

# AN OVERVIEW TO THE IMMEDIATE RELEASE ANTI-COAGULANT DRUGS/ NOVEL RAPID RELEASE ANTI-COAGULANTS: AN OVERVIEW

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## Abstract

***Anticoagulants remain the primary plan for the prevention and treatment of thrombosis. Warfarin and heparins have been the main anticoagulants used until the past decade. the appearance of newer target-specific anticoagulants has brought us easier and inversely effective agents, although no specific antidotes are yet available. This article provides an overview of new rapid-release anticoagulants pharmacology and PKPD studies.***

***Keyword: Anticoagulants, Antithrombotic therapy, Factor Xa inhibitors, Immediate release anticoagulants, Low molecular weight heparins, venous thromboembolism, Vitamin K dependent coagulation***

## 1.INTRODUCTION

Anticoagulants, generally known as blood thinners, are chemical substances that help or reduce the coagulation of blood, dragging the clotting time. Some of them do naturally in blood-eating animals such as leeches and mosquitoes, where they help keep the bite area unclotted long enough for the beast to gain some blood. As a class of specifics, anticoagulants are used in remedies for thrombotic diseases. Oral anticoagulants(OACs) are taken by numerous people in lozenge or tablet form, and colorful intravenous anticoagulant lozenge forms are used in hospitals. Some anticoagulants are used in medical outfits, similar to sample tubes, blood transfusion bags, heart–lung machines, and dialysis equipment. One of the first anticoagulants, warfarin, was at first approved as a rodenticide. Anticoagulants are closely connected to antiplatelet drugs and thrombolytic drugs by working

the various pathways of blood coagulation. Specifically, antiplatelet drugs prevent platelet aggregation (clumping together), while anticoagulants prevent specific pathways of the coagulation cascade, which occurs after the initial platelet aggregation but before the formation of fibrin and stable aggregated platelet products (1).

Anticoagulants are the mainstay of treatment for stroke and systemic embolism inhibition in patients with atrial fibrillation (AF) or flutter. They can be used as well for the prevention and treatment of venous thromboembolism (VTE) and treatment of thrombus formation in other places. This class of medicine must be used carefully because using them mistakenly can lead to either ineffective prevention of clot formation or bleeding. It is vital for the clinician who uses any of these anticoagulants to just a basic understanding of their pharmacology and evidence of use (1). Through the now available agents, instant anticoagulation can only be achieved with parenteral anticoagulants (such as unfractionated heparin, low molecular weight heparin, or fondaparinux). Extended anticoagulant therapy currently involves the use of vitamin K antagonists (mainly warfarin) (2).

Unfractionated heparin binds to several plasma proteins, which subsidize to its variable anticoagulant response. In adding, unfractionated heparin is associated with the threat of developing heparin-induced thrombocytopenia and osteoporosis. Accordingly, rigorous and frequent coagulation monitoring is needed. Low molecular weight heparins, derived from unfractionated heparin by chemical or enzymatic depolymerisation, exhibit more probable anticoagulation and can be given at fixed doses without

coagulation monitoring. However, both unfractionated heparin and low molecular weight heparins require parenteral administration, which limits their use in the outpatient setting. Although low molecular weight heparins can also cause heparin-induced thrombocytopenia, this risk is lower compared with unfractionated heparin (3).

Vitamin K antagonists first introduced further than 60 years ago were until recently the only orally active anticoagulants available for clinical use. They produce an anticoagulant effect by interfering with the  $\gamma$ -carboxylation of vitamin K dependent coagulation Factors II, VII, IX, and X. In addition to their slow onset of action, vitamin K antagonists are also challenging to use in clinical practice since they have a narrow therapeutic window, unpredictable pharmacokinetics and pharmacodynamics, and several food-drug, and drug-drug interactions. Therefore, their use necessitates frequent coagulation monitoring and dose adjustment (4). It is apparent that traditional anticoagulants are all associated with drawbacks like the slow onset of action, unpredictable patient response, narrow therapeutic window, multiple food and drug interactions, etc. and there is an increasing need for new and better anticoagulant agents (2).

In search for an ideal anticoagulant agent, some preferred properties are oral administration, rapid onset of action, Wide therapeutic window, Minimal interactions with foods and other drugs, Predictable pharmacokinetics and pharmacodynamics, Low non-specific binding, Obtainability of an antidote, No unpredicted toxicities and Suitable costs (5).

Novel oral anticoagulants contain direct inhibitors of thrombin, factor Xa, and factor IXa. Designed to provide additional streamlined anticoagulation than warfarin, these agents can be given without routine coagulation monitoring. Ximelagatran, the first oral direct thrombin inhibitor, is as effective and safe as warfarin for the prevention of cardioembolic events in patients with atrial fibrillation (6).

Novel anticoagulants target specific steps in coagulation. This review paper presents a simplified view of the coagulation system and highlights the targets of new anticoagulants, reviews the pharmacology of the

new agents, and describes the results of immediate-release formulations of Novel anticoagulant agents.

## 2. MEDICAL USES:

The usage of anticoagulants is a choice based on the risks and benefits of anticoagulation. The major risk of anticoagulation therapy is the increased risk of bleeding. In the well people, the increased risk of bleeding is minimal, but those who have taken recent surgery, cerebral aneurysms, and other situations may have too great a risk of bleeding. Usually, the benefit of anticoagulation is the prevention of or reduction of the progression of thromboembolic disease. Some indications for anticoagulant therapy that are known to have benefited from therapy include:

- Atrial fibrillation — commonly forms an atrial appendage clot
- Coronary artery disease
- Deep vein thrombosis — can lead to pulmonary embolism
- Ischemic stroke
- Hypercoagulable states (e.g., Factor V Leiden) — can lead to deep vein thrombosis
- Mechanical heart valves
- Myocardial infarction
- Pulmonary embolism
- Restenosis from stents
- Cardiopulmonary bypass (or any other surgeries requiring temporary aortic occlusion)
- Heart failure

In these cases, anticoagulation therapy can prevent the formation of dangerous clots or prevent the growth of clots.

The choice to begin therapeutic anticoagulation frequently involves the use of multiple bleeding risk predictable outcome tools as non-invasive pre-test stratifications due to the potential for bleeding while on blood thinning agents. Among these tools are HAS-BLED, ATRIA, HEMORR2HAGES, and CHA2DS2-VASc. The risk of bleeding using the aforementioned risk assessment tools must then be weighed against the thrombotic risk to formally determine the patient's overall benefit in starting anticoagulation therapy.

### 3. INSIGHTS OF COAGULATION CASCADE:

The coagulation cascade as it is now understood has experienced a shift in understanding, from the intrinsic and extrinsic pathways, to a more all-encompassing model. This model incorporates an understanding of not only the accretive pattern of activation of zymogens, but also the intricate interlinking of the pathways, a better understanding of nonsupervisory mechanisms, the conception of the necessity of cellular surfaces upon which these reactions take place, and the energy of several crucial factors within the pathway, to achieve applicable and regulated hemostasis (7).

The coagulation cascade involves the activation of a series of clotting factors, which are proteins that are involved in blood clotting. Each clotting factor is a serine protease, an enzyme that speeds up the breakdown of another protein. The clotting factors are originally in an inactive form called zymogens. When placed with its glycoprotein co-factor, the clotting factor is actuated and is then capable to catalyze the next reaction. Coagulation consists of three pathways, the extrinsic, intrinsic, and common pathways, that interact together to form a stable blood clot. The extrinsic and intrinsic coagulation pathways both lead into the final common pathway by independently activating factor X (8)

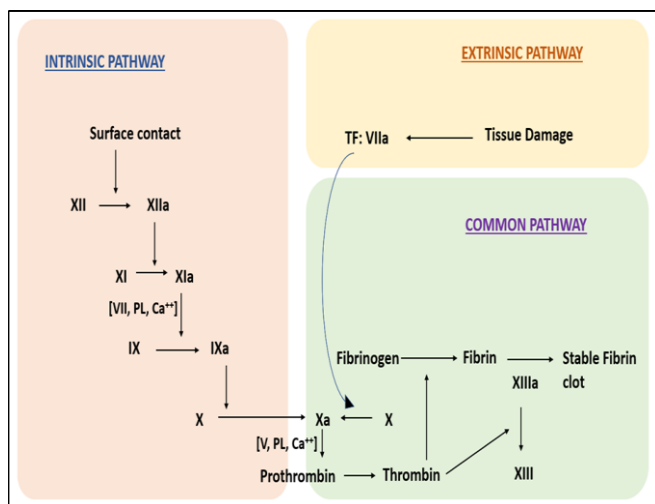


Figure 1: Blood Coagulation Cascade (XII Hageman factor, a serine protease; XI - Plasma thromboplastin, antecedent serine protease; IX Christmas factor, serine protease; VII Stable factor, serine protease; XIII - Fibrin stabilizing factor, a transglutaminase; PL- Platelet

membrane phospholipid; Ca<sup>++</sup> - Calcium ions; TF - Tissue Factor)

#### 3.1. Extrinsic pathway:

It is considered the first step in plasma-mediated hemostasis. It is actuated by TF III (Tissue Factor III), which is expressed in the subendothelial tissue. Under normal physiological conditions, normal vascular endothelium minimizes contact between TF and plasma procoagulants, but vascular insult disclosures TF which bind with factor VII and activates VIIa and calcium to promote the conversion of factor X to Xa (Figure 1) (9).

#### 3.2. Intrinsic Pathway:

The intrinsic pathway is initiated by factors that are present within the blood. By exposure to negatively charged particles and surfaces, FXII can be actuated and it serves as the central element of the contact system that includes PKK (prekallikrein) and HK (high molecular weight kinogen). Activation of the intrinsic pathway can be enhanced by the conduct of both PKK and HK. During the process of contact activation, originally generated FXIIa can activate PKK forming  $\alpha$ KK ( $\alpha$ -kallikrein) that can itself activate FXII initiation of a positive feedback loop. FXII also converts factor IX to IXa which combines with factor VIII and calcium ions on the platelet surface to form a factor X activating complex (Figure 1) (10).

#### 3.3. Common Pathway:

This pathway begins at factor X which is initiated to factor Xa. The process of actuating factor Xa is a complicated response. Tenase is the complex that cleaves factor X into factor Xa. Tenase has two forms: extrinsic, containing factor VII, factor III (tissue factor), and Ca<sup>2+</sup>, or intrinsic, made up of cofactor factor VIII, factor IXA, a phospholipid, and Ca<sup>2+</sup>. Once actuated to factor Xa, it goes on to actuate factor II (prothrombin) into factor IIa (thrombin). Also, factor Xa requires factor V as a cofactor to cleave prothrombin into thrombin. Factor IIa (thrombin) goes on to activate fibrinogen into fibrin. Thrombin also goes on to actuate other factors in the intrinsic pathway (factor XI) as well as cofactors V and VIII and factor XIII. Fibrin subunits come together to form fibrin strands, and factor XIII acts on fibrin strands

to form a fibrin mesh. This mesh helps to stabilize the platelet plug (Figure 1) (11).

Once the injured blood vessel has healed, the clot is no longer required, and the body initiates the process of clot dissolution or fibrinolysis. Plasmin is the main enzyme of the fibrinolytic system. It is synthesized in the liver as the proenzyme plasminogen and then out into circulation. Plasminogen is a glycoprotein and the native form (Glu-plasminogen) has glutamic acid at its N-terminal. Plasminogen cannot cleave fibrin, but has an affinity for fibrin and is thus combined into the clot. It is then transformed to plasmin by two distinct activators: Plasmin then functions as a serine protease. It cleaves fibrin to soluble fibrin degradation products. Plasmin stimulates further plasmin making by producing more active forms of t-PA and u-PA. Plasmin converts Glu-plasminogen to modified forms with lysine at the N-terminal (Lys-plasminogen). Lys-plasminogen is a more favorable substrate for plasminogen activators. Plasmin thereby has positive feedback on its product (12).

Understanding the coagulation cascade is needed for diagnosing and managing many bleeding and clotting disorders. Medical interventions, such as anticoagulant medications and clotting factors replacement treatments are designed to target specific stages in the cascade to restore the balance and avoid complications.

#### 4. NOVEL RAPID-RELEASE ANTICOAGULANT AGENTS:

Anticoagulant pharmacopeia was, up until the early 2000s, restricted to warfarin, heparin, and its derivatives, and aspirin. The limitations of these agents (inter-patient variability in response, the need for ongoing monitoring, thrombocytopenia, and the need for parenteral administration) have necessitated the development of newer agents. Presently, a new variety of drugs (Table 1), effective orally and targeting novel areas in the coagulation cascade, are in widespread use for conditions such as prophylaxis of thrombo-embolic phenomena in inherited and acquired conditions, atrial fibrillation, patients with mechanical heart valves and prophylaxis and treatment of DVT and pulmonary embolism (13)

**TABLE 1: NOVEL ANTI-COAGULANT DRUGS**

<b>Class of Drugs</b>	<b>Mode of Action</b>	<b>Examples</b>
<b>Anti-platelet agents</b>	P2Y12 receptor inhibition	Clopidogrel, Prasugrel and Ticagrelor
<b>Novel rapid release Anticoagulants</b>	Direct thrombin inhibition	Dabigatran
	Factor Xa inhibition	Rivaroxaban, Apixaban

##### 4.1. Anti-Platelet agents:

These agents act on the P2Y12 receptor, irreversibly blocking adenosine diphosphate activation of this receptor, therefore disrupting the downstream signal transduction, with a net result of decreased stability of platelet aggregation. The most commonly utilized agent, clopidogrel, is administered orally once daily as a prodrug, which is metabolized to an active compound through the liver's cytochrome P450 (CYP) system. Genetic polymorphisms (CYP 2C19)<sup>11</sup> have been implicated in the altered metabolism of clopidogrel, resulting in decreased effectiveness of the medication, with clinical consequences. Clopidogrel is used at a dose of 75 mg daily. Whereas several daily doses are required to achieve a steady state, a loading dose of at least 300 mg of clopidogrel produces a rapid onset of pharmacodynamic action. Prasugrel also has the same mode of action to that as Clopidogrel. Prasugrel has faster peak effectiveness and increased potency in comparison with clopidogrel (14,15).

##### 4.2. Novel rapid release Anticoagulants:

Novel rapid-release Anticoagulants are a group of medications that directly inhibit specific clotting factors in the coagulation cascade. They offer several advantages over traditional anticoagulants like warfarin,

including predictable pharmacokinetics, fewer drug interactions, and less need for routine monitoring. Dabigatran, rivaroxaban, and apixaban are novel oral anticoagulants that offer major advantages over current agents. They have a rapid onset and more predictable anticoagulant response that eliminates the need for monitoring (16). Dabigatran etexilate mesylate is a prodrug. After oral administration, non-specific plasma and hepatic esterases hydrolyze the complex into the active anticoagulant, dabigatran. Dabigatran is DTI that exerts its action through reversible, competitive required to the active site on thrombin. (Table 2) Likewise, dabigatran ultimately exerts an anti-platelet effect by reducing thrombin’s impact on promoting platelet activation and aggregation Dabigatran is removed through renal filtration with up to 80 % of the dose emitted unchanged in urine. Dabigatran’s mean terminal elimination half-life is extended in patients with severe renal dysfunction. There is no antidote existing to reverse or diminish dabigatran’s anticoagulant effect (17).

In 2019, the FDA approved rivaroxaban for hospitalized mature patients with an acute medical illness at threat for thromboembolic complications due to restricted mobility and other threat factors. Rivaroxaban was the

first orally dosed, direct Factor Xa inhibitor, a small-particles oxazolidinone derivative. It fixes directly and reversibly to Factor Xa via the S1 and S4 pockets. Metabolism of this medication occurs in the liver via oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 mechanism. Elimination occurs generally via urine 66% and partially via feces 28%. Rivaroxaban is administered orally with a half-life of 5 to 9 hours (maybe longer in older individuals [e.g., 11 to 13 hours]). The dose ranges from 2.5 mg two times daily to 20 mg once daily and does not need monitoring (Table 2) (18,19). Apixaban is a new oral anticoagulant (NOAC) approved by the US Food and Drug Administration (FDA) in 2012 for usage in patients with non-valvular atrial fibrillation to decrease the risk of stroke and blood clots. Later, in 2014, it was accepted to treat deep venous thrombosis (DVT) and pulmonary embolism (PE). Apixaban is an extremely selective direct factor Xa inhibitor, blocking the propagation phase of the coagulation cascade. It uses its effect on both free and clot-bound factor Xa. It has dose line pharmacokinetics up to 10mg dose. Its complete bioavailability is 50% and achieves the peak plasma concentration in 3 to 4 hrs (20).

**TABLE 2: CLINICAL PROFILE OF NOVEL ANTICOAGULANT AGENTS**

<b>Name of Drug</b>	<b>Dabigatran</b>	<b>Rivaroxaban</b>	<b>Apixaban</b>
<b>Mode of action</b>	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
<b>Prodrug</b>	Yes	No	No
<b>Absorption</b>	Rapid	Rapid	3-4 hrs
<b>Volume of distribution</b>	50-70 L	50 L	21 L
<b>Half-life</b>	12–17 hrs	5-9 hrs (young) 11-13 hrs (elderly)	12 hrs
<b>Bioavailability</b>	6 %	66%	50%
<b>Time to reach Plasma peak level</b>	0.5-2 hrs	2-4 hrs	1-4 hrs
<b>Protein binding</b>	35%	92-95%	87%
<b>Liver Metabolism</b>	No	Yes	Yes

<b>Renal excretion</b>	80%	35%	25%
<b>Doses</b>	75 mg, 110 mg, 150 mg	2.5 mg, 10 mg, 15 mg, 20 mg	2.5 mg, 5 mg
<b>Dosage form</b>	Capsule	Tablet	Tablet

## 5. INVESTIGATIONAL ANTICOAGULANTS: FUTURE THERAPIES:

Not unexpectedly various companies have decided to pull the plug on different anticoagulants in the pipeline later considering the crowded market and the strengthened competition in this field. At least 3 direct FXa inhibitors have been unobtainable at the Phase II stage: Darexaban maleate (Astellas Pharma), Letaxaban (Takeda), and Eribaxaban (Pfizer). However, others are carrying on the research and development based on the already evident drawbacks of the novel anticoagulants currently on the market (21). Betrixaban and LY517717 are agents in the pipeline that may fill the gap left by others in terms of anticoagulation in patients with renal failure and polypharmacy. Once more, betrixaban is the only oral agent in which a specific antidote is already being tested. Among others, BMS593214, BMS26208, and FIX ASOs are novel agents in initial experimental phases that have wide therapeutic windows and low bleeding tendencies. Various targets have multiple physiological roles several of which are still unknown. Thrombin and TF are examples of coagulation factors with many physiologic tasks. We will wait and see if inhibitors to these coagulation factors will show pleiotropic effects (22).

Aptamers are a class of structured nonbiological single-stranded nucleic acid macromolecules that can bind to protein targets with high affinity and specificity. NU172 is a through high-affinity antithrombin aptamer with a small duration of action in vivo. NU172 is managed by incessant infusion during cardiopulmonary bypass or other surgical procedures to maintain a state of anticoagulation with a rapid return to hemostasis once the infusion ceases. HD1-22 is a bivalent aptamer that binds to thrombin with high affinity. In adding, it has been presented that HD1-22 binds with a related affinity to prothrombin, resultant in the inhibition of prothrombin activation. The strong thrombin-inhibiting activity, together with the availability of a rapid-acting

antidote strategy, creates HD1-22 an interesting anticoagulant candidate, mainly for use in clinical situations where effective anticoagulation and rapid reversal of the anticoagulant effect are mandatory (23,24).

## 6. CONCLUSION:

Important interest has turned to finding attractive options for classical anticoagulants. Some new anticoagulants have formerly made it to the market after some significant results from large-scale trials, affecting the investigation of the agents in the pipeline. The probable fierce competition for a rather narrow market has had a different impact on the development of experimental anticoagulants: some have been discontinued; others are concentrating on a niche of patients not covered by the presently approved innovative anticoagulants. The efficacy of FXI inhibition in this setting suggests that feedback activation of FXI by thrombin is essential for thrombus growth and stabilization. Although most of the existing attention is concentrated on FXI inhibitors, by inhibiting the root cause of clotting on medical devices and extracorporeal circuits, FXII inhibitors may be better than FXI inhibitors for this suggestion. With a plethora of new agents under examination and a wide array of phase 2 trials ongoing, the clinical probability of FXI and FXII inhibitors should become clearer over the next few years.

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## 8. CONFLICTS OF INTEREST:

Authors have no conflicts of interest to declare.

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