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Chapter

# Direct Oral Anticoagulants and Vitamin K Antagonists: Role in Thrombotic Damage, Safety, and Indications

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## Abstract

This chapter is intended to discuss the available oral anticoagulants, including vitamin K antagonists and the Direct Oral Anticoagulants such as dabigatran, apixaban, rivaroxaban, and edoxaban. It will review their basic pharmacology, pharmacokinetics, pharmacodynamics, dosage forms, clinical indications, and place in therapy. Finally, this chapter will also discuss the currently available reversal agents.

**Keywords:** anticoagulants, vitamin K antagonists, direct oral anticoagulants, reversal agents

## 1. Introduction

Thromboembolic diseases are a leading source of morbidity and death in the United States. Thrombosis can happen in either the arteries or the veins. Acute myocardial infarction (MI), ischemic stroke, and limb gangrene are all caused by arterial thrombosis. Deep vein thrombosis (DVT), which can cause post-thrombotic syndrome, and pulmonary embolism (PE), which can be fatal or cause thromboembolic pulmonary hypertension, are both examples of venous thromboembolism (VTE). Arterial thrombosis is usually managed using antiplatelet therapy. On the other hand, VTE episodes are typically managed using anticoagulant therapy [1].

Anticoagulant drugs are the mainstay of therapy for many thrombotic disorders. The selection of one agent over the other is usually guided by balancing the risks versus the benefits of these anticoagulants. Also, it requires deep knowledge and understanding of the clinical pharmacology, efficacy, safety, and clinical outcomes for each of these anticoagulants.

Historically. Jay McLean and William Henry Howell discovered heparin a century ago, in 1914. However, it was first used in clinical practice in the 1940s. It's given subcutaneously or intravenously, and it binds to antithrombin. This will improve its capacity to inactivate several clotting factors such as thrombin, factor Xa, and factor IXa [2]. Later on, several oral and parenteral antithrombotic agents are used to prevent and treat thrombotic episodes. In 1940, Karl Link and colleagues

discovered warfarin which is a vitamin-k antagonist. Warfarin was first marketed as a rodenticide. Later on, it was adopted for therapeutic usage as an anticoagulant [3].

In 2003, the discovery of ximelagatran showed that a particular oral thrombin inhibitor might be safe and effective in a range of thrombotic diseases, paving the way for introducing a new class of anticoagulants [4]. Following these advancements, a major millstone was declared in the field of anticoagulation. Several direct oral anticoagulants (DOACs) targeting factors Xa and II were introduced from 2007 to 2014. According to several landmark randomized studies, they were shown to be equally safe and efficacious as warfarin in preventing and treating venous thromboembolism and stroke prevention in atrial fibrillation. These advancements led to an enormous change in the landscape of managing thrombotic events [5].

This chapter is intended to review the currently available oral anticoagulants, including vitamin K antagonists (VKA), such as warfarin, and the (DOACs) such as dabigatran, apixaban, rivaroxaban, and edoxaban. In addition, it will discuss periprocedural management of anticoagulants, reversal modalities and highlight the major future advancements in the field of anticoagulation.

## 2. Vitamin K Antagonists

Warfarin is a vitamin K antagonist that was approved by the US Food and Drug Authority (FDA) in 1954 for stroke prevention. It is approved in many other indications such as managing and preventing VTE. Until recently, it was the only oral agent approved for these indications. However, more oral anticoagulants have been approved that possess more advantages and better pharmacokinetic properties. However, warfarin still a widely used medication to prevent blood clotting disorders. Warfarin administration remains a challenge despite being used for more than 60 years. Warfarin has a narrow therapeutic index and monitored regularly using international normalized ratio (INR). Duo to it inter and intra individual variation in response and multiple drug and food interactions, warfarin was replaced as a first line anticoagulant agent [6].

### 2.1 Mechanism of action

Warfarin exerts it anticoagulant effect by interfering with vitamin K epoxide reductase in the liver which serve as a cofactor for the carboxylation of glutamate to γ-carboxyglutamates. This process leads to the inhibition of vitamin K–dependent γ-carboxylation of factors II, VII, IX, and X. However, Vitamin K antagonist does not inhibit the existing γ-carboxyglutamates that can lead to delay in its anticoagulant effect [6].

### 2.2 Pharmacology

Warfarin consists of a racemic mixture of S-warfarin and R-warfarin, in which the S- form being more active. It has high bioavailability with rapid absorption from the gastrointestinal tract. After drug administration, warfarin reaches maximum concentration within 90 mins. Warfarin is highly albumin bound with a half-life of 36–42 hours. Warfarin is metabolized mainly in the liver through the cytochrome P450 (CYP) enzymes. However, the two isomers and metabolized through a different pathway in the liver. CYP2C9 is associated with the metabolism of the more potent S-warfarin whereas R-warfarin mainly metabolized by CYP1A2 and CYP3A4 [6].

### 2.3 Indication and dosing

Warfarin has multiple indications including venous thrombosis, prosthetic heart valves and more commonly arterial fibrillation. Usually, the starting dose for warfarin is 5–10 mg daily. However, lower doses can be initiated for patients at high risk of bleeding. Patients with known genetic polymorphism in CYP2C9 or VKORC1 can be more sensitive to warfarin. Also, elderly patients, patients with chronic kidney disease or patients on other medications that can cause bleeding can be initiated at a lower dose and up titrated to INR goal. Duo to its delayed antithrombotic effect, patients with established clot or high risk for thrombosis are bridged with a fast-acting parenteral anticoagulant. Commonly, heparin or enoxaparin are given concomitantly with warfarin until INR is at goal for 2 consecutive days with a minimum of 5 days on parenteral anticoagulant [6].

### 2.4 Monitoring

Warfarin is a drug known for its narrow therapeutic index as well as having multiple drug and food interactions. Therefore, continuous monitoring is important to ensure anticoagulation efficacy is achieved and severe side effects are avoided. INR is calculated from prothrombin time which is a test that measures how long a clot is formed in a blood sample is performed when patients are on warfarin. Mostly, warfarin is given to achieve an INR goal of 2–3. However, patients with a mechanical mitral valves or mechanical aortic valve replacement with Starr-Edwards or disc valves have a higher INR target of 2.5–3.5 duo to higher thromboembolic risk [6].

### 2.5 Side effects

One of the major risks associated with using warfarin is bleeding and the severity of bleeding can vary. Majority of bleeding side effect is seen when INR supratherapeutic. Therefore, INR monitored and maintained at target is essential to minimize bleeding risk. There are several approaches to manage a supratherapeutic INR and the choice usually depends on the present or absent of bleeding, severity of bleeding and magnitude in which INR increased. Skin necrosis is a rare complication associated with warfarin administration in patients with protein C or S deficiency [6].

### 2.6 Drug interaction

Warfarin can interact with large number of medications. Drugs can cause pharmacodynamic or pharmacokinetic interaction with warfarin. Pharmacokinetic interactions involve medications that inhibit or induce CYP2C9, CYP1A2 or CYP3A4 which can alter warfarin concentration. Inhibitors of the CYP enzymes can interfere with warfarin metabolism that leads to higher warfarin concentration. However, CYP enzyme inducers can increase warfarin removal, therefore, decrease its effect. Pharmacodynamic interaction can occur when warfarin given with other anticoagulants, antiplatelet, non-steroidal anti-inflammatory drugs, or serotonin Reuptake Inhibitors. In which, these drugs can increase risk of bleeding [6].

## 3. Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) have been introduced to the market initially in 2010 as a potential alternative for warfarin. They possess many advantages over warfarin that placed them as the first-line anticoagulant option for many

indications. These agents include apixaban, rivaroxaban, edoxaban, and dabigatran. All of these agents do not require regular monitoring of their anticoagulant effect and they achieve the target anticoagulation level shortly given their fast onset of action compared to warfarin. These significant advantages placed these agents as the preferred anticoagulant option by patients and clinicians [7].

### 3.1 Mechanism of action

Factor Xa is a crucial coagulation factor in the coagulation cascade that leads to the formation of thrombin and clot generation. Apixaban, rivaroxaban, and edoxaban, bind directly and reversibly to factor Xa and inhibit its action leading to a strong anticoagulation activity. On the other side, dabigatran inhibits directly factor IIa (thrombin), leading to the prevention of clot formation [8].

### 3.2 Pharmacology

Apixaban binds directly to factor Xa when free and when thrombin bound. It has a bioavailability of approximately 50% and reaches a plasma peak in about 2 hours with maximum plasma concentration in about 3 to 4 hours. It has a half-life of approximately 12 hours after oral administration necessitating twice-daily dosing. It is metabolized mainly by CYP3A4 and eliminated in both urine and feces. Renal elimination accounts for 27% of total clearance. Apixaban has no interaction with food but is a substrate of P-glycoprotein (P-gp) and CYP3A4 requiring vigilant review of concurrent medications for possible drug–drug interactions [9].

Dabigatran is the active form of the prodrug dabigatran etexilate, which binds thrombin directly and competitively inhibiting its activity. The approximate bioavailability of dabigatran after oral administration is 3–7%, with peak plasma concentration achievement within 2 hours. The bioavailability increased to 75% after the pellets were taken without the capsule. Therefore, the capsules should not be broken, chewed, or opened before administration. The half-life of dabigatran is approximately 12–17 hours, necessitating twice-daily dosing. Dabigatran is mainly eliminated in the urine with a renal clearance of roughly 80%. It is a substrate of P-gp and therefore, it carries a risk for drug–drug interactions [9].

Edoxaban binds selectively to factor Xa and inhibits its action without the need for a cofactor (i.e., antithrombin III). It has a bioavailability of approximately 62% and reaches a peak plasma concentration in about 1 to 2 hours. It has a half-life of approximately 10–14 hours, and 50% of the total clearance is through urine. Therefore, edoxaban blood levels are increased or decreased in patients with poor or good renal function. Edoxaban is a substrate for P-gp and CYP3A4, increasing the risk for drug–drug interactions [9].

Rivaroxaban is a selective inhibitor of factor Xa with no requirement for a cofactor (i.e., antithrombin III) with no direct effect on platelet aggregation. It has a very high bioavailability following oral administration of 2.5 mg and 10 mg doses reaching 80–100%. Administration with food increases the bioavailability of rivaroxaban. Therefore, it should be taken with food. Peak plasma concentration is achieved in about 2 to 4 hours. It has a renal clearance of up to 30%. Rivaroxaban is a substrate for P-gp increasing the risk of drug–drug interactions [9]. **Table 1** summarizes the pharmacological properties of DOACs.

### 3.3 Indications and dosing

DOACs are currently used in different indications, including reducing the incidence of stroke in patients with NVAF, treatment of acute VTE, and reducing

| | Apixaban | Dabigatran | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| Mechanism of action | Factor Xa | Thrombin | Factor Xa | Factor Xa |
| Pro-drug | No | Yes | No | No |
| Bioavailability | 50% | 3%-7% | 62% | 66%-80% |
| Time to peak | 2 hours | 2 hours | 1-2 hours | 2-4 hours |
| Half-life | 12 hours | 12-17 hours | 12-14 hours | 9-13 hours |
| Protein binding | 87% | 35% | 55% | 90% |
| Renal elimination | 27% | 80% | 50% | 30% |
| Substrate of CYP3A4 | Yes | No | Yes | Yes |
| Substrate of P-gp | Yes | Yes | Yes | Yes |
| Dialyzable | No | Yes | No | No |

**Table 1.**
*Pharmacological properties of DOACs.*

the risk of recurrent VTE. Finally, apixaban, rivaroxaban, and dabigatran have been approved by US FDA and European Medical Agency (EMA) for thromboprophylaxis post orthopedic surgeries (i.e., knee and hip replacements). Apixaban and rivaroxaban are approved for post-knee and hip replacement surgeries, and dabigatran is only approved for post-hip replacement surgery. In addition, rivaroxaban is also approved for VTE prophylaxis in acutely ill medical patients at risk for thromboembolic complications, not at high risk of bleeding [9]. **Table 2** illustrates the usual dosing recommendations for the various indications.

### 3.4 Monitoring

DOACs possess the advantage of having predictable pharmacokinetic and pharmacodynamic properties making their regular monitoring of blood levels or coagulation factors not necessary. This provides a great advantage and more convenience to patients than the traditional anticoagulant warfarin. Currently, there are no validated and clinically feasible tests to measure the anticoagulant effect of DOACs on daily basis. Besides, routine monitoring of kidney function is necessary to ensure appropriate clearance of DOACs as all of them have varying degrees of renal elimination. This becomes of high importance when dealing with end-stage renal disease patients or patients on hemodialysis. Monitoring hepatic function every 6 to 12 months is recommended as all DOACs except dabigatran are metabolized by the liver. Regular follow-up on patient adherence is also encouraged to ensure the safety and efficacy of the anticoagulation given their short duration of action [9].

### 3.5 Side effects

As with all anticoagulants, the main severe and concerning side effect is bleeding. Careful watching of signs and symptoms of bleeding and proper patient education on identifying them is crucial. Dyspepsia is another reported side effect more linked to dabigatran. Taking dabigatran with food should help with minimizing dyspepsia as the body tolerates the medication with time [10].

### 3.6 Choosing an anticoagulant agent

Warfarin could be an appealing anticoagulant option in many cases. For example, it could be an adequate option to be sued in patients with an estimated creatinine

| Apixaban | Dabigatran | Edoxaban | Rivaroxaban |
|---|---|---|---|
| **Stroke prevention in nonvalvular atrial fibrillation (NVAF)** | | | |
| 5 mg PO BID<br>2.5 mg PO BID if two of the following occurs:<br>• Age ≥ 80 years<br>• Scr ≥ 1.5 mg/dl<br>• Weight ≤ 60 kg | 150 mg PO BID | 60 mg PO once daily<br>• Not recommended with CrCl > 95 ml/min | 20 mg PO once daily |
| **Treatment of acute venous thromboembolism (VTE)** | | | |
| 10 mg PO BID for 7 days, then 5 mg PO BID | Following 5-10 days of initial parenteral therapy: 150 mg PO BID | Following 5-10 days of initial parenteral therapy:<br>• Weight > 60 kg: 60 mg PO once daily<br>• Weight ≤ 60 kg: 30 mg PO once daily | 15 mg PO BID for 21 days, then 20 mg PO once daily |
| **Reduction in the risk of recurrent VTE** | | | |
| 2.5 mg PO BID | 150 mg PO BID | Not approved | 10 mg PO once daily |
| **Post-knee/hip replacement DVT prophylaxis** | | | |
| 2.5 mg PO BID 12-24 hours post-op<br>• Hip replacement duration: 35 days<br>• Knee replacement duration: 12 days | Hip replacement only: 110 mg PO 1-4 hours post-surgery, then 220 mg PO once daily for 28-35 days | Not approved | 10 mg PO once daily 6-10 hours post-op<br>• Hip replacement duration: 35 days<br>• Knee replacement duration: 12 days |
| **VTE prophylaxis in acutely ill medical patients at risk for thromboembolic complications, not at high risk of bleeding** | | | |
| Not approved | Not approved | Not approved | 10 mg PO once daily in the hospital and after hospital discharge for a total duration of 31-39 days |

**Table 2.**
*DOACs approved indications and recommended doses for normal kidney patients.*

clearance (CrCl) of less than 30 mL/min as those individuals were excluded from many clinical trials that compared warfarin to the DOACs. Also, it could be used in patients with poor medication adherence. This is mainly because many of the currently available DOACs are dosed to be taken twice daily. This could affect patient adherence. In addition, the presence of laboratory assessment modalities like the INR can identify poor medication adherence. Despite the long list of interacting medications with warfarin, the use of *warfarin could be preferred as dose adjustments based on INR monitoring can facilitate titration of the anticoagulant response. Warfarin remains the least expensive anticoagulant currently available. This could make it a reasonable option for individuals who cannot afford the more costly options* [11].

DOACs are considered the first line option in many indications given their predicted pharmacokinetics and pharmacodynamics which minimizes the need for regular drug monitoring compared to warfarin. They are dosed either once daily

or twice daily and do not have significant drug-food interactions. Patients with various degrees of renal impairment (i.e. CrCL <30 ml/min) were excluded from the DOACs' pivotal trials, therefore their use in this certain population is debatable. However, apixaban, for example has good pharmacokinetic data supporting its use in hemodialysis (HD) patients as it has very low renal clearance that accounts for only 25%. Currently, apixaban is recommended for stroke prevention in atrial fibrillation patients with end stage renal disease (ESRD) on HD. On the other hand, patients with poor compliance may benefit more from being on warfarin rather than DOACs as the effect of warfarin stays longer than DOACs. If a patient misses one dose of warfarin, the INR would still be in the therapeutic range for one or more days. Finally, the need to monitor kidney function with DOACs still exists and crucial to assess the need for renal dose adjustments [12, 13].

### 3.7 Periprocedural management of anticoagulation

Management of anticoagulation before and after surgeries such as thrombectomy is very crucial safety step to ensure safe and effective surgical interventions with minimal chances for bleedings. The appropriate knowledge of anticoagulants pharmacokinetics properties and the degree of bleeding risk of the procedure are two essential factors to formulate an appropriate periprocedural anticoagulation plan. Special considerations should be taken with individuals with impaired renal or liver functions [14].

| Procedure Bleeding Risk | DOAC | Warfarin |
|---|---|---|
| **Minimal** | • Omit anticoagulant on the day of procedure | • No interruption needed |
| **Low** | • Omit anticoagulant one day before the procedure<br>• Reinitiate anticoagulant one day after the procedure<br>• For individuals receiving dabigatran with CrCl 30 to 50 mL/min: omit two days before procedure. | • Assess thromboembolic risk:<br>• Low – moderate risk: interrupt 5 days before the procedure without parenteral anticoagulant bridging<br>• High risk: interrupt 5 days before the procedure with parenteral anticoagulant bridging |
| **Moderate** | • Omit anticoagulant one day before the procedure<br>• Reinitiate anticoagulant one day after the procedure | • Assess thromboembolic risk:<br>• Low – moderate risk: interrupt 5 days before the procedure without parenteral anticoagulant bridging<br>• High risk: interrupt 5 days before the procedure with parenteral anticoagulant bridging<br>• Reinitiate warfarin postoperatively once hemostasis is attained |
| **High** | • Omit anticoagulant two day before the procedure<br>• Reinitiate anticoagulant two day after the procedure<br>• For individuals receiving dabigatran with CrCl 30 to 50 mL/min: omit four days before procedure | • interrupt 5 days before the procedure with parenteral anticoagulant bridging<br>• Reinitiate warfarin postoperatively once hemostasis is attained |

**Table 3.**
*Periprocedural management of anticoagulants.*

In patients who are on a DOAC and going into a minimal risk procedure, omitting one dose of the anticoagulant on the day of the procedure is sufficient. However, in low or moderate risk procedures, the anticoagulant should be omitted for one day before the procedure and restart one day after the procedure. In high-risk procedures, omitting the DOAC agent two days before and after the procedure would reasonable. **Table 3** summarizes the periprocedural management of anticoagulants.

On the other side, patients who are on warfarin and undergoing minimal risk procedures, interruption of anticoagulation is not necessary. However, in other low and moderate risk procedures, warfarin should be interrupted with mostly no need for bridging. In high risk, interruption of anticoagulation is needed with bridging. Discontinuation of warfarin should be done five days before the procedure. When bridging is required, starting enoxaparin three days before the procedure is reasonable with last dose being given 24 hours before the procedure. In patients with various degrees of renal impairments may require longer interruption periods as clearance of the anticoagulant may become delayed. **Table 3** summarizes the periprocedural management of anticoagulants.

## 4. Reversal Agents

### 4.1 Warfarin reversal modalities

Holding or discontinuing warfarin as a solo strategy may be adequate in asymptomatic patients with an elevated INR value and a low risk for bleeding. Certain patient may require further agents to be administered such as, Vitamin K (phytonadione), Prothrombin Complex Concentrate (PCC), and Fresh frozen plasma (FFP) [15].

#### *4.1.1 Vitamin K (Phytonadione)*

Exogenous vitamin K level helps reestablishing the hepatic formation of vitamin K–dependent clotting factors. When exogenous vitamin K is given, it can continue to be reduced and converted to its active form, KH2, which results with functional clotting factors despite recent warfarin administration. Vitamin K dose and route of administration vary depends on the bleeding magnitude. It can be given as 2–5 mg PO/IV for minor bleeding events and 5–10 IV for major bleed. Although they are rare, anaphylactic reactions and temporary warfarin resistance have been reported with vitamin K use IV vitamin K normalizes the INR quicker than PO. It only takes 8–12 hours with IV administration and might take up to 24–48 hours following oral administration [15].

#### *4.1.2 Prothrombin Complex Concentrate (PCC)*

Clotting factor replenishing, and it can enchase platelet activation. These clotting factors are 25-fold more concentrated than blood. Recombinant activated factor VII (FVIIa) (NovoSeven®) contains activated factor VII can directly activate thrombin generation by binding to tissue factor. PCC products are differentiated by the type of clotting factors they consist of. The 3-factor PCC consist of clotting factors II, IX, and X. The 4-factor PCC 4 consist of clotting factors II, IX, X, and VII (4PCC). Activated 4-factor PCC consist of II, IX, X, and VIIa. All PCC products have natural anticoagulants protein C and protein S. and all PCC products contain heparin, except Profilnine® (3-factor PCC) [15].

PCC dosing is based on factor IX and activated versus non-activated pertains to factor VII. Normally each single-dose vial of PCC is mixed with 10–40 mL of sterile water. Fixed dose PCC for non-intracranial hemorrhagic (ICH) bleed is usually 1000 units while in ICH, it is 1500–2000 units. The other modality to dose PCC is INR and weight driven dose. In patients with INR of 2 to less than 4, the dose is 25 units/kg. In patients with INR of 4–6,, the dose is 35 units/kg. In patients with INR of more than 6, the dose is 50 units/kg. PCC dose might need to be rounded up or down to the nearest available vial size. The acceptable dose adjusting margin is institution dependent (usually 5–10%). Infusion related allergic reactions, heparin-induced thrombocytopenia (with exception of Profilnine®) and low acceptable risk of thrombosis have been reported in patients receiving PCC therapy [15].

#### *4.1.3 Fresh frozen plasma (FFP)*

FFP is not a specific reversal agent. It contains all coagulation factors, including II, VII, IX, and X in diluted inactive form. Moreover, it contains fibrinogen and platelet. There is no specific recommendation when it comes to FFP dosing, but usually it is given as 10–30 mL/kg (1-unit FFP has a volume of 250 mL). Transfusion reactions, volume overload, infection, and transfusion-related lung injury have been reported in patients receiving FFP therapy [15].

### 4.2 Direct thrombin inhibitors reversal agents

#### *4.2.1 Idarucizumab*

Idarucizumab is a humanized monoclonal antibody fragment that has been developed specifically to reverse the anticoagulation effect of dabigatran [9]. Idarucizumab is indicated for emergent surgery/urgent procedures In life-threatening or uncontrolled bleeding. It is given as a total dose of 5 grams (two separate doses of 2.5 g diluted in 50 mL vials) intravenous infusion over 5 minutes. Idarucizumab carries a warning for inducing thromboembolic events. The thrombotic rate in REVERSE-AD trial was 4.8% at 1 month. The risks of hypersensitivity and severe adverse reactions in patients with hereditary fructose intolerance are reported in the packaging insert due to sorbitol excipient. Among patients who received Idarucizumab, 5% or more experienced hypokalemia, pneumonia, pyrexia, and delirium [9].

#### *4.2.2 Prothrombin Complex Concentrates (PCC)*

Inconsistent data was reported regarding the efficacy of PCC in reversing dabigatran based on its laboratory abnormalities. When PCC is used, aPCC such as FEIBA may be preferred. The thrombin generation following PCC administration is dose dependent. Currently most guidelines recommend aPCC 50 units/kg to be given when an emergent reversal is needed for dabigatran. Because of the presence of activated clotting factors, and higher prothrombin and thrombin content in aPCC, the risk of thrombosis is expected to be higher with aPCC than with PCC [9].

### 4.3 Anti-Xa inhibitors reversal agents

#### *4.3.1 Andexanet alfa*

Andexanet alpha is a recombinant modified human “decoy” factor Xa protein, and it works through a competitive binding mechanism with high specificity to

direct and indirect anti-Xa agents; to restore the activity of factor Xa and reverses the anticoagulant effect. In May 2018, the FDA approved Andexxa® for the reversal of apixaban and rivaroxaban in the setting of life-threatening or uncontrolled major bleeding. Later, the European Medicine Agency (EMA) gave it a 'conditional authorization' in 2019 using the trade name of (Ondexxya®)[9].

Andexanet alpha dosing is either 400 mg IV bolus followed by continuous IV infusion or 800 mg IV bolus followed by 960 mg continuous IV infusion, based on drug, dose, and timing. Treatment with the high dose would cost $49,500 for the drug alone. It is available as 100-mg dry powder vials. It needs to be reconstituted with 10 mL SWFI with typical dissolution time of 3 minutes. Most common reported issues related to andexanet alfa include flushing and fever which may be an infusion related side effect in study performed in healthy volunteers. Albeit the decoy mechanism of action of this drug, the most common side effects in patients with major bleeding events were thromboembolism including DVTs, myocardial infarction and ischemic stroke which was reported in 10% in the ANEXXA-4 trial.

*4.3.2 Prothrombin Complex Concentrates (PCCs)*

Variable data have been reported on the role of PCC in anti-Xa as potential reversal strategies. Multiple guidelines suggest using PCCs as alternative method to andexanet alfa. However, multiple reports demonstrated similar efficacy and safety profile for PCCs when used for major bleed induced by rivaroxaban, apixaban, or edoxaban. Many clinicians may prefer PCCs over andexanet alfa based on the cost difference in addition to the lack of high-quality head-to-head comparisons. Dosing may have a range between 25 and 50 units/kg based on actual body weight [9].

## 5. Ongoing research on anticoagulant therapy

The anti-factor Xa inhibitors have achieved so many milestones and currently are recommended by most well-respected clinical guidelines. This mechanism of action is becoming so appealing for many manufacturers to design new agents that specifically target factor Xa. Darexaban and nokxaban are two new potential agents that may see the light soon and attain the guidelines recommendations for many clinical indications. They have still not been approved by neither the US FDA nor the EMA but their Phase II trials are promising with comparable safety and efficacy data to current approved DOACs. On the other side, currently approved DOACs are being tested for many other indications and we may see further utilization of these agents on a wider range of patient population. Drugs targeting other coagulation factors such as factor XI and XII are also being developed [16–19].

## 6. Conclusion

Several anticoagulant agents could be used to manage thrombotic events. However, it is essential to consider thrombectomy over anticoagulant therapy in acute settings. This is mainly due to the fact that limited data exist on the use of VKA or DOACs in the acute treatment of patients with ischemic stroke. Anticoagulants could be reserved as a secondary prevention strategy in many thrombotic disorders.

## Conflict of interest

The authors declare no conflict of interest.

## Notes/thanks/other declarations

None.

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