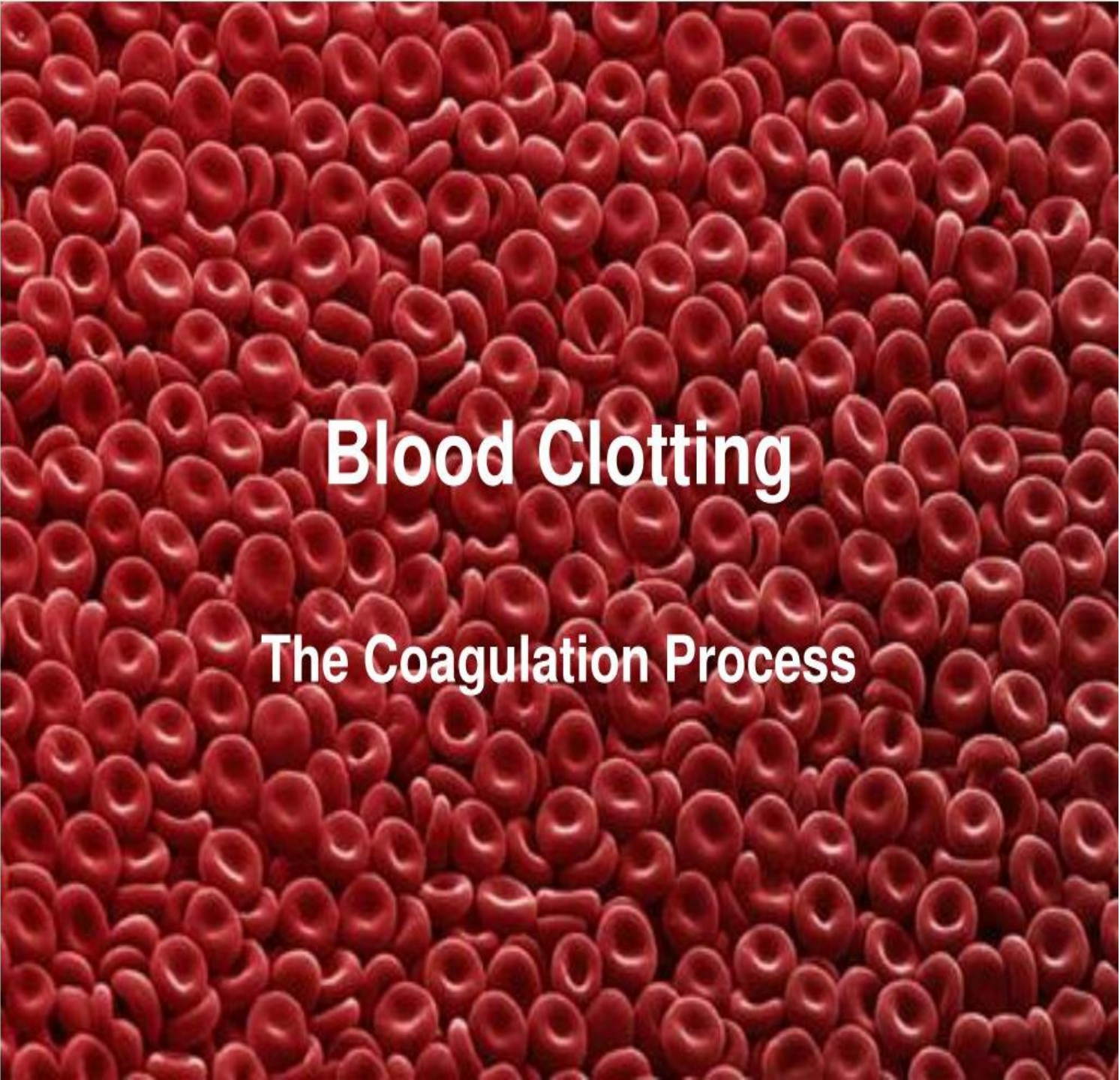


Anticoagulants & antiplatelets 2

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BCPS

A dense, close-up microscopic view of numerous red blood cells, which are biconcave and reddish in color, filling the entire right half of the slide.

Blood Clotting

The Coagulation Process

Blood Coagulation

The coagulation process that generates thrombin consists of two interrelated pathways, the extrinsic and the intrinsic systems. The extrinsic system is initiated by the activation of clotting factor VII by tissue factor (also known as thromboplastin). Tissue factor is a membrane protein that is normally separated from the blood by the endothelial cells that line the vasculature. However, in response to vascular injury, tissue factor becomes exposed to blood. There, it can bind and activate factor VII, initiating the extrinsic pathway. The intrinsic system is triggered by the activation of clotting factor XII. This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.

The three pathways that makeup the classical blood coagulation pathway

Intrinsic

surface contact

XII → XII_a

XI → XI_a

IX → IX_a

(VIII, PL, Ca⁺⁺)

X → X_a

(V, PL, Ca⁺⁺)

prothrombin

thrombin

(serine protease)

fibrinogen

fibrin

stable fibrin
clot

XII – Hageman factor, a serine protease

XI – Plasma thromboplastin, antecedent serine protease

IX – Christmas factor, serine protease

VII – Stable factor, serine protease

XIII – Fibrin stabilising factor, a transglutaminase

PL – Platelet membrane phospholipid

Ca⁺⁺ – Calcium ions

TF – Tissue Factor

(_a = active form)

Extrinsic

TF:VII_a

tissue damage

Common

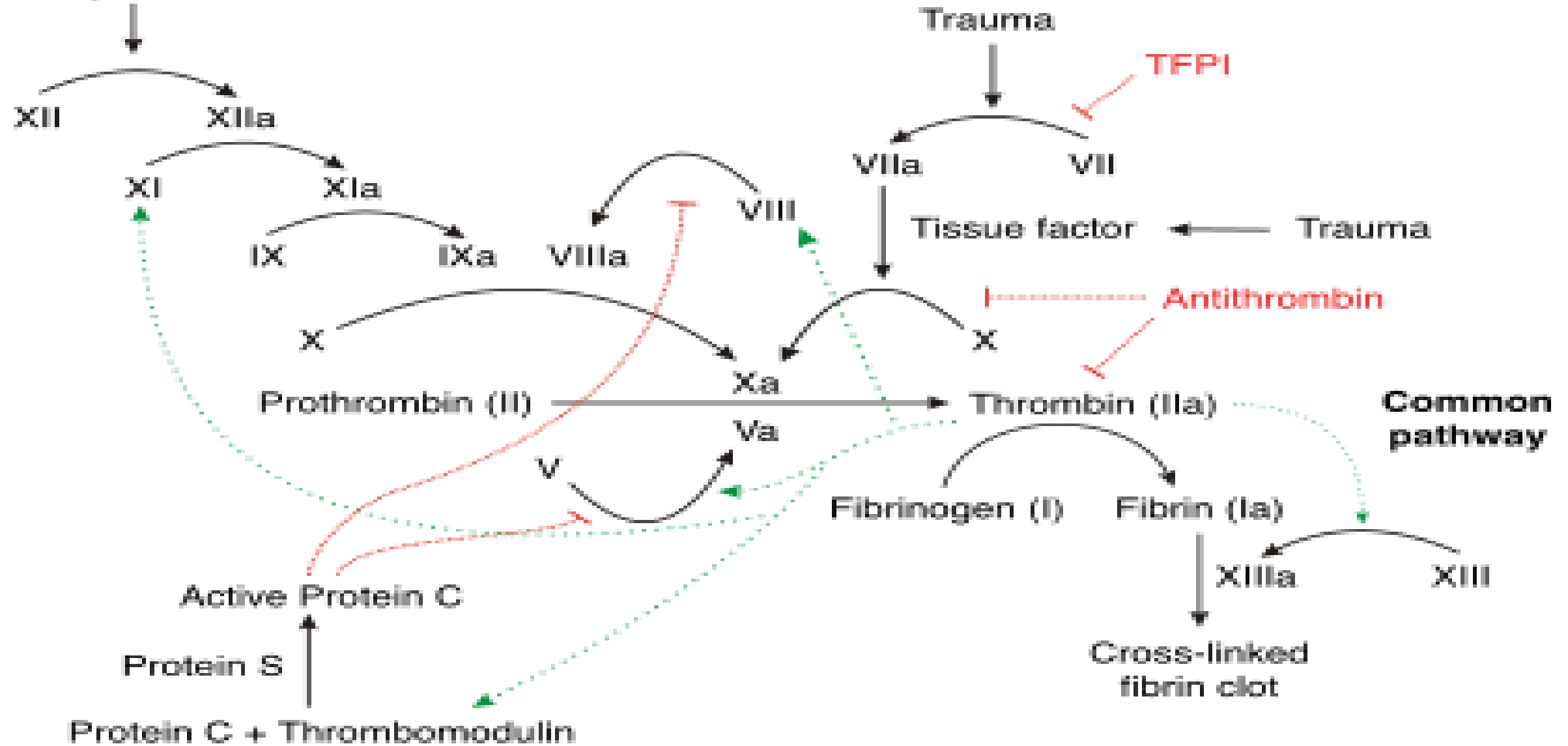
XIII

XIII_a

Contact activation (intrinsic) pathway

Tissue factor (extrinsic) pathway

Damaged surface



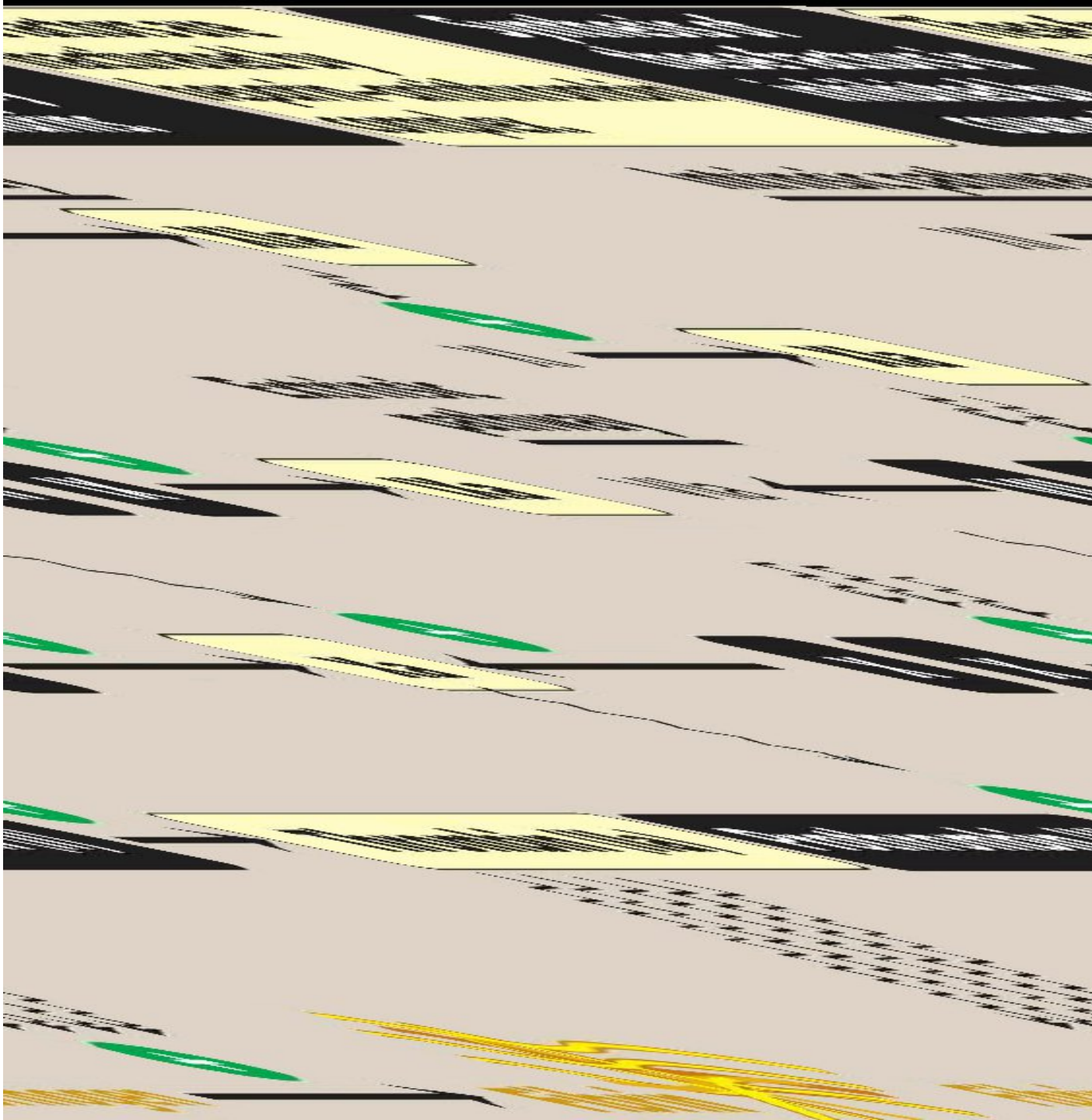
All clotting factors are proteins and synthesized in liver except:

- factor IV: calcium
- factor VIII carrier protein vonWillebrand factor

- Coagulation cascade is activated by 2 pathways, the extrinsic and intrinsic which culminates into a common pathway. The factors involved in common pathway can be remembered by a mnemonic:

1 X 2 X 5 = 10.

- Factor II (prothrombin): when activated to thrombin, activates factor I and XIII
- Factor V (labile factor): when activated, activates factor II
- Factor X (Stuart power factor): activated by both intrinsic and extrinsic pathway; when activated activates factor II

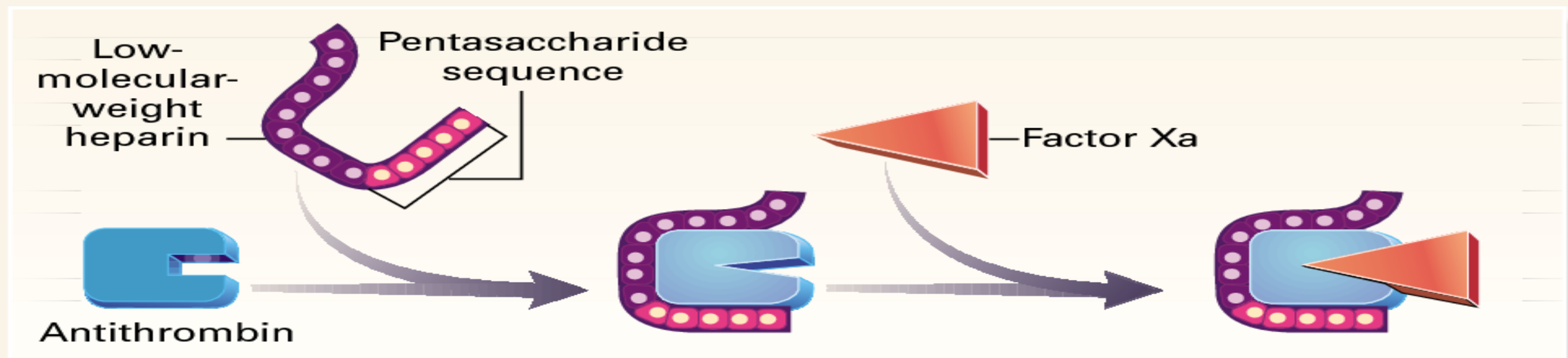
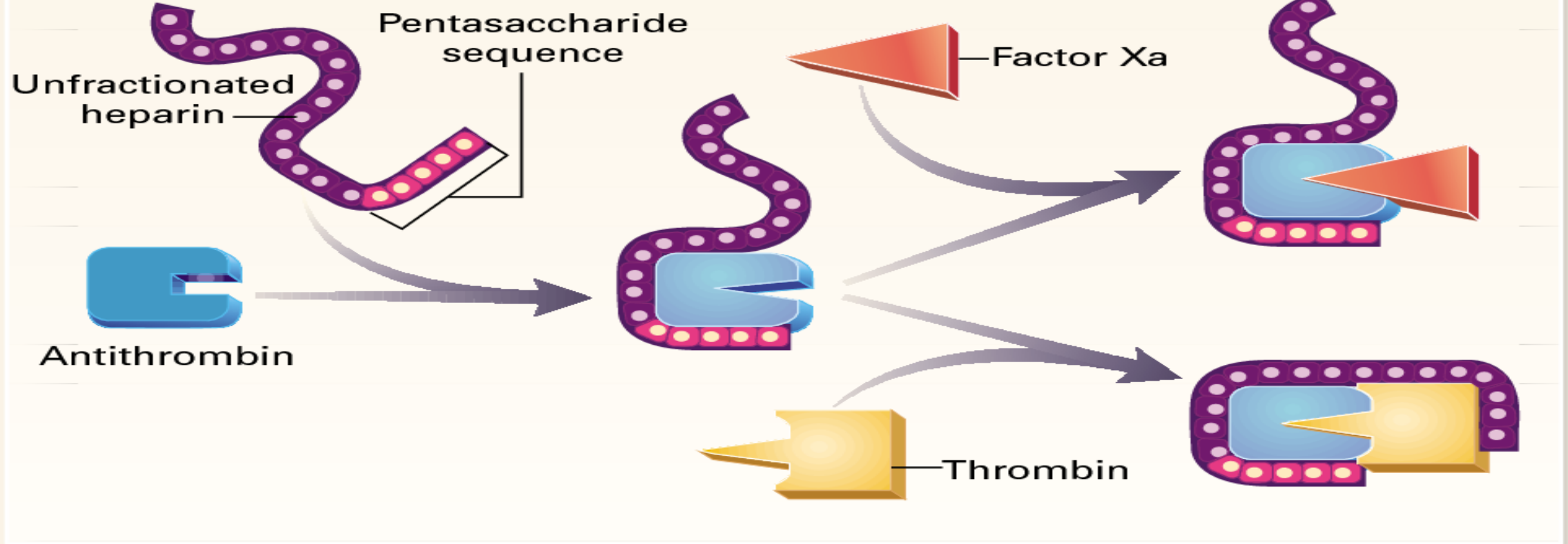


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Parenteral Anticoagulants

Heparin and low molecular weight heparins(Enoxaparin, Dalteparin)

Heparin is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi. Heparin occurs naturally as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown. It is extracted for commercial use from porcine intestinal mucosa. Unfractionated heparin is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights. It is strongly acidic because of the presence of sulfate and carboxylic acid groups. The realization that low molecular weight forms of heparin (LMWHs) can also act as anticoagulants led to the isolation of enoxaparin and dalteparin, produced by depolymerization of unfractionated heparin. The LMWHs are heterogeneous compounds



Mechanism of action

Heparin acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors. Antithrombin III is an α globulin that inhibits serine proteases of thrombin (factor IIa) and factor Xa. In the absence of heparin, antithrombin III interacts very slowly with thrombin and factor Xa. When heparin molecules bind to antithrombin III, a conformational change occurs that catalyzes the inhibition of thrombin about 1000-fold. LMWHs complex with antithrombin III and inactivate factor Xa (including that located on platelet surfaces) but do not bind as avidly to thrombin. A unique pentasaccharide sequence contained in heparin and LMWHs permits their binding to antithrombin III

Therapeutic use

Heparin and the LMWHs limit the expansion of thrombi by preventing fibrin formation. These agents are used for the treatment of acute venous thromboembolism (DVT or PE). Heparin and LMWHs are also used for prophylaxis of postoperative venous thrombosis in patients undergoing surgery (for example, hip replacement) and those with acute MI. These drugs are the anticoagulants of choice for treating pregnant women, because they do not cross the placenta, due to their large size and negative charge. LMWHs do not require the same intense monitoring as heparin, thereby saving laboratory costs and nursing time. These advantages make LMWHs useful for both inpatient and outpatient therapy.

Pharmacokinetics

Heparin must be administered subcutaneously or intravenously, because the drug does not readily cross membranes. The LMWHs are usually administered subcutaneously. [Note: Enoxaparin can be administered intravenously in the treatment of MI.] Heparin is often initiated as an intravenous bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of heparin, titrated to the desired level of anticoagulation according to the activated partial thromboplastin time (aPTT) or anti-Xa level. Whereas the anticoagulant effect with heparin occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection), the maximum anti-factor Xa activity of the LMWHs occurs about 4 hours after subcutaneous injection. It is usually not necessary to monitor coagulation values with LMWHs because the plasma levels and pharmacokinetics of these drugs are more predictable. However, in renally impaired, pregnant, and obese patients, monitoring of factor Xa levels is recommended with LMWHs.

- In the blood, heparin binds to many proteins that neutralize its activity, causing unpredictable pharmacokinetics. Heparin binding to plasma proteins is variable in patients with thromboembolic diseases. Although generally restricted to the circulation, heparin is taken up by the monocyte/macrophage system, and it undergoes depolymerization and desulfation to inactive products. The inactive metabolites, as well as some of the parent heparin undergo renal excretion. The LMWHs are primarily eliminated in the urine. Therefore, renal insufficiency prolongs the half-life of LMWH, and the dose of LMWH should be reduced in patients with renal impairment. The half-life of heparin is approximately 1.5 hours, whereas the half-life of the LMWHs is longer than that of heparin, ranging from 3 to 12 hours.

Adverse effects

The chief complication of heparin and LMWH therapy is bleeding. Careful monitoring of the patient and laboratory parameters is required to minimize bleeding. Excessive bleeding may be managed by discontinuing the drug or by treating with protamine sulfate. When infused slowly, the latter combines ionically with heparin to form a stable, 1:1 inactive complex. It is important that the dosage of protamine sulfate is carefully titrated (1 mg for every 100 units of heparin administered), because protamine sulfate is a weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential. Heparin preparations are obtained from porcine sources and, therefore, may be antigenic. Possible adverse reactions include chills, fever, urticaria, and anaphylactic shock.

In addition, osteoporosis has been observed in patients on long-term heparin therapy. Heparin and LMWHs are contraindicated in patients who

Heparin Induced Thrombocytopenia

HIT

- Heparin-induced thrombocytopenia (HIT) is a life-threatening complication of exposure to heparin (eg, unfractionated heparin, low molecular weight [LMW] heparin) that occurs in a small percentage of patients exposed, regardless of the dose, schedule, or route of administration. HIT results from an autoantibody directed against endogenous platelet factor 4 (PF4) in complex with heparin. This antibody activates platelets and can cause catastrophic arterial and venous thrombosis. Untreated HIT has a mortality rate as high as 20 percent; although with improved recognition and early intervention, mortality rates have been reported as below 2 percent.

HIT type I versus type II – There are two forms of HIT, only one of which is clinically significant. Distinction between these two forms of HIT is made based on clinical parameters such as the timing and degree of platelet count drop, and laboratory testing if needed.

- HIT type I (HIT I) is a mild, transient drop in platelet count that typically occurs within the first two days of heparin exposure. The platelet count typically returns to normal with continued heparin administration. The mechanism appears to be a direct effect of heparin on platelets, causing non-immune platelet aggregation. The typical platelet count nadir is approximately 100,000/microL. This form of HIT is not considered clinically significant, is not associated with thrombosis, and patients can be managed expectantly without discontinuation of heparin.

- HIT type II (HIT II) is a clinically significant syndrome due to antibodies to platelet factor 4 (PF4) complexed to heparin, referred to as "HIT antibodies" or "PF4/heparin antibodies". These antibodies can cause thrombosis along with thrombocytopenia; hence, this syndrome has also been called heparin-induced thrombocytopenia and thrombosis (HITT). The risk of thrombosis, including life-threatening limb gangrene, persists until both heparin is eliminated and a non-heparin anticoagulant is initiated.

Argatroban

Argatroban is a synthetic parenteral anticoagulant that is derived from L-arginine. It is a direct thrombin inhibitor . Argatroban is used for the prophylaxis or treatment of venous thromboembolism in patients with HIT, and it is also approved for use during PCI in patients who have or are at risk for developing HIT. Anticoagulant effects are immediate. Argatroban is metabolized in the liver and has a half-life of about 39 to 51 minutes. Dose reduction is recommended for patients with hepatic impairment. Monitoring includes aPTT, hemoglobin, and hematocrit. As with other anticoagulants, the major side effect is bleeding.

Bivalirudin and desirudin

Bivalirudin and desirudin are parenteral anticoagulants that are analogs of hirudin, a thrombin inhibitor derived from saliva of the medicinal leech. These drugs are selective direct thrombin inhibitors that reversibly inhibit the catalytic site of both free and clot-bound thrombin. Bivalirudin is an alternative to heparin in patients undergoing PCI who have or are at risk for developing HIT and also in patients with unstable angina undergoing angioplasty. In patients with normal renal function, the half-life of bivalirudin is 25 minutes. Dosage adjustments are required in patients with renal impairment. Desirudin is indicated for the prevention of DVT



Fondaparinux

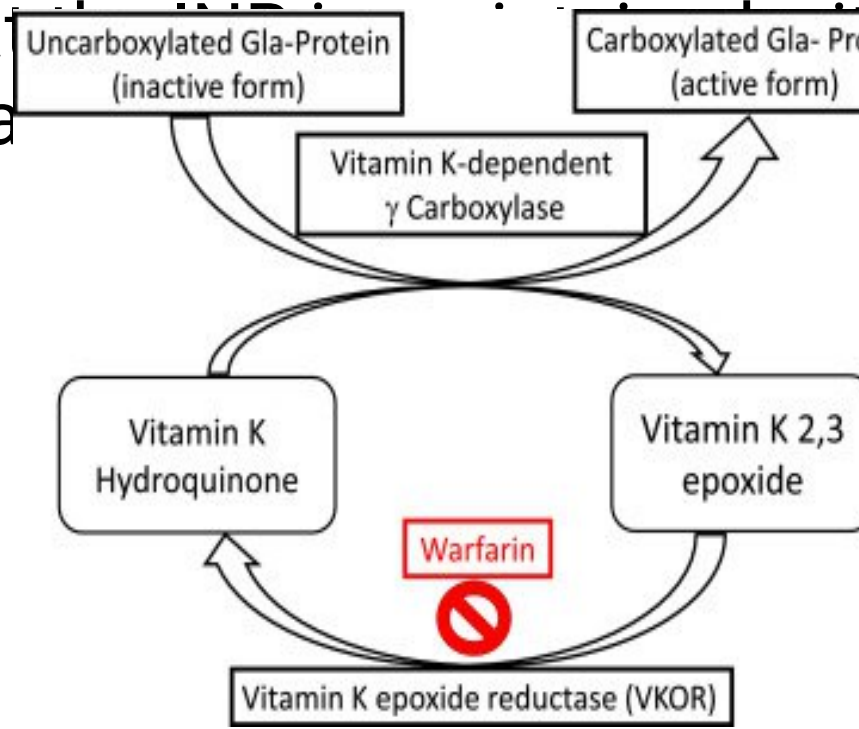
Fondaparinux is a synthetically derived pentasaccharide anticoagulant that selectively inhibits factor Xa. By selectively binding to antithrombin III, fondaparinux potentiates (300- to 1000-fold) the innate neutralization of factor Xa by antithrombin III. Fondaparinux is approved for use in the treatment of DVT and PE and for the prophylaxis of venous thromboembolism in the setting of orthopedic and abdominal surgery. The drug is well absorbed from the subcutaneous route with a predictable pharmacokinetic profile and, therefore, requires less monitoring than heparin. Fondaparinux is eliminated in the urine mainly as unchanged drug with an elimination half-life of 17 to 21 hours. It is contraindicated in patients with severe renal impairment. Bleeding is the major side effect of fondaparinux. There is no available agent for the reversal of bleeding associated with fondaparinux. HIT is less likely with fondaparinux than with heparin but is still a possibility

Oral anticoagulants

Vitamin K Antagonists

Coumarin anticoagulants owe their action to the ability to antagonize the cofactor functions of vitamin K. The only coumarin anticoagulant available in the United States is warfarin. The international normalized ratio (INR) is the standard by which the anticoagulant activity of warfarin therapy is monitored. Warfarin has a narrow therapeutic index.

Therefore, it is important that the INR be maintained in the optimal range as much as possible, and the degree of anticoagulation required



Warfarin

Mechanism of action

Factors II, VII, IX, and X require vitamin K as a cofactor for their synthesis by the liver. These factors undergo vitamin K–dependent posttranslational modification, whereby a number of their glutamic acid residues are carboxylated to form γ -carboxyglutamic acid residues. The γ -carboxyglutamyl residues bind calcium ions, which are essential for interaction between the coagulation factors and platelet membranes. In the carboxylation reactions, the vitamin K–dependent carboxylase fixes CO_2 to form the new COOH group on glutamic acid. The reduced vitamin K cofactor is converted to vitamin K epoxide during the reaction. Vitamin K is regenerated from the epoxide by vitamin K epoxide reductase, the enzyme that is inhibited by warfarin. Warfarin treatment results in the production of clotting factors with diminished activity (10% to 40% of normal), due to the lack of sufficient γ -carboxyglutamyl side chains. Unlike heparin, the anticoagulant effects of warfarin are not observed immediately after drug administration. Instead, peak effects may be delayed for 72 to 96 hours, which is the time required to deplete the pool of circulating clotting factors. The anticoagulant effects of warfarin can be overcome by the administration of vitamin K. However, reversal following administration of vitamin K takes approximately 24 hours.

Consider half-lives of inhibited clotting factors: factor VII = 6 hours, factor IX = 24 hours, factor X = 36 hours, factor II = 72 hours

Therapeutic use

Warfarin is used in the prevention and treatment of DVT and PE, stroke prevention, stroke prevention in the setting of atrial fibrillation and/or prosthetic heart valves, protein C and S deficiency, and antiphospholipid syndrome. It is also used for prevention of venous thromboembolism following orthopedic surgery.

Pharmacokinetics

Warfarin is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation). Warfarin is highly bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk. However, drugs that have a greater affinity for the albumin-binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity. Drugs that affect warfarin binding to plasma proteins can lead to variability in the therapeutic response to warfarin. Warfarin readily crosses the placental barrier. The mean half-life of warfarin is approximately 40 hours, but this value is highly variable among individuals. Warfarin is metabolized by the CYP450 system (mainly CYP2C9) to inactive components. After conjugation to glucuronic acid, the inactive metabolites are excreted in urine and feces. Agents that affect the metabolism of warfarin may alter its therapeutic effect. Warfarin is also metabolized by intestinal bacteria to inactive components.

Follow-up INR monitoring

- i. INR values on a specific day are the result of warfarin doses taken over the previous 3–4 days, and dosing changes made on a specific day are not fully represented in the INR for 3–5 days. Takes 5–7 days to see the full effect of a stable warfarin dose
- ii. If the INR is out of the therapeutic range in the outpatient setting, increase or decrease the cumulative weekly dose by 5%–20%, depending on the INR; if the INR is greater than 4.5, consider holding one or two doses before resuming at the reduced dose.
- iii. In the setting of continuous nasogastric feeding, consider holding the feeds 1 hour before and after the dose.
- iv. If the INR is previously stable or therapeutic and a single out-of-range INR is 0.5 or less above or below the therapeutic range, current dosing can be continued; the INR should be rechecked within 1–2 weeks.
- v. In general, no need to adjust dose if INR is within 0.1 of goal, but would monitor more closely (especially if below goal)
- vi. If the INR decreases to 1.8 or less, the risk of ischemic stroke in NVAF increases by 60%, whereas the risk of bleeding does not significantly increase until the INR is greater than 4.0 (better to be a little high than a little low).
- vii. VKA therapy is well managed when the individual patient's time in therapeutic range (TTR) is greater than 65%–70%. If this level of TTR is not achieved, strategies should be implemented to improve the patient's TTR (e.g., more frequent monitoring, better control of diet, alcohol, drug interactions, referral to a dedicated anticoagulation clinic), or therapy should be changed to a DOAC.

INR	Bleeding	Action
5.0–9.0	Standard risk	Recommend omit 1–2 doses warfarin (1C)
	High risk	Suggest omit 1 dose warfarin and give 1.0–2.5 mg oral vitamin K (2A)
>9.0	No bleeding	Recommend holding warfarin and giving 2.5–5.0 mg oral vitamin K (1B)
Any	Major bleeding	Recommend holding warfarin and giving 10 mg iv vitamin K and giving FFP or PCC or rFVIIa (1C)

Adverse effects

The principal adverse effect of warfarin is bleeding. Minor bleeding may be treated by withdrawal of the drug or administration of oral vitamin K, but severe bleeding may require greater doses of vitamin K given intravenously. Whole blood, frozen plasma, and plasma concentrates of blood factors may also be used for rapid reversal of warfarin. Skin lesions and necrosis are rare complications of warfarin therapy. Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from platelet therapy. Warfarin is teratogenic.

Absolute Contraindications	Some Relative Contraindications
• The presence of a severe or active bleeding diathesis • Non-adherence to medication and INR monitoring • Pregnancy²⁸ (avoided at least during the first trimester and from about 2 to 4 weeks before delivery) • Allergy or intolerance to warfarin (consider warfarin alternative – Nicoumalone)	• Uncontrolled hypertension (> 160/100 mm Hg) • Severe liver disease • Recent surgery and procedures involving the nervous system, spine or eye

Abbreviation: INR = international normalized ratio.
Footnote: *For a complete list of contraindications, refer to the product monograph.

Direct Oral Anticoagulants DOAC

Dabigatran

1. Mechanism of action

Dabigatran etexilate is the prodrug of the active moiety dabigatran, which is an oral direct thrombin inhibitor. Both clot-bound thrombin and free thrombin are inhibited by dabigatran.

2. Therapeutic use

Dabigatran is approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It may also be used in the treatment of DVT and PE in patients who have already received parenteral anticoagulants and as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE. The drug is contraindicated in patients with mechanical prosthetic heart valves and is not recommended in patients with bioprosthetic heart valves.

Direct oral factor Xa inhibitors

Mechanism of action

Apixaban, betrixaban, edoxaban, and rivaroxaban are oral inhibitors of factor Xa. Inhibition of factor Xa reduces the production of thrombin (IIa) from prothrombin.

Therapeutic use

With the exception of betrixaban, these agents are approved for prevention of stroke in nonvalvular atrial fibrillation, as well as the treatment of DVT and PE. Rivaroxaban and apixaban are also used as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE. Betrixaban is indicated for the prophylaxis of DVT and PE in at-risk hospitalized medical patients.

DOAC Pharmacologic Properties

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct IIa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Bioavailability	3%–7%	66% without food, 80%–100% with food	50%	62%
Onset of anticoagulant activity	1.5 hr	2–4 hr	2–3 hr	1–2 hr
Half-life ^a	12–17 hr	9–13 hr	12 hr	9–10 hr
Renal clearance	80%	36%	27%	50%
Protein binding	35%	90%	87%	55%
Removed by dialysis	Yes	No	No	No
P-gp transport	Yes	Yes	Yes	Yes
Hepatic metabolism	None	CYP 3A4/5 and CYP2J2	CYP3A4/5	Minimal (4% CYP3A4/5)

^aHalf-life can be increased in patients with severe illness with renal and/or hepatic failure

Dosing of DOACs in NVAF

Avoid Use ^a	Agent	Standard Dosing	Dose Adjustment ^a
• CrCl < 15 mL/min • Dialysis 150 mg twice daily with meals dronedarone, diltiazem, and clarithromycin	Dabigatran	150 mg twice daily	• CrCl 15–30 mL/min/1.73 m² • CrCl 30–50 mL/min/1.73 m² with ketoconazole or
• CrCl 15–30 mL/min/1.73 m² with amiodarone, verapamil, ketoconazole, dronedarone, diltiazem, and clarithromycin • Rifampin • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide			
• CrCl 15–50 mL/min/1.73 m² • Dialysis^b	• Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan) • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide		Rivaroxaban 20 mg once daily with meals

Agent	Standard Dosing	Dose Adjustment ^a	Avoid Use ^a
a (age ≥ 80 yr, or SCr ≥ 1.5 mg/dL) strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan) • Dialysis^{b,c}	• Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • If on 2.5 mg twice daily – Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan) • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and, enzalutamide	Apixaban 5 mg twice daily	2.5 mg twice daily • Two of three criteria: age ≥ 75 yr, weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL) • Use with caution with strong P-gp inhibitors
once daily	30 mg once daily • CrCl 15–50 mL/min/1.73 m²	• CrCl > 95 mL/min/1.73 m² • CrCl < 15 mL/min/1.73 m² • Dialysis • Rifampin • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and, enzalutamide	Edoxaban 60 mg once daily

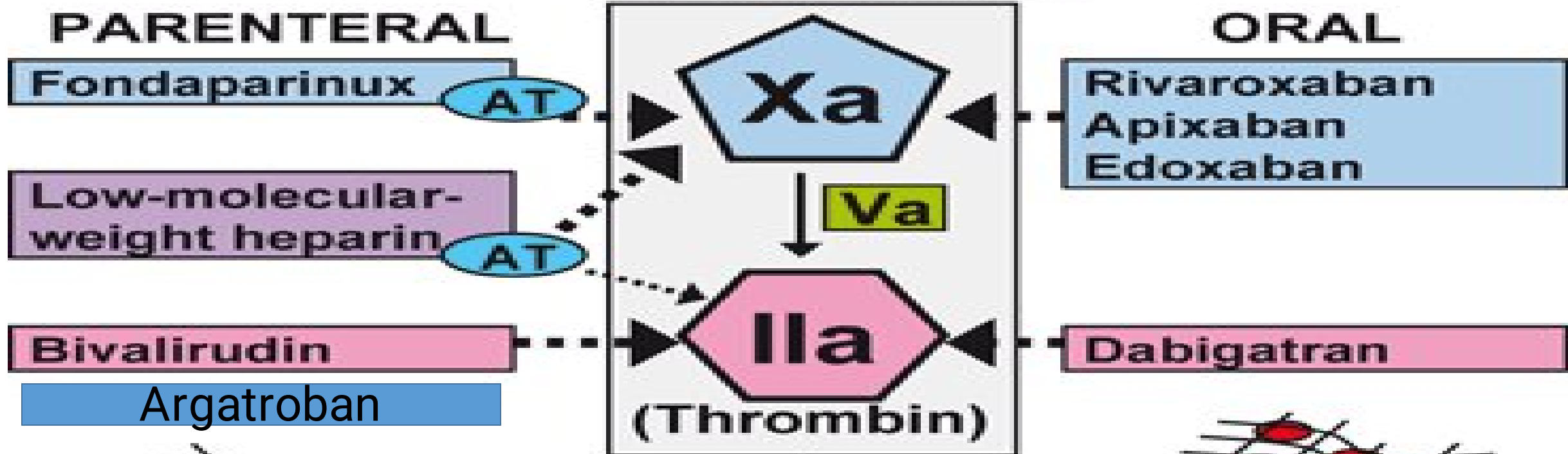
Intrinsic pathway Amplification

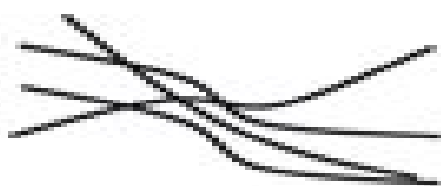


Extrinsic pathway Initiation



PROPAGATION




Fibrinogen

THROMBUS
FORMATION


Fibrin
thrombus

STROKE PREVENTION IN NONVALVULAR ATRIAL FIBRILLATION

Definitions

1. Paroxysmal AF: AF that terminates spontaneously or with intervention within 7 days
2. Persistent AF: Continuous AF that is sustained more than 7 days
3. Longstanding persistent AF: Continuous AF for more than 12 months
4. Permanent AF: Decision of the patient and clinician to stop further attempts to restore and/or maintain normal sinus rhythm and remain in AF
5. NVAf: When discussing the role of direct oral anticoagulants (DOACs), NVAf represents patients without moderate or severe mitral stenosis and those with mechanical heart valves, including patients receiving transcatheter aortic valve replacement (TAVR).

Stroke

1. NVAf increases the risk of stroke by 5-fold compared with patients without AF.
2. AF is responsible for 15%–20% of all strokes.

Risk Stratification for Antithrombotic Therapy Using the CHA₂DS₂-VASc Score_a

	Score	Risk Factor
	1	CHF or LVEF ≤ 40%
	1	Hypertension
	2	Age ≥ 75 yr
	1	Diabetes
thromboembolism	2	Stroke, TIA
vascular disease	1	Vascular
65–74 yr	1	Age
sex category (female)	1	Sex

CHA ₂ DS ₂ -VASc Score of 0 in men or 1 in women	CHA ₂ DS ₂ -VASc Score of 1 in men or 2 in women	CHA ₂ DS ₂ -VASc Score of 2 in men or 3 in women	CHA ₂ DS ₂ -VASc Score of 3 or more in men or 4 or more in women
It is reasonable to omit antithrombotic therapy or consider aspirin	Consider no antithrombotic therapy, oral anticoagulation, or aspirin	Oral anticoagulant therapy is indicated. DOAC over warfarin in DOAC-eligible patients	Reasonable to consider oral anticoagulation over warfarin in DOAC-eligible patients

Components and Bleeding Rates of the HAS-BLED Score

Points		Risk Factors		
	1		Hypertension (systolic BP > 160 mm Hg)	
	1 or 2		Abnormal renal or liver function ^a	
	1		History of stroke	
	1		History of bleeding ^b	
	1		Labile INRs ^c	
	1		Older adults (age > 65)	
	1 or 2		Drugs or alcohol excess ^d	
% of Patients		Risk of Major Bleeding/Yr		Score
	26		1.1%	0
	42		1.9%	1
	24		1.9%	2
3	6		3.7%	
4	2		8.7%	
5	<1		12.5%	
>5	<1%		Undetermined	

-Should not be used to determine who does not receive therapy(Warfarin), but more to balance the risk of stroke with the risk of bleeding.

-unreliable with DOACs.

Thrombolytic Drugs (ALTEPLASE, TENECTEPLASE)

Acute thromboembolic disease in selected patients may be treated by the administration of drugs that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots.

Mechanism of action

The thrombolytic agents act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi. Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as aspirin, or antithrombotics such as heparin.

Therapeutic use

Originally used for the treatment of DVT and serious PE, thrombolytic drugs are currently used less frequently because of tendency to cause serious bleeding. For MI, intracoronary delivery of the drugs is the most reliable in terms of achieving recanalization. However, cardiac catheterization may not be possible in the 2- to 6-hour “therapeutic window,” beyond which significant myocardial salvage becomes less likely. Thus, thrombolytic agents are usually administered intravenously. Thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions. They are also used to dissolve clots that result in strokes.

Alteplase has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. Thus, alteplase is said to be “fibrin selective” at low doses.

Alteplase is approved for the treatment of MI, massive PE, and acute ischemic stroke. Tenecteplase is approved only for use in acute MI.

Treatment of Acute events(stroke)

1. Heparin

- a. Good data on outcomes unavailable; generally not recommended for stroke treatment at therapeutic doses; increases risk of hemorrhagic transformation; heparin is often used for deep venous thrombosis prevention at a dose of 10,000–15,000 units/day given subcutaneously
- b. Avoid in hemorrhagic stroke.

2. Streptokinase: Should be avoided because of excess mortality

3. Tissue plasminogen activator (Alteplase)

- a. Within 4½ hours of symptom onset
- b. Three-month outcome significantly improved (decreased disability)
- c. Intracerebral hemorrhage increased but no increase in mortality
- d. Dose 0.9 mg/kg intravenously (maximum is 90 mg), with 10% as a bolus and the remainder over 1 hour. The bolus should be administered within 60 minutes of hospital arrival.
- e. Antiplatelet agents should be held for 24 hours after tissue plasminogen activator administration.

Exclusion criteria

- i. Intracranial bleeding (or history) or subarachnoid bleeding
- ii. Other active internal bleeding
- iii. Intracranial/spinal surgery, head trauma, stroke within 3 months
- iv. Major surgery or serious trauma within 2 weeks, if risk of bleeding outweighs the anticipated benefits of reduced stroke-related neurologic deficits
- v. Gastrointestinal (GI) hemorrhage within 3 weeks or structural GI malignancy
- vi. Blood pressure greater than 185/110 mm Hg. If medications are given to lower blood pressure,
blood pressure should be stabilized before beginning treatment and maintained below 180/105 mm Hg for at least the first 24 hours after treatment.
- vii. Glucose less than 50 mg/dL or greater than 400 mg/dL, unless subsequently normalized
- viii. Arterial puncture at a noncompressible site within 1 week
- ix. Intracranial intra-axial neoplasm, arteriovenous malformation, or giant unruptured and unsecured aneurysm

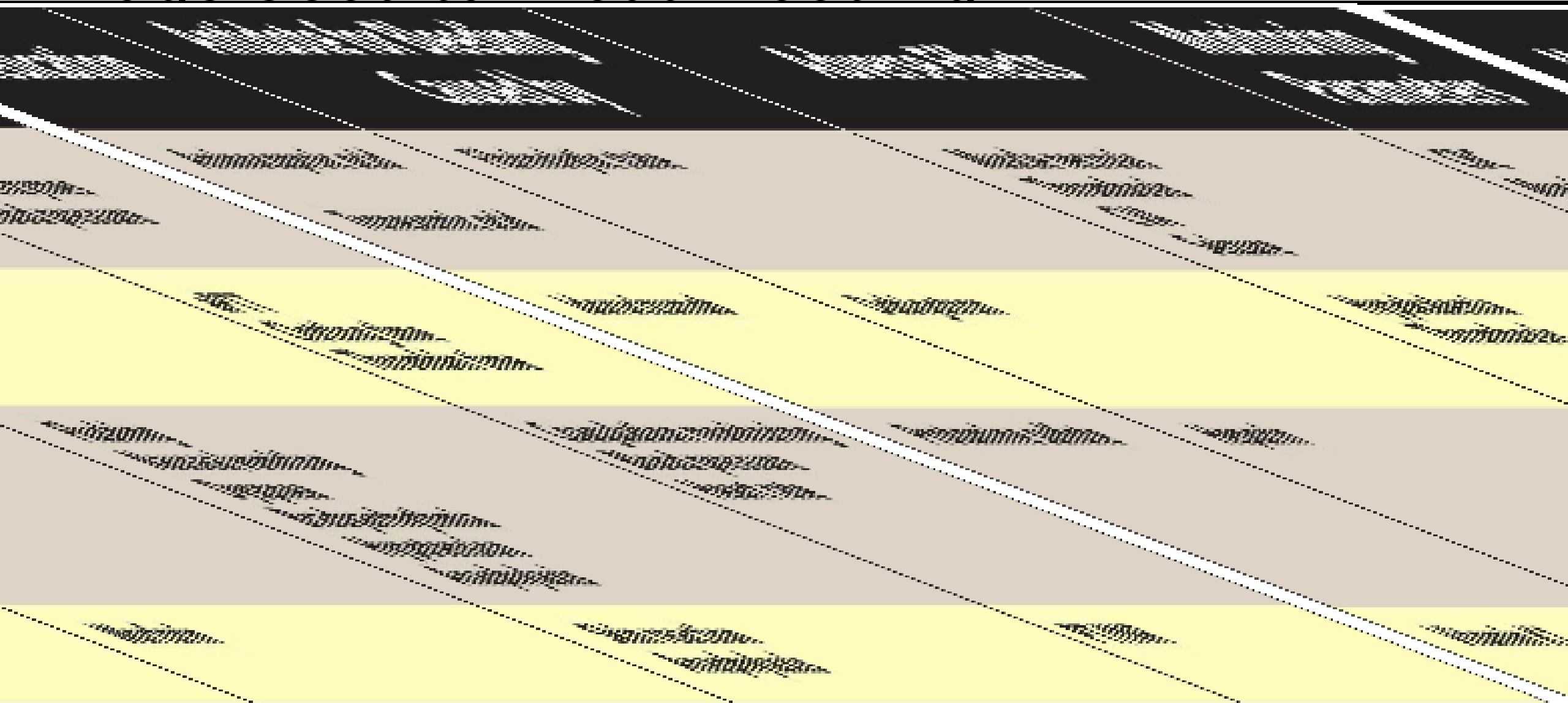
x. INR greater than 1.7, activated partial thromboplastin time greater than 40 seconds, prothrombin time greater than 15 seconds, platelet count less than 100,000 cells/m³, patients who have received a dose of low-molecular-weight heparin within the previous 24 hours, or patients who have taken direct thrombin inhibitors or direct factor Xa inhibitors in the previous 48 hours

xi. Infective endocarditis

xii. Pregnancy, if the anticipated benefits of treating moderate to severe stroke do not outweigh the anticipated risks of uterine bleeding

xiii. Additional criteria for the 3- to 4½-hour period have largely been abandoned. Benefit of treatment with NIH Stroke Scale greater than 25 in this time is uncertain

Drugs Used to Treat Bleeding



Drug	Indication	Contraindications	Monitoring
Protamine	Reverses heparin	None	None
Desmopressin	Platelet dysfunction	None	None
Tranexamic acid	Fibrinolysis	None	None
Vitamin K	Vitamin K deficiency	None	None
Factor VIIa	Factor VII deficiency	None	None
Factor VIII	Factor VIII deficiency	None	None
Factor IX	Factor IX deficiency	None	None
Factor X	Factor X deficiency	None	None
Factor XI	Factor XI deficiency	None	None
Factor XII	Factor XII deficiency	None	None
Factor XIII	Factor XIII deficiency	None	None
Factor XIV	Factor XIV deficiency	None	None
Factor XV	Factor XV deficiency	None	None
Factor XVI	Factor XVI deficiency	None	None
Factor XVII	Factor XVII deficiency	None	None
Factor XVIII	Factor XVIII deficiency	None	None
Factor XIX	Factor XIX deficiency	None	None
Factor XX	Factor XX deficiency	None	None
Factor XXI	Factor XXI deficiency	None	None
Factor XXII	Factor XXII deficiency	None	None
Factor XXIII	Factor XXIII deficiency	None	None
Factor XXIV	Factor XXIV deficiency	None	None
Factor XXV	Factor XXV deficiency	None	None
Factor XXVI	Factor XXVI deficiency	None	None
Factor XXVII	Factor XXVII deficiency	None	None
Factor XXVIII	Factor XXVIII deficiency	None	None
Factor XXIX	Factor XXIX deficiency	None	None
Factor XXX	Factor XXX deficiency	None	None

Summary of drugs used to treat bleeding. aPTT = activated partial thromboplastin time, CBC = complete blood count, CVA = cerebrovascular accident, INR = international normalized ratio, PT = prothrombin time.

Andexaa

injection, lyophilized powder for reconstitution

100mg/single-use vial

Factor Xa Reversal

Indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed because of life-threatening or uncontrolled bleeding

There are 2 dosage regimens (low dose or high dose) to choose from

Safety and efficacy of an additional dose has not been established

Low or high dose regimens

Low dose

Initial IV bolus: 400 mg IV; target infusion rate of 30 mg/min

Follow-on IV infusion: 4 mg/min IV for up to 120 min

High dose

Initial IV bolus: 800 mg IV; target infusion rate of 30 mg/min

Follow-on IV infusion: 8 mg/min IV for up to 120 min

Mechanism of Action

Exerts its procoagulant effect by binding and sequestering the FXa inhibitors, rivaroxaban and apixaban

Another observed procoagulant effect is its ability to bind and inhibit the activity of tissue factor pathway inhibitor (TFPI); inhibiting TFPI activity can increase tissue factor-initiated thrombin generation

Distribution

Vd: 5 L; ~equivalent to blood volume

Elimination

Half-life: 5-7 hr

Clearance: 4.3 L/hr