Journal of Health Informatics in Developing Countries
http://www.jhidc.org/
Vol. 16 No. 1, 2022

Submitted: Jan 24th, 2022 Accepted: April 17th, 2022

Medication Errors associated with Direct Oral Anticoagulants: A Systematic Review

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Abstract

Background: Direct oral anticoagulants (DOACs) have favorable safety and efficacy outcomes in treating and preventing different thrombotic events compared to warfarin. DOACs are mainly eliminated through the kidney; therefore, poor renal function is one of the important patient-related factors related to DOACs prescription errors. Our objective was to systematically review evidence related to the prevalence, risk factors, and characteristics of inappropriate DOACs prescription practices.

Methods: The search was conducted in PubMed and Scopus databases from 2011to 2021. We included any study that involved DOACs use among adults >18. Modified Newcastle-Ottawa Scale was used to assess the quality of selected articles.

Results: As a result of our search strategy, we found 19 articles that met the inclusion criteria. The prevalence of DOACs inappropriate prescription ranged from 6% to 60%. The most commonly reported inappropriate prescription was underdosing. Renal impairment was an important factor related to inappropriate DOACs prescriptions.

Conclusion: Appropriateness of the DOACs prescription practice remains a concern, with underdosing as the most reported dosing-related problem. Renal impairment among the patients-related factors increases the risk of inappropriate dosing.

Keywords: Medication error; Preventable adverse drug event; Medication-related harm; Inappropriate prescribing; Anticoagulants.

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1. Introduction

Direct oral anticoagulants (DOACs) that include rivaroxaban, apixaban, edoxaban, and dabigatran are indicated for treatment or prophylaxis of several conditions such as stroke prevention, non-valvular atrial fibrillation, venous thromboembolic events and total hip or knee replacement surgery. Dabigatran was the first direct oral anticoagulant and had favorable results in clinical practice [1]. DOACs have a rapid onset of action, fewer drug and food interactions, and less bleeding risk than warfarin [1,2] For DOACs, there is a lack of evidence on their use when patients have renal insufficiency [2].

Over one-third of the adverse drug events (ADE) are preventable, and anticoagulants are considered a high-risk medication, therefore, more prone to errors than the other drugs classes [3,4]. Errors in DOACs prescription occur because of the knowledge gap about DOACs safe practices.1 Renal impairment is an important factor to consider while prescribing DOACs [5,6,7]. Dose adjustment is needed if the patient has at least two of the three conditions, i.e., age > 80, bodyweight < 60 kg, and serum creatinine >1.5 mg/dL [8,9]. This is important to avoid adverse effects among patients with renal impairment [10]. According to the American Heart Association, direct oral anticoagulants are approved for patients with creatinine clearance of less than 30 ml/min in some cases [11]. With this background, it is also important to remember that guidelines related to dose adjustment depend on the type of DOACs and the creatinine clearance [1].

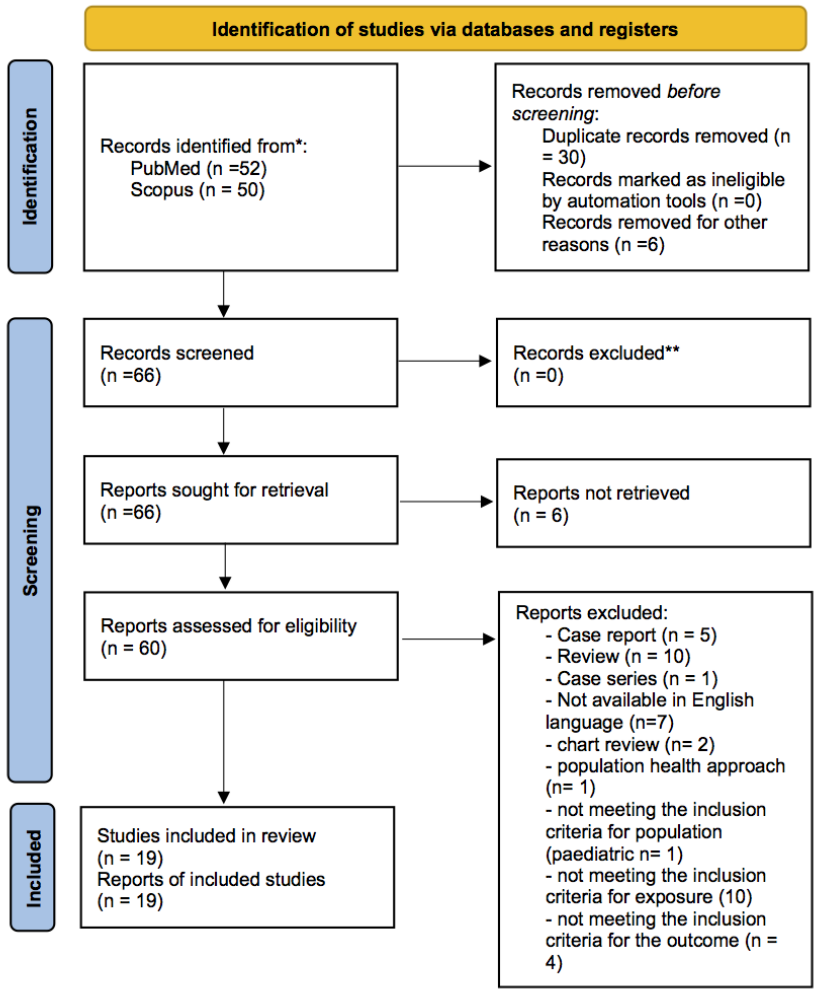
A previous systematic review and meta-analysis published intended to assess the efficacy and safety of direct oral anticoagulants compared with warfarin among atrial fibrillation patients with chronic kidney disease. The review reveals that DOACs are similar to warfarin in efficacy and safety and did not increase the risk of major bleeding among atrial fibrillation patients with chronic moderate kidney impairment. The review did not include patients with creatinine clearance of less than 15, so their findings do not apply to patients with advanced kidney disease [36] Another published review studied the safety and efficacy of the DOACs for treating venous thromboembolism patients with renal impairment. the included studies were phase 3 trials that did not include patients with creatinine clearance of less than 25 ml/min, confirming the lack of evidence related to DOACs prescription among patients with advanced renal failure [2].

With the expanding use of direct oral anticoagulants, there are some challenging situations regarding the appropriate selection of DOACs, dose, duration, and use with the high-risk population. Several factors are needed to be considered to avoid inappropriate prescription of DOACs. To assess the relationship between DOACs improper use and renal insufficiency, we conducted a systematic review to find relevant literature on the prevalence and risk factors of inappropriate DOACs prescriptions. In these studies, we also explored the nature of DOACs inappropriate prescription.

2. Subjects and Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) checklist [12]. The search was conducted on PubMed and Scopus databases from 2011-2021. We used search terms for PubMed; ("Medication Errors"[Mesh] or "medication error*" [tw] or "preventable adverse drug event*" [tw] or “medication related harm” [tw] or “inappropriate prescribing”) AND ("Anticoagulants"[Mesh] or "anticoagulant*" [tw]). For Scopus we just removed the Mesh words. The search strategy is reported on PRISMA flowchart (Figure1). EndNote was used to remove the duplicate articles. Two reviewers screened the articles based on title, abstract, and full articles.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

2.1.Inclusion and exclusion criteria:

We included any study involving DOACs use among adults >18; thus studies conducted on warfarin only or those studies which did not include DOACs were excluded. We limited our search to English language.

2.2.Assessment of the quality:

Modified Newcastle-Ottawa Scale (NOS) for appraisal of non-randomized controlled studies adopted to assess the methodological quality of the included studies [35] the assessment was done independently for each study by two reviewers (Table 1).

Table (1) Modified Newcastle-Ottawa scale for appraisal of non- randomized controlled studies.

Study/ domain	Study group	attrition	Exposure measure	Outcome measure	Investigators blinded	Confounders identified	Statistical adjustment	Funding source
Rahmanza [13] 2020	Y	N	Y	Y	NR	Y	Y	Y
Feng [14] 2020	Y	N	Y	Y	Y	Y	NR	N
Godino [15] 2020	Y	Y	Y	Y	NR	Y	NR	Y
Alrowily [16] 2021	Y	Y	Y	NR	N	Y	N	Y
Pharithi [17] 2018	Y	Y	NR	Y	Y	Y	Y	N
Sennesael [18] 2018	Y	Y	Y	Y	NR	Y	NR	N
Bruneau [19] 2019	Y	Y	Y	NR	N	Y	Y	Y
Larock [20] 2015	Y	NR	Y	Y	Y	NR	NR	N
Zhang [21] 2020	Y	NR	Y	Y	NR	Y	Y	Y
Ting [22] 2020	Y	N	Y	Y	Y	Y	N	N
Dreijer [23] 2018	Y	NR	Y	Y	N	NR	NR	Y
Desai [24] 2013	NR	N	Y	Y	N	Y	Y	Y
Cardoso [25] 2020	Y	NR	Y	N	NR	Y	Y	Y
Elewa [26] 2017	Y	Y	Y	Y	N	Y	Y	N
Mascolo [27] 2019	Y	Y	Y	Y	NR	Y	NR	Y
Viprey [28] 2016	Y	NR	Y	N	Y	Y	Y	N
Ferrat [29] 2021	Y	N	Y	Y	N	Y	Y	Y
Getachew [30] 2016	Y	Y	N	Y	NR	Y	Y	Y
Whitworth [34]2017	Y	N	Y	Y	NR	Y	Y	Y

Y= Yes; N= No; NR= Not reported

2.3.Data collection:

The data from each article is summarized in a table containing; the author, year of the study, country, sample size, study design, assessment of the exposure, assessment of the outcome, and the main results of each study (Table 2).

Table (2) Details of the studies selected in the systematic review

Author/ year	Country/ region	Sample size	Study design	Assessment of the exposure	Assessment of the outcome	Results
Rahmanza et al [13] 2020	Switzerland	107	Cohort study	computerized export from the hospital utilizes an electronic health care system (KISIM).	HAS-BLED score.	Therapeutic duplication of anticoagulants occurred in 6.7% of patients who received direct oral anticoagulants (DOACs)
Feng et al [14] 2020	US	3634 patients.	Cohort study	ICD-9-CM ICD- 10-CM	Self-reports	20.7% were potentially inappropriate.
Godino et al [15] 2020	Italy	760 patients	Cohort study	The 2018 European Heart Rhythm Association Practical Guide on the use of nonvitamin K antagonist oral anticoagulants in patients with atrial fibrillation	International Society of Thrombosis and Hemostasis classification (ISTH)	An inappropriate DOACs dose was prescribed in 96 patients (12.6%), 68% of which underdosing, and 32% higher dose.
Alrowily et al [16] 2021	Saudi arabia.	109 reported errors	Cohort study	-Saudi Food and Drug Authority pharmacovigilance database - local incidents reporting system	-Saudi Food and Drug Authority pharmacovigilance database - local incidents reporting system	Prescribing error was the most common error type representing 81.4% of all errors. Apixaban was the most frequent drug associated with error reporting with 134 (67.3%) incidents.
Pharithi et al [17] 2018	Ireland	348 patients	Cohort study	By reviewing of non-vitamin K antagonist anticoagulant (NOAC) prescriptions	CHA2DS2–VASC score	20.4% (n= 70) had inaccurate prescriptions; 92.9% (n = 65) underdosed and 7.1% (n = 5) on inappropriately higher doses
Sennesael et al [18] 2018	Belgium	89 patients	Cohort study	Medication Appropriateness Index (MAI)	European Medicines Agency definitions	53% of DOAC -related serious ADRs considered potentially preventable.

Bruneau et al [19] 2019	France	157 patients	Cohort study	summary of product characteristics (SPC) guidelines	SPC guidelines	34 (22.4%) prescriptions were inappropriate at discharge. Underdosing represent 17% of dosing errors, and over-dosing 4.6% of dosing errors at discharge.
Larock et al [20] 2015	Belgium	69 patients	Cohort study	Medication Appropriateness Index	HAS-BLED bleeding risk score	16 patients (23%) had 1 inappropriate criterion, and an additional 18 (26%) had more than 1 inappropriate criterion.
Zhang et al [21] 2020	Netherlands	770 patient's prescripti-on	Cohort study	Manual record reviewing	modified version of the Medication Appropriateness Index (MAI)	(34.6%) had at least met one inappropriate criterion for a DOAC prescription reduced renal function (eGFR < 50 mL/min) (OR=2.35; p<0.001) a diagnosis of atrial fibrillation (OR=1.87; p=0.004), and 'prescribed by surgeons' (OR=1.9; p=0.013) were independently associated with inappropriateness of prescribing.
Ting et al [22] 2020	USA	207 patients	Cohort study	FDA-labeled dosing recommendat-ion.	International Society on Thrombosis and Haemostasis (ISTH)	61 (29.5%) patients received inappropriate dosing, with 43 (70.5%) being under-dosed and 18 (29.5%) being over-dosed.
Dreijer et al [23] 2018	Netherlands	1000	Cross-sectional	Central Medication incidents Registration (CMR)	(LSKA; Dutch guideline on inte-grated antithrombotic care)	Anticoagulants were involved in 8.3% of the medication error reports DOACs were (3%) which is the lowest one among all anticoagulants.
Desai et al [24] 2013	USA	32 176 Medication errors	Cross-sectional	Reviewing Self-reported ME.	Medication Error Quality Initiative (MEQI)	Anticoagulants drugs errors versus other drugs OR=1.79 (95% CI 1.20-2.66)
Cardoso et al [25] 2020	Portugal	858 patients	Cross-sectional	By reviewing Medical Records.	HAS-BLED score	(42 patients [4.9%] with supratherapeutic dosing and 218 [25.4%] with infratherapeutic dosing ITD). Effect of Chronic kidney disease on ITD (odds ratio, 0.22; 95% CI, 0.258e0.678; P < 0.001).

Elewa et al [26] 2017	Qatar	1049	Cross-sectional	By reviewing medical records for anticoagulants prescriptions.	based on approved dosing and indications in Canada and the United States.	Factors associated with inappropriate dosing included dabigatran prescriptions (OR= 7.6, 95% CI: 5.5-10.5) and poor renal function (OR = 14.6, 95% CI: 3.6-58.4) Factors associated with inappropriate indication Dabigatran OR = 2.9 95% CI=1.3-6.5
Mascolo et al [27] 2019	*Singapore*	453	Cross-sectional	Individual Case Safety Reports (ICSRs)	bleeding categorized by system organ class (SOC)	8.6% of preventable cases was related to DOACs.
Viprey et al [28] 2016	France	1213	Cross-sectional	ICD-10 and diagnosis-related group (DRG)	Pharmaceutical Care Network Europe Classification System.	A too low drug dose was the most frequent DRP* 4.7% followed by a too high drug dose 3.1% Contraindication 0.4% and pharmacokinetic problem requiring dose adjustment 0.2%
Ferrat et al [29] 2021	France	1111 patients	Cross-sectional	European Medicines Agency	The HAS-BLED and CHA_2DS_2-VASc scores	438 patients (39.4%) had received at least one inappropriate prescription. Reduced kidney function association with underdosing OR= 0.59 (95% CI 0.42-0.83) and over-dosing 3.28 (95%CI 1.34-8.08)
Getachew et al [30] 2016	Ethiopia	156 patients	Cross-sectional	STOPP/START criteria	The Screening Tool for Older Person's Prescription/ Screening	(51.4%) were identified as potentially inappropriate medications.
Whitworth et al [34] 2017	USA	120 patients	retrospective cohort	Medication Appropriateness Index (MAI)	Medication Appropriateness Index (MAI)	(60.0%) IP, the most frequent inappropriate criteria were dosage (33.0%)

3. Results

3.1.Quality assessment:

According to The NOS visual assessment, no study met all the criteria. There was no clear justification in some studies regarding the validity of exposure or the outcome measures and whether the investigator was blinded. Out of all studies, 10 (52.6%) met 6 out of 8 criteria, while 7 (36.8%) met 5

criteria. The remaining 2 (10.5%) met 4 criteria, and we did not include those two studies in the analysis. (Table1) Six high-quality studies showed that inappropriate prescribing ranged from 6% to 51%.

3.2.Included studies characteristics:

Among 19 studies included, 11 studies (57.9%) used cohort study design, and 8 studies (42.1%) used cross-sectional study design. Two cross-sectional study designs were multicenter, one single-center, four from reporting systems, and one from a cohort study.

The included studies involved approximately 44,386 patients from either hospital admissions or medication errors records. Two US studies (10.5%) involved the highest sample, 32,176 patients from medication errors reports and 3,634 from the hospital registry. Further, 4 studies (21.1%) included over a thousand patients in each study, and the remaining 13 studies (68.4%) comprised less than thousand patients in each study. Additionally, considering the geographical spread of the included studies, 4 were conducted in the United States and 3 in France, 2 in Belgium and 2 in Netherland, 1 in each of Switzerland, Italy, Ireland, Portugal, Saudi Arabia, Qatar, Singapore, and Ethiopia. (Table 2)

More than half of the included studies, i.e., 13 studies (68.4%) used the "inappropriate prescribing" term and included the subtypes of the prescribing error "overdosing, underdosing...". Moreover, 3 studies (15.8%) used the medication errors term, 1 study (5.3%) used the preventable cases of adverse drug events, 1 (5.3%) used misdoing term, and 1 study (5.3%) used therapeutic duplication term. The definition of inappropriate prescribing varies throughout the studies as 4 studies (21.1%) used the medication appropriateness index definition, and 2 (10.5%) studies developed their definition. Also, 2 studies (10.5%) retrieved the definition from previous studies, and 2 studies (10.5%) did not provide a clear definition. The remaining studies used 9 (47.4%) studies used different definitions. The data was obtained either by reviewing hospital medication records or by using national incident reporting databases. Due to the large variability of the study design, definitions, and scales of measurements, the methodological heterogeneity was high.

3.3.Main results

The most commonly inappropriate prescribing was related to dosage, reported in 9 studies (47.4%). Underdosing was reported in 6 studies (31.6%). Underdosing was more common than overdosing across all the studies. Rivaroxaban, dabigatran, and apixaban were the most commonly reported medications associated with errors. Out of all the studies included, 5 studies (26.3%) assessed the medication errors among DOACs and compared them with the other medications, and 2 studies (10.5%) assessed the preventability of the adverse drugs events related to DOACs. The percentage of preventable drug events reported in these two studies was 8.6% and 50%. We observed that a comparative "inappropriate prescription rate" among the medications is difficult to assess because it is unclear and not

unified throughout all the studies. The prevalence of DOACs inappropriate prescribing estimated in 13 studies (68%) ranged from 6% to 60%.

3.4.Contributory factors:

While assessing contributory factors, it was found that 13 studies (68%) reported the contributory factors correlated with DOACs inappropriate prescribing. The most common ones assessed were the patients' related factors such as age (older adult > 65), gender (female > males), weight, renal and hepatic function, comorbidities, history of bleeding, thromboembolic events, and previous use of vitamin K antagonist. Notably, renal impairment was largely discussed as a risk factor that could lead to inappropriate prescribing cause the kidney mainly eliminates all the agents.

4. Discussion

Patient-related factors mainly affected the prescribing appropriateness of DOACs. Dosing-related problem was the most reported concern, particularly underdosing was the highest across all the studies reporting the subtypes of dosing inappropriateness. Renal impairment was an important risk factor for inappropriate prescription of DOACs. In most studies, the inappropriate prescribing assessment was according to the severity of the bleeding (HAS-BLED score) and the thromboembolic events (CHA2DS2–VASC score).

Some studies reported other factors like atrial fibrillation as an indication or whether surgeons wrote the prescription as being independently associated with inappropriate prescribing. In this review only reduced renal function was considered. We could not assess the most frequent factor related to errors due to the disparities between the study settings and the DOACs indications. Some studies only assessed two agents: dabigatran and rivaroxaban or rivaroxaban and apixaban. Other studies compare DOACs with warfarin.

The three studies that used the medication errors reporting systems were inconsistent, limiting the ability to compare the results. One study compares the DOACs with the other anticoagulants. Another study compared it with different classes. Only one study compares the DOACs agents individually in terms of medication errors; apixaban was more prone to errors, followed by rivaroxaban and dabigatran [16,23,24].

A previous systematic review discussed prescription errors as the most common type of medications errors, particularly dosing-related errors with high-risk medications [31]. Thomas et al. found that the definition and reporting of medication errors for any subtype is inconsistent despite their study conducted in the middle east and the healthcare system being not quite different from each other [31] Another systematic review was done to assess the suboptimal use of oral anticoagulants among atrial

fibrillation patients found that adoption of the DOACs varies across the counties, leading to preventing the improvement of prescribing practice [32] This review intended to investigate only DOACs and assess one of the most reported risk factors, i.e., renal impairment, and its effects on the prescribing practices.

A systematic review of thirty-eight systematic reviews and meta-analysis was done to assess the risk and benefits of all classes of anticoagulants. The result did not apply to severe renal impairment, other comorbidities, and polypharmacy as these were the circumstances in which the inappropriate prescribing practices was found [33]. The majority of the studies did not give a clear recommendation regarding prescription patterns of DOACs among patients with severe renal failure.

Our findings should encourage clinicians to improve the safe practice of DOACs and consider the patients-related factors. Few studies reported wrong prescriptions by non-cardiologist, which shows that this practice may be avoided to prevent unwarranted complications. Further studies are needed to provide the best DOACs use among renal impairment patients.

This systematic review has several limitations; our findings were from different countries, so other factors might be related to the healthcare system and the level of DOACs introduced in practice. We only assessed the renal impairment among the individual patient-level factors, while the other factors may also be important. The classifications of kidney diseases differ throughout the studies. Moreover, there might be under-reporting among the studies that extract the data from the reporting system. We limited this review to English articles and did not search grey literature. In addition, this systematic review suffers from limitations related to poor internal validity of some studies. Further research is needed to investigate the prescribing practice, contributary factors, and interventions to improve the prescribing of DOACs.

5. Conclusion

Appropriateness of the DOACs prescribing practice remains a concern, with underdosing as the most reported dosing-related problem. Renal impairment among the patients-related factors increases the risk of inappropriate dosing.

6. Declarations

6.1.Conflict of Interest Statement

The authors have no conflict of interests to declare.

6.2.Funding Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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