Chapter

Pharmacological Review of Anticoagulants

Hobart Owen Ng Tsai

Abstract

The art and science of anticoagulation have never gotten more complicated than it has now. Newer anticoagulants have entered the market and have provided more options to the patients and healthcare professionals. This chapter will review the basic physiology of hemostasis, pharmacology of the anticoagulants, and how these medications are used in the clinical setting. The mechanism of action, pharmacokinetics and pharmacodynamics, clinical evidence of use and clinical pearls, laboratory monitoring in clinical practice, and adverse effects will be examined individually for each drug considered. This chapter will serve as a review for the practicing clinician and a thorough introduction for the beginning reader.

Keywords: anticoagulants, warfarin, heparin, low molecular weight heparin, enoxaparin, dabigatran, rivaroxaban, apixaban, edoxaban

1. Introduction

Anticoagulants are the mainstay of treatment for stroke and systemic embolism prevention in patients with atrial fibrillation (AF) or flutter. They can be used as well for prevention and treatment of venous thromboembolism (VTE) and treatment of thrombus formation in other places. This class of medications must be used carefully because using them incorrectly can lead to either ineffective prevention of clot formation or bleeding. It is vital for the clinician who uses any of these anticoagulants to have a basic understanding of their pharmacology and evidence of use.

2. The coagulation cascade

The coagulation system is composed of two separate pathways that convene on a single pathway. The two pathways are extrinsic pathway and intrinsic pathway. Injury to the endothelial system exposes *tissue factor* out in the bloodstream. The extrinsic pathway begins with factor VII. Circulating factor VII in the bloodstream will then get activated to factor VIIa when they come into contact with tissue factor. Factor VIIa then converts factors X and IX to factor Xa and IXa, respectively. The presence of factor IXa, together with factor VIIIa, work to produce more factor Xa. Factor Xa and factor Va then activate factor II (prothrombin) to factor IIa (thrombin). Factor IIa then converts fibrinogen to fibrin [1, 2].

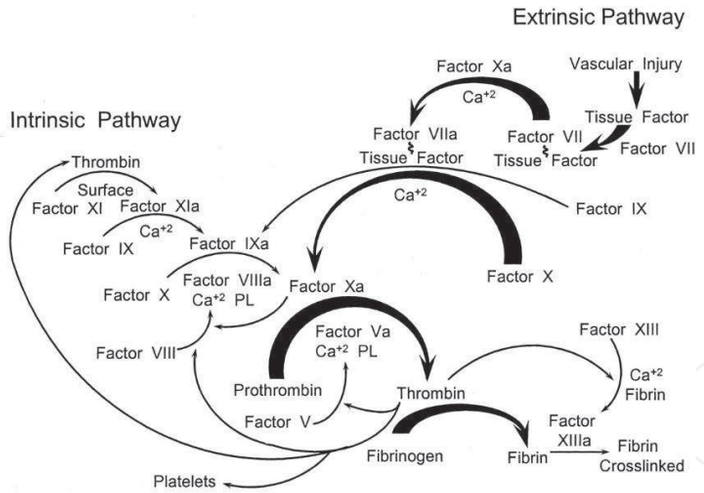

Figure 1.
Coagulation cascade showing the intrinsic, extrinsic, and common pathway. Reprint with permission from [30].

The result of this cascade is the production of fibrin molecules that bind to GPIIb/IIIa receptors on platelets and hold them together to form a platelet plug. The extrinsic pathway is what protects humans when bleeding occurs involving trauma to the vasculature or when the blood comes in contact with extravascular tissues [1, 2].

The intrinsic pathway gets activated upon trauma to the blood or when the blood gets exposed to collagen found on damaged blood vessels. At the beginning of the intrinsic pathway activation, exposure of factor XII to collagen, for example, stimulates a configurational change in factor XII to become factor XIIa. Together the help of high molecular weight kininogen and prekallikrein, factor XIIa enzymatically activates factor XI to XIa. Factor XIa in turn activates factor IX to IXa. Factor IXa then works with factor VIIIa to convert factor X to Xa. Factor Xa then converts factor II to factor IIa, which in turn activates fibrinogen to fibrin [1, 2].

The extrinsic pathway and intrinsic pathway converge as the common pathway when factor X gets converted to factor Xa [1, 2] (see **Figure 1**).

3. Basic and clinical pharmacology of the anticoagulants

3.1 Unfractionated heparin (UFH)

3.1.1 Mechanism of action

Unfractionated heparin is a long string of glycosaminoglycan molecules that can range from 3000 to 30,000 Daltons. UFH with its specific pentasaccharide sequence binds to antithrombin III and catalyzes its efficiency in inhibiting factor Xa and IIa in a ratio of 1: 1. However, not all heparin molecules given are active; only about a third of the heparin molecules in a solution contain the required pentasaccharide sequence [1–3].

3.1.2 ADME

Heparin is not absorbed orally and is given either subcutaneously (SQ) or intravenously (IV). Heparin is highly protein bound and is cleared in the bloodstream by endothelial cells and macrophages. The half-life of heparin increases as the dose increases; it can vary from 1 hour at a dose of 100 units/kg to 2.5 h for 400 units/kg to 5 h for 800 units/kg. In general, the clinical effect of IV UFH dissipates 4–6 hours after stopping the infusion [1–3].

3.1.3 Clinical use

UFH can be either given SQ or IV as mentioned above. However, SQ administration of UFH has erratic bioavailability. Hence, SQ is not a preferred route if a patient requires treatment dose of UFH. Clinical studies have also shown a higher rate of treatment failure rate with SQ compared to IV heparin [3, 4]. For VTE prophylaxis, SQ administration of UFH would suffice. The usual dose is 5000 units q8-12h [4].

Initial dosing of IV UFH depends on the indication. Besides VTE treatment, IV UFH can also be used for patients with acute coronary syndrome, as a bridging agent for patients with atrial fibrillation, mechanical valves, etc. The dose of IV UFH could be either a fixed dose or a weight-based dose. A study by Raschke et al. [3] compared fixed dose vs. weight-based dose of IV heparin in patients with venous and arterial thromboembolism. In that study, significantly more patients (97%) in the weight-based dosing group achieved an Activated Partial Thromboplastin Time (aPTT) > 1.5x the baseline within 24 hours vs. the fixed dose group (77%), leading the authors to conclude that weight-based dosing is superior to fixed dose IV heparin [3, 4]. The 2016 Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism and the 2012 American College of Chest Physicians (ACCP) Guidelines on Antithrombotic Therapy and Prevention of Thrombosis Supplement on Parenteral Anticoagulants list both fixed dose and weight-based dose for IV heparin [3].

3.1.4 Monitoring

There are two ways of monitoring the heparin activity in the body. These are the aPTT and Activated Clotting Time (ACT). The usual aPTT target for a therapeutic effect of heparin is 1.5–2x the baseline, which is equivalent to an anti-factor Xa activity of 0.3–0.7 units/ml [1, 3, 4]. The target aPTT varies based on what reagent is used to measure it. Thus, the clinician should check with the institution's laboratory for the target aPTT for patients receiving IV heparin. When using IV UFH for treating heparin or for bridging purposes, the aPTT is used. Another lab test used to monitor heparin is the ACT. ACT is available as a point-of-care test and is used when patients are receiving high doses of heparin. ACT can be seen being used in instances such as during cardiopulmonary bypass surgery and percutaneous coronary intervention. The target ACT varies based on the indication. ACT is reported in seconds and denotes how long it takes for the blood to clot.

3.1.5 Adverse effects

Patients on heparin also need close monitoring of platelet counts. Thrombocytopenia could be a consequence of heparin infusion and severe reaction called heparin-induced thrombocytopenia (HIT) may occur [1–5]. There are two kinds of heparin-induced thrombocytopenia: HIT type 1 and HIT type 2. HIT Type 1, which may also be called heparin-associated thrombocytopenia, is a benign, transient drop in platelets counts usually within the first 2–4 days after initiation of heparin infusion. Platelet counts rarely go below 100,000 [3–6]. The mechanism behind HIT type 1 is unknown but may involve dilutional effect or decreased platelet production associated with the acute illness [6].

The other more serious reaction, which is HIT type 2, involves antibody formation against heparin-platelet factor 4 complex. Heparin may bind to platelet factor-4 (PF 4), which is a cationic protein product of platelets that binds heparin and prevents heparin from binding with antithrombin. The heparin-PF4 complex is highly antigenic and induces the formation of IgG molecules against it. The IgG

molecule-heparin-PF 4 complex binds to platelets and activates it, further releasing more PF4. The activated platelets with bound IgG-heparin-PF 4 complex also produce prothrombotic molecules that may cause thrombosis [3–6]. HIT type 2 can cause both arterial and venous thromboses, although venous thrombosis is more common. The activated platelets with bound IgG-heparin-PF 4 get removed from the body quickly, hence causing thrombocytopenia [6].

For the treatment of HIT, the American Society of Hematology 2018 guidelines for the management of venous thromboembolism: heparin-induced thrombocytopenia suggests use of non-heparin options such as argatroban (a direct thrombin inhibitor), fondaparinux (an ant-factor Xa inhibitor), or DOAC (specifically rivaroxaban due to most experience at a dose of 15 mg twice a day for 3 weeks if thrombosis is present, or 15 mg twice a day until the platelet counts have recovered to $\geq 150 \times 10^9$/L, then followed by 20 mg daily if there is an indication for continued anticoagulation) [7].

3.1.6 Reversibility

In the event of bleeding, heparin can be reversed with protamine sulfate. Protamine is a cationic protein from fish sperm that can bind to heparin (which is anionic) and neutralize heparin immediately [1]. 1 mg of protamine reverses approximately 100 units of heparin, with a maximum dose of 50 mg at a time. For patients who are receiving continuous IV heparin infusion, only the last 2–3 hours dose of heparin given needs to be taken into when calculating the dose for protamine. For patients who received SQ heparin, protamine has to be given as a prolonged infusion. aPTT can be used to monitor the efficacy of protamine. One needs to be careful when giving protamine as protamine itself is prothrombotic [3, 5].

3.2 Low molecular weight heparin (LMWH)

There are various preparations of LMWH available in the market. Some examples are enoxaparin, dalteparin, tinzaparin, etc. The rest of the discussion in this section will focus on enoxaparin.

3.2.1 Mechanism of action

LMWH's are shorter molecular version of UFH. They are only a third of the size of UFH. Same as UFH, LMWH bind to antithrombin and catalyzes its efficiency. But unlike UFH, the combination LMWH-antithrombin is only capable of deactivating factor Xa and very little factor IIa [1, 3, 5].

3.2.2 ADME

Enoxaparin can be either given SQ or IV depending on the indication. It is predominantly cleared renally hence dose adjustment is needed in patients with renal impairment (when Cockcroft-Gault calculated creatinine clearance is <30 ml/min). It has a half-life of 3–6 hours and reaches peak concentration 3–5 hours after SQ injection [1, 3–5].

3.2.3 Clinical use

Enoxaparin can be given as a once a day or twice daily dosing. Once daily dosing is not advisable in certain populations such as obese patients because the effect of enoxaparin would not last for 24 hours [4]. The dose varies based on the indication.

It can be used for VTE treatment and prophylaxis, arterial thromboses, bridging agent for patients with atrial fibrillation, mechanical valves, etc. It is easier to use in practice than IV heparin if full treatment dose is needed as there is no laboratory monitoring required.

3.2.4 Monitoring

The activity of LMWH is more predictable than UFH. Hence, monitoring is not needed when LMWH is given. However, its anticoagulation effects may be determined by checking the anti-factor Xa activity. Several guidelines including the 2016 Guidelines for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism and the 2018 American Society of Hematology guidelines for the management of venous thromboembolism: optimal management of anticoagulation therapy do not suggest routing monitoring of anti-factor Xa activity due to uncertainties regarding its clinical utility and its cost-effectiveness [4, 8]. Additionally, there is currently no standardized method of adjusting the dose of enoxaparin based on anti-factor Xa activity [8], except for pediatric patients.

3.2.5 Adverse effects

As with any anticoagulants, bleeding is a major concern for patients receiving LMWH. Hematoma surrounding the injection site may also appear if patients rub on the injection site. In terms of major side effects, LMWH has a lower incidence of HIT type 2 compared to UFH. However, patients who have a history of HIT type 2 should best avoid LMWH if antibodies are still present.

3.2.6 Reversibility

In cases of bleeding, enoxaparin may be partially reversed with protamine if it was given within 8 hours. Protamine can only reverse 65–70% of enoxaparin at most [5]. Protamine neutralizes anti factor IIa bound to the LMWH-antithrombin complex completely but only variably to factor Xa bound to the LMWH-antithrombin complex [3, 5].

3.3 Warfarin

3.3.1 Mechanism of action

Warfarin has been used around since the early 1930s but it was not used clinically until the 1950s. Warfarin is the oldest oral anticoagulant around. Warfarin inhibits vitamin K epoxide reductase (VKOR) that leads to the decrease in production of factors II, VII, IX, and X. These factors depend on vitamin K for carboxylation in order to become active. In addition to these four factors, vitamin K also decrease the production of protein C and S, which also depend on carboxylation to become active [5, 9, 10] (See **Figure 2**).

3.3.2 ADME

Warfarin is present as a racemic mixture of two enantiomers, S-warfarin and R-warfarin. S warfarin is about three times more potent than R-warfarin. The S-warfarin is metabolized by CYP 2C9, whereas R-warfarin is metabolized by CYP 1A1, 1A2, and 3A4. Hence, any metabolic interactions involving these enzymes, especially 2C9, would affect the clinical efficacy and safety of warfarin significantly [9, 10].

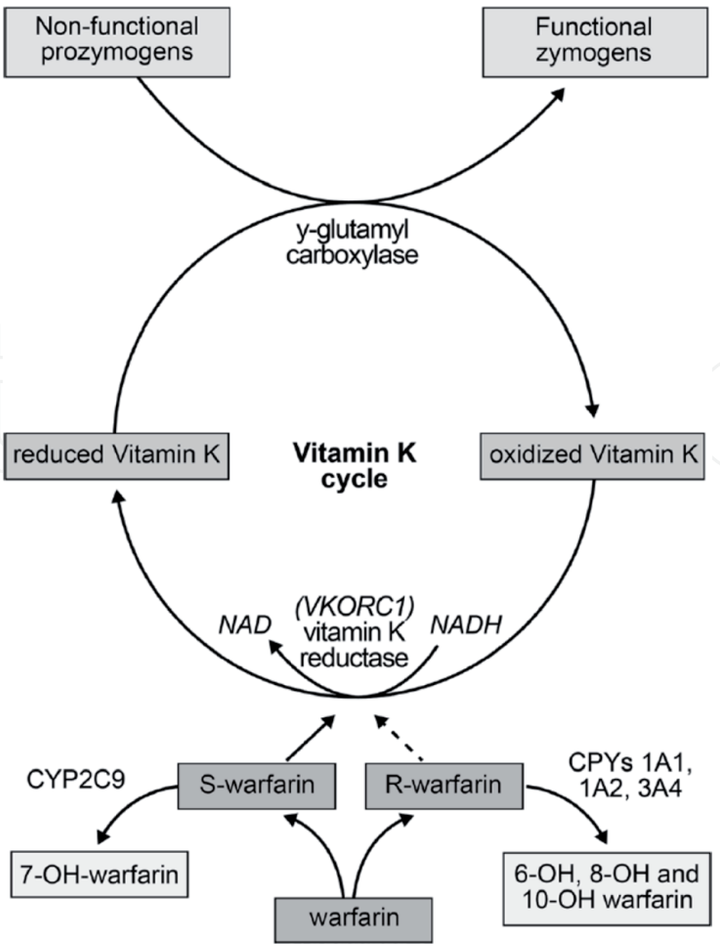

Figure 2.
Vitamin K cycle showing where warfarin acts and the enzymes that metabolize each enantiomer. Reprint with permission from [16].

Warfarin is readily absorbed and is almost 100% bioavailable. It has similar volume of distribution as albumin (0.11–0.18 L/kg) and is metabolized by the liver. It is a highly protein-bound drug (>98%) and has a half-life of 36–42 hours (R-warfarin 45 hours, S-warfarin 29 hours). Advances in genetics have elucidated that polymorphisms in the gene that encode VKOR (VKORC1) and CYP2C9 enzyme dramatically affect the dose requirement of a patient [9, 10]. Dose calculators based on the genetic polymorphisms of these two enzymes exist and some of them are available online. How accurate they are is still a question. It should be noted that each patient's warfarin dose requirement does not rely only on genes. Genetics can only account for 30–50% of each patient's dose requirement. Diet, medical condition, and drugs (including supplements) have a role to play as well in determining how much warfarin one needs.

3.3.3 Clinical use

Clinically, warfarin is used for various conditions such as prevention of stroke and systemic embolism in patients with atrial fibrillation or atrial flutter, treatment and prevention of venous thromboembolism, cerebral venous thrombosis, etc. Clinicians have the most experience with warfarin and warfarin has a wider range of indications than the direct-acting oral anticoagulants (DOACs).

There are several published sample algorithms on initiation and dosing of warfarin. Several institutions also have in-house protocols and dose adjustment guidelines

for patients on warfarin. However, due to the multiple factors that can affect warfarin, the protocols may not be necessarily apt to follow. Picking the correct warfarin dose to start patients on and adjusting of warfarin doses subsequently is usually not as simple clinically. Choosing what dose to start patients on require a thorough review of that patient's medical condition, weighing thrombotic risk against bleeding risk, and having considerable experience in managing patients on warfarin.

3.3.4 Monitoring

Upon initiation, it takes about 2–3 days usually to see an increase on the international normalized ratio (INR) and about 5–7 days to see the full effect of warfarin on INR (corresponding approximately to the amount of time it takes for factor IIa to be depleted). A usual starting dose is 5 mg. Smaller doses such as 2 or 3 mg may be given in patients who are elderly or who are expected to have lesser dose requirements (e.g., CKD patients, patients with lighter body weight, presence of drugs that could raise the INR). Due to the delayed effect of warfarin, it may be overlapped with some faster-acting anticoagulants such as heparin, enoxaparin, or DOACs if immediate anticoagulation is needed.

INR is affected mainly by three factors, namely, drugs including natural supplements, patient's medical condition, and diet and lifestyle. These factors need to be considered when dosing a patient and when an explanation for a subtherapeutic or supratherapeutic INR is being sought.

3.3.5 Adverse effects

The most important adverse effect of warfarin is bleeding. Bleeding risk increases when the INR is >4. The risk of bleed is generally <3% annually if INR is kept between 2 and 3 [1]. If bleeding occurs and warfarin has to be reversed, patients should be given IV Vitamin K and Prothrombin Complex Concentrate (PCC). Fresh frozen plasma (FFP) may also be used as an alternative to PCC but it carries some disadvantages such as delayed administration due to thawing, and infusion of large volumes of fluid [9, 10].

Other notable adverse effects of warfarin include skin necrosis, which occurs 3–8 days after initiation of warfarin [5]. Skin lesions appear due to thrombi in the capillaries and veins. They are usually found in areas rich with fatty tissue such as the breast, abdomen, and extremities. Skin lesion may occur in two types of patients. First is in patients treated with warfarin who have active HIT. Second is in patients who have protein S and/or C deficiency. The exact pathophysiology is not known but may be due to the abrupt drop in protein S and/or C before factors IIa, VIIa, IXa, and Xa drops sufficiently that cause the scale to tip over to the prothrombotic side. In such events, warfarin may be started slowly with concurrent heparin. Stop heparin when INR has reached the therapeutic range [10, 11].

Another adverse effect is purple toe syndrome that occurs 3–10 weeks after initiation of warfarin. The exact pathophysiology is not known but may be due to cholesterol deposits embolizing from the arterioles when the patient develops microbleeds in the atherosclerotic arterioles. The cholesterol emboli could occlude the arteries downstream. It can be reversed when it is discovered early and when warfarin is discontinued. Otherwise, it may lead to gangrene necessitating amputation [5, 11–13].

Other less serious adverse effects include osteoporosis, alopecia, etc. [5, 10]. Warfarin has also been associated with acute kidney injury termed warfarin-related nephropathy.

3.4 Dabigatran

3.4.1 Mechanism of action

Dabigatran is a competitive direct thrombin (factor IIa) inhibitor. It binds to both free and clot-bound thrombin [1, 5, 10, 14]. This is in contrast to heparin which can only bind to free thrombin. As a result, fibrinogen cannot be converted to fibrin. Parenteral direct factor IIa inhibitors have been available in the market before the introduction of dabigatran. Some examples are argatroban, bivalirudin, etc.

3.4.2 ADME

Dabigatran has low oral bioavailability of only 3–7% and is a substrate of P-glycoprotein (P-gp). It comes as a prodrug called dabigatran etexilate that gets hydrolyzed to dabigatran. It reaches its peak concentration about 2 hours after ingestion. Dabigatran is 35% bound to protein and is highly (80%) renally excreted. Dabigatran is 50–60% dialyzable, an important point to take note of especially in cases of toxicity. It has a half-life of 12–17 hours and is dosed twice a day [15, 16] (see **Table 1**).

3.4.3 Clinical use

Dabigatran was the first medication under the new class of medications called novel oral anticoagulants (NOAC) or Direct-acting Oral Anticoagulant (DOAC). Dabigatran is approved for stroke and systemic embolism (SSE) prevention for patients with non-valvular atrial fibrillation, treatment of VTE, and VTE prophylaxis post-hip replacement.

Dabigatran is available in three doses: 75, 110, and 150 mg. Some countries, in the United States, for example, only have 75 and 150 mg. As with the other NOACs, dabigatran can be given without the need for any monitoring of anticoagulation intensity. However, renal function must be monitored carefully as dabigatran is highly renally cleared (80% of the drug).

In terms of efficacy as compared to warfarin for SSE prevention, dabigatran 110 mg has similar efficacy to warfarin titrated to an INR of 2–3. Dabigatran

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target(s)	IIa, VIIa, IXa, Xa	IIa	Xa	Xa	Xa
Prodrug	No	Yes	No	No	No
Bioavailability (%)	80–100	6.5 (pH dependent)	80	50	62
Volume of distribution (L)	10	50–70	50	23	>300
Peak effect	4–5 days	1.5–3 h	2–4 h	1–3 h	1–2 h
Half-life[a]	40 h	12–17 h	5–9 h	9–14 h	10–14 h
Renal elimination	None	80 %	33 %	25 %	35–50 %
Protein binding (%)	>99	35	90	87	55
Dialyzable	No	Yes	No	No	Possible
Interactions	Many	P-gp	3A4, P-gp	3A4, P-gp	P-gp
Coagulation monitoring	Yes	No	No	No	No
Antidote	Vitamin K	Idarucizumab	No	No	No
Lab measure	INR	aPTT	PT	Anti-Xa	Anti-Xa
		TT, ECT	Anti-Xa		

[a] Normal renal function

P-gp P glycoprotein, *3A4* cytochrome P450 3A4, *INR* international normalized ratio, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *TT* thrombin time, *dTT* dilute thrombin time, *ECT* ecarin clotting time

Table 1.
Pharmacokinetic and pharmacodynamic properties of the different oral anticoagulants. Reprint with permission from [16].

150 mg, on the other hand, is superior to warfarin titrated to an INR of 2–3. The superiority is mainly driven by a decrease in stroke events among patients taking dabigatran 150 mg. This is based on the RE-LY (Dabigatran versus Warfarin in Patients with Atrial Fibrillation) trial that led to the approval of dabigatran. In terms of bleeding risk, dabigatran 110 mg has lower overall major bleeding risk, similar gastrointestinal (GI) bleeding risk, and lower intracranial hemorrhage (ICH) compared to warfarin. With regards to dabigatran 150 mg vs. warfarin, dabigatran 150 mg has a similar overall bleeding risk, higher rates of GI bleed, and similar ICH risk compared to warfarin. These have to be taken into consideration when choosing which DOAC is more suitable for a patient [17] (see **Table 2**).

In terms of VTE treatment, dabigatran is not inferior to warfarin in terms of efficacy and safety based on the RE-COVER and RE-COVER II studies [17] (see **Table 3**). One caveat in its use for VTE treatment is that it requires a parenteral lead-in of at least 5 days with UFH or LMWH based on how it was carried out in the studies [19].

3.4.4 Monitoring

No pharmacodynamic monitoring is needed for any of the DOACs including dabigatran. Dabigatran has little effect on prothrombin time (PT) and INR. With regards to the activated partial thromboplastin time (aPTT), a normal aPTT does not exclude the presence of dabigatran. More sensitive tests for dabigatran are Thrombin Time (TT), Ecarin Clotting Time (ECT) and Diluted Thrombin Time (dTT) [20, 21] (see **Table 1**).

3.4.5 Adverse effects

Dabigatran, being a blood thinner, has bleeding as its main side effect. Careful consideration of the bleeding risk factors of the patients needs to be done prior to prescribing dabigatran 150 mg twice daily. History of prior GI bleeding, peptic ulcer disease, colonic angiodysplasia, and other pathologies that predispose a patient to GI bleeding are some practical issues that the prescriber needs to be mindful of. Dyspepsia, abdominal pain, and abdominal discomfort are other side effects that occurred more frequently compared to warfarin [5, 16]. The RE-LY trial has raised concerns about increased myocardial infarction (MI) risk among patients taking dabigatran but the US Food and Drug Administration (FDA) has not found an increase MI risk among patients taking dabigatran in its observational study [22]. Because dabigatran is highly renally cleared, the serum creatinine and creatinine clearance has to be regularly monitored.

3.5 Rivaroxaban

3.5.1 Mechanism of action

Rivaroxaban is the first direct factor Xa inhibitor [16]. It therefore prevents the formation of factor II to factor IIa. It acts one step higher on the coagulation cascade compared to dabigatran. Rivaroxaban is able to bind to both free and clot-bound factor Xa due to its small size (436 g/mol) [10].

3.5.2 ADME

Rivaroxaban has good bioavailability of 66% when taken without food. The bioavailability dramatically increases when it is taken with food to 80–100%.

Characteristics	RE-LY (dabigatran)	ROCKET AF (rivaroxaban)	ARISTOTLE (apixaban)	ENGAGE AF (edoxaban)
Design	Randomized, open label[a]	Randomized, DB/DD	Randomized, DB/DD	Randomized, DB/DD
Dosing	150 mg, 110 mg twice daily	20 mg daily	5 mg twice daily	60 mg, 30 mg daily
Dose adjustment/criteria	No	If CrCl 30–49 mL/min then 15 mg	If ≥2 factors: age ≥80 years, body weight <60 kg, creat ≥1.5 mg/dL then 2.5 mg	If CrCl 30–50 mL/min or weight ≤60 kg or potent P-gp inhibitor[b] then 50 % dose
CrCl exclusion	30 mL/min	30 mL/min	25 mL/min	30 mL/min
$CHADS_2$ score inclusion criteria	≥1	≥2	≥1	≥2
Primary efficacy endpoint	Stroke/TIA and SE	Stroke/TIA and SE	Stroke/TIA and SE	Stroke/TIA and SE
Primary safety endpoint	Major bleeding	Major plus CRNM bleeding	Major bleeding	Major bleeding
Trial size	18,113	14,264	18,201	21,105
Age (years), median (IQR)	72±9[c]	73 (65–78)	70 (63–76)	72 (64–78)
$CHADS_2$ (mean)	2.1	3.5	2.1	2.8
$CHADS_2$ ≥3 (%)	32	87	30	53
Heart failure	32	62	35	57
Stroke/TIA or SE	20[d]	55	19	28
Median follow-up (years)	2.0	1.9	1.8	2.8
Early discontinuation				
DOAC (%)	20.7/21.2	35.4	25.3	33.0/34.3
VKA (%)	16.6	34.6	27.5	34.4

CRNM clinically relevant non-major bleeding, *DB/DD* double blind, double dummy, *IQR* interquartile range, *DOAC* direct oral anticoagulant, *SE* systemic embolism, *TIA* transient ischemic attack, *VKA* vitamin K antagonist, *CrCl* creatinine clearance

[a] Patients were unblended with respect to dabigatran or warfarin assignment; however, all investigators, coordinating center members, the steering committee, the event adjudication committee, and the sponsor were blinded during event ascertainment and analyses

[b] Strong P-gp inhibitors such as dronedarone, quinidine, or verapamil

[c] Mean±SD

[d] No data on SE

DOAC vs VKA HR (95 % CI)	RE-LY[a] (dabigatran) 110 mg 150 mg	ROCKET AF (rivaroxaban) 20 mg	ARISTOTLE (apixaban) 5 mg	ENGAGE AF-TIMI 48 (edoxaban) 30 mg 60 mg
Ischemic stroke	1.11 (0.89–1.40)[a]	0.94 (0.75–1.17)	0.92 (0.74–1.13)	***1.41 (1.19–1.67) p < 0.001***
	0.76 (0.60–0.98)[a] p = 0.03			1.00 (0.83–1.19)
Systemic embolism	Not reported	**0.23 (0.09–0.61) p = 0.003**	0.87 (0.44–1.75)	1.24 (0.72–2.15)
				0.65 (0.34–1.24)
Hemorrhagic stroke	**0.31 (0.17–0.56) p < .0001**	**0.59 (0.37–0.93 p = 0.024)**	**0.51 (0.35–0.75) p < 0.001**	**0.33 (0.22–0.50) p < 0.001**
	0.26 (0.14–0.49 p < 0.001			**0.54 (0.38–0.77) p < 0.001**
Major bleed	**0.80 (0.69–0.93) p = 0.003**	1.04 (0.90–1.20)	**0.69 (0.60–0.80) p < 0.001**	**0.47 (0.41–0.55) p < 0.001**
	0.93 (0.81–1.07) p = 0.3			**0.80 (0.71–0.91) p < 0.001**
Intracranial bleed	**0.31 (0.20–0.47) p < 0.001**	**0.67 (0.47–0.93) p = 0.02**	**0.42 (0.30–0.58) p < 0.001**	**0.30 (0.21–0.43) p < 0.001**
	0.40 (0.27–0.60) p < 0.001			**0.47 (0.34–0.63) p < 0.001**
Gastrointestinal bleed	1.10 (0.86–1.41)	***3.2 vs 2.2[b] p < 0.001***	0.89 (0.70–1.15)	**0.67 (0.53–0.83) p < 0.001**
	1.50 (1.19–1.89) p < 0.001			***1.23 (1.02–1.50) p = 0.03***
All-cause mortality	0.91 (0.80–1.03)	0.85 (0.70–1.02)	**0.89 (0.80–0.98) p = 0.047**	**0.87 (0.79–0.96) p = 0.006**
	0.88 (0.77–1.00) p = 0.051			0.92 (0.83–1.01)
Cardiovascular mortality	0.90 (0.77–1.06)[a]	0.89 (0.73–1.10)	0.89 (0.76–1.04)	**0.85 (0.76–0.96) p = 0.008**
	0.85 (0.72–0.99)[a] p = 0.04			**0.86 (0.77–0.97) p = 0.013**

Bold font indicates significantly better result of DOAC in relation to warfarin. Bold and italic font indicates significantly worse result of DOAC compared to warfarin

[a] RE-LY reported relative risk instead of hazard ratio (HR); ischemic or uncertain stroke instead ischemic stroke, and vascular mortality instead cardiovascular mortality

[b] Incidence/year (%), HR not reported

Table 2.
Characteristics, efficacy, and safety data of warfarin vs. DOACs for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation. Adapted from [31] under Creative Commons (CC BY) Attribution 4.0 International License.

Rivaroxaban reaches its peak concentration about 2–4 hours after ingestion. Rivaroxaban is highly protein bound at 95%. Two-thirds of the drug is degraded by the liver via CYP3A4 and CYP3A5, and CYP2J2 to a lesser extent, half of which is then excreted renally and the other half is excreted by the hepato-biliary route into the feces. The remaining one-third of the drug is excreted renally. Rivaroxaban is a P-gp substrate both at the gut and at the kidney, hence

Trial	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER	RE-COVER II	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Year	2009	2014	2010	2012	2013	2013
Design	Double-blind	Double-blind	Open-label	Open-label	Double-blind	Double-blind
# of patients	2539	2589	3449	4832	5395	8292
LMHW/ heparin bridge	Yes	Yes	No	No	No	Yes
Treatment protocol	Dabigatran 150 mg BID	Dabigatran 150 mg BID	Rivaroxaban 15 mg BID for 3 weeks; then 20 mg daily	Rivaroxaban 15 mg BID for 3 weeks; then 20 mg daily	Apixaban 10 mg BID for 7 days; then 5 mg BID	Edoxaban 60 mg daily; or 30 mg daily for patients w/CrCl 30–50 ml/min, weight ≤ 60 kg, or receiving P-glycoprotein inhibitors
Duration of therapy (months)	6	6	3, 6, or 12	3, 6, or 12	6	≤ 12
Primary efficacy outcome	Recurrent VTE and related death	Recurrent VTE and related death	Recurrent VTE	Recurrent VTE	Recurrent VTE and related death	Recurrent VTE and related death
Event rate of primary efficacy outcome: NOAC vs. VKA	2.4% vs. 2.1%	2.3% vs. 2.2%	2.1% vs. 3.0%	2.1% vs. 1.8%	2.3% vs. 2.7%	3.2% vs. 3.5%
Hazard ratio (HR), 95% confidence interval (CI)	1.10 (0.65–1.84) *P*<0.001	1.08 (0.64–1.80) *P*<0.001	0.68 (0.44–1.04) *P*<0.001	1.12 (0.75–1.68) *P* = 0.003	0.84 (0.60–1.18) *P*<0.001	0.89 (0.70–1.13) *P*<0.001
Primary safety outcome	Major bleed	Major bleed	Major or CRNM bleed	Major or CRNM bleed	Major bleed	Major or CRNM bleed
Event rate of primary safety outcome: NOAC vs. VKA	1.6% vs. 1.9%	1.2% vs. 1.7%	8.1% vs. 8.1%	10.3% vs. 11.4%	0.6% vs. 1.8%	8.5% vs. 10.3%
HR, 95% CI	0.82 (0.45–1.48)	0.69 (0.36–1.32)	0.97 (0.76–1.22) *P* = 0.77	0.90 (0.76–1.07) *P* = 0.23	0.31 (0.17–0.55) *P*<0.001	0.81 (0.71–0.94) *P* = 0.004

BID twice daily dosing, *CrCl* creatinine clearance, *CRNM* clinically relevant nonmajor, *DVT* deep vein thrombosis, *LMWH* low molecular weight heparin, *NOAC* non vitamin K oral anticoagulant, *PE* pulmonary embolism, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

Table 3.
Efficacy and safety data of DOACs venous thromboembolism treatment. Adapted from [18] under Creative Commons (CC BY) Attribution 4.0 International License.

drug–drug interaction between rivaroxaban and P-gp substrates, inhibitors, or inducers must be taken note of. The half-life of rivaroxaban is about 5–9 hours for the younger patients. It has a longer half-life of 11–13 hours among the elderly [15, 16] (see **Table 1**).

3.5.3 Clinical use

Rivaroxaban comes in various strengths of 2.5, 10, 15, and 20 mg tablets. It is approved for stroke and systemic embolism prevention in patients with non-valvular AF, VTE treatment and prophylaxis including patients who had Total Knee Replacement (TKR) and Total Hip Replacement (THR), and for cardiovascular risk reduction among patients with Coronary Artery Disease (CAD) or Peripheral Artery Disease (PAD) in the United States.

For SSE prevention in patients with non-valvular AF, rivaroxaban has demonstrated non-inferiority both in efficacy and safety compared to warfarin. Careful examination of the data from the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) trial shows that rivaroxaban has higher GI bleeding rates but lower ICH rates compared to warfarin [23] (see **Table 2**).

For VTE treatment, rivaroxaban is non-inferior as well compared to warfarin (see **Table 3**). However, the initial treatment dose is 15 mg twice daily × 3 weeks followed by 20 mg daily [18]. The reason for the twice daily dosing is likely due to the need for a higher concentration for clot resolution and prevention of further propagation, knowing that the risk of VTE occurrence is highest during the first 3–4 weeks [24].

At a dose of 2.5 mg twice daily in combination with aspirin and either clopidogrel or ticlopidine, rivaroxaban has shown small 16% relative risk reduction, or 1.6% absolute risk reduction (NNT = 63) for death due to cardiovascular causes, MI, or stroke. This is at the backdrop of higher bleeding events (NNH = 83 for TIMI major bleeding events not associated with CABG) [25]. Patients subjected to rivaroxaban 2.5 mg twice daily need to be carefully selected.

3.5.4 Monitoring

No routine laboratory monitoring is needed for rivaroxaban for its pharmacodynamic effect. Rivaroxaban may affect PT/INR depending on the reagent used; elevated PT/INR may signal the presence of the drug but rivaroxaban cannot be excluded even if the PT/INR is normal [15, 20, 21]. Rivaroxaban may affect aPTT but less so compared to PT/INR. The best test to measure for the effect of the drug is via anti-factor Xa assay [20, 21], which is not routinely available in most hospital laboratories. Patient's serum creatinine and creatinine clearance should be periodically monitored to see if dose adjustment might be needed.

3.5.5 Adverse effects

Bleeding is the adverse effect of utmost concern among patients started on rivaroxaban. Patients with history of GI bleeding should select other oral anticoagulants besides rivaroxaban due to its higher GI bleed risk when studied against warfarin.

3.6 Apixaban

3.6.1 Mechanism of action

Similar to rivaroxaban, apixaban is also a direct factor Xa inhibitor [16, 26]. It thus inhibits one step higher on the coagulation cascade compared to dabigatran. It binds to both free and clot-bound factor Xa.

3.6.2 ADME

Apixaban has a bioavailability of 50% and is an active drug itself. It is also a substrate of P-gp. It reaches peak concentration 2–4 hours after ingestion. It is

highly protein bound as well at 87%. Apixaban is cleared both via renal and non-renal pathway. Fifty percent of the drug is excreted into the feces unchanged, 27% is also excreted in the urine unchanged. The remaining (~25%) undergoes metabolism by CYP3A4 and by other minor CYP enzymes such as CYP1A2, 2J2, 2C8, 2C9, and 2C19. It has a half-life of 9–14 hours [15, 16, 19, 26] (see **Table 1**).

3.6.3 Clinical use

Apixaban is approved in the US for SSE in patients with non-valvular AF, VTE treatment and prophylaxis, including patients' post-TKR and post-THR, and for long-term recurrent VTE prophylaxis. It comes in two strengths of 2.5 and 5 mg tablets.

In the Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) trial, apixaban demonstrated superiority over warfarin titrated to an INR of 2–3 with relative risk reduction of 21%, absolute risk reduction of 0.33% giving an NNT of 303. This statistically significant result is driven mainly by a decrease in hemorrhagic stroke rates. In terms of bleeding events, apixaban demonstrated 31% less bleeding compared to warfarin, mainly driven by decrease in ICH and bleeding other than GI bleeding rates. Of note, apixaban has similar GI bleeding rates versus warfarin. Apixaban is used at a dose of 5 mg twice daily for SSE prevention (see **Table 2**). The dose is reduced to 2.5 mg twice daily if two out of the three following criteria are met: weight of ≤60 kg, serum creatinine of >1.5 mg/dl, or age of ≥80 years old according to the drug label. It should be noted that patients with CrCl of <25 ml/min are not included in the trial and hence other countries do not allow use of apixaban in patients with CrCl of <25 ml/min [27]. However, in the US, apixaban can be used at a dose of 2.5 mg twice daily even in patients with end-stage renal disease, including patients on dialysis, based on pharmacokinetic modeling.

For the treatment of VTE, apixaban is non-inferior to warfarin but has lower bleeding episodes (see **Table 3**). Apixaban is started at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily [19, 26]. Similarly, apixaban should be avoided in patients with CrCl of <25 ml/min as these patients were excluded in the trial.

3.6.4 Monitoring

Apixaban does not require any laboratory monitoring as well. PT/INR is even less sensitive to apixaban compared to rivaroxaban. Anti-factor Xa assay specifically calibrated to apixaban is a sensitive test that could detect the presence and could give the quantity of the drug present in the sample. However, anti-factor Xa assay for DOACs are not readily available in most hospital laboratories [20, 21, 26].

3.6.5 Adverse effects

Patients on apixaban need to watch for bleeding, though apixaban has a better safety profile than warfarin.

3.7 Edoxaban

3.7.1 Mechanism of action

Edoxaban is also a direct factor Xa inhibitor, like rivaroxaban and apixaban [16].

3.7.2 ADME

Edoxaban is 62% bioavailable and is a P-gp substrate as well. Peak concentration occurs 1–2 hours after ingestion of edoxaban. Edoxaban is cleared both renally and

non-renally in a 50-50 manner. Fifty percent of the drug is metabolized hepatically via hydrolysis. Only 4% of the drug is metabolized by CYP3A4. The remaining 50% of the drug is excreted renally. It has a half-life of 10–14 hours [15, 19, 28] (see **Table 1**).

3.7.3 Clinical use

Edoxaban is approved both for SSE prevention in patients with non-valvular AF and VTE treatment. In the Edoxaban versus Warfarin in Patients with Atrial Fibrillation (ENGAGE AF-TIMI 48) trial, edoxaban has shown to be non-inferior to warfarin for SSE prevention [28] (see **Table 2**). However, a separate analysis that was published shows that at CrCl of >95 ml/min, edoxaban is not as protective as warfarin against SSE. Patients with CrCl >95 ml/min have lower edoxaban concentration likely due to higher clearance of the drug among those with CrCl of 95 ml/min [29]. Hence, edoxaban is not approved by the US FDA for use among patients with CrCl of >95 ml/min. In terms of bleeding episodes, edoxaban has lesser bleeding risk than warfarin. Edoxaban comes in 30 and 60 mg doses. The 30 mg dose is used if patients have CrCL of 30–50 ml/min, weighs ≤60 kg, or is on verapamil, quinidine, or dronedarone (medication that are strong P-gp inhibitors) [28].

For the treatment of VTE, edoxaban is non-inferior to warfarin in terms of efficacy and has a lesser bleeding occurrence (see **Table 3**). There is no FDA recommendation whether it should be avoided in patients with CrCl > 95 ml/min due to lack of studies. However, it would seem prudent to also do the same for patients with VTE [18].

3.7.4 Monitoring

Edoxaban does not require monitoring like other DOACs. Similar to rivaroxaban and apixaban, PT/INR has low sensitivity towards edoxaban's pharmacodynamic effect and is therefore not a good laboratory test to check on the presence of the drug. Anti-factor Xa assay calibrated to edoxaban remains to be the most sensitive test for edoxaban so far [20, 21, 28].

3.7.5 Adverse effects

Edoxaban has demonstrated lesser bleeding risk compared to warfarin in the clinical phase III studies.

4. Conclusion

The use of anticoagulants requires holistic evaluation of the patient and careful balancing of the thrombotic and bleeding risks of the patient. Understanding the pharmacology, pharmacodynamics, pharmacokinetics, and clinical evidence behind the use of these drugs will help the clinician in selecting the best therapy for the patient.

Conflict of interest

The author has no conflict of interest to declare.

Notes/thanks/other declarations

None.

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Author details

Hobart Owen Ng Tsai
Khoo Teck Puat Hospital, Singapore

*Address all correspondence to: hngtsai@gmail.com

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