (mean \pm SD) | 16.53 ± 4.56 | 16.09 ± 4.05 | 15.48 ± 4.93 | 0.44 |
| Correct-answer percentage (mean \pm SD) | $47.22\% \pm 13.03\%$ | $45.98\% \pm 11.58\%$ | $44.23\% \pm 14.08\%$ | 0.51 |
| Number of participants with $>50\%$ correct answers | 30 | 14 | 16 | |

† t-test and independent t-test were used to compare age, score, and practice years.

* p-value <0.05 is significant

Table 2. participants' knowledge in survey areas (n=95)

| Anticoagulant type | Correct-answer percentage (mean \pm SD) | p-value* | |
|--------------------|---|----------|-------|
| Enoxaparin | $39.85\% \pm 19.31\%$ | | 0.001 |
| Warfarin | $60.23\% \pm 16.41\%$ | 0.001 | 0.001 |
| DOAC | $40.81\% \pm 18.55\%$ | | |
| Rivaroxaban | $43.51\% \pm 18.02\%$ | | |
| Apixaban | $38.12\% \pm 18.88\%$ | | 0.23 |

† Abbreviations: Direct oral anticoagulant (DOAC), standard deviation (SD)

‡ ANOVA was used to compare subgroups.

* p-value <0.05 is significant.

Table 3. Participants' responses to 35 questions about anticoagulants usage and safety (n=95)

| Awareness of anticoagulant safety (n) | | | | | | | | | | | |
|---|-----|-----|-----|------------------------|-----|-----|-----|----------------------|-----|-----|-----|
| Agree Respondents | | | | Don't know Respondents | | | | Disagree Respondents | | | |
| RIV | APX | WAR | ENO | RIV | APX | WAR | ENO | RIV | APX | WAR | ENO |
| A specific antidote for each anticoagulant is available in Iran's pharmaceutical market | | | | | | | | | | | |
| 10 | 10 | 88 | 21 | 50 | 54 | 3 | 51 | 35 | 31 | 4 | 23 |
| This anticoagulant is contraindicated in patients with cancer for treating DVT, PTE, ... | | | | | | | | | | | |
| 6 | 9 | 9 | 3 | 48 | 46 | 47 | 48 | 41 | 40 | 39 | 44 |
| This anticoagulant is contraindicated in pregnancy for treating DVT, PE, ... | | | | | | | | | | | |
| 29 | 31 | 82 | 18 | 20 | 17 | 4 | 33 | 46 | 47 | 9 | 44 |
| This anticoagulant is contraindicated in patients with renal impairment (GFR<15ml/min) | | | | | | | | | | | |
| 51 | 46 | 23 | 29 | 30 | 34 | 30 | 30 | 14 | 15 | 42 | 36 |
| This anticoagulant is contraindicated in patients with severe hepatic insufficiency | | | | | | | | | | | |
| 46 | 42 | 21 | 27 | 23 | 35 | 30 | 33 | 16 | 18 | 44 | 35 |
| This anticoagulant is contraindicated in patients with a history of gastric ulcer | | | | | | | | | | | |
| 48 | 48 | 25 | 25 | 12 | 12 | 20 | 15 | 35 | 35 | 50 | 55 |
| Awareness of patient counselling (dispensing) considerations for oral anticoagulants | | | | | | | | | | | |
| RIV | APX | WAR | RIV | APX | WAR | RIV | APX | WAR | RIV | APX | WAR |
| Strong inducers of CYP 3A4 such as phenytoin and carbamazepine interact with this medication and should be avoided | | | | | | | | | | | |
| 75 | 70 | 88 | 10 | 14 | 3 | 10 | 11 | | | | 4 |
| Leafy green vegetables such as spinach interact with this anticoagulant | | | | | | | | | | | |
| 52 | 46 | 76 | 11 | 16 | 6 | 32 | 33 | | | | 13 |
| This anticoagulant has a specific consideration to be administered with meal | | | | | | | | | | | |
| 28 | 26 | 82 | 39 | 39 | 7 | 28 | 30 | | | | 6 |
| Awareness of patient counselling (dispensing) considerations for enoxaparin | | | | | | | | | | | |
| Enoxaparin should be injected subcutaneously into abdomen, except for the 5 cm area around your belly button | | | | | | | | | | | |
| | 37 | | | 29 | | | 29 | | | | |
| Should refer to doctor immediately if patient experiences ecchymosis, epistaxis or bleeding associated with anticoagulant | | | | | | | | | | | |
| | 92 | | | 3 | | | 0 | | | | |

Abbreviations: Rivaroxaban (RIV), Apixaban (APX), Warfarin (WAR), Enoxaparin (ENO), Deep vein thrombosis (DVT), Pulmonary embolism (PE).

Although we did not observe a desirable level of knowledge in our study population, Vakili et al. reported acceptable awareness about DOACs (64.94 ± 5.84%). This difference in results may be due to about one third of the mentioned study's population being non-community pharmacists, and the different contents of the questionnaire used [21]. On the other hand, our result was in line with Gadrđan et al., which asserted that pharmacist confidence level in providing pharmacy counseling on DOAC compared to warfarin and enoxaparin [22].

Considering our results and results from similar studies in Iran, it seems that lack of enough knowledge about anticoagulants in Iranian pharmacists is an issue to be kept in mind when planning and organizing for continuous medical education programs.

It has been observed that approximately 60 % of patients who use medications for the long term do not read the package insert, meaning the pharmacists serve as the primary source of information, especially on the correct administration and dose [23]. However, contrary to these ideal facts, a significant fraction of our participants (pharmacists themselves) were unaware of the correct route of enoxaparin injection and necessity of full stomach at the time of using rivaroxaban in doses ≥ 15 mg/day (score of 26.58% ± 14.11%) [24, 25] This puts the patient at significant risk of therapy harm and inefficiency.

4. Conclusion

This study showed that community pharmacist's knowledge on utilization, safety and interactions of commonly prescribed anticoagulants was non-satisfactory, with an average correct answer score of 16.58 ± 4.56 out of 35 questions. Considering the crucial role of pharmacists in providing patient counseling, it is essential to ensure their professional competence to promote good patient care.

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References

- Kim JH, Lim K-M, Gwak HS. New anticoagulants for the prevention and treatment of venous thromboembolism. *Biomolecules & therapeutics*. 2017;25(5):461.
- Lippi G, Mattiuzzi C, Cervellin G, Favaloro EJ. Direct oral anticoagulants: analysis of worldwide use and popularity using Google Trends. *Ann Transl Med*. 2017;5(16):322.
- Mazzolai L, Aboyans V, Ageno W, Agnelli G, Alatri A, Bauersachs R, et al. Diagnosis and management of acute deep vein

- thrombosis: a joint consensus document from the European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. *Eur Heart J*. 2018;39(47):4208-18.
4. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2):e44S-e88S.
 5. QuarterWatch (2016 Annual Report) [Last accessed on 2018 Oct 6]. Part II: Oral Anticoagulants—The Nation's Top Risk of Acute Injury from Drugs | Institute for Safe Medication Practices.
 6. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;39(16):1330-33.
 7. Witt DM, Clark NP, Kaatz S, Schnurr T, Ansell JE. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41(1):187-205.
 8. Entezari-Maleki T, Dousti S, Hamishehkar H, Gholami K. A systematic review on comparing 2 common models for management of warfarin therapy; pharmacist-led service versus usual medical care. *J Clin Pharmacol*. 2016;56(1):24-38.
 9. Tschol N, Lai D, Tilley JA, Wong H, Brown GR. Comparison of physician-and pharmacist-managed warfarin sodium treatment in open heart surgery patients. *The Canadian journal of cardiology*. 2003;19(12):1413-7.
 10. Fahimi F, Sharif-Kashani B, Hossein-Ahmadi Z, Salamzadeh J, Namdar R, Mousavi S, et al. The first pharmacist-based warfarin-monitoring service in Iran. *Journal of Pharmaceutical Health Services Research*. 2011;2(1):59-62.
 11. Elewa H, Jalali F, Khudair N, Hassaballah N, Abdelsamad O, Mohammed S. Evaluation of pharmacist-based compared to doctor-based anticoagulation management in Q atar. *Journal of evaluation in clinical practice*. 2016;22(3):433-8.
 12. Fuentes AV, Pineda MD, Venkata KCN. Comprehension of Top 200 Prescribed Drugs in the US as a Resource for Pharmacy Teaching, Training and Practice. *Pharmacy (Basel)*. 2018;6(2).
 13. Enoxaparin. In: Lexi-drugs online [database on the Internet]. Hudson (OH): Lexicomp, Inc.; 2021[updated 12 Sep 2020; cited 9 Apr 2020]. Available from: <http://online.lexi.com>. Subscription required to view. [Internet]. 2020.
 14. Rivaroxaban. In: Lexi-drugs online [database on the Internet]. Hudson (OH): Lexicomp, Inc.; 2021[updated 12 Sep 2020; cited 9 Apr 2020]. Available from: <http://online.lexi.com>. Subscription required to view. [Internet]. 2020.
 15. Cronbach LJ, Shavelson RJ. My current thoughts on coefficient alpha and successor procedures. *Educational and psychological measurement*. 2004;64(3):391-418.
 16. Ghaibi S, Ipema H, Gabay M. ASHP guidelines on the pharmacist's role in providing drug information. *American Journal of Health-System Pharmacy*. 2015;72(7):573-7.
 17. Burns A. Medication therapy management in pharmacy practice: core elements of an MTM service model (version 2.0). *Journal of the American Pharmacists Association*. 2008;48(3):341-53.
 18. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-52.
 19. Lip GY, Banerjee A, Boriani G, en Chiang C, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154(5):1121-201.
 20. Hawes EM. Patient Education on Oral Anticoagulation. *Pharmacy (Basel)*. 2018;6(2).
 21. Urlick BY, Meggs EV. Towards a greater professional standing: evolution of pharmacy practice and education, 1920–2020. *Pharmacy*. 2019;7(3):98.
 22. El-Bardissy A, Elewa H, Khalil A, Mekkawi W, Mohammed S, Kassem M, et al. Assessing Pharmacists Knowledge and Attitude Toward the Direct Oral Anticoagulants in Qatar. *Clin Appl Thromb Hemost*. 2020;26:1076029620933946.
 23. Mohamed AA, Alnewais ME, Ibrahim YA, Zaitoun MF. Pharmacists' warfarin therapy knowledge and counseling practices in the Eastern Province, Saudi Arabia: A cross-sectional study. *J Pharm Bioallied Sci*. 2020;12(3):289-94.
 24. Papastergiou J, Kheir N, Ladova K, Rydant S, De Rango F, Antoniou S, et al. Pharmacists' confidence when providing pharmaceutical care on anticoagulants, a multinational survey. *Int J Clin Pharm*. 2017;39(6):1282-90.
 25. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22):3317-59.
 26. Mueck W, Stampfuss J, Kubitz D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet*. 2014;53(1):1-16.
 27. Raynor D, Silcock J, Knapp P, Edmondson H. How do patients use medicine information leaflets in the UK? *International Journal of Pharmacy Practice*. 2007;15(3):209-18.