Introduction

Venous thromboembolism (VTE) and atrial fibrillation (AF) are major burdens on the healthcare system. The average occurrence of venous thromboembolism annually is around 108 per 100,000 person-year.[1]

For many years, oral vitamin K antagonists (VKAs) were the drug of choice in managing VTE. VKAs treatment is safe and effective if therapeutic international normalized ratio (INR) maintained on the target. However, achieving a stable, therapeutic international normalized ratio (INR) can be difficult and challenging in the context of drug and food interactions and liver disorder, resulting in undertreatment which increases the risk of thromboembolism or overtreatment which might cause bleeding. Herein, we provide an overview of DOACs indications, use in specific comorbidities, monitoring parameters, perioperative management, and reversal agents.

Keywords: Anticoagulant, DOACs, effective, factor Xa, overview, rivaroxaban

Abstract

Venous thromboembolism (VTE) and atrial fibrillation (AF) is a major burden on the healthcare system. The average occurrence of venous thromboembolism annually is around 108 per 100,000 person-year.[1]

DOACs have transformed treatment of coagulation disorder, and now, it is the leading treatment for stroke prevention in AF and VTE prophylaxis and treatment. For more many years, oral vitamin K antagonists (VKAs) were the drug of choice in managing VTE. VKAs treatment is safe and effective if therapeutic international normalized ratio (INR) maintained on the target. However, achieving a stable, therapeutic international normalized ratio (INR) can be difficult and challenging in the context of drug and food interactions and liver disorder, resulting in undertreatment which increases the risk of thromboembolism or overtreatment which might cause bleeding.[2] Furthermore, their unpredictable pharmacokinetics and pharmacodynamics necessitate the need for routine laboratory which is posing a difficulty for both patients and doctors alike.

In 2010 the launch of direct oral anticoagulants (DOACs) led to shift from using VKAs due to their efficacy, standardized dosing, reduced monitoring, less frequent follow-up, fewer interactions with food or drugs, generally lower rate of adverse events and immediate drug onset and offset.[3,4]

DOACs are now the preferred medication for VTE treatment and prevention and stroke prevention in patients with AF.[5]

DOACs are categorized into two classes: direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban, and betrixaban).

Herein, we provide an overview of DOACs indications, use in specific medical conditions, monitoring parameters, perioperative management, and reversal agents.

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**Indications of DOACs**

Apixaban, edoxaban, rivaroxaban, and dabigatran are approved for reducing the risk of stroke in AF patients as well as VTE treatment and prophylaxis.\[6\]

Rivaroxaban has unique indications as the first DOAC licensed for use in acute coronary syndrome (ACS) and in combination with aspirin to lessen major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).\[7,8\] The other DOACs are at this time being assessed for their role in percutaneous coronary intervention.\[9,10,11\]

**DOACs in Specific Comorbidities**

1. **Cancer-Associated Thromboembolism:**

   Active cancer increases the risk of arterial and VTE and bleeding as well. Traditionally, the preferred agent of choice of VTE with cancer has been low molecular weight heparin (LMWH).\[12\] The current view for the treatment of VTE related to cancer support the use of apixaban over LMWH and other DOACs. Major guidelines now recommend the use of DOACs in cancer-related VTE treatment.\[13-15\]

2. **Renal disease:**

   All DOACs therapies eliminated by the kidneys and reeducation in glomerular filtration rate must be considered when considering these agents. The most renally eliminated DOACs is Dabigatran, kidneys clear 80% of it, followed by edoxaban 50%, rivaroxaban 35%, apixaban 27%, while betrixaban has the lowest clearance by 11%.\[14\]

   Importantly, severe renal dysfunction (CrCl < 30 mL/min) or dialysis patients have been excluded from Phase III trials of DOACs.\[17\]

   However, growing data are being produced about the safety of using DOACs (apixaban in particular) in severely reduced kidney function and dialysis patients and in 2014, these drugs started receiving U.S. Food and Drug Administration (FDA) approvals or, rather, labeled dosing guidance for use in dialysis patients constructed from pharmacokinetic and pharmacodynamic studies.\[18-23\]

   Clinical trials such as the Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease study (NCT02933697) and the Strategies for the Management of Atrial Fibrillation in Patients Receiving Hemodialysis (NCT03987711) study are underway.\[21\]

3. **Liver impairment:**

   Liver disease represents another major global health burden and is associated with both thrombotic and bleeding complications.\[22\] At first, patients with advanced liver disease were thought to have what is called “auto-anticoagulation”, particularly with a baseline INR, in which they were believed to have an increased risk of hemorrhage and a low risk of thrombosis. However, latest data have refuted and acknowledged an increased prevalence of thrombotic complications in liver disease patients.\[23\]

   As in patient with severe renal dysfunction patients with liver disease have been excluded from the clinical trials of DOACs.

   All DOACs undergo certain degree of hepatic metabolism; therefore, any reduction in liver function might influence the effect of these medications. The use of DOACs in patients with hepatic impairment are based on the Child-Pugh classification system.\[24\]

   All DOACs are contraindicated in patients with severe hepatic disease in which warfarin is the only suggested anticoagulant medication.\[25\]

4. **Pregnancy**

   Pregnancy is a known factor for VTE. Moreover, AF is a common disorder in women of fertile age with heart disease and may warrant anticoagulation therapy.\[26\]

   As pregnancy is considered as hypercoagulative state, the usefulness of anticoagulation may not be effective during pregnancy due to multiple factors as increase of glomerular filtration rate through pregnancy lead to increased renal elimination and fibrinogen levels are elevated during the pregnancy DOAC dosages could be inadequate in pregnant women.\[27\]

   Currently, LMWH are the standard for the prevention and treatment of venous thromboembolism during pregnancy.\[28\] There are no adequate data on the use of DOACs in pregnant women and the current guidelines recommend against DOAC use throughout pregnancy.\[29\]

**Monitoring Parameters**

The FDA has not approved any method to monitor the anticoagulant effect of DOACs. Qualitative laboratory test such as activated partial thromboplastin time, thrombin time, and prothrombin time might be used. However, these tests are lacking the adequacy to assess the degree of anticoagulation as seen with INR for VKAs. Despite having no established clinical role, directly assessing the anticoagulation effects using anti-factor Xa levels, drug concentrations in plasma, dilute thrombin time, and ecarin thrombin time can be used.\[30\]

**Perioperative Management**

The timing of halting DOACs before the interventions depends on the half-life of the drug, kidney function, and the possibility of bleeding.\[31\] Procedures associated with a very low risk of
bleeding might not require disconnection of DOACs, whereas high-risk procedures require interruption of the DOAC at least 48 hours prior to surgery. If hemostasis achieved DOACs can be resumed at 6–12 hours following low-risk procedures, and at 48 hours following high-risk procedures.[32]

**Reversal Agents**

During life threatening bleeding anticoagulation reversal is a key component of maintaining the patient and the choice to reverse anticoagulation should evaluate the benefit–risk ratio of supporting hemostasis versus post-reversal thrombosis.[33]

For several years, the first-line option for the reversal of anticoagulation was prothrombin complex concentrate (PCC). Two specific reversal agents are now available: idarucizumab for dabigatran and andexanet alfa for apixaban and rivaroxaban.[30,34]

Table 1 summaries the doses for reversal agents.

**Conclusion**

DOACs have refashioned anticoagulant medication and becoming the foundation treatment for stroke prevention in AF and VTE prophylaxis and treatment, and the list of other indications is expanding. There are many considerations that will affect appropriate efficacy and safety end points when recommending DOAC therapy, and this review aims to address these circumstances.

**List of abbreviation**

Vitamin K antagonists (VKAs)
Venous thromboembolism (VTE)
International normalized ratio (INR)
Chronic coronary artery disease (CAD)
Peripheral artery disease (PAD)
Low molecular weight heparin (LMWH)
Prothrombin complex concentrate (PCC).

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**Conflicts of interest**

There are no conflicts of interest.

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**Table 1: Reversal agents’ doses**

| Reversal agent | Timing of Last Dose | Andexanet alfa | 4-factor PCC |
|----------------|---------------------|--------------|--------------|
|                | <8 h or Unknown     | Low dose     | PCC can be given at a dose of 50 units/kg, or a fixed-dose regimen (2000 or 2500 units) can be used |
|                | ≥8 h                | Low dose     |               |
| Apixaban       | ≤ 5 mg              | Low dose     |               |
| Rivaroxaban    | > 5 mg or unknown   | High dose    |               |
|                | ≤10 mg              | Low dose     |               |
|                | >10 mg or unknown   | High dose    |               |

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