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Contributory factors and patient harm including deaths associated direct acting oral anticoagulants (DOACs) medication incidents: evaluation of real world data reported to the National Reporting and Learning System

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ABSTRACT

Introduction: Direct oral anticoagulants (DOACs) are considered high risk medicines and are frequently associated with medication errors. The nature of incidents and associated outcomes of such incidents are poorly understood.

Areas covered: Using a national patient safety reporting database, the National Reporting and Learning System (NRLS), this study aimed to report the contributory factors and outcomes including severe harm and deaths related to all safety incidents involving DOACs reported in England and Wales between 2017–2019. Reason's accident causation model was used to classify the incidents.

Expert opinion: A total of 15,730 incident reports were analyzed. A total of 25 deaths were reported with a further 270 and 55 incidents leading to moderate and severe harm, respectively. A further 8.8% ($n = 1381$) of incidents were associated with low degree of harm. The majority of the incidents involved active failures ($n = 13776$; 87.58) including duplication of anticoagulant therapies, patients being discharged without DOACs, non-consideration of renal function, and lack of commencement of DOACs post-surgery suggesting preventability of such reported incidents. This study shows that medication incidents involving DOACs have the potential to cause severe harm and deaths, and there is a need to promote guideline adherence through education, training, and decision support technologies.

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Safety incidents; Direct acting oral anticoagulants; National reporting and learning system; DOACs; Contributory factors

1. Introduction

Direct oral anticoagulants (DOACs) have been recognized as one of the most commonly concerned drug classes in relation to safety incidents [1,2]. A recent study showed approximately 12% of all severe and fatal medication errors in hospitals constituted the use of anticoagulants including DOACs [3]. The lack of long-term clinical experiences and the need for careful consideration of risk and benefit profiles make DOACs, the likely candidates for medication errors, particularly prescribing errors [4]. DOACs are now the most commonly prescribed oral anticoagulants in the UK accounting to over 60% of total quantity prescribed [5]. A recently published systematic review of 32 studies concluded that one in five prescriptions of DOACs have errors in prescribing [pooled prescribing error rate of 20% (95% CI 15–25%; I2 = 96%; 95% PrI 4–43%)] [6]. However, the review identified that data on circumstances, contributory factors, and likelihood of harm were scant.

Medication errors can be detrimental to patient safety, yet they are a common occurrence in clinical practice [7]. A recent estimate suggested that 66 million out of 237 million medication errors which occurred in England in the year are potentially clinically significant [8]. The WHO 'Global Patient Safety Challenge: Medication Without Harm' had set a global challenge which aimed to reduce severe avoidable medication-related harm by 50% by 2022 [9]. Errors can occur throughout the medication use processes including storage, distribution, prescribing, compounding, preparing, dispensing and administration, and during monitoring [10].

The National Health Service (NHS) England aims to promote safety culture and to monitor spontaneously reported safety incidents by healthcare professionals (HCPs) or patients through the National Reporting and Learning System (NRLS) [11]. The NRLS allows safety incidents in relation to healthcare and healthcare interventions to be reported from all healthcare settings from England and Wales, collated and analyzed to prevent future incidents and promote patient safety. The NRLS database offers excellent opportunity to identify circumstances and contributory factors in relation to medication errors involving DOACs.

The NRLS defines a 'patient safety incident' as 'any unintended or unexpected incident, which could have or did lead to harm for one or more patients receiving health care' [12]. The focus of this paper was on patient safety incidents that were specifically related to DOACs use. Incidents are likely to

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have resulted due to errors in the process of prescribing, preparing, dispensing, administering, monitoring, or through suboptimal advice. Additionally, safety incidents also include near misses and never events. Near misses are defined as prevented medicine-related patient safety incidents which could have led to patient harm, while 'never events' are serious, largely preventable patient safety incidents that should not occur if HCPs have implemented existing national guidance or safety recommendations as in case of administration of medication by the wrong route and overdose of high-risk medication despite the published policy [12]. This study aimed to analyze and report the nature, severity of harm, and types of all medication incidents related to DOACs submitted through all clinical settings across England and Wales to the NRLS database. An in-depth evaluation of all incidents associated with severe harm and deaths were conducted.

2. Methods

2.1. Study design

This study constitutes a mixed-methods analysis of retrospectively collected NRLS data in relation to DOACs safety incidents, contributory factors, degree of harm, and prevention strategies as recommended by organizations responsible for reporting of errors.

2.2. Data Source and inclusion criteria

The NRLS is presently managed by NHS Improvement, which receives over three million patient safety incident reports each year [13]. Incidents reported to NRLS between 1 January 2017 to 31 December 2019 were included. Five DOACs that are licensed and used in the NHS in England and Wales were considered for inclusion namely: dabigatran, rivaroxaban, edoxaban, apixaban, and betrixaban. Reports without drug name or not related to DOACs were excluded. A complete list of search terms is available in Supplementary material Table 1. The data of incident reports included patients age, drug name, indication, severity, type and subtype of medication errors, and location, as well as free-text data usually describing 'what happened,' 'apparent causes,' and 'actions preventing reoccurrence.'

Data on severity resulting from harm as entered by the reporter in the database were classified as- 'no harm occurred;' to 'low,' 'moderate,' or 'severe harm,' which respectively caused minimal, temporal, or permanent harm to one or more persons or fatal incidents[13]. The primary author (AA) checked all entries for completeness, accuracy of descriptions around severity of harm, and applying the inclusion/exclusion criteria. A sample of 10% of these data was validated by two other authors (VP and ZA).

2.3. Data Analysis

Frequency tables were generated to report incidents including drug name, age, care setting of occurrence, description of what happen, medication use process stage, medication error category, and degree of harm. The narrative descriptions of contributory factors and prevention strategies in relation to all incidents resulting in moderate harm, severe harm, or death of the patient were analyzed based on Reason's model [14]. Reason's Accident Causation model is a theoretical framework and is most commonly used to inform investigation on the nature and causes of incidents. Incidents can be classified into active failures (such as slips or lapses), those caused by error-producing conditions and latent failures (or system related). Two members of the research team (AA and VP) familiarized themselves by reading the incident-free text description. Incidents were considered irrelevant if the error was not directly associated with DOACs. All free texts data related associated with medication safety incidents involving death and severe and moderate harm were thematically analyzed.

2.4. Ethical approval

The University of Birmingham's Ethics Committee reviewed and approved this study (ERN_20–0551). NHS Improvement granted approval to share the NRLS data with University of Birmingham (Ref:5199/10 December 2020).

3. Results

A total of 24,322 incident reports were identified from the search. During the data cleaning phase, 8592 incidents were excluded as they were duplicate, irrelevant, or insufficient as shown in Figure 1. A total of 15,730 (64.7%) anonymized DOACs medications incident reports were quantitatively analyzed and categorized according to Reason's accident causation model into active failures ($n = 13776$; 87.58%), followed by error-provoking conditions ($n = 1601$; 10.18%) and latent failures ($n = 353$; 2.24%) as shown in Table 1.

The majority of the active failures were related to mistakes ($n = 6286$; 45.63%). For instance, 'Patient was prescribed Apixaban 25 mg BD. The dose was supposed to be 2.5 mg instead of 25 mg.' Error-provoking conditions contributed to the over a tenth of incidents ($n = 1601$; 10.18%), and within this category, poor documentation constituted the highest reasons ($n = 704$; 43.97%). For instance, 'nurse mentioned that 6 doses of dabigatran had not been signed in anticoagulant chart since admission … missed doses?' Latent failure constituted 2.24% of incidents ($n = 353$) mainly owing to the lack of training ($n = 203$; 57.51%). For instance, 'The patient was prescribed Apixaban, but dalteparin still continued because … trainings of anticoagulants medication a bit lacking.'

3.1. Degree of harm

The NRLS definition of harm is provided in Supplementary material Table 2, and the results of the quantitative analysis for the degree of harm are demonstrated in Supplementary

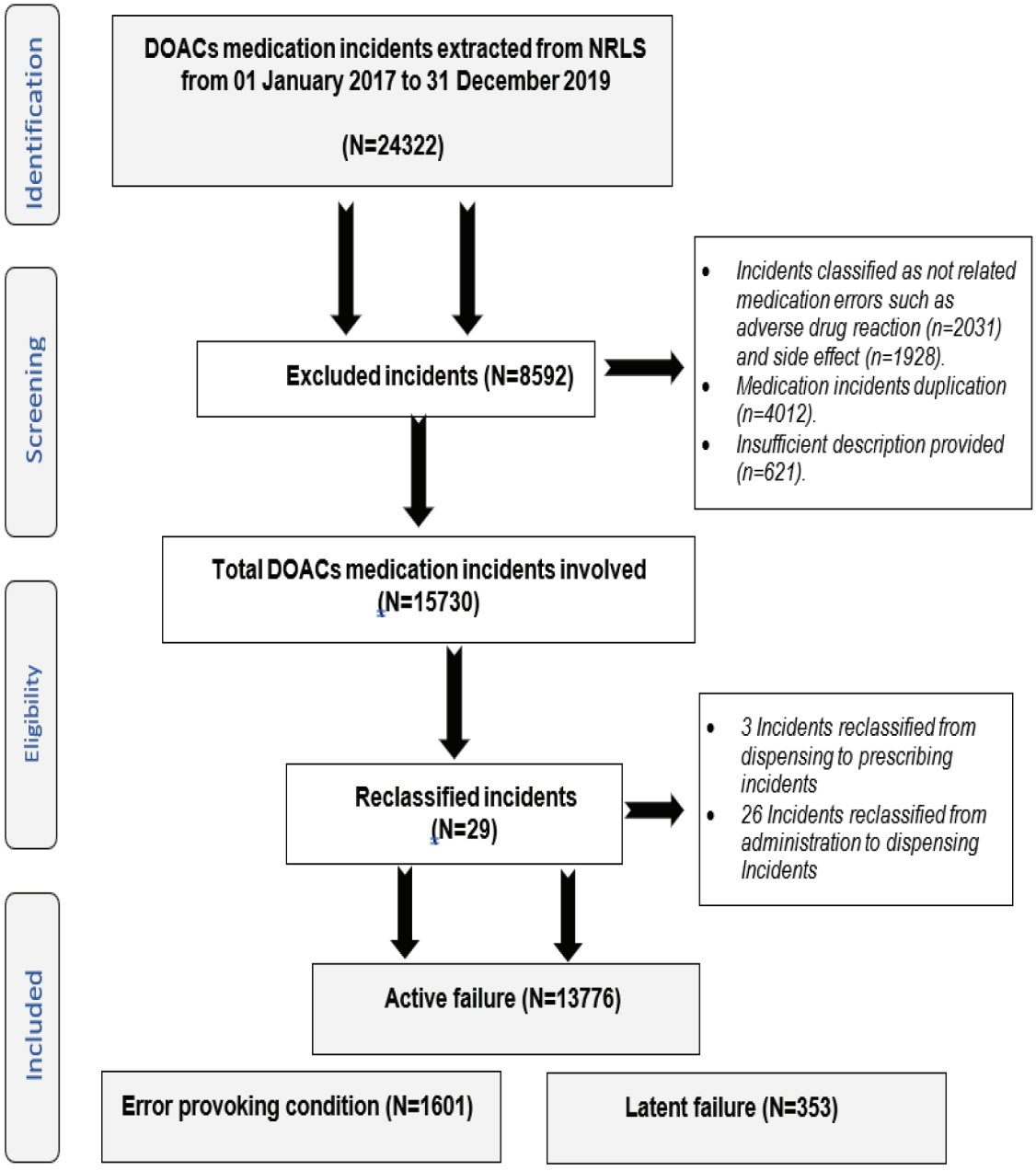

Figure 1. National Reporting and Learning Dataset used for the evaluation of incidents related to directly-acting oral anticoagulants.

material Table 3. While the majority of the incidents (n = 13999; 89%) were associated with no harm and low degree of harm (n = 1381; 8.8%), a total of 325 incidents were related to moderate or severe harm [moderate: 270 incidents (1.70%) and 55 (0.30%) severe harm]. A further 25 (0.20%) incidents led to deaths.

The majority of the incidents known to have caused either moderate harm, severe harm, or deaths occurred in age category 76 to 85 years (104; 29.7%). In total, 44.6% (n = 156) were reported to relate to prescribing, followed by administration (80; 22.8%) and dispensing of medication (60; 17.1%). Wrongful omission of DOACs (70; 20%), followed by contra-indication to the use of the medicine in relation to concomitant drugs prescribed or patients' clinical conditions (52; 15.4%) and wrong/unclear dose or strength of DOACs (43; 12.5%) were the three most common types of medication error reported among these incidents.

3.2. Incidents leading to deaths

Majority of the 25 incidents leading to deaths were reported to have been contributed by active failures caused by mistakes (n = 13; 52%). Free text data in relation to every incident leading to death were analyzed and presented in Table 2. For example, a physician prescribed apixaban to a patient (who was 56–65 years old) only on the drug chart and wrote 'see anticoagulation chart' without writing the same order on the anticoagulation chart. This mistake in prescribing was assumed to have led to death because of the omitted medicine used by the patient before admission.

Table 1. Medication incidents related to direct oral anticoagulants (DOACs) categorized as per the Reason's accident causation model.

	N	%
Active failures		
Slips	5903	42.85%
Lapses	970	7.04%
Mistakes	6286	45.63%
Violations	358	2.60%
Lack of knowledge	259	1.88%
Total	13776	87.58%
Error provoking conditions		
Insufficient staff	28	1.75%
Patient condition(s)	145	9.06%
Poor communication	215	13.43%
Lack of experience	27	1.69%
Distractions	94	5.87%
Look alike drugs	378	23.61%
Poor documentation	704	43.97%
Illegible orders	10	0.62%
Total	1601	10.18%
Latent failures		
Heavy workload	86	24.36%
Lack of training	203	57.51%
Organization factors	27	7.65%
Blame culture	10	2.83%
Supervisory issues	6	1.70%
Organizational policy issues	12	3.40%
Information resource issues	9	2.55%
Total	353	2.24%
Total Errors	15730	100%

3.3. Incidents leading to severe to moderate harm

Qualitative analysis of the examples of severe errors are depicted in Table 3 and represent slips, mistakes, and latent failures. One of the examples documented in the database is related to the lack of experience and training of cardiologist staff in regard DOACs causing latent failure because of contraindication to drugs or condition. In this case, the patient (who was 66–75 years old) was admitted with chest pain and was on apixaban for managing previous stroke. The patient received fondaparinux to treat ACS while already on apixaban. Afterward, the patient was readmitted with hemorrhagic stroke because of the errors in prescriptions due to the lack of experience from the cardiologists. Further examples are presented in Table 3.

Most of the incidents leading to moderate harm (84.8%, 229) were caused by active failure of which the majority were caused by mistakes (49.3%; $n = 113$). Poor documentation was the most prevalent reason in relation to error provoking conditions (35.1%; $n = 35$). Heavy workload and lack of training contributed equally ($n = 2$) and were linked to the occurrence of the latent failures. For example, patient received coadministration of dalteparin with apixaban for evening dose, and this was reported to have happened because of the heavy workload of the nurses that led to losing concentration in managing the patient's medications and lack of consulting the physician after prescribing dalteparin while the patient was already on apixaban. Further examples are demonstrated in Table 4.

3.4. Medications involved and indication

Apixaban represented the highest number of reported incidents accounting for the majority of the incidents ($n = 8127$; 52.0%) followed by rivaroxaban ($n = 5658$; 36.0%), edoxaban ($n = 937$; 6.0%), dabigatran ($n = 787$;5.0%), and unspecified of DOACs ($n = 221$; 1.0%) as shown in Supplementary material Figure 1.

3.5. Indication for medication use

Atrial fibrillation showed highest number related to the medication incidents (59.50%; $n = 9340$) followed by deep vein thrombosis (DVT) ($n = 4625$; 29.40%), pulmonary embolism (PE) ($n = 1510$; 9.60%), and other conditions ($n = 255$; 2.0%) as shown in Supplementary material figure S2.

3.6. Incidents per stage of medication use process

The highest number of medication incidents were reported to occur during the prescribing stage ($n = 6614$; 42.0%). The second highest category of reported medication incidents was reported to involve administration stage ($n = 4581$; 29.10%), followed by medication dispensing ($n = 2557$; 16.30%), monitoring/follow-up ($n = 571$; 3.60%), and advice ($n = 357$; 2.30%), and the least number was reported in the supply stage or OTC drugs use stage ($n = 48$; 0.30%). A total of 6.4% ($n = 1002$) incidents were categorized as 'other' which included storage, response to treatment, order communication, and product labeling and packaging. Detailed data and examples of incidents per stage of medication use process are provided in Supplementary material Tables 4 and 5.

3.7. Safety incidents per medication error category

The most common errors resulting in an incident were omission ($n = 3437$; 21.90%) followed by contraindication to the use of the medicine in relation to drugs or conditions ($n = 2223$; 14.1%), followed by wrong/unclear dose or strength ($n = 2188$; 13.90%) and wrong drug/medicine ($n = 1714$; 10.9%). Table 5 presents data on proportion of safety incidents per stage of medication error category with some examples.

3.8. Patient age

Patients aged 76 to 85 years were most commonly involved covering over a quarter of all incidents (28.53%; $n = 4487$), followed by patients above 85 years old (22.38%; $n = 3520$), as shown in Supplementary material figure S3.

3.9. Safety incidents per care setting

Cardiology wards in the hospitals had the highest proportion of medication reports for DOACs incidents ($n = 7346$; 46.70%), followed by acute medical ward ($n = 3311$; 21.10%). Community pharmacies had also a relatively high rate of error report ($n = 1696$; 10.80%). Results are provided in Supplementary material table S6.

Table 2. Detailed descriptions of incidents leading to deaths with the assigned medication process stage, error type and nature of contributing factor.

Incident information	Incident description	Remedial actions proposed
Error type: Wrong/unclear dose or strength Degree of harm: Death Patient age (years): 76 to 85 Medication process: Dispensing Drug name: Apixaban Accident causation model: Active failure (Slips)	A patient had Apixaban 5 mg tablet twice daily was prescribed a box of Apixaban 5 mg. A box of Apixaban 2.5 mg was dispensed by mistake.	- Avoid active failure/slips.– Double verification by two pharmacists before dispensing. - Double verification by two pharmacists before dispensing.
Error type: Wrong/ transposed/omitted medicine label Degree of harm: Death Patient age (years): 76 to 85 Medication process: Monitoring Drug name: Apixaban Accident causation model: Active failure (Lapses)	Discharge medication dispensed for patient, when checking the patient own medication cupboard, a box of Apixaban was found that had a different patient name on and was labeled from hospital	- Avoid active failure/lapses.– Double check labeling information including patient and drug names especially in high alert medications before dispensing.– Monitor proper medication use. - Double check labeling information including patient and drug names especially in high alert medications before dispensing. - Monitor proper medication use.
Error type: Omitted medicine Degree of harm: Death Patient age (years): 56 to 65 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Patient admitted and usually takes Apixaban twice daily, however has only had it administer once daily, Apixaban was prescribed on meds chart and not on the blue anticoagulation chart on the prescription chart it is written saying see anticoagulation chart however there was no chart seen.	- Avoid active failure/mistakes in prescribing.– Ensure proper prescribing in both medication and blue anticoagulation chart. - Ensure conformity between both charts.– Ensure immediate escalation and proper communication between the nurse and the physician before drug administration. - Ensure proper prescribing in both medication and blue anticoagulation chart. - Ensure conformity between both charts. - Ensure immediate escalation and proper communication between the nurse and the physician before drug administration.
Error type: Contra-indication to drugs or condition Degree of harm: Death Patient age (years): 56 to 65 Medication process: Administration Drug name: Rivaroxaban Accident causation model: Active failure (Lack knowledge)	Patient received Dalteparin and Rivaroxaban on the same day failure to cancel Dalteparin prescription when commencing DOACs therapy, patient had severe bleeding and died.	- Avoid active failure/Improve knowledge -– Nurses to receive proper educationregarding administration, starting, stopping anticoagulants.– Nurses to communicate with the physicianregarding administering such drugs together. - Nurses to receive proper education regarding administration, starting, stopping anticoagulants. - Nurses to communicate with the physician regarding administering such drugs together.
Error type: Contra-indication to drugs or condition Degree of harm: Death Patient age (years): 46 to 55 Medication process: Monitoring Drug name: Rivaroxaban Accident causation model: Error provoking condition (Patient condition)	Elderly Patient prescribed rivaroxaban by secondary care. Elderly frail patient with eGFR: 19 unsuitable for rivaroxaban. Secondary care alerted and rivaroxaban changed to Warfarin but unfortunately, patient had severe bleeding and died.	- Avoid error provoking condition.- Monitor kidney function (eGFR) in elderlyfrail patients before prescribing rivaroxabanor any DOACs. - Monitor kidney function (eGFR) in elderly frail patients before prescribing rivaroxaban or any DOACs.
Error type: Wrong drug/ medicine Degree of harm: Death Patient age (years): 26 to 35 Medication process: Dispensing Drug name: Apixaban Accident causation model: Error provoking condition (LASA)	Dispensing 2 days of Apixaban instead of Aripiprazole issued as a TTO. Patient had felt unwell and admitted, CT scan show recently brain injury and hemorrhage finally, patient had coma and died.	- Avoid error provoking condition. - Segregate and double check LASA beforedispensing.- Double checking/verification for orders bytwo pharmacists before dispensing. - Segregate and double check LASA before dispensing. - Double checking/verification for orders by two pharmacists before dispensing.
Error type: ADRs (when used as intended) Degree of harm: Death Patient age (years): 66 to 75 Medication process: Monitoring Drug name: Apixaban Accident causation model: Error provoking condition (Patient condition)	A patient suffered from very fast AF. After stabilization the patient was taken for a CT scan of the head, which revealed significant bleeding. On review of notes and drug chart it was noticed that the patient was on apixaban for AF, but this was not stopped despite a very low platelet count of 3 and 2 in the last 24 to 48 hours. The patient deteriorated and died.	- Avoid error provoking condition.- monitor the blood count and platelet level before/after commence treatment. - monitor the blood count and platelet level before/after commence treatment.

(*Continued*)

Table 2. (Continued).

Incident information	Incident description	Remedial actions proposed
Error type: ADRs(when used as intended) Degree of harm: Death Patient age (years): 76 to 85 Medication process: Prescribing Drug name: Apixaban Accident causation model: Latent failure (Lack of training)	Junior doctor (trainee) admitted one patient with chest pain diagnosed as ACS 'NSTEMI.' Treated with medication aspirin, ticagrelor, fondaparinux and bisoprolol. However, the patient was already on Apixaban for AF not taken any for 7 days prior to admission. The patient did not have any Apixaban on the evening but did have a dose on the morning. However, the patient had sudden deterioration and reduced level of consciousness with l sided weakness and inattention. She was intubated for CT scan which showed a large Intracerebral hemorrhage.	- Avoid latent failure. - Double checking/verification for diagnosis and identify patient history before order any medication.Ensure proper training for junior doctor. - Double checking/verification for diagnosis and identify patient history before order any medication. - Ensure proper training for junior doctor.
Error type: Unknown Degree of harm: Death Patient age (years): 66 to 75 Medication process: Prescribing Drug name: Rivaroxaban Accident causation model: Active failure (Mistakes)	Patient prescribed double dose of rivaroxaban for AF. Patient admitted with heavy epistaxis and nose packed. Arrested over night. Cause of death patient had haemopericardium, ruptured left ventricle, mitral valve, and coronary artery disease.	- Avoid active failure/mistake– Avoid mistakes while prescribing.- Double checking/verification of orders bydoctor and pharmacists. - Avoid mistakes while prescribing. - Double checking/verification of orders by doctor and pharmacists.
Error type: Omitted medicine/ingredient Degree of harm: Death Patient age (years): 76 to 85 Medication process: Administration Drug name: Dabigatran Accident causation model: Active failure (Slips)	- Patient was prescribed dabigatran for AF but it wasn't given for 2 days before the patient suffered a large ischemic stroke, clexane treatment dose is indicated when there is no availability of the oral tablets. When she was found with reduced responsiveness by the nursing staff patient was transferred from ward, but patient quickly deteriorated and died.	- Avoid active failure/slips– Ensure drug available in the ward and properadministration anticoagulants by nurses.- Double checking/verification of ordersbefore administer drug. - Ensure drug available in the ward and proper administration anticoagulants by nurses. - Double checking/verification of orders before administer drug.
Error type: Contra-indication to drugs or condition Degree of harm: Death Patient age (years): unknown Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Patient was prescribed enoxaparin at night after his surgery and his usual on apixaban dose was restarted today morning. The patient received enoxaparin on evening and then apixaban on morning. Apixaban should have been restarted on evening when clexane dose was due. The Patient pass away unfortunately.	- Avoid active failure/mistake - Ensure and double check when shouldresume DOACs after surgery. - Ensure and double check when should resume DOACs after surgery.
Error type: Wrong/unclear dose or strength Degree of harm: Death Patient age (years): 56 to 65 Medication process: Prescribing Drug name: Rivaroxaban Accident causation model: Active failure (Mistakes)	Patient on rivaroxaban 15 mg OD was prescribed on admission. Nurse saw the chart there was a piece of paper attached to the prescription chart saying that in patients dose rivaroxaban was 15 mg BD. It seems that based off of this, someone has circled a second daily dose of rivaroxaban (the dose for treatment of embolism, which was not her diagnosis) without signing or dating this change or questioning the dose and the patient's current dose was found to be 20 mg OD once investigated.The wrong dose and timings of DOACs drug was prescribed due to an error.	- Avoid active failure/mistake - Ensure and double check when should DOACs after surgery. - Ensure and double check when should DOACs after surgery.
Error type: other Degree of harm: Death Patient age (years): Over 85 Medication process: Administration Drug name: Rivaroxaban Accident causation model: Active failure (Slips)	Nurse had failed to administer for medication due at certain time. Rivaroxaban written on medication chart for another patient.	- Avoid active failure/slips - Ensure and double check which DOACscommence for right patient. - Ensure and double check which DOACs commence for right patient.
Error type: Omitted medicine/ingredient Degree of harm: Death Patient age (years): unknown (Frail elderly) Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Patient admitted with PE. VTE risk assessed no pharmaceutical prophylaxis given. Stockings correctly prescribed but patient declined. Patient should start apixaban 2.5 mg BID. However, apixaban appears never to have been prescribed or given. She died in hospital on cause of death PE.	-Avoid active failure/mistake– Ensure council patient of risk not wear the stocking and risk if declined–Ensure commence and administer the drug to patient.- - Ensure council patient of risk not wear the stocking and risk if declined. - Ensure commence and administer the drug to patient.-

(*Continued*)

Table 2. (Continued).

Incident information	Incident description	Remedial actions proposed
Error type: Contra-indication to drugs or condition Degree of harm: Death Patient age (years): 56 to 65 Medication process: Prescribing Drug name: Rivaroxaban Accident causation model: Active failure (Mistakes)	Patient prescribed tinzaparin and rivaroxaban concurrently and had been administered medication by nursing staff for 3 days. Doctor reports no clear reason as to why both tinzaparin and rivaroxaban prescribed. Doctor reports it being a busy night shift – this may have been a contributing factor.	- Avoid active failure/mistake - Ensure and double check which DOACscommence for patient. - Mitigate night duty for staff and ensureenough staff not short. - Ensure and double check which DOACs commence for patient. - Mitigate night duty for staff and ensure enough staff not short.
Error type: Contra-indication to drugs or condition Degree of harm: Death Patient age (years): 66 to 75 Medication process: Prescribing Drug name: Edoxaban Accident causation model: Active failure (Mistakes)	Patient admitted from other hospital with view to surgical intervention. Doctor documented that apixaban omitted 5 days before intervention. Drug chart showed was given at previous hospital.	- Avoid active failure/mistake– Ensure and double check when DOACscommence for patient prior to transfer andlisting for surgery. - Ensure and double check when DOACs commence for patient prior to transfer and listing for surgery.
Error type: other Degree of harm: Death Patient age (years): 76 to 85 Medication process: Dispensing Drug name: Apixaban Accident causation model: Active failure (Slips)	The patient was given her medication for discharge, but in her bag was other medication rivaroxaban intended for another patient (with a similar looking name).	- Avoid active failure/slips– Ensure and double check medication forright patient name and address beforedischarge patient. - Ensure and double check medication for right patient name and address before discharge patient.
Error type: Omitted medicine/ingredient Degree of harm: Death Patient age (years): Over 85 Medication process: Dispensing Drug name: Rivaroxaban Accident causation model: Active failure (Slips)	The nurse was counseling a patient and noticed the apixaban 5 mg wasn't in the bag. she went on pharmacy to see if they had dispensed or not, but it had not dispensed yet.	- Avoid active failure/slips - Ensure and double check medicationbefore discharge patient. - Engage with all clinical pharmacist to activelymonitor and ensure high standards in theclinical check process. - Ensure and double check medication before discharge patient. - Engage with all clinical pharmacist to actively monitor and ensure high standards in the clinical check process.
Error type: Contra-indication to drugs or condition Degree of harm: Death Patient age (years): 76 to 85 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	A patient transfer to the ward (B) from ward (A) on the evening shift and was given apixaban twice daily as well as tinzaparin at evening. The apixaban and tinzaparin had been prescribed together in 1st ward several days ago and the nurses on ward (B) did not administer the tinzaparin as the patient was on apixaban and they were aware not to give the two together. The nurses on ward (A) gave the apixaban and the tinzaparin until it was spotted the following morning by the pharmacist.	- Avoid active failure/Mistake-Double checking/verification for orders byPharmacists and nurse before administeringdrug - Inform to the nurse in charge and explainedthat nurses should be aware of the need tobe vigilant whenever they are givingmedication–inform nurses staff not supposed to beprescribed together and significantly increasethe risk of bleeding if given together. - Double checking/verification for orders by Pharmacists and nurse before administering drug. - Inform to the nurse in charge and explained that nurses should be aware of the need to be vigilant whenever they are giving medication. - inform nurses staff not supposed to be prescribed together and significantly increase the risk of bleeding if given together.
Error type: Omitted medicine/ingredient Degree of harm: Death Patient age (years): Over 85 years Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	patient admitted overnight post AF ablation procedure. Morning medication round noted only apixaban and insulin prescribed. Checked only apixaban 8 tablet oral medications plus insulin.	-Avoid active failure/Mistake - Ensure and double check right DOACsfor patient prior procedure. - Patients admitted for overnight care shouldhave all their usual medications prescribedas well as those required post procedure. - Ensure and double check right DOACs for patient prior procedure. - Patients admitted for overnight care should have all their usual medications prescribed as well as those required post procedure.

(*Continued*)

Table 2. (Continued).

Incident information	Incident description	Remedial actions proposed
Error type: Omitted medicine/ingredient Degree of harm: Death Patient age (years): 56 to 65 Medication process: Prescribing Drug name: Rivaroxaban Accident causation model: Active failure (Mistakes)	Patient usually takes apixaban BID. However, has only had it administered OD for the last 3 days. Apixaban was prescribed on medication chart and not on the blue anticoagulation chart. On the prescription chart it is written saying see anticoagulation chart however there was no chart seen.	- Avoid active failure/Mistake - Ensure and double check right DOACsdose for patient in all related chart. - Nurses staff should ensure that if drug chartsays this we escalate immediately as to notcause any delay/omission of treatment - Doctors also need to be ensuring that thereis an anticoagulant chart prescribed if needsto be so nurses can give correct DOACs. - Ensure and double check right DOACs dose for patient in all related chart. - Nurses staff should ensure that if drug chart says this we escalate immediately as to not cause any delay/omission of treatment - Doctors also need to be ensuring that there is an anticoagulant chart prescribed if needs to be so nurses can give correct DOACs.
Error type: Other Degree of harm: Death Patient age (years): 76 to 85 Medication process: Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Patient had admitted with stroke. Apixaban were stopped whilst on surgery may be planned for spinal abscess. Planned to hold apixaban. On the after day noted no need for surgery but apixaban were not recommended. patient had severe stroke. patient still made no improvement, severely disabled and deteriorated his case then died.	- Avoid active failure/Mistake - Ensure and double check when stop/resume DOACs for patient prior procedure. - Ensure and double check when stop/resume DOACs for patient prior procedure.
Error type: Other Degree of harm: Death Patient age (years): 36 to 45 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Patient admitted with PE. and prescribed apixaban 10 mg BID for 7 days then 5 mg BID long term by junior doctor. chart shows the apixaban 10 mg BID for 7 days but not written for the 5 mg BID for long term.	- Avoid active failure/Mistake - Ensure training Junior doctor for how toprescribe drugs following a initial week longloading dose. - Improve supervision for junior physicians. - Ensure pharmacy provided education for thejuniors and seniors are aware how thisprescription should be prescribed. - Reenforced with medical team that dailydrug chart review is mandatory for allpatients - Pharmacy explore an alert canbe introduced on system to prompt thedoctors when a loading dose regime ispresent without a maintenance dose. - Ensure training Junior doctor for how to prescribe drugs following a initial week long loading dose. - Improve supervision for junior physicians. - Ensure pharmacy provided education for the juniors and seniors are aware how this prescription should be prescribed. - Reenforced with medical team that daily drug chart review is mandatory for all patients - Pharmacy explore an alert can be introduced on system to prompt the doctors when a loading dose regime is present without a maintenance dose.
Error type: Other Degree of harm: Death Patient age (years): 36 to 45 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Senior Doctor admitted Patient and diagnosed with AF and prescribed apixaban BID, 2nd day patient assessed with thrombosis team and prescribed apixaban OD. Patient still in wrong frequency for many days. Patient had severe bleeding and deteriorated.	- Avoid active failure/Mistake - Ensure good communication between HCP steam - Engage all clinical pharmacist to activelymonitor and ensure high standards in theclinical check process. - Ensure good communication between HCPs team. - Engage all clinical pharmacist to actively monitor and ensure high standards in the clinical check process.
Error type: Contra-indication to drugs or condition Degree of harm: Death Patient age (years): Over 85 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Patient with AKI and planed for discharge. Although medicines reviewed for nephrotoxic drugs it was not identified that apixaban contraindicated as in AKI (eGFR deteriorated from 31 to 19, CrCl would have been closer to 15). Patient developed hemorrhage into left kidney causing pain, worsening AKI and deteriorated his case then died.	-Avoid active failure/Mistake–Ensure all Junior doctor be aware ofthe medicines safety update sent andinforming Apixaban now contraindicated inAKI patients - Doubled check of renal function before commencing apixaban. - Ensure all Junior doctor be aware of the medicines safety update sent and informing Apixaban now contraindicated in AKI patients. - Doubled check of renal function before commencing apixaban.

Note: * LASA: Look Alike Sound Alike; TTO: To take out; DOAC: Direct Oral Anti-Coagulant; eGFR: Estimated glomerular filtration rate; AKI: Acute kidney injury; ACS: Acute coronary syndrome; OD: Once daily; BID: Twice daily; Crcl: Creatinine clearance; AF: Atrial fibrillation;; PE: Pulmonary embolism; VTE: Venous thromboembolism, NSTEMI: Non-ST elevation myocardial infarction; HCPs: Health care professionals.

Table 3. Examples of incidents associated with severe harm.

Incident information	Incident description	Remedial actions proposed
Error type: Omitted medicine Degree of harm: Severe Patient age (years): Over 85 Medication process: Administration Drug name: Edoxaban Accident causation model: Active failure (Slips)	Edoxaban prescribed on admission but not administered for 3 days (two days on ward 1, one day on ward 2), Patient developed sudden loss of vision due to embolic central retinal artery occlusion. Very likely that this was the direct result of omission of edoxaban	- Avoid Active failure/Slips - Ensure proper and timely administration of prescribed anticoagulants by nurses. - Ensure proper and timely administration of prescribed anticoagulants by nurses.
Error type: Wrong quantity Degree of harm: Severe Patient age (years): Over 85 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Patient dose of apixaban was not reduced in spite of the advanced age (96 years) and deteriorating renal function. Creatinine 199. Patient was discharged later that day.	- Avoid Active failure/mistakes - Consider dose adjusting based on kidney function tests before prescribing such drugs - Introduce alerts for performing kidney function tests before prescribing such drugs. - Add it to the AF management guidelines and improve physicians' knowledge regarding these issues. - Consider dose adjusting based on kidney function tests before prescribing such drugs. - Introduce alerts for performing kidney function tests before prescribing such drugs. - Add it to the AF management guidelines and improve physicians' knowledge regarding these issues.
Error type: Wrong drug /medicine Degree of harm: Severe Patient age (years): 66 to 75 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	patient was on rivaroxaban and was not told to stop this before surgery. Was documented that he bleed easily, on rivaroxaban but omitted to mention previous DVT	- Avoid active failure/mistakes in prescribing. - Ensure deprescribing of rivaroxaban beforesurgery. - Ensure deprescribing of rivaroxaban before surgery.
Error type: Others Degree of harm: Severe Patient age (years): Over 85 Medication process: Advice Drug name: Apixaban Accident causation model: Error provoking condition (poor communication)	Patient was referred to Social for ongoing support with this, they visited patient to assess. The patient declined their input, so they did not continue to visit, patient did not have understanding of risks associated with declining support & had been compliant with Social. Health dept were not aware of this and therefore patient missed his evening dose of rivaroxaban.	- Avoid error provoking condition. - Improve communication with patients and provide proper patient education. - Improve communication with patients and provide proper patient education.
Error type: Contra-indication to drugs or condition Degree of harm: Severe Patient age (years): 66 to 75 Medication process: Prescribing Drug name: Apixaban Accident causation model: Latent failure (Lack of training)	Patient admitted with chest pain, patient was on apixaban for previous stroke, received ACS treatment including fondaparinux. He received fondaparinux while the patient already on apixaban. Patient readmitted with Haemorrhagic stroke.	- Avoid latent failure/lack of training. - Ensure proper training. - Improve awareness regarding updated guidelines. - Ensure proper training. - Improve awareness regarding updated guidelines.
Error type: Wrong drug/medicine Degree of harm: Severe Patient age (years): 66 to 75 Medication process: Prescribing Drug name: Apixaban Accident causation model: Latent failure (Supervisory issues)	Emergency admission of patient with thrombosed mechanical valve, Patient with mechanical mitral valve had warfarin discontinued and apixaban prescribed instead by Cardiology team. apixaban does not work on mechanical valves and is not licensed for that use	- Avoid latent failure/lack of training. - Ensure proper training of cardiology team. - Improve supervision for junior physicians. - Ensure proper training of cardiology team. - Improve supervision for junior physicians.

Note: * DVT: Deep vein thrombosis; AF: Atrial fibrillation; ACS: Acute coronary syndrome.

4. Discussion

4.1. Statement of key findings

To our knowledge, this is the first study evaluating the medication incidents relating to DOACs using a large national reporting dataset. Of the 15,730 incidents analyzed, a total of 11% incidents were associated with some degree of harm, including severe and moderate harm, ontributing to deaths. The present study showed that apixaban and rivaroxaban were amongst the medications most associated with safety incidents. The majority of all incidents (68%) involved patients aged 66 years and above and occurred in cardiology and acute medical wards in hospitals.

4.2. Interpretation of findings

A recent study showed that apixaban was the most commonly prescribed oral anticoagulants in the UK in 2019 accounting for 38% of all prescribed items [5]. This study by Afzal et al [5] showed that while the highest number of adverse drug reactions reported to the Medicines and Healthcare Regulatory Agency (MHRA) in the UK amongst all anticoagulants was apixaban (643 events reported in 2019), the number of ADRs per 100,000 items were similar to other DOACs such as rivaroxaban. This suggests that the higher number of incidents related to apixaban in our study was linked with higher prescribing volume rather than its adverse event profile.

Table 4. Examples of incidents associated with moderate harm.

Incident information	Incident description	Remedial actions proposed
Error type: Wrong/unclear dose or strength Degree of harm: Moderate Patient age (years): 66 to 75 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Slips)	Patient admitted with PE On the discharge summary it states: apixaban 10 mg OD last dose. Then 5 mg OD in 3 months. apixaban dose should be 10 mg BID for 1 week followed by reducing dose of 5 mg BID until follow up in hematology clinic. Patient has the potential to extend the PE if the dose is OD.	- Avoid active failure/Slips. - Avoid mistakes in dosing while prescribing. - Avoid Loss of concentration and fatigue
Error type: Wrong drug/medicine Degree of harm: Moderate Patient age (years): Over 85 Medication process: Prescribing Drug name: Apixaban Accident causation model: Active failure (Mistakes)	Patient was switched from rivaroxaban to apixaban. Rivaroxaban was clearly marked as stopped on the system, however when the community pharmacy requested rivaroxaban the medication was restarted by a GP. The patient did not take the rivaroxaban as they were aware the medication was meant to be changed to apixaban.	- Avoid active failure. - Avoid mistakes in prescribing. - Avoid prescribing stopped drugs.
Error type: Omitted medicine Degree of harm: Moderate Patient age (years): 76 to 85 Medication process: Administration Drug name: Apixaban Accident causation model: Active failure (Violations)	Patient on enoxaparin for VTE prophylaxis. She refused to administer 16 doses in different days within a month and had multiple PE. She was then treated with higher dose of enoxaparin for one week. Afterwards, it was switched to apixaban twice a day dosing, and over the weekend, the patient had refused both the evening doses. This was the second time in this patient's admission she had refused a critical medicine, and there was no referral to the medical team.	- Avoid active failure/Violations. - Improve patients' education toward proper medication administration. - Proper education and counseling for patient
Error type: Mismatching between patient and medicine Degree of harm: Moderate Patient age (years): 76 to 85 Medication process: Prescribing Drug name: Apixaban Accident causation model: Error provoking condition (Patient condition)	Patient with past medical history including stroke, hypertension, AF and recurrent UTIs. He was on Apixaban and stopped by GP due to recurrent hematuria. Apixaban changed to clopidogrel by GP. Patient arrived to ward with diagnosis of PE.	- Avoid Error provoking condition. - Assess Patient condition thoroughly before deprescribing/prescribing medications. - Double check patient comorbidities
Error type: Wrong drug/medicine Degree of harm: Moderate Patient age (years): 36 to 45 Medication process: Dispensing Drug name: Apixaban Accident causation model: Error provoking condition(LASA)	Rivaroxaban 20 mg tablets were supplied in error instead of rosuvastatin 20 mg tablets.	- Avoid error provoking condition. - Segregate and double check LASA before dispensing. - Improve awareness of such incidences. - Double checking/verification of orders by two pharmacists before dispensing.
Error type: Contra-indication to drugs or conditions Degree of harm: Moderate Patient age (years): 36 to 45 Medication process: Prescribing (Administration?) Drug name: Apixaban Accident causation model: Latent failure (Heavy workload)	Dalteparin given with apixaban for evening dose. Staffing pressures and workload versus junior nurses not aware and lost in concentration dealing with managing a patient medication.	- Avoid latent failure/Heavy workload. - Improve staff education. - Balancing heavy workload - Reducing staff stress

Note: * DVT: Deep vein thrombosis; ACS: Acute coronary syndrome; OD: Once daily; BID: Twice daily; PE: Pulmonary embolism; GP: General practitioner; VTE: Venous thromboembolism; UTIs: urinary tract infections; GP: General practitioner; PE: pulmonary embolism: NSTEMI: Non-ST elevation myocardial infarction; TTO: To. take out; DOAC: Direct Oral Anti-Coagulant.

The findings of our study corroborate well with the results of other studies around DOAC errors. A study conducted in a large University hospital in the West Midlands region of England reported prescribers' active failure contributed to the majority of DOAC-related incidents [15]. Another retrospective study investigated severe medication errors (MEs) reported to the National Supervisory Authority for Welfare and Health (Valvira) in Finland and conveyed similar results as most of the errors occurred in prescribing, administration, and monitoring phases of the medication process due to mainly active failure causes [16]. Omission error had the highest prevalence among medication errors category in the present study, similar to other studies conducted in tertiary care hospitals in England, Wales, and India [17,18].

4.3. Strengths and limitations

This study has the advantages of using a big national database with extensive information on safety incidents. Availability of free-text description of the safety incidents added value to our study through qualitative analysis. However, researchers noted a lack of a systematized way of narrative reporting. Due to the voluntary nature of the error reporting system, errors are likely to have been under-reported, leading to selection or reporting bias.

Table 5. Proportion and examples of safety incidents per stage of medication error category.

Medication Error Category	N(%)	Examples
Omitted medicine/ingredient	3437 (21.9%)	'TTO was dispensed for patient. A nurse on the ward realized that anticoagulant medicines (Apixaban 2.5 mg tablets) was missing from the TTO, and the nurse phoned pharmacy about the missing medication.'
Contra-indication to the use of the medicine in relation to drugs or conditions	2223 (14.1%)	'Patient received rivaroxaban 20 mg and dalteparin sodium 5000 units for 2 weeks. Patient should not have been receiving both medicines.'
Wrong/unclear dose or strength	2188 (13.9%)	'Inappropriate dose of rivaroxaban had been prescribed for a patient with reduced renal function for treatment of DVT. The patient was prescribed 15 mg BID for 21 days, followed by 20 mg OD maintenance dosing. The patients' renal function was 41 mL/min; therefore, she should have been prescribed maintenance dose of 15 mg OD.'
Wrong drug/medicine	1714 (10.9%)	'Cardiology registrar prescribed 110 mg rivaroxaban by mistake 110 mg is the normal dose of dabigatran.'
Wrong frequency	993(6.3%)	'Patient prescribed edoxaban 60 mg BID. Asked doctor to change it to once daily.'
Mismatching between patient and medicine	707(4.5%)	'Patient was given wrong drug. two patients with the same surname on ward. The wrong patient was given rivaroxaban 15 mg and already taken these medications.'
Wrong quantity	602(3.8%)	'Prescription required for one month supply of rivaroxaban 20 mg tablets. But unfortunately, only 2 weeks supply.'
Wrong method of preparation/supply	229(1.5%)	'Patient prescribed 2.5 mgs of apixaban BID. the pharmacy supplied 5 mgs. the Label written 2.5 mgs take one tablet BID. There are 6 tablets missing from the box.'
Wrong/omitted verbal patient directions	167(1.1%)	'Patient was discharged on apixaban without receiving the relevant counseling. Doctor stated on the discharge letter that he had been counseled about the use and side effects of apixaban and he has been given information.'
Wrong/transposed/omitted medicine label	131(0.8%)	'Care home telephoned because patient had been discharged at the weekend with an unlabeled packet of apixaban tablets. They are unable to use it as it is unlabeled.'
Wrong storage	86(0.5%)	'During a check for discharge planning, I found in the current patient drug locker a box of opened rivaroxaban 20 mg tablets that belonged to a previous patient on the ward.'
Adverse drug reaction (when used as intended)	73(0.5%)	'Patient on apixaban 5 mg BID and been prescribed clarithromycin. Manufacturer of apixaban advises to rather avoid taking apixaban while on clarithromycin.'
Wrong formulation	66(0.4%)	'Patient given rivaroxaban and apixaban at the same time and they belong in the same group of drugs.'
Wrong/omitted/passed expiry date	51(0.3%)	'Patient prescribed rivaroxaban with passed expiry date'
Wrong/omitted patient information leaflet	36(0.2%)	'Patient attended for a colonoscopy. Patient had taken apixaban as usual and not received any information on when must be stopping apixaban before procedure.'
Patient allergic to treatment	26(0.2%)	'Patient prescribed rivaroxaban for DVT. Pharmacy had supplied medication. The medication was listed as an " allergy" for patient on drug chart.'
Wrong route	17(0.1%)	'Rivaroxaban and enoxaparin 4 mg SC OD concomitantly administered. Rivaroxaban administered via NG tube and its not suitable for NG administration.'
Unknown	249 (1.6%)	'Patient had been discharged with rivaroxaban 10 mg for VTE prophylaxis from nursing staff and also dabigatran 110 mg from pharmacy for VTE prophylaxis. patient reported had been taking both medications on discharge.'
Other	2735 (17.4%)	'Patient initiated on apixaban for AF. Prophylactic enoxaparin not discontinued when apixaban initiated so patient received concomitant apixaban and enoxaparin for 2 consecutive days.'
Total	15730 (100%)	

Note: * OD: Once daily; BID: Twice daily; TTO: To take out; DVT: Deep vein thrombosis; SC: Subcutaneous; NG: Nasogastric; VTE: Venous thromboembolism; AF: Atrial fibrillation.

Previous studies describe barriers such as lack of time, fear of blame, lack of knowledge, and forgetfulness amongst key barriers to incident reporting [19,20]. Furthermore, the researchers had limited information about patient's clinical conditions, risk factors, and comorbidities. Therefore, independent evaluation of the causality of the harm with the DOACs could not be undertaken. Error-provoking conditions relating to charting mistakes might include other medications that could have also contributed to the adverse outcomes. Finally, we were unable to identify and classify the incidents linked to the actions of different HCPs and their hierarchy, including senior or junior doctors, nurses, and pharmacists, due to the narratives being often incomplete. Such evaluation will be useful in identifying target populations in future interventions.

5. Conclusion

The findings from this large-scale study involving a national incident reporting dataset suggests that medication incidents involving DOACs are a common occurrence and have led to severe harm and deaths. Most of the DOACs incidents were related to active failures, such as slips and mistakes, as well as through poor documentation and communication and lack of training. Given their proven effectiveness and ease of use, it is imperative to promote safer prescribing and use of DOACs. Health organizations should invest in the continuous professional development, promoting guideline adherence and interventions that have been shown effective in minimizing medication and specifically DOAC related errors.

6. Expert opinion

DOACs related incidents are common in healthcare settings, and this study shows that the incidents can lead to fatal outcomes as well as various degrees of harm with many of these being preventable. Based on Reason's accident causation model, the present study also showed that the majority of

DOACs-pertaining safety incidents were due to active failures of slips and mistakes followed by poor documentation and communication and lack of training. Examples include missed doses, duplication of anticoagulant therapies, patient being discharged without DOACs, and lack of commencement or adjustment of DOACs post-surgery. There is a need to promote guideline adherence through education, training, and decision support technologies, given the majority of DOAC errors related to active failures.

Many of the reported incidents leading to harm were related to the lack of dose adjustments as per renal function. Dose adjustments is key to optimizing treatment and reducing the risk of bleeding. Creatinine clearance (CrCl) instead of eGFR has been advised to determine dosage adjustments for DOACs [21]. Mandating renal functions in prescriptions is likely to minimize errors. Multifaceted interventions involving the use of clinical pharmacists in ward rounds and technological and educational support have been shown to be effective in reducing errors [22,23].

This study could be used as guidance for policy makers, safety professionals, as well as the clinical practitioners to pay attention for omission errors and contraindications while prescribing, dispensing, and administering DOACs. Given the significant impact that such preventable incidents can have on patient-related outcomes, some of the omissions or delays of DOACs could provoke significant patient harm that necessitate further and expensive health care. Health organizations should focus on training their clinicians on DOACs pharmacotherapy and on human factors associated with medication errors such as mistakes in prescribing and encouraging clinician to follow evidence-based clinical guidelines or pathways to improve prescribing practice of such medications. It is also important to perform clinical audits of reported safety incidents and disseminate recommendations for clinical practice improvements. Pharmacists can play an important role in ensuring safety practices through participation and leadership in anticoagulant stewardship programs, which emphasize the use of evidence base in decision making as well as appropriate prescribing, dispensing, and follow-up practices [24]. In addition, pharmacists could play important role in prevention action through medication reviews and medication reconciliation upon admission, care transfer and on discharge, and through their wider roles in prescription and non-prescription medicines counseling and advice in the community [25,26] to help minimizing administration errors. In addition to implementing anticoagulation stewardship and providing anticoagulation management, pharmacist-based ambulatory care anticoagulation clinics can also promote patient safety [27].

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Data availability statement

All data corresponding to this work are provided with the manuscript.

Author contributions Statement

The authors confirm contribution to the paper as follows: study conception and design: A Alrowily, Z Jalal and V Paudyal; data collection: A Alrowily and V Paudyal; The primary author (A Alrowily) was responsible for cleaning up of data and applying the inclusion/exclusion criteria. A sample of 10% of these data was validated by two other authors V Paudyal and Z Jalal. Analysis and interpretation of results: A Alrowily, Z Jalal; Draft manuscript preparation: A Alrowily. All authors reviewed the results and approved the final version of the manuscript prior to submission.References

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