Journal of Thrombosis and Thrombolysis (2019) 47:146–154
https://doi.org/10.1007/s11239-018-1752-9

Direct oral anticoagulants: a review of common medication errors

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Published online: 8 October 2018

Abstract
Stroke and venous thromboembolism continues to be a major cause of morbidity and mortality worldwide. The use of anticoagulation therapy has proven effective in the prevention of stroke and management of thromboembolism; however, initiating treatment may bear clinical burden given the capacity of these agents to cause bleeding. Originally, warfarin has been primarily used, but with the approval of direct oral anticoagulants, therapeutic recommendations have shifted to direct oral anticoagulants for first line therapy for venous thromboembolism for patients without cancer. As compared to warfarin, direct oral anticoagulants are associated with predictable pharmacokinetic profiles, lower bleeding risks, and minimal drug interactions. Complexities in the medication use process can however heighten the risks of causing adverse events. The purpose of this article is to describe common medication errors associated with direct oral anticoagulants, provide practical guidance on the management of direct oral anticoagulants, and suggest strategies to reduce errors. Efforts to minimize medication errors involve the participation of an interdisciplinary team that has standardized policies, risk reduction strategies, and guiding principles to achieve optimal therapeutic outcomes. Current primary literature is not robust in assessment of clinical impact of medication errors associated with DOACs but reports of adverse drug events have been noted. Future studies should be guided to assess clinical outcomes associated with medication errors and identify potential clinical interventions to optimize therapy.

Keywords Anticoagulation · DOAC · Medication error · Risk reduction

Highlights

- Anticoagulants are primarily associated with bleeding adverse events, however other adverse reactions may also occur due to medication errors.
- Varying indications and complexities in regimens can contribute to the inappropriate use of direct oral anticoagulants.
- Risk reduction strategies to minimize errors should be identified and implemented into institutional practices.
- The inclusion of routine monitoring of direct oral anticoagulants may be necessary to ensure therapeutic outcomes.

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Introduction

Thromboembolic events associated with atrial fibrillation (AFib) and venous thrombosis (VTE), are leading causes of morbidity and mortality worldwide [1]. Anticoagulants are indicated for the prevention and/or treatment of VTE and thromboembolic complications associated with AFib such as stroke [2–6]. Oral anticoagulants have been utilized for years with the development of vitamin K antagonist, warfarin, in 1954 [6]. It is estimated that more than 6 million patients in the United States (US) are treated with anticoagulants [7]. Use of anticoagulation is an essential treatment modality for patients yet carries substantial risks of adverse events. Clinical use of oral anticoagulant therapy has expanded considerably since the approval of direct oral anticoagulants (DOACs). Among them are apixaban, dabigatran, edoxaban, and rivaroxaban. An additional agent, betrixaban received final US Food and Drug Administration (FDA) approval in June 2017. These agents exert their anticoagulant effects, by directly inhibiting thrombin (dabigatran) or factor Xa (apixaban, rivaroxaban, edoxaban, and betrixaban) [2–5].

FDA approved indications and doses are included in Table 1 [2–5].

Historically, warfarin has been considered the "standard" of therapy, but the fixed-dose regimen, absence of drug monitoring, and fewer drug–drug interactions of DOACs has caused a paradigm shift in treatment guidelines and prescribing patterns of healthcare providers [8, 9]. Global registry data indicate that prescriptions for DOACs have surpassed that of VKA [8]. Advantages of using DOACs over VKA include reaching a more rapid anticoagulant effect within hours after first dose, achieving similar (and in some cases superior) effectiveness compared to VKA, and eliminating the need for routine international normalized ratio (INR) testing [9–11]. Although highly effective, all anticoagulants are associated with bleeding risks [12]. Quarter Watch estimates 6.3% of patients exposed to an anticoagulant for one year will need to visit the emergency room [13]. Clinical trials have noted variances in bleeding outcomes in patients receiving DOACs versus VKA therapy [14]. The efficacy and safety of DOACs for stroke prevention in AFib have been established in four phase III trials. Dabigatran, apixaban, rivaroxaban, and edoxaban were studied in the following trials: randomization evaluation of long-term anticoagulant therapy (RE-LY), apixaban for the prevention of stroke in subjects with atrial fibrillation (ARISTOTLE), rivaroxaban once daily oral direct factor Xa inhibitor compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET-AF), and effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48 (ENGAGE AF-TIMI 48), respectively [15–17]. A meta-analysis pooling the results of the four pivotal clinical trials in patients with non-valvular atrial fibrillation (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48) included 42, 411 patients receiving a DOAC and 29, 272 patients receiving a VKA [18].

The analysis confirmed that DOACs had significant reduction rates in hemorrhagic stroke and intracranial hemorrhage compared to VKA and less severe major bleeding events [18]. Although, the trials did confirm that major bleeding with a DOAC is less severe in nature than VKA therapy, the RE-LY, ROCKET, and ENGAGE-AF -TIMI trials did show that gastrointestinal bleeding is higher with dabigatran 150 mg, rivaroxaban, and edoxaban than VKA [15–17]. While the ARISTOTLE trial demonstrated that adverse events occurred in almost equal proportions of patients in the apixaban and warfarin arms [15].

When DOACs are not prescribed or utilized appropriately, the incidence of adverse events can increase. In fact, anticoagulant drugs–led by rivaroxaban–accounted for 21,996 reports of severe injuries in the US, including 3,018 reported deaths, per the Institute for Safe Medication Practices (ISMP) analysis of 2016 FDA adverse event data [13]. The majority of these injuries (n = 17,218) were from hemorrhages, making bleeding one of the most frequently reported serious adverse drug effects of all types [13]. Although data is limited on the clinical impact of adverse events associated with medication errors involving DOACs, studies have identified errors at the prescribing, dispensing and administration stages of the medication use process [19–23].

Inappropriate prescribing

DOACs are marketed for having fixed dosing as compared to warfarin, due to a wider therapeutic index and more predictable pharmacokinetic and pharmacodynamic properties [20]. When determining the appropriate dose for a patient, factors such as the indication, physiological properties and clinical parameters (age, weight, renal insufficiency, interacting drugs) of the patient should be taken into consideration [21]. The complexity of these DOAC specific parameters make their appropriate prescribing highly challenging [23].

Several studies have examined DOAC use and prescribing patterns in patients to assess compliance of patients' prescriptions to guidelines and manufacturer recommendation [19–25]. According to a subgroup analysis regarding off label dosing of non-VKA oral anticoagulants of the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase III (ORBIT-AF III) trial, almost one in eight of US patients in the community received a DOAC dose inconsistent with labeling [19]. Two prospective studies conducted to evaluate the appropriateness of prescribing dabigatran and rivaroxaban in patients with non-valvular atrial fibrillation (NVAF) in the clinic setting found that the choice of drug and dosage were the most frequent inappropriate criterion among patients [24, 25]. The appropriateness of prescribing was assessed using the following criteria: indication, preferred choice, modalities and practicability of administration, drug–drug interactions (DDIs), drug-disease interactions, duplication, and duration from the Medication Appropriate Index (MAI) tool [26]. Some studies have identified rivaroxaban and apixaban most commonly associated with an inappropriate dose [19–23]. This could be potentially related to the dosing guidance specificity in patients with renal impairment or in the presence of drug interactions. Use of the Cockcroft–Gault method to calculate a patient's renal function is mainly used, but certain patient populations are at risk for dosing discordance when advanced age, extremes in weight, or female gender are taken into consideration.

Although the clinical impact of adverse events associated with inappropriate prescribing has not been well established among various clinical studies, some have identified thrombotic and bleeding risks associated with suboptimal prescribing [19, 22, 23]. In a retrospective cohort analysis of

Table 1 Indications and dosing recommendations for DOACs

Indication	Apixaban	Betrixaban	Dabigatran	Edoxaban	Rivaroxaban
DVT/PE prophylaxis	2.5 mg twice daily after at least 6 months of treatment *(reduction in risk of recurrence)*	160 mg as single dose on day 1, followed by 80 mg once daily for 35–42 days	150 mg twice daily		10 mg once daily with/without food, after at least 6 months of standard anticoagulation treatment *(reduction in the risk recurrence)*
DVT/PE treatment	10 mg twice daily for 7 days, then 5 mg twice daily		150 mg twice daily	If patient weight > 60 kg: 60 mg once daily after 5 to 10 days with parenteral anticoagulant < 60 kg: 30 mg once daily	15 mg twice daily × 21 days, then 20 mg once daily with food
Postoperative DVT prophylaxis after knee replacement	2.5 mg twice daily beginning 12–24 h postoperatively; duration 12 days				10 mg once daily for 12 days
Postoperative DVT prophylaxis after hip replacement	2.5 mg twice daily beginning 12–24 h postoperatively; duration 35 days		110 mg 1–4 h post-surgery and after achieving homeostasis, then 220 mg once daily for 28–35 days		10 mg once daily for 35 days
Prevention of stroke and systemic embolism NVAF	5 mg twice daily		150 mg twice daily	60 mg once daily; Do NOT use in patients with a CrCl > 95 ml/min due to increased risk of stroke	20 mg once daily with food
Dosing in the Presence of Renal Impairment	2.5 mg twice daily if any two of the following are present: age ≥ 80, weight ≤ 60 kg, SCr ≥ 1.5	If CrCl ≥ 15 to < 30 ml/min: initial 80 mg single dose, followed by 40 mg once daily for 35–42 days	CrCl < 30 ml/min not recommended for VTE treatment or prophylaxis If CrCl 15–30 ml/min: 75 mg twice daily for NVAF	If CrCl 15–50 ml/min: 30 mg once daily for prevention of stroke in NVAF If CrCl 15–50 ml/min or weight ≤ 60 kg, reduce dose to 30 mg once daily for treatment of DVT or PE	If CrCl < 30 ml/min: avoid use for VTE treatment or prophylaxis If CrCl 15–50 ml/min: 15 mg once daily with food for prevention of stroke in NAVF, if CrCl < 15 ml/min avoid use
Dosing in the presence of drug interactions	In the presence of dual strong CYP3A4 or P-gp inhibitors: reduce dose by 50% Avoid use if patient is already indicated to use 2.5 mg twice daily	In the presence of dual strong CYP3A4 or P-glycoprotein inhibitors: reduce initial and maintenance dose by 50% Avoid use if patient also has severe renal impairment	Avoid concomitant use with rifampin Treatment of DVT/PE: If CrCl < 50 ml/min avoid use with any P-gp inhibitor NVAF: If CrCl 30–50 ml/min and given with dronedarone or systemic ketoconazole: 75 mg twice daily CrCl < 30 ml/min and any P-gp inhibitor: avoid concurrent use	Avoid concomitant use with rifampin Treatment of DVT/PE: In the presence of P-gp inhibitors reduce dose to 30 mg once daily	Avoid concomitant use with combined P-gp and strong CYP3A4 inhibitors or inducers

SCr serum creatinine, *CrCl* creatinine clearance, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *VTE* venous thromboembolism, *NVAF* non-valvar atrial fibrillation, *P-gp* P-glycoprotein, *CYP3A4* cytochrome P450 3A4

168 DOAC patients, three events of each, recurrent venous thromboembolism and major bleeding, were associated with inappropriately dosed DOACs [22]. While, Whitworth et al. found that the odds of bleeding doubled with each inappropriate use and adverse events [23]. Overall, an increase in cardiovascular hospitalizations can be associated with patients who are considered under dosed, while overdosing is associated with increased all-cause mortality as compared with recommended dosing [19].

Commonly used coagulation assays (e.g., activated partial thromboplastin time and prothrombin time) are available across all institutions and are easy to perform but lack the necessary sensitivity and specificity to be reliable for monitoring patients on DOACs [27]. The lack of routine monitoring, stable dosage regimen, and lesser interaction with drugs are some possible reasons why DOACs are less likely to be discontinued and are often seen as an advantage over warfarin [28]. However, situations exist when having a reliable method to assess the presence of an anticoagulant would be useful. The potential indications for coagulation testing may include emergency situations (e.g. trauma, urgent surgery, or acute bleed), overdose, acute thrombosis, medication adherence, and potential DDIs [29, 30]. Some studies have indicated that DOACs non-adherence rates have reached up to 50% if no special measures were taken [24, 31, 32].

While DOACs have fewer DDIs than warfarin, the pharmacodynamics of DOACs can be enhanced by several drug classes, including other anticoagulants, antiplatelet, and nonsteroidal anti-inflammatory drugs (NSAIDs). The concomitant administration of these classes in addition to DOACs can cause an increased incidence of hemorrhage. A subgroup analysis examining concomitant use of rivaroxaban and NSAIDs found a 2.5-fold higher rate of major bleeding compared to those who were not taking NSAIDs [33]. Many of the drug interactions involving DOACs are dependent on varying degrees of P-glycoprotein (P-gp) and cytochrome P450 (3A4) pathways [34]. There is a substantial number of drugs that inhibit the P-gp system which as a result may enhance the absorption of DOACs [34]. These include antiretrovirals, certain macrolides, some psychotropic and, importantly, cardiovascular drugs such as amiodarone and verapamil, which are frequently used in conjunction with DOACs for rate or rhythm control in atrial fibrillation [34]. Alternatively, there are also drugs, P-gp or CYP 3A4 inducers, that will reduce levels of DOACS with variable magnitude such as certain anticonvulsants and herbal supplements for example St. John's Wort [34]. Therapeutic management may require DOAC dosage adjustments or the avoidance of the concomitant use due to alterations in DOAC concentrations or increased risk of bleeding (Fig. 1).

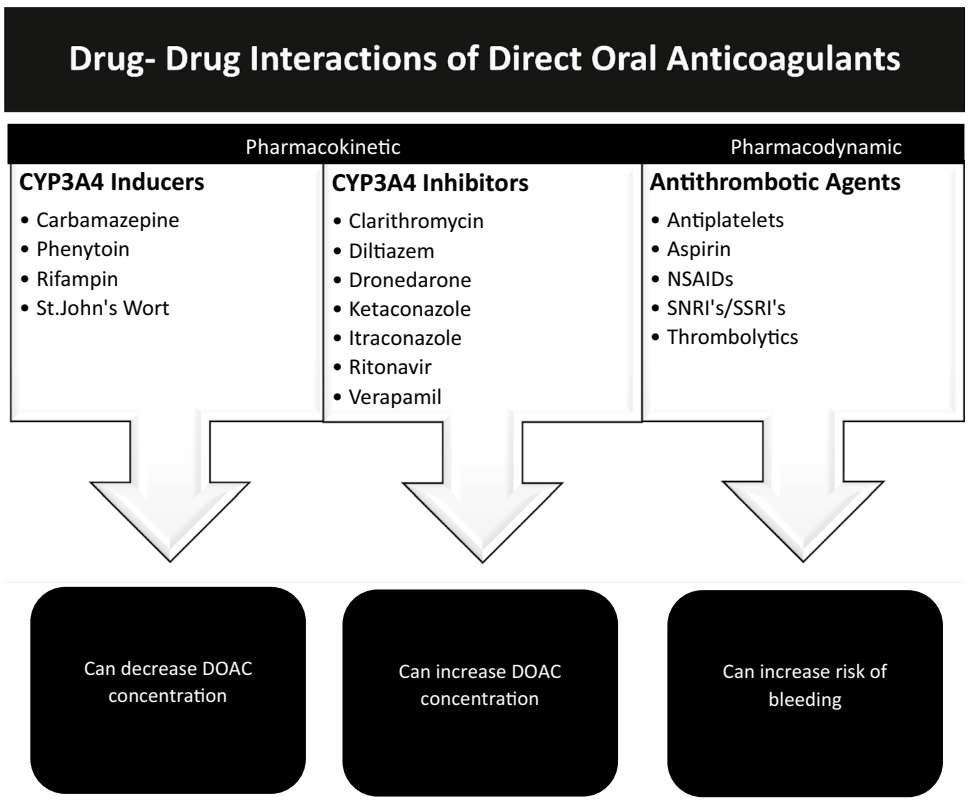

Fig. 1 Clinically relevant pharmacokinetic and pharmacodynamic drug–drug interactions with DOACs and potential effects on DOAC therapy. *CYP3A4* cytochrome P450 3A4; *NSAIDs* nonsteroidal anti-inflammatory drugs; *SNRI* serotonin-norepinephrine reuptake inhibitors, *SSRI* selective serotonin reuptake inhibitor

Administration and dispensing

During the dispensing and administration stages of the medication use process, the focus is to ensure that the medication dispensed is concordant with the prescribed drug. Issues with dispensing and administration have been identified in the ambulatory and inpatient settings and may occur due to discontinuity of care across health sectors and interdisciplinary teams [35]. Errors that have been reported with DOACs at these stages include improper storage, administration of DOACs, and omission of dose. One of the recommendations to reduce medication errors and harm is to use the "five rights": the right patient, the right drug, the right dose, the right route, and the right time [36].

Although studies have not identified clinical impact associated with errors of storage and administration of DOACs, it has been mentioned that some health care providers lack knowledge regarding the storage and administration of these medications. In the survey of health care providers, only half the respondents knew that dabigatran should not be crushed or exposed to moisture, and that rivaroxaban 20 mg should be taken with food [37].

The omission of an anticoagulant can pose a significant risk at which the patient can experience a thromboembolic event. Previously, various terms such as non-vitamin K or novel oral anticoagulants, often abbreviated as "NOAC" or target specific oral anticoagulants (TSOAC) were used to describe direct oral anticoagulants. However, the ISMP identified "NOAC" as an error-prone abbreviation due to being misconstrued as "no anticoagulation. There is at least one reported account where the term "NOAC" written in the medical record was interpreted as meaning "no anticoagulation" potentially resulting in the patient not receiving the critical therapy that was intended [38]. In addition, lapses with "hold orders" in the inpatient setting can also lead to omission of therapy, when the medication is not re-initiated when appropriate. An example could be described as "holding" two to three doses of a DOAC for a procedure.

A descriptive Danish study conducted by Henrisken et al. showed potentially fatal and serious events were most frequently associated with sector change (admission to or discharge from hospital or undergoing surgery) and resulted from insufficient or excess dosing [35]. Although the study did not highlight differences between anticoagulant drug classes, it did show anticoagulants are associated with serious and potentially fatal adverse events to patients during a sector change [35].

Periprocedural management of DOACs

In 2017, the American College of Cardiology released a consensus statement regarding the periprocedural management of DOAC's for patients with non-valvular atrial fibrillation to provide practical guidance in the bridging or interruption of therapy [39]. Clinical considerations for periprocedural management regarding interruption of therapy are dependent on predisposing factors, procedural bleed risk, and kidney function [39]. The exact duration for which a DOAC should be withheld is also dependent on the specified agent.

Given the pharmacokinetic profiles of DOACs and their short-half lives, reinitiating a DOAC will render the patient therapeutically anticoagulated within hours after the first full dose and bridge therapy is generally not required [39]. Prior to reinitiating DOAC therapy, practitioners should ensure complete homeostasis [39]. Patient related-factors and risk of procedural site bleed could potentiate the likelihood of bleeding complications. Resuming DOAC therapy may be a cumbersome task for practitioners, as they are tasked with minimizing preoperative thrombotic risks with temporary interruption of anticoagulation therapy and postoperative bleeding risks associated with resumption of therapy. Following procedures with low post procedural bleed risk, DOAC therapy could be resumed sooner than with high post procedural bleed risks [39]. In the setting of neuraxial anesthesia, the American Society of Regional Anesthesia and Pain Management does recommend discontinuing DOAC's prior to neuraxial procedures due to increased risk of spinal or epidural hematoma [40]. All DOAC's carry a black box warning regarding their use in the setting of neuraxial anesthesia and reinitiating DOAC therapy is dependent on the specific agent and could vary from at least 24–72 h after the procedure [40]. Clinical considerations for procedural management regarding the interruption and reinstitution of DOAC therapy is listed in Table 2.

Use of reversal agents

In the event of a life-threatening or uncontrolled bleeding event, there are currently two reversal agents, coagulation factor Xa, recombinant, inactivated-zhzo and idarucizumab marketed for specific DOACs. Coagulation factor Xa, recombinant, inactivated-zhzo was recently approved for the reversal of apixaban and rivaroxaban [41]. It is not indicated for the treatment of bleeding related to any factor Xa inhibitors other than apixaban or rivaroxaban. Dosing of coagulation factor Xa, recombinant, inactivated-zhzo is

Table 2 Considerations for the periprocedural interruption and reinstiution of DOACs

Temporary interruption of DOAC therapy
Factor xa inhibitors (apixaban, betrixaban, edoxaban, rivaroxaban)
Low bleed risk (e.g. cataract surgery)
If CrCl ≥30, discontinue ≥ 24 h
If CrCl 15–29, discontinue ≥ 36 h
If CrCl is < 15, consider Xa level and/or ≥48 h; no data available
Procedure unknown, intermediate, or high bleed risk (e.g., pacemaker or cardioverter-defibrillatior device implantation)
If CrCl is ≥ 30, discontinue ≥ 48 h
If CrCl is < 30, consider Xa level and/or ≥ 72 h; no data available
Direct thrombin inhibitor (dabigatran)
Low bleed risk
If CrCl ≥ 80, discontinue DOAC ≥24 h
If CrCl 50–79, discontinue ≥ 36 h
If CrCl 30–49, discontinue ≥ 48 h
If CrCl 15–29, discontinue ≥ 72 h
If CrCl < 15, consider direct thrombin time assay and/or ≥ 96 h; no data available
Procedure unknown, intermediate, or high bleed risk
If CrCl ≥ 80, discontinue DOAC ≥ 48 h
If CrCl 50–79, discontinue ≥ 72 h
If CrCl 30–49, discontinue ≥ 96 h
If CrCl 15–29, discontinue ≥ 120 h
If CrCl < 15, consider direct thrombin time assay and/or ≥ 96 h; no data available consider direct thrombin time assay
Restarting DOAC therapy
General considerations
Establish that hemostasis has been achieved
Ensure the patient can tolerate oral medications
DOAC dosing should reflect postprocedural renal function
Generally bridge therapy with a parenteral agent is not required
Low post procedural bleed risk
Reasonable to reinitiate DOAC within 24 h of procedure. Consider using reduced dose on the evening after the procedure
High post procedural bleed risk
Reasonable to reinitiate DOAC 48–72 h after the procedure

based upon the dose of rivaroxaban and apixaban and the time since last administration. Treatment consists of either a single 400- or 800-mg intravenous bolus dose, followed by an infusion at a rate of 4 or 8 mg/min for up to 120 min [41]. Dosing and administration recommendations with the use of factor Xa, recombinant, inactivated-zhzho are included in algorithm (Fig. 2).

However, practitioners should be cautioned with the use of coagulation factor Xa, recombinant, inactivated-zhzo due to reports of arterial and venous thromboembolic events and sudden deaths observed within 30 days of use according to early reports from the Andexanet Alfa for acute major bleeding associated with factor Xa inhibitors (ANNEXA-4) study [42].

Idarucizumab is a humanized monoclonal antibody fragment that binds directly to dabigatran, neutralizing its activity [43]. Idarucizumab is indicated in patients treated with dabigatran when the reversal of the anticoagulants effects of dabigatran is needed. The recommended dose of Idarucizumab is 5 g provided as 2 separate vials each containing 2.5 g [43]. Idarucizumab is administered intravenously as a bolus injection or as two consecutive infusions of 2.5 g over 5 min to 10 min each (administered no more than 15 min apart) [43].

With reversing any anticoagulation agent, there is a risk of exposing patients to thrombotic risks of their underlying disease. The clinical benefit should be assessed prior to initiation of any reversal agents to mitigate any risks that may be associated with reversal therapy.

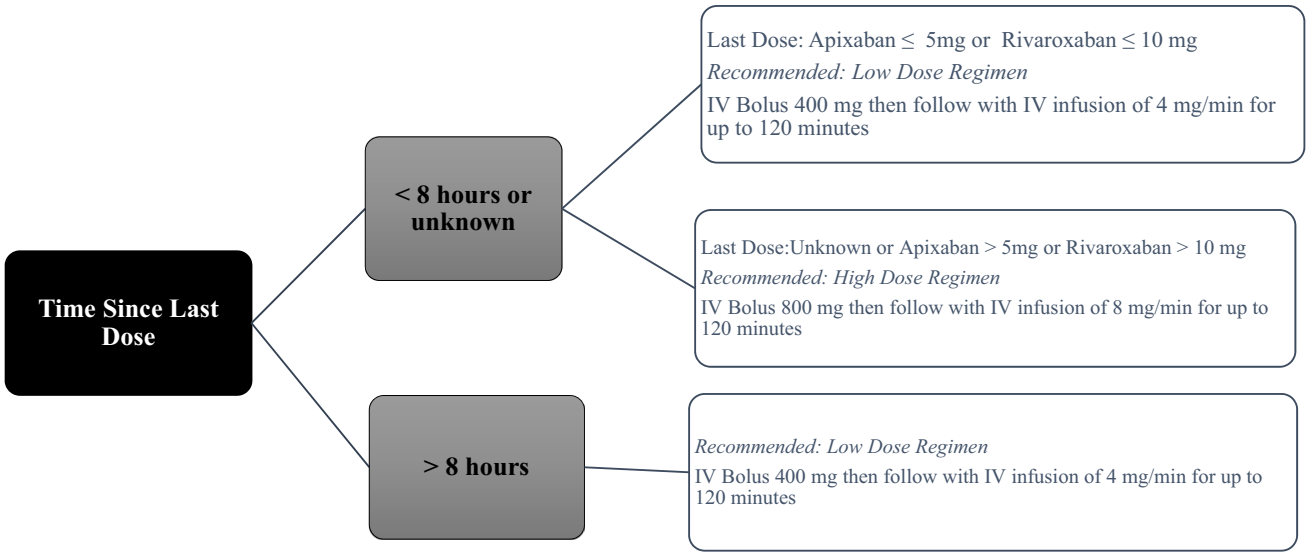

Fig. 2 The recommended dosing regimens for coagulation factor Xa recombinant inactivated zhzo, based on specific factor Xa inhibitor, dose of FXa inhibitor, and time since the patient's last dose

Risk reduction strategies

Opportunities for lowering risks of medications errors exist for healthcare providers to optimize patient care and outcomes. The anti-thrombotic self-assessment tool and 10 key system elements of medication use provided by the ISMP could evaluate current systems related to the use of anticoagulant agents, proactively identify potential improvement areas and opportunities for reducing patient harm [44]. Prior to initiating a DOAC agent, pertinent patient demographic information (age, actual body weight) and clinical information such as clinical indication and most recent laboratory data (renal and hepatic function) can assist with selecting the appropriate medication and prevent complications in therapy. Dosage adjustments may be necessary for patients dependent upon renal function, age, or weight. Patients that are not candidates for DOAC therapy include those with several renal dysfunction, mechanical valve prosthesis, and women who are pregnant [45]. A standardized protocol in which computer order entry system alerts healthcare practitioners of duplicate class orders for anticoagulants and highlights potentially dangerous DDIs could mitigate the risks of administration and dispensing errors. In addition, the computer order entry system should be directly interfaced with the laboratory system in which abnormal values automatically notify practitioners for a potential need for modification of therapy [44, 46].

Medication reconciliation should be performed for all patients at times of sector transfer, which includes hospital admission/discharge and peri-operative management. Serious incidents and sometimes fatality may occur when a patient is transitioning care, in which insufficient or excess anticoagulation is administered. Upon patient discharge, verify that the patient will be able to obtain the medication prescribed.

Warfarin is a practical option for patients who may be underinsured or financially unstable, if their level of anticoagulation can be monitored properly. In patients with mechanical heart valves, warfarin provides excellent protection against thromboembolic complications [47]. Dabigatran was compared to warfarin in patients with mechanical heart valves in a Phase II Study (RE-ALIGN) [47]. The study was discontinued early due to excess thromboembolic and bleeding events in the patients randomized to the dabigatran group [47].

Conclusion

As DOACs continue to be integrated in to clinical practice, it is important to utilize and manage these agents appropriately. Results from studies describe improper DOAC utilization and potentially inappropriate prescribing, which may advertently lead to adverse events. Varying indications and complexities in dosing regimens, renal function, and drug–drug interactions can contribute to the inappropriate prescribing of DOACs. In addition, patient-related factors such as advanced age, comorbid cardiovascular conditions, and compliance could play an integral role in risk stratification to identify patients at an increased risk of bleeding events. Due to the differences among the oral anticoagulants, it is important for healthcare providers to utilize these agents appropriately to achieve the safest and most efficacious use to optimize patient outcomes. Possible interventions to

reduce medication errors involve strengthening the education of healthcare providers, establishing DOAC management protocols, and implementing anticoagulant services for all patients when they are discharged from the hospital and transition care to the outpatient setting.

Funding This study was performed without financial support.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants This article does not contain any studies with human participants performed by any of the authors.

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