



## Research Article

# Efficacy and Safety of Warfarin Therapy: Comparison Between Specialized INR Clinic and General Medical Clinic

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### Abstract

**Background:** Although warfarin is known as effective oral anticoagulant to prevent thromboembolic events, its' narrow therapeutic index requires ambient and good follow-up to reduce its therapeutic complications. There is a continuous debate whether the best practice to accomplish this goal is in a specialized international normalized ratio clinic (INR-C) or in a general medical clinic (General-C). Few, if any, studies have been done in Sudan to compare the safety and efficacy of anticoagulant therapy in those clinics. Thus, the objective of this study was to compare the efficacy and safety of anticoagulant therapy in INR-C and in General-C.

**Methods:** This is a prospective hospital-based study where 200 patients were divided into two groups (group A and B) of 100 patients. Group A were in the INR-C at Ahmed Gasim specialized hospital and group B in the General-Cat AL-Shaab teaching hospital. The study was conducted from September 2019 to April 2020. All patients were on warfarin treatment and regular follow-ups were conducted. Demographic and clinical data were collected and analyzed statistically using SPSS version 20. Ethical approval was obtained from the ethical committee of the Sudanese Medical Specialization Board (SMSB).

**Results:** Of the 200 patients, 118/59% were females and 82/41% were males. Target international normalized ratio (INR) for group (A) was achieved in 56% of the patients in the first visit, increased to 63% in the second visit, and 75% in the third follow-up, compared with 24% of the patients from group (B) in the initial and second follow-up visit, to 43% in the third visit ( $P$  value=0.05). Knowledge about drug and food interaction of coagulation agents was higher (91%) among patients in group (A) compared with group (B) (56%). Drug interaction awareness was found in 89% of the patients in group (A) compared with only 40% in group (B) ( $P$  value=0.05).

Major bleeding was reported in 2% and 14% of the patients of group (A) and (B) respectively, whereas minor bleeding was seen in 4% of group (A) and 11% of group (B).

**Conclusion:** The study showed that INR-C is more efficient and safer for patients on regular warfarin therapy compared with the General-C.

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## 1. Introduction

Warfarin is an oral anticoagulant frequently used to control and prevent thromboembolic disorders [1]. Due to the diverse genetic profile of humans, the anticoagulant effect of warfarin must be monitored based on the international normalized ratio (INR) to ensure an accurate and safe dose of warfarin that is within the therapeutic range for each patient [2]. For the purposes of follow-up of patients on warfarin therapy, some authors favor specialized international normalized ratio clinics (INR-C) whereas others argue in favor of general medical clinics (General-C) that may very well achieve similar therapeutic outcomes [3,4]. The anticoagulant thrombosis center has high clinical and laboratory expertise which provides diagnosis, treatment, and follow-up of patients with thromboembolic events [5]. To achieve these goals, such clinics must provide patients with individualized anticoagulation education, management, and close follow-up to ensure that their INR values remain within the therapeutic goals by maintaining a therapeutic range (TTR) at or above 70% that is associated with clinical benefit in terms of efficacy and safety [6].

## 2. Material and Methods

This study is a cross-sectional prospective hospital-based study that includes 200 patients, all on warfarin therapy. Of those, 100 patients were recruited from the INR-C at Ahmed Gasim specialized hospital (group A), and the remaining 100 patients were from General-C at AL-Shaab teaching hospital (group B), from September 2019 to April 2020. The demographic and clinical data including INR was collected using a predesigned questionnaire. The ethical approval was obtained from the ethical committee of the Sudanese Medical Specialization Board (SMSB).

The data were analyzed using SPSS program version 20 and the results were expressed as mean  $\pm$  the standard deviation. Frequency count was done on the data and the result was reported as a percentage. The results were considered statistically significant if the *P* value < 0.05.

## 3. Results

The results of both groups revealed that 118 (59%) of the patients were females and 82 (41%) were males of which 32% were >60 years of age, 23% were between 50–60 years, 18.5% were between 40–49 years, and 26.5% were aged less than 40 years.

The results also showed that 119 (59.5%) patients were the inhabitants of Khartoum State, 40 (20%) patients were from central states, 24 (12%) patients were from western states, 13 (6.5%) patients from **eastern** states, and only 4 (2%) patients were from **Western** states.

Of the 200 patients included in the study, 144/72% were unemployed, 28/14% worked in manual labor, 14/7% were governmental employees, and 14/7% were from the private sector.

The indications for warfarin therapy of the patients of group (A) were mechanical heart valve replacement in 47%, atrial fibrillation in 28%, rheumatic heart disease in 13%, cardiomyopathy in 8%, pulmonary embolism in 3%, and deep vein thromboembolism in 1%. These indications were assigned for 17%, 29%, 31%, 17%, 3%, 4%, and 0% of the patients in group (B) respectively ( $P$  value=0.05: statistically significant difference).

Almost all patients (98%) from Ahmed Gasim specialized hospital were lifelong users of warfarin compared with (85%) of the patients at AL-Shaab teaching hospital.

The frequency of follow-up was monthly for 89% of the patients, weekly for 9%, and yearly for 2% of the patients in group (A) compared to 86%, 14%, and 0% of the patients in group (B) respectively ( $P$  value < 0.05: statistically significant difference).

Patient's knowledge about warfarin/food and warfarin/other medications interaction was reported by 91% and 89% of the patients in group (A) compared to 65% and 40% of the patients in group (B) respectively ( $P$  value < 0.05: statistically significant difference) (Table 1).

TABLE 1: The level of knowledge in INR-C (group A) and General-C (group B).

		Group	
		A	B
Knowledge about drug diet interaction	Yes	91	65
	No	9	35
Knowledge about medications that should not be used	Yes	89	40
	No	11	60

$P$  value = 0.014 < 0.05 significant

Major bleeding was reported in 2% of the patients attending the INR-C (group A), whereas 4% experienced minor bleeding. For those attending General-C (group B) 14% reported major bleeding and 11% experienced minor bleeding (Table 2).

First, second, and third INR targets were reached in 56%, 63%, and 75% of the patients attending INR-C (group A), compared with 24%, 24%, and 43% of patients attending

TABLE 2: The complications and management percent of warfarin therapy in patients on regular follow up in INR-C (group A) and General-C (group B).

Complications during treatment	Group	
	A	B
No complication seen	94	75
Major bleeding (hospital attendance)	2	14
Minor bleeding (no attendance)	4	11
Measures required for patients		
No measures needed	0	14
Managed at outpatient	2	6
Admitted to hospital	4	5
Management of complications		
Observation	4	16
Vitamin K	2	5
Fresh frozen plasma	0	2
Blood transfusion	0	2
Possible risk factors for complications		
<b>Full compliance this is not a risk factor</b>	94	75
No compliance	6	10
Stopped medications	0	15

*P* value = 0.012 < 0.05 significant

General-C (group B) respectively (*P* value < 0.05: statistically significant difference) (Table 3).

TABLE 3: Time in therapeutic range (TTR) measurements in INR-C (group A) and General-C (group B).

TTR measurements		Group	
		A	B
First visit	Below target	38	59
	Within target range	56	24
	Above target	6	17
Second visit	Below target	30	56
	Within target range	63	24
	Above target	7	20
Third visit	Below target	21	45
	Within target range	75	43
	Above target	4	12

*P* value = 0.025 > 0.05 significant

## 4. Discussion

Although new-generation oral anticoagulants are increasingly being introduced, warfarin remains the best choice for patients with mechanical prosthetic valves and valvular AF, especially in developing countries in which the incidence of rheumatic heart disease remains high; thus, valvular AF (atrial fibrillation) is a serious health problem in many developing countries including Sudan [7]. The present study showed, as have many other studies, the crucial role of INR-C not only in the control of TTR but also in reducing the incidence of major and minor bleeding, increasing drug interaction knowledge among patients, and finally, better patients compliance among those attending INR-C (group A) [8].

INR monitoring can be performed in hospitals, general outpatient clinics, and specialized INR outpatient clinics. In addition to that it can be self-monitored in selective cases [9].

Several studies revealed that a vast majority of thromboembolic and bleeding events happened once the INR is outside the therapeutic range that is, higher INR increases the risk of bleeding, whereas lower INR increases the risk of thromboembolism [10]. Our results showed lower mean TTR in patients with major events (bleeding and ischemic events) compared with those with no major events. Moreover, we have shown that the type of follow-up clinic is an independent predictor of major events.

According to our knowledge, this is the first ever study in Sudan that compared the warfarin patient's follow-up in INR-C and General-C. The results suggested that patients attending INR-C had higher TTR levels and decreased bleeding and ischemia events rates. Thus, by increasing the number of INR-C in Sudan, we can ensure a good quality of warfarin follow-up and reduced morbidity.

It was very important to assess and compare the level of the drug interaction knowledge provided by the two clinics (INR-C and the General-C clinic), especially in developing countries where most of the patients are semiliterate. For such patients, one may expect low compliance to warfarin that may lead to significant complications [11,12]. The results of the present study showed clearly that patients attending INR-C were more knowledgeable about coagulation drugs interaction with food and with other medications compared with patients attending General-C ( $P$  value < 0.05: statistically significant difference). Moreover, patients' good compliance that is, attending follow-ups was seen in the INR-C in contrast to poor compliance in the General-C [13].

Although major and minor bleeding were reported in both clinics, yet they were far less in patients attending the INR-C. Similar to previous studies, it was shown that the only common side effect of warfarin is bleeding [14,15].

In this study, the measures done for patients with complications in group (A) were admission to the hospital 4(66.6%) and management as outpatients 2(33.4%), while in group (B) no measure was taken in 14 cases (56%), management at outpatient clinic 6 (24%), and admission in the hospital 5(20%). Management of complications were observation for 4 (66.7%) and vitamin K for 2(33.4%) in group (A) patients. For group (B) no management was done for 14 (56%), vitamin K for 5 (20%), fresh frozen plasma for 2 (7%), observation 2(8%), and blood transfusion 2 (8%) ( $P$  value < 0.05: significant difference). The risk factors of complications were noncompliance in 6(6%) of the patients in group (A), while in group (B) the risk for complications were stopping of medications 15(15%) and no compliance 10(10%) ( $P$  value < 0.05: statistically significant difference) [16].

In this study, the INR target value was reported in (75) in group (A) compared to (43) in group (B),  $P$  value < 0.05: significant difference. These results were similar to those of Li *et al.* in China who assessed the knowledge level regarding warfarin therapy among its users and identified the factors that significantly influence anticoagulation control [17]. Alghadeeer *et al.* investigated the differences in anticoagulation control of warfarin using TTR between pharmacists and other health-care providers. They enrolled 62 patients, of them 33 were in a pharmacist-led clinic and 29 in a physician-led clinic. TTR levels showed significant increase among patients in the pharmacist-led clinic (82%) compared to the physician-led clinic (24%) ( $p < 0.001$ ). In 27 patients followed by physicians and prospectively by clinical pharmacists, TTR increased during clinical pharmacists' care ( $91.70\% \pm 2.93\%$ ) versus ( $61.39\% \pm 5.11\%$ ) during physician care;  $p < 0.001$ ) [11].

The results of the present study showed that the TTR levels of the patients followed in INR-C were significantly higher than in patients who attended General-C. Moreover, it also showed lower rates of combined minor and major bleeding and ischemic events in INR-C compared with those attending the General-C. These results showed the benefits and importance of the INR-C for patients on warfarin therapy. The only negative argument may be the high cost of INR-C services, especially in countries with low-health resources such as Sudan. On the other hand, the high standard of service provided by the INR-C argues in its favor since it reduces morbidity and mortality.

## 5. Conclusion

Based on the study results, one may conclude that the INR-C is more efficient and safer for follow-up of patients on warfarin therapy compared to General-C. In spite of the high cost of running INR-C in countries with low-health resources, the overall health outcome is beyond comparison with the General-C considering the expected complications and the high-concomitant cost.

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## Ethical Considerations

The ethical approval was obtained from the ethical committee of the Sudanese Medical Specialization Board (SMSB).

## Competing Interests

Authors declare no conflict of interest.

## Availability of Data and Material

Data is available with corresponding author upon request.

## Funding

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## References

- [1] Robinson, A. A., Trankle, C. R., Eubanks, G., Schumann, C., Thompson, P., Wallace, R. L., Gottiparthi, S., Ruth, B., Kramer, C. M., Salerno, M., Bilchick, K. C., Deen, C., Kontos, M. C., & Dent, J. (2020). Off-label use of direct oral anticoagulants compared with warfarin for left ventricular thrombi. *JAMA Cardiology*, 5(6), 685–692. <https://doi.org/10.1001/jamacardio.2020.0652>

- [2] Michaels, K., Regan, E. N. (2013). Teaching patients INR self-management. *Nursing2020*, 43(5):67–9. <https://doi.org/10.1097/01.NURSE.0000428711.89001.61>
- [3] van Walraven, C., Jennings, A., Oake, N., Fergusson, D., & Forster, A. J. (2006). Effect of study setting on anticoagulation control: A systematic review and metaregression. *Chest*, 129(5), 1155–1166. <https://doi.org/10.1378/chest.129.5.1155>
- [4] Pell, J. P., & Alcock, J. (1994). Monitoring anticoagulant control in general practice: Comparison of management in areas with and without access to hospital anticoagulant. *The British Journal of General Practice*, 44(385), 357–358.
- [5] Testa, S., Paoletti, O., Zimmermann, A., Bassi, L., Zambelli, S., Cancellieri, E. (2012). The role of anticoagulation clinics in the era of new oral anticoagulants. *Thrombosis*, 2012, 835356. <https://doi.org/10.1155/2012/835356>
- [6] Morgan, C. L., McEwan, P., Tukiendorf, A., Robinson, P. A., Clemens, A., & Plumb, J. M. (2009). Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. *Thrombosis Research*, 124(1), 37–41. <https://doi.org/10.1016/j.thromres.2008.09.016>
- [7] Zhao, S. J., Zhao, H. W., Wang, X. P., Gao, C. Y., Qin, Y. H., Cai, H. X., Chen, B. Y., & Cao, J. J. (2016). [Current status of warfarin therapy in Chinese patients with nonvalvular atrial fibrillation: A single center analysis]. *Zhonghua Xin Xue Guan Bing Za Zhi*, 44(11), 940–944.
- [8] Chiquette, E., Amato, M. G., & Bussey, H. I. (1998). Comparison of an anticoagulation clinic with usual medical care: Anticoagulation control, patient outcomes, and health care costs. *Archives of Internal Medicine*, 158(15), 1641–1647. <https://doi.org/10.1001/archinte.158.15.1641>
- [9] Lafata, J. E., Martin, S. A., Kaatz, S., & Ward, R. E. (2000). The cost-effectiveness of different management strategies for patients on chronic warfarin therapy. *Journal of General Internal Medicine*, 15(1), 31–37. <https://doi.org/10.1046/j.1525-1497.2000.01239.x>
- [10] Brown, D. G., Wilkerson, E. C., & Love, W. E. (2015). A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. *Journal of the American Academy of Dermatology*, 72(3), 524–534. <https://doi.org/10.1016/j.jaad.2014.10.027>
- [11] Alghadeer, S., Alzahrani, A. A., Alalayet, W. Y., Alkharashi, A. A., & Alarifi, M. N. (2020). Anticoagulation Control of Warfarin in Pharmacist-Led Clinics Versus Physician-Led Clinics: A Prospective Observational Study. *Risk Management and Healthcare Policy*, 13, 1175–1179. <https://doi.org/10.2147/RMHP.S248222>



- [12] Kuruvilla, M., & Gurk-Turner, C. (2001). A review of warfarin dosing and monitoring. *Proceedings - Baylor University. Medical Center*, 14(3), 305–306. <https://doi.org/10.1080/08998280.2001.11927781>
- [13] Lee, Y.-P., & Schommer, J. C. (1996). Effect of a pharmacist-managed anticoagulation clinic on warfarin-related hospital readmissions. *American Journal of Health-System Pharmacy*, 53(13), 1580–1583. <https://doi.org/10.1093/ajhp/53.13.1580>
- [14] Shoeb, M., & Fang, M. C. (2013). Assessing bleeding risk in patients taking anticoagulants. *Journal of Thrombosis and Thrombolysis*, 35(3), 312–319. <https://doi.org/10.1007/s11239-013-0899-7>
- [15] Camm, A. J., Lip, G. Y., De Caterina, R. (2012). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Europace*, 14, 1385–1413.
- [16] Al-Momany, N. H., Makahleh, Z. M., Al-Omari, N. A., Al-Sarayreh, H. A., & Momani, R. O. (2019). Analysis of factors that interrupt with INR control in the first anticoagulation clinic monitoring Jordanian patients. *Clinical and Applied Thrombosis/Hemostasis*, 25, 1076029619870252. <https://doi.org/10.1177/1076029619870252>
- [17] Li, X., Sun, S., Wang, Q., Chen, B., Zhao, Z., & Xu, X. (2018). Assessment of patients' warfarin knowledge and anticoagulation control at a joint physician- and pharmacist-managed clinic in China. *Patient Preference and Adherence*, 12, 783–791. <https://doi.org/10.2147/PPA.S156734>