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Warfarin adherence and anticoagulation control in atrial fibrillation patients: a systematic review

M. ABABNEH[1], S.A. NASSER[1], A. RABABA'H[1], F. ABABNEH[2]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan
[2]Department of Orthopedic Surgery, Royal Medical Services, Amman, Jordan

Abstract. – OBJECTIVE: This paper aims to review the literature systematically on warfarin adherence in patients with atrial fibrillation and to assess the anticoagulation control focused on patient clinical outcomes. Atrial Fibrillation (AF) is a cardiac disease defined by abnormal heart rhythm, which significantly impacts a patient's health status, quality of life, and heart output, and thus a greater risk of stroke and hospitalization. Most AF patients should be managed with long-term anticoagulation, either with vitamin K antagonists such as warfarin or new oral anticoagulants (NOACs). Anticoagulants have been a core in treating AF and weighing the consequences of thrombosis with the risk of bleeding. This systematic review aimed to assess the impact of warfarin adherence on AF patients.

MATERIALS AND METHODS: A systematic search of the literature was conducted on electronic databases of PubMed/MEDLINE, EBSCO, Cochrane library, Google, and Google Scholar from January 2011 to April 2021 to determine studies that reported warfarin adherence on patients with atrial fibrillation.

RESULTS: Out of 1429 titles and abstracts were retrieved, 12 studies fulfilled and met the inclusion criteria. From the included studies, two were carried out in Brazil and one from the following nations: Libya, Jordan, Iran, KSA, Canada, Malaysia, Bahrain, UAE, Singapore, and the USA. The study designs identified were cross-section, retrospective, and prospective studies. Warfarin adherence was influenced by multiple causes, including pharmaceutical services, the number of medications, and warfarin knowledge regarding anticoagulation control. Warfarin adherence illustrates its positive association with TTR and INR as a measure of anticoagulation control.

CONCLUSIONS: While the available evidence is limited, this systematic review demonstrated a positive finding of the association between warfarin adherence and anticoagulation control in patients with AF.

Key Words:
Atrial fibrillation, Warfarin, Adherence, Anti-coagulation control.

Introduction

Atrial Fibrillation (AF) is a cardiac disorder characterized by irregular heart rhythm[1,2], which has a substantial effect on a patient's health status, quality of life, and heart output and resulting in frequent hospitalization, higher risk of stroke, and reduced productivity[3]. The most common form is Non-Valvular AF (NVAF), which arises in the absence of mitral valve repair, rheumatic mitral valve disorder, or a prosthetic heart valve[1,4]. The Centers for Disease Control and Prevention (CDC) predicted that 12.1 million individuals in the United States would have AF by 2030. In addition, atrial fibrillation was listed on 175,326 death certificates in 2018 and is the primary cause of mortality in 25,845 cases[5]. Notably, it is anticipated that 6-12 million people in the United States will have AF by 2050 and 17.9 million individuals in Europe by 2060[6-8].

Since AF significantly raises the likelihood of stroke, effective preventive therapy is critical and key management priority[1,9,10]. According to the European Society of Cardiology (ESC) guidelines, the vast majority of AF patients should be treated with continuous anticoagulation, either with vitamin K antagonists like warfarin or new oral anticoagulants (NOACs)[10].

Anticoagulants have been the cornerstone in treating AF and balancing the consequences of thromboembolism with the likelihood of hemorrhage. For years, warfarin has been shown to effectively manage thromboembolism in non-valvular atrial fibrillation (NVAF)[9,10]. Warfarin with a dose adjustment has been shown to decrease stroke by 64%[11,12]; nevertheless, there are also clinical issues involved with warfarin utilization[13].

Warfarin is a racemic isomer complex that inhibits the formation of the coagulation factors depending on vitamin K. Warfarin effective dosage vary substantially between individuals due to genetic alterations of its receptor, metabolism through cytochrome P450 (CYP), and interaction with sev-

Corresponding Author: Mera A. Ababneh, Ph.D; e-mail: mababneh@just.edu.jo

eral medications, green vegetables, and vitamins[14]. Warfarin treatment is difficult because of its narrow therapeutic index, and patients are prone to increase the risk of thromboembolism or bleeding[15].

Monitoring and close supervision of the International Normalized Ratio (INR) in patients treated with warfarin decrease the incidence of bleeding and thrombosis[15]. Considerably, multiple studies, including a systematic review stated that time in therapeutic range (TTR) and INR variability assess various aspects of warfarin treatment management: the TTR evaluates the intensity of warfarin therapy with a high TTR indicating a reduced probability of stroke or bleeding[9,15-17]. Patients with a higher TTR value had favorable outcomes; for instance, reduction in the risk of strokes, severe hemorrhagic incidents, and mortality[18]. In comparison, the INR variation is a predictor of the stability of warfarin therapy, with low variation suggesting a low probability of adverse events[17].

Various rating methods can be used to measure the risk of stroke in AF patients. The most widely deployed risk stratification scheme is CHA2DS2-VASc (cardiac failure or impairment, hypertension, age 65-74 [1 point] or 75 years [2 points], diabetes mellitus, and previous stroke/transient ischemic attack or thromboembolism [2 points]-vascular disorder, and sex classification [female]) score[19,20].

Patient noncompliance remains one of the most difficult challenges in the healthcare sector. Adherence problems, particularly with medications with a narrow therapeutic index, can increase risks and medical expenses. Patients on warfarin treatment have difficulty sustaining proper adherence, which significantly impacts anticoagulation control[21]. Warfarin has a narrow therapeutic index, which entails regular monitoring and strict patient adherence to obtain treatment outcomes[22].

It is vital to enhance patients' awareness and knowledge about the complications and benefits of anticoagulant medications and to ensure that they have a thorough understanding of warfarin intake, drug reactions, and frequent monitoring. Furthermore, non-adherence to warfarin treatment is associated with more variable anticoagulation control, which may contribute to the patients' lack of awareness[23].

Materials and Methods

Literature Search and Study Design

This systematic review was established using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method, which compiles results related to primary outcomes from all published studies and improves results' reliability for warfarin adherence and anticoagulation control. A systematic search of PubMed/MEDLINE, EBSCO, Cochrane library, Google, and Google Scholar were searched for studies assessing the association between warfarin adherence and anticoagulation control in patients with atrial fibrillation, which included citations from the period of January 2011 to April 2021. The following keywords were used in the search criteria: "warfarin", "warfarin adherence", "association", "atrial fibrillation", "anticoagulation control", "Time in Therapeutic Range", "TTR', "International Normalized Ratio", "INR".

Study Selection

Identified abstracts were included based on the following criteria: the study should target patients with AF treated with warfarin, full-text article, English language, inpatient or outpatient setting. Article papers were qualified for Full-text review. Studies that did not provide warfarin adherence, anticoagulation control, did not assess any primary outcomes, or were conducted in animal facilities were omitted.

Data Extraction

After the abstract and title reviews were screened, full-text versions of the articles were retrieved for evaluation. After assessment of inclusion criteria, a total of 12 studies were included in this study. The data extracted from the reported studies included study design, settings, intervention, publication year, duration of research, and outcomes.

Results

In total, 1429 titles and abstracts were obtained from electronic databases. Additionally, we analyzed 1423 abstracts; 35 studies were selected for full-text review, with 12 articles fulfilling the inclusion criteria. PRISMA chart illustrates an outline of the study selection (Figure 1).

Results by Regions and Study Design

An outline for the included articles is illustrated in Table I. Among the 12 studies, two studies were conducted in Brazil[24,25]. One study was carried out in each country of the following: Libya[26], Jordan[27], Iran[28], KSA[29], Canada[30], Malaysia[31], Bahrain[32], UAE[33], Singapore[34], USA[35].

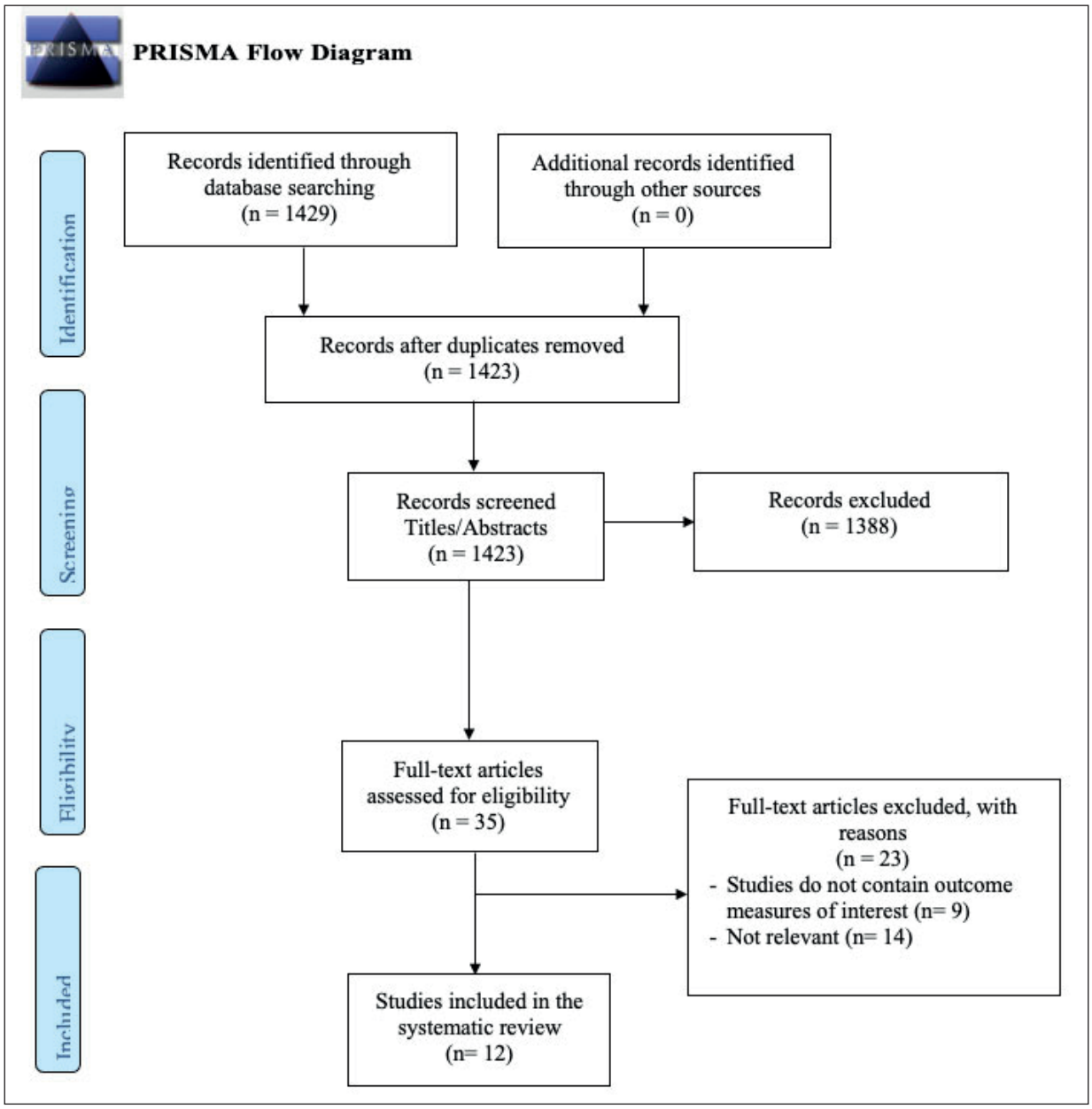

Figure 1. PRISMA chart.

The study design of the total twelve identified studies was as follows: seven cross-sectional studies[26-29,32,34,35] three prospective studies[24,25,33], and two retrospective cohorts[30,31].

Reported Outcomes

Role of Pharmaceutical Care Services in Warfarin Adherence

In this systematic review, two studies highlighted the role of pharmaceutical care services regarding warfarin adherence[25,31]. Aidit et al[31] conducted a retrospective study in Malaysia from 2009-2014, they addressed a pre protocol group (under standard medical team management known as (UMC), and a post protocol group called warfarin medication therapy adherence clinic (WMTAC), which was mainly headed by a pharmacist and played an expanded part in patient counseling and education. Therefore, the post protocol group was given the authority to carry out the protocol and recommend any dose modification and/or the continuity of warfarin treatment.

Table I. Outline for the included articles.

Author	Country	Study design	Settings	Sample Size	Participants	Predictor	Outcome
Ahmed et al[26], 2021	Libya	Cross-sectional, Oct 2017 - Jan 2018	Tripoli University Hospital	88 recruited patients	Adult patients >18 years who had been on warfarin >3 months	Assess adherence to warfarin therapy was measured by (MMAS-8)	Assess INR and TTR
Ababneh et al[27], 2016	Jordan	Cross-sectional convenience sample	Two hospitals in northern Jordan	331 recruited outpatients	Adult outpatients >18 years	Assess adherence to warfarin therapy was measured by (MMAS-8)	Evaluate TTR and INR
Farsad et al[28], 2016	Iran	Cross-sectional, Sep 2014 to Mar 2015	Outpatient anticoagulant center of Shaheed Rajaie Hospital	470 patients	Adults with NVAF (30-85) years old & taking warfarin for >3 months	Use Rosendaal method	Evaluate TTR
Balkhi et al[29], 2018	KSA	Cross-sectional, 1 June to 31 Aug 2016	Anticoagulation clinic King Fahad Hospital	298 patients	18 years ≥ on warfarin therapy for ≥ 6 months	Assessed medication adherence using the MAQ	Assess INR targets
Marcatto et al[24], 2021	Brazil	Prospective, 2016-2018	Tertiary hospital	262 patients	Patients≥18 years old, with NVAF	Obtained the TTR value by the Rosendaal method	Basal TTR, TTR after 12 weeks, TTR of 1 year after the end of pharmaceutical care
Mcalister et al[30], 2018	Canada	Retrospective cohort, 1 Jan 2008 and 31 Mar 2015	The Canadian province of Alberta using routinely collected health data	57 669 patients	Adult ≥18 years old with NVAF patients on warfarin for ≥ 1 month	Frequency of (INR) testing and the Rosendaal TTR with timing zero set at 31 days after the first warfarin dispensing	Assess TTR
Marcatto et al[25], 2018	Brazil	Retrospective descriptive and prospective	Heart Institute	268 patients	Adult patients >18 years with AF and low TTR <50%	Adherence assessment was calculated through surveys and pill counts	Evaluate a pharmacist's warfarin management with poor TTR
Aidit et al[31], 2017	Malaysia	Retrospective cohort, 2009 to 2014	Cardiology referral hospital	151 subjects	Adult patients ≥ 18 years with AF	Using Rosendaal method,	Assess INR, bleeding events, TTR & common drug interaction, pharmacist management
Sridharan et al[32], 2020	Bahrain	Cross-sectional, May-Oct 2019	Tertiary care hospital	150 patients	Adult patients with AF	PACT-2 questionnaire and MMAS-8	Assess INR
Shehab et al[33], 2012	UAE	Prospective cross-sectional, Dec (2009 -2010)	Al Ain hospital	160 patients	Inpatient & outpatient taking Warfarin treatment for >3 months	10- item warfarin audit questionnaire, Monitor adherence, and medical staff	Assess INR
Wang et al[34], 2014	Singapore	Cross-sectional convenience sample Nov 2012 -Apr 2013	General Hospital	183 patients	Adult patients ≥ 21 years	Warfarin refill records to calculate refill adherence	Assess INR & TTR
Oramasionwu et al[35], 2014	USA	May-Nov 2013	Ambulatory anticoagulation clinics in two North Carolina towns	198 subjects recruited	Adults ≥ 18, on warfarin for ≥ 6 months & patients had TTR of at least 65%.	Using Rosendaal's method	Health literacy & anticoagulation management as determined by TTR

Abbreviations: MMAS-8: 8-item Morisky Medication Adherence Scale, TTR: time in therapeutic range, MAQ: Medication Adherence Questionnaire, PACT-2: perception of anticoagulant treatment questionnaire, INR: international normalization ratio.

Hence, there were substantial correlations among the usual medical care (UMC) category and pharmacist-led WMTAC with regard to TTR ($p = 0.01$) and INR ($p = 0.02$) levels. The positive engagement of pharmacists in the WMTAC clinic had a beneficial effect, where the expanded therapeutic INR range ($p = 0.04$) was notably higher in the WMTAC category[31].

Furthermore, Marcatto et al[25] evaluated the pharmacist's role in warfarin management in patients with low anticoagulation therapy control (Time in the Therapeutic Range <TTR 50%). The adherence assessment was calculated through surveys and pill counts. The comparison of basal TTR measured on the three most recent INR readings (before the prospective phase) and TTR of 4 weeks (determined by assessing the INR readings from visits 0 to 4 in the prospective phase). Also, basal TTR and TTR of 12 weeks measured based on the INR results from visits 0 to 12, in the prospective phase of the study, the results have reported substantial differences (0.144 ± 0.010 *vs.* 0.382 ± 0.016 and 0.144 ± 0.010 *vs.* 0.543 ± 0.014, $p < 0.001$), respectively[25].

Thus, the authors revealed that the average TTR one year prior (retrospective phase) was lower than that of the TTR reading after 12 weeks of pharmacist-driven care (prospective phase) (0.320 ± 0.015; 0.540 ± 0.015, $p < 0.001$). Taken together, these findings highlight the role of pharmaceutical care which enhanced TTR quality in patients with AF and with low anticoagulation control with warfarin[25].

Warfarin with TTR Control Based on the Number of Medications

One study demonstrated the effect of the number of medications on the level of TTR control on NVAF patients. Of the studied groups with a sample size of 470 patients, 37.3% were in a good level of control (TTR > 70%), 24.6% were within the level of the intermediate control (50% <TTR < 70%) and 38.1% were in a bad control (TTR < 50%). An important indicator of poor control was identified in the number of drugs exceeding four medications (OR = 2.06; 95% CI, 1.87, 2.23). The average TTR of the patients was (54.9 %) which was under the good control range[28].

Impact of Warfarin Knowledge and Adherence on TTR

Ababneh et al[27] illustrated the impact of warfarin knowledge on warfarin adherence on anticoagulation control in outpatients with AF. The authors used the Morisky Medication Adherence Scale (MMAS-8). Fifty-four percent of the study subjects (n=331) were adherent (MMAS-8 = 8). Compared to non-adherent participants, adherent patients have a higher likelihood of having better anticoagulation control which was measured by a validated Morisky Medication Adherence Scale (MMAS-8 ≤ 7). Moreover, MMAS-8 adherence ratings were shown to be significantly related to warfarin-knowledge scoring (Spearman's q = 0.291, $p = 0.000$). The percentage of the recruited patients in the adherent group was higher than those in the non-adherent group regarding counseling about warfarin-drug treatment (42 *vs.* 26 %, OR = 2.06, 95 % CI [1.29-3.30] $p = 0.002$)[27].

More recent evidence by Ahmed et al[26] reported that 76.2% (n=88) of patients adhered to warfarin (MMAS score ≥6), and 20.45% were high adherent to warfarin (MMAS score=8). The median score was 6 (interquartile range 6–7). Also, they used the Oral Anticoagulation Knowledge (OAK) assessment and found a notable positive correlation with TTR. There was a strong positive relationship and statistically significant among drug adherence and TTR as an indication of INR control (rs [86] = 0.472, $p<0.0001$)[26].

Discussion

To the best of our knowledge, this is the first systematic review that evaluates the relationship between warfarin adherence and anticoagulation control in AF patients. The conspicuous observation to emerge from the data was the notable impact of adherence on anticoagulation management (TTR and INR) and the role of pharmaceutical care management to achieve a targeted therapeutic outcome of warfarin treatment.

Adherence to medication in the long term, particularly cardiovascular treatments, is considered a crucial challenge for patients and healthcare professionals[36,37]. This is especially true for drugs with a narrow therapeutic range, including warfarin. Unfortunately, despite obtaining instruction and awareness on the necessity of warfarin adherence, patients continue to struggle with maintaining acceptable levels of adherence, impacting their level of anticoagulation management[36].

A study by Kimmel et al[36] demonstrated a substantial correlation between non-adherent and below anticoagulation levels. For example, there was a 14% increase in the likelihood of under anticoagulation readings for every 10% rise in missing tablet bottle openings ($p<.001$); whereas patients

who had additional pills bottle openings on > 10% of days had a marked increase in over anticoagulation (adjusted odds ratio, 1.73; 95 % CI, 1.09-2.74). Thus, maintaining sufficient adherence to the warfarin regimen is challenging for patients, and this poor adherence has a major impact on anticoagulation management[36]. This is similar to our outcomes that support Marcatto et al[25] where the adherence assessment was calculated through surveys and pill counts. The comparison of basal TTR measured on the three most recent INR readings (before the prospective phase) and TTR of 4 weeks (determined by assessing the INR readings from visits 0 to 4, in the prospective phase), basal TTR and TTR of 12 weeks analyzed based on the INR results from visits 0 to 12, in the prospective phase, which reported substantial differences (0.144 ± 0.010 *vs.* 0.382 ± 0.016 and 0.144 ± 0.010 *vs.* 0.543 ± 0.014, $p < 0.001$), respectively[25].

Marcatto et al[25] have identified that the average TTR one year prior (retrospective phase) was lower than that of the TTR reading after 12 weeks of pharmacist-driven care (prospective phase) (0.320 ± 0.015; 0.540 ± 0.015, $p < 0.001$). In summary, the role of pharmaceutical care services enhanced TTR quality in patients with AF and with low anticoagulation control with warfarin[25].

In our review, we found that Farsad et al[28] study demonstrated the effect of the number of medications on the level of TTR control on NVAF patients. The study is in line with retrospective observational research that evaluated the quality of anticoagulation control through TTR employing the Rosendaal method. The effect on INR management was statistically substantial, with higher TTR readings in patients with non-polypharmacy usage compared to the polypharmacy group (42 % *vs.* 57.1 %, $p = 0.03$) and in patients with less often visits to warfarin clinic (18 ± 4.8 *vs.* 22.3 ± 5.5, $p = 0.001$)[38].

Patients in the poor-quality anticoagulation cohort were more frequently to go for outpatient warfarin clinic visits (22.3 ± 5.5 *vs.* 18 ± 4.4, $p = 0.001$) and have a higher percentage of polypharmacy (57.1% *vs.* 42%, $p = 0.03$)[38].

Amongst the included papers, Wang et al[34] yielded that patients who were more knowledgeable ($r = 0.24$, $p = 0.001$) and less worried ($rs = -0.23$, $p = 0.002$) were correlated with greater satisfaction. Increased awareness and satisfaction have been attributed to better adherence to warfarin (rs = 0.21 and 0.16; $p = 0.01$ and 0.046). Good INR management was correlated with better awareness, higher satisfaction, fewer worries, and better warfarin adherence ($p = 0.003$, 0.02, 0.03, and 0.003, respectively)[34]. On the contrary, Kim et al[39] stated that medication adherence was not correlated with a good anticoagulation level as assessed by INR. On the other hand, the adherent category had considerably more knowledge about warfarin than the nonadherent category (7.20 ± 1.70 *vs.* 6.56 ± 1.84, $p = .026$)[39].

Conclusions

It is plausible that some limitations may influence the results obtained in our systematic review, owing to the small number of eligible studies that were included due to the limited studies that were in line with our objective, and they were published in English; the keywords were used from databases were also in the English language. Some articles might have been written and published in other languages, but they were not included in our study. Notwithstanding the limitations of this study, our findings suggest that engagement and collaboration between patients and healthcare providers should be reinforced to promote adherence to warfarin regimens. Additionally, interactions with patients may assist healthcare practitioners in identifying patients' issues and offering them the needed support. Counseling patients and enhancing their knowledge of warfarin intake will encourage them to become more engaged; thus will increase warfarin adherence and maintain good anticoagulant control.

Conflict of Interests

The authors declare that they have no conflict of interests.

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