

Assessment of Adverse Drug Reactions to Direct Oral Anticoagulants in Real-World Cardiac Practice

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Article History

Received: 21.09.2025

Revised: 30.09.2025

Accepted: 22.10.2025

Published: 11.11.2025

Abstract: Direct oral anticoagulants (DOACs) have become a favoured alternative to classic vitamin K antagonists in the prevention of thromboembolic events in adult patients with cardiac disorders (atrial fibrillation and venous thromboembolism). Their effectiveness and convenience are not disputed, but there are limited real-world data on the adverse drug reactions (ADRs). The purpose of the study was to evaluate the occurrence, nature, and risk factors of ADRs in case of DOAC therapy in everyday clinical practice. The prospective study was an observational study conducted within six months where patients undergoing the DOACs included (dabigatran, rivaroxaban, apixaban or edoxaban) were involved in tertiary care cardiology unit. The identification of ADRs was based on interviews with patients, physical examination, and analysis of laboratory research and categorization was made based on the severity and involvement of the system organ. ADRs were reported in 28 out of 150 enrolled patients (18.7 percent) and minor bleeding, gastrointestinal discomfort, and increased liver enzymes were the most common. The predictors of ADR occurrence were age, comorbidities, polypharmacy, and renal impairment. The results underscore the need to use continuous monitoring, patient education, and risk analysis at the individual level to maximize the safety of DOAC treatment in the practice of cardiology.

Keywords: Direct oral anticoagulants, adverse drug reactions, atrial fibrillation, real-world practice, bleeding, patient safety, polypharmacy.

INTRODUCTION

DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban are a major achievement in the treatment of anticoagulation. In contrast to the traditional vitamin K antagonists (VKAs), e.g. warfarin, DOACs have predictable pharmacokinetics, constant dosing regimens, rapid absorption, and there is limited food or drug interactions. These benefits have seen DOACs become the stroke prevention therapy of choice in non-valvular atrial fibrillation, as well as in the treatment and prophylaxis of venous thromboembolism [1].

Although proven in their efficacy, DOAC therapy is also linked to the possible adverse drug reactions (ADRs), which may compromise the patient safety and treatment outcomes. Small and significant bleeding, GIT disturbances, high liver enzymes, and changes in renal functioning are the most frequently reported ADRs. Such reactions may be caused by pharmacodynamic and pharmacokinetic differences in people, polypharmacy, old age and comorbidities like chronic kidney disease, liver disease or cardiovascular diseases. The reason of identifying and controlling these ADRs is very important in preventing complications, preventing termination of therapy and enhancing adherence and clinical outcome [2].

Although randomized controlled trials (RCTs) offer controlled data on safety and effectiveness, this method is prone to rule out the elderly, patients with multiple comorbid conditions, or patients taking multiple medications. Therefore, RCT results are not likely to be representative of the actual occurrences and trend of ADRs. It is thus necessary to fill this gap by observational studies in routine clinical environments to capture the range of ADRs in standard therapeutic settings [3].

The proposed study will evaluate the occurrence, nature, severity, and risk factors of ADRs in the use of DOACs in real cardiac practice. Being informed about the nature of the patients, their therapy, and profiles of ADRs, clinicians would be able to include particular monitoring processes, optimize the dose rise or fall, patient educational work in universities, and improve the overall safety and efficacy of anticoagulants therapy. The study will most probably contribute to the evidence-based decision-making and the patient's-centered approach in the cardiology practice [4].

MATERIALS AND METHODS

Study Design and Setting

The research was prospective and observational study which was conducted within a duration of six months at the Department of Cardiology of a teaching hospital that

is of tertiary level. The aim of the research was to identify some adverse drug reactions (ADRs) of direct oral anticoagulants (DOACs) in clinical practice [5].

Study Population

The revision incorporated patients by atrial fibrillation, venous thromboembolism, or any other cardiac indication over the age of 18 years and had been prescribed any DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) [6].

Inclusion Criteria

- Patients under DOAC therapy at least 1 month before enrolment.
- Patients with informed consent to attend follow-up visits [7].

Exclusion Criteria

- Vital patients taking concomitant vitamin K antagonists (e.g. warfarin).
- Patients who are recognized designate hypersensitive to DOACs.
- Pregnant or lactating women.

- These contraindicated patients who are hepatically or renal impaired to take DOAC severely [8].

Data Collection

Demographic information (age, gender), past medical history (indication of anticoagulation, comorbidities), type of DOAC and dose, and other concomitants were taken. The ADRs were identified by following up patients via out-patient visits and telephone interviews. Objective evidence of drug-effects was checked in laboratory investigation such as complete blood count, liver and renal functioning tests [9].

Evaluation of Adverse Drug Reactions

The identification of ADRs involved patient interviews, physical examination and lab tests. The intensity of ADRs was categorized as per the World Health Organization (WHO)-UMC causality scale as certain, probable, possible, or unlikely. ADRs were further divided in terms of involvement and severity of the system organs (mild, moderate, severe) [10].

Outcome Measures

- Type and incidence of ADRs on DOAC therapy.
- Severity, clinical impact of ADRs.
- Ages, comorbidities, polypharmacy, and renal functioning are some of the factors that contribute to the occurrence of ADRs [11].

Statistical Analysis

The data were compared with the SPSS software (version 25.0). Continuous variables were presented as mean $\pm$ standard deviation (SD), and categorical variables were presented as frequencies and percentages. Associations between categorical variables were determined by chi-square test or Fishers exact test and those between continuous variables by Student t - test. There was a p-value of less than 0.05 that was regarded as significant [12].

Ethical Considerations

The Institutional Ethics Committee approved the study protocol. All the participants gave informed consent in writing. Patient confidentiality was upheld during the research and all ADRs were reported as per the pharmacovigilance requirements (Figure 1) [13].

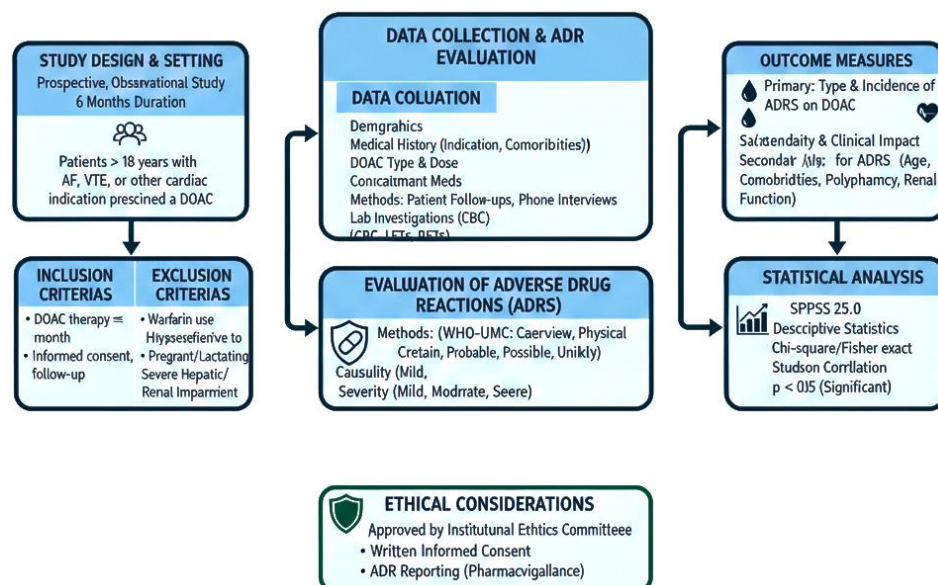


Figure 1: Research Methodology

RESULTS

The study was conducted on a total of 150 patients undergoing direct oral anticoagulants (DOACs). There were 88 (58.7) males and 62 (41.3) females among them and their mean age was 63.5 ± 9.2 years. Atrial fibrillation (70%), venous thromboembolism (20%), and other conditions of the heart were the most significant signs of DOAC therapy. The comorbid conditions were as follows hypertension (62%), diabetes mellitus (45%), chronic kidney disease (18%), and ischemic heart disease (35%)(Table 1).

Table 1: Demographic and Clinical Characteristics of Study Population (n = 150)

Parameter	Category	Number of Patients (n)	Percentage (%)
Gender	Male	88	58.7
	Female	62	41.3
Mean Age (years)	—	63.5 ± 9.2	—
Age Groups	<50	25	16.7
	50-64	62	41.3
	≥65	63	42.0
Indication for DOAC therapy	Atrial fibrillation	105	70.0
	Venous thromboembolism	30	20.0
	Other cardiac conditions	15	10.0
Comorbidities	Hypertension	93	62.0
	Diabetes mellitus	68	45.3
	Chronic kidney disease	27	18.0
	Ischemic heart disease	53	35.3

Adverse Drug Reactions (ADRs) Incidence and Types

The study had 150 patients where 28 (18.7%) of the cases had ADRs throughout the study period. The most common ADRs that were reported included:

- Minor bleeding events (n = 12, 8%)
- Gastrointestinal problems, such as nausea and dyspepsia (n = 8, 5.3%)
- Elevated liver enzymes (n = 5, 3.3%)
- Rashes on the skin or an allergic reaction (n = 3, 2%) (Table 2, Figure 2)

Table 2: Incidence and Types of Adverse Drug Reactions (ADRs)

Type of ADR	Number of Patients (n)	Percentage (%)
Minor bleeding	12	8.0
Gastrointestinal disturbances	8	5.3
Elevated liver enzymes	5	3.3
Skin rashes/allergic reactions	3	2.0
Total ADRs	28	18.7

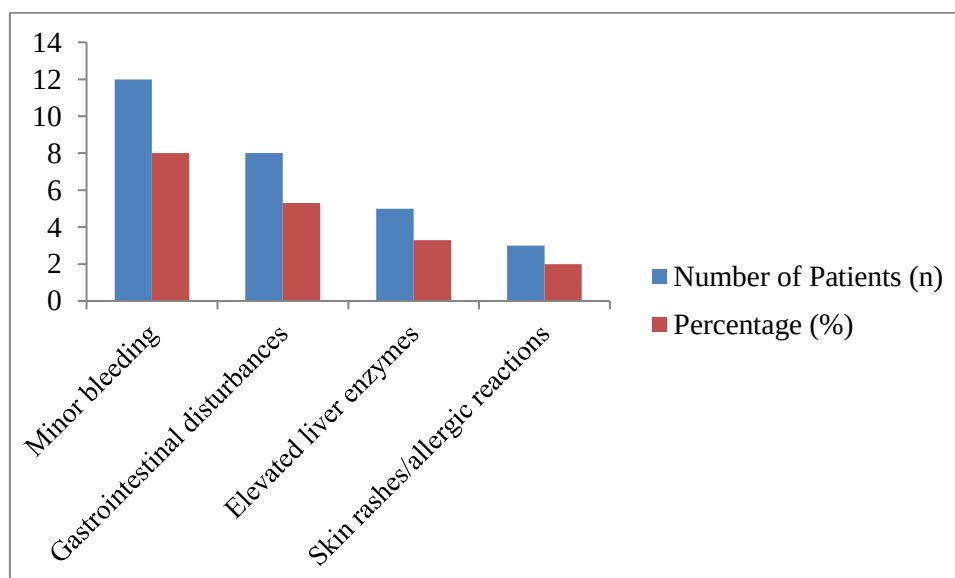


Figure 2: Graphical presentation of Incidence and Types of Adverse Drug Reactions (ADRs)

Severity of ADRs

The majority of ADRs (n = 20, 71.4 percent) were mild and did not need any alteration of therapy. Moderate ADRs (n= 7, 25 percent) necessitated dose modification or a pause in the treatment. There was only one patient (3.6) who had a severe ADR (major gastrointestinal bleeding) that required hospitalization and a discontinuation of the DOAC (Table 3).

Table 3: Severity of Adverse Drug Reactions

Severity Level	Number of Patients (n)	Percentage (%)	Clinical Action Taken
Mild	20	71.4	No change in therapy
Moderate	7	25.0	Dose adjustment or temporary stop
Severe	1	3.6	Hospitalization and therapy discontinuation

Risk Factors for ADRs

The contribution factor analysis showed that the likelihood of the ADR appearance was increased in:

- Patients aged ≥ 65 years ($p = 0.03$)
- Individuals with several comorbidities, in particular, chronic kidney disease ($p = 0.02$).
- Polypharmacy (5 or more concomitant medications) ($p = 0.01$) (Table 4)

Table 4: Risk Factors Associated with ADRs

Risk Factor	Number of Patients with ADR (n)	Statistical Significance (p-value)
Age ≥ 65 years	15	0.03
Multiple comorbidities	12	0.02
Polypharmacy (≥ 5 drugs)	14	0.01
Female gender	13	0.08 (not significant)

The incidence of ADRs on DOAC users was 18.7 in total. The most common ADRs were minor bleeding and gastrointestinal disturbances. Those who are very old, have comorbid conditions, and taking multidrugs were at increased risk. Most of ADRs were slight and easily controllable, with minimal adverse incidences. These findings suggest that although DOACs are considered to be relatively safe in clinical practice involving cardiac patients, regular monitoring, patient education, and dose-adjustment in vulnerable populations are crucial to reduce ADRs, achieving the best therapy outcomes.

DISCUSSION

The current paper evaluated the adverse drug reactions (ADRs) of direct oral anticoagulant (DOACs) in actual cardiac practice. In the 150 patients who were the subjects of the research, 28 (18.7) of the patients had ADRs and this indicates that DOACs are safe in general, but there are very high chance of patients having side effects. This incidence is also in line with the previous observational studies that show ADR rates of 15-20 percent in a normal clinical environment [14].

The number of minor bleeding events was the most commonly reported ADRs (8%), then gastrointestinal disturbances (5.3%), and increased liver enzymes (3.3%). The results are in line with the clinical trial data and post-marketing surveillance reports that list bleeding and gastrointestinal reactions as frequent reactions of DOAC. The majority of the ADRs were mild (71.4 percent) and did not necessitate discontinuation of therapy (only one patient had a severe ADR and had to be hospitalized). This supports the positive safety profile of DOACs particularly compared to the conventional vitamin K antagonists that are linked to increased major bleeding and more frequent monitoring necessities [15].

Risk factor analysis indicated that the older age (65 years and above), comorbidity, and polypharmacy were found

to be enormous predisposing factors of ADR. The pharmacokinetics and pharmacodynamics of the elderly patients can be changed, their renal functioning can be weakened, and the medications can be combined and amplify the bleeding or other negative outcomes. It is also possible that patients with several comorbid conditions, including chronic kidney disease or liver impairment, are prone to increased drug accumulation and toxicity. The findings prove the significance of personalized treatment, dose change, and close observation in the risk groups [16].

The findings indicate that careful pharmacovigilance should be practiced in the routine cardiac practice. Patients need to be trained by clinicians on how to identify the onset of ADRs, perform regular lab checks, and patient-specific risk factors to choose the type and dosage of DOAC. Moreover, it can be noted that the simplification of drug schedules and other unwarranted polypharmacy can further decrease the number of ADRs [17].

These trends have been recorded previously with minor bleeding as the most prevalent ADR and severe events as being rather uncommon. Nevertheless, it is common in real-world studies to record slightly higher ADR rates compared to a clinical trial because older people and comorbidities have been included, unlike in RCTs. This

accentuates the significance of observational studies in going through the entire range of DOAC safety in various patient groups [18].

All together, the DOACs have an excellent safety profile in the actual cardiac practice, and the majority of ADRs are mild and treatable. However, the high-risk groups of patients, patient education, and active surveillance should also be considered to reduce the adverse effect and maximize the efficacy of the therapy [19].

CONCLUSION

The paper has shown that direct oral anticoagulants (DOACs) are universally typically safe and tolerable in clinical practice in cardiac units; a large proportion of adverse drug reactions (ADRs) are mild and can be managed. The most common ADRs were minor bleeding and gastrointestinal disorders, and severe reactions were uncommon. The age, comorbidities, and polypharmacy were observed as the risk factors that affect ADR occurrence significantly. The results demonstrate the need to focus on the personalized treatment, patient education, and frequent monitoring to make the DOAC treatment safer. Such strategies can be implemented to streamline the results of treatment, reduce complications and achieve successful anticoagulation of patients with cardiac conditions.

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