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Prevalence and characteristics of potential drug-drug interactions in hospitalized atrial fibrillation patients receiving anticoagulant therapy

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ABSTRACT

Background: Anticoagulants are essential for stroke prophylaxis in atrial fibrillation but carry significant interaction potential with commonly used medications. Understanding the prevalence and characteristic of these interactions is crucial for optimizing therapy.

Objective: To assess the prevalence and characteristics of potential drug-drug interactions (DDIs) in hospitalized atrial fibrillation patients receiving anticoagulant therapy.

Methods: This retrospective, descriptive observational study analyzed medical records of 324 atrial fibrillation patients hospitalized between January 2019 and December 2021 at a regional hospital in Banyumas Regency. Potential DDIs were assessed using Lexicomp, Drugs.com, and Merck Manual databases, and categorized by severity, mechanism, and clinical manifestation.

Results: Of 1,249 identified DDI events, most were moderate in severity (83.27%) and primarily involved warfarin (69.73%). Pharmacodynamic mechanisms predominated (51.24%), and decreased anticoagulant efficacy was the most common potential clinical manifestation (64.21%). Warfarin accounted for most pharmacokinetic (10.49%) and pharmacodynamic (32.42%) interactions. Elderly patients (>65 years) constituted the largest population group (40.74%), and most patients (65.74%) had atrial fibrillation as a secondary diagnosis.

Conclusion: The high prevalence of potential DDIs involving anticoagulants in hospitalized atrial fibrillation patients underscores the need for vigilant medication management, particularly for patients receiving warfarin and those with multiple comorbidities.

Keywords: atrial fibrillation, anticoagulants, drug-drug interactions, warfarin, medication safety

Introduction

Atrial fibrillation is the most common heart rhythm disorder, marked by uncoordinated atrial contractions and a rapid ventricular response [1]. The prevalence of atrial fibrillation has increased by 33% over the past 20 years. In 2017, the global prevalence of atrial fibrillation reached 37.534 million cases (4,977 cases per million population), and it is expected to increase by more than 60% by 2050 [2].

Anticoagulants are one of the primary treatments for atrial fibrillation patients [3]. Anticoagulants are the primary choice for stroke prophylaxis in atrial fibrillation patients. They can be administered orally, such as vitamin K antagonists like warfarin and new oral anticoagulants (NOACs) like edoxaban and rivaroxaban. Intravenous anticoagulants, on the other hand, belong to the group of indirect thrombin inhibitors, including enoxaparin, fondaparinux, and heparin [4].

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An essential aspect of ensuring the quality and safety of anticoagulant therapy is the management of drug interactions [5]. It is estimated that nearly 80% of atrial fibrillation patients will receive medications that can interact with oral anticoagulants throughout their lifetime [6]. Vitamin K antagonist anticoagulants, such as warfarin, are narrow therapeutic index drugs with a high risk of life-threatening drug-related events. They top the list of drugs with interactions, with warfarin known to interact with over 500 drugs [7,8]. NOACs have a higher safety profile and are less affected by interactions, but potential interactions still need monitoring and consideration [7]. Rivaroxaban and edoxaban have interactions with 332 and 248 drugs, respectively [9].

Unmanaged drug interactions with anticoagulants can lead to serious clinical consequences, including increased risk of major bleeding events or reduced therapeutic efficacy resulting in thrombotic complications. The prediction of drug interactions can occur before administering medications to patients [10]. Despite available information on potential drug interactions, a gap remains in understanding their actual incidence and patterns in clinical settings, particularly among hospitalized patients with atrial fibrillation.

New information about anticoagulant drug interactions continues to evolve, making it crucial for pharmacists to regularly consult databases and literature to stay updated on these interactions. Moreover, the management of drug interactions can lead to improved clinical outcomes and the prevention of adverse effects in patients undergoing anticoagulant treatment [5]. This study's focus on hospitalized patients with atrial fibrillation provides valuable insights into medication management in this high-risk population. Therefore, this study was conducted to assess the prevalence of potential drug-drug interactions in patients receiving anticoagulant therapy.

Methods

Design study and population

This was a retrospective, descriptive observational study of medical records from atrial fibrillation patients between January 2019 and December 2021 at one of the regional hospitals in Banyumas Regency. Data collection was conducted from September to December 2022 using total sampling. From the available population, 324 patients met the following inclusion criteria: a) Inpatients diagnosed with atrial fibrillation and flutter with the International Classification of Diseases (ICD-10) code: I48; b) aged ⩾17 years; c) receiving anticoagulant drugs via oral, subcutaneous, and/or intravenous routes. There were no exclusion criteria in this study.

Ethical consideration

This research received ethical approval from the Ethics Commission of RSUD Prof. Dr. Margono Soekarjo (approval number: 420/04627, granted on April 14, 2022).

Research instrument

The patient medical record data used in this study was documented on a Case Report Form (CRF) sheet, which includes the medical record number, patient identity (initial name, gender, and age), diagnosis (primary and secondary), as well as details about anticoagulant therapy and other administered treatments (type, dose, administration frequency, and route of administration).

Data analysis

Data were analyzed descriptively, including patient characteristics (age, gender, and atrial fibrillation diagnosis), the profile of anticoagulant use (monotherapy and switch therapy), and the incidence of potential interactions among anticoagulant drugs (quantity, severity, mechanism, and clinical manifestations).

Potential drug-drug interactions (DDIs) were assessed using three complementary databases: the Lexicomp database on UpToDate [11], Drugs Interaction Checker on Drugs.com [9], and Drug Info on Merck Manual [12]. These databases were selected to provide comprehensive coverage of potential interactions. In cases of discrepancies between databases regarding interaction severity or clinical significance, Lexicomp in UpToDate was used as the reference. The severity of interactions was classified according to the Lexicomp rating system as contraindicated, major, moderate, minor, or no interaction. The analyzed interactions included those between anticoagulant drugs and interactions between anticoagulant drugs and other medications used by the patient.

Results

Patient characteristic and profile of anticoagulants use

A total of 324 patients met the inclusion criteria in this study. The results showed that the majority

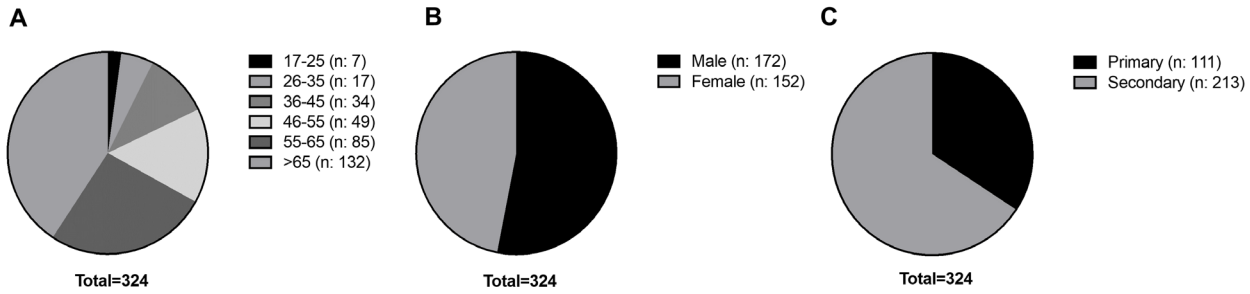

Figure 1. Patient characteristics. (A) Age, (B) Gender, (C) Diagnosis of atrial fibrillation

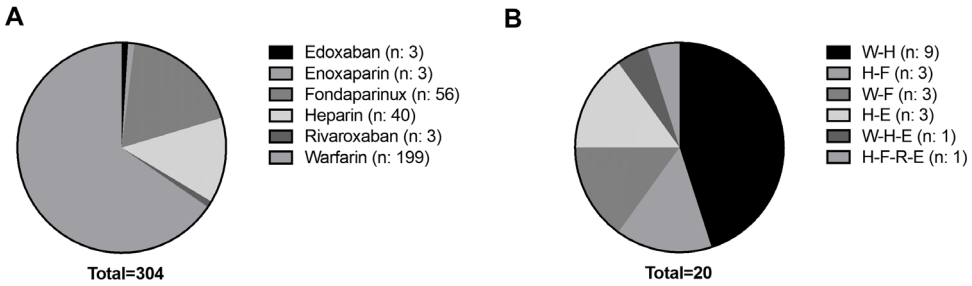

Figure 2. Profile of anticoagulants use. (A) Monotherapy (n=304), (B) Switch therapy (n=20). W-H (warfarin to heparin), H-F (heparin to fondaparinux), W-F (warfarin to fondaparinux), H-E (heparin to enoxaparin), W-H-E (warfarin to heparin to enoxaparin), H-F-R-E (heparin to fondaparinux to rivaroxaban to enoxaparin)

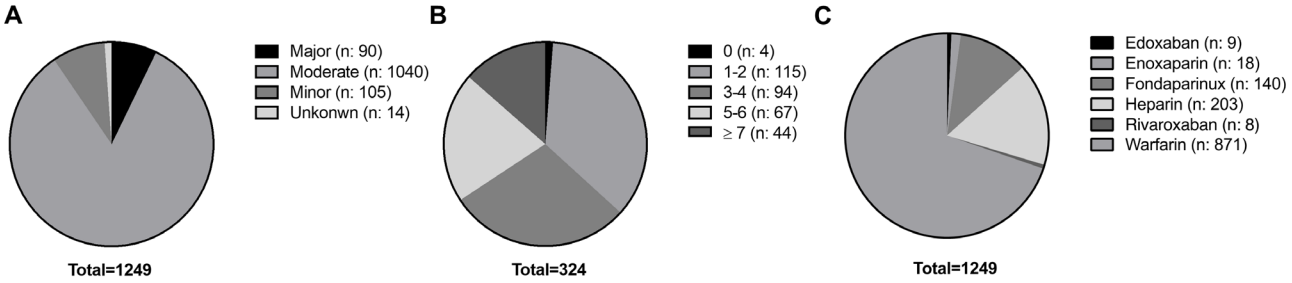

Figure 3. Severity level and number of potential DDI events. (A) Severity level of potential DDIs of anticoagulants*, (B) Number of potential DDI events, (C) Number of Potential DDIs events per anticoagulant*. *: more than one severity per anticoagulant

of the patients were elderly, aged over 65 years (132 patients; 40.74%), with a higher proportion of males (53.09%) than females (46.91%) (Figure 1A,B). These findings are consistent with the global prevalence of atrial fibrillation, where in 2017, there were 37.534 million cases with a male-to-female ratio of 1.11:1 [2].

Most patients (65.74%) had atrial fibrillation as a secondary diagnosis rather than a primary diagnosis. Among patients with other primary diagnoses, myocardial infarction (71 patients, 21.91%) and congestive heart failure (42 patients, 12.96%) were the most common conditions (Figure 1C).

In this study, patients received various types of anticoagulants treatments, either as monotherapy or switch therapy (Figure 2).

Potential drug-drug interactions of anticoagulants

Nearly all patients (n:320 patients or 98.90%) experienced potential drug-drug interactions (DDIs) involving anticoagulants. The majority of potential interactions (83.27%) were classified as *moderate* in severity (Figure 3A). Potential *major* DDIs were associated with warfarin (61 events), heparin (9 events), edoxaban (8 events), fondaparinux (7 events), and rivaroxaban (5 events).

Figure 3B shows the distribution of potential DDI events per patient and per anticoagulant. Most patients (35.49%) experienced 1-2 potential DDIs. Warfarin was associated with the highest number of potential interactions (69.73% of all DDIs) (Figure 3C), reflecting its widespread use and complex interaction profile.

Table 1. Mechanism of potential DDIs of anticoagulants

No	Anticoagulants	Pharmacokinetics	Pharmacodynamics	Unknown
1	Edoxaban	1	4	4
2	Enoxaparin	0	4	14
3	Fondaparinux	0	140	0
4	Heparin	0	85	118
5	Rivaroxaban	5	2	1
6	Warfarin	131	405	335

Table 2. Manifestations of anticoagulants DDIs

Anticoagulants	Manifestations of interaction	n (%)
Edoxaban	Bleeding	8 (0.64%)
	Decreased Efficacy (coagulation)	1 (0.08%)
Enoxaparin	Bleeding	10 (0.80%)
	Hyperkalemia	8 (0.64%)
Fondaparinux	Bleeding	140 (11.21%)
Heparin	Bleeding	55 (4.40%)
	Decreased Efficacy (coagulation)	43 (3.44%)
	Hyperkalemia	105 (8.41%)
Rivaroxaban	Bleeding	7 (0.56%)
	Decreased Efficacy (coagulation)	1 (0.08%)
Warfarin	Bleeding	71 (5.69%)
	Decreased Efficacy (coagulation)	800 (64.05%)
Total		**1249 (100%)**

The analysis of potential DDIs is categorized into three groups based on their mechanisms: pharmacokinetic, pharmacodynamic, and unknown mechanisms. The majority of potential DDIs with pharmacokinetic and pharmacodynamic mechanisms involved warfarin, accounting for 131 events (10.49%) and 405 events (32.42%), respectively (Table 1).

Pharmacodynamic interactions were the most prevalent mechanism, accounting for 640 events (51.24% of all interactions). These interactions primarily involved warfarin (405 events, 32.42%) and fondaparinux (140 events, 11.21%), suggesting that these anticoagulants frequently interact with other medications through altered pharmacological effect rather than changes in drug concentration.

Pharmacokinetic interactions, which involve alterations in drug absorption, distribution, metabolism, or excretion, were less common overall (137 events, 10.97%). Warfarin was responsible for the vast majority of these interactions (131 events, 10.49%), reflecting its complex metabolism through the cytochrome P450 enzyme system and high protein binding. The other anticoagulants demonstrated minimal pharmacokinetic interactions, with rivaroxaban (5 events, 0.40%) and edoxaban (1 event, 0.08%) showing only a few instances.

A substantial proportion of interactions (472 events, 37.79%) had unknown mechanisms, particularly with warfarin (335 events, 26.82%) and heparin (118 events, 9.45%). This highlights a significant knowledge gap in understanding how these medications interact with concomitant drugs, potentially complicating clinical management decisions.

The predominance of warfarin across all interaction mechanisms is consistent with its known complex pharmacological profile and extensive drug interaction potential compared to other anticoagulants. These findings emphasize the need for careful medication

management, particularly when warfarin is prescribed alongside other medications.

Table 2 presents the clinical manifestations of anticoagulant drug-drug interactions observed in the study. The most common clinical manifestation across all anticoagulants was decreased efficacy of anticoagulation (67.65% of all interactions), with warfarin accounting for the vast majority of these cases (800 events, 64.05% of total interactions). This finding is particularly significant as decreased efficacy could potentially lead to thrombotic events in these already at-risk patients.

Bleeding risk was the second most common manifestation, occurring across all anticoagulant types. Fondaparinux was associated with the highest number of bleeding-risk interactions (140 events, 11.21%), followed by warfarin (71 events, 5.69%) and heparin (55 events, 4.40%). This aligns with the known safety profiles of these medications.

Hyperkalemia was identified as a potential manifestation specifically with heparin (105 events, 8.41%) and enoxaparin (8 events, 0.64%), representing an important metabolic complication that requires monitoring in patients receiving these agents.

These findings underscore the importance of vigilant monitoring for both decreased therapeutic effect and increased bleeding risk when anticoagulants are administered concurrently with other medications, particularly for patients receiving warfarin, which was involved in nearly 70% of all potential drug interactions identified in this study.

Discussions

This study revealed a strikingly high prevalence of potential drug-drug interactions (DDIs) among hospitalized atrial fibrillation patients receiving anticoagulant therapy, with 98.90% of patients experiencing at least one potential interaction. Warfarin was the predominant anticoagulant associated with these interactions, accounting for 69.73% of all identified DDIs. The majority of interactions were classified as moderate in severity (83.27%), with pharmacodynamic mechanisms (51.24%) being most common, and decreased anticoagulant efficacy (64.21%) representing the primary clinical concern. These findings highlight the significant challenges in medication management for this patient population.

Advanced age is a well-established risk factor for atrial fibrillation due to structural cardiac changes that can trigger the condition [13]. Our results confirmed this association, with elderly individuals aged over 65 years predominating among atrial fibrillation patients (40.74%). This aligns with global epidemiological data showing that the increase in atrial fibrillation cases is most notable in the 65-69 age group, with 0.526 million new cases recorded in 2017, following similar patterns observed in those over 70 years of age in 2007 and 1997 [2].

The slight male predominance observed in our study (53.09% vs. 46.91%) is consistent with the global male-to-female ratio of 1.11:1 reported in epidemiological studies [2]. Furthermore, the high proportion of patients with atrial fibrillation as a secondary diagnosis (65.74%) reflects the strong association between atrial fibrillation and other cardiovascular diseases. Atrial fibrillation is known to increase the risk of additional cardiovascular conditions, including a five-fold higher risk of stroke and a three-fold higher risk of heart failure [14]. This explains why myocardial infarction (21.91%) and congestive heart failure (12.96%) were the most common primary diagnoses in our patient population.

Warfarin was the most frequently prescribed anticoagulant (61.42% as monotherapy), despite the increasing availability of direct oral anticoagulants (DOACs). The choice of appropriate anticoagulant is typically determined using the SAME-TT2R2 score, which considers sex, age, medical history, treatment, tobacco use, and race. Patients with a SAME-TT2R2 score of ⩽2 are predicted to have a good time-in-therapeutic tange (TTR), making vitamin K antagonists like warfarin the recommended choice [15]. While DOACs are now generally preferred for stroke prevention in patients with atrial fibrillation, warfarin remains widely used due to multiple factors, including its lower cost, provider unfamiliarity with newer agents, concerns about the reversibility of DOACs, and prior authorization barriers limiting access [16].

The relatively low use of NOACs observed in our study (only 0.93% for rivaroxaban and 0.93% for edoxaban) contrasts with current guidelines recommending them as first-line agents. This discrepancy likely reflects regional practice patterns, economic constraints, and the study's time frame, which may not fully capture recent shifts toward NOAC adoption.

The prevalence of potential DDIs in our study was remarkably high (98.90% of patients), which aligns with previous research showing increased interaction risk in cardiovascular patients due to the complexity of

pharmacotherapy. This high prevalence is also linked to older age, extended hospital stays, and polytherapy [17], all of which were common features in our patient population.

The predominance of warfarin in DDIs (871 events; 69.73%) is not surprising given its widespread use and complex interaction profile. While over 500 types of drug interactions are known to occur with warfarin, limited data are available regarding their clinical significance. Some drug interactions with warfarin become clinically relevant only in specific situations, such as in patients with genetic polymorphisms in CYP2C9 substrates [8].

Regarding the severity of these DDIs, the majority were of moderate severity (83.27%), with major drug interactions accounting for 7.20% of events. This distribution is concerning, as moderate interactions may worsen the patient's condition and necessitate additional treatment or extended hospitalization, while major interactions can be life-threatening or lead to permanent damage [11].

Pharmacokinetic and pharmacodynamic interaction mechanisms have distinct clinical implications. In our study, pharmacodynamic interactions predominated (51.24% of all interactions), particularly with warfarin (32.42%) and fondaparinux (11.21%). This suggests that these anticoagulants frequently interact with other medications through altered pharmacological responses rather than changes in drug concentration.

Warfarin's pharmacokinetic interactions (10.49% of total) primarily occurred with spironolactone during the metabolic phase (127 events). As a CYP3A4 inhibitor, spironolactone can inhibit warfarin metabolism, potentially leading to bleeding complications. This interaction is classified as moderate in severity [11]. Drug-drug interactions that enhance warfarin's effects typically increase International Normalized Ratio (INR) and require careful monitoring [7,20,21].

For pharmacodynamic mechanisms, warfarin had a notable potential interaction with paracetamol (42 cases). The paracetamol metabolite (NAPQI) inhibits the vitamin K reductase enzyme, increasing bleeding risk. This interaction is also of moderate severity, necessitating monitoring of warfarin's effects when initiating or discontinuing paracetamol [11].

The finding that decreased efficacy of anticoagulation was the most common potential clinical manifestation (64.21% of all interactions) is particularly concerning, as it could lead to thrombotic events in these already high-risk patients. Conversely, bleeding risk was identified across all anticoagulant types, with fondaparinux associated with the highest number of bleeding-risk interactions (11.21%), followed by warfarin (5.69%) and heparin (4.40%). Hyperkalemia was identified specifically with heparin (8.41%) and enoxaparin (0.64%), representing an important metabolic complication that requires monitoring.

These findings have several important implications for clinical practice. First, medication reconciliation and review should be standard practice for all hospitalized atrial fibrillation patients, particularly those receiving warfarin. Second, electronic prescribing systems with built-in drug interaction alerts could help identify potential problems before they occur. Third, for patients on warfarin with multiple medications, more frequent INR monitoring may be necessary, especially when medications are added or removed from the regimen.

For NOACs, despite their lower interaction potential compared to warfarin, clinicians should remain vigilant about specific interaction pairs, particularly with antifungals, antiretrovirals, and certain antibiotics. The lower prevalence of NOAC interactions in our study (0.72% for edoxaban and 0.64% for rivaroxaban) may partly reflect their limited use rather than inherently lower interaction risk.

This study provides valuable insights into medication management in hospitalized patients with atrial fibrillation. However, several limitations must be acknowledged. First, we examined only the potential for drug interactions based on patients' medication history in medical records without monitoring actual clinical outcomes. The identified interactions may not always manifest clinically or accurately reflect the patient's condition. Second, the single-center design may limit generalizability to other settings or regions with different prescribing patterns.

Future research should focus on prospective studies that correlate potential drug interactions with actual clinical outcomes such as bleeding events, thrombotic complications, or hospital readmissions. Additionally, intervention studies testing various strategies to reduce clinically significant drug interactions in this population would be valuable. As NOAC use continues to increase, more research is needed to better understand their real-world interaction profiles compared to warfarin.

Conclusion

In conclusion, the extremely high prevalence of potential drug-drug interactions involving anticoagulants in hospitalized atrial fibrillation patients underscores the need for vigilant medication management, particularly for patients receiving warfarin. Clinicians should be especially attentive to interactions that may decrease anticoagulant efficacy, as these represented the most common potential clinical manifestation in our study.

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Conflict of interest

None.

Author contributions

DLI, MWS, NEE: Conceptualization, Methodology; AP: Collecting data; DLI, AP, MWS: Analyzing the data; DLI, AP: led the drafting of the manuscript to which all authors contributed with the revision. All authors agreed to the final version of the manuscript.

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