Oral Anticoagulants: Optimizing Venous Thromboembolism Management

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Abstract:
A decade ago, oral anticoagulants were limited to Vitamin K antagonists, i.e., warfarin. Since 2010, the US Food and Drug Administration has approved several non-Vitamin K oral anticoagulants: dabigatran is a direct thrombin inhibitor, while apixaban, edoxaban, and rivaroxaban are direct factor Xa inhibitors. Oral anticoagulants are used for the management of several venous thromboembolism (VTE) events, including the prevention of stroke in nonvalvular atrial fibrillation; acute coronary syndromes; treatment of VTE; and VTE prophylaxis after total hip or knee replacement. In this review article, we address the main indications, dosages, bleeding and reversal agents, pharmacokinetic and pharmacodynamic properties, and methods of switching between oral anticoagulants.

Keywords:
Anticoagulants, bleeding, management, reversal agent, venous thromboembolism

Introduction

Hemostasis is defined as a continuous balance between thrombus formation and disbanding thrombus. This process is regulated by several different system interactions between platelets cascade and the endothelium tissue of the vascular system, coagulation cascade, and the fibrinolytic system. Coagulation cascade involves a series of interactions that induce thrombin production, and consist of two pathways between the contact activation pathway and the tissue factor pathway (previously named the intrinsic and extrinsic systems, respectively). The two pathways apparently catalyze the conversion of factor X to Xa independently, which is the beginning of the common pathway. In the common pathway, prothrombin is converted to thrombin, which subsequently catalyzes the production of fibrin from fibrinogen, eventually leading to the formation of the matrix of the clot by stabilizing the aggregated platelets.

Exposure to anticoagulants, such as warfarin, were the reference drugs in the treatment and prevention of many arterial and venous thromboembolic (VTE) events. However, several non-Vitamin K oral anticoagulants (NOACs) have been approved that interfere with the activity of factor Xa (apixaban, edoxaban and rivaroxaban) or thrombin (dabigatran). In patients with nonvalvular atrial fibrillation (NVAF), NOACs are the first-line therapy in both the American Heart Association and European Society of Cardiology guidelines for prevention of stroke. This review highlights the practical considerations for the use of anticoagulants, including dosing recommendations, pharmacodynamic and pharmacokinetic properties, monitoring, bleeding and reversal, switching between oral anticoagulants, and prescribing in specific clinical situations.

Warfarin

Warfarin exerts its anticoagulant activity by inhibiting Vitamin K 2,3-epoxide reductase thus blocking the Vitamin K cycle in the hepatocyte, preventing formation of Vitamin K antagonists, such as warfarin, were the reference drugs in the treatment and prevention of many arterial and venous thromboembolic (VTE) events.
the active form of the Vitamin K-dependent clotting factors II, VII, IX and X, as well as the regulatory natural anticoagulant protein C, S, and Z. Warfarin has been used since its approval by Food and Drug Administration (FDA) in 1954. Indications of warfarin include chronic use for management of thrombotic events, and prevention of VTE diseases in patients with atrial fibrillation and mechanical heart valves, or those at high risk of developing VTE events after surgery. Warfarin is available orally in various strengths and can thus be initiated with a dose ranging from 5 to 10 mg and based on international normalized ratio (INR) results, the dose may be adjusted. Due to the variability in the prothrombin time (PT) reagent sensitivity, INR was introduced to standardize the measurement of PT prolongation between different laboratories. Warfarin half-life ranges between 20 and 60 h, and the duration lasts up to 5 days. It is primarily metabolized through the cytochrome P450 system, the primary enzymes that metabolize warfarin, and induction or inhibition of this enzymes system can increase the INR significantly.

### Bleeding and Reversal of Warfarin

Bleeding is the main concern with regard to adverse events associated with warfarin and is linked to elevated INR >5. Furthermore, several risk factors leading to warfarin associated bleeding include elderly, cancer, chronic kidney disease (CKD), liver failure, elevated blood pressure, prior stroke, alcohol and antiplatelet agents. Warfarin effects can be reversed by several available agents, including Vitamin K (phytonadione), prothrombin complex concentrates (PCCs), or fresh frozen plasma (FFP). The current practice guidelines worldwide, including the American College of Chest Physicians, recommend PCC as the first-line factor replacement therapy rather than FFP. The management algorithm for reversal of elevated INR with or without bleeding is presented in Figure 1.

![Management of elevated INR in patients receiving warfarin](image)

**Figure 1:** Management algorithm for reversal elevated INR with or without bleeding. INR = International normalized ratio; PCC = Prothrombin complex concentrate; FFP = Fresh frozen plasma
The Non-Vitamin K Oral Anticoagulants

Although warfarin is the most effective anticoagulant in the management of VTE events, its limitation of frequent monitoring, labile INR results requiring frequent dose adjustment to achieve therapeutic target, dietary and drug interaction, and the risks of bleeding have led to efforts to develop NOACs. These agents have proven efficacy in the treatment and prevention of VTE, as well as prevention of embolic disease in NVAF. NOACs exert their anticoagulant property that targets the activity of factor Xa or thrombin within the coagulation cascade [Figure 2]. As a class of anticoagulants, NOACs have more favorable pharmacokinetic properties [Table 1][13‑16] thus eliminating the need for laboratory monitoring, lower drug–drug and food interaction, and standard dosing.[6]

Direct Factor Xa Inhibitors

Apixaban, edoxaban, and rivaroxaban are orally available with highly specific factor Xa inhibitors. All these anticoagulants have been used in the management of VTE and stroke in patients with NVAF [Table 2].[17,14‑16]

Apixaban

Apixaban is an oral direct factor Xa inhibitor. It is FDA approved for reduction in the risk of thromboembolism or stroke in NVAF and for the management and prevention of VTE, including recurrent VTE and VTE after major surgery.[17,18] The absorption of apixaban following oral administration is very rapid and it may be given with or without a meal. The elimination half-life for apixaban in healthy controls is approximately 12 h. Dosing administration primarily depends on the treatment indication, the age of the patient, serum creatinine clearance (CrCl), and body weight. At the recommendation of the manufacturer, the dose should be reduced in patients with two out of the following three: age 80≥ years, serum creatinine of 1.5 mg/dl or greater, and body weight ≤60 kg. The peak plasma concentration of apixaban is achieved at 1–3 h, and it is

![Figure 2: Non-Vitamin K oral anticoagulants' mechanism of action in the coagulation cascade](image)

| Table 1: Selected pharmacodynamic and pharmacokinetic properties of non-Vitamin K oral anticoagulants[13‑16] |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Property                        | Apixaban        | Edoxaban        | Rivaroxaban     | Dabigatran      |
| Target of action                | Factor Xa       | Factor Xa       | Factor Xa       | Thrombin        |
| Prodrug                         | No              | No              | No              | Yes             |
| Crush tablet                    | Yes             | No data         | Yes             | No (do not crush) |
| Bioavailability (%)             | 50              | 62              | 90              | 6               |
| Achievement of peak concentration (h) | 3-4             | 1-2             | 2-4             | 1-3             |
| Half-life (h)                   | 8-15            | 10-14           | 5-9             | 12-17           |
| Protein binding (%)             | 87              | 55              | 93              | 35              |
| Renal clearance (%)             | 27              | 50              | 36              | 80              |
| Monitoring                      | None            | None            | None            | None            |
| Interaction                     | CYP3A4          | P-gp and CYP3A4 | P-gp            |                 |
| Food effects                    | No effect       | No effect       | 20 mg and 15 mg with food, and 10 mg dose with/without food | No effect |

CYP3A4=Cytochrome P450 3A4; P-gp=P-glycoprotein
metabolized mainly by the liver and excreted in urine and feces. Apixaban requires no dose reduction in mild hepatic failure but should not be used in moderate to severe hepatic failure.\[18\] In coadministration with ketoconazole, itraconazole, or clarithromycin, a strong dual inhibitor of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), a reduced dose of 2.5 mg twice daily should be considered, and patients already receiving a reduced dose should avoid concomitant coadministration with these drugs. Concomitant use of apixaban and strong dual inhibitors of CYP3A4 and P-gp (rifampin, carbamazepine, and phenytoin) decrease their efficacy and their use with apixaban should be avoided.\[19\]

### Edoxaban

Edoxaban, approved by the FDA in January 2015 for use in stroke prevention in NVAF and for prophylaxis and treatment of VTE, is a tablet available in doses of 30 and 60 mg administered once daily. The recommended dose is 60 mg to prevent stroke or systemic embolism and for VTE treatment, or 30 mg for VTE treatment in patients weighing <60 kg. In patients with high CrCl (>95 mL/min), edoxaban should not be prescribed to prevent the increased risk of ischemic stroke.\[14,20\]

### Direct Thrombin Inhibitor

#### Dabigatran

Dabigatran is a reversible direct thrombin inhibitor approved for the prevention of embolic complications associated with NVAF, treatment of VTE, reducing the risk of recurrent VTE, and prophylaxis of VTE in hip replacement surgery [Table 2]. Dabigatran is available as an oral prodrug, converted to the active form following oral

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### Table 2: Indications and dosages of non-Vitamin K oral anticoagulants

| Indications | Apixaban | Edoxaban | Rivaroxaban | Dabigatran |
|-------------|----------|----------|-------------|------------|
| NVAF        | 5 mg po bid | CrCl >95 mL/min: Should be avoided (drug may be cleared too rapidly and adequate drug levels not attained) | CrCl >50 mL/min: 20 mg po daily with food | CrCl >30 mL/min: 150 mg po bid |
|             | 2.5 mg po bid: If ≥2 of the following: Age ≥80, weight ≤60 kg or Cr ≥1.5 mg/dl | CrCl 51-95 mL/min: 60 mg po once daily | CrCl 15-50 mL/min: 15 mg po daily with food | CrCl 15-30 mL/min: 75 mg po bid |
|             | CrCl <25 mL/min: No data | CrCl 15-50 mL/min: 30 mg po once daily | CrCl <15 mL/min: Should be avoided | CrCl <15 mL/min: Should be avoided |
| VTE treatment | 10 mg bid for 7 days, then 5 mg po bid | CrCl >50 mL/min: 60 mg po once daily | CrCl ≥30 mL/min: 15 mg po bid for 21 days, then 20 mg po daily | For VTE treatment, an initial 5-10 days of parenteral anticoagulation is required before initiating dabigatran |
|             | CrCl <25 mL/min: No data | CrCl 15-50 mL/min or weight ≤60 kg or on P-gp inhibitor: 30 mg po once daily | CrCl <30 mL/min: Should be avoided | CrCl >30 mL/min: 150 mg po bid |
| VTE secondary prevention | 2.5 mg po bid | No approval | CrCl ≥30 mL/min: 20 mg po daily. May consider 10 mg po daily* | See recommended dosage for VTE treatment |
|             | CrCl <25 mL/min: No data | CrCl <30 mL/min: Should be avoided | CrCl <30 mL/min: Should be avoided | CrCl ≤30 mL/min: Should be avoided |
| VTE prophylaxis in THR and TKR | THR: 2.5 mg bid po for 35 days | No approval | Start 6-10 h postoperative | THR |
|             | TKR: 2.5 mg po bid for 12 days | THR: 10 mg po daily for 35 days | TKR: 10 mg po daily for 12 days | CrCl >30 mL/min: 110 mg for the first day, then 220 mg po daily |
|             | Start 12-24 h after surgery | TKR: 10 mg po daily for 12 days | CrCl <30 mL/min: Should be avoided | CrCl ≤30 mL/min or on dialysis: No data |
|             | CrCl <25 mL/min: No data | TKR: 10 mg po daily for 12 days | CrCl <50 mL/min with concomitant use of P-gp inhibitor: Avoid co-administration | CrCl <50 mL/min with concomitant use of P-gp inhibitor: Avoid co-administration |

CrCl=Creatinine clearance; P-gp=P-glycoprotein; NVAF=Nonvalvular atrial fibrillation; VTE=Venous thromboembolism; THR=Total hip replacement; TKR=Total knee replacement.
administration. Like the other agents, it has predictable pharmacokinetic and pharmacodynamic effects, so no routine coagulation monitoring is necessary.\textsuperscript{[16,22]}

**Non-Vitamin K oral anticoagulants monitoring**

There are no specific laboratory tools to monitor NOACs. The main advantage of these agents is that they have predictable pharmacokinetics and pharmacodynamic effects, so no routine coagulation monitoring is necessary. Antifactor Xa level assay was primarily developed and calibrated for monitoring the effect of low molecular weight heparin (LMWH); however, this assay can be utilized to monitor or confirm overdose of factor Xa inhibitors.\textsuperscript{[23]}

Likewise, activated partial thromboplastin time (aPTT) can be utilized as a surrogate to monitor the action of the DTIs; however, the level of elevation of the aPTT does not reflect the level of elevation of DTI effect.\textsuperscript{[24]}

**Bleeding and reversal of non-Vitamin K oral anticoagulants**

The primary adverse event of NOACs is bleeding, including gastrointestinal intracranial bleeding. Dependent on the severity of the clinical scenario and taking into account the relatively short half-life of NOACs, interruption of the drug may often be sufficient to secure bleeding events. However, if urgent reversal of anticoagulation is deemed necessary, additional measure could be considered. Idarucizumab has been approved to reverse the action of dabigatran in many countries for patients with active bleeding or urgent surgical intervention. Idarucizumab is a humanized monoclonal antibody fragment that has a 350 times stronger affinity to bind to dabigatran than the affinity between thrombin and dabigatran.\textsuperscript{[25]}

Andexanet alfa is a recombinant protein analogue of factor Xa to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors with high affinity.\textsuperscript{[26]}

Andexanet is reverse the anticoagulant effect of apixaban, rivaroxaban and edoxaban, without evidence of clinical side effects, and approved by the FDA.\textsuperscript{[27,28]}

**Switching between oral anticoagulants**

Clinical situations of patients must be evaluated in order to determine the appropriate oral anticoagulants. Involvement of patients in decision making empowers them and improves healthcare services and outcomes. NOACs do not require the frequent blood monitoring or dietary restrictions associated with warfarin prescribing. However, NOACs are not recommended for some patients, such as those with CKD, hemodialysis, pregnancy, or lactating mothers. Clinicians have a major role in initiating the oral anticoagulants, choosing the appropriate agent and switching from warfarin to one of the NOAC agents or vice versa for eligible patients (Table 3).\textsuperscript{[17,14‑16]}

**Specific Clinical Situations**

**Elderly**

From the mid-1900s until 2010, warfarin was the only therapy given for the prevention of cardioembolic stroke.\textsuperscript{[32]}

The safety of NOACs in the elderly population (≥ 65 years) was assessed and found that the incidence of major bleeding during NOAC therapy was 1.37 per 100 person-year over a mean of 2.6 years. The deterioration of renal function compared to the baseline was the main finding associated with the risk of bleeding.\textsuperscript{[33]}

In a meta-analysis of randomized controlled trials comparing NOACs with warfarin therapy in patients aged ≥ 75 years, NOACs were similar in causing bleeding events and were equal or more effective.\textsuperscript{[34]}

In practice, renal function and drug adherence need to be monitored for the safety of elderly taking NOACs.\textsuperscript{[35]}
**Table 3: Switching between the oral anticoagulants**

| From        | VK antagonist | Direct FXa inhibitors | DTI         |
|------------|---------------|-----------------------|-------------|
| Warfarin*  | Apixaban      | Rivaroxaban          | Edoxaban    |
| Start warfarin and discontinue apixaban when INR <2 | Discontinue warfarin and start rivaroxaban when INR <2 | Discontinue warfarin and start edoxaban when INR <2.5 | Discontinue warfarin and start dabigatran when INR <2 |
| Apixaban   | Start warfarin and discontinue apixaban 3 days later; monitor INR more frequently | Discontinue apixaban and start rivaroxaban when the next scheduled dose of apixaban would have been due | Discontinue apixaban and start edoxaban when the next scheduled dose of apixaban would have been due | Discontinue apixaban and start dabigatran when the next scheduled dose of apixaban would have been due |
| Rivaroxaban| Start warfarin and discontinue apixaban 3 days later; monitor INR more frequent | Discontinue rivaroxaban and start apixaban when the next scheduled dose of rivaroxaban would have been due | Discontinue rivaroxaban and start edoxaban when the next scheduled dose of rivaroxaban would have been due | Discontinue rivaroxaban and start dabigatran when the next scheduled dose of rivaroxaban would have been due |
| Edoxaban   | Start warfarin and discontinue edoxaban 3 days later; monitor INR more frequent | Discontinue edoxaban and start apixaban when the next scheduled dose of edoxaban would have been due | Discontinue edoxaban and start rivaroxaban when the next scheduled dose of edoxaban would have been due | Discontinue edoxaban and start dabigatran when the next scheduled dose of edoxaban would have been due |
| Dabigatran | CrCl >50 mL/min: Start dabigatran 3 days later | Discontinue dabigatran and start apixaban when the next scheduled dose of dabigatran would have been due | Discontinue dabigatran and start rivaroxaban when the next scheduled dose of dabigatran would have been due | Discontinue dabigatran and start edoxaban when the next scheduled dose of dabigatran would have been due |
|           | CrCl >31-50 mL/min: Start dabigatran 2 days later |                        |             |
|           | CrCl >15-30 mL/min: Start warfarin and discontinue dabigatran 1 day later |                        |             |

*Alternatively discontinue NOAC agents and start bridging therapy using unfractionated heparin or low molecular weight heparin and warfarin at the time as NOAC agents, and continue until desired INR achieved. CrCl = Creatinine clearance; NOAC = Non-Vitamin K oral anticoagulant; INR = International normalized ratio

**Pregnancy and lactation**

Pregnancy is a hypercoagulable state and pregnant women have five times increased risk of VTE events during gestation trimesters, and the risk continues up to 3 months postpartum.[38] The teratogenic effects of warfarin (category D) prevent its use specifically during the first and third trimesters of pregnancy; therefore, females of childbearing age must be advised to not conceive while on warfarin. NOAC dosing in pregnancy has not been studied so there are no approved recommendations.[17,14-16,37,38] During pregnancy, the current option for treatment and prevention of VTE and NVAF is heparin; LMWH is preferred over UFH and is typically used throughout the majority of the pregnancy for women who meet the criteria for either prophylactic or therapeutic anticoagulation.[38,39]

As it is not known if NOACs are excreted in mother’s breast milk, a decision should be made to discontinue lactation or switch to parenteral or warfarin therapy.[17,14-16,38]

**Obesity**

The guidance statements from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (SSC of the ISTH) recommend appropriate standard dosing of the NOACs in patients with a BMI ≤40 kg/m² and weight ≤120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in NVAF.[40] There are limited available studies and the available evidence of low drug exposures, low peak concentrations, and decreased half-lives which may lead to insufficient drug amounts in patients with extremes of weight; therefore the guidance statements advise against the use of NOACs in patients with a BMI of >40 kg/m² and weight >120 kg.[40] However, a retrospective cohort study analyzed 64 adult patients with a BMI >40 kg/m² and weight >120 kg who were prescribed NOACs (apixaban, dabigatran or rivaroxaban) for NVAF. The incidence rate of ischemic stroke or transient ischemic attack was lower (1.75%/year) in the NOAC group than that (2.07%/year) in the warfarin group (rate ratio = 0.84; 95% confidence interval [CI] = 0.23–3.14; P = 0.80). Furthermore, the
incidence rate of major bleeding was lower (2.18%/year) in the NOAC group than that (4.97%/year) in the warfarin group (rate ratio = 0.44; 95% CI = 0.15–1.25; P = 0.11). The authors concluded that, after further analysis of the data collected for each NOAC specifically, apixaban and rivaroxaban may be prescribed as an alternative to warfarin for NVAF in extreme weight individuals. Dabigatran prescribing in extremely obese patients needs caution until further investigations are conducted.[46]

Cancer
VTE is a predominant event in patients with active cancer.[42] The current guidelines still promote LMWH in patients with active cancer for up to 6 months.[43, 44] However, NOACs have been recommended by SSC of the ISTH for the treatment and prevention of VTE in patient with cancer. They suggest the use of specific NOACs for cancer patients who have had an acute VTE event.[45]

Mechanical heart valves
NOAC clinical trials usually exclude patients with a mechanical heart valve, and uncertainty remains as to whether the use of NOACs is safe or effective in this population. Specific NOAC agents have either not been evaluated or have limited data available.[46] Warfarin remains the gold standard for the prevention of VTE events in patients with mechanical heart valves.

Chronic kidney disease on dialysis
The benefit and risk of complication such as bleeding with the use of NOACs in CKD and dialysis patients with VTE still need to be investigated. Clinicians should be cautious and consider dose adjustment when deciding to use NOACs for this population.[47] Apixaban, renal clearance 27%, may be considered as an alternative option to warfarin in patients with CKD and dialysis.

Pediatrics
Warfarin is the standard oral anticoagulant therapy used in pediatric patients who need long-term treatment. The starting dose of warfarin is 0.2 mg/kg and the dose must be adjusted based on the INR result.[48] Similar limitations of warfarin use is seen in pediatrics as with adult population. Drug dosage form is another limitation as warfarin is available only as tablets and many infants are unable to swallow so require liquid dosage form. However, the guidelines supporting the use of NOACs in pediatric patients have not yet been released due to the lack of data. The benefit and risk must be assessed before initiating NOAC therapy; the availability of oral suspension makes NOACs a better option for the pediatric population. Currently, FDA has approved two reversal agents for NOACs to be used in adults,[25–28] [Figure 2]. The use of these reversal agents needs clinical trials to examine the safety and efficacy in the pediatric population, and therefore recommendations and data are lacking.

Drug Interaction
Drug interactions with NOACs therapy are less than that with warfarin; however, CYP3A4 and P-gp are liver enzymes that metabolize apixaban and rivaroxaban. Dabigatran and edoxaban are broken down only by the P-gp transporter system. The coadministration of enzyme inhibitors can delay NOACs’ metabolism and increase the blood concentration, leading to potentiated anticoagulant effects, which may result in bleeding. In contrast, enzyme inducers can increase NOACs’ metabolism and decrease the blood concentration, and could therefore induce VTE events.

Conclusion
The growing usage of NOACs in clinical practice is influenced by the clinicians’ experience and understanding of their convenience of prescribing, and better pharmacokinetic properties, including rapid onset and offset effects, fixed dosing, low food and drug interactions, shorter half-life, and no requirement for regular laboratory monitoring; furthermore, methods exist to reverse their anticoagulation effects.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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