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Pharmacist-Managed Anticoagulation Services for Warfarin Management in Tertiary Hospitals: The Egyptian Experience

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Abstract: *Background:* Warfarin is widely regarded as the main anticoagulant in lowering the risk of thromboembolism. This study used indicators to compare pharmacist-managed anticoagulation services, using a well-prepared protocol, with physician-managed anticoagulation services. *Methods:* A retrospective prospective pilot study was conducted to compare patient outcomes before and after transitioning patients to pharmacist-managed anticoagulation services, comparing the proportion of those with therapeutic international normalized ratio (INR), subtherapeutic INR, and supratherapeutic INR, as well as their bleeding occurrences as indicators of assuring quality care. *Results:* A significant improvement in anticoagulation management was noted in the transition to pharmacist-managed anticoagulation services. The proportion of those with subtherapeutic INR decreased from 61.8% to 11.8% ($p < 0.001$), those with supratherapeutic INR decreased from 20.6% to 2.9% ($p < 0.001$), those with therapeutic INR increased from 17.6% to 85.3% ($p < 0.001$), and the occurrence of bleeding decreased from 11.8% to 0.0%, without significant difference in warfarin doses (median from 4 before the transition to 5 after); in addition, the time to reach therapeutic INR decreased from 12-24 weeks to 2-8 weeks after transitioning to pharmacist-managed anticoagulation services. *Conclusion:* Pharmacist-managed anticoagulation services are considered safer and more effective than physician-managed anticoagulation services alone in terms of patients' adherence and satisfaction, which provide an excellent opportunity for quality assurance care.

Keywords: Pharmacist-managed anticoagulation services; Warfarin; Anticoagulation clinic; Therapeutic drug monitoring

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1. Background

Warfarin management poses several challenges. For most indications, the main challenge is to administer an optimal effective dose required to maintain the target international normalized ratio (INR) between 2 and 3 [1].

Patients should be closely monitored following each dose. The drug begins to exert its antithrombotic effects between twenty-four and thirty-six hours after administration; however, antithrombotic effects are not observed until around the fifth day of treatment. Not only is the response to warfarin delayed, but it is also unpredictable due to various circumstances, including sensitivity to warfarin, varied drug clearance rates, and varying half-lives of vitamin K-dependent clotting factors. Drug interactions and certain dietary habits have a significant impact on how patients respond to warfarin. The second challenge is the severity of its adverse reactions [2].

According to previous meta-analysis, the use of warfarin is associated with a 0.6% annual risk of bleeding-related death and a 9.6% annual risk of a significant or mild bleeding event, with the risk being highest at the start of medical assistance [3]. While numerous risk factors for bleeding have been identified, including comorbidities, advanced age, and concurrent medications, the risk is frequently mitigated with less intensive medical intervention. Less intensive medical assistance is commonly defined as an INR goal of 3 against an INR goal of more than 3 [3].

There are currently evidence-based guidelines for warfarin administration [4]. Raising the quality of health care, enhancing patient safety, and minimizing errors are all obstacles to bridging the gap between evidence-based guidelines and actual clinical practice. In order to optimize warfarin administration, a standard protocol should be used. Standardization is one method for bridging this gap. Developing and testing a protocol will ensue a systematic and effective implementation of the principles. A standard protocol has been adopted to promote the optimization of warfarin administration [4,5].

Currently, warfarin is the most commonly prescribed oral anticoagulant around the world. Despite warfarin's potential benefits in the management of thromboembolic disorders, major adverse events, such as hemorrhage and thromboembolic events, have been reported when the INR is not controlled within the therapeutic range [1,2]. It cannot be denied that optimal INR management leads to a reduction in anticoagulation-related adverse reactions [6].

According to available research and the recommendation by the American College of Chest Physicians, anticoagulation management service (AMS) can improve the quality of care and reduce complications related to anticoagulant therapy [7,8]. There are now four primary methods for administering oral anticoagulation therapy: usual medical care (UMC), pharmacist-managed anticoagulation services (PMAS), nurse-managed anticoagulation services, and patient-directed models. Under the UMC model, the management of warfarin is directed by a primary health care practitioner, and in the majority of cases, a physician [7,9].

In PMAS, the administration of warfarin is directed by a trained pharmacist, usually in a primary care clinic, using a designed protocol that has been approved by physicians. In such clinics, the pharmacist's primary responsibilities include visiting patients and assessing their medical conditions, adjusting warfarin doses based on INR results, patient consultation and education, monitoring patients for anticoagulation-related adverse effects, as well as checking drug and dietary interactions with warfarin [7,10].

The INR was developed in 1982 by the World Health Organization's Expert Committee on Biologic Standardization in response to global disparities in thromboplastin sensitivity in reporting prothrombin time [11]. Inadequate management of warfarin can result in subtherapeutic or supratherapeutic INR readings, thus increasing the risk of acute or recurrent thromboembolic or bleeding events.

The aim of this study was to assess whether transitioning patients from physician-managed anticoagulation services to pharmacist-managed anticoagulation services will improve the quality of

anticoagulation care.

2. Methods

From March to April 2019, the most recent resources and guidelines on warfarin use were searched, followed by data collection from Chest guidelines – Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition [9], the 2017 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [8], the 2019 protocols for outpatient oral anticoagulation with vitamin K antagonists by Oxford Hemophilia and Thrombosis Center [12], the Michigan Anticoagulation Quality Improvement Initiative (MAQI) anticoagulation toolkit [13], and the new guidelines from the Thrombosis and Hemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism [10].

A protocol for the safe use of warfarin was developed. The protocol included warfarin indications, duration of administration, INR targets for each indication, contraindications, drug-drug and drug-food interactions, warfarin sensitivity, maintenance monitoring and dose adjustment based on INR results, specific concerns about using warfarin, as well as patient education on the drug regimen.

The warfarin protocol was applied to 34 patients in Abo-Kir General Hospital from June 2019 to September 2019, using a patient-specific approach. The INR of the patients was monitored, and the pharmacists documented data for age, gender, indication, and a weekly progressive note (INR and any new patient observation) in the medical chart.

A retrospective prospective pilot study was conducted to compare patient outcomes before and after the implementation of the protocol. The outcomes were the proportion of patients in the therapeutic INR range, the time required to achieve this range, as well as those in the subtherapeutic and supratherapeutic INR ranges.

3. Results

3.1. Demographics

Thirty-four patients underwent the transition process from physician-managed anticoagulation services to pharmacist-managed anticoagulation services. Their demographics and indication for warfarin are shown in **Figure 1** and **Figure 2**, respectively. The distribution of the studied cases based on demographic data and indication for warfarin is shown in **Table 1**.

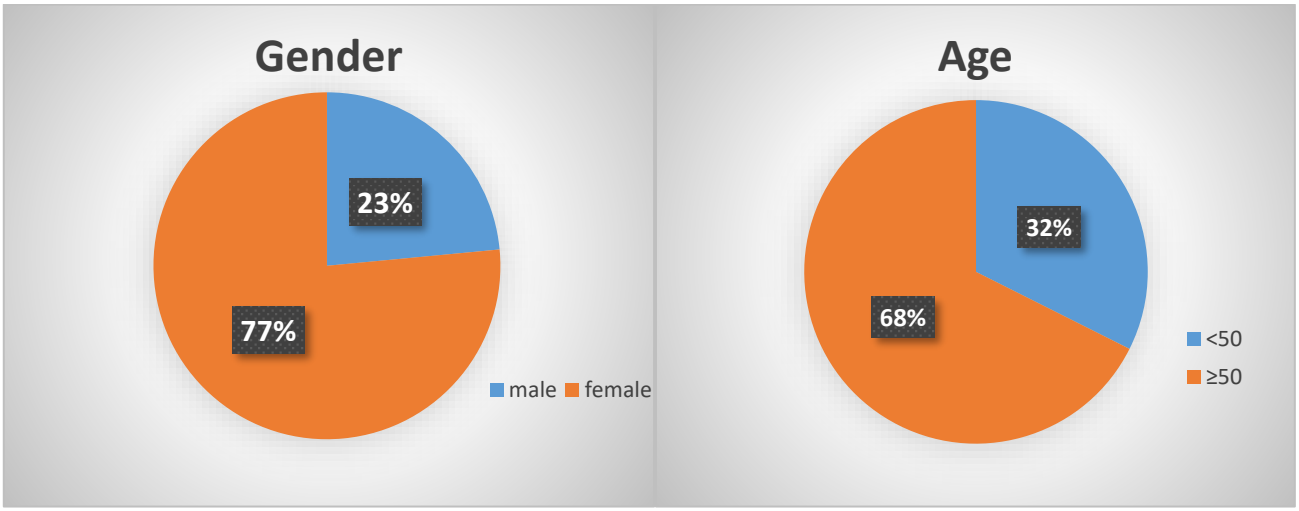

Figure 1. Distribution of studied cases according to gender and age (n = 34)

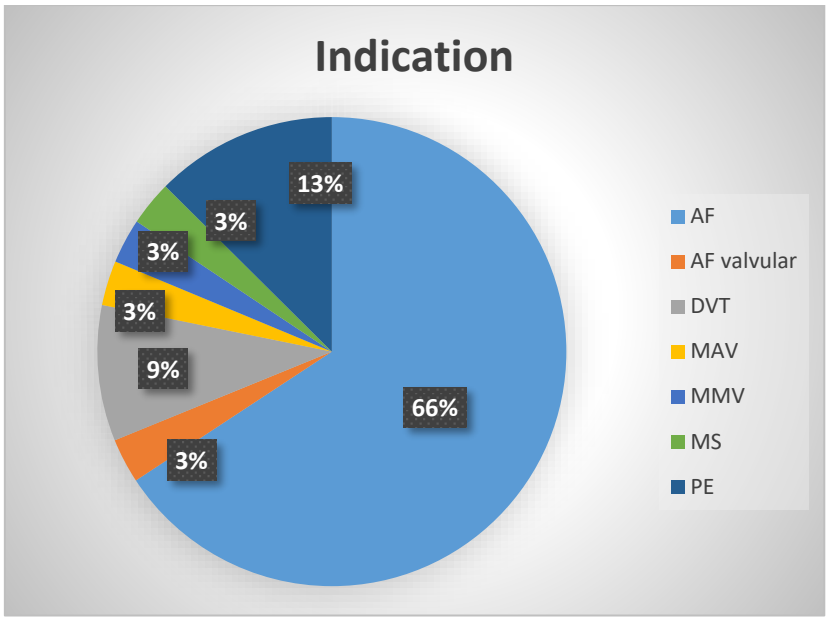

Figure 2. Distribution of studied cases according to the indication of warfarin

Note: AF: atrial fibrillation; DVT: deep vein thrombosis; MAV: mechanical aortic valve; MMV: mechanical mitral valve; MS: mitral stenosis; PE: pulmonary embolism

Table 1. Distribution of the studied cases based on demographic data and indication for warfarin (n = 34)

Demographics	**Number**	**Percentage (%)**
Sex		
Male	8	23.5
Female	26	76.5
Age (years)		
< 50	11	32.4
≥ 50	23	67.6
Min. – Max.	30.0 – 85.0	
Mean ± SD	14.89 ± 55.74	
Median	54.50	
Indication	**Number**	**Percentage (%)**
AF	21	61.8
AF valvular	1	2.9
DVT	3	8.8
Mechanical aortic valve	1	2.9
Mechanical mitral	1	2.9
Mitral stenosis	1	2.9
PE	4	11.8
Rheumatic mitral valve	2	5.9

3.2. Warfarin monitoring

A significant improvement in anticoagulation control was observed in the transition to pharmacist-managed anticoagulation services. The proportion of patients in the subtherapeutic INR range decreased from 61.8% to 11.8% ($p < 0.001$), while in the supratherapeutic INR range, a decrease was seen from 20.6% to 2.9% ($p < 0.001$), and in the therapeutic INR range, a significant increase was noted from 17.6% to 85.3% ($p <$

0.001); the occurrence of bleeding among patients reduced from 11.8% to 0.0% without a significant difference in the dose of warfarin (median from 4 to 5 prior to transitioning to pharmacist-managed anticoagulant services); a reduction in the time taken to reach therapeutic INR from 12-24 weeks to 2-8 weeks after transitioning to pharmacist-managed anticoagulation services was also noted. **Figure 3**, **Table 2**, and **Table 3** show the anticoagulation control before and after the transition.

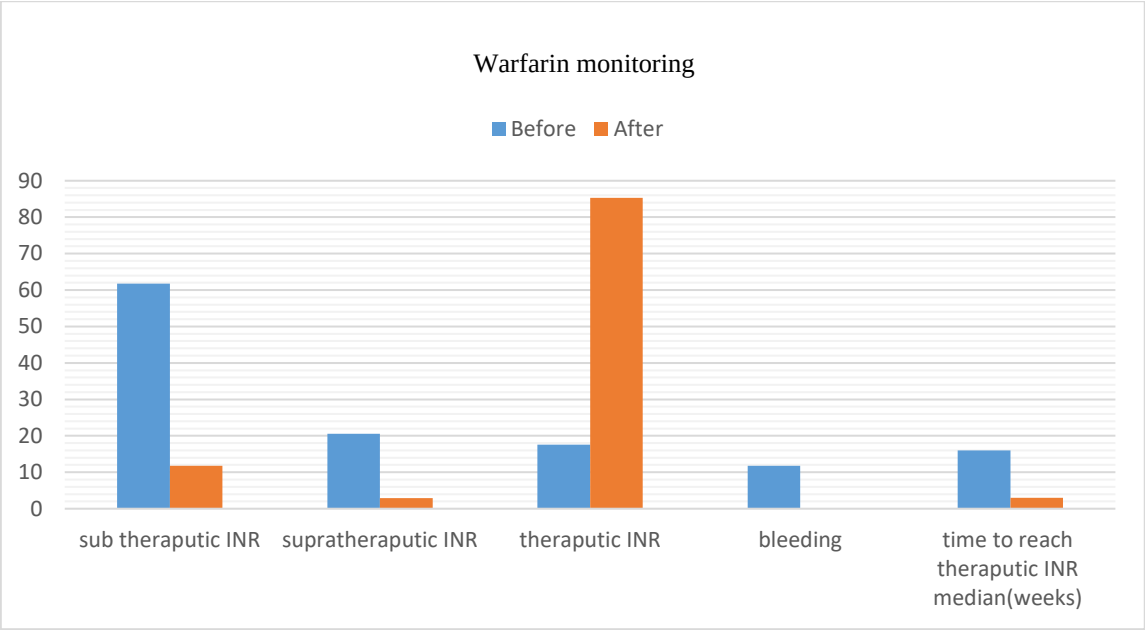

Figure 3. Comparison between the two studied periods

Table 2. Comparison between the two studied periods based on warfarin (n = 34)

Warfarin	Before	After	Z	*p*
Min. – Max.	1.0 – 8.50	0.50 – 15.0		
Mean ± SD.	1.87 ± 4.40	2.49 ± 5.07	1.681	0.093
Median	4.0	5.0		

Note: Z: Wilcoxon signed-rank test; *p*: *p* value for comparing the studied periods

Table 3. Comparison between the two studied periods based on INR

INR	Before		After		*p*
	Number	Percentage (%)	Number	Percentage (%)	
Subtherapeutic	21	61.8	4	11.8	$^{McN}p < 0.001$*
Supratherapeutic	7	20.6	1	2.9	$^{McN}p = 0.031$*
Therapeutic	6	17.6	29	85.3	$^{McN}p < 0.001$*
Bleeding	4	11.8	0	0.0	$^{McN}p = 0.125$
Min. – Max.	1.19 – 10.0		1.40 – 3.58		
Mean ± SD	1.87 ± 2.41		0.42 ± 2.29		0.381
Median	1.75		2.30		

Note: Z: Wilcoxon signed-rank test; McN: McNemar's test; *p*: *p* value for comparing studied periods; *: statistically significant at $p \leq 0.05$

4. Discussion

This study revealed that the detailed dosing protocol used by pharmacists with minimal physician oversight reduced the number of patients with an INR that was higher or lower than the target range and the occurrence of bleeding when compared to the standard practice of dosing by an individual provider.

It is possible that the personal care provided by the pharmacists aided in the improvement of control, as each patient's chart was reviewed weekly for laboratory values. Previous research has shown that ineffective monitoring can aggravate control [14]. Even if the lack of oversight contributes to poor control, the protocol enables the use of existing pharmacy resources in the care of patients.

This small pilot study demonstrated that a warfarin protocol implemented through pharmacist-managed anticoagulation services is an effective method for ensuring compliance with the most recent evidence-based guidelines for warfarin administration as well as an effective and safe use of warfarin. The majority of physician service lines were pleased with having pharmacists manage their patients in using warfarin, and the results were extremely positive.

Numerous additional studies have demonstrated the effectiveness of warfarin protocols implemented through pharmacist-managed anticoagulation services [15-17]. For example, in a 2005 study involving 6,645 inpatients and outpatients, the patients in the intervention group, who received a centralized, pharmacist-managed anticoagulation monitoring service, were 39% less prone to having an anticoagulation-related complication than those in the control group [18]. A retrospective study of 717,396 Medicare patients, treated in 1995, revealed that hospitals without pharmacist-managed anticoagulation services for warfarin therapy had 6.20% higher death rates, 5.86% longer hospital stay, 2.16% higher Medicare charges, as well as 8.09% and higher rates of bleeding complications [19]. As with previous pilot studies, the sample size of this study was small, which has always been a significant limitation.

5. Conclusion and recommendation

This study concludes that the management of warfarin by pharmacists using the warfarin protocol is safer and more effective than being under the care of physicians alone. It increases patient satisfaction, adherence, and participation in the care plan. Using their knowledge of drug interactions and dose monitoring offers an excellent opportunity for providing quality assurance care. Given the rapid pace of change in health care, it is essential to have measurement tools and guidelines, such as protocols, in place. Further studies involving larger sample size are recommended to reinforce the protocol.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Pirmohamed M, 2006, Warfarin: Almost 60 Years Old and Still Causing Problems. Br J Clin Pharmacol, 62(5): 509.

[2] Oake N, Jennings A, Forste AJ, et al., 2008, Anticoagulation Intensity and Outcomes Among Patients Prescribed Oral Anticoagulant Therapy: A Systematic Review and Meta-Analysis. CMAJ, 179(3): 235-244.

[3] Landefeld CS, Beyth RJ, 1993, Anticoagulant-Related Bleeding: Clinical Epidemiology, Prediction, and Prevention. Am J Med, 95(3): 315-328.

[4] Kuruvilla M, Gurk-Turner C, 2001, A Review of Warfarin Dosing and Monitoring. Proc (Bayl Univ Med Cent), 14(3): 305-306.

[5] Hamrah MS, Hamrah MH, Hamrah MH, et al., 2019, An Overview of Anticoagulants. CPQ Medicine, 6: 3.

[6] Yimer NS, Abiye AA, Hussen SU, et al., 2021, Anticoagulation Control, Outcomes, and Associated Factors in Patients with Atrial Fibrillation Receiving Warfarin at Tertiary Care Hospital in Ethiopia. Clin Appl Thromb Hemost, 27: 10760296211049786.

[7] Sylvester KW, Ting C, Lewin A, et al., 2018, Expanding Anticoagulation Management Services to Include Direct Oral Anticoagulants. J Thromb Thrombolysis, 45(2): 274-280.

[8] Schmidt GA, Girard TD, Kress JP, et al., 2017, Liberation from Mechanical Ventilation in Critically Ill Adults: Executive Summary of an Official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline. Chest, 151(1): 160-165.

[9] Holbrook A, Schulman S, Witt DM, et al., 2012, Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(2): e152S-e184S.

[10] Tran HA, Gibbs H, Merriman E, et al., 2019, New Guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the Diagnosis and Management of Venous Thromboembolism. Med J Aust, 210(5): 227-235.

[11] Saelim W, Boonmuang P, Suphanklang J, et al., 2020, Clinical Factor Related to International Normalized Ratio Changes in Warfarin Users Who Underwent Heart Valve Replacement at Warfarin Clinic of Phramongkutklao Hospital. Thai Bulletin of Pharmaceutical Science, 15(2): 73-79.

[12] Helin T, Joutsi-Korhonen L, Lassila R, 2019, Clinical Use and Laboratory Testing of Oral Anticoagulation Therapy: Experience from Finland. Annals of Blood, 4: 17.

[13] Barnes GD, Kaatz S, Golgotiu V, et al., 2013, Use of Warfarin for Venous Thromboembolism Prophylaxis Following Knee and Hip Arthroplasty: Results of the Michigan Anticoagulation Quality Improvement Initiative (MAQI2). Journal of Thrombosis and Thrombolysis, 35(1): 10-14.

[14] Dawson NL, Klipa D, O'Brien AK, et al., 2011, Oral Anticoagulation in the Hospital: Analysis of Patients at Risk. Journal of Thrombosis and Thrombolysis, 31(1): 22-26.

[15] Kose E, An T, Kikkawa A, 2018, Assessment of Oral Anticoagulation Control at Pharmacist-Managed Clinics: A Retrospective Cohort Study. Pharmazie, 73(6): 356-360.

[16] Daniels PR, Manning DM, Moriarty JP, et al., 2018, Improving Inpatient Warfarin Therapy Safety Using a Pharmacist-Managed Protocol. BMJ, 7(2): e000290.

[17] Sargin M, Tasdemir MM, Kuplay H, et al., 2019, Retrospective Cohort Study for Evaluating the INR Monitoring Patterns in Patients with Deep Vein Thrombosis in Daily Practice: Analysis of 2010-2013 Database of a Tertiary Care Center. Phlebology, 34(5): 317-323.

[18] Anich KV, Witt DM, Delate T, et al., 2005, A Descriptive Evaluation of Routine Complete Blood Count Monitoring in Patients Receiving Anticoagulation Therapy. J Thromb Thrombolysis, 20(3): 183-188.

[19] Chiquette E, Amato M, Bussey HI, 1998, Comparison of an Anticoagulation Clinic with Usual Medical Care: Atrial Fibrillation and Prophylaxis in Italian Inpatients 229 Anticoagulation Control, Patient Outcomes, and Health Care Costs. Archives of Internal Medicine, 158(15): 1641-1647.