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Original Research Article

A study of drug-drug interactions involving direct oral anticoagulants for discharged patients in Sana'a city, Yemen

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Abstract

Background: Direct oral anticoagulants (DOACs) are fast-acting agents for blood clots, offering a favorable risk-benefit profile with significant reductions in stroke, intracranial hemorrhage, and mortality compared to warfarin. However, combining treatments can lead to drug-drug interactions (DDIs), affecting DOACs' exposure or pharmacological activities. The risk and severity of DDIs vary among DOACs, and they are particularly concerning for patients with major comorbidities requiring additional therapies.

Objective: To evaluate the prevalence and severity of the potential DDIs of DOACs among adult patients (18 years or older) who have received DOACs therapy at hospital discharge.

Methodology: This cross-sectional study was conducted at two hospitals in Sana'a from January 2022 to January 2023. The study data included demographic, clinical, and drug-therapy-related variables, which was collected from paper medical records. Drug interactions were identified using updated Lexicomp online software.

Results: Out of 146 patients, there were 140 (95.9%) individuals who had a total of 733 clinically significant DDIs. Specifically, 113 (77.4%) individuals had a total of 184 clinically significant DDIs with DOACs. 165 (89.7%) of which were category D, 14 (7.6%) of which were category X, and only 5 (2.7%) of which were category C DDIs with DOACs. There was also an association between advanced age, co-morbidities, and concomitant drug with the presence of DDI with DOACs.

Conclusion: The most potential drug interactions with DOACs was with aspirin (54.3%), clopidogrel (33.2%), Enoxaparin (6%)) and diltiazem (1.1%). It was also noticed that category D DDIs with DOACs was the most common, followed by category X DDIs with DOACs.

Keywords: Concomitant therapies Direct oral anticoagulants, Drug-drug interactions, Lexicomp

Introduction

Blood coagulation and platelet-mediated primary hemostasis have evolved as important defense mechanisms against bleeding. The coagulation system is triggered in response to rupture of endothelium, which allows exposure of blood to the extravascular tissue. The responses of the coagulation system are coordinated with the formation of the platelet plug that initially occludes the vascular lesion. Anticoagulant mechanisms ensure careful control of coagulation and, under normal conditions, they prevail over the procoagulant forces. Disturbances of the natural balance between the procoagulant and anticoagulant systems due to genetic or acquired factors may result in bleeding or thrombotic diseases [1].

Anticoagulants drugs are used for treating and preventing embolic events and derive their effect by acting at different sites of the coagulation cascade. Some act directly by enzyme inhibition, while others indirectly, by binding to antithrombin or by preventing their synthesis from the liver. Drug-drug interaction (DDI) is defined as the change in the drug effect when a second drug is taken concurrently. Many drugs interact with each other in many ways. When two drugs interact with each other, this interaction results in either increasing the effect of one or both of them or in preventing one or both of them from doing their activity. Types, mechanisms, and yields of DDIs vary variably [2].

DDIs may be either pharmacokinetic (PK) or pharmacodynamical (PD). Pharmacokinetic drug-drug interaction occurs when one drug hinders either: the absorption, distribution, metabolism, or excretion of the other drug. Pharmacodynamical drug-drug interaction, on the other hand, occurs when two drugs are administered and one of them alters the pharmacologic effect of the other, either by increasing or decreasing it. Decreasing the activity of a drug (antagonism) usually ends up with therapeutic failure, while increasing (synergism or addition) the activity of the drug results in increasing its toxicity [3].

Some risk factors contribute to increased DDIs. Using multiple medications at the same time is surely the main reason. Patients who have multiple conditions (comorbidities) are more subjected to DDIs due to the use of multiple drugs at the same time (polypharmacy). Impaired kidney or liver functions make the body unable to get rid of excess concentrations of medication substances. Some medical conditions make the patients susceptible to DDIs as well [4].

DDIs vary in severity and risk levels. Some drugs, if given together, yield a life-threatening interaction. In such cases, the drugs should not have given together and an alternative agent should be used instead. Other drugs would cause an interaction but that interaction is not that serious, and the drugs can be given and monitoring for signs of the interactions is required. Still, some drugs can cause mild interactions and nothing serious would happen if they were given together. DDIs vary in severity levels according to the mechanism by which they interact [3].

When two drugs interact with each other resulting in altering the process that each one should cause and undergo, this is called DDIs. These interactions vary depending on many factors and mechanisms. The severity of DDIs also varies. DDIs can reduce a

drug's effectiveness, induce unanticipated adverse effects, or enhance a drug's action. It occurs when a patient's response to a drug is altered by food, medication, or illness. When two or more medications react with one another, this is referred to as a drug-drug interaction. Drug interactions are a frequent cause of adverse medication responses and increased patient hospitalization rates. Drug interactions are more common among patients with co-morbidities, especially the elderly [3].

The most common chronic conditions from which the older adults suffer often include cardiovascular disease, diabetes mellitus, and chronic kidney disease. Cardiovascular disease is common in older adults and atrial fibrillation (AF) is the most common type of cardiac arrhythmia worldwide and its prevalence is increasing due to the ageing population and other risk factors and comorbidities [5].

The direct oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban, and edoxaban are becoming the most commonly prescribed drug for preventing ischemic stroke in patients with non-valvular atrial fibrillation, for other cardiovascular disease that increase risk of thromboembolic event and for the treatment and prevention of venous thromboembolism (VTE) [5].

DOACs have broadened the landscape of oral anticoagulant therapy for almost a decade. They were first approved for the prevention of VTE after hip or knee replacement surgery [6]. Since 2011, they have also been indicated for stroke prevention in patients with non-valvular atrial fibrillation as well as for the treatment and secondary prevention of VTE. In 2016, the guidelines issued by the European Society of Cardiology and the American College of Chest Physicians recommended DOACs over vitamin K antagonists (VKAs) in eligible patients [7].

Initially, VKAs were the only feasible oral anticoagulants. There is a substantial downside with the use of VKAs such as increased risk of bleeding, narrow therapeutic index, individualized dosing based on INR, and many more. Direct oral anticoagulants resolved these issues to a remarkable extent. It is at least as effective as traditional anticoagulants and is convenient to administer as it is given as fixed doses without routine coagulation monitoring. It has a predictable and consistent PK-PD profile. Unlike VKAs, DOACs have more predictable PK-PD properties. Due to this appreciable characteristic, DOACs are used at fixed doses without periodic monitoring of coagulation parameters [8].

DOACs act by two different mechanisms. Based on this, it is grouped as direct thrombin inhibitor and direct factor Xa inhibitor. The former category inhibits coagulation by directly binding to thrombin and prevents the formation of fibrin by restricting thrombin from breaking fibrinogen. The latter group inhibits factor Xa, which is trypsin-like serine protease that plays a critical role in the blood coagulation cascade. It has a principal position in linking the intrinsic and extrinsic pathways to the final common coagulation pathway. These agents bind directly to factor Xa and prevent it from cleaving prothrombin to thrombin [9].

Pharmacokinetic profile varies among agents in this family. All DOACs absorbed rapidly following administration. Food intake has a

variable effect on DOACs absorption; Rivaroxaban is more effectively absorbed when taken with food, however, there is no effect of the presence of food in the stomach on absorption of Edoxaban, apixabana and dabigatran. Most of DOACs extensively bound to plasma protein, and as a result, systemic exposure unbound active drug is low. DOACs metabolism is variable; dabigatran metabolized by the glucoronic acid conjunction. Apixaban metabolized by cyp3A4, cyp1A2, cyp2j2, cyp2bC8, cyp2C9 and cyp19. Edoxaban metabolized by Cyp3A4. Rivaroxaban metabolized by cyp2A4 and cyp2j2. Patients with hepatic impairment are at increased risk of bleeding complications and thrombotic events [5].

Most DOACs therapies are eliminated by the kidneys to varying degrees, and alterations in renal clearance must be taken into account when dosing these agents. Recommended dosing regimens are nevertheless based on clinical characteristics (weight, age, renal function) and some co-medications. DOACs are anticoagulation pharmacotherapy used for the prevention of thrombosis in several cardiovascular contexts. DOACs are categorized into two main classes: oral direct factor Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban, and Betrixaban) and direct thrombin inhibitors (Dabigatran) [8].

While DOACs have many beneficial effects, they are usually well-tolerated with few side effects. The main side effect is bleeding, which can range from minor (e.g., slight bruising or occasional bleeding from the gums when bruising teeth) to serious bleeding (e.g., vomiting blood, blood in the stools/urine, or bleeding inside your head) [10].

Our study has been designed to evaluate the prevalence and severity of DOACs-related DDIs, identify common interacting drugs and mechanisms, and assess the associations with comorbidities, age, and polypharmacy; those will impact on the Improving Patient Safety by avoiding harmful drug combinations, reducing the risk of adverse effects and enhancing patient safety. Although, Optimized Treatment Plans by knowing which drugs interact with DOACs, doctors can create more effective treatment plans tailored to individual patients, especially those with comorbidities and on polypharmacy. Moreover, the finding of this study will help in the improvement of informed decision-making, enhanced clinical guidelines, and aid to personalize medicine.

Impact Statements

This study proclaims that the presence of the interactions of direct oral anticoagulants will result in either increased toxicity, risk of bleeding, and adverse effects that in turn lead to less adherence by the patients to the medications, or decreased effectiveness that results in therapeutic and prevention failure.

Evaluating the prevalence and severity levels of DDIs of direct oral anticoagulants among adults will lead to increased knowledge about DOACs-drug interactions and their severity levels, and how they should be avoided and managed. Our study has been designed to evaluate the prevalence and severity levels of DDIs of direct oral anticoagulants among adults in Sana'a city, Yemen.

Aims and Objectives of the Study

The current study intends to investigate the prevalence and severity of drug interactions

(DDIs) with DOACs among patients aged 18 and over, who have received DOACs therapy from January 2022 to January 2023 in Sana'a city. Specifically, this study aims to:

1.Evaluate the prevalence and severity of DOACs-related DDIs.

2.Identify the common interacting drugs and mechanisms.

3.Assess the associations between DOACs-Drug Interactions and comorbidities, age, and polypharmacy.

Methods

Study Design

This is a retrospective cross-sectional study of all patients who attended the clinic and were diagnosed with cardiovascular diseases or venous thromboembolism. Data were collected through a retrospective review of paper medical records of all of the patients who were managed at the clinic between January 2022 and January 2023.

Study Period and Setting

This study was carried out from January 2022 to January 2023. The sample of this study was selected from the files of the patients discharged from Lebanon Hospital and Cardiac Center-Military Hospital, in Sana’a city.

The Study Sample

The sample of this study was purposively selected from of 1523 patient files that were examined during the study period. The study sample included 146 files of patients aged 18 and over who received DOACs between January 2022 and January 2023.

Inclusion Criteria

Patients' medical records in the hospitals database were filtered by diagnosis and time of discharge. Medical records of patients with cardiovascular disease that increase thromboembolism events who received DOACs therapy and discharged from the hospitals between January 2022 and January 2023 were included .

Exclusion Criteria

Medical records of male and female patients younger than 18 years old and medical records of patients who did not receive DOACs therapy were excluded.

Data Collection

Data were recorded in a predesigned data-collecting format. The data collected included name, age, gender, diagnosis, medications with their dosages and frequencies of dosing. The presence of drug interactions was investigated using Lexicomp online software and recorded in the bottom of the format. Lexicomp is a DDI database for healthcare providers and requires a subscription for access. It has been developed in various platforms, such as mobile applications, online, or desktop software [11]. According to Lexicomp, drug interactions are categorized into five risk rating levels: A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy modification), and X (avoid combination). These categories indicate the level of urgency and the actions needed to respond to a potential drug interaction.

Principally, paper medical records of adult patients receiving DOACs therapy were used for collecting the required data for the study. The obtained data were written down in a

predesigned data-collecting format. The medications found to be used by the patients including an agent from DOACs drugs were checked for the presence of any drug interaction using the interaction checker Lexicomp and written down in the same format of the patient.

Statistical Analysis

Data were statistically analyzed using the statistical package for social science (SPSS version 21) for categorical data, frequency, and percentage. Statistical differences among groups were evaluated using Pearson's chi-squared test: A p-value <0.05 was considered statistically significant.

Ethical Approval

The study was approved by the Faculty of Clinical Pharmacy at 21 September University for Medical & Applied Sciences and by the ethical committees of the hospitals targeted in this study.

Results

Demographic Data

A total of 1523 patient files were examined. 146 prescriptions were found to include DOACs. Accordingly, 146 patient files were selected for examination in this study. The mean age of the patients was 58 years old (± SD 11 years). In parallel, gender was distributed, as shown in **(Table 1)**, where 111 (76%) were male and 35 (24%) were female.

DOACs Drugs

The results obtained from the identified DOACs disclose that apixaban was prescribed for 111 (76.03%) of the patients while rivaroxaban was prescribed for 36 (24.66%) of the patients.

It was also found that 86 (58.9%) of the patients had two comorbidities, 35 (23.9%) of them had three comorbidities, and 7 (4.8%) of them had four comorbidities. The majority of the patients were diagnosed with IHD.

Table 1. Demographic Characteristics of the Patients Receiving DOACS.

Demographic Data	Number of prescriptions	Percentage%
Age		
<40	8	5.48%
40-49	22	15.07%
50-59	53	36.3%
60-69	48	32.88%
70-79	10	6.85%
≥80	5	3.42%
Gender		
Male	111	76%
Female	35	24%
Diagnosis		
IHD	65	23.99%
Post-PCI	34	12.55%
Diabetes Mellitus	23	8.49%
Atrial Fibrillation	13	4.8%
Deep Vein Thrombosis	3	1.11%
Others	133	49.06%

Concomitant Drugs The concomitant drugs that were prescribed along with DOACs were analyzed as well. Their average number was 6.89 (±SD 2.118). Aspirin, beta-blockers, pantoprazole, statins, and clopidogrel were the most common drugs prescribed with DOACs. All co-administered drugs and their percentages are listed in **Table2.**

Table 2. Concomitant Medications co-Prescribed Medications with DOACs

Concurrently Used Drug			Concurrently Used Drug			Concurrently Used Drug		
Medication	**No.**	**%**	**Medication**	**No.**	**%**	**Medication**	**No.**	**%**
Aspirin	97	66.4%	**Levocarnitine**	6	4.1%	**Salbutamol**	2	1.4%
Bisoprolol	81	55.5%	**Acetylcysteine**	5	3.4%	**Vitamin D3**	2	1.4%
Pantoprazole	67	45.9%	**Sitagliptin**	5	3.4%	**Allopurinol**	1	0.7%
Atorvastatin	66	45.2%	**Ciprofloxacin**	4	2.7%	**Cefepime**	1	0.7%
Clopidogrel	58	39.7%	**Glibenclamide**	4	2.7%	**Cefixime**	1	0.7%
Spironolactone	49	33.6%	**Glimepiride**	4	2.7%	**Cefoperazone**	1	0.7%
Torsemide	46	31.5%	**Paracetamol**	4	2.7%	**Cortisone**	1	0.7%
Linezolid	43	29.5%	**Potassium gluconate**	4	2.7%	**Dexamethasone**	1	0.7%
Rosuvastatin	33	22.6%	**Vitamin B**	4	2.7%	**Diclofenac Na**	1	0.7%
Furosemide	23	15.8%	**Albumin**	3	2.1%	**Dobutamine**	1	0.7%
Carvedilol	22	15.1%	**Amiloride**	3	2.1%	**Domperidone**	1	0.7%
Nitroglycerin	20	13.7%	**Amlodipine**	3	2.1%	**Escitalopram**	1	0.7%
Dapagliflozin	18	12.3%	**Cefuroxime**	3	2.1%	**Fentanyl**	1	0.7%
Metformin	13	8.9%	**Ferrous sulfate**	3	2.1%	**Flupenthixol**	1	0.7%
Enoxaparin	12	8.2%	**Folic acid**	3	2.1%	**Heparin**	1	0.7%
Sacubitril/Valsartan	12	8.2%	**Isosorbide dinitrate**	3	2.1%	**lansoprazole**	1	0.7%
Ramipril	11	7.5%	**Valsartan**	3	2.1%	**Melitracen**	1	0.7%
Digoxin	10	6.8%	**Candesartan**	2	1.4%	**Meloxicam**	1	0.7%
Losartan	10	6.8%	**Diltiazem**	2	1.4%	**Metoprolol**	1	0.7%
Amoxicillin/ clavulanic	9	6.2%	**Gliclazide**	2	1.4%	**Omeprazole**	1	0.7%
Empagliflozin	8	5.5%	**Levothyroxine**	2	1.4%	**Ondansetron**	1	0.7%
Amiodarone	7	4.8%	**Metronidazole**	2	1.4%	**Ranitidine**	1	0.7%
Hydrochlorothiazide	7	4.8%	**Nebivolol**	2	1.4%	**Sacubitril**	1	0.7%
Insulin	7	4.8%	**Phenoxymethylpenicillin**	2	1.4%	**Tramadol**	1	0.7%
Ceftriaxone	**6**	**4.1%**	**Piperacillin**	**2**	**1.4%**	**Warfarin**	1	**0.7%**

DOACs-Drug Interactions, according to Lexicomp

The Prevalence of Potential DOACS-Drug Interactions

Broadly, there were 140 (95.9%) patients out of 146 patients who had a total of 733 clinically significant drug-drug interactions. Category C represented 513 (70%), category D represented 204 (27.8%), and category X represented 16 (2.2%) of those drug-drug interactions.

Specifically, given that only categories C, D, and X are clinically significant, the result show that out of 146 patients, there were 113 (77.4%) individuals who had a total of 184 (25.1%) clinically significant DOACs-drug interactions, as shown in **Table 3.**

Table 3. The Prevalence of Clinically Significant and DOACs-Drug Interactions

Interactions	No. of patients	Percent of patients	No. of DDIs
General DDIs	140	95.9%	733
DOACs-Drug DDIs	113	77.4%	184

Remarkably, the study found that the age group between 50-59 is associated with the most DOACs-drug interactions **(Figure 1).**

As displayed in Table 4, apixaban was prescribed for 111 (76%) of the patients and rivaroxaban was prescribed for 36 (24.66%) of the patients. Besides, out of 184 DOACs-drug interactions, apixaban accounted for 126 (68.5%) of the patients whereas rivaroxaban accounted for 58 (31.5%) of them.

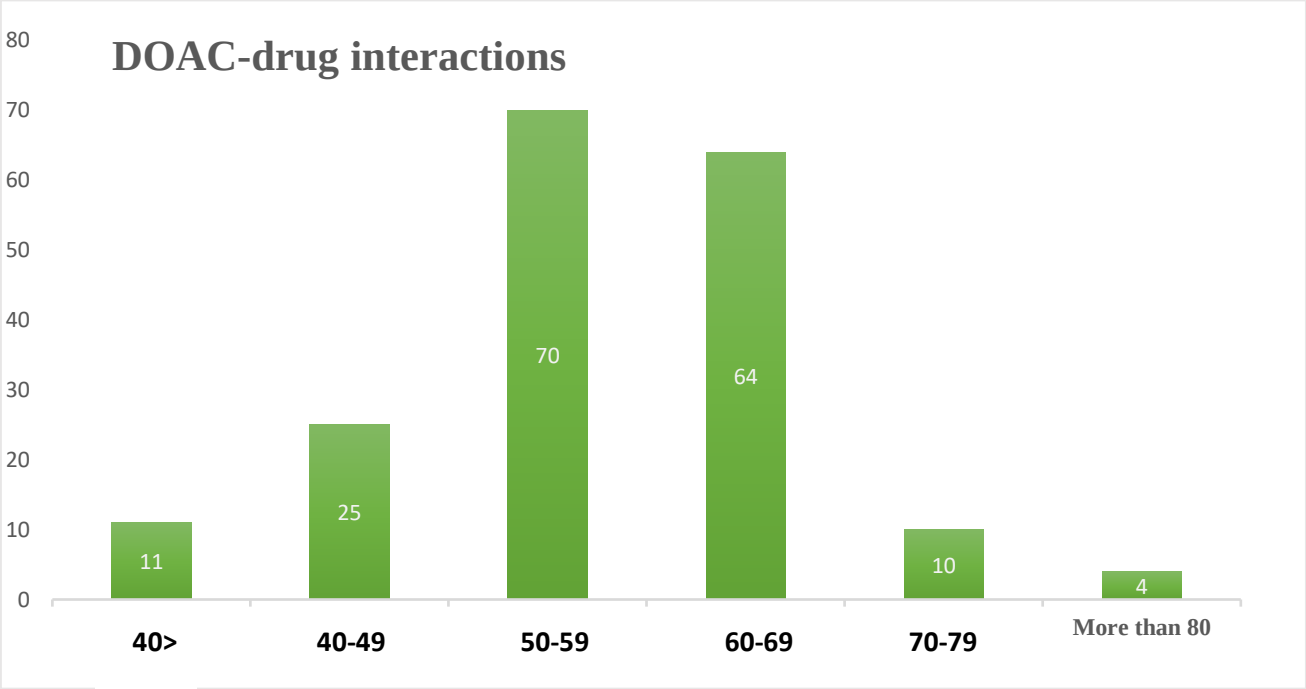

Figure 1. Association of DOACS-Drug Interactions with the Age Group

Table 4. Distribution of DOACs Agents Among Patients

DOACs agents	No. of Prescriptions	No. of Interactions
Apixaban	111 (76%)	126 (68.5%)
Rivaroxaban	36 (24.66%)	58 (31.5%)

Factors that might Affect the Occurrence of DOACs-Drug Interactions

When examining the factors that might affect the occurrence of DOACs-drug interactions, it was found that the number of comorbidities was associated with more concomitant drugs (0.308, p-value < 0.0001). Consequently, the number of concomitant drugs was shown to be strongly associated with more DOACS-drug interactions (0.386 p-value < 0.0001). By the same token, the increased number of comorbidities is directly associated with an increased number of DOACS-drug interactions (0.194, p-value < 0.05). **Table 5** illustrates the degree of correlation between the factors that were found to affect the occurrence of DOACs-drug interactions.

Table 5. Correlation between the Most Important Factors that Might Affect the Occurrence of DOACs-Drug Interactions.

		No. of comorbidities	No. of DOACs-DDIs	No. of drugs
No. of comorbidities	Pearson Correlation	1	0.194*	0.308**
	Sig. (2-tailed)		0.019	0.000
	N	146	146	146
No. of DOACs-DDIs	Pearson Correlation	0.194*	1	0.386**
	Sig. (2-tailed)	0.019		0.000
	N	146	146	146
No. of drugs	Pearson Correlation	0.308**	0.386**	1
	Sig. (2-tailed)	0.000	0.000	
	N	146	146	146

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Potentially Interacting Drugs with DOACs

When analyzing the drugs that were involved in the identified DOACs-drug interactions, aspirin, clopidogrel, enoxaparin and diltiazem were found to be responsible for most DOACs-drug interactions.

Table 6. Percent of each Potentially Interacting Drug with DOACs According to Lexicomp

Interacting drug	Number of prescriptions	Percent%	The Severity
Aspirin	100	54.35%	D
Clopidogrel	61	33.15%	D
Enoxaparin	11	5.98 %	X
Apixaban with Rivaroxaban	2	1.09 %	X
Diltiazem	2	1.09%	C
Heparin	1	0.54%	X
Diclofenac Na	1	0.54%	D
Meloxicam	1	0.54%	D
Escitalopram	1	0.54%	C
Fluoxetine	1	0.54%	C
Indomethacin	1	0.54%	D
Warfarin	1	0.54%	C
Ibuprofen	1	0.54%	D
Total	184	100.0%	

The Severity of the Potential DOACs-Drug Interactions

Equally important, the severity of the potential DOACS-drug interactions was analyzed, revealing that out of 184 DOACS-drug interactions, 5 (2.7%) were of category C, 165 (89.7%) were of category D, and 14 (7.6 %) were of category X interactions. This distribution is shown in **Table 7.**

Table 7. Percentage of the Severity Levels of DOACS-Drug Interactions

Severity	Number of Prescriptions	Percent%
C (Monitor Therapy)	5	2.7%
D (Consider Therapy Modification)	165	89.7%
X (Avoid Combination)	14	7.6%

Mechanism of the Potential DOACs-Drug Interactions

Lastly, the potential mechanism by which the DOACs interacted with other medications has a pharmacokinetic basis in 3 (1.6%) of the interactions and most DOACS-drug interaction has a pharmacodynamic basis in 181 (98.4%) of them. **Table 8** illustrates the mechanism of DOACS-drug interactions.

Table 8. Mechanism of DOACS-Drug Interactions

	No. of DDIs	Percent%
Pharmacodynamic	181	98.4%
Pharmacokinetic	3	1.6%

Discussion

It was found that out of 146 patients, 86 (58.9%) had two comorbidities while 35 (23.9%) had three comorbidities, and the vast majority of the patients were diagnosed with IHD.

It was also found that the mean number of concomitant prescribed medications along with DOACs was 6.89 (± SD 2.118).

Besides, most commonly co-prescribed medications included aspirin, beta blockers, pantoprazole, statins and clopidogrel.

Our findings revealed that 77.4% of patients experienced clinically significant DOACs-drug interactions; a total of 184 DDI with DOACs were found in 140 prescriptions out of 146 prescriptions. This aligns with previous studies such as Badreldin et al. (2020) and Forbes and Polasek (2017), which reported interaction rates between 37% and 78%. [12,13] The high prevalence in our study may be attributed to the widespread use of polypharmacy in cardiovascular patients.

PD-DDIs were more frequent in patients of this study compared to PK-DDIs (98.4% versus 1.6%, respectively). However, the percentage 98.4% found in our study was higher than of other studies, which could be attributed to the increased use of antiplatelet therapy in our population compared to the other studies. This could be explained by the fact that IHD and PCI were more prevalent in population of this study which may necessitate the use of an antiplatelet for primary and secondary propose.

This study also revealed that as the number of comorbidities increase, the potential DDIs with DOACs increase as well (0.194, p-value < 0.05). The strong correlation between polypharmacy and DOACs interactions ($r = 0.386$, $p < 0.0001$) is expected, as older patients with cardiovascular diseases often require multiple medications.

Most DOACS interactions were classified as category D (89.7%), meaning that the patient should be considered for therapy modification. Additionally, the patient has a substantial chance of an adverse drug reactions, which increase the likelihood of hospitalization and category X (7.6%), indicating that the medications should be avoided. Only (2.7%) of the interactions were classified as category C, meaning that the patient's medications should be monitored. The severity of the interactions not mentioned in other studies such as Badreldin (2020) and Forbes and Polasek (2017) [12,13], by which our study fills this gap. Only Ersoy's (2021) study mentioned the severity of interactions, which in accordance with our study claimed that the majority of significant DDI with DOACs is category D. [14]

It was also found that the most frequently reported DDIs of DOACS were with antiplatelet and NSAID, such as Aspirin, Clopidogrel, Enoxaparin and Diltiazem. These findings are also consistent with the findings of the study made by Ersoy (2021). [14]

Another study was conducted in Saudi Arabia by Badreldin (2020), reporting that NSAIDs and Antiplatelet were the most frequent interacting class of medications with DOACs. [12]
Concurrent use of DOACs and other medications may increase or decrease the effectiveness of some medications. It may also increase the risk of bleeding and gastrointestinal symptoms.
In this study, DOACs were prescribed with aspirin in 100 (54.35%) and clopidogrel in 61 (33.15%) of 140 prescriptions. The use of DOACs in conjunction with antiplatelet therapy (aspirin and/or clopidogrel) showed increase in the risk of major bleeding. The postulated mechanism for this potential interaction was that both agents affect the

pharmacological effect of the DOACs by agonizing its effect. This study showed that DDI of DOACs were mostly observed among the patients whose age was 50 and 59. This is because nearly at this age, a patient usually has several chronic diseases, especially CVD, which require anticoagulation therapy to prevent further consequences.

The majority of DOACs medication interactions may be avoided by adhering to best practices in clinical care and clinical pharmacology, such as avoiding complicated treatment regimens, utilizing a single pharmacy for all prescriptions, and recognizing patient risk factors.

Strengths and Limitations

The present study was the first study to investigate potential DDIs with DOACs in adult patients in Yemen. The results needed to be interpreted with caution because the present study have several limitations. Firstly, the current study was retrospective observational in nature. Secondary, we examined drug interactions of DOACs, but we did not know co-medications' interactions with each other. Moreover, the study examined drug interactions only from one online application. It could be argued that other drug interaction software like Micromedex, In Facts, Medscape, and others online applications of drugs interactions checkers could have different results. However, several reports have shown that Lexicomp was the most accurate and comprehensive software among the drug interactions software.

Conclusion and Recommendations

This study found that 77.4% of patients receiving DOACs experienced clinically significant drug-drug interactions, primarily in category D (89.7%) and category X (7.6%). Most interactions were pharmacodynamic in nature. The key risk factors for DOACs-drug interactions included advanced age, polypharmacy, and multiple comorbidities.According to the results obtained in this study, we recommend:

1.Adhering to best practices in clinical care and pharmacotherapy such as avoiding complicated treatment regimens and recognizing patient risk factors.

2.Patients' co-medications should be checked regularly in order to support the risk assessment for excessive bleeding or thrombotic events due to DDIs.

3.Close monitoring for excessive bleeding or thrombotic events when DOACs used in combination.

4.Health care professionals should use drug-drug interaction checkers such as Lexicomp, Medscape, and Micromedex.

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