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Navigating the Principles and Practice of Oral Anticoagulant Therapy: A Comprehensive Healthcare Guide

Julliyan Dilleban[1,*], Venkateshan Narayanan[2], Deephiha E.[3], Balakrishnan K.[3], Bhavani Suba Niranjana M.[3], Thenraja S.[1]

Abstract

Oral anticoagulant therapy plays a critical role in the prevention and treatment of thromboembolic disorders, including atrial fibrillation (AF), venous thromboembolism (VTE), and mechanical heart valve replacement. This research article aims to provide a comprehensive overview of the principles and practice of oral anticoagulant therapy, focusing on the mechanisms of action, pharmacokinetics, clinical indications, monitoring, and management of associated complications. The cornerstone of oral anticoagulant therapy includes vitamin K antagonists (VKAs), such as warfarin and direct oral anticoagulants (DOACs) including dabigatran, rivaroxaban, apixaban, and edoxaban. VKAs exert their anticoagulant effects by inhibiting the synthesis of vitamin K-dependent coagulation factors, while DOACs directly target specific coagulation factors, offering more predictable pharmacokinetics and fewer drug interactions compared to VKAs. Clinical indications for oral anticoagulant therapy vary depending on the underlying thromboembolic disorder. For instance, in patients with AF, anticoagulation is recommended to reduce the risk of stroke and systemic embolism, with risk stratification guided by scoring systems, such as CHA2DS2-VASc. Similarly, in patients with VTE, oral anticoagulants are used for both acute treatment and long-term prevention of recurrence, with the choice of agent influenced by factors, such as renal function and bleeding risk.

Keywords: Vitamin K antagonists, clinical indications, warfarin, atrial fibrillation, pregnancy, special population

***Author for Correspondence**
Julliyan Dilleban
E-mail: julliyandilleban@akcp.ac.in

[1]Assistant Professor, Department of Pharmacy Practice, Arulmigu Kalsalingam College of Pharmacy, Krishnankoil, Virudhunagar, Tamil Nadu, India.
[2]Professor, Department of Pharmacy Practice, Arulmigu Kalsalingam College of Pharmacy, Krishnankoil, Virudhunagar, Tamil Nadu, India.
[3]PharmD Intern, Department of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Virudhunagar, Tamil Nadu, India.

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INTRODUCTION

Thrombosis is the leading cause of venous thromboembolism, heart attack and strokes. Anticoagulants are the drugs used to reduce the coagulability of blood. Fasting acting anticoagulants are the agents used to treat and prevent venous thromboembolism [1]. Physicians have used warfarin for the management of various thrombotic disorders for more than Decades. Warfarin therapy should be frequently monitored due to the variable dose response, interactions, such as drug–drug and drug-food interaction and narrow therapeutic index. Over the past 30 years, intravenous & subcutaneous agents, such as unfractionated heparin, direct thrombin inhibitors, and pentasaccharide has been introduced [2]. Warfarin is used to inhibit the synthesis of antithrombotic factors protein C and protein S and in the synthesis of vitamin K dependent clotting factors, such as II, VII, IX, X [3].

EVOLUTION OF ANTICOAGULANTS

Thromboembolic disorders are the emerging cause of morbidity and mortality in many countries. Anticoagulants are used to treat venous thromboembolism (VTE) which includes Deep vein thrombosis (DVT) and pulmonary embolism (PE) [4]. It is also recommended to treat acute coronary syndrome to prevent stroke in patients with atrial fibrillation. Heparins, such as unfractionated heparin, low molecular weight heparin (LMWH) and vitamin K antagonist (VKA), such as warfarin, phenprocoumon, acenocoumarol are used to treat these thrombotic disorders (Table 1) [5].

Table 1. Evolution of anticoagulant.

Year	Anticoagulant Drug
1940s	Unfractionated heparin
1950s	Warfarin
1980s	Low molecular weight heparins
1990s	Parenteral direct thrombin inhibitors
2002	Fondaparinux
2010	Dabigatran
2011	Rivaroxaban
2012	Apixaban
2014	Edoxaban

UNFRACTIONATED HEPARIN (UFH) & LOW MOLECULAR WEIGHT HEPARINS (LMWH)

UFH was discovered in 1914 and later it was introduced in 1960 to clinical practice. A cofactor is required for UFH to produce its anticoagulant effect. Intravenous (or) subcutaneous administration of UFH binds anti thrombin and then inactivates the thrombin, factor X_a and IX_a which is responsible for the clot formation. This anticoagulant effect of UFH is produced if only UFH contains at least 18 saccharide units, which bind with antithrombin and inactivate the conversion of prothrombin to thrombin. While UFH is administered, the activated partial thromboplastin time should be monitored in patients with long term therapy. UFH has complications, such as Heparin-induced thrombocytopenia and osteoporosis.

LMWH are the compounds derived from UFH by the process of chemical (or) enzymatic deploymerisation reaction. LMWH, such as Enoxaparin, dalteparin, nactroparin, tinzaparin, certoparin, reviparin, ardeparin and bemiparin which are administered subcutaneously. UFH and LMWH minimize the VTE complications in hip (or) knee arthroplasty and has higher risk in patients including heart failure and acute inflammatory diseases. Patients with acute coronary syndrome, UFH and LMWH can be combined with aspirin and clopidogrel. In the 1980s, LMWH replaced the UFH because of its efficiency and safety. Nowadays, LMWH is suggested for the acute & long-term management of cancer associated with VTE [5].

VITAMIN K ANTAGONISTS (VKA)

Warfarin, antagonist of vitamin K produces its anticoagulant property by interrupting the factors, such as FII, FVII, FIX, FX and anticoagulation proteins (protein C&S). INR should be monitored, and frequent dose adjustments should be necessary during warfarin therapy. VKA is effective in decreasing the VTE recurrence and cardio embolic stroke in non-valvar atrial fibrillation. And also, it reduces the risk of hemorrhage [5]. Even warfarin is an effective oral anticoagulant, it has some drawbacks, such as reduced onset of action, drug interactions which either increase or decrease its anticoagulant activity. Monitoring INR while using warfarin may reduce the risk of hemorrhage and thrombosis.

ANTICOAGULANTS IN CURRENT PRACTICE

Several study results confirmed that DOACs have higher safety and efficacy when compared with VKAs [6]. Acute phase, long-term phase and an extended phase are the three important phases in the management of DVT. Acute phase is managed using Heparinoids (or) fondaparinux while Warfarin is used for long-term effect in conditions like cancer associated with DVT, low molecular weight heparin is prescribed for at least 3 months. Regular monitoring & dose – adjustment of warfarin is necessary for narrow therapeutic window and pharmacokinetic interactions. Recently FDA approved the certain novel oral anticoagulants (NOACs) were approved by FDA to treat VTE, knee and hip arthroplasty and stroke prevention in atrial fibrillation [7]. Emerging Anti-Xa therapy brings a great impact in treating acute coronary syndrome and thrombolysis in myocardial infarction, there is notable change in death rate of cardiovascular disease following administration of rivaroxaban dose of either 2.5mg (or) 5mg twice daily, either aspirin (or) dual antiplatelet therapy (Table 2) [8].

Table 2. Suggested therapeutic range for oral anticoagulant therapy [4].

Indications	INR
• Venous thrombosis- Prophylaxis (higher risk surgery)	
• Venous thrombosis	
• Pulmonary embolism	2.0–3.0
• To prevent systemic embolism	
Tissue heart valves	
Acute myocardial infarction	
Valvar heart disease	
Atrial fibrillation	
• Mechanical prosthetic valves (high risk)	2.5–3.5

DIRECT ORAL ANTICOAGULANTS (DOACs)

Direct Xa inhibitors, such as edoxaban, apixaban and rivaroxaban and dabigatran are new direct anticoagulants which have developed. DOACs are also known as new oral anticoagulants (NOACs) or Target specific oral anticoagulants (TSOACs) which particularly inhibit the clotting factors II_a or X_a. International society of thrombosis and hemostasis states that DOACs are the preferred name used to treat the thrombotic disorder. DOACs have higher efficacy and safety, thereby lowers the chances of bleeding when compared with warfarin [9].

Oral vitamin K antagonists are used to treat and prevent the arterial and venous thromboembolic events because of its efficacy and safety. But it increased the risk of thromboembolism (or) bleeding. Direct oral anticoagulants, such as dabigatran, rivaroxaban, apixaban and edoxaban were compared with warfarin for stroke prevention in atrial fibrillation. The International society on Thrombosis and Hemostasis recommended to use DOACs, they directly inhibit the protein C and protein S in the coagulation cascade pathway, in other hand VKAs inhibit the synthesis of vitamin K dependent clotting factors [8].

DOACs are more convenient to administer to patients while compared with VKAs and have rapid onset and offset of action, fewer drug-drug, and drug-food interactions, lower the risk of bleeding and can administer without the need of laboratory monitoring. But it has some disadvantages includes high cost of treatment, depends upon renal clearance and may predispose at risk-patients to gastrointestinal bleeding [10].

NEWER GENERATION ANTICOAGULANTS

Recently new oral anticoagulants, such as apixaban, dabigatran and rivaroxaban have been developed to prevent and treat thromboembolic diseases and stroke with atrial fibrillation [2–11].

NEED OF NEW ORAL ANTICOAGULANTS

NOACs are developed to overcome the following factors:

1. Slow onset of action.
2. Drug-drug or drug-food interactions.
3. Necessity of regular monitoring to adjust dose.
4. Narrow therapeutic window.
5. Polymorphism, age, perioperative management.

DABIGATRAN ETEXILATE

After oral administration of Dabigatran etexilate which is converted into Dabigatran by the enzyme esterases. Dabigatran has predictable pharmacokinetic and pharmacodynamics properties, and it does not interact with atorvastatin (or) non-steroidal anti-inflammatory drug, such as diclofenac, but it is contraindicated with quinidine [12].

RIVAROXABAN

Rivaroxaban, an oral direct factor X_a inhibitor, has predictable and dose-dependent pharmacokinetic and pharmacodynamics properties. It is not interacted with acetyl salicylic acid (aspirin) or clopidogrel and NSAIDs and contraindicated with Ketoconazole (or) ritonavir [12].

Table 3. Comparing the characteristics of new oral anticoagulants [2, 10–11].

	Rivaroxaban	**Apixaban**	**Dabigatran Etexilate**
Target	**Clotting Factor Xa**	**Clotting Factor Xa**	**Clotting Factor IIa**
Molecular weight	436	460	628
Prodrug	No	No	No
Bioavailability (%)	~80	~50	6-7
Time to peak (h)	2-3	1-2	1.5
Half-life (%)	7-11	8-14	14-17
Renal excretion (%)	66*	~25	>80
Antidote	None	None	None

DOAC'S IN SPECIAL POPULATION

Nowadays, DOACs are widely used to treat the thrombotic disorders in many developed countries. But DOACs has some uncertainties in patients with chronic kidney disease, elderly patients, drug-drug interactions, patients with higher body mass index. Here are some recommended uses of DOACs in special population (Tables 3 & 4) [13].

Table 4. Overview of Safety of Anticoagulants During Gestation and Lactation Period [14].

z	**Safety During Gestation**	**Safety During Lactation**	**Evidence-Based Overview**
Heparins	Yes	Yes	It does not cross the placental barrier.
Vitamin K antagonist	No	Yes	It may cross the placental barrier, which may lead to Coumadin embryopathy during 6^{th} and 12^{th} week, and may also result in fetal bleeding and neurodevelopmental deficits.
Direct oral anticoagulants	No	No	It may cross the placental barrier.
Danaparoid	Yes	Yes	It does not cross the placental barrier.
Fondaparinux	Probably Yes	Yes	It may cross the placental barrier, but some limited study data suggest that it is safe to the fetus.

PREGNANCY

In the management of venous thromboembolism (VTE) during pregnancy, low molecular weight heparins (LMWHs), such as danaparoid are typically preferred due to their inability to cross the placental barrier and lack of teratogenic effects. However, subcutaneous administration of LMWHs can result in local bruising and skin reactions at the injection site. For instance, an 11-week pregnant patient presenting with left-sided chest pain exacerbated by inspiration over the past three days and shortness of breath for one day was treated with a daily dose of 14,000 IU of tinzaparin, adjusted according to her body mass index, alongside tramadol and acetaminophen for pain management [14, 15]. In contrast, research on direct oral anticoagulants (DOACs) during pregnancy indicates potential risks. A study involving 339 cases of DOAC exposure during pregnancy revealed that 56% resulted in live births, 22.2% in miscarriages, 21.8% in elective terminations, and 3.67% in fetal abnormalities. These outcomes suggest a higher incidence of adverse effects compared to LMWHs [16]. Consequently, while DOACs offer advantages in non-pregnant populations, their use in pregnant patients is associated with greater risks, reinforcing the preference for LMWHs in this context.

CHRONIC KIDNEY DISEASE

In patients with chronic kidney disease (CKD), dose adjustments for direct oral anticoagulants (DOACs) are crucial to mitigate the risk of bleeding and ensure efficacy. For apixaban, the standard dose of 5 mg twice daily is reduced to 2.5 mg twice daily in patients with a creatinine clearance (CrCl) >30 mL/min to prevent stroke in non-valvular atrial fibrillation (AF). The dose of apixaban is similarly adjusted when CrCl falls between 15-30 mL/min. Dabigatran, typically dosed at 150 mg twice daily, is reduced to 110 mg twice daily in patients with elevated bleeding risk. In the United States, dabigatran is also approved at a reduced dose of 75 mg twice daily for those with a CrCl of 15-29 mL/min. Edoxaban is administered at 60 mg once daily, with a dose reduction recommended for patients weighing less than 60 kg or with a CrCl of 15-49 mL/min. Similarly, rivaroxaban is typically dosed at 20 mg once daily but is reduced to 15 mg once daily when CrCl is between 15-49 mL/min [13]. Adjusting DOAC doses in CKD patients is essential to balance efficacy and safety, considering the altered pharmacokinetics associated with impaired renal function.

GERIATRICS

In managing atrial fibrillation (AF) among elderly patients, the Systematic Assessment of Geriatric Elements in Atrial Fibrillation (SAGE-AF) study highlights the importance of evaluating factors, such as frailty, cognitive and sensory impairments, social isolation, and depression. These assessments guide the prescription of direct oral anticoagulants (DOACs), with dosing adjustments tailored to each patient's age, renal function, body weight, and any potential drug-drug interactions [17]. When it comes to treating venous thromboembolism (VTE) in elderly patients, DOACs have shown benefits compared to low molecular weight heparins (LMWHs) and vitamin K antagonists (VKAs). They are associated with lower rates of mortality, bleeding, and recurrence, indicating that DOACs might offer a safer and more effective alternative to traditional anticoagulants for this population [18–20].

ATRIAL FIBRILLATION AND PERCUTANEOUS CORONARY INTERVENTION

To prevent the recurrence of atherosclerosis and thrombosis in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) is commonly employed. This regimen typically includes aspirin combined with a P2Y12 inhibitor, such as clopidogrel, prasugrel, or ticagrelor. For patients with concurrent atrial fibrillation (AF), triple antithrombotic therapy is often required. This approach combines DAPT with an anticoagulant, usually a vitamin K antagonist (VKA), to provide comprehensive protection against thromboembolic events while carefully managing the increased risk of bleeding complications [19].

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CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding the publication of this article.

CONCLUSIONS

Warfarin stands as a reliable oral anticoagulant in the prevention of thrombotic disorders and embolic stroke in patients with atrial fibrillation. Its mechanism, which inhibits the synthesis of vitamin K-dependent clotting factors and antithrombotic factors, underscores its efficacy. Regular monitoring of INR levels is imperative to gauge potential bleeding events during the therapy. Moreover, emerging evidence suggests that Direct Oral Anticoagulants (DOACs), like dabigatran, Rivaroxaban, and Apixaban, offer comparable, if not superior, efficacy to Warfarin. This underscores the evolving landscapes of anticoagulant therapy, offering clinicians and patients a broader array of options for effective management.

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