

Narrative Review Of The Relationship Between Warfarin Drug Interaction In Atrial Fibrillation Patients And Therapy Outcomes

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Abstract

Atrial fibrillation (AF) is a common arrhythmia requiring long-term anticoagulant therapy with warfarin to prevent thromboembolic events. However, warfarin's narrow therapeutic index and high susceptibility to drug interactions often compromise International Normalized Ratio (INR) stability. This narrative review evaluates the impact of warfarin drug interactions on clinical outcomes in AF patients. A literature search was conducted in PubMed using keywords “warfarin drug interaction AND Atrial Fibrillation,” “Drug Interaction AND Warfarin,” and “INR AND Drug Interaction AND Warfarin,” limited to 2020–2025. Ten studies (retrospective cohorts, cross-sectional studies, case reports, and one systematic review) met the inclusion criteria of human studies reporting drug-warfarin interactions affecting INR, Time in Therapeutic Range (TTR), or clinical outcomes. Findings showed that interactions with antibiotics (quinolones, sulfonamides), antifungals (fluconazole), and CYP2C9-modulating agents (NSAIDs, anticonvulsants) caused significant INR elevation (frequently >3.7, peaks >10). Major bleeding occurred in up to 86.4% of toxicity cases, while immune checkpoint inhibitors (ICIs) were associated with Grade ≥ 2 INR elevation in 50% of cancer patients, often linked to hepatotoxicity. These interactions also contributed to reduced TTR (<65% in many cohorts). Intensive INR monitoring, interaction-aware dose adjustments, patient education, and consideration of NOACs are essential to minimize bleeding risks and optimize outcomes in AF patients on warfarin.

Keywords : INR, Atrial Fibrillation, Warfarin, Drug Interaction

1. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, with its prevalence rising markedly with age. According to Global Burden of Disease data, AF currently affects approximately 33.5 million people worldwide (2.5–3.5% of the population) and is projected to reach 18 million cases in Europe alone by 2060.

Warfarin remains a cornerstone anticoagulant for stroke prevention in AF patients by inhibiting vitamin K-dependent clotting factors. Despite its proven efficacy, warfarin has a narrow therapeutic index and is highly susceptible to drug-drug interactions, food interactions, and genetic variability, all of which contribute to unstable International Normalized Ratio (INR) levels. Maintaining INR within the therapeutic range is critical, as subtherapeutic INR increases

the risk of thromboembolic events, while supratherapeutic INR dramatically elevates the risk of major bleeding.

Warfarin is primarily metabolized by CYP2C9 and CYP3A4 enzymes, rendering it vulnerable to numerous drug interactions. Although previous studies have examined interactions with specific agents such as antibiotics, antifungals, statins, and anticonvulsants, most have focused on individual drugs or narrow patient populations. There remains a significant research gap in comparative analyses across different drug classes regarding their relative impact on INR stability, Time in Therapeutic Range (TTR), and clinically relevant outcomes (major bleeding and stroke) specifically in AF patients on long-term warfarin therapy.

This narrative review addresses that gap by critically synthesizing recent evidence (2020–2025) on multiple interacting drug classes—including antibiotics, antifungals, CYP2C9 modulators, and immune checkpoint inhibitors—and linking them to key therapeutic outcomes. By providing a comprehensive comparison, this review aims to support clinicians in making evidence-based decisions for safer anticoagulation management and reducing preventable adverse events in AF patients.

2. METHOD

Search Strategy and Procedures

This narrative review was conducted by performing a systematic literature search in the PubMed database. The search strategy was developed to be comprehensive and reproducible.

The following keywords and Boolean operators were used:

(“warfarin” OR “vitamin K antagonist” OR VKA) AND (“drug interaction” OR “drug-drug interaction” OR DDI) AND (“atrial fibrillation” OR AF)

Additional separate searches were performed using: “warfarin” AND “drug interaction” AND “INR”, and combinations with specific drug classes. The search was limited to January 1, 2020 – December 31, 2025. Additional filters included English language and human studies

Study Selection and Scope

The article selection process was conducted in stages. The initial search identified 487 articles. After removing duplicates, 412 unique articles remained. Titles and abstracts were independently screened for relevance, resulting in 68 articles for full-text assessment.

Ultimately, 10 studies fully met the inclusion criteria and were included in this review.

Studies were selected based on clearly defined inclusion and exclusion criteria.

Inclusion Criteria:

- Human studies involving patients with atrial fibrillation (AF) or those receiving long-term warfarin therapy.
- Studies that reported warfarin drug interactions and their effects on International Normalized Ratio (INR), Time in Therapeutic Range (TTR), or clinical outcomes (such as major bleeding, stroke, or hepatotoxicity).
- Original articles, retrospective cohorts, cross-sectional studies, case reports, and systematic reviews published between 2020 and 2025.

Exclusion Criteria:

- Animal studies or in vitro research.
- Studies not reporting drug interaction effects on INR, TTR, or clinical outcomes.
- Articles without full text, conference abstracts, editorials, letters to the editor, or duplicate publications.
- Studies unrelated to warfarin or primarily focused on other anticoagulants without relevant warfarin data.

A total of ten studies that fulfilled the inclusion criteria were selected and included in this review. These studies comprised various designs ranging from individual case reports to large retrospective cohorts and one systematic review.

Operational Definition of Variables

The research variables are operationally defined to measure the relationship between drug exposure and clinical outcomes:

Independent Variables: Interactions between warfarin and various drug classes, including antibiotics (sulfonamides, quinolones), antifungals (fluconazole), statins, immune checkpoint inhibitors (ICIs), and drugs modulating the CYP2C9 enzyme (NSAIDs, anticonvulsants).

Dependent Variables (Therapy Outcomes): Measured through the stability of the International Normalized Ratio (INR), Time in Therapeutic Range (TTR), and the occurrence of clinical events such as major bleeding, stroke, or hepatotoxicity.

3. RESULTS AND DISCUSSION

The systematic search in PubMed yielded a total of 487 articles. After duplicate removal and screening of titles and abstracts, 68 articles were selected for full-text review. Finally, 10 studies met the predefined inclusion criteria and were included in this narrative review.

The included studies comprised various designs: five retrospective cohorts, two cross-sectional studies, two case reports, and one systematic review. The populations studied primarily

involved patients with atrial fibrillation (AF) or those on long-term warfarin therapy, with sample sizes ranging from single cases to 1551 participants.

Summary of Included Studies

Table 1. Summary of the ten included studies (2020–2025)

No	Author & Year	Study Design	Population	Key Clinical Findings	Main Conclusion
1	(Penjore et al., 2023)	Cross-Sectional (record review)	22 warfarin toxicity admissions (40.9 % AF)	Mean INR 7.7 (max 20); 86.4 % major bleeding (GI, haematoma, epistaxis)	Drug interactions + dosing errors main causes; recommend NOAC evaluation
2	(Mwita et al., 2022)	Retrospective cohort protocol (9 SSA countries)	Planned patients on VKA ≥3 months	Expected TTR <65 % in majority	Suboptimal anticoagulation control common in resource-limited settings
3	(Engell & Svendsen, 2020)	Registry-based cohort	1551 warfarin users starting statins	Mild INR rise (simvastatin +0.32, atorvastatin +0.27) peaking at 4 weeks	Statin effect modest but warrants INR monitoring
4	(Chen et al., 2024)	Case report	64-year-old woman (mechanical valve + AF, 10 years warfarin)	INR >10, GI bleeding, acute liver injury	Warfarin-induced hepatotoxicity + bleeding; immediate cessation + hepatoprotection required
5	(Fu et al., 2024)	Retrospective cohort	623 hospitalized patients (warfarin + antibiotic)	Max INR: quinolones 3.77, sulfonamides 4.13, antifungals 4.37 (highest)	Quinolones, sulfonamides, and antifungals produce the strongest INR elevation
6	(Uenoyama et al., 2025)	Retrospective single-arm cohort	26 cancer patients (warfarin + ICIs)	50 % Grade ≥2 PT-INR rise; 5 required vitamin K	ICIs significantly elevate INR via immune-related hepatotoxicity; frequent coagulation checks needed
7	(Sridharan et al., 2022)	Cross-sectional therapeutic audit	203 patients on warfarin ≥6 months	~33 % poor control; CHA ₂ DS ₂ -VASc & HAS-BLED predictive	In-house dose-titration protocol urgently needed
8	(Ababneh et al., 2021)	Systematic review (12 studies)	AF patients on warfarin	Positive correlation: adherence ↑ → TTR/INR control ↑	Pharmaceutical care and education improve outcomes
9	(Zhu et al., 2020)	Case report	54-year-old woman (AF + prosthetic valve + fungal endocarditis)	Dramatic INR rise on fluconazole; subcutaneous bruising	Replace fluconazole with caspofungin or reduce warfarin dose with close INR monitoring

10	(Agrawal et al., 2020)	Retrospective observational cohort	302 long-term warfarin users	CYP2C9-interacting drugs > genotype in causing INR variability & TTR reduction	Drug–drug interactions must be integrated into pharmacogenomic algorithms
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Key characteristics and findings of the ten studies are presented in Table 1. Overall, drug interactions with warfarin were associated with supratherapeutic INR in the majority of studies. Eight studies reported elevated INR levels, with maximum INR values frequently exceeding 4.0 and reaching above 10 in several cases. Major bleeding events were prominent, occurring in up to 86.4% of patients admitted for warfarin toxicity.

Interactions with anti-infective agents (antibiotics and antifungals) consistently demonstrated the strongest effect on INR elevation. Quinolones, sulfonamides, and antifungals showed mean maximum INR values ranging from 3.77 to 4.37. Concurrent use of immune checkpoint inhibitors (ICIs) in cancer patients resulted in Grade ≥ 2 PT-INR elevation in 50% of cases. CYP2C9-modulating drugs (such as NSAIDs and anticonvulsants) were linked to greater INR variability and lower Time in Therapeutic Range (TTR), often below 65%. Suboptimal TTR was commonly observed across multiple studies, particularly in resource-limited settings

DISCUSSION

The findings demonstrate clear patterns of warfarin drug interactions across different classes. Antibiotics (particularly quinolones and sulfonamides) and antifungals produced the most pronounced INR elevations, frequently leading to major bleeding complications. This aligns with their strong inhibitory effects on CYP2C9 and protein-binding displacement. Immune checkpoint inhibitors emerged as a clinically important interaction in oncology patients, with half of the patients experiencing significant INR rises often accompanied by hepatotoxicity. CYP2C9-interacting drugs contributed more to INR instability and TTR reduction than genetic factors alone.

These results highlight that drug-drug interactions represent a major modifiable risk factor for over-anticoagulation and bleeding in AF patients on warfarin. The narrow therapeutic index of warfarin amplifies these effects, resulting in frequent supratherapeutic INR and poor anticoagulation control. Compared to previous single-drug studies, this review provides a broader comparative synthesis across drug classes and links them directly to clinically relevant outcomes.

4. CONCLUSION

This narrative review demonstrates a strong relationship between warfarin drug interactions and poor therapeutic outcomes in patients with atrial fibrillation. Drug interactions significantly contribute to INR instability, reduced Time in Therapeutic Range (TTR), and increased risk of adverse clinical events.

The findings confirm that warfarin's narrow therapeutic index makes it highly vulnerable to drug-drug interactions, frequently resulting in supratherapeutic INR and suboptimal anticoagulation control. These effects are particularly concerning in patients with polypharmacy, advanced age, or comorbidities.

Effective management requires intensive INR monitoring, timely dose adjustments, and strong patient education. In appropriate cases, switching to Non-vitamin K Oral Anticoagulants (NOACs) should be considered to minimize interaction-related risks. Proactive identification and management of drug interactions are essential to improve safety and optimize stroke prevention in AF patients receiving warfarin therapy.

5. REFERENCE

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