WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 12, 247-265. Review Article ISSN 2277–7105

A NOVEL ANTICOAGULANT THERAPY REVIEW

Priyanshi Jain[1]*, Riya Mondal, Aditya Pant[2] and Dr. B. S. Sonigara[3]

[1*]B. Pharm. Student (BNCP).

[2]Asst. Prof. (Department of Pharmacology, BNCP).

[3]Asst. Prof. (Department of Chemistry, BNCP).

Article Received on
29 April 2025,

Revised on 19 May 2025,
Accepted on 08 June 2025,

DOI: 10.20959/wjpr202512-37134

***Corresponding Author**

Priyanshi Jain

B. Pharm. Student (BNCP).

ABSTRACT

Novel oral anticoagulants (NOACs) also termed as, direct oral anticoagulants (DOACs) have revolutionised the management of thromboembolic disorders, offering improved efficacy and safety profiles over traditional agents such as warfarin, including narrow therapeutic window, drug-food interaction, and need for routine monitoring. This review provides an overview of the current state of novel anticoagulants, mainly focusing on DOACs targeting factor Xa and thrombin, which includes direct thrombin inhibitors and factor Xa inhibitor. We discuss the pharmacological properties, clinical efficacy and the safety for various clinical conditions like venous thromboembolism, atrial fibrillation and stroke. We also discuss developments in reversal agents by examining current evidence and the challenges. Finally, we highlight the ongoing research and future in development of novel anticoagulants.

INTRODUCTION

Anticoagulants therapies are used to prevent blood clots and are found to be effective in managing thromboembolic events in conditions like atrial fibrillations, venous thromboembolism (VTE), and coronary artery disease, as well as in patients with prosthetic heart valves. While arterial clots (platelet-rich and fibrin-poor, the so-called white clots) are usually generated at sites of vascular injury under high shear rates and are responsible for myocardial infarction and stroke, venous clots (fibrin- and red blood cell-rich and platelet-poor, the so-called red clots) cause venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).[4]

Venous thromboembolism (VTE) is the third leading cardiovascular diagnosis after a heart attack and stroke. Historically, vitamin K antagonists, such as warfarin, and aspirin, were the only anticoagulants that has been in clinical use as an antithrombotic for almost a half century. The risk for bleeding and the inconvenience for laboratory monitoring, dose adjustment and drug or food interactions are the main limits for VKAs while parenteral administration is the main limit for heparin and fondaparinux.[5] The therapeutic dose of warfarin for individuals also varies, reflecting differences in dietary vitamin K consumption, drug interactions and genetic polymorphisms in enzymes of warfarin metabolism. As a result, patient education, compliance and frequent monitoring are essential to ensure anticoagulation remains in the narrow therapeutic window.[6]

Novel oral anticoagulants (NOACs) are relatively new medications that offer many of these potential benefits like offering great convenience in administration, minor food-drug interaction and no need of frequent monitoring. The 2 classes of NOACs are direct thrombin inhibitors and direct factor Xa inhibitors. Dabigatran (Pradaxa) is currently the only direct thrombin inhibitor and was the first NOAC approved in 2010. Factor Xa inhibitors include rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa). NOACs like rivaroxaban and apixaban, can be administered without the need for initial parenteral anticoagulation and they can be given in fixed doses with no, or lesser need for monitoring the anticoagulant effect. Without the need for parenteral anticoagulation for some of the NOACs, there is potential for patients with low risk pulmonary embolisms to be discharged early and managed at home.[7] The risk of intracranial bleeding is 52 % lower with NOACS than with warfarin, with extremes ranging from 33 to 70 %. Such benefit is applicable to different NOACs, and independent of the time-in-therapeutic range under warfarin. Patients at increased risk for intra-cranial bleeding (renal dysfunction, or prior stroke or intra-cranial bleeding) should benefit most from switching to NOACs.[8] By synthesising existing literature, this review seeks to provide a valuable resource for researchers and practitioners interested in the novel anticoagulant therapies and its future directions.

Conventional Anticoagulant Agents

Conventional anticoagulant agents are mainly, unfractionated heparin(UH), low-molecular-weight heparins (LMWHs),the synthetic pentasaccharide fondaparinux, and vitamin K antagonists such as warfarin and related drugs. The direct thrombin inhibitors bivalirudin and

lepirudin are only licensed for restricted indications, such as acute coronary syndromes and the thrombotic complications of heparin-induced thrombocytopenia.[9]

Unfractionated heparin and Low-molecular-weight heparins

Heparin is the most widely used anticoagulant in the world. Unfractionated Heparin (UFH) is a fast-acting blood thinner that works together with antithrombin, a natural protein in the body, to block clot formation. Specifically, UFH binds to antithrombin and enhances its ability to inhibit two of the body's most potent clotting factors – factor Xa and factor IIa.[10] Molecules of heparin with fewer than 18 saccharides lack the chain length to bridge between thrombin and AT and therefore are unable to inhibit thrombin. LMWHs are compounds formed due to depolymerization or fractionation, with having short polysaccharide chains and low-molecular weight. All of the anticoagulant, pharmacokinetic, and other biological differences between unfractionated heparin (UFH) and LMWH can be explained by the relatively lower binding properties of LMWH. Compared with UFH, LMWHs have reduced ability to inactivate thrombin because the smaller fragments cannot bind simultaneously to AT and thrombin. In contrast, because bridging between AT and factor Xa is less critical for anti–factor Xa activity, the smaller fragments inactivate factor Xa almost as well as do larger molecules. UFH and LMWH have been consistently found to reduce VTE complications in hip or knee arthroplasty and in the setting of high-risk medical conditions (heart failure, acute inflammatory diseases, prolonged immobilisation in bed) by approximately 60%. They are also administered, along with dual antiplatelet therapy (e.g., aspirin and clopidogrel) in patients with acute coronary syndromes, whether or not managed with revascularization treatment. Indeed, besides reducing mortality and morbidity related to VTE in cancer patients, accumulating experimental and clinical data suggest that LMWH significantly improve overall survival by a direct effect on the development and metastasization of cancer itself.[11]

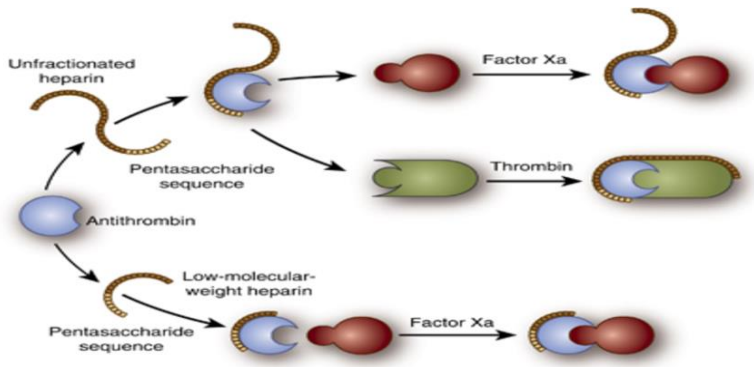

Figure 1: Mechanism of action of low molecular weight heparin.

Vitamin K Antagonist

Warfarin inhibits the synthesis of vitamin K-dependent clotting factors, reducing clotting ability. Close monitoring of prothrombin time (PT) and the international normalized ratio (INR) is essential to ensure therapeutic effectiveness and minimize adverse events, such as bleeding.[12] For reversal of excessive anticoagulation by warfarin, AVK withdrawal, oral or parenteral vitamin K administration, prothrombin complex or fresh frozen plasma may be used, depending on the excess of anticoagulation, the existence and site of active bleeding, patient characteristics and the indication for AVK. In over-anticoagulated patients, vitamin K aims at rapid lowering of the international normalized ratio (INR) into a safe range to reduce the risk of major bleeding and therefore improving patient outcome without exposing the patient to the risk of thromboembolism due to overcorrection, resistance to AVK, or an allergic reaction to the medication. As vitamin K administration via the intravenous route may be complicated by anaphylactoid reactions, and via the subcutaneous route by cutaneous reactions, oral administration is preferred. Overcorrection of the INR or resistance to warfarin is unlikely if the above doses of vitamin K are used. Vitamin K is less effective for over-anticoagulation after treatment with acenocoumarol or phenprocoumon than after treatment with warfarin.[13]

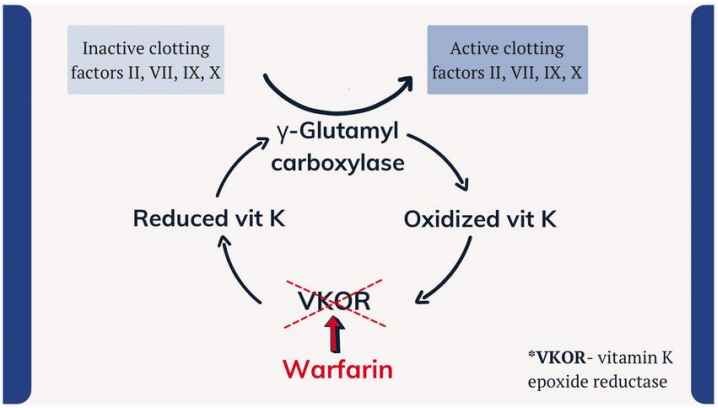

Figure 2: Mechanism of action of warfarin (Vitamin K antagonist).

New Oral Anticoagulants

The limitations of warfarin and heparin lead to developments of new oral anticoagulant agents selectively targeting specific steps in the coagulation cascade which, besides having a high efficacy and safety profile, have the advantage of being orally administered at fixed dosages with a lower need for laboratory monitoring.14 Newer anticoagulants, novel oral anticoagulants (NOAC) or directly acting oral anticoagulants (DOAC) include a direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and

edoxaban). NOACs are the present promising alternatives to warfarin due to their lower bleeding risk, fixed dosages, and lack of routine laboratory monitoring.[15]

The characteristics of NOACs are mentioned in the table below

Table 1: Characteristics of NAOCs.

Characteristics		Direct thrombin inhibitor	Factor Xa inhibitors		
		Dabigratan	*Apixaban*	*Edoxaban*	*Rivaroxaban*
Bioavailability (%)		3–7	50	62	80
Time to peak concentration (hours)		1–3	1–3	1–3	2–4
Half-life (hours)		12–17	8–15	8–10	7–13
Renal clearance (%)		80	25	35	33
Dosing regimen		110–150 mg twice daily	2.5–5 mg twice daily	15–30 mg once daily	10–20 mg once daily; 15 mg once or twice daily
Metabolism		P-glycoprotein	P-glycoprotein, CYP3A4	P-glycoprotein, CYP3A4	P-glycoprotein, CYP3A4
Approved indications	Non-valvular AF	North America, Europe	North America, Europe	United States	North America, Europe
	VTE treatment	United States, Europe	United States, Europe	Unites States	North America, Europe
	VTE prevention	Canada, Europe	Canada, Europe	Japan	North America, Europe

Direct Thrombin Inhibitor

Direct thrombin inhibitors (DTIs) bind directly to thrombin and do not require a cofactor such as antithrombin to exert their effect. DTIs can inhibit both soluble thrombin and fibrin-bound thrombin.[16] Thrombin has an active site and 2 secondary binding exosites. Exosite 1 acts as a dock for substrates such as fibrin to promote orientation for active site binding. Exosite 2 is the heparin-binding domain. Dabigatran is a univalent direct thrombin inhibitor that binds to the active site, thereby inactivating both fibrin-bound and unbound (ie, free) thrombin. Indirect thrombin inhibitors such as unfractionated heparin and low-molecular-weight heparin cannot inhibit fibrin-bound thrombin. The ability to inhibit fibrin-bound thrombin is an important theoretical advantage of dabigatran over the heparins because bound thrombin can continue to trigger thrombus expansion.[17] Dabigatran etexilate is an orally administered direct thrombin inhibitor, developed to overcome the limited oral bioavailability of dabigatran. Once absorbed from the gastrointestinal tract, it is rapidly converted to the active form dabigatran. Dabigatran circulates in the blood with a half-life of 12–17 h, which allows oral administration once a day. With a low potential for drug-drug interactions and a predictable anticoagulant effect, dabigatran etexilate can be administered in fixed doses without need for monitoring coagulation.[18] Recently, the safety profile of dabigatran (150 and 75 mg BD) in real US clinical practice has been reported in an elderly Medicare cohort with non-valvular AF.20 Compared with warfarin, dabigatran was associated with a reduced risk of ischaemic stroke, intracranial haemorrhage and mortality, but with an increased risk of

major GI bleeding. These results were stronger in the subgroup treated with dabigatran 150 mg BD. Around 16% of patients received dabigatran 75 mg BD and among these, none of the study outcomes were statistically significantly different from warfarin except for a lower risk of intracranial haemorrhage with dabigatran. Unfortunately, known severe renal impairment was only present in up to 7% of the subgroup of dabigatran 75 mg BD and results must be interpreted carefully.[19]

Factor Xa Inhibitor

Factor Xa is responsible for the conversion of prothrombin into thrombin which then cleaves fibrinogen to create the fibrin clot. Factor Xa represents an attractive target for antithrombotic drugs as blockade of factor Xa permits inhibition of both the extrinsic and intrinsic coagulation pathways. Several factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban, have been approved for certain conditions, and are also in clinical development for other indications.[20]

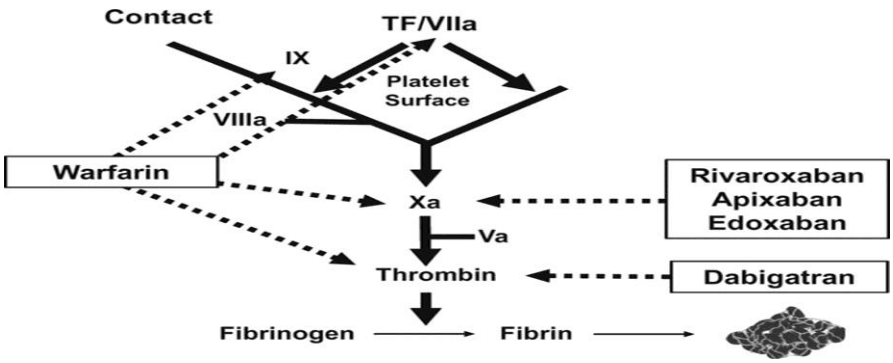

Figure 3: Site of action of Warfarin and NAOCs.

A) Rivaroxaban- Pharmacokinetic and pharmacodynamic effects

Rivaroxaban is a novel factor Xa inhibitor that exhibits predictable pharmacokinetics, with high oral bioavailability, rapid onset of action (achieves maximum plasma concentration in 1.5–2.0 h), and no known food interactions. The 10 mg tablet has a bioavailability of 80–100% and is not affected by food, whereas the 20 mg tablet has only a 66% bioavailability that will increase when taken with food. After ingestion, rivaroxaban reaches peak concentration within 2–4. Rivaroxaban has a plasma protein binding of 92–95% to which it binds mainly to albumin. In addition, 51% of rivaroxaban is metabolized by cytochrome P (CYP)3A4 and CYP2J2 to inactive metabolites and most of the drug is excreted in the urine.[21]

Elimination of rivaroxaban from plasma occurs with a terminal half-life of 5–9 h in young individuals, and with a terminal half-life of 12–13 h in subjects aged >75 years. Available data indicate that body weight, age, and gender do not have a clinically relevant effect on the pharmacokinetics and pharmacodynamics of rivaroxaban, and it thus can be administered in fixed doses without coagulation monitoring. Although no specific antidote is known for rivaroxaban, preclinical data suggested that recombinant factor VIIa and activated prothrombin complex concentrate may reverse the effects of high-dose rivaroxaban. Patients with severe renal function (CrCl less than 15 ml/min) should avoid rivaroxaban treatment. Correspondingly, rivaroxaban should not be used in patients with Child-Pugh B or C hepatic impairment. Rivaroxaban is a pregnancy category C and it is unknown whether rivaroxaban is excreted in breast milk.[22]

B) Apixaban- Pharmacokinetic and pharmacodynamic effects

Apixaban is a direct, reversible, competitive, and selective inhibitor of factor Xa and the last NOAC approved by the FDA and EMA for the prevention of stroke and embolism in non-valvular AF. It is well absorbed achieving peak plasma concentration in 1 –4 h. Apixaban achieves a bioavailability of 50% after oral administration and is not affected by food. The protein binding is 87% to plasma proteins and apixaban is metabolized mostly through CYP3A4 to inactive metabolites. Apixaban is eliminated by the urine and feces with urine accounting for 27% of the clearance. The half-life for apixaban is 12 hours. Adverse events and contraindications for apixaban are limited to bleeding events. Patients with the characteristic of low body weight alone have not been found to have differences in apixaban exposure. Similarly, geriatric patients with normal body weight and renal function also had normal apixaban exposure. Although there is limited data of the use of apixaban in pregnancy or breast-feeding, it is pregnancy category B.[23] The maximum plasma concentration (Cmax) of apixaban occurs 3–4h after oral administration. The absorption of apixaban appears to occur primarily in the small intestine and decreases progressively throughout the gastro-intestinal tract. Compared with oral administration, the bioavailability of 2.5mg of apixaban solution was approximately 60% and 84% lower when released in the distal small bowel and ascending colon, respectively. For oral doses up to 10mg, the absolute bioavailability of apixaban is ~ 50%, resulting from the incomplete absorption and first-pass metabolism in the gut and liver. The volume of distribution is approximately 21 L, suggesting distribution mainly into extracellular fluid, which comprises vascular and interstitial fluid. The blood to plasma ratio of apixaban is 0.9:1 in humans, suggesting that apixaban is uniformly distributed

between plasma and red blood cells. It is unknown whether apixaban or its metabolites are excreted in human breast milk. The apparent elimination half-life ($t_{1/2}$) is ~ 12 h. Elimination involves multiple pathways, including metabolism as well as biliary and renal elimination of the unchanged parent compound and direct intestinal excretion. Apixaban is not a high-extraction-ratio drug.[24] The metabolic pathways for apixaban include O-demeth-ylation, hydroxylation, and sulfation of hydroxylated O-dem-ethyl apixaban, with metabolism primarily occurring via cytochrome P450 (CYP) 3A4/5, with minor contributions from CYP1A2, CYP2C8, CYP2C9, CYP2C19, andCYP2J2. After an oral dose of apixaban, unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites present.[25]

C) Edoxaban- Pharmacokinetic and pharmacodynamic effects

Edoxaban belongs to the class of direct oral anticoagulants (DOACs) and is used for the treatment of pulmonary embolism (PE), deep venous thrombosis (DVT), and to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) following 5 to 10 days of initial therapy with a parenteral anticoagulant. This drug exerts its therapeutic effects by inhibiting factor Xa directly, selectively, and reversibly as part of its mechanism of action. In contrast to the widely used anticoagulant warfarin, edoxaban offers the advantage of fewer monitoring requirements, lower risk of substantial bleeding, and infrequent drug interactions.[26] This drug is also an orally active factor Xa inhibitor with a half-life of 10 to 14 hours, and it has the same indications as rivaroxaban and apixaban. It is given at a fixed rate with no monitoring. The typical dosage is 30 or 60 mg once daily. Possible improvements in efficacy and/or safety with monitoring have been suggested.[26] The pharmacokinetics of edoxaban have been studied in many healthy volunteer studies. Single oral doses of 10–180 mg were administered to healthy subjects. Edoxaban exhibits generally linear and dose-proportional pharmacokinetics. Following oral administration, edoxaban reaches peak plasma concentration (C_{max}) values within 1–2 h. Edoxaban is widely distributed in the body, with a steady-state volume of distribution (V_{ss}) (arithmetic mean ± standard deviation) of 107 ± 19.9 L. The total clearance of edoxaban is estimated to be 21.8 ± 3.03 L/h, with renal and non-renal clearance contributing almost equally. Renal clearance is estimated to be about 10.7 ± 3.00 L/h. The terminal elimination half-life is approximately 10–14 h. Both single- and multiple-dose administration result in C_{max} within 1–2 h after dosing, followed by a biphasic decline. Oral bioavailability is 62 %. Edoxaban is primarily absorbed in the upper gastrointestinal tract, with approximately 13 % absorbed in the colon. The

disposition of edoxaban is biphasic and is described by a 2-compartment model. The (mean ± standard deviation) V_{ss} is 107 ± 19.9 L. In vitro, five phase 1 edoxaban metabolites were detected in human liver microsomes: M-1, M-4, M-5, M-6 and a hydroxylated metabolite at the *N*,*N*-dimethylcarbamoyl group of edoxaban (hydroxymethyl edoxaban) (M-7). The formation of the human-unique metabolite M-4 is catalysed by carboxylesterase-1 (CES1) present in human liver microsomes and in the cytosol. Cytochrome P450 isoenzyme (CYP) 3A4 mediates the formation of M-5 and hydroxymethyl edoxaban in the presence of nicotinamide adenine dinucleotide phosphate (NADPH). M-8, a minor metabolite, is postulated to arise spontaneously (non-enzymatically) through an intermediary, hydroxymethyl edoxaban, formed via CYP3A4/5.Edoxaban has a minimal inhibitory effect on CYPs (IC_{50} ≥100 µM). It shows a weak inhibitory effect on P-gp, OATP1B1 and OATP1B3 (IC_{50} ≥50 µM), and a minimal effect on other drug transporters (OAT1, OAT3, OCT1 and OCT2; IC_{50}≥100 µM). In human hepatocytes, edoxaban and the metabolites M-4 and M-1 do not induce gene expression of CYP1A2, CYP3A4 or multidrug resistance protein 1 (MDR1; P-gp) (data on file). Thus, at clinical concentrations, edoxaban is unlikely to affect the pharmacokinetics of other drugs that are substrates of CYPs or transporters, such as P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. The in vitro total plasma protein binding of edoxaban at concentrations of 0.2–5 µg/mL is about 55 %, whereas the human-unique metabolite M-4 is approximately 80 % bound to plasma proteins over a concentration range of 0.2–2 µg/mL. Edoxaban partitions almost equally in blood (46 %) and plasma. Edoxaban is primarily eliminated unchanged in urine and through biliary secretion, with metabolism contributing to a lesser extent towards total clearance. Renal clearance of unchanged drugs contributes approximately 50 % to total clearance, with the remaining 50 % non-renal clearance occurring through metabolism and biliary secretion. The oral half-life of edoxaban (10–14 h) suggests distribution and redistribution resulting in a higher terminal-phase volume of distribution, possibly due to enterohepatic recirculation.[27]

Table 2: Mechanism of action of NAOCs.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Reversible thrombin inhibitor	Reversible Factor Xa inhibitor	Reversible Factor Xa inhibitor	Reversible Factor Xa inhibitor
Prodrug	Yes	No	No	No
Pharmacokinetics	Bioavailability 6.5% Time to peak effect in 1-2 hours Half-life 12-17 hours Plasma protein binding 35% Metabolism - Serum esterases and non-CYP hepatic enzymes Excretion - urine 80%, feces 20%	Bioavailability > 90% Time to peak effect in 2-4 hours Half-life 5-9 hours Plasma protein binding > 80% Metabolism - CYP 3A4/5, CYP2J2 hydrolysis Excretion - urine 70%, feces 30%	Bioavailability 50% Time to peak effect in 3-4 hours Half-life 9-11 hours Plasma protein binding 87% Metabolism - CYP 3A4/5 (major) Excretion - urine 25%, feces 75%	Bioavailability 62% Time to peak effect in 1.5 hours Half-life 10-14 hours Plasma protein binding 55% Metabolism - CYP < 4%, Hydrolysis (major) Excretion - urine 35% feces 65%
PT/INR	Not used	Prolonged: suggests excessive bleeding risk	Not used	Not used
aPTT	>2x ULN suggests excessive bleeding risk	Not used	Not used	Not used
Absorption with food	No effect	+39% more; mandatory intake with food	No effect	No effect
Renal/Hepatic Monitoring	Renal function	Renal and hepatic function	Renal and hepatic function	Renal function
Dosing	CrCl > 30 mL/min 150 mg PO twice daily CrCl < 30 mL/min Not recommended	CrCl > 50 mL/min 20 mg PO Daily CrCl 30-50 mL/min 15 mg PO Daily CrCl < 30 mL/min Not recommended	5 mg PO twice daily 2.5 mg PO twice daily if 2 or more of the following > 80 years, < 60 kg, Serum Creatinine > 1.5 mg/dL CrCl < 30 mL/min Not recommended	CrCl 50 - 95 mL/min 60 mg PO once daily CrCl 15 - 50 mL/min 30 mg PO once daily CrCl > 95 mL/min Not recommended CrCl < 15 mL/min Not recommended

Clinical Applications

Stroke prevention in Atrial fibrosis

AF is characterised by the anarchic (fast and disorganised) and unpredictable contraction of atrial muscle fibres. This arrhythmia appears on an electrocardiogram as an absence of P-waves and irregular R-R intervals. It is usually associated with tachycardia. The resulting asynchrony leads to ineffective contraction, decreased ventricular ejection fraction and blood pooling, predisposing to coagulation inside the atrium and increasing the risk of thromboembolic events. The efficacy of antiarrhythmic drugs is unpredictable, depending mainly on the duration of AF and the patient's underlying heart disease. Moreover, antiarrhythmic drug treatment can cause proarrhythmia. AF can also recur after catheter ablation. Given the uncertain success of attempts to directly treat AF, it is therefore important to manage the attendant increased risk of thromboembolic events; most patients with AF will eventually need anticoagulant therapy to prevent thromboembolism. Although VKAs

improve prognosis by reducing thromboembolic events, they have diverse clinical limitations.[1] VKAs significantly increase the risk of minor and major bleeding complications, of which intracranial haemorrhage is particularly harmful. Regular monitoring and dose adjustments are thus essential to keep patients within the narrow therapeutic range throughout VKA treatment.[28] Rivaroxaban was shown to have an efficacy similar to warfarin, dabigatran (150 mg dose) was statistically superior to warfarin in the prevention of stroke or systemic embolic events and apixaban reduced stroke or systemic embolism. A major advantage of new anticoagulants is that they are less susceptible to the dietary and drug interactions that confound warfarin management. However, even though the need for INR monitoring is considered a detriment of warfarin therapy, it does provide an objective way to assess and respond to nonadherence and a monitoring tool in case of bleeding or thrombosis. The inability to accurately monitor the new anticoagulants may be troublesome in patients with chronic kidney disease whose dosing needs will vary according to renal function. PT may be used to measure the effect of rivaroxaban and anti-FXa may be used to measure apixaban in clinical settings. Dabigatran has shown difficulties with dyspepsia and gastrointestinal hemorrhage, while neither rivaroxaban nor apixaban seemed to have this particular adverse-event profile in clinical trials. The data are strongest for apixaban. It was superior to warfarin and aspirin in the reduction of stroke and systemic embolism but was the only one of the three to also show a significant reduction in bleeding as well. There was a strong trend towards a reduction in mortality with dabigatran and rivaroxaban, but apixaban had a significant mortality reduction compared to warfarin. Of the new agents only rivaroxaban is a once-a-day medication, which might be more convenient and able to increase adherence. Until recently, the main drawback of novel anticoagulants was the lack of an agent to reverse their effects. Now, however, various clinically-effective antidotes have been developed. To date, four extensive randomised clinical trials comparing four DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) with warfarin in different cohorts of patients with nonvalvular AF have been published.[29]

Prevention and treatment of VTE and PE

Venous thromboembolism (VTE), a disease entity comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent and potentially life-threatening event. To date different agents are available for the effective treatment of acute VTE and the prevention of recurrence. For several years, the standard of care was the subcutaneous application of a low molecular weight heparin (LMWH) or fondaparinux, followed by a vitamin K antagonist

(VKA). DOAC significantly simplifies VTE treatment because they are administered in fixed doses and no routine monitoring is needed. Moreover, in meta-analyses DOAC were associated with a significantly lower risk of bleeding complications. The efficacy of rivaroxaban in the treatment of acute DVT and PE was demonstrated in two large open-label trials (Einstein DVT and Einstein PE). These studies compared rivaroxaban with the standard of care treatment (LMWH followed by VKA) and were designed as non-inferiority studies. In both studies rivaroxaban proved as effective as LMWH followed by VKA with similar bleeding rates. Apixaban was tested in the AMPLIFY study, a double-dummy double-blind trial, and was non-inferior compared to standard treatment. Major bleeding occurred less frequently under the treatment with apixaban. In the AMPLIFY Extension study patients were randomized into two different doses of apixaban (5 or 2.5 mg twice daily) or placebo for testing VTE recurrence during 12 months of extended treatment. Both treatment doses of apixaban similarly reduced the risk of recurrent VTE without an increased risk of major bleeding. Dabigatran was non-inferior compared to standard treatment and no differences with regard to major bleeding episodes were found.[30] Thus, although edoxaban and rivaroxaban were more effective than dalteparin for preventing recurrence in cancer patients, they were associated with more bleeding. Therefore, there is a need for safer anticoagulants, and FXII and FXI are being pursued as targets for the development of such agents. The goal of anticoagulation therapy is to attenuate thrombosis without perturbing hemostasis. Although DOACs come closer to this goal than VKAs, bleeding is not eliminated with DOACs. This is particularly evident in patients with cancer-associated VTE. Thus, in patients without active cancer, a meta-analysis revealed that DOACs are at least as effective as VKAs, but are associated with a 40% reduction in the risk of major bleeding. The excess in major bleeding events with DOACs were mostly gastrointestinal bleeds that occurred in patients with gastrointestinal cancers, whereas most of the clinically relevant non-major bleeding events occurred in patients with gastrointestinal or urological cancers. Therefore, because of the increased risk of bleeding, DOACs can only be used in selected patients with VTE with active cancer. advances in anticoagulation have simplified VTE prevention and treatment. The next frontier is development of safer anticoagulants for VTE treatment in cancer patients and the introduction of novel strategies to reduce the risk of CTEPH and PTS.[31]

Use in orthopedic surgery

Patients undergoing major orthopaedic surgery, including total hip arthroplasty, total knee arthroplasty and hip fracture surgery, are at high risk of developing post-operative deep vein

thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE). With contemporary surgical techniques and current methods of VTE prophylaxis, about 1–3% of patients develop a symptomatic DVT and 0.2–1.1% a PE within 35 days of surgery. LMWH and fondaparinux are often stopped because of the inconvenience of parenteral administration. Consequently, there is a clear need for oral agents that are effective, safe and do not require routine coagulation monitoring. The development of novel oral agents for VTE prevention have focused on the development of non-peptidic, orally available, small molecules that directly inhibit one of two key serine proteases in the coagulation cascade, thrombin (activated Factor II) and activated Factor X (FXa). The direct thrombin inhibitor, dabigatran etexilate (referred to as dabigatran hereafter), and the selective FXa inhibitors, rivaroxaban and apixaban, are approved in many countries for the prevention of VTE in patients undergoing hip or knee arthroplasty. Rivaroxaban is the only one of these agents approved by the US Food and Drug Administration for prophylaxis of DVT, which may lead to PE, in adults undergoing hip or knee replacement surgery. Edoxaban is another oral FXa inhibitor that has been approved in Japan for the same indication. These agents may satisfy the clinical need for improved thromboprophylaxis.[32]

Safety, efficacy and comparative studies

NOACs have a favourable benefit-risk profile, they are associated–as any anticoagulant–with a risk of bleeding. In addition, treatment may need to be interrupted in patients who need surgery or other procedures. When a patient is known or suspected to be on NOAC treatment presents for emergency care, careful medical history taking is required to determine which NOAC, if any, is taken, which dose regimen is used, and when the last dose was taken (i.e. whether the drug level is pre- or post-peak). It is also essential to identify co-morbidities and concomitant treatments associated with an increased risk of bleeding. As the half-lives of NOACs are influenced by renal function and patients with renal failure will be at increased risk of bleeding complications as a result of the faulty renal elimination, assessment of creatinine clearance is important to evaluate when restoration of haemostasis can be expected after cessation of NOAC treatment. Measuring the anticoagulant effect of NOACs may also be helpful to guide emergency care.[33]

A recent pooled analysis of results from multiple population-based cohort studies from Europe and Canada (421,523 NVAF patients) showed a slightly higher risk of MB for rivaroxaban (HR 1.11), whereas a lower risk of MB was observed for apixaban (HR 0.76)

and dabigatran (HR 0.85) compared to VKAs**.** Superior effectiveness (ischemic stroke/SE HR: 0.82) and safety (ICH/GIB HR: 0.58) outcomes of Apixaban versus Rivaroxaban have been reported in a US nationwide commercial health care claims database. Compared to other DOACs or VKAs, there is scant real-world evidence on the efficacy and safety of edoxaban, which is the last licensed DOAC. In the only study available on AF patients from a large German health insurance database (globally enrolling 21,038 patients), edoxaban demonstrated a favorable safety profile with lower risk of MB compared to rivaroxaban (HR 0.74) and VKA (HR 0.47), while no differences in the risk of MB were found between edoxaban and apixaban or dabigatran. Other recent systematic review and meta-analyses found that among three DOACs (apixaban, dabigatran, rivaroxaban), apixaban had the most favorable safety profile, with lower risk of MB. No significant difference was observed in the risk of stroke/SE between DOACs.[34]

Reversal agents and antidotes

Until recently, only bypass agents were available for bleeding on NOAC therapy. However, now direct molecular antagonists that inhibit the anticoagulant activity have been developed. The latter class of agents act by binding to and sequestering the active drug (Idarucizumab or Andexanet alfa) or occupying the anticoagulant drug's active site through non-covalent hydrogen bonding (Aripazine, Ciraparantag, [PER977]). Bypass agents are pro-haemostatic clotting factors that can activate coagulation despite presence of coagulation inhibitors. Prothrombin Complex Concentrates (PCCs), activated PCCs (aPCCs) and recombinant FVIIa (rFVIIa) have been suggested for consideration within many local institutional bleeding management protocols. However it is important to note that efficacy testing for NOAC effect reversal has been limited to animal studies and small healthy human volunteer studies and to date there are no controlled clinical studies of reversal therapy in bleeding patients taking oral Xa inhibitors. Importantly, these agents carry an inherent pro-thrombotic risk and are expensive.

Idarucizumab for Dabigatran- Idarucizumab is a humanized monoclonal antibody fragment developed as a specific reversal agent for dabigatran. It binds with high affinity (350 times higher than that of thrombin) to both free and thrombin-bound dabigatran, and its binding is effectively irreversible. In healthy volunteers with normal renal function, peak plasma concentrations were achieved at the end of a five-minute infusion, and idarucizumab was demonstrated to have an initial half-life of 47 minutes. Despite its short plasma half-life,

however, idarucizumab bound to all of the dabigatran present in plasma within minutes. Idarucizumab is primarily eliminated, so drug exposure is increased in patients with impaired renal function. However, such patients also have elevated dabigatran concentrations, since this agent is also predominantly renally cleared. Notably, idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran. The median maximum percentage of reversal of dabigatran was 100% [95% confidence interval (CI): 100–100] as assessed by either dilute thrombin time or ecarin clotting time.[35]

Andexanet alfa for factor Xa inhibitor- Andexanet alfa (andexanet) is a specific reversal agent that is designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors. Andexanet is a recombinant modified human factor Xa decoy protein that is catalytically inactive but that retains the ability to bind factor Xa inhibitors in the active site with high affinity and a 1:1 stoichiometric ratio. Andexanet binds and sequesters factor Xa inhibitors within the vascular space, thereby restoring the activity of endogenous factor Xa and reducing levels of anticoagulant activity, as assessed by measurement of thrombin generation and anti–factor Xa activity, the latter of which is a direct measure of the anticoagulant activity.[36] Use of the drug should be limited to reverse anticoagulation if needed due to life-threatening or uncontrolled bleeding. The use of Andexanet Alfa to reverse the effects of edoxaban is currently off-label because more extensive studies are needed to determine its efficacy and safety for this treatment.[37]

Advantages of NAOCs

NOACs become popular in the market due to advantages over traditional anticoagulants. Some of the many advantages are dealt with here. Firstly, it has erased the need for heparin bridging as it has sudden onset as well as offset action, which eliminates the chances of bleeding if the patient requires surgical treatments. Along with these benefits, the rapid onset and offset actions mean any patient with acute thrombosis does not require any initial treatment with a parenteral anticoagulant. Its popularity accounts not only for its predictable anticoagulant effects which in turn reduce the need for a routine coagulation monitoring but also its convenience for the patients as NOACs have fixed daily oral doses. This is possible since they have predictable PK properties and absolute bioavailability, regardless of the demographic variables. Most importantly, the actions of NOACs are not affected by the intake of foods. Hence, the patient does not need to avoid certain foods or put any dietary restrictions. Also, due to the wide therapeutic window, the chances of bleeding complications

are exponentially reduced. NOACs have specific coagulation enzyme targets; therefore, off-target adverse effects are almost nil. It also shows greater efficacy in patients having atrial fibrillation. And they are less prone to have intracranial haemorrhage (ICH) with an exception for dabigatran (150 mg of the drug causes equal rate of ICH as warfarin). Lastly, the studies show that NOACs have minimal interactions with other drugs. It permits the concomitant administration of other drugs with NOACs. It is unlike VKAs which exhibit a wide range of drug interactions.[38]

Challenges of NAOCs

Even though NOACs brought about several advantages over VKAs, there still exist some challenges that need to be overcome. Even though current guidelines favour the use of NOACs, there are several domains that need contemplation and studies to guarantee the safe and effective use of the drug. It lacks empirical evidence on its proper use which makes clinicians less interested to switch over to NOACs. Some of the main demerits are addressed below. The drug acquisition costs are higher for NOACs compared to VKAs; hence, it limits the usage. This makes the healthcare system prefer warfarin over NOACs though INR is poorly controlled with it. Unlike warfarin, NOACs lack the need for routine investigation of the drug in plasma or modification of dose except for emergency situations where the drug exposure assessment is required. This arena demands a large number of studies, because most of the tests are not reliable and provide accurate tests. There is only limited evidence available to assess the coagulation testing ability. Primarily, specific tests are still not routinely available in many centres. Even if available, the expertise is not available round the clock. Thus, it is difficult to assess the level of coagulation in emergency situations. Also, there are no international calibration standards for the assays. Thus, there are chances for considerable variations between laboratories. There is no system to optimize non-compliance of NOACs like VKAs. This is due to the shorter half-life of the drugs. Thus patients require follow-up to ensure their medication compliance. The endurance with NOACs is unsatisfactory and efforts are in progress to enhance compliance. Switching from NOAC to warfarin is a bit complex. Warfarin shows gradual onset of action (5–10 days). Thus, NOACs should be administered along with warfarin till the INR is in the desired value. Once sole therapy is in place, the INR should be re-evaluated 24 h after the last dose of NOACs. This is done to guarantee adequate anticoagulation. Close monitoring of INR is suggested for the first month until stable INR values are achieved. For CKD patients, a yearly examination of renal function is advised especially for dabigatran (80% elimination renally). The current

ESC guidelines state that the use of NOACs is undesirable in CKD patients having CrCl < 30 ml/min. Administration of NOACs is not suggested in patients with AF and undergoing haemodialysis. The dose adjustments are done according to the patient characteristics outlined in the monograph of each agent since there is very little evidence in suggestion to improve safety levels of the drug in relation to clinical characteristics like age, renal function, and concomitant medications. Dose adjustment for patients at extremes of body weight is still debated upon as data on these clinical trials are insufficient at present. There are limited studies with regard to the usage of NOACs in pregnant women and breast feeding mothers along with patients having hepatic disease. Whether it is safe for long-term use or not has not yet been confirmed.[39]

CONCLUSION

In conclusion, this review has highlighted the significant advancements In novel anticoagulant therapies offering promising alternatives to traditional vitamin K Antagonist These agents demonstrate comparable or superior efficiency in preventing thromboembolic events with improved safety profiles, particularly regarding intracranial hemorrhage. Their predictable pharmacokinetic and pharmacodynamics, with absence of routine monitoring, offer significant advantages in terms of patient convenience and adherence.

However, the landscape of anticoagulant therapy continues to evolve. Further research is warranted to fully elucidate the long term safety and effectiveness of these NAOCs across patient population and clinical scenarios. Areas requiring ongoing investment include optimal management of bleeding complications, the development of more universally affecting reversal agents, and the cost-effectiveness of these in routine clinical practice. Ultimately, the choice of anticoagulant therapy should be individualised, considering patient- specific risk factors, lifestyles, and preferences. As our understanding of homeostasis and thrombosis deepens the further clinical data emerge, novel anticoagulants are poised to play an increasingly central role in prevention and treatment of thromboembolic disorders, potentially leading to imported patient outcomes and reduced burden of these life- threatening conditions.

REFERENCE

1. Franchini et al., “The Evolution of Anticoagulant Therapy.”
2. Becattini, Vedovati, and Agnelli, “Old and New Oral Anticoagulants for Venous Thromboembolism and Atrial Fibrillation.”

3. Jo and Barnes, “Role of Novel Oral Anticoagulants in the Management and Prevention of Venous Thromboembolism.”
4. Jennifer L. Cruz and Katherine Summers, “Novel Oral Anticoagulants.”
5. Verdecchia et al., “Why Switch from Warfarin to NOACs?”
6. Mannucci and and Franchini, “Old and New Anticoagulant Drugs.”
7. Qiu et al., “Pharmacological and Clinical Application of Heparin Progress.”
8. “Unfractionated Heparin (UFH) - Blood Clots.”
9. Franchini et al., “The Evolution of Anticoagulant Therapy,” March 2016.
10. Patel et al., “Warfarin.”
11. Hanslik and Prinseau, “The Use of Vitamin K in Patients on Anticoagulant Therapy.”
12. Franchini et al., “The Evolution of Anticoagulant Therapy,” March 2016.
13. “Direct Oral Anticoagulants | Department of Pharmacy Services | UC Davis Health.”
14. Lee and Ansell, “Direct Thrombin Inhibitors.”
15. Hankey and Eikelboom, “Dabigatran Etexilate.”
16. Kong et al., “Direct Thrombin Inhibitors.”
17. Hankey and Eikelboom, “Dabigatran Etexilate.”
18. Shantsila and Lip, “Factor Xa Inhibitors.”
19. McCarty and Robinson, “Factor Xa Inhibitors.”
20. Almarshad et al., “Use of Direct Oral Anticoagulants in Daily Practice.”
21. McCarty and Robinson, “Factor Xa Inhibitors.”
22. “(PDF) Apixaban: A Clinical Pharmacokinetic and Pharmacodynamic Review.”
23. Byon et al., “Apixaban.”
24. “(PDF) Apixaban: A Clinical Pharmacokinetic and Pharmacodynamic Review.”
25. Padda and Chowdhury, “Edoxaban.”
26. California, “Assessing Novel Oral Anticoagulants.”
27. Parasrampuria and Truitt, “Pharmacokinetics and Pharmacodynamics of Edoxaban, a Non-Vitamin K Antagonist Oral Anticoagulant That Inhibits Clotting Factor Xa.”
28. Martínez-Rubio et al., “Using Direct Oral Anticoagulants in Patients with Atrial Fibrillation.”
29. Norgard et al., “Novel Anticoagulants in Atrial Fibrillation Stroke Prevention.”
30. Thaler, Pabinger, and Ay, “Anticoagulant Treatment of Deep Vein Thrombosis and Pulmonary Embolism.”
31. Weitz and Chan, “Novel Antithrombotic Strategies for Treatment of Venous Thromboembolism.”

32. Quinlan and Eriksson, “Novel Oral Anticoagulants for Thromboprophylaxis after Orthopaedic Surgery.”
33. Eikelboom et al., “Emergency Care of Patients Receiving Non-Vitamin K Antagonist Oral Anticoagulants.”
34. Ballestri et al., “Risk and Management of Bleeding Complications with Direct Oral Anticoagulants in Patients with Atrial Fibrillation and Venous Thromboembolism.”
35. Abed et al., “Reversal Agents in the Era of NOACs.”
36. Siegal et al., “Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity.”
37. “Anticoagulation Reversal Agents - LabCE.Com, Laboratory Continuing Education.”
38. Paul et al., “NOACs.”