

Heparins and related parenteral anticoagulants

Injected anticoagulants that work by supercharging the body's own antithrombin, separated from one another by chain length - which decides whether thrombin as well as factor Xa is inhibited, how predictable the effect is, and how likely the immune reaction called heparin-induced thrombocytopenia becomes.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/heparins>

Content updated: 2026-08-20

Quick revision

One Liner: Most drugs in this group work indirectly, by making antithrombin - a natural clotting brake already in the blood - work far harder than it otherwise would, and among those agents almost every difference comes down to how long the sugar chain is. The intravenous direct thrombin inhibitors are the contrast: they block thrombin themselves and need no cofactor.

1. Heparin binds antithrombin III and changes its shape, greatly increasing its ability to inactivate thrombin and factor Xa. [1]
2. To inhibit thrombin, the heparin molecule must be long enough to hold antithrombin and thrombin together on the same chain; inhibiting factor Xa needs only the short binding sequence. [2][1]
3. That length requirement is the whole reason unfractionated heparin blocks both thrombin and factor Xa while low-molecular-weight heparin acts mainly through factor Xa. [2]
4. Fondaparinux is the logical endpoint of shortening the chain: a synthetic pentasaccharide of just five sugars that potentiates antithrombin's neutralisation of factor Xa by roughly three hundredfold and does not inactivate thrombin at all. [7][3]
5. None of these drugs is absorbed from the gut, so all are given by injection or infusion. [1][2]
6. Unfractionated heparin has a short, dose-dependent half-life measured in well under a couple of hours, which is what makes it the agent of choice when anticoagulation may need to be switched off quickly. [1]
7. Unfractionated heparin is monitored with the activated partial thromboplastin time, or with activated clotting time during bypass, extracorporeal support and coronary intervention. [1]
8. Low-molecular-weight heparin has a longer half-life and a more predictable response, so it is usually given at a fixed weight-based dose without routine monitoring. [2]
9. Heparin-induced thrombocytopenia type II is the signature adverse effect of the class: an immune, antibody-mediated reaction that paradoxically causes clotting rather than bleeding. [3]
10. The antibody is directed at a complex of heparin with platelet factor 4, and it activates platelets by binding their Fc receptor, which is what drives the hypercoagulable state. [3]
11. Because antibodies take time to form, type II usually appears after about five to fourteen days of heparin, but can appear on the first day if there was exposure within the previous few months. [3]
12. Type I is different: a non-immune, mild, early fall in platelets that resolves on its own even if heparin continues. [3][1]
13. Risk of heparin-induced thrombocytopenia tracks chain length - higher with unfractionated heparin than with low-molecular-weight heparin, and fondaparinux does not cause it and does not react with the antibodies. [3]
14. Protamine neutralises unfractionated heparin within about five minutes by forming an inactive salt with it, but reverses low-molecular-weight heparin only partly and has no useful effect on fondaparinux. [4][1]
15. Direct thrombin inhibitors given intravenously - argatroban and bivalirudin - are the alternatives used when heparin has to be stopped because of heparin-induced thrombocytopenia. [5][6]
16. Beyond bleeding, chronic heparin use is associated with osteopenia and osteoporosis, and heparin can impair aldosterone synthesis and raise potassium. [1]

Overview

1. The heparins are the parenteral anticoagulants of hospital practice. They are used to prevent and treat venous thrombosis and pulmonary embolism, in atrial fibrillation, during cardiac surgery, extracorporeal circulation and dialysis, in acute coronary syndromes and coronary intervention, in acute limb ischaemia, and in consumptive coagulopathies such as disseminated intravascular coagulation. What unites them is not a chemical structure but a mechanism: none of them attacks a clotting factor itself, and all of them work by making a protein the patient already has - antithrombin - far more effective than it normally is. [1]
2. Antithrombin is a natural inhibitor that slowly inactivates thrombin and factor Xa. Heparin binds it and changes its shape, and the inactivation that would have taken a long time now happens quickly. The catch is geometry. Neutralising factor Xa needs only the short sugar sequence that binds antithrombin, but neutralising thrombin requires the heparin chain to be long enough to hold antithrombin and thrombin against each other at the same time. Unfractionated heparin, with chains averaging around forty-five sugar units, can do both. Low-molecular-weight heparin, averaging about fifteen, mostly cannot reach thrombin. Fondaparinux, a synthetic chain of exactly five sugars, cannot reach it at all. [1][2][3][7]
3. The practical differences follow from that. Unfractionated heparin is given intravenously, has a short and dose-dependent half-life, produces a variable response between patients, and therefore needs measurement - usually the activated partial thromboplastin time, or the activated clotting time in the operating theatre and catheter laboratory. Those same properties make it the preferred agent when anticoagulation may have to be switched off at short notice. Low-molecular-weight heparin is injected under the skin, is absorbed almost completely, lasts longer, behaves predictably enough for fixed weight-based dosing without routine monitoring, and is cleared substantially by the kidney, so kidney function matters. Fondaparinux sits further along the same line again, with a much longer half-life and near-complete renal elimination of unchanged drug. [1][2][7]
4. The adverse effect that defines this class is not bleeding, common though bleeding is. It is heparin-induced thrombocytopenia - specifically its immune form, in which IgG antibodies against a complex of heparin and platelet factor 4 activate platelets and produce a severe hypercoagulable state. The platelet count falls, and the danger is clotting rather than haemorrhage. Because chain length governs how readily those complexes form, the risk is greatest with unfractionated heparin, lower with low-molecular-weight heparin, and absent with fondaparinux. When it occurs, every form of heparin is stopped and replaced with an anticoagulant that does not cross-react, in practice an intravenous direct thrombin inhibitor such as argatroban or bivalirudin. [3][5][6]

Classification and drug examples

Intro: The natural way to divide this group is by how long the sugar chain is, because that determines which clotting factors are reached. The intravenous direct thrombin inhibitors are included because they are the parenteral anticoagulants used when a heparin cannot be, and because contrasting them with heparin is the clearest way to see what indirect inhibition means.

1. Name: Unfractionated heparin

1. Note: Long, heterogeneous chains averaging around forty-five sugar units. Long enough to bridge antithrombin to thrombin, so both thrombin and factor Xa are inhibited. Short-acting, variable between patients, and therefore monitored.

Name: Heparin

Unfractionated heparin

Route: Intravenous or subcutaneous

Note: The reference agent of the class, used for treatment and prophylaxis of thrombosis, during cardiac surgery, extracorporeal circulation and dialysis, and in consumptive coagulopathies; its rapid onset and adjustable dosing make it the preferred agent where circumstances may change quickly. [1] [1][3]

2. Name: Low-molecular-weight heparins

2. Note: Shorter, fragmented chains averaging around fifteen sugar units, so the effect is directed mainly at factor Xa. More predictable, longer acting, given subcutaneously and usually without routine monitoring.

1. Name: Enoxaparin

1. Route: Subcutaneous (with an intravenous route used around coronary intervention)

1. Note: The lower-molecular-weight of the two agents described here; subcutaneous bioavailability is essentially complete, and exposure rises in severe kidney impairment so a reduced dose is advised. [2]

2. Name: Dalteparin

2. Route: Subcutaneous or intravenous

2. Note: Slightly larger on average than enoxaparin, with a correspondingly different pharmacodynamic profile; its half-life is longer after subcutaneous than after intravenous administration because absorption is the slow step. [2][3]

3. Name: Synthetic pentasaccharide

3. Note: The antithrombin binding sequence alone, with nothing left over. Selective for factor Xa, with no action on thrombin and no platelet effect, and it does not provoke or react with heparin-induced antibodies.

Name: Fondaparinux

Fondaparinux sodium

Route: Subcutaneous

Note: Binds antithrombin specifically and does not bind platelet factor 4 or red cells; eliminated in the urine largely unchanged, with a much longer half-life than any heparin, and contraindicated in severe kidney impairment. [7][3] [7][3]

4. Name: Intravenous direct thrombin inhibitors

4. Note: Not heparins at all, and included as the contrast: they bind thrombin themselves and need no cofactor, which is why they remain effective when antithrombin is deficient and why they are the substitutes after heparin-induced thrombocytopenia.

1. Name: Argatroban

1. Route: Intravenous

1. Note: A synthetic compound based on the structure of L-arginine that binds reversibly at the active site of thrombin; approved for prophylaxis and treatment of thrombosis in heparin-induced thrombocytopenia and for coronary intervention in patients with or at risk of it. [5]

2. Name: Bivalirudin

2. Route: Intravenous

2. Note: Binds thrombin at both the catalytic site and the anion-binding exosite, acting on thrombin within a thrombus as well as in the circulation, and does not bind platelet factor 4. [6] [5][6]

Mechanism of action

Summary: Heparins bind antithrombin and change its shape so that it inactivates thrombin and factor Xa far faster than it otherwise would. How much of that dual effect survives depends on chain length: a long chain can hold antithrombin and thrombin together, a short one can only present antithrombin to factor Xa.

Target: Antithrombin III, and through it thrombin (factor IIa) and factor Xa; the direct thrombin inhibitors included for contrast bind thrombin itself

1. Step: 1

1. Title: Antithrombin is already there, working slowly

1. Detail: Antithrombin III is a natural regulatory protein circulating in plasma that inactivates several clotting enzymes, most importantly thrombin and factor Xa. On its own it does this slowly enough that clotting proceeds normally. [1]

2. Step: 2

2. Title: Heparin binds antithrombin and changes its shape

2. Detail: Heparin binds antithrombin through a specific pentasaccharide sequence, inducing a conformational change that dramatically increases its inhibitory activity. Fondaparinux, which is that sequence and nothing else, is stated to

potentiate antithrombin's neutralisation of factor Xa by about three hundredfold. [1][7]

3. Step: 3

3. Title: Factor Xa inhibition needs only the binding sequence

3. Detail: Once antithrombin is activated, it can neutralise factor Xa without any further help from the heparin molecule. This is why every drug in the group, however short, retains anti-factor Xa activity. [2][7]

4. Step: 4

4. Title: Thrombin inhibition needs a long chain as well

4. Detail: To inactivate thrombin, the heparin molecule must provide a binding site for thrombin alongside the one for antithrombin, holding both on the same chain. Only the longer chains of unfractionated heparin can do this, which is why unfractionated heparin inhibits both targets and has a faster onset of anticoagulant action. [2]

5. Step: 5

5. Title: Blocking either target stops fibrin forming

5. Detail: Inactivating factor Xa means prothrombin is not converted to thrombin; inactivating thrombin means fibrinogen is not converted to fibrin. Either way the final common pathway is interrupted and no stable clot forms, which prolongs clotting times without affecting bleeding time. [2][1]

6. Step: 6

6. Title: The effect is capped by how much antithrombin there is

6. Detail: Because the drug works through a cofactor, its effect depends on the patient's antithrombin level. Inflammation, major thrombosis, malignancy, the postoperative state and inherited deficiency all reduce the response, a phenomenon described as heparin resistance. [1]

7. Step: 7

7. Title: Long chains also bind platelet factor 4, which is where the immune problem starts

7. Detail: Platelet factor 4 is positively charged and binds negatively charged heparin with high affinity. The shorter the chain and the smaller the molecule, the less readily it binds plasma proteins and cell surfaces, which is why the risk of the immune reaction falls from unfractionated heparin to low-molecular-weight heparin and disappears with fondaparinux. [3]

8. Step: 8

8. Title: Direct thrombin inhibitors bypass the cofactor entirely

8. Detail: Argatroban binds reversibly at the active site of thrombin, and bivalirudin binds both the catalytic site and the anion-binding exosite, in circulating and clot-bound thrombin alike. Neither needs antithrombin, and bivalirudin does not bind platelet factor 4, which is what makes them usable after heparin-induced thrombocytopenia. [5][6]

9. Step: 9

9. Title: Protamine reverses by charge, not by receptor

9. Detail: Protamine is a positively charged arginine-rich peptide that forms an inactive salt aggregate with strongly negatively charged unfractionated heparin, neutralising it within about five minutes. Because the interaction depends on charge and chain size, it reverses low-molecular-weight heparin only partly. [4]

Major clinical uses

1. Drug: Unfractionated heparin

1. Indication: Prevention and treatment of venous thromboembolism, and anticoagulation in atrial fibrillation

1. Line: first-line parenteral option

1. Note: An approved indication covering deep vein thrombosis and pulmonary embolism; where a vitamin K antagonist is being started for acute venous thromboembolism, guidance directs initial parenteral therapy with a heparin or fondaparinux. [1]

2. Drug: Unfractionated heparin

2. Indication: Anticoagulation during cardiac surgery, cardiopulmonary bypass, extracorporeal circulation and dialysis

2. Line: standard of care

2. Note: Clotting time is measured before bypass begins and at intervals during it, because the response to a weight-based bolus varies substantially between patients. [1]
3. Drug: Unfractionated heparin
3. Indication: Acute coronary syndrome and percutaneous coronary intervention
3. Line: recommended parenteral anticoagulant
3. Note: Guidance directs parenteral anticoagulation from diagnosis, before angiography and through the procedure, because thrombin generation and platelet activation make this a period of high thrombotic risk; a direct thrombin inhibitor is substituted where heparin-induced thrombocytopenia is known or suspected. [1]
4. Drug: Unfractionated heparin
4. Indication: Acute limb ischaemia
4. Line: prompt first-line treatment
4. Note: Given at diagnosis unless contraindicated, to prevent the clot extending while revascularisation is planned; rapid onset and adjustable dosing are the stated reasons for preferring it here. [1]
5. Drug: Low-molecular-weight heparin
5. Indication: Prophylaxis and treatment of venous thromboembolism, including in hospitalised and surgical patients
5. Line: first-line subcutaneous option
5. Note: Used on acute or elective hospital admission for prophylaxis, and for treatment of established deep vein thrombosis and pulmonary embolism; recommended for thromboprophylaxis in hospitalised medical patients and in surgical and high-risk ambulatory cancer patients. [2]
6. Drug: Low-molecular-weight heparin
6. Indication: Anticoagulation in pregnancy, and bridging around planned procedures
6. Line: preferred where an oral agent is unsuitable
6. Note: The oral agents cross the placenta and pose fetal risk, so a subcutaneous agent is used instead; low-molecular-weight heparin is also the preferred bridging option for patients at high thromboembolic risk around surgery, and it may be used where there is a risk of recurrent miscarriage. [2]
7. Drug: Fondaparinux
7. Indication: Prophylaxis of deep vein thrombosis after hip fracture, hip replacement, knee replacement or abdominal surgery
7. Line: approved prophylaxis
7. Note: Started only after bleeding has been controlled following surgery; extended prophylaxis is described after hip fracture surgery. [7]
8. Drug: Fondaparinux
8. Indication: Anticoagulation in a patient with a history of heparin-induced thrombocytopenia
8. Line: alternative to a heparin
8. Note: Described as safe to use in patients with a history of the reaction, and potentially in treating the acute episode, because it neither causes the reaction nor reacts with the antibodies. [3]
9. Drug: Argatroban and bivalirudin
9. Indication: Anticoagulation in heparin-induced thrombocytopenia, and during coronary intervention in affected patients
9. Line: first-line non-heparin option
9. Note: Argatroban is approved for prophylaxis and treatment of thrombosis in this setting and for coronary intervention in patients with or at risk of it; bivalirudin is indicated for intervention including in affected patients and is endorsed in interventional cardiology guidance. [5][6]

Pharmacokinetics

1. Drug: Unfractionated heparin
1. Route: Intravenous or subcutaneous

1. Absorption: Not absorbed from the gastrointestinal tract, so it must be given parenterally; intravenous injection gives a rapid onset and quickly reaches peak plasma concentration
1. Metabolism: Not degraded enzymatically; cleared by the liver and by uptake into the reticuloendothelial system
1. Elimination: A rapid saturable phase mediated by binding to endothelial cells, macrophages and plasma proteins, followed by a slower first-order phase
1. Half Life: Short and dose-dependent, well under a couple of hours, and longer in older patients
1. Dose Adjust: Titrated against the activated partial thromboplastin time using an institutional nomogram, or against activated clotting time during bypass, extracorporeal support and coronary intervention; anti-factor Xa activity is used where those tests are unreliable [1]
2. Drug: Enoxaparin
2. Route: Subcutaneous, with an intravenous route around coronary intervention
2. Absorption: Essentially complete after subcutaneous injection, with maximum anti-factor Xa activity a few hours later
2. Metabolism: Hepatic desulfation and depolymerisation into smaller fragments with reduced potency
2. Elimination: Partly renal, with a proportion of anti-factor Xa activity recovered in urine within a day
2. Half Life: Several hours after a single subcutaneous dose, and longer with repeated dosing
2. Dose Adjust: Reduced in severe kidney impairment for both treatment and prophylaxis; no adjustment is advised across the moderate range, and body weight influences the regimen [2]
3. Drug: Dalteparin
3. Route: Subcutaneous or intravenous
3. Absorption: High but not complete subcutaneous bioavailability, with peak anti-factor Xa activity a few hours after injection
3. Metabolism: As for the class, by hepatic desulfation and depolymerisation
3. Elimination: Renal, and prolonged in chronic kidney disease requiring haemodialysis
3. Half Life: A few hours after intravenous administration, and longer after subcutaneous injection because absorption is the rate-limiting step
3. Dose Adjust: Adjusted in severe kidney impairment according to the labelling [2]
4. Drug: Fondaparinux
4. Route: Subcutaneous
4. Absorption: Rapid and complete after subcutaneous injection
4. Metabolism: Not appreciably metabolised; it binds antithrombin specifically and does not bind platelet factor 4, other plasma proteins or red cells to any significant extent
4. Elimination: Eliminated in the urine mainly as unchanged drug, with most of a dose recovered within three days in people with normal kidney function
4. Half Life: Substantially longer than any heparin, so the anticoagulant effect persists for days after the last dose and longer still if kidney function is impaired
4. Dose Adjust: Contraindicated in severe kidney impairment for prophylaxis or treatment of venous thromboembolism, and stopped immediately if severe impairment develops during treatment [7]
1. The monitoring test follows the mechanism. Unfractionated heparin inhibits thrombin, which the activated partial thromboplastin time detects, while the shorter agents act mainly on factor Xa, so anti-factor Xa activity is the measurement used when a level is needed at all. [1][2]
2. Kidney function matters progressively more as the chain gets shorter: unfractionated heparin is cleared by the liver and the reticuloendothelial system, low-molecular-weight heparins are partly renal, and fondaparinux leaves almost entirely in the urine unchanged. [1][2][7]
3. Heparin used only to keep an intravenous line open is not therapeutic anticoagulation, and that use has declined because even small exposures carry risk. [1]
4. This page gives no dose regimens by design. Doses depend on indication, body weight, kidney function, the monitoring target and local protocol, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Bleeding

1. Detail: The most significant complication and the one that governs monitoring. Patients are watched for new bleeding such as blood in the urine or stool, and for bruising, a petechial rash and nosebleeds. [1]

2. Effect: Mild thrombocytopenia

2. Detail: A fall in platelets occurs in a substantial minority of heparin-treated patients and is usually mild and of no clinical consequence; the concern is distinguishing it from the immune form. [1]

3. Effect: Injection site reactions

3. Detail: Local reactions are common with subcutaneous administration, and patients frequently dislike self-injection because of pain or bleeding at the site - a real determinant of which anticoagulant is chosen for long courses. [1][2]

4. Effect: Hyperkalaemia

4. Detail: Heparin can impair aldosterone synthesis, and the resulting rise in potassium matters most in kidney impairment, diabetes, metabolic acidosis, or when a potassium-sparing drug is also being taken. [1]

1. Effect: Heparin-induced thrombocytopenia, type II

1. Detail: An immune, antibody-mediated reaction that usually appears after about five to fourteen days of exposure, or on the first day if there has been exposure within the preceding few months. It produces an intensely hypercoagulable state, with up to half of affected patients developing a thromboembolic complication and a substantial reported mortality.

1. Action: Assessed with the 4T score at the bedside. Above the action threshold, all heparin exposure - including flushes, coated catheters and dialysate - is stopped and a non-heparin anticoagulant started, with antibody and functional testing sent to confirm the diagnosis. [3][1]

2. Effect: Thrombosis complicating heparin-induced thrombocytopenia

2. Detail: Deep vein thrombosis, pulmonary embolism and skin necrosis are the commonest complications, and both venous and arterial territories can be involved. Risk is highest in the first days but the prothrombotic state persists for weeks after heparin is stopped.

2. Action: Treated as an indication for full therapeutic anticoagulation with a non-cross-reacting agent rather than for observation. [3]

3. Effect: Warfarin-associated skin necrosis in acute heparin-induced thrombocytopenia

3. Detail: Starting or continuing warfarin during the acute phase lowers protein C and S further in a patient who is already hypercoagulable, and skin necrosis is a recognised consequence.

3. Action: Where warfarin has recently been started, the source describes holding it and giving vitamin K to restore protein C and S stores before anticoagulation is transitioned. [3]

4. Effect: Osteopenia and osteoporosis with prolonged use

4. Detail: Linked to chronic heparin therapy rather than to short courses, and one of the reasons long-term parenteral anticoagulation is avoided where an alternative exists.

4. Action: Considered when parenteral anticoagulation is expected to continue for a long period, particularly in pregnancy where oral options are unsuitable. [1]

5. Effect: Spinal or epidural haematoma

5. Detail: Bleeding into the spinal canal can follow neuraxial anaesthesia or spinal puncture in a patient anticoagulated with a low-molecular-weight heparin, a heparinoid or fondaparinux, and may cause long-term or permanent paralysis.

5. Action: The risks and benefits are weighed before any neuraxial procedure, and patients are watched afterwards for midline back pain, numbness, tingling or weakness in the legs, and bladder or bowel disturbance. [7]

6. Effect: Protamine reactions

6. Detail: Anaphylaxis with hypotension, bronchoconstriction and bradycardia is the commonest serious reaction, and pulmonary hypertension from thromboxane A2 release can be catastrophic, raising pulmonary vascular resistance many times over.

6. Action: Given by slow infusion, often after a small test dose, and usually through a peripheral rather than a central line; suspected anaphylaxis is treated as any other perioperative anaphylaxis. [4]

1. Drug: Unfractionated heparin

1. Effect: The highest risk of heparin-induced thrombocytopenia in the group, because its long heterogeneous chains bind platelet factor 4 most readily; it also carries the hyperkalaemia and long-term bone effects. [3][1]

2. Drug: Low-molecular-weight heparins

2. Effect: Lower risk of the immune reaction than unfractionated heparin, but not zero, and accumulation in severe kidney impairment is the practical hazard that distinguishes them. [3][2]

3. Drug: Fondaparinux

3. Effect: Does not cause heparin-induced thrombocytopenia and does not react with the antibodies, but its long half-life and near-complete renal elimination mean the effect cannot be quickly withdrawn and it is contraindicated in severe kidney impairment. [3][7]

4. Drug: Protamine

4. Effect: In excess it becomes an anticoagulant in its own right, impairing platelet function, interfering with clotting factors and stimulating clot breakdown, so over-dosing worsens rather than corrects the bleeding. [4]

Contraindications, precautions and interactions

1. Active major bleeding, which is a stated contraindication for fondaparinux and the situation in which anticoagulation is stopped rather than adjusted. [7]

2. Bacterial endocarditis, listed as a contraindication for fondaparinux and as a caution for heparin because of the bleeding risk. [7][1]

3. Severe kidney impairment in a patient being considered for fondaparinux for prophylaxis or treatment of venous thromboembolism. [7]

4. Continued heparin of any kind once immune heparin-induced thrombocytopenia is suspected above the action threshold, including line flushes, heparin-coated catheters and heparin in dialysate. [3]

1. Severe uncontrolled hypertension, and major surgery involving the brain, spinal cord or eye, both of which raise the consequences of any bleeding. [1]

2. Recent or ongoing spinal tap or spinal anaesthesia, given the risk of bleeding into the spinal canal. [1][7]

3. Haematological disorders including haemophilia, thrombocytopenia and vascular purpura. [1]

4. Hereditary antithrombin III deficiency in a patient also receiving antithrombin III concentrate, where the heparin requirement falls. [1]

5. Ulcerative lesions of the gastrointestinal tract, or continuous gastric or intestinal drainage. [1]

6. Liver disease and menstruation, both listed among the situations calling for particular care. [1]

7. Older age, in whom equivalent doses of unfractionated heparin produce higher plasma concentrations and slower elimination can prolong the activated partial thromboplastin time. [1]

1. With: Warfarin during the acute phase of heparin-induced thrombocytopenia

1. Effect: Lowering protein C and S in an already hypercoagulable patient risks skin necrosis, so warfarin recently started is held and vitamin K given to replete those stores. [3]

2. With: Other drugs affecting haemostasis

2. Effect: Antiplatelet agents and other anticoagulants add bleeding risk, which is why parenteral anticoagulation alongside dual antiplatelet therapy in acute coronary syndrome is a deliberate, time-limited decision. [1]

3. With: Potassium-sparing medicines

3. Effect: Compound heparin's suppression of aldosterone synthesis, raising the risk of hyperkalaemia, particularly alongside kidney impairment, diabetes or metabolic acidosis. [1]

4. With: Antithrombin III concentrate

4. Effect: Restores the cofactor heparin depends on, so the heparin requirement falls and the dose is reduced in patients with hereditary deficiency receiving it. [1]

5. With: Protamine

5. Effect: Neutralises unfractionated heparin by charge within about five minutes; the amount needed is calculated from how much heparin was given in the preceding hours, because heparin's short half-life means the requirement falls quickly with time. [4][1]

6. With: Aspirin before cardiac surgery

6. Effect: Suggested in some studies to reduce protamine-induced pulmonary hypertension, since the mechanism is attributed to thromboxane A2 release and aspirin suppresses thromboxane production irreversibly. [4]

7. With: Transition from low-molecular-weight heparin to unfractionated heparin before delivery

7. Effect: Guidance for pregnant patients with mechanical valve prostheses directs a switch to unfractionated heparin well before a scheduled delivery, so that anticoagulation can be turned off quickly if needed. [2]

Comparison tables

1. Title: Chain length and what it changes

1. Caption: The single organising idea of the class. Properties are for learning; agent choice and dosing are clinical decisions from a current prescribing reference.

1. Key: agent

1. Label: Agent

1. Is Row Header: true

2. Key: length

2. Label: Average chain length

3. Key: targets

3. Label: Targets inhibited

4. Key: monitoring

4. Label: Routine monitoring

5. Key: hit

5. Label: Heparin-induced thrombocytopenia risk

1. Agent: Unfractionated heparin

1. Length: About forty-five saccharide units

1. Targets: Thrombin and factor Xa

1. Monitoring: Activated partial thromboplastin time, or activated clotting time in procedural settings

1. Hit: Highest [3][1]

2. Agent: Low-molecular-weight heparin

2. Length: About fifteen saccharide units

2. Targets: Mainly factor Xa

2. Monitoring: Not routine; anti-factor Xa activity where a level is needed

2. Hit: Lower than unfractionated heparin [2][3]

3. Agent: Fondaparinux

3. Length: Exactly five saccharide units

3. Targets: Factor Xa only; no action on thrombin and no platelet effect

3. Monitoring: Not routine

3. Hit: Does not cause it and does not react with the antibodies [7][3]

4. Agent: Argatroban and bivalirudin

4. Length: Not saccharides - small direct inhibitors

4. Targets: Thrombin, bound directly and without antithrombin

4. Monitoring: Titrated in the setting in which they are used

4. Hit: Non-immune; used as the substitute after the reaction [5][6]

2. Title: The two forms of heparin-associated thrombocytopenia

2. Caption: Distinguishing them is the entire point of the 4T score, because the management is opposite.

1. Key: feature

1. Label: Feature

1. Is Row Header: true

2. Key: type1

2. Label: Type I

3. Key: type2

3. Label: Type II (immune)

1. Feature: Mechanism

1. Type1: Non-immune direct interaction with platelets

1. Type2: IgG antibodies against the heparin-platelet factor 4 complex activating platelets through the Fc receptor [3][1]

2. Feature: Timing

2. Type1: Early, within the first day or two of starting

2. Type2: Usually after about five to fourteen days, or immediately on re-exposure within the preceding few months [3]

3. Feature: Severity

3. Type1: Mild, with no complications

3. Type2: Severe, with a hypercoagulable state and life-threatening complications [3]

4. Feature: What happens if heparin continues

4. Type1: Platelet count normalises on its own

4. Type2: The self-amplifying cycle continues and thrombosis risk rises [3]

5. Feature: Management

5. Type1: Heparin may continue while other causes are sought

5. Type2: All heparin stopped and a non-heparin anticoagulant started at once [3][1]

High-yield exam pearls

1. Pearl: Chain length explains almost everything in this class.

1. Why: Unfractionated heparin averages around forty-five sugar units, low-molecular-weight heparin around fifteen, and fondaparinux exactly five. That single number predicts the target profile, the predictability of the dose response, and the risk of the immune reaction. [3]

2. Pearl: Heparin does not dissolve anything and does not affect bleeding time.

2. Why: It prolongs the time blood takes to clot, but it has no fibrinolytic action and does not act on platelets. The distinction separates it cleanly from the thrombolytics and from the antiplatelet drugs. [1][7]

3. Pearl: Heparin-induced thrombocytopenia presents as clotting, not bleeding.

3. Why: Up to half of affected patients develop a thromboembolic complication and the reported mortality is substantial, so a falling platelet count in a heparin-treated patient is a thrombotic emergency rather than a reason to worry mainly about haemorrhage. [3]

4. Pearl: The prothrombotic state of heparin-induced thrombocytopenia outlasts the heparin.

4. Why: Risk of complications is highest in the first days, but the hypercoagulable state persists for weeks after heparin is stopped, which is why an alternative anticoagulant is started rather than simply withdrawing the drug. [3]

5. Pearl: Warfarin must not be the immediate substitute in acute heparin-induced thrombocytopenia.

5. Why: Warfarin lowers protein C and S first, and in an already hypercoagulable patient that precipitates skin necrosis; where warfarin has just been started, the source describes holding it and giving vitamin K to restore those stores. [3]

6. Pearl: The 4T score comes before the laboratory test, not after it.

6. Why: It scores thrombocytopenia, timing, thrombosis and other causes, and a score at or above the action threshold triggers immediate withdrawal of all heparin and a non-heparin anticoagulant while antibody testing is sent. [3][1]

7. Pearl: The platelet factor 4 immunoassay rules out; the serotonin release assay rules in.

7. Why: The immunoassay is highly sensitive with a strong negative predictive value but poor specificity because it

detects antibody classes not involved in the disease. The functional serotonin release assay measures actual platelet activation and is the confirmatory test. [3]

8. Pearl: Heparin resistance is usually about antithrombin, not about the heparin.

8. Why: Since heparin works only through antithrombin, states that consume or lack it - systemic inflammation, major thrombosis, malignancy, the postoperative state, inherited deficiency - blunt the response, and anti-factor Xa monitoring is used when the activated partial thromboplastin time becomes unreliable. [1]

9. Pearl: Protamine is not a benign antidote.

9. Why: Given too fast or in excess it causes hypotension, pulmonary vasoconstriction, pulmonary hypertension and anaphylaxis, and excess protamine is itself anticoagulant - impairing platelet function, interfering with clotting factors and promoting clot breakdown. [4]

10. Pearl: Bivalirudin does not bind platelet factor 4.

10. Why: That is the mechanistic reason it does not cross-react with heparin-induced thrombocytopenia antibodies, which is exactly why a direct thrombin inhibitor is the substitute rather than another heparin. [6]

Common exam traps

1. Trap: Calling heparin a direct factor Xa inhibitor.

1. Correction: Heparin has no anticoagulant activity of its own. It accelerates antithrombin, which is the molecule that actually inactivates thrombin and factor Xa, and that is why it is described as indirect. [1][5]

2. Trap: Assuming low-molecular-weight heparin is simply a smaller dose of the same drug.

2. Correction: The shorter chain cannot bridge antithrombin to thrombin, so the effect is directed at factor Xa. That changes the monitoring test, the predictability of the response, the reversibility with protamine and the risk of the immune reaction. [2][4]

3. Trap: Treating every fall in platelets on heparin as heparin-induced thrombocytopenia.

3. Correction: Mild thrombocytopenia is common and often clinically unimportant, and type I is a non-immune early drop that resolves on its own. The dangerous form is the immune type II, which is what the 4T score is designed to identify. [1][3]

4. Trap: Stopping heparin and considering the problem solved.

4. Correction: Withdrawal alone leaves the patient in a hypercoagulable state that persists for weeks, so an alternative anticoagulant that does not cross-react with the antibodies is started at the same time. [3]

5. Trap: Forgetting that line flushes and coated catheters count as heparin exposure.

5. Correction: No amount is too small to trigger the reaction, and management explicitly requires stopping all forms of heparin, including flushes, heparin-coated catheters and heparin in dialysate. [3]

6. Trap: Expecting protamine to reverse anything with heparin in its description.

6. Correction: It fully neutralises unfractionated heparin, gives only partial and uncertain reversal of low-molecular-weight heparin, and that low-molecular-weight use is not an approved indication. It is not a general antidote for the class. [4]

7. Trap: Assuming the activated clotting time and the activated partial thromboplastin time are interchangeable.

7. Correction: The activated clotting time is a less sensitive, point-of-care test reserved for settings such as bypass, extracorporeal support and coronary intervention, whereas the activated partial thromboplastin time is the routine measure for therapeutic infusions. [1]

Self-test questions

1. Question: How does heparin produce its anticoagulant effect?

1. By binding thrombin directly and blocking its active site

2. By binding antithrombin III and greatly enhancing its inactivation of thrombin and factor Xa

3. By blocking the synthesis of clotting factors in the liver

4. By converting plasminogen to plasmin

1. Explanation: Heparin binds antithrombin III and induces a conformational change that greatly increases its ability to inactivate clotting factors, most importantly thrombin and factor Xa. The drug itself has no direct action on those enzymes. [1]

2. Question: Why does low-molecular-weight heparin act mainly on factor Xa rather than on thrombin?

1. It binds a different site on antithrombin
2. Its chain is too short to hold antithrombin and thrombin together simultaneously
3. It is destroyed by thrombin before it can act
4. It works without antithrombin altogether

2. Explanation: Inhibiting thrombin requires the heparin molecule to bridge antithrombin and thrombin on the same chain, which needs a long saccharide chain. Factor Xa inhibition requires only the antithrombin binding sequence, so a shorter chain retains it. [2]

3. Question: Which anticoagulant is a synthetic pentasaccharide that does not cause heparin-induced thrombocytopenia?

1. Enoxaparin
2. Dalteparin
3. Fondaparinux
4. Unfractionated heparin

3. Explanation: Fondaparinux consists of only the five sugars that make up the antithrombin binding sequence. Because it is too small to form the complexes that provoke the immune response, it does not cause the reaction and does not react with heparin-induced antibodies. [3][7]

4. Question: What is the immunological basis of type II heparin-induced thrombocytopenia?

1. IgE antibodies against heparin causing mast cell degranulation
2. IgG antibodies against a heparin-platelet factor 4 complex that activate platelets via the Fc receptor
3. Direct toxicity of heparin to megakaryocytes
4. Complement-mediated lysis of platelets without antibody involvement

4. Explanation: Platelet factor 4 binds heparin with high affinity, and IgG raised against that complex engages the platelet Fc receptor. Activated platelets release more platelet factor 4 and prothrombotic mediators, driving a self-amplifying hypercoagulable cycle. [3]

5. Question: A patient develops type II heparin-induced thrombocytopenia. What is the correct immediate management approach?

1. Stop heparin and observe, since the platelet count will recover
2. Stop all forms of heparin and start a non-heparin anticoagulant
3. Switch to a lower dose of the same heparin
4. Start warfarin immediately as the sole replacement

5. Explanation: All heparin exposure is stopped, including flushes and coated catheters, and an alternative anticoagulant is started because the prothrombotic state persists for weeks. Warfarin alone is not appropriate acutely, since falling protein C risks skin necrosis. [3]

6. Question: Which laboratory test is the confirmatory, functional test for heparin-induced thrombocytopenia?

1. Platelet factor 4 immunoassay
2. Activated partial thromboplastin time
3. Serotonin release assay
4. Anti-factor Xa activity

6. Explanation: The immunoassay detects antibodies and is sensitive but poorly specific, so it is best at ruling the diagnosis out. The serotonin release assay measures whether the patient's antibodies actually activate platelets in the presence of heparin, and is the gold standard for confirmation. [3]

7. Question: Which statement about protamine is correct?

1. It reverses fondaparinux completely

2. It neutralises unfractionated heparin rapidly by forming an inactive salt complex
3. It has no adverse effects of clinical importance
4. It works by displacing heparin from antithrombin
7. Explanation: Protamine is a positively charged peptide that forms an inactive salt aggregate with the strongly negatively charged heparin molecule, neutralising it within about five minutes. Reversal of low-molecular-weight heparin is partial only, and protamine carries a real risk of anaphylaxis and pulmonary hypertension. [4]
8. Question: Why is an intravenous direct thrombin inhibitor chosen after heparin-induced thrombocytopenia?
 1. It works faster than any heparin
 2. It does not bind platelet factor 4 and so does not cross-react with the causative antibodies
 3. It has no bleeding risk
 4. It can be given by mouth
8. Explanation: Bivalirudin binds thrombin at its catalytic site and anion-binding exosite and does not bind platelet factor 4, so there is no cross-reactivity with heparin-induced antibodies. Argatroban is likewise a direct, non-immune inhibitor and is licensed for this setting. [6][5]
9. Question: A patient on unfractionated heparin is not achieving the expected effect despite escalating infusion rates. What is the most likely explanation?
 1. Antithrombin deficiency or consumption, so-called heparin resistance
 2. The patient has developed antibodies that destroy heparin
 3. Heparin is being cleared by the kidney too quickly
 4. The patient has an inherited excess of antithrombin
9. Explanation: Heparin acts only through antithrombin, so inflammation, major thrombosis, malignancy, the postoperative state and inherited antithrombin deficiency all blunt the response. In these situations anti-factor Xa monitoring is used because the activated partial thromboplastin time becomes unreliable. [1]

Frequently asked questions

1. Question: Why is heparin called an indirect anticoagulant?
 1. Answer: Because it does not attack any clotting factor itself. It binds antithrombin, a natural inhibitor already present in the blood, and changes its shape so that antithrombin inactivates thrombin and factor Xa far more quickly. Remove the antithrombin and heparin does nothing, which is why states that deplete it blunt the drug's effect. [1][5]
2. Question: What actually makes low-molecular-weight heparin different?
 2. Answer: Only the length of the sugar chain, but that one difference cascades. A short chain cannot bridge antithrombin to thrombin, so it works mainly on factor Xa. It also binds fewer plasma proteins and cells, which makes the dose response more predictable, allows fixed weight-based dosing without routine monitoring, and lowers the risk of the immune reaction. [2][3]
3. Question: Why is unfractionated heparin still used when the alternatives are more convenient?
 3. Answer: Because it can be switched off. Its half-life is short and dose-dependent, the infusion rate can be changed minute by minute, and protamine neutralises it quickly and completely. That combination is what makes it the agent of choice during cardiac surgery, on extracorporeal circulation, in dialysis, in acute limb ischaemia and around delivery in a patient with a mechanical valve. [1][4][2]
4. Question: Why does a drug that prevents clotting end up causing clots?
 4. Answer: Because in immune heparin-induced thrombocytopenia the problem is not the drug's pharmacology but an antibody. IgG bound to heparin-platelet factor 4 complexes engages the platelet Fc receptor and activates platelets, which release more platelet factor 4 and prothrombotic mediators, activating still more platelets. Platelets are consumed, so the count falls, while the activated ones drive thrombosis. [3]
5. Question: How is heparin-induced thrombocytopenia diagnosed?
 5. Answer: Clinically first, with the 4T score, which weighs the degree of thrombocytopenia, the timing, the presence of thrombosis and whether another cause is likely. At or above the action threshold, heparin is stopped and an alternative

started immediately, without waiting for laboratory results. The immunoassay for antibodies is then used to rule out and the functional serotonin release assay to confirm. [3][1]

6. Question: Is protamine an antidote for the whole class?

6. Answer: No. It fully neutralises unfractionated heparin, forming an inactive salt with it within about five minutes. Reversal of low-molecular-weight heparin is partial and of uncertain degree, and that use is not an approved indication. Protamine also carries real hazards of its own - anaphylaxis, pulmonary hypertension, and an anticoagulant effect if too much is given. [4]

7. Question: What is heparin resistance?

7. Answer: It usually means there is not enough working antithrombin for the heparin to act on. Systemic inflammation, extensive thrombosis, myocardial infarction, malignancy, the postoperative state and inherited antithrombin deficiency are the situations named. In these patients the activated partial thromboplastin time becomes an unreliable guide, and anti-factor Xa activity is used instead. [1]

8. Question: Why is a low-molecular-weight heparin used in pregnancy rather than an oral anticoagulant?

8. Answer: Because the oral agents cross the placenta and pose risks to the developing fetus, whereas these large molecules do not. The trade-off is daily injections and, over long courses, the bone effects associated with prolonged heparin use, which is why the choice is reviewed rather than assumed. [2][1]

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