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Drug Interactions of Anticoagulants: Mechanisms, Clinical Implications, and Strategies to Prevent and Manage Interactions

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ABSTRACT

Introduction: Anticoagulants are one of the most commonly used medications to prevent and treat thromboembolic disorders. However, they have a narrow therapeutic index, which makes them very prone to clinically important drug, food, and disease interactions. The result can be a loss of efficacy and thrombotic events or an increased anticoagulant effect with major bleeding. **Methods:** This review aims to outline current evidence related to anticoagulant interaction profiles from pharmacological, clinical, and guideline-based data. Mechanistic data on vitamin K antagonists, heparins, direct oral anticoagulants, and factor XIa inhibitors were reviewed, along with documented drug-drug, drug-food, and drug-disease interactions. Risk reduction strategies, including laboratory monitoring, medication reconciliation, renal/hepatic assessment, patient counseling, and multidisciplinary interventions, were assessed. **Results:** Vitamin K antagonists, especially warfarin, have extensive pharmacokinetic and pharmacodynamic drug interactions related to CYP450 enzymes, P-glycoprotein modulation, and dietary vitamin K. Heparins have fewer metabolic drug interactions but have a significant additive bleeding risk when used concurrently with antiplatelets, fibrinolytics, or NSAIDs. Food factors that may alter anticoagulant response include vitamin K-rich vegetables, herbal supplements, and excessive alcohol intake. Comorbidities that further modify anticoagulant safety and efficacy include hepatic and renal impairment, bleeding disorders, thrombocytopenia, and recent surgery. Optimal management includes individualized monitoring; INR, aPTT, and/or anti-Xa or drug levels; structured medication review and organ function assessment; patient education; and multidisciplinary involvement. **Conclusion:** Anticoagulant interactions significantly affect therapeutic outcomes and patient safety. Clinicians can optimize anticoagulant therapy and minimize bleeding or thrombotic complications in diverse clinical settings by integrating vigilant monitoring, systematic reconciliation, patient-centered counseling, and collaborative care.

1 INTRODUCTION

Anticoagulants are pharmacological agents that prevent or delay blood clot formation by blocking one or more steps in the coagulation process. They play an important role in the management and prevention of various thromboembolic events such as deep vein thrombosis, stroke, pulmonary embolism and heart attack [1-4]. Given their widespread clinical use and narrow therapeutic index, understanding anticoagulant pharmacology and potential interactions is crucial to optimizing both safety and efficacy.

Anticoagulants are among the most prescribed medications globally, and their use has demonstrated a sharp increase over the last decade, highlighting their increasing clinical importance and the need for careful management of drug–drug interactions. In the United States, the use of DOACs in patients having atrial fibrillation increased from 4.7% in 2011 to 47.9% in 2020, whereas warfarin use decreased from 52.4% to 17.7% during the same time. Similar upward trends have been reported globally; for example, DOAC prescriptions in the United Kingdom increased from 9% of all anticoagulant prescriptions in 2014 to 74% in 2019, though some

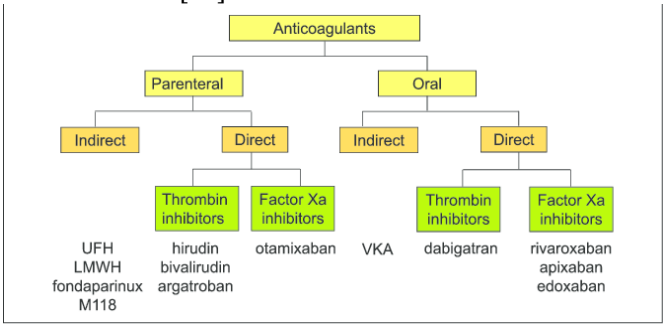
regional variations persist [5-7]. This shift toward DOACs-especially in the elderly, polypharmacy-prone populations-emphasizes an urgent need to understand and mitigate clinically significant anticoagulant interactions. This review, therefore, focuses on the mechanisms, clinical relevance, and prevention strategies of anticoagulant drug interactions.

1.1 Classification of Anticoagulants

Anticoagulants are broadly classified based on their route of administration into oral and parenteral agents:

Figure 1

Classification of anticoagulants based on route of administration [15]



1.2 Importance of Anticoagulants

Anticoagulants prevent clot formation and embolic complications across venous and arterial disorders, are central in AF, VTE, and some coronary settings, and include parenteral agents, VKAs, and direct oral agents with distinct mechanisms, clear outcome benefits, and important bleeding and monitoring trade-offs [8,9]. Anticoagulants reduce the chance of thrombus formation and embolic propagation; therefore, are useful in the prevention of systemic embolism, stroke, and pulmonary embolism. They are cornerstone therapies to reduce arterial thromboembolism (notably in atrial fibrillation) and venous thromboembolism (VTE) outcomes in cardiovascular practice [10,11]. They are also used in acute coronary syndrome [12,17], Prosthetic valves and rheumatic disease [13], and ischemic stroke [17].

1.3 Relevance of drug interactions to safety and efficacy

Drug interactions are the greatest determinant of the safety and efficacy of pharmacotherapy. Interaction in case of anticoagulants with other drugs, foods, or patient conditions is especially important since these medications have a narrow therapeutic index; therefore, a minor change in plasma concentration can cause under-anticoagulation or over-anticoagulation [14]. In clinical practice, many patients on anticoagulants have polypharmacy (for example, in atrial fibrillation, venous thromboembolism, or coronary disease) and thus are more susceptible of drug-drug interactions [15,17]. From the efficacy side, a drug interaction that reduces anticoagulant effect may lead to thromboembolic events (stroke, DVT/PE, prosthetic valve thrombosis) despite treatment. From the safety side, a drug interaction that increases anticoagulant effect (or adds bleeding risk via another mechanism) may result in major bleeding (intracranial, gastrointestinal, etc.) [16,17].

1.4 Scope and Aims of the Review

The objective of this review is to evaluate thoroughly the drug interactions of anticoagulants, which are critical because of their narrow therapeutic window and widespread utilization in treating patients with a variety of thromboembolic disorders. Minor pharmacologic interactions can create a significant imbalance between thrombosis and hemorrhage by altering the narrow margin between the two states; therefore, identifying and managing such interactions is essential to ensure both effectiveness and patient safety. The mechanisms of interaction of anticoagulants (pharmacokinetics, pharmacodynamics, and disease-specific) will be discussed within each class of drugs (vitamin K antagonists, heparins, and direct oral anticoagulants). The impact of food intake, comorbid conditions, and other concomitantly prescribed medications on the anticoagulant response will also be emphasized. Practical methods to minimize undesirable effects from drug interactions, specifically, therapeutic drug monitoring, medication reconciliation, educating patients regarding their medications, and coordinating care among multiple health professionals, will be discussed. In general, the purpose of the review is to emphasize the clinical importance of understanding the above-mentioned drug interactions and to present a methodically constructed framework to identify, detect, and manage such interactions in order to prevent undesirable consequences.

2 Pharmacological Basis of Interactions

2.1 General Mechanism of Action

Anticoagulants work by interfering with the coagulation cascade, which is responsible for the formation of fibrin clots.

Vitamin K Antagonists: including Warfarin and acenocoumarol, inhibit the synthesis of vitamin K-dependent factors [16,19,20,22].

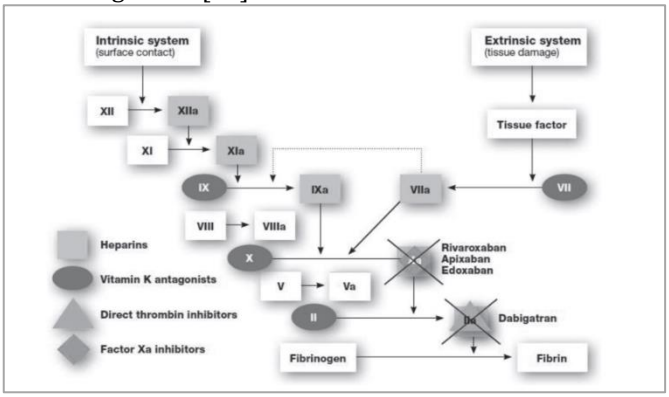
Indirect thrombin inhibitors: including unfractionated heparin (UFH), LMWH, potentiate antithrombin III, inhibiting IIa and Xa [20].

Direct Oral Anticoagulants: including Factor Xa inhibitors (Rivaroxaban, Apixaban and Fondaparinux) and Direct thrombin inhibitors (Bivalirudin, Argatroban and Dabigatran) [20].

Factor XIa Inhibitor: including Asundexian inhibits factor XIa, reducing thrombin generation [29,30,32].

Figure 2

coagulation cascade overview and primary site(s) of action of anticoagulants [24]



Vitamin K Antagonists

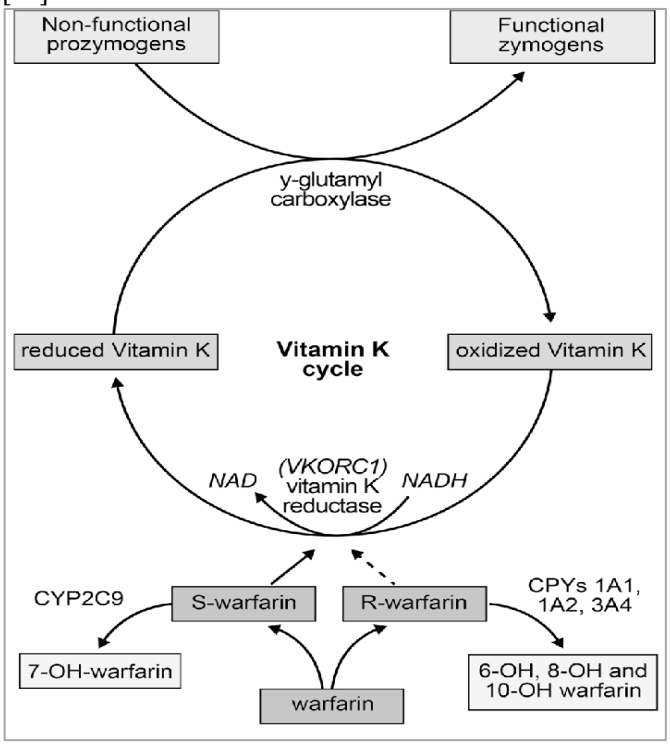
Vitamin K antagonists include warfarin and acenocoumarol.

Warfarin

Warfarin works by inhibits the vitamin K epoxide reductase complex, thereby reducing the synthesis of clotting factors II, VII, IX, and X. It also inhibits anticoagulant proteins C and S [16,19,20,24].

Figure 3

Mechanism of action of Vitamin K antagonist (Warfarin) [21]



Warfarin is indicated for:

- Treatment and prophylaxis of pulmonary embolism and venous thrombosis.
- Treatment and prophylaxis of various embolic complications associated with cardiac valve replacement or atrial fibrillation.
- Lowers the risk of death, recurrent myocardial infarction, and post-MI stroke or systemic embolism [19].

Metabolism and Excretion

Warfarin is extensively metabolized by the Hepatic system. CYP 450 system is involved in its metabolism, particularly CYP isoenzymes (1A2, 2C8, 2C9, 2C19, 3A4 and 2C18). Inactive metabolites are excreted by renal excretion. It is a substrate as well as an inhibitor of hepatic P-gp [19].

Indirect Thrombin Inhibitors

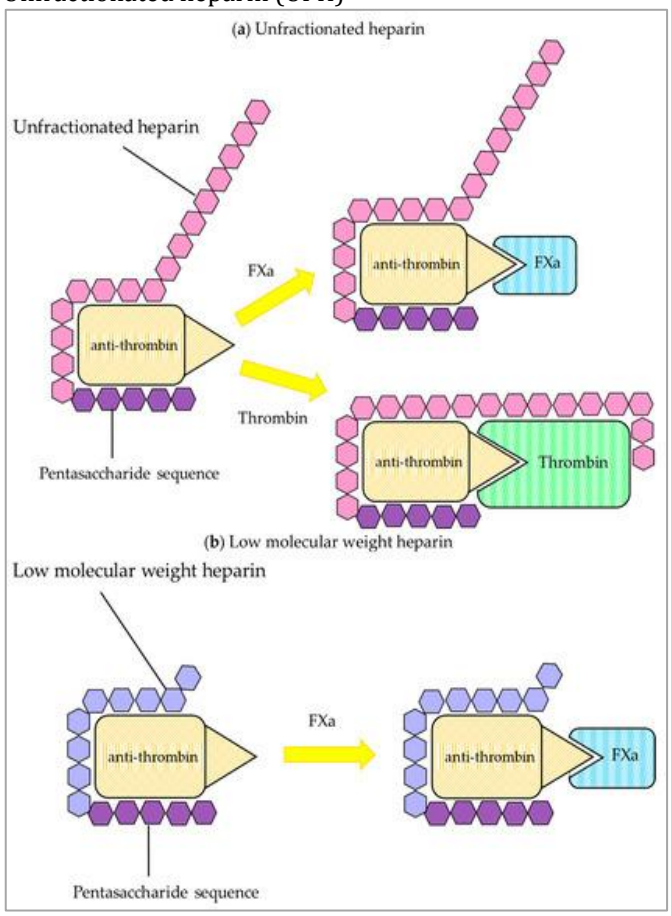
Including Unfractionated Heparin (UFH), LMWH.

Heparin

Unfractionated heparin inhibits both thrombin and factor Xa. Thrombin binding requires high-molecular-weight heparin, while low-molecular-weight heparin (LMWH) mainly enhances antithrombin's inactivation of factor Xa [20,23].

Figure 4

Inactivation of coagulation factors by heparin. (a) Unfractionated heparin (UFH)



(b) Low molecular weight heparin (LMWH) [20]

Heparin is Indicated for

- prevention and management of venous thrombosis,
- treatment of thromboembolic disorders,
- management of disseminated intravascular coagulation (DIC), and
- prevention of clot formation during artificial dialysis and extracorporeal circulation [20,23].

Metabolism and Excretion

Eliminated primarily by the reticuloendothelial system. A small fraction is excreted in urine. It is not metabolized by CYP450 or its isoenzymes. Heparin undergoes biphasic elimination - an initial rapid, saturable, zero-order phase via endothelial and macrophage binding - followed by a slow first-order phase. Accordingly, its half-life is dose-dependent, between 0.5-2 hours. In elderly patients, reduced clearance leads to higher plasma levels and prolongation of aPTT [19,23].

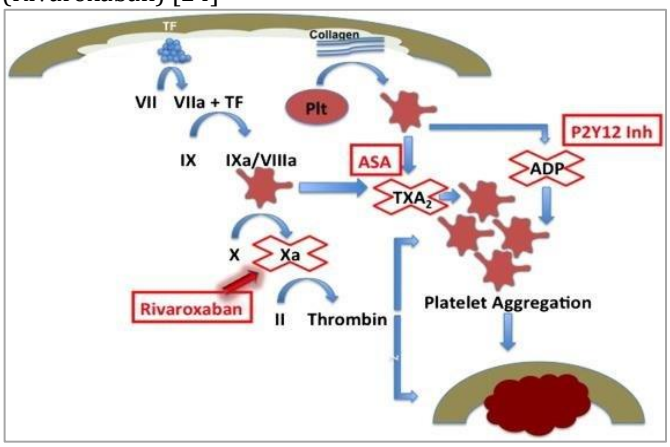
Direct Oral Anticoagulants

including Rivaroxaban, apixaban, edoxaban, dabigatran

Rivaroxaban

They exert dose-dependent inhibition of factor Xa, the first enzyme in the common pathway. Rivaroxaban directly binds to the active site of factor Xa, blocking both free and clot-bound forms and suppressing prothrombinase activity [24,25].

Figure 5
Mechanism of action of direct oral anticoagulant (Rivaroxaban) [24]



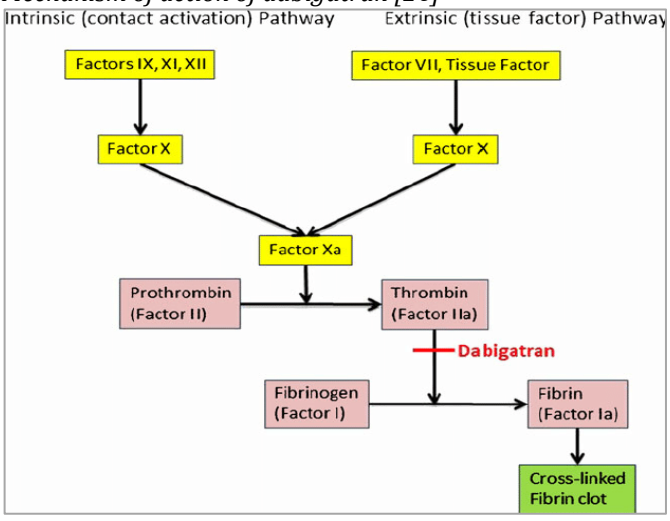
Rivaroxaban is indicated for:

- Preventing blood clots in patients who are undergoing surgery for the replacement of a knee or a hip.
- Lowering chances of DVT recurrence.
- Preventing Strokes in Patients with arrhythmias.
- treatment of acute VTE and prevention of its recurrence.
- lowering the ongoing risk of venous thromboembolic events and
- secondary prevention in patients with acute coronary syndrome or peripheral arterial disease [19,25].

Metabolism and excretion
Hepatic metabolism of the drug occurs via oxidative pathways primarily involving CYP3A4/5 and CYP2J2. Excretion occurs predominantly through the urine (66%) and to a lesser extent via the feces (28%). Substrate of P-gp and Substrate of ABCG2 (BCRP) [19,25].

Dabigatran
Dabigatran etexilate is a prodrug, and it is converted into its active moiety, dabigatran, in the body. It is a direct inhibitor of thrombin [24,26,27].

Figure 6
Mechanism of action of dabigatran [26]



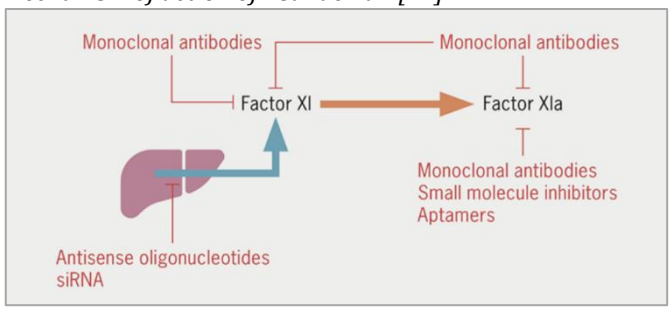
Dabigatran is indicated for:

- Prevention of systemic embolism or stroke in patients with NVAF.
- Treatment of PE and DVT in patients that are being treated with a parenteral anticoagulant.
- Reduces the risk of recurrent PE and DVT.
- Prophylaxis of PE and DVT in patients who have with a history of hip replacement surgery [19,28].

Metabolism and excretion:
Hepatic metabolism up to 20% by glucuronidation (phase II). Renal excretion is 80% excreted in unchanged form. Biliary excretion is approximately 20%. Not metabolized by CYP enzymes. Substrate of P-gp [19,24].

Factor XIa Inhibitor
Asundexian
It is a direct, oral, and reversible inhibitor of activated factor XI (FXIa) [29-32].

Figure 7
Mechanism of action of Asundexian [32]



Asundexian is Indicated for

- stroke prevention of atrial fibrillation,
- Acute coronary syndrome and
- venous thromboembolism [31].

Metabolism and Excretion
It is predominantly excreted via feces and, to a lesser extent, excreted in the urine either as a product of amide hydrolysis or as an unchanged drug. It is a P-gp substrate. Mainly metabolized by carboxylesterase-1 and, to a lesser extent, via CYP3A4 [31].

2.2 Interaction of Anticoagulants
Anticoagulants are a class of drugs most prone to clinically significant interactions. Warfarin alone has more than 200 identified drug interactions, though the strength of evidence varies across sources. Many such interactions result from altered metabolism via cytochrome P450 enzymes, displacement from plasma protein binding sites, or interference with vitamin K-containing foods. Heparins, on the other hand, are less susceptible to metabolic interactions but may exhibit additive pharmacodynamic effects when combined with other agents that affect hemostasis, such as antiplatelets or NSAIDs. Direct oral anticoagulants, designed to minimize variability, are also vulnerable to modulators of P-glycoprotein and CYP3A4. These interactions can result in either diminished anticoagulant efficacy, increased thrombotic risk, or excessive anticoagulant effect, predisposing to major bleeding. Knowledge of the interactions of these drugs is therefore critical for optimizing safety and efficacy in anticoagulant therapy [19,24,39].

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Table 1
Drug-Drug Interactions of Anticoagulants

Class	Drug	Interaction	Remarks	References
Vitamin K antagonists	Warfarin	Antimicrobials, fibrinolytics, other anticoagulants, antiarrhythmic drugs, nonsteroidal anti-inflammatory agents, and antiplatelet medications.	When warfarin is given with any of these drugs, dose adjustment and close monitoring is required.	[16,24].
		Can potentiate warfarin action: Felodipine, citalopram, ciprofloxacin, zileuton, miconazole, losartan, trichloroacetic acid (from chloral hydrate), amlodipine, clofibrate, sertraline, erythromycin, ibuprofen, propranolol, cotrimoxazole, metronidazole, quinidine, piroxicam, omeprazole, voriconazole, fluconazole, isoniazid, diltiazem, phenylbutazone, fenofibrate, cimetidine, amiodarone, propafenone, anabolic steroids, valsartan, entacapone, sulfinpyrazone.	Try to avoid using them together. If they must be given at the same time, check the INR more often and adjust the warfarin dose accordingly.	[19,24,39]
		Can cause Inhibition of Warfarin action: Ribavirin, phenobarbital, griseofulvin, carbamazepine, sucralfate, mercaptopurine, mesalamine, cholestyramine, rifampin, nafcillin, barbiturates	Try to avoid using them together. If they must be given at the same time, check the INR more often and adjust the warfarin dose accordingly.	[19,24,39]
Vitamin K antagonists	Acenocoumarol	Itraconazole, metronidazole and co-trimoxazol.	increases the risk of over-anticoagulation	[33]
		Aminoglutethimide	Concurrent use causes a decline in hypoprothrombinemic effect. Hepatic microsomal enzymes are being induced by aminoglutethimide which reults in enhanced metabolism of oral anticoagulants	[34]
		Antithyroid Agents	Effects of oral anticoagulants is decreased due to becreased metabolism of clotting factors.	[34]
		Fluconazole, Aspirin, Lepirudin, Low Molecular Weight Heparins, Anticoagulants, Piroxicam, Salicylates, Tamoxifen, Thrombolytic Agents, Treprostinil, Amiodarone, Voriconazole, Zotepine, Flurbiprofen, Fenofibrate, Clarithromycin, NSAIDs	Concomitant use can increase the risk of bleeding.	[34]
		Tricyclic Antidepressants	Increases the bioavailability of acenocoumarol	[34]
Indirect thrombin inhibitors	Heparin (Unfractionated heparin)	Thrombolytics	Concurrent administration of thrombolytics increases the risk of bleeding	[23]
		Platelet inhibitors:	Concomitant use can cause bleeding	[23]
		Oral anticoagulants	Should be used with caution in pateints taking oral anticoagulants	[23]
		digoxin, tetracyclines, and nitroglycerin	Possibility of intraction (can reduce anticoagulant effect of heoarin)	[23]
		ACE inhibitors and ARBs	Co-administration can cause hyperkalemic effect	[24]
		Nitroglycerin	Serum concentrations of heparin can be decreased by concomitant use.	[24]
		Omega-3 fatty acids and NSAIDs	coadministration with heparin causes enhanced anti-coagulant effect.	[24]
		progestin and estrogen	Anticoagulant action can be diminished when using Concomitantly with heparin.	[24]
Indirect thrombin inhibitors	Enoxaparin (LMWH)	NSAIDs, other anticoagulants and platelet inhibitors.	increasing the risk of developing epidural or spinal hematomas	[35]
Indirect thrombin inhibitors	Dalteparin (LMWH)	platelet aggregation inhibitors, thrombolytic drugs and oral anticoagulants	Concomitant administration increases the risk of bleeding	[36]
Direct Oral Anticoagulants	Fondaparinux (Factor Xa inhibitors)	Aspirin, other anticoagulants, Warfarin, Heparin, other NSAIDs.	increases the risk of bleeding.	[37]

Direct oral Anticoagulants	Apixaban (Factor Xa inhibitors)	Can be affected by drugs that induce or inhibit the activity of cytochrome P450 enzymes	Avoid concomitant use	[17].
		Affected by drugs that modify cytochrome P450 enzyme function	Avoid concomitant use	[17].
	Rivaroxaban, (Factor Xa inhibitors)	Affected by drugs that modify cytochrome P450 enzyme function	Avoid concomitant use	[17].
		Breast cancer resistance protein Bcrp (ABCG2) inhibitors, CYP3A inhibitors, P-glycoprotein inhibitors.	Inhibitors of rivaroxaban	[25]
		Other anticoagulants, including: apixaban, unfractionated heparin, dabigatran, fondaparinux, warfarin, low molecular weight heparins (e.g., enoxaparin).	Concomitant use should be avoided	[25]
		Amiodarone	Combination of Rivaroxaban and Amiodarone Increases Bleeding	[38]
Direct Oral Anticoagulants	Dabigatran (Direct thrombin inhibitors)	Inducers of P-gp (eg, rifampin)	Avoid concomitant use	[19,24]
		Inhibitors of P-gp (eg, ketoconazole and dronedarone)	Avoid concomitant use	[19,24]
		Dronedarone	Dronedarone should not be used concomitantly with dabigatran because it augments the levels of the dabigatran up to 2-fold	[24]
		antacids and proton pump inhibitors	Concomitant use decreases drug absorption	[24]
		Rifampicin, ketoconazole, and quinidine.	Concomitant use with dabigatran decreases its bioavailability	[24]
		anticoagulant or antiplatelet	Avoid concomitant use	[24]
		clopidogrel	When clopidogrel is administration with dabigatran it can cause and increasein Cmax and AUC of dabigatran to 40% and 30% respectively.	[24]

Table 2

Drug Food Interactions of Anticoagulants

Class	Drug	Interaction	Remark	References
Vitamin K Antagonists	Warfarin	Vitamin K-containing foods	Vitamin K reduces warfarin's effectiveness in the body Examples of vitamin K–rich foods are kale, spinach, Brussels sprouts, and green tea leaves.	[16,24].
		Alcohol and Grapefruit juice	bleeding complications can occur due to enhanced warfarin action.	[16,24]
		Green Tea	contains a minimal amount of vitamin K. Interaction is dose-dependent. High does reduce PT-INR	[24]
		Chamomile	inhibitory effect mainly on CYP1A2, and slightly on CYP3A4 and CYP2C9	[24]
		Soybeans	inhibit CYP3A4 and CYP2C9, which can reduce action of warfarin.	[24]
		Mango	They are rich in retinol, which inhibits CYP2C19. Even small amounts of mango can raise PT-INR.	[24]
		St. John's wort	Induces 2C9, 3A4 and CYP1A2, which causes increase in the clearance and decrease in the plasma concentration of warfarin.	[23]
		Green leafy vegetables	Causes a decrease in PT-INR	[23]
		Ginseng	The Active component of ginseng is Ginsenosides, it act inhibits CYP1A2, thromboxane formation and platelet aggregation.	[23]
Vitamin K antagonists	Acenocoumarol	Foods containing Vitamin K	Effect of oral anticoagulants can be antagonized by Foods rich in vitamin K.	[34]
		Garlic	when taken orally, it can inhibit platelet aggregation. antiplatelet effect of garlic, along with an anticoagulant, increases the risk for bleeding complications	[34]
Indirect thrombin inhibitors	Heparin (Unfractionated heparin)	Vitamin K-rich food	decreased action of heparin	[24]
		soy foods	affecting heparin efficacy	[24]

			Ginseng, garlic, onion, cannabis, green tea, and ginger.	When combined with heparin,it can increase the risk of bleeding.	[24]
Indirect thrombin inhibitors	Enoxaparin (LMWH)		pork	Contraindicated	[71]
Direct Oral Anticoagulants	Dabigatran (Direct thrombin inhibitors)		St. John's wort	Potent inducer of P-glycoprotein and CYP3A4, it is anticipated to decrease the plasma concentrations of dabigatran	[24]
			Garlic	antiplatelet properties of garlic can increase the risk.	[24]
			Echinacea flavonoids	By inhibiting P-gp activity, it may increase the concentration of factor Xa inhibitors in the plasma.	[24]

Table 3

Drug-Disease interactions of Anticoagulants

Drug		Interaction	Remarks/management	Reference
Vitamin K Antagonists	Warfarin	HIT	Warfarin is contraindicated in HIT	[66]
		Renal impairment	Warfarin may accumulate in the body due to decreased renal function.	[16]
		Significant hemorrhage risk	Warfarin should not be used in patients who have active gastrointestinal ulcers, bleeding in the respiratory or urinary tracts, bleeding in the central nervous system, a dissecting aortic aneurysm, or those undergoing epidural or spinal punctures.	[16]
		Recent surgery resulted in large open surfaces of the eye, central nervous system, or traumatic surgery.	Warfarin is contraindicated.	[16]
		Bleeding linked with pericardial effusion, bacterial endocarditis or pericarditis.	Warfarin is contraindicated.	[16]
		Major regional or lumbar block anesthesia	Warfarin is contraindicated.	[16]
		Malignant hypertension	Warfarin is contraindicated.	[16]
Vitamin K Antagonists	Acenocoumarol	deficiency of ascorbic acid	Contraindicated	[34]
		bacterial endocarditis	Contraindicated	[34]
		blood dyscrasias or other disorders of the blood having an elevated risk of hemorrhage	Contraindicated	[34]
		cerebral aneurysm or cerebrovascular hemorrhage	Contraindicated	[34]
		Situations where fibrinolytic activity is high, such as after lung, prostate, or uterine surgery	Contraindicated	[34]
		Aortic dissection.	Contraindicated	[34]
		A known hypersensitivity reaction to acenocoumarol or other drugs in the coumarin class	Contraindicated	[34]
		Severe hypertension	Contraindicated	[34]
		Extensive surgical procedures or regional anesthesia blocks	Contraindicated	[34]
Indirect thrombin inhibitors	Heparin (Unfractionated heparin)	Heparin-Induced Thrombocytopenia	If heparin-induced thrombocytopenia occurs, start a non-heparin anticoagulant therapy.	[23,41-44,47]
		Bleeding disorders	Heparin is contraindicated in bleeding disorders. Heparin itself can also cause bleeding, which depends upon several factors such as gender, state of illness, and drug therapy, particularly aspirin.	[23,45-47]
		Hypersensitivity	It is contraindicated in patients having hypersensitivity to heparin	[23,47]
		vaccine-induced immune thrombotic thrombocytopenia (VITT)	For patients presenting with cerebral venous thrombosis and low platelet counts, if vaccine-induced immune thrombotic thrombocytopenia is suspected or confirmed, heparin should not be used; instead, non-heparin anticoagulants are recommended.	[48,49]
		hereditary antithrombin III deficiency	To reduce the risk of bleeding, heparin dosage should be adjusted	[23]
Indirect thrombin inhibitors	Enoxaparin (LMWH)	Renal insufficiency	Dose adjustment is required in patients with renal impairment.	[35,50-52]

		acute coronary syndrome	In acute coronary syndrome, enoxaparin use warrants close monitoring in patients ≥65 years, with prior bleeding events, or with a history of oral anticoagulant therapy, due to elevated bleeding risk.	[53]
		Active bleeding	Active bleeding within 48-72 hours	[35,56]
		Hypersensitivity	contraindicated	[35,56,71]
		Recent head trauma	Contraindicated	[56]
		Multiple traumas with high bleeding risk	Contraindicated	[56]
		Low platelet count	Contraindicated	[56]
		Neonates with a previous hypersensitivity reaction to benzyl alcohol.	Contraindicated	[35,71]
Indirect thrombin inhibitors	Dalteparin (LMWH)	bleeding disorders	Contraindicated	[54,56]
		thrombocytopenia	Contraindicated	[33,54]
		liver disease	Contraindicated	[54]
		uncontrolled hypertension	Contraindicated	[33,54]
		Patient with positive platelet aggregation test with Dalteparin	Contraindicated	[54]
		Diabetic retinopathy	contraindicated	[54]
		Cancer	Patients with cancer undergoing regional anaesthesia	[55]
		Severe renal impairment	It is contraindicated in trauma patient with severe renal impairment	[56]
		existing hemorrhagic conditions	contraindicated	[36]
		hemorrhagic or ischemic stoke	contraindicated	[36]
		hypersensitivity	contraindicated	[36]
Indirect thrombin inhibitors	Nadroparin (LMWH)	Renal impairment	Dose adjustment is required	[57]
		thrombocytopenia		[58]
Direct Oral Anticoagulants	Fondaparinux (Factor Xa inhibitors)	Renal insufficiency	contraindicated in those patients with severe renal impairment (CrCl <30 mL/min)	[37,59-65]
		active major bleeding	contraindicated	[37]
		bacterial endocarditis	Contraindicated	[37]
		Fondaparinux-related thrombocytopenia	Contraindicated	[37]
		hypersensitivity to fondaparinux	contraindicated	[37]
	Betrixaban (Factor Xa inhibitors)	hypersensitivity	Avoid	[68]
		Renal impairment	For patients with renal impairment, dose adjustment of direct factor Xa inhibitors should be considered when creatinine clearance is below 30 mL/min, and these drugs should be avoided if creatinine clearance falls under 15 mL/min	[68]
		hepatic impaired	Dose adjustment is required	[68]
	Rivaroxaban (Factor Xa inhibitors)	hepatic impairment	Not recommended in patients with liver disease (including those classified as Child-Pugh B or C), having coagulopathy and an increased risk of clinically significant bleeding	[25,68,69]
		Renal impairment	Avoid patients with CrCl < 30 mL/min	[61,68,70]
		Allery	Severe hypersensitivity to rivaroxaban	[25]
		Active pathological bleeding	Contraindicated	[25]
		Antiphospholipid syndrome	not recommended in patients having triple-positive antiphospholipid syndrome	[25]
		Atrial fibrillation with end-stage CKD	Rivaroxaban is not recommended	[25]
		Valvular disease	Avoid in patients having mechanical valve or those with moderate to severe mitral stenosis. It is also not recommended in patients with prosthetic heart valves or rheumatic heart disease.	[25]
		Congenital or acquired bleeding disorders	Contraindicated	[25]
		Uncontrolled, severe arterial hypertension	Contraindicated	[25]
		Active ulcerative GI disease	Contraindicated	[25]
		vascular retinopathy	Contraindicated	[25]
		bronchiectasis	Contraindicated	[25]
	Apixaban (Factor Xa inhibitors)	hepatic impairment	Because apixaban is metabolized hepatically, it is contraindicated in patients having significant hepatic disease.	[61,68,69]

		Renal impairment	Should be avoided in patients with a creatinine clearance below 25 mL/min or serum creatinine exceeding 2.5 mg/dL.	[61,68,70]
	Edoxaban (Factor Xa inhibitors)	Renal impairment	Should not be used in patients whose creatinine clearance is less than 15 mL/min	[61,68,70]
		hepatic impairment	Should not be used in hepatic impairment	[68,61]
	Dabigatran (Direct thrombin inhibitor)	Renal impairment	Since dabigatran is primarily eliminated by the kidneys, it should not be used in patients with a creatinine clearance below 30 mL/min.	[61,68,69 ,70]
		Hepatic impairment	Avoid in patients with hepatic impairment	[61]
Others	Hirudin-based thrombin inhibitors	Renal impairment	Hirudin dosage should be lowered in patients with a creatinine clearance below 60 mL/min, and the drug should not be used in individuals with renal failure.	[63]
	Lepirudin	Renal Impairment	Lepirudin should be administered cautiously at a reduced dose in patients with serum creatinine levels above 1.6 mg/dL (141.4 µmol/L), and it should not be used in individuals undergoing hemodialysis or with acute renal failure.	[66]
	Argatroban	hepatic dysfunction	Should be avoided or used with adjusted dose	[67]

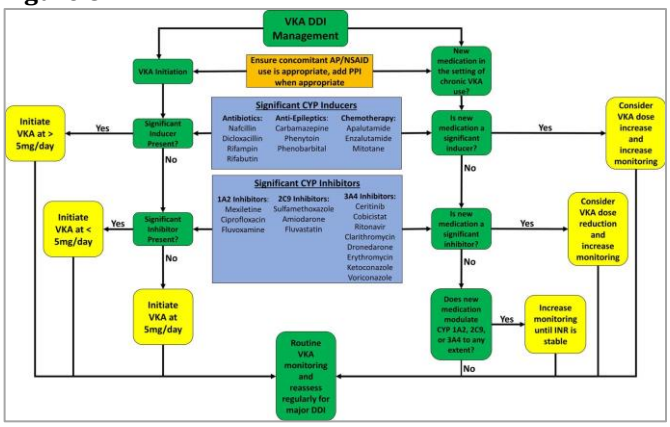
3 Clinical Implications and Strategies to Prevent and Manage Interactions

3.1 Monitoring

Monitoring involves choosing the right test for the right drug and using it to detect any clinically important interactions.

International Normalized Ratio (INR): It is considered to be a standard test for monitoring effects of VKAs like warfarin because these agents work by decreasing vitamin K-dependent clotting factors (II, VII, IX and X) [14, 72]. After starting warfarin treatment, frequent INR checks (every 3-5 days) are performed until stable, and the same is the case when there is any concomitant drug or food variation, considering the high interaction potential of warfarin. The monitoring interval can be extended (up to 12 weeks) if the INRs are stable over months, if there are no new interacting medications or dietary changes. Clinically, too high INRs mean risk of major bleeding, and too low reflects potential thrombosis; therefore, any considerable fluctuations should trigger a review of diet and possible interactions [72, 73]. VKA (warfarin) associated drug interactions can be screened and managed by clinicians using the simple algorithmic depiction given below.

Figure 8



An approach for handling warfarin-related drug-drug interactions both during the initiation phase and when introducing a new interacting medication to patients already receiving long-term warfarin therapy. Abbreviations: AP, antiplatelet; CYP, cytochrome P450; DDI, drug-drug interaction; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; VKA, vitamin K antagonist [14].

Activated Partial Thromboplastin Time (aPTT) for Unfractionated Heparin (UFH): It is another useful procedure, as it reflects coagulation pathways affected by heparin (via antithrombin III-mediated inhibition of IIa and Xa). Altered aPTT may reflect changed heparin effects due to dose adjustments, binding variations, age, renal/hepatic dysfunction, or concurrent drugs that affect hemostasis. Frequent aPTT monitoring is necessary in patients taking UFH who may start or stop using another drug (antiplatelet or a fibrinolytic) to detect possible bleeding risks. Obesity or altered binding/clearance states can result in variation of aPTT results [74,75].

Anti-Xa / Drug-specific level monitoring for Low Molecular Weight Heparin (LMWH) & Dabigatran / Rivaroxaban / Apixaban (DOACs): Anti-Xa monitoring for patients on LMWH or DOACs is not required as frequently as INR for VKAs. However, conditions like potential drug interactions, bleeding, or thrombosis on therapy necessitate careful monitoring. In the context of DOACs, anti-Xa assays have to be performed for specific drugs (rivaroxaban or apixaban) because the heparin-calibrated assay standards can misrepresent DOAC levels, resulting in misinterpretation. Situations like major bleeding or urgent surgery necessitate knowledge of DOAC levels or anti-Xa activity to help make reversal or delay decisions. If a patient on a DOAC starts an unmonitored and strong inhibitor of P-gp/CYP3A4 (e.g., ketoconazole), they may develop high anticoagulant levels leading to bleeding risk; conversely, a strong inducer may lower levels and increase thrombotic risk. Monitoring these high-risk situations helps in detection [14, 74, 76, 77].

3.2 Careful medication reconciliation at initiation and follow-up

Polypharmacy continues to be among the leading causes of clinically important anticoagulant interactions, especially in elderly patients having atrial fibrillation and venous thromboembolism (AF/VTE) who take multiple interacting medications. Unintentional co-prescription of inhibitors/inducers and anticoagulants/antiplatelets overlapping can be prevented by systematic reconciliation at admission, discharge, and clinical visits of the patient

[14,79]. Before dose or medication alterations, using a standardized checklist (including prescription drugs, OTC, herbal supplements, and topical agents) and consultation with up-to-date drug interaction resources, as well as flagging risky combinations or those requiring intensive monitoring (e.g., strong CYP3A4 + P-gp inhibitors with apixaban/rivaroxaban; rifampicin or carbamazepine with DOACs), certain complications can be avoided [78].

3.3 Routine renal and hepatic function monitoring

DOACs, especially dabigatran, are cleared renally. Creatinine clearance should be assessed before initiation and dose adjustments or avoidance may be needed at established criteria [76, 80]. Agents that are metabolized by the liver, for example, CYP3A4 substrates such as rivaroxaban/apixaban, require thorough assessment of hepatic impairment, as severe hepatic disease is often a contraindication [81]. Complications can be avoided by establishing monitoring intervals, e.g., 1–3 months after initiation/change, then at least annually or more frequently if unstable renal/hepatic disease or when interacting drugs are added.

3.4 Patient education

Patient counselling can be very beneficial in avoiding common preventable interactions. They should be advised to keep their dietary vitamin K consistent (if on VKAs), avoid starting or stopping any herbal products or OTC NSAIDs without consulting their physician, limit alcohol consumption, and inform their physician of any prescription alterations from other providers or pharmacies [82]. They can be provided with written counselling, an easy-to-understand anticoagulant card, pharmacist counselling, and follow-up. They should be advised to report in case of any associated ADRs like bruising, melena, or a new severe headache.

3.5 Switching to alternative anticoagulants when the risk is unacceptable

Sometimes switching to alternative anticoagulants is the only plausible option left, especially when therapy becomes unsafe or unmanageable due to unavoidable interactions. In patients receiving strong enzyme inducers (rifampicin, carbamazepine) or inhibitors (ritonavir-boosted antiretrovirals), which are chronic interacting drugs, the anticoagulant level is significantly altered [14, 83]. It is also appropriate in severe renal or hepatic impairment that limits DOAC use, or when INR monitoring for VKA is unreliable due to compliance or access issues. Switching should follow drug-specific protocols, such as overlapping UFH/LMWH with warfarin until INR is therapeutic or applying a 24-48 hr washout when moving from DOACs to parenteral agents based on renal function.

3.6 Multidisciplinary collaboration

Integrated efforts of pharmacists and specialized anticoagulation clinics in patient care can improve safety by ensuring considerable factors like accurate dosing, detecting interactions early, and enhancing patient education, significantly reducing bleeding and thrombotic complications. Not only can prescribing errors be avoided, but also better patient care can be ensured by multidisciplinary coordination and interdisciplinary communication. A practical approach is to establish local protocols where the addition of high-risk interacting drugs (e.g., strong CYP3A4/P-gp inhibitors or antiplatelets) automatically triggers a pharmacist review to adjust or monitor therapy [84].

CONCLUSION

Anticoagulants remain indispensable in the prevention and management of thromboembolic disorders, but their safety and therapeutic success are profoundly influenced by drug–drug, drug–food, and drug–disease interactions. This review illustrates that such interactions can significantly alter anticoagulant absorption, metabolism, clearance, and pharmacodynamic response, thereby increasing the risk of either thrombosis due to subtherapeutic levels or major bleeding from excessive anticoagulation. Warfarin exhibits the highest interaction burden, whereas DOACs, though more predictable, are still susceptible to potent modulators of CYP3A4 and P-gp. Heparins and LMWHs also pose notable additive risks, particularly when combined with other agents affecting hemostasis. This includes a multifaceted, evidence-based approach to optimizing anticoagulant therapy, such as laboratory monitoring where appropriate, routine assessment of renal and hepatic function, systematic medication reconciliation, and proactive patient education regarding diet, herbal supplements, and OTC medications. In high-risk scenarios where interactions cannot be mitigated, switching to an alternative anticoagulant or adjusting the therapeutic strategy becomes important. Multidisciplinary collaboration among clinicians, pharmacists, and specialized anticoagulation services significantly enhances safety and clinical outcomes. Enhanced awareness and systematic management of anticoagulant interactions are important for effective, individualized, and safe anticoagulation across diverse populations.

REFERENCES

1. Heestermans, M., Poenou, G., Hamzeh-Cognasse, H., Cognasse, F., & Bertoletti, L. (2022). Anticoagulants: A short history, their mechanism of action, pharmacology, and indications. *Cells*, *11*(20), 3214. https://doi.org/10.3390/cells11203214
2. Kholmukhamedov, A., Subbotin, D., Gorin, A., & Ilyassov, R. (2025). Anticoagulation management: Current landscape and future trends. *Journal of Clinical Medicine*, *14*(5), 1647. https://doi.org/10.3390/jcm14051647
3. Warzycka, K., Maliszewska, K., Woźniak, K., Gardian-Baj, M., Jung, M., Hedesz, P., Jung, M., Doryń, A., Jędral, K., Włodarczyk, A., & Szczerbiak, A. (2024). Anticoagulants - The past, the present, the future - A systematic review. *Journal of Education, Health and Sport*, *68*, 49539. https://doi.org/10.12775/jehs.2024.68.49539

4. Institute for Quality and Efficiency in Health Care (IQWiG). (2022, October 25). In brief: What are anticoagulants? In Informed Health.org [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK279433/
5. Grymonprez, M., Simoens, C., Steurbaut, S., De Backer, T. L., & Lahousse, L. (2021). Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: A systematic review and meta-analysis. *EP Europace*, *24*(6), 887-898. https://doi.org/10.1093/europace/euab303
6. Navar, A. M., Kolkailah, A. A., Overton, R., Shah, N. P., Rousseau, J. F., Flaker, G. C., Pignone, M. P., & Peterson, E. D. (2022). Trends in oral anticoagulant use among 436 864 patients with atrial fibrillation in community practice, 2011 to 2020. *Journal of the American Heart Association*, *11*(22). https://doi.org/10.1161/jaha.122.026723
7. Chen, Q., Lapane, K., Nunes, A. P., Tjia, J., Hugunin, J., & Alcusky, M. (2021). Prevalence and the factors associated with oral anticoagulant use among nursing home residents. *Journal of Clinical Pharmacy and Therapeutics*, *46*(6), 1714-1728. https://doi.org/10.1111/jcpt.13508
8. Chan, N. C., Eikelboom, J. W., & Weitz, J. I. (2016). Evolving treatments for arterial and venous thrombosis. *Circulation Research*, *118*(9), 1409-1424. https://doi.org/10.1161/circresaha.116.306925
9. Taylor, J., Stiepel, H. R., & Keefe, N. (2022). Anticoagulation and antiplatelet agents in peripheral arterial interventions. *Seminars in Interventional Radiology*, *39*(04), 364-372. https://doi.org/10.1055/s-0042-1757314
10. Kanagasabapathy, P., Chowdary, P., & Gatt, A. (2010). Alternatives to warfarin-the next generation of anticoagulants. *Cardiovascular Therapeutics*, *29*(6), e80-e88. https://doi.org/10.1111/j.1755-5922.2010.00197.x
11. Larson, E. A., German, D. M., Shatzel, J., & DeLoughery, T. G. (2018). Anticoagulation in the cardiac patient: A concise review. *European Journal of Haematology*, *102*(1), 3-19. https://doi.org/10.1111/ejh.13171
12. Ahrens, I., Bode, C., & Zirlik, A. (2014). Anticoagulation during and after acute coronary syndrome. *Hämostaseologie*, *34*(01), 72-77.
13. Kaneko, T., & Aranki, S. F. (2013). Anticoagulation for prosthetic valves. *Thrombosis*, *2013*, 1-4. https://doi.org/10.1155/2013/346752
14. Taylor, J., Stiepel, H. R., & Keefe, N. (2022). Anticoagulation and antiplatelet agents in peripheral arterial interventions. *Seminars in Interventional Radiology*, *39*(04), 364-372. https://doi.org/10.1055/s-0042-1757314
15. Wang, C., Wu, V. C., Chang, K., Tu, H., Kuo, C., Huang, Y., Chu, P., Kuo, C., & Chang, S. (2019). Assessing major bleeding risk in atrial fibrillation patients concurrently taking non-vitamin K antagonist oral anticoagulants and antiepileptic drugs. *European Heart Journal - Cardiovascular Pharmacotherapy*, *6*(3), 147-154. https://doi.org/10.1093/ehjcvp/pvz035
16. Patel, S., Singh, R., Preuss, C. V., & Patel, N. (2024). Warfarin. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470313/
17. Ferri, N., Colombo, E., Tenconi, M., Baldessin, L., & Corsini, A. (2022). Drug-drug interactions of direct oral anticoagulants (DOACs): From pharmacological to clinical practice. *Pharmaceutics*, *14*(6), 1120. https://doi.org/10.3390/pharmaceutics14061120
18. De Caterina, R., Husted, S., Wallentin, L., Andreotti, F., Arnesen, H., Bachmann, F., ... & Weitz, J. I. (2013). General mechanisms of coagulation and targets of anticoagulants (Section I). *Thrombosis and haemostasis*, *109*(04), 569-579. https://doi.org/10.1160/TH12-10-0772
19. DeWald, T. A. (2018). Pharmacokinetics, mechanisms of action, and indications. *Coagulation and Hematology in Neurological Surgery. An Issue of Neurosurgery Clinics of North America E-Book*, *29*(4), 503.
20. Kumano, O., Akatsuchi, K., & Amiral, J. (2021). Updates on anticoagulation and laboratory tools for therapy monitoring of heparin, vitamin K antagonists and direct oral anticoagulants. *Biomedicines*, *9*(3), 264. https://doi.org/10.3390/biomedicines9030264
21. Nutescu, E. A., Burnett, A., Fanikos, J., Spinler, S., & Wittkowsky, A. (2016). Erratum to: Pharmacology of anticoagulants used in the treatment of venous thromboembolism. *Journal of Thrombosis and Thrombolysis*, *42*(2), 296-311. https://doi.org/10.1007/s11239-016-1363-2
22. Elkhazraji, A., Rharrit, S., Uwingabiye, J., Zahid, H., Ibrahimi, A., & Messaoudi, N. (2018). Hypersensitivity to Acenocoumarol Revealing a Homozygous Mutation for VKORC1-1639 G> A and VKORC1 1173 C> T and Heterozygous for CYP2C9* 2 and CYP2C9* 3. *International Journal of Medical Research & Health Sciences*, *7*(3), 66-72.
23. Patel, B., Gupta, V., & Ahsan, F. (2012). PEG–PLGA based large porous particles for pulmonary delivery of a highly soluble drug, low molecular weight heparin. Journal of controlled release, 162(2), 310-320. https://www.ncbi.nlm.nih.gov/books/NBK538247/
24. Singh, R., & Emmady, P. D. (2023). Rivaroxaban. In *StatPearls [Internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557502/
25. Ganetsky, M., Babu, K. M., Salhanick, S. D., Brown, R. S., & Boyer, E. W. (2011). Dabigatran: Review of pharmacology and management of bleeding complications of this novel oral anticoagulant. *Journal of Medical Toxicology*, *7*(4), 281-287. https://doi.org/10.1007/s13181-011-0178-y
26. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Dabigatran. [Updated 2017 Nov 5]. https://www.ncbi.nlm.nih.gov/books/NBK547924/
27. Amaraneni, A., Chippa, V., Goldin, J., & Rettew, A. C. (2024). Anticoagulation safety. In *StatPearls [Internet]*. StatPearls Publishing.

https://www.ncbi.nlm.nih.gov/books/NBK519025/
28. Heitmeier, S., Visser, M., Tersteegen, A., Dietze-Torres, J., Glunz, J., Gerdes, C., Laux, V., Stampfuss, J., & Roehrig, S. (2022). Pharmacological profile of asundexian, a novel, orally bioavailable inhibitor of factor Xia. *Journal of Thrombosis and Haemostasis*, *20*(6), 1400-1411. https://doi.org/10.1111/jth.15700
29. Kanefendt, F., Brase, C., Jungmann, N., Fricke, R., Engelen, A., & Schmitz, S. (2024). Pharmacokinetics of asundexian with combined CYP3A and P-GP inhibitors and an inducer: Target in vitro and in vivo studies. *British Journal of Clinical Pharmacology*, *90*(4), 1036-1049. https://doi.org/10.1111/bcp.15981
30. Ferri, N., Colombo, E., & Corsini, A. (2024). Drug–drug interactions of FXI inhibitors: Clinical relevance. *Hematology Reports*, *16*(1), 151-163. https://doi.org/10.3390/hematolrep16010016
31. Sammut, M. A., Elamin, N., & Storey, R. F. (2024). Factor XI and XIa inhibition: A new approach to anticoagulant therapy. *The British Journal of Cardiology*, *31*(2), 018. https://doi.org/10.5837/bjc.2024.018
32. Becker, M. L., Van Uden, R. C., Giezen, T. J., Meijer, K., Houtenbos, I., & Van den Bemt, P. M. (2020). Drug-drug interactions with metronidazole and itraconazole in patients using acenocoumarol. *European Journal of Clinical Pharmacology*, *76*(10), 1457-1464. https://doi.org/10.1007/s00228-020-02930-z
33. Minigh, J. (2008). Acenocoumarol. *xPharm: The Comprehensive Pharmacology Reference*, 1-12. https://doi.org/10.1016/b978-008055232-3.61156-0
34. Jupalli, A., & Iqbal, A. M. (2023). Enoxaparin. In *StatPearls [Internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK539865/
35. Harvison, P. J. (2007). Dalteparin. *xPharm: The Comprehensive Pharmacology Reference*, 1-4. https://doi.org/10.1016/b978-008055232-3.61540-5
36. McKeage, K., & Lyseng-Williamson, K. A. (2010). Fondaparinux: a pharmacoeconomic review of its use in the management of non-ST-segment elevation acute coronary syndrome. *PharmacoEconomics*, *28*(8), 687-698. https://doi.org/10.2165/11205130-000000000-00000
37. Wang, Z., Li, X., Zou, Y., Li, X., & Lv, Q. (2023). Combination of Rivaroxaban and Amiodarone increases bleeding in patients with atrial fibrillation. *Annals of Pharmacotherapy*, *58*(8), 761-770. https://doi.org/10.1177/10600280231211306
38. Vazquez, S. R. (2018). Drug-drug interactions in an era of multiple anticoagulants: A focus on clinically relevant drug interactions. *Blood*, *132*(21), 2230-2239. https://doi.org/10.1182/blood-2018-06-848747
39. Ho, K. H., Van Hove, M., & Leng, G. (2020). Trends in anticoagulant prescribing: A review of local policies in English primary care. *BMC Health Services Research*, *20*(1). https://doi.org/10.1186/s12913-020-5058-1
40. Arepally, G. M. (2017). Heparin-induced thrombocytopenia. *Blood*, *129*(21), 2864-2872. https://doi.org/10.1182/blood-2016-11-709873
41. Arepally, G. M., & Cines, D. B. (2020). Pathogenesis of heparin-induced thrombocytopenia. *Translational Research*, *225*, 131-140. https://doi.org/10.1016/j.trsl.2020.04.014
42. Warkentin, T. E. (2023). Autoimmune heparin-induced Thrombocytopenia. *Journal of Clinical Medicine*, *12*(21), 6921. https://doi.org/10.3390/jcm12216921
43. May, J., Westbrook, B., & Cuker, A. (2023). Heparin-induced thrombocytopenia: An illustrated review. *Research and Practice in Thrombosis and Haemostasis*, *7*(5), 100283. https://doi.org/10.1016/j.rpth.2023.100283
44. Walker, A. M. (1980). Predictors of bleeding during heparin therapy. *JAMA: The Journal of the American Medical Association*, *244*(11), 1209. https://doi.org/10.1001/jama.1980.03310110019020
45. Gervin, A. S. (1975). Complications of heparin therapy. *Surgery, Gynecology & Obstetrics*, *140*(5), 789-796.
46. Lowinger, J., & Maxwell, D. (2009). Heparins for venous thromboembolism prophylaxis - safety issues. *Australian Prescriber*, *32*(4), 108-112. https://doi.org/10.18773/austprescr.2009.051
47. Ferro, J. M., Sousa, D. A., Coutinho, J. M., & Martinelli, I. (2021). European stroke organization interim expert opinion on cerebral venous thrombosis occurring after SARS-Cov-2 vaccination. *European Stroke Journal*, *6*(3), CXVI-CXXI. https://doi.org/10.1177/23969873211030842
48. Pavord, S., Lester, W., & Hunt, B. J. (2021). Clinical features of VITT. Reply. *The New England journal of medicine*, *386*(1), 10-1056. https://doi.org/10.1056/nejmc2118473
49. Atiq, F., Van den Bemt, P. M., Leebeek, F. W., Van Gelder, T., & Versmissen, J. (2015). A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency. *European Journal of Clinical Pharmacology*, *71*(8), 921-929. https://doi.org/10.1007/s00228-015-1880-5
50. Bazinet, A., Almanric, K., Brunet, C., Turcotte, I., Martineau, J., Caron, S., Blais, N., & Lalonde, L. (2005). Dosage of enoxaparin among obese and renal impairment patients. *Thrombosis Research*, *116*(1), 41-50. https://doi.org/10.1016/j.thromres.2004.10.004
51. Meneveau, N. (2009). Safety evaluation of enoxaparin in currently approved indications. *Expert Opinion on Drug Safety*, *8*(6), 745-754. https://doi.org/10.1517/14740330903352498
52. Weerasaksanti, A., Siwamogsatham, S., Kunlamas, Y., & Bunditanukul, K. (2023). Factors associated with bleeding events from enoxaparin used for patients

with acute coronary syndrome. *BMC Cardiovascular Disorders*, *23*(1). https://doi.org/10.1186/s12872-023-03278-9
53. Soroka, S., Agharazii, M., Donnelly, S., Roy, L., Muirhead, N., Cournoyer, S., MacKinnon, M., Pannu, N., Barrett, B., Madore, F., Tennankore, K., Wilson, J., Hilton, F., Sherman, N., Wolter, K., Orazem, J., & Feugère, G. (2018). An adjustable Dalteparin sodium dose regimen for the prevention of clotting in the extracorporeal circuit in hemodialysis: A clinical trial of safety and efficacy (the PARROT study). *Canadian Journal of Kidney Health and Disease*, *5*. https://doi.org/10.1177/2054358118809104
54. Coleman, R., & MacCallum, P. (2010). Treatment and secondary prevention of venous thromboembolism in cancer. British Journal of Cancer, 102(S1), S17-S23. https://doi.org/10.1038/sj.bjc.6605601
55. Gunning, A. C., Maier, R. V., De Rooij, D., Leenen, L. P., & Hietbrink, F. (2019). Venous thromboembolism (VTE) prophylaxis in severely injured patients: An international comparative assessment. *European Journal of Trauma and Emergency Surgery*, *47*(1), 137-143. https://doi.org/10.1007/s00068-019-01208-z
56. Russcher, M., Josephus Jitta, N., Kraaijenhagen, R. J., Fijnheer, R., Pasker-de Jong, P. C., & Gaillard, C. A. (2013). Preemptive dosage reduction of nadroparin in patients with renal failure: A retrospective case series. *Clinical Kidney Journal*, *6*(5), 473-477. https://doi.org/10.1093/ckj/sft083
57. Malinauskiene, L., Aleksandraviciute, L., Kryzauskaite, L., & Savlan, I. (2021). Rare complication of nadroparin injections: Skin necrosis and heparin-induced thrombocytopenia syndrome. https://doi.org/10.22541/au.163336068.80729964/v1
58. Kopp, S. L., Vandermeulen, E., McBane, R. D., Perlas, A., Leffert, L., & Horlocker, T. (2025). Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American society of Regional Anesthesia and Pain Medicine evidence-based guidelines (fifth edition). *Regional Anesthesia & Pain Medicine*, rapm-2024-105766. https://doi.org/10.1136/rapm-2024-105766
59. Smythe, M. A., Priziola, J., Dobesh, P. P., Wirth, D., Cuker, A., & Wittkowsky, A. K. (2016). Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. *Journal of Thrombosis and Thrombolysis*, *41*(1), 165-186. https://doi.org/10.1007/s11239-015-1315-2
60. Streiff, M. B., Agnelli, G., Connors, J. M., Crowther, M., Eichinger, S., Lopes, R., McBane, R. D., Moll, S., & Ansell, J. (2016). Guidance for the treatment of deep vein thrombosis and pulmonary embolism. *Journal of Thrombosis and Thrombolysis*, *41*(1), 32-67. https://doi.org/10.1007/s11239-015-1317-0
61. Jones, A., & Al-Horani, R. A. (2023). Venous thromboembolism prophylaxis in major orthopedic surgeries and factor Xia inhibitors. *Medical Sciences*, *11*(3), 49. https://doi.org/10.3390/medsci11030049
62. Garcia, D. A., Baglin, T. P., Weitz, J. I., & Samama, M. M. (2012). Parenteral anticoagulants. *Chest*, *141*(2), e24S-e43S. https://doi.org/10.1378/chest.11-2291
63. Alquwaizani, M., Buckley, L., Adams, C., & Fanikos, J. (2013). Anticoagulants: A review of the pharmacology, dosing, and complications. *Current Emergency and Hospital Medicine Reports*, *1*(2), 83-97. https://doi.org/10.1007/s40138-013-0014-6
64. Onwuzo, C., Olukorode, J., Sange, W., Tanna, S. J., Osaghae, O. W., Hassan, A., Kristilere, H., Orimoloye, D. A., Omokore, O., Ganiyu, B., Fayemi, T., & Addeh, E. (2023). A review of the preventive strategies for venous thromboembolism in hospitalized patients. *Cureus*. https://doi.org/10.7759/cureus.48421
65. Ahmed, I., Majeed, A., & Powell, R. (2007). Heparin induced thrombocytopenia: Diagnosis and management update. *Postgraduate Medical Journal*, *83*(983), 575-582. https://doi.org/10.1136/pgmj.2007.059188
66. Cuker, A., Arepally, G. M., Chong, B. H., Cines, D. B., Greinacher, A., Gruel, Y., Linkins, L. A., Rodner, S. B., Selleng, S., Warkentin, T. E., Wex, A., Mustafa, R. A., Morgan, R. L., & Santesso, N. (2018). American Society of Hematology 2018 guidelines for management of venous thromboembolism: Heparin-induced thrombocytopenia. *Blood Advances*, *2*(22), 3360-3392. https://doi.org/10.1182/bloodadvances.2018024489
67. Wu, M., Schuster, M., & Tadros, M. (2019). Update on management of Portal vein thrombosis and the role of novel anticoagulants. *Journal of Clinical and Translational Hepatology*, *7*(X), 1-11. https://doi.org/10.14218/jcth.2018.00057
68. Ribic, C., & Crowther, M. (2016). Thrombosis and anticoagulation in the setting of renal or liver disease. *Hematology*, *2016*(1), 188-195. https://doi.org/10.1182/asheducation-2016.1.188
69. Gomez-Outes, A., Suarez-Gea, M. L., Lecumberri, R., Terleira-Fernandez, A., & Vargas-Castrillon, E. (2014). Direct oral anticoagulants in the treatment of venous thromboembolism, with a focus on patients with pulmonary embolism: An evidence-based review. *Vascular Health and Risk Management*, 627. https://doi.org/10.2147/vhrm.s50543
70. Ingle, R. G., & Agarwal, A. S. (2014). A world of low molecular weight heparins (LMWHs) enoxaparin as a promising moiety—A review. *Carbohydrate Polymers*, *106*, 148-153. https://doi.org/10.1016/j.carbpol.2014.01.100
71. Kuruvilla, M., & Gurk-Turner, C. (2001). A review of warfarin dosing and monitoring. *Baylor University Medical Center Proceedings*, *14*(3), 305-306. https://doi.org/10.1080/08998280.2001.11927781
72. Holbrook, A., Schulman, S., Witt, D. M., Vandvik, P. O., Fish, J., Kovacs, M. J., Svensson, P. J., Veenstra, D. L., Crowther, M., & Guyatt, G. H. (2012). Evidence-based management of anticoagulant therapy. *Chest*, *141*(2), e152S-e184S. https://doi.org/10.1378/chest.11-2295

73. Qiao, J., & Tran, M. (2024). Challenges to laboratory monitoring of direct oral anticoagulants. *Clinical and Applied Thrombosis/Hemostasis*, *30*. https://doi.org/10.1177/10760296241241524
74. Lardinois, B., Hardy, M., Michaux, I., Horlait, G., Rotens, T., Jacqmin, H., Lessire, S., Bulpa, P., Dive, A., & Mullier, F. (2022). Monitoring of unfractionated heparin therapy in the intensive care unit using a point-of-care aPTT: A comparative, longitudinal observational study with laboratory-based aPTT and anti-xa activity measurement. *Journal of Clinical Medicine*, *11*(5), 1338. https://doi.org/10.3390/jcm11051338
75. Mithoowani, S., & Siegal, D. (2024). DOACs: Role of anti-xa and drug level monitoring. *Hematology*, *2024*(1), 178-185. https://doi.org/10.1182/hematology.2024000666
76. Moser, K. A., & Smock, K. J. (2021). Direct oral anticoagulant (DOAC) interference in hemostasis assays. *Hematology*, *2021*(1), 129-133. https://doi.org/10.1182/hematology.2021000241
77. Wuyts, S. C., Moor, J. D., Jochmans, K., Cortoos, P., Vandervorst, F., Steurbaut, S., Dupont, A. G., & Cornu, P. (2025). Prescriptions of cyp3a4- and P-GP inducers for patients on direct oral anticoagulants: Bridging the gap between epidemiology and patient management for optimal thromboembolic event prevention. *British Journal of Clinical Pharmacology*, *91*(4), 1114-1131. https://doi.org/10.1002/bcp.70007
78. Guo, X., Li, M., Du, X., Jiang, C., Li, S., Tang, R., Sang, C., Yu, R., Long, D., Dong, J., & Ma, C. (2022). Multimorbidity, polypharmacy and inappropriate prescribing in elderly patients with atrial fibrillation: A report from the China atrial fibrillation registry study. *Frontiers in Cardiovascular Medicine*, *9*. https://doi.org/10.3389/fcvm.2022.988799
79. Medicines and Healthcare products Regulatory Agency. (2023, May 25). Direct-acting oral anticoagulants (DOACs): paediatric formulations; reminder of dose adjustments in patients with renal impairment. GOV.UK. https://www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-paediatric-formulations-reminder-of-dose-adjustments-in-patients-with-renal-impairment
80. Costache, R. S., Dragomirică, A. S., Gheorghe, B. E., Balaban, V. D., Stanciu, S. M., Jinga, M., & Costache, D. O. (2023). Oral anticoagulation in patients with chronic liver disease. *Medicina*, *59*(2), 346. https://doi.org/10.3390/medicina59020346
81. Martins, A. S., Monteiro, C., & Duarte, A. P. (2025). Risks of oral anticoagulants: Interactions with drugs and medicinal plants. *Scientia Pharmaceutica*, *93*(3), 35. https://doi.org/10.3390/scipharm93030035
82. Hwang, K. W., Choi, J. H., Lee, S. Y., Lee, S. H., Chon, M. K., Lee, J., Kim, H., Kim, Y., Choi, H. O., Kim, J. S., Park, Y., Kim, J. H., Chun, K. J., Nam, G., & Choi, K. (2023). Oral anticoagulants and concurrent rifampin administration in tuberculosis patients with non-valvular atrial fibrillation. *BMC Cardiovascular Disorders*, *23*(1). https://doi.org/10.1186/s12872-023-03212-z
83. El-Bosily, H. M., Abd El Meguid, K. R., Sabri, N. A., & Ahmed, M. A. (2025). Clinical pharmacist-led anticoagulation stewardship program: Improve physician adherence to evidence-based guidelines and reduce anticoagulant-related medication errors. *Future Journal of Pharmaceutical Sciences*, *11*(1). https://doi.org/10.1186/s43094-025-00791-w