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Drug-drug Interactions between Warfarin and Antimicrobials: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Introduction: Warfarin is a highly effective oral anticoagulant; however, its use is confined due to a valid concern about bleeding. This systematic review investigates the drug-drug interactions that may occur in patients on warfarin therapy and the use of antimicrobials.
Methodology: PubMed, Web of Science, Science Direct, EBSCO, and Cochrane library were searched. Study articles were screened by title and abstract using Rayyan QCRI then a full-text assessment was conducted.
Results: Eleven studies were included, with a total of 83438 patients. The included studies have reported different antibiotics were associated with bleeding events in patients on warfarin therapy. Three studies associated reported GIT bleeding. Older adults and patients who underwent valve replacement surgery and were on warfarin therapy were found to have an increase in INR with associated antibiotic use.
Conclusion: Patients on warfarin run the risk of a variety of drug interactions. Most interactions but not all—increase the risk of bleeding, and the majority of these are linked to higher international normalised ratios. The good news for doctors is that most common drug interactions with warfarin are triggered by a small number of well-known drug classes, and their effects are shown through a small number of pathways, many of which are clear. The risk of harm brought on by drug interactions can be decreased by being aware of these guidelines, using thoughtful prescription practises, and exercising judicious monitoring when new medications are added to regimens containing warfarin.

Keywords: Warfarin; antimicrobials; drug interaction; bleeding; systematic review.

1. INTRODUCTION

Warfarin, which is a vitamin K antagonist oral anticoagulant, is commonly prescribed to prevent major events, including stroke, venous thromboembolism (VTE), and other thromboembolic sequelae in atrial fibrillation patients and mechanical heart valves [1,2]. Warfarin has been prescribed less frequently recently due to the availability of direct oral anticoagulants (DOACs) in clinical settings [3,4]. Warfarin, however, continues to be the anticoagulant of choice for a large portion of patients who prefer to stay on it, have diseases that necessitate warfarin, or when the additional expense of DOACs is not afforded [5].

To prevent potentially fatal consequences from both under- and over-coagulation, warfarin has a narrow therapeutic range and requires routine monitoring [6]. The risk of severe bleeding among warfarin users has been linked to a wide variety of medications [7,8].

Warfarin users frequently take antibiotics concurrently, and this increases the risk of overanticoagulation [9]. Patients who take warfarin tend to be older, have numerous comorbidities, and take multiple drugs concurrently, all of which can raise their risk of bleeding and make managing their underlying medical disorders more challenging [10]. The principal mechanisms by which antibiotics interact with warfarin to enhance the hazard of major bleeding events is through disturbance of intestinal flora that synthesizes vitamin K and inhibition of cytochrome p450, which metabolizes warfarin [11].

Warfarin has a long history of being the gold standard of anticoagulant therapy, but its limited therapeutic window poses certain clinical difficulties. The unpredictability of a patient's international normalized ratio (INR) and sporadic adverse effects are frequently attributed to the drug's propensity for drug-drug interactions with other drugs [12]. Additionally, clinicians who routinely manage multimorbid diseases requiring numerous concurrent treatments usually worry about drug-drug interactions. Clinicians require reliable information to support their decisions since clinical decision support systems usually base their warnings on high-quality surrogate data, such as medication levels or INR [6,13]. This systematic review aims to investigate the drug-drug interactions that may occur in patients on continuous warfarin therapy and the use of antimicrobials.

2. METHODOLOGY

This systematic review was conducted in accordance with established guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA).

Study Design: This was a systematic Review.

Study duration: From November to December 2022.

Study condition: The main objective of this systematic review is to investigate the drug-drug interactions between warfarin use and antimicrobials.

Search strategy: A comprehensive literature search was conducted in five major databases, including PubMed, Web of Science, Science Direct, EBSCO, and Cochrane Library, to identify the relevant literature. Our search was limited to English, and each database's specific requirements were taken into account. The right studies were located using the following keywords, which were transformed into Mesh terms in PubMed; "Drug-drug interactions," "concurrent," "risk," "hazard," "bleeding," "warfarin," "vitamin K antagonist," "anti-vitamin K," "antimicrobials," and "antibiotics." The appropriate keywords were paired with "OR" and "AND" Boolean operators. The search results comprised English, full-text publications, freely available articles, and human trials.

2.1 Selection Criteria

Inclusion criteria: The subjects were chosen for addition founded on their applicability to the research, which has the following criteria; male or female patients on warfarin use who received antibiotic treatment.

Exclusion criteria: All other articles, ongoing studies, and assessments of previous studies that did not concentrate on one of these concerns were excluded.

Data extraction: To check for duplicate results from the search technique, we employed Rayyan (QCRI) [14]. By limiting the combined search results based on a set of inclusion/exclusion criteria, the researchers were able to determine the relevancy of the titles and abstracts. The reviewers looked over the entire texts of the papers that met the criteria for inclusion. The authors discussed how to resolve conflicts. The qualified study was added using a made-up data extraction form. The authors extracted data about the study titles, authors, study year, study designs, population type, participant number, mean age, gender, antibiotic used, follow-up duration, interaction recorded, and main outcomes.

Strategy for data synthesis: A qualitative description of the included study components and outcomes was provided in summary tables produced from the data collected from the eligible studies. Following data extraction for the systematic review, the best strategy to use the data from the included study articles was chosen. Studies that met the full-text inclusion criteria but did not provide any data on the interaction between warfarin therapy and antibiotics use were excluded.

3. RESULTS

3.1 Search Results

A total of 842 study articles resulted from the systematic search, and then 80 duplicates were removed. Title and abstract screening were conducted on 762 studies, and 577 studies were excluded. 185 reports were sought for retrieval, and only 10 articles were not retrieved. Finally, 175 studies were screened for full-text assessment; 92 were excluded for wrong study outcomes, 52 for unavailable data on drug-drug interaction between warfarin therapy and antibiotics, and 22 for the wrong population type. Eleven eligible study articles were included in this systematic review. A summary of the study selection process in Fig. 1.

3.2 Characteristics of the Included Studies

A total of 11 studies were included in this review, with 83438 patients on warfarin therapy who received antibiotics. Five studies were case-control studies [15,16,17,18,19], five were retrospective cohort studies [20,21,22,23,24], and one was a prospective study [25]. Six studies were conducted in the USA [15,16,20,21,23,24], three in Canada [17,18,19], one in Australia [22], and one in Pakistan [25]. The follow-up duration ranged from 5 days [16] to 1 year [15]. The studies we investigated have reported different antibiotics were associated with bleeding events in patients on warfarin therapy [15,16,17,18,19,20,21,22,24,25]. Three studies associated reported GIT bleeding [16,18,19]. Older adults [24] and patients who underwent valve replacement surgery and were on warfarin therapy [25] were found to have an increase in INR with associated antibiotic use.

Table 1. A summary of characteristics of the included study articles

Study	Country	Study designs	Population type	Participants (n)	Male (n)	Mean age	Antibiotic used	Follow-up	Type of intervention	Key findings
Baillargeon et al. [15]	USA	Case-control	Older adults receiving warfarin	798	279	66 to more than 85	Azole antifungals	1 year	Severe bleeding and hospitalization	Exposure to antibiotics, particularly azole antifungals, was linked to an increased hazard of bleeding among elderly chronic warfarin users.
Schelleman et al. [16]	USA	Case-control	Patients on warfarin	11444	NA	NA	Fluoroquinolones, Sulfonamides, and Azole Antifungals	5 days	GIT bleeding	Patients on warfarin had a higher risk of significant GIT bleeding right after getting an antibiotic, which may indicate that the illness itself or its effects increase patient risk.
Lane et al. [20]	USA	Retrospective cohort	Patients on warfarin	22,722	21702	69.5 ± 10.8	Cotrimoxazole	NA	Severe bleeding and hospitalization	Major bleeding events are more likely to occur when high-risk antibiotics are provided to warfarin users.
Lane et al. [20]	Canada	Case-control	Older adults receiving warfarin	4269	2134	79 ± 6.9	Cefuroxime	14 days	Severe bleeding and hospitalization	Warfarin and levofloxacin have a severe medication interaction that is linked to clinically significant hemorrhage.
Zhang et al. [21]	USA	Retrospective cohort	Patients on warfarin	17,895	8828	64.29 ± 14.6	Metronidazole and cephalosporins	7 days	Severe bleeding and hospitalization	When administrated with warfarin, metronidazole or cephalosporins has a severe interaction that results in significant hemorrhage.
Fischer et al. [18]	Canada	Case-control	Patients on warfarin	2151	1128	74-85	Cotrimoxazole	NA	Upper GIT bleeding	Cotrimoxazole has a considerably higher risk of UGI tract bleeding than other regularly prescribed antibiotics among elderly people taking warfarin.
Vitry et al. [22]	Australia	Retrospective cohort	Veterans on warfarin	17661	11277	81.8 ± 4.4	Different antibiotics, including; macrolides, trimethoprim, and metronidazole	28	Severe bleeding and hospitalization	Aspirin, when administrated with warfarin, has a severe interaction that results in significant hemorrhage.
Clark et al. [23]	USA	Retrospective cohort	Patients on warfarin	5857	2843	70.3 ± 13.1	Oral antibiotics	30 days	Clinically relevant bleeding	Patients using warfarin are more likely to experience excessive anticoagulation with or without exposure to antibiotics if they experience an acute upper respiratory tract infection.
Ghaswalla et al. [19]	USA	Retrospective cohort	Older adults receiving warfarin	205	NA	70-81	Amoxicillin, azithromycin, cephalexin, ciprofloxacin, levofloxacin, or moxifloxacin	14 days	Severe bleeding with or without hospitalization	Antibiotics may cause a rise in INR in elderly patients receiving continuous warfarin treatment.
Liaqat et al. [24]	Pakistan	Prospective	Patients who had valve replacement surgery and on warfarin	75	46	47 ± 12.2	Levofloxacin and moxifloxacin	7 days	Bleeding events	Antibiotics may cause a rise in INR in elderly patients with valve replacement and receiving continuous warfarin treatment.

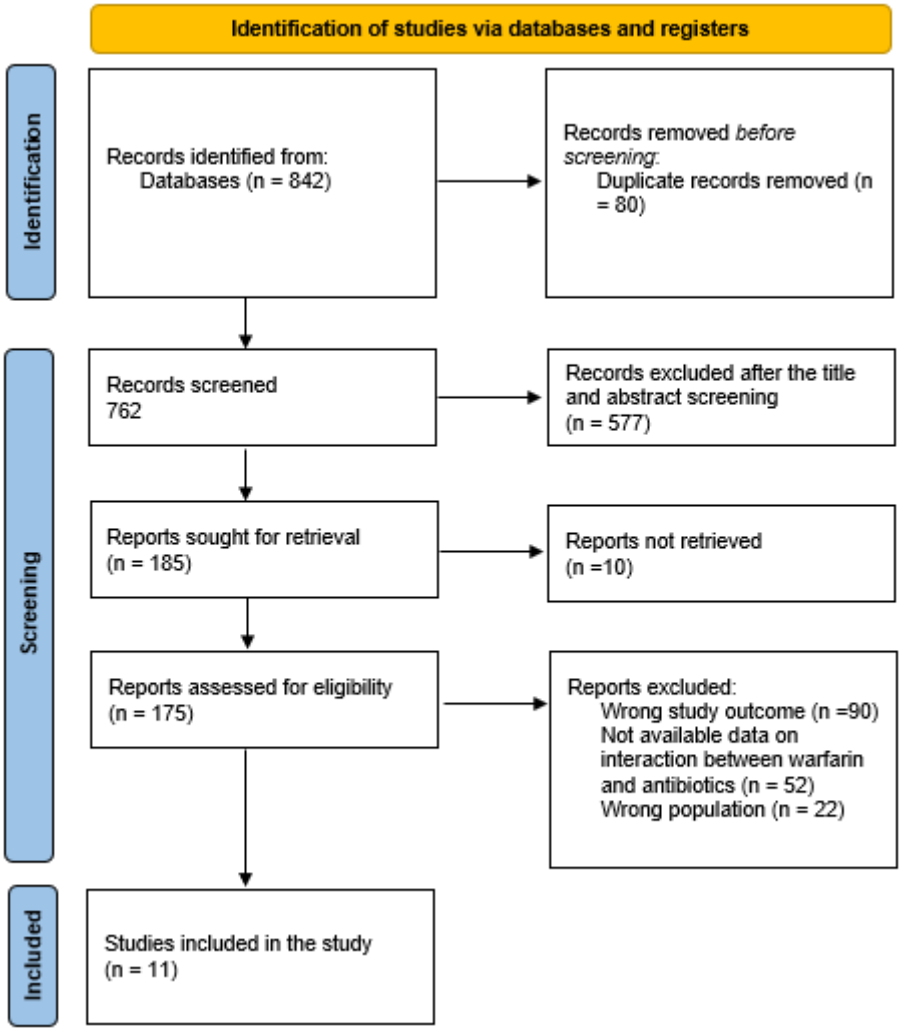

Fig. 1. Presents the PRISMA flowchart

4. DISCUSSION

This updated systematic review demonstrates an increase in warfarin interactions with antibiotics reports, supporting both the anticoagulant's widespread use and its use with other antimicrobials [6]. This study has demonstrated the bleeding risk of antimicrobials and antifungal use among patients on warfarin therapy. These bleeding events included mainly upper GIT bleeding.

The vitamin K status, which is partially reliant on the manufacture of vitamin K2 (menaquinone) by intestinal bacteria, affects the hypoprothrombinemia response to warfarin. Many antibiotics change the composition of the gut flora, which makes warfarin work better [25]. Although interactions of this kind are foreseeable, it is difficult to foretell how they will manifest. When adding any antibiotic to a regimen that includes warfarin, Holbrook et al. has rightly advised caution [6], but some antibiotics additionally decrease the hepatic metabolism of warfarin and thus deserve special consideration. Cotrimoxazole, metronidazole, and, to a lesser extent, macrolides and fluoroquinolones are some of these antibiotics.

All of the anti-infectives that were looked at, including ones that were not typically thought to interact with warfarin (such as amoxicillin and cephalexin), increased the likelihood of hospitalization for GI bleeding [2]. Cotrimoxazole and fluconazole, out of all the investigated anti-infectives, were most likely to have a real drug-drug interaction with warfarin [26].

The present study reported that older adults and patients who underwent valve replacement

surgery and were on warfarin therapy were found to have an increase in INR with associated antibiotic use. Warfarin has a relatively limited therapeutic range, and a variety of things, including diet and drug interactions and the health of the patients receiving warfarin therapy, can change how anticoagulant it is. Warfarin takes roughly 5.5 days on average to show its enhanced hypoprothrombinemia impact [27]. Any factor that affects the pharmacodynamics and/or pharmacokinetics of warfarin can lead to INR levels that are either subtherapeutic or supratherapeutic, which can have major consequences, including further thromboembolic or bleeding events [28].

The most serious clinical side effect related to drug interactions between warfarin and other medications is bleeding. Anticoagulation intensity is the main element that affects bleeding risk, and it has been noted that significant bleeding (such as cerebral and intraperitoneal bleeding) is more likely to occur when the INR is above 4. INR levels of more than 5 generally result in a substantial rise in bleeding problems and hospitalization. Warfarin is prone to a variety of medication interactions since it is metabolized by the hepatic microsomal enzyme system, primarily by the CYP2C9 enzyme. In patients with underlying high-risk cardiac diseases connected to a cardiac prosthetic valve, the American Heart Association (AHA) advises antimicrobial preventive regimens. As a result of drug-drug interactions with warfarin, certain antimicrobials, including azithromycin, erythromycin, cimetidine, fibrates, amiodarone, ciprofloxacin, ofloxacin, and sulfamethoxazole-trimethoprim—can raise INR levels and increase the risk of concerns related to bleeding [29].

In summary, patients on warfarin are at risk for a wide range of medication interactions. Most, but not all, interactions increase the risk of bleeding, and most of these are also associated with raised international normalized ratios. Fortunately for physicians, typical drug interactions with warfarin are precipitated by a small number of well-known medication classes, and their effects are manifested by a small number of mechanisms, many of which are obvious. By being aware of these guidelines, exercising deliberate prescription practises, and exercising prudent monitoring when new medications are introduced to regimens containing warfarin, the risk of harm resulting from drug interactions can be reduced.

5. CONCLUSION

This study has demonstrated that using antimicrobials and antifungals while taking warfarin medication increases the risk of bleeding. These bleeding incidents mostly included upper GIT bleeding. Antibiotic use was reported to raise INR in the elderly and patients who had valve replacement surgery and were taking warfarin therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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