

Antiplatelet agents

Drugs that blunt platelet activation at one of four points - thromboxane synthesis, the P2Y₁₂ ADP receptor, the glycoprotein IIb/IIIa receptor, or cyclic nucleotide breakdown - and are separated from one another by whether they need metabolic activation and whether their binding is reversible.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/antiplatelet-agents>

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Quick revision

One Liner: Antiplatelet drugs interrupt platelet activation at a small number of well-defined points, and almost every examinable distinction inside the class comes down to which point an agent acts at, whether it has to be metabolically activated first, and whether its binding to the target is reversible.

1. Aspirin irreversibly inhibits cyclooxygenase-1, abolishing platelet thromboxane A₂ production, so its antiplatelet effect long outlasts the brief presence of the acetylating molecule in plasma. [4][3]
2. Platelets have no nucleus and cannot resynthesise cyclooxygenase, so recovery after aspirin depends on new platelets entering the circulation over roughly seven to ten days. [4]
3. Clopidogrel and prasugrel are thienopyridine prodrugs that require hepatic cytochrome P450 bioactivation before they can block the platelet P2Y₁₂ receptor. [3][5][6]
4. Ticagrelor is not a prodrug: it is active at the receptor as given, and it and its approximately equipotent metabolite interact reversibly with the platelet P2Y₁₂ receptor. [10][3]
5. Cangrelor is an intravenous, directly acting P2Y₁₂ antagonist that reaches maximum platelet inhibition within minutes and allows normal platelet function to return within about an hour of stopping the infusion. [7]
6. Clopidogrel activation depends on CYP2C19, so a loss-of-function allele leaves the patient unable to generate enough active metabolite to inhibit platelet activity. [5]
7. Prasugrel carries a boxed warning for potentially fatal bleeding and is contraindicated in anyone with a prior stroke or transient ischaemic attack. [6]
8. Glycoprotein IIb/IIIa inhibitors block the receptor that mediates the final common step of aggregation, and they are parenteral agents used around the acute phase of coronary intervention. [3][2]
9. Dipyridamole and cilostazol inhibit phosphodiesterase and so raise platelet cyclic nucleotide levels, producing vasodilation alongside the antiplatelet effect. [3][8][9]
10. Cilostazol is contraindicated in heart failure because phosphodiesterase inhibitors showed decreased survival compared with placebo in class III to IV heart failure. [9]
11. Dyspnoea is characteristic of ticagrelor, is usually mild to moderate in intensity, and often resolved while treatment continued. [10]
12. Thrombotic thrombocytopenic purpura is a rare but serious reaction reported with clopidogrel and combines thrombocytopenia, microangiopathic haemolytic anaemia, neurological signs and renal dysfunction. [5]
13. There is no specific antidote for any antiplatelet medication, so management of severe haemorrhage is supportive and may require transfusion of blood products. [3]
14. Bleeding complications dominate the adverse-effect profile of every agent in this class whatever its mechanism, and they are what governs how agents are combined. [2][3]

Overview

1. Antiplatelet drugs are used where the clot that matters is platelet-rich and arterial: coronary, cerebrovascular and peripheral arterial disease. They divide first into oral and parenteral agents, and the oral agents subdivide further according to the mechanism they act through. Understanding the class means holding four mechanisms in mind at

once - cyclooxygenase inhibition, P2Y₁₂ receptor blockade, glycoprotein IIb/IIIa receptor blockade and phosphodiesterase inhibition - because spectrum of use, onset, offset and monitoring all follow the mechanism rather than the indication. [2]

2. Aspirin was the first antiplatelet medication and remains the reference point for the whole class. It is a cyclooxygenase inhibitor, and its defining property is that the inhibition of cyclooxygenase-1 is irreversible, achieved by acetylating a serine residue in the enzyme's active site. Since the circulating platelet has no nucleus and cannot replace the enzyme, the block persists for that platelet's whole life, and recovery of aggregation depends on the arrival of new platelets rather than on clearance of the drug. [2][4]

3. The P2Y₁₂ inhibitors are where most examination detail sits, because the agents differ on two independent axes. The first is whether the drug must be bioactivated: clopidogrel and prasugrel are thienopyridine prodrugs converted by hepatic cytochrome P450 enzymes, while ticagrelor and the intravenous agent cangrelor act directly. The second is whether the binding is reversible: clopidogrel and prasugrel block the receptor irreversibly, whereas ticagrelor and cangrelor do not. Those two axes together explain the differences in how quickly the drugs start working, how predictably they work, and how quickly their effect wears off. [3][5][6][7][10]

4. Whatever the mechanism, bleeding is the effect that dominates. Ecchymosis, haematuria, epistaxis, gastrointestinal bleeding and frank haemorrhage recur across the class, and the contraindications that matter most are active pathological bleeding, a history of intracranial haemorrhage, significant thrombocytopenia and severely uncontrolled hypertension. Because no antiplatelet drug has a specific antidote, the management of major bleeding is supportive, and that asymmetry - easy to start, hard to reverse - is the reason prescribing decisions in this class are weighed so carefully. [2][3]

Classification and drug examples

Intro: The class is grouped by the point in platelet activation at which each agent acts. Within the P2Y₁₂ group the further split - prodrug against directly acting, irreversible against reversible - is the distinction most often examined.

1. Name: Cyclooxygenase inhibitors

1. Note: Represented in antiplatelet practice by aspirin, which was the first drug of the class. It reduces production of thromboxane A₂, the mediator platelets need for aggregation.

Name: Aspirin

Acetylsalicylic acid

Route: Oral (also available rectally)

Note: Irreversibly inhibits cyclooxygenase-1 by acetylation and additionally acetylates cyclooxygenase-2, altering rather than abolishing that enzyme's activity. [4][2] [2][4]

2. Name: Oral P2Y₁₂ receptor inhibitors

2. Note: All block adenosine diphosphate-induced platelet aggregation at the P2Y₁₂ receptor, but they differ in whether they require metabolic activation and in whether the block is reversible.

1. Name: Clopidogrel

1. Route: Oral

1. Note: A thienopyridine prodrug requiring two-step bioactivation through CYP2C19 and CYP3A4; its active metabolite inhibits the platelet for the life of that platelet. [5]

2. Name: Prasugrel

2. Route: Oral

2. Note: A thienopyridine prodrug that achieves greater inhibition of platelet aggregation than clopidogrel, at the cost of a higher bleeding risk and a boxed warning. [6]

3. Name: Ticagrelor

3. Route: Oral

3. Note: Directly active rather than a prodrug; ticagrelor and its approximately equipotent metabolite interact reversibly with the P2Y₁₂ receptor. [10][3] [2][3]

3. Name: Intravenous P2Y₁₂ receptor inhibitors

3. Note: A single agent whose value is its speed in both directions: full effect within minutes of starting and recovery within about an hour of stopping.

Name: Cangrelor

Route: Intravenous infusion

Note: Direct-acting, requiring no hepatic metabolism, and reversible; its elimination half-life is a matter of minutes, which is what makes the effect so easy to switch off. [7] [7]

4. Name: Glycoprotein IIb/IIIa inhibitors

4. Note: These block the receptor that cross-links platelets in the final common step of aggregation. They exist only as parenteral agents and are used in the acute phase of acute coronary syndrome, before or during percutaneous coronary intervention.

1. Name: Eptifibatide

1. Route: Intravenous

1. Note: Blocks the glycoprotein IIb/IIIa receptor on the platelet surface; available only parenterally and used over a short period around intervention. [3][2]

2. Name: Tirofiban

2. Route: Intravenous

2. Note: The other glycoprotein IIb/IIIa inhibitor in routine parenteral use during the acute phase of acute coronary syndrome. [2] [2][3]

5. Name: Phosphodiesterase inhibitors

5. Note: These raise platelet cyclic nucleotide levels rather than blocking a surface receptor, so vasodilation accompanies the antiplatelet effect and shapes both their uses and their adverse effects.

1. Name: Dipyridamole

1. Route: Oral and intravenous

1. Note: Acts predominantly by inhibiting phosphodiesterase and adenosine deaminase, raising cyclic adenosine and guanine monophosphate and reversibly inhibiting aggregation. [8]

2. Name: Cilostazol

2. Route: Oral

2. Note: A phosphodiesterase III inhibitor that suppresses breakdown of cyclic adenosine monophosphate, producing antiplatelet activity and arterial vasodilation together. [9] [3][8][9]

6. Name: Protease-activated receptor-1 antagonists

6. Note: A separate mechanism that interrupts thrombin-mediated platelet activation rather than the thromboxane or adenosine diphosphate pathways.

Name: Vorapaxar

Route: Oral

Note: Named in the source literature as the protease-activated receptor-1 antagonist of this class; it is the least commonly encountered antiplatelet mechanism in practice. [2] [2]

Mechanism of action

Summary: Platelets are recruited into a growing arterial thrombus through several reinforcing pathways, and each antiplatelet subclass interrupts one of them: aspirin removes thromboxane A₂, the P2Y₁₂ inhibitors remove the adenosine diphosphate signal, the glycoprotein IIb/IIIa inhibitors block the receptor that actually cross-links platelets, and the phosphodiesterase inhibitors raise the intracellular cyclic nucleotides that hold platelets in a resting state.

Target: Platelet cyclooxygenase-1, the P2Y₁₂ adenosine diphosphate receptor, the glycoprotein IIb/IIIa receptor, platelet phosphodiesterase and the protease-activated receptor-1

1. Step: 1

1. Title: Platelet activation converges on one receptor

1. Detail: Thromboxane A₂, adenosine diphosphate and thrombin each activate the platelet through their own receptor, but all of them converge on the glycoprotein IIb/IIIa complex, which is what allows platelets to bind one another. Every drug in this class works either upstream of that convergence or at it. [3][5]

2. Step: 2

2. Title: Aspirin acetylates cyclooxygenase-1

2. Detail: Aspirin's acetyl group is transferred covalently to a serine residue in the cyclooxygenase-1 active site, abolishing the enzyme's cyclooxygenase activity. Thromboxane A₂ synthesis stops, and because the modification is covalent, no recovery of that enzyme molecule is possible. [4]

3. Step: 3

3. Title: The anucleate platelet cannot rebuild the enzyme

3. Detail: A circulating platelet has no nucleus and so cannot transcribe a replacement cyclooxygenase. Suppression of aggregation therefore lasts until the affected platelets are replaced, approximately seven to ten days, which is why the effect is described in terms of the platelet lifespan rather than a drug half-life. [4]

4. Step: 4

4. Title: P2Y₁₂ blockade removes the adenosine diphosphate amplification signal

4. Detail: Blocking the P2Y₁₂ receptor prevents adenosine diphosphate-induced platelet aggregation and, downstream, prevents activation of the glycoprotein IIb/IIIa complex. This is why P2Y₁₂ blockade adds meaningfully to aspirin rather than duplicating it. [2][5]

5. Step: 5

5. Title: Some P2Y₁₂ inhibitors must be bioactivated first

5. Detail: Clopidogrel and prasugrel are prodrugs converted by hepatic cytochrome P450 enzymes into the metabolite that actually binds the receptor. That extra step is where variability enters: only a minority of an oral clopidogrel dose survives esterase hydrolysis to become active, and CYP2C19 genotype changes how much is generated. [5][6]

6. Step: 6

6. Title: Reversibility decides how the effect wears off

6. Detail: Clopidogrel and prasugrel bind irreversibly, so their effect is tied to platelet turnover. Ticagrelor interacts reversibly, and cangrelor is reversible with an elimination half-life of minutes, so recovery there follows clearance of the drug instead. [3][7][10]

7. Step: 7

7. Title: Glycoprotein IIb/IIIa blockade acts at the final step

7. Detail: Eptifibatide and tirofiban occupy the glycoprotein IIb/IIIa receptors on the platelet surface, preventing the cross-linking on which aggregation depends. Acting at the convergence point produces intense inhibition, which is why these agents are reserved for short parenteral use in the acute setting. [3][2]

8. Step: 8

8. Title: Phosphodiesterase inhibition works through cyclic nucleotides

8. Detail: Dipyridamole and cilostazol raise intracellular cyclic adenosine monophosphate by suppressing its breakdown, which reversibly inhibits aggregation and, in the vessel wall, produces vasodilation. That second action explains dipyridamole's role in stress testing and cilostazol's benefit in claudication. [3][8][9]

Major clinical uses

1. Drug: Aspirin

1. Indication: Prevention of cardiovascular and cerebrovascular events

1. Line: foundational

1. Note: Low-dose aspirin is the long-standing foundation of secondary prevention, and its suppression of thromboxane A₂ synthesis is what underlies that use. [4]

2. Drug: Clopidogrel

2. Indication: Unstable angina and non-ST-elevation myocardial infarction

2. Line: alternative P2Y12 option

2. Note: A regulator-approved acute coronary syndrome indication, but guidance reserves it rather than leading with it: it is the P2Y12 inhibitor chosen for patients who also need ongoing oral anticoagulation, or who are at high bleeding risk, or in whom prasugrel and ticagrelor are unsuitable. It remains the agent used where ST-elevation infarction is managed with fibrinolytic therapy. [5][1]

3. Drug: Clopidogrel

3. Indication: Secondary prevention after myocardial infarction, stroke or peripheral arterial disease

3. Line: long-term

3. Note: Its approved secondary-prevention indications span all three arterial territories rather than the coronary circulation alone. [5]

4. Drug: Prasugrel

4. Indication: Acute coronary syndrome managed with percutaneous coronary intervention

4. Line: first-line P2Y12 option

4. Note: Offered as part of dual antiplatelet therapy with aspirin for acute coronary syndrome managed interventional; the greater platelet inhibition is paired with a higher bleeding risk, particularly where urgent bypass surgery may follow. [6]

5. Drug: Ticagrelor

5. Indication: Acute coronary syndrome or a history of myocardial infarction

5. Line: first-line P2Y12 option

5. Note: Offered as part of dual antiplatelet therapy with aspirin in acute coronary syndrome, including where percutaneous intervention is not indicated unless bleeding risk is high. Labelled to reduce the risk of cardiovascular death, myocardial infarction and stroke in this population, and separately in coronary artery disease at high risk of a first such event. [10][1]

6. Drug: Cangrelor

6. Indication: Reduction of periprocedural thrombotic events during percutaneous coronary intervention

6. Line: procedural

6. Note: Approved for patients who have not already received a P2Y12 inhibitor and are not receiving a glycoprotein IIb/IIIa inhibitor; its minute-scale onset and offset suit the procedural window. [7]

7. Drug: Eptifibatide and tirofiban

7. Indication: Acute phase of acute coronary syndrome, before or during intervention

7. Line: short-term parenteral adjunct

7. Note: Used for a short period in the acute setting only; these agents exist in parenteral form alone, so they have no role in chronic outpatient therapy. [2]

8. Drug: Dipyridamole

8. Indication: Adjunct for prevention of thromboembolism after cardiac valve replacement, and stroke prevention in combination with aspirin

8. Line: adjunct

8. Note: The valve indication is the regulator-approved one; the combination with extended-release dipyridamole for stroke prevention rests on trial evidence showing a reduced risk of stroke compared with placebo. [8]

9. Drug: Dipyridamole

9. Indication: Pharmacological stress agent in thallium nuclear stress testing

9. Line: diagnostic

9. Note: A diagnostic rather than therapeutic use, and the reason oral dipyridamole is withheld before adenosinergic stress testing to avoid an interaction. [8]

10. Drug: Cilostazol

10. Indication: Intermittent claudication in peripheral vascular disease

10. Line: symptomatic

10. Note: Improves walking distance by dilating affected arteries and improving blood flow and oxygen delivery, so the benefit sought is symptomatic rather than preventive. [9]

Pharmacokinetics

1. Drug: Aspirin

1. Route: Oral

1. Absorption: Absorbed from the upper gastrointestinal tract; the platelet effect is established well before the drug leaves the body

1. Metabolism: Rapidly hydrolysed to salicylate, so exposure to the intact acetylating molecule is brief

1. Elimination: Salicylate and its conjugates are cleared renally

1. Half Life: Plasma half-life is short, but the pharmacodynamic effect lasts roughly seven to ten days

1. Dose Adjust: Avoided in children and adolescents during or after viral illness, and in glucose-6-phosphate dehydrogenase deficiency [4]

2. Drug: Clopidogrel

2. Route: Oral

2. Absorption: Absorbed orally, but only about a sixth of the dose escapes esterase hydrolysis to enter the activation pathway

2. Metabolism: Two-step hepatic bioactivation involving CYP2C19 and CYP3A4

2. Elimination: Excreted as inactive metabolites

2. Half Life: Plasma exposure is brief, while receptor blockade persists for the life of the platelet

2. Dose Adjust: Effect is reduced by CYP2C19 loss-of-function alleles and by CYP2C19-inhibiting proton pump inhibitors [5]

3. Drug: Prasugrel

3. Route: Oral

3. Absorption: Absorbed orally as an inactive thienopyridine prodrug

3. Metabolism: Hepatic conversion to the active metabolite that blocks the P2Y₁₂ receptor

3. Elimination: Cleared as inactive metabolites

3. Half Life: Antiplatelet effect lasts the lifespan of the platelet, with function recovering over about five to nine days after withdrawal

3. Dose Adjust: Bleeding risk is increased in patients above seventy-five years of age and at low body weight [6]

4. Drug: Ticagrelor

4. Route: Oral

4. Absorption: Absorbed orally and active at the receptor without any activation step

4. Metabolism: Hepatic, generating a metabolite approximately equipotent with the parent drug

4. Elimination: Cleared predominantly by non-renal routes

4. Half Life: Short enough that recovery of platelet function follows drug clearance rather than platelet turnover

4. Dose Adjust: Contraindicated rather than adjusted in active pathological bleeding and after intracranial haemorrhage [10][3]

5. Drug: Cangrelor

5. Route: Intravenous

5. Absorption: Given by infusion, so there is no absorption phase and no bioactivation step

5. Metabolism: Inactivated directly rather than requiring hepatic conversion

5. Elimination: Very rapid, which is what allows platelet function to return within about an hour of stopping

5. Half Life: Approximately three to six minutes

5. Dose Adjust: No dose change, but the transition to an oral P2Y₁₂ inhibitor must respect the receptor-occupancy interaction [7]

6. Drug: Dipyridamole

- 6. Route: Oral and intravenous
- 6. Absorption: Oral for antiplatelet use; intravenous when it is used as a stress agent
- 6. Metabolism: Hepatic conjugation to a glucuronide
- 6. Elimination: Excreted largely in bile rather than urine
- 6. Half Life: Extended-release formulations are what make once-daily-style oral use practical
- 6. Dose Adjust: Generally avoided in older patients because of orthostatic hypotension, and withheld before adenosinergic stress testing [8]
- 7. Drug: Cilostazol
- 7. Route: Oral
- 7. Absorption: Absorbed orally
- 7. Metabolism: Hepatic, through CYP3A4 and CYP2C19
- 7. Elimination: Metabolites are cleared predominantly in urine
- 7. Half Life: Long enough that the effect builds over several days of regular use
- 7. Dose Adjust: Reduced when combined with CYP3A4 or CYP2C19 inhibitors, and the drug is avoided altogether in heart failure [9]
- 1. Route follows the clinical situation rather than the mechanism: the glycoprotein IIb/IIIa inhibitors and cangrelor exist only as parenteral agents used around intervention, while aspirin and the oral P2Y₁₂ inhibitors carry long-term therapy. [2][7]
- 2. For irreversible agents, the pharmacodynamic half-life is the platelet lifespan and not the plasma half-life, which is the single most useful pharmacokinetic idea in this class. [4][5][6]
- 3. Genotype matters here in a way it does not for most cardiovascular drugs: clopidogrel's dependence on CYP2C19 bioactivation makes loss-of-function alleles a direct determinant of achieved platelet inhibition. [5]
- 4. This page gives no dose regimens by design. Doses depend on indication, formulation, comorbidity, renal and hepatic function and metaboliser status, and belong in a prescribing reference used by the treating clinician.

Adverse effects

- 1. Effect: Minor bleeding and bruising
- 1. Detail: Ecchymosis, haematuria and epistaxis recur across the whole class and are the everyday expression of reduced platelet function. [2]
- 2. Effect: Gastrointestinal irritation with aspirin
- 2. Detail: The commonest adverse effect of aspirin ranges from gastritis through to frank gastrointestinal bleeding, and it is the reason gastric protection is so often discussed alongside it. [4]
- 3. Effect: Dyspnoea with ticagrelor
- 3. Detail: Breathlessness affected about a fifth of patients in the THEMIS population, was usually mild to moderate in intensity, and often resolved during continued treatment. [10]
- 4. Effect: Headache and dizziness with the phosphodiesterase inhibitors
- 4. Detail: Headache is among the most frequent effects of both dipyridamole and cilostazol, and dizziness is common with dipyridamole; both reflect the vasodilator component of the mechanism. [8][9]
- 5. Effect: Palpitations and diarrhoea with cilostazol
- 5. Detail: Diarrhoea and palpitations are among its most frequently reported effects, and a modest rise in heart rate typically accompanies treatment. [9]
- 1. Effect: Major haemorrhage
- 1. Detail: Significant and sometimes fatal bleeding is the defining serious risk of every agent in the class, and prasugrel and ticagrelor both carry boxed warnings to that effect.
- 1. Action: Urgent clinical assessment with supportive care; no specific antidote exists, and severe haemorrhage may require resuscitation with packed red blood cells and platelets. [3][6][10]
- 2. Effect: Intracranial haemorrhage

2. Detail: A prior stroke or transient ischaemic attack raises this risk sufficiently that it becomes a contraindication to prasugrel, and a history of intracranial haemorrhage contraindicates ticagrelor.
2. Action: Treated as a neurological emergency; the drug history is established immediately because it changes both prognosis and supportive management. [6][10]
3. Effect: Thrombotic thrombocytopenic purpura with clopidogrel
3. Detail: A rare but serious condition characterised by thrombocytopenia, microangiopathic haemolytic anaemia, neurological signs and renal dysfunction.
3. Action: Recognised as a haematological emergency requiring urgent plasmapheresis, so any new thrombocytopenia with neurological change on clopidogrel is investigated promptly. [5]
4. Effect: Ventricular pauses and bradyarrhythmias with ticagrelor
4. Detail: The label states that ticagrelor can cause ventricular pauses, and bradyarrhythmias including atrioventricular block have been reported after marketing. Patients with sick sinus syndrome or high-degree block were excluded from the clinical studies.
4. Action: Cardiac rhythm is assessed when syncope, presyncope or symptomatic bradycardia develops during treatment. [10]
5. Effect: Reduced survival with phosphodiesterase inhibition in advanced heart failure
5. Detail: Drugs of this mechanism demonstrated decreased survival compared with placebo in class III to IV heart failure, which is why cilostazol is contraindicated across grades of heart failure.
5. Action: Cardiac function is established before cilostazol is considered, and the drug is not used where heart failure is present. [9]
6. Effect: Reye syndrome with aspirin in children
6. Detail: A rare but serious paediatric complication associated with aspirin given during or after viral illness.
6. Action: Aspirin is not used for antipyresis or analgesia in children and adolescents in that setting; its paediatric use is restricted to specific indications directed by a specialist. [4]
1. Drug: Aspirin
1. Effect: Haemolytic anaemia in glucose-6-phosphate dehydrogenase deficiency, and Reye syndrome in children after viral illness. [4]
2. Drug: Clopidogrel
2. Effect: Thrombotic thrombocytopenic purpura, and hypersensitivity reactions including rash and angio-oedema. [5]
3. Drug: Prasugrel
3. Effect: A boxed warning for potentially fatal bleeding, with particular concern where urgent coronary artery bypass grafting may be needed. [6]
4. Drug: Ticagrelor
4. Effect: Dyspnoea and ventricular pauses, neither of which is shared by the thienopyridines. [10]
5. Drug: Dipyridamole
5. Effect: Chest pain and exacerbation of angina, particularly with intravenous administration during stress testing, and orthostatic hypotension. [8]
6. Drug: Cangrelor
6. Effect: Thrombocytopenia, hypersensitivity, hypotension and infusion-site reactions in addition to bleeding. [7]

Contraindications, precautions and interactions

1. Active pathological bleeding, which contraindicates antiplatelet therapy generally and is stated explicitly for ticagrelor and cangrelor. [2][10][7]
2. A history of intracranial haemorrhage, listed among the contraindications for the class and specifically for ticagrelor. [2][10]
3. Prior stroke or transient ischaemic attack in a patient being considered for prasugrel, because of the heightened haemorrhagic risk. [6]

4. Heart failure of any grade in a patient being considered for cilostazol, reflecting the survival signal seen with phosphodiesterase inhibitors. [9]
5. Aspirin in children or adolescents during or after a viral illness, because of the association with Reye syndrome. [4]
1. Significant thrombocytopenia, which appears in the class-level contraindication list because platelet number and platelet function compound one another. [2]
2. Severe uncontrolled hypertension, which raises the haemorrhagic consequences of any degree of platelet inhibition. [2]
3. Advanced age and low body weight in patients receiving prasugrel, both of which are recognised markers of increased bleeding risk. [6]
4. Bleeding disorders and peptic ulcer disease in patients receiving aspirin, together with glucose-6-phosphate dehydrogenase deficiency. [4]
5. Older patients receiving dipyridamole, in whom orthostatic hypotension has led to advice that the oral drug is generally avoided, while its use in intravenous stress testing remains acceptable. [8]
6. Sick sinus syndrome and high-degree atrioventricular block in patients considered for ticagrelor, since such patients were excluded from the clinical studies. [10]
7. Severe hepatic or renal impairment in patients considered for cilostazol, alongside supraventricular arrhythmia and established heart disease. [9]
1. With: CYP2C19-inhibiting proton pump inhibitors
1. Effect: Omeprazole and lansoprazole reduce the bioactivation of clopidogrel and therefore the platelet inhibition achieved; rabeprazole is regarded as probably safe because it is minimally affected by CYP2C19. [5]
2. With: Non-steroidal anti-inflammatory drugs
2. Effect: Combined use with clopidogrel increases the risk of gastrointestinal bleeding. [5]
3. With: Oral anticoagulants such as warfarin
3. Effect: Concurrent administration with an antiplatelet agent elevates bleeding risk, so the combination is a deliberate decision rather than a default. [5]
4. With: Other antiplatelet agents
4. Effect: Simultaneous use increases haemorrhage through additive platelet inhibition, which is the central trade-off in dual antiplatelet therapy. [5]
5. With: Cangrelor with clopidogrel or prasugrel
5. Effect: Receptor occupancy by cangrelor blocks the binding of those active metabolites, so the oral agent is administered after the infusion is discontinued; ticagrelor may be given at any point. [7]
6. With: Adenosinergic stress testing
6. Effect: Oral dipyridamole is withheld before adenosine-based stress testing because the combination is hazardous. [8]
7. With: CYP3A4 and CYP2C19 inhibitors with cilostazol
7. Effect: Inhibition of either pathway raises cilostazol exposure and calls for a reduced dose determined from a prescribing reference. [9]
8. With: Digoxin with ticagrelor
8. Effect: The label directs that digoxin levels are monitored when ticagrelor is started or its dose is changed. [10]

Comparison tables

1. Title: P2Y₁₂ inhibitors side by side
1. Caption: Activation requirement and reversibility are independent properties, and together they explain the differences in onset, predictability and offset. Actual therapy is governed by a current prescribing reference.
1. Key: drug
1. Label: Drug
1. Is Row Header: true

- 2. Key: route
- 2. Label: Route
- 3. Key: activation
- 3. Label: Needs bioactivation?
- 4. Key: binding
- 4. Label: Receptor binding
- 5. Key: offset
- 5. Label: How the effect wears off
- 1. Drug: Clopidogrel
- 1. Route: Oral
- 1. Activation: Yes - two-step hepatic conversion via CYP2C19 and CYP3A4
- 1. Binding: Irreversible
- 1. Offset: Tracks platelet turnover, about seven to ten days [5]
- 2. Drug: Prasugrel
- 2. Route: Oral
- 2. Activation: Yes - hepatic conversion to an active metabolite
- 2. Binding: Irreversible
- 2. Offset: Platelet function recovers over about five to nine days [6]
- 3. Drug: Ticagrelor
- 3. Route: Oral
- 3. Activation: No - active as given, with an approximately equipotent metabolite
- 3. Binding: Reversible
- 3. Offset: Follows clearance of the drug rather than platelet turnover [10][3]
- 4. Drug: Cangrelor
- 4. Route: Intravenous infusion
- 4. Activation: No - direct-acting, no hepatic metabolism required
- 4. Binding: Reversible
- 4. Offset: Normal platelet function returns within about an hour of stopping [7]
- 2. Title: Mechanism, route and signature problem across the class
- 2. Caption: One row per mechanism, showing where the drug acts and the adverse effect most characteristic of that group. Bleeding risk applies to every row and is not repeated.
- 1. Key: group
- 1. Label: Group
- 1. Is Row Header: true
- 2. Key: target
- 2. Label: Molecular target
- 3. Key: route
- 3. Label: Route
- 4. Key: signature
- 4. Label: Signature problem
- 1. Group: Cyclooxygenase inhibitor (aspirin)
- 1. Target: Cyclooxygenase-1, acetylated irreversibly
- 1. Route: Oral
- 1. Signature: Gastrointestinal irritation and bleeding; Reye syndrome in children [4]
- 2. Group: Oral P2Y12 inhibitors
- 2. Target: Platelet P2Y12 adenosine diphosphate receptor
- 2. Route: Oral

- 2. Signature: Variable response with clopidogrel; dyspnoea with ticagrelor [5][10]
- 3. Group: Intravenous P2Y₁₂ inhibitor
- 3. Target: Platelet P2Y₁₂ adenosine diphosphate receptor
- 3. Route: Intravenous infusion
- 3. Signature: Interaction that blocks thienopyridines given during the infusion [7]
- 4. Group: Glycoprotein IIb/IIIa inhibitors
- 4. Target: Glycoprotein IIb/IIIa receptor on the platelet surface
- 4. Route: Intravenous only
- 4. Signature: Intense inhibition restricted to short use around intervention [3][2]
- 5. Group: Phosphodiesterase inhibitors
- 5. Target: Platelet phosphodiesterase, raising cyclic adenosine monophosphate
- 5. Route: Oral, and intravenous for dipyridamole stress testing
- 5. Signature: Headache and vasodilator effects; heart failure contraindication for cilostazol [8][9]

High-yield exam pearls

- 1. Pearl: Aspirin works by covalently acetylating a serine residue in the active site of cyclooxygenase-1.
- 1. Why: The covalent modification is exactly what makes the inhibition irreversible, and it is the property that separates aspirin from ibuprofen and naproxen, which block the same enzyme reversibly. [4]
- 2. Pearl: Reversible binding is the single property that sets ticagrelor apart from clopidogrel and prasugrel.
- 2. Why: It means the return of platelet function follows clearance of the drug rather than the turnover of the whole platelet pool, which is the reasoning behind every question comparing the three orally administered agents. [3][10]
- 3. Pearl: Only a small fraction of an oral clopidogrel dose ever reaches the active metabolite.
- 3. Why: Most of the absorbed drug is diverted by esterase hydrolysis, and that narrow bioactivation margin is why genotype and interacting drugs shift the achieved level of platelet inhibition so much. [5]
- 4. Pearl: Clopidogrel or prasugrel given during a cangrelor infusion cannot be relied on to work.
- 4. Why: Cangrelor occupies the P2Y₁₂ receptor so densely that the active metabolites of those thienopyridines cannot bind, which is why the transition is made after the infusion stops; ticagrelor is the stated exception and may be given at any point. [7]
- 5. Pearl: Dipyridamole appears in cardiology twice: as an antiplatelet adjunct and as a pharmacological stress agent.
- 5. Why: The same adenosine-mediated vasodilation that supports its antiplatelet role is what makes it useful in thallium nuclear stress testing, and it also explains the interaction with adenosinergic testing. [8]
- 6. Pearl: Prasugrel's headline contraindication is a neurological history rather than a bleeding one.
- 6. Why: Prior stroke or transient ischaemic attack shifts the balance toward intracranial haemorrhage, which outweighs the greater platelet inhibition prasugrel achieves compared with clopidogrel. [6]
- 7. Pearl: Cilostazol is the antiplatelet drug whose absolute contraindication is a cardiac diagnosis.
- 7. Why: Phosphodiesterase inhibitors as a group demonstrated decreased survival compared with placebo in advanced heart failure, so the restriction is about mortality rather than about haemorrhage. [9]
- 8. Pearl: Reye syndrome is the reason aspirin is avoided in children and adolescents during or after viral illness.
- 8. Why: It is the one classic aspirin restriction driven by age and infection rather than by bleeding risk, and it is a reliable examination item. [4]

Common exam traps

- 1. Trap: Assuming all three orally administered P2Y₁₂ inhibitors are prodrugs.
- 1. Correction: Clopidogrel and prasugrel are prodrugs that need hepatic activation, whereas ticagrelor binds the receptor directly and reversibly without requiring conversion. [3][10]
- 2. Trap: Treating aspirin and the other non-steroidal anti-inflammatory drugs as interchangeable at the platelet.
- 2. Correction: Aspirin abolishes cyclooxygenase-1 activity irreversibly by acetylation, while the other agents in that

family block the enzyme reversibly, so their platelet effect ends as the drug is cleared. [4]

3. Trap: Expecting platelet function to recover as soon as an irreversible agent is withdrawn.

3. Correction: After aspirin, clopidogrel or prasugrel the recovery of platelet function tracks turnover of the platelet pool over several days rather than the plasma half-life of the drug. [4][5][6]

4. Trap: Reading breathlessness in a patient on ticagrelor as heart failure or as a hypersensitivity reaction.

4. Correction: Dyspnoea is a recognised and common effect of ticagrelor itself, was usually mild to moderate, and often resolved during continued treatment, so it is assessed rather than assumed to be another diagnosis. [10]

5. Trap: Assuming a specific reversal agent exists for antiplatelet-related haemorrhage.

5. Correction: No specific antidote is available for any antiplatelet medication, and care of severe haemorrhage is supportive, which may include resuscitation with packed red blood cells and platelets. [3]

6. Trap: Pairing clopidogrel reflexively with omeprazole for gastric protection.

6. Correction: Omeprazole and lansoprazole inhibit CYP2C19 and reduce clopidogrel activation, whereas rabeprazole is considered probably safe because it is minimally affected by that enzyme. [5]

Self-test questions

1. Question: Which statement correctly describes how aspirin inhibits platelet cyclooxygenase?

1. It competitively and reversibly occupies the active site, so the effect ends when plasma levels fall
2. It covalently acetylates a serine residue in the cyclooxygenase-1 active site, abolishing enzyme activity irreversibly
3. It prevents transcription of the cyclooxygenase gene inside the circulating platelet
4. It chelates the calcium required for cyclooxygenase catalysis

1. Explanation: Aspirin transfers its acetyl group to a serine residue in the cyclooxygenase-1 active site. Because the modification is covalent and the anucleate platelet cannot make new enzyme, thromboxane A2 production stays suppressed for the lifespan of that platelet. [4]

2. Question: A patient is a CYP2C19 poor metaboliser. Which oral antiplatelet agent is most likely to under-perform for that reason?

1. Ticagrelor
2. Aspirin
3. Clopidogrel
4. Dipyridamole

2. Explanation: Clopidogrel is a prodrug whose two-step bioactivation depends on CYP2C19. A loss-of-function allele leaves the patient unable to generate sufficient active metabolite, producing high on-treatment platelet reactivity. [5]

3. Question: Which P2Y₁₂ inhibitor binds its receptor reversibly?

1. Clopidogrel
2. Prasugrel
3. Ticagrelor
4. None of them; all P2Y₁₂ inhibitors bind irreversibly

3. Explanation: Ticagrelor and its metabolite interact reversibly with the platelet P2Y₁₂ receptor, while clopidogrel and prasugrel are prodrugs whose active metabolites block the receptor irreversibly. [3][10]

4. Question: Why is an oral thienopyridine given after, rather than during, a cangrelor infusion?

1. Cangrelor induces the cytochrome enzymes that activate thienopyridines
2. Cangrelor occupies the P2Y₁₂ receptor so densely that thienopyridine active metabolites cannot bind
3. The combination causes an immediate hypertensive crisis
4. Cangrelor prevents intestinal absorption of oral tablets

4. Explanation: High receptor occupancy by cangrelor prevents the active metabolites of clopidogrel and prasugrel from reaching the receptor, so those agents are started once the infusion has been discontinued. Ticagrelor is the stated exception. [7]

5. Question: Which antiplatelet agent is absolutely contraindicated by a history of stroke or transient ischaemic attack?

1. Clopidogrel
2. Dipyridamole
3. Prasugrel
4. Cangrelor
5. Explanation: Prasugrel is contraindicated after a prior stroke or transient ischaemic attack because of the heightened risk of haemorrhage in that group, and it separately carries a boxed warning for potentially fatal bleeding. [6]
6. Question: Cilostazol is contraindicated in heart failure. What is the stated reason?
 1. It causes profound bradycardia that heart failure patients tolerate poorly
 2. Phosphodiesterase inhibitors demonstrated decreased survival compared with placebo in class III to IV heart failure
 3. It accumulates in patients with reduced renal perfusion and causes fatal bleeding
 4. It antagonises every beta blocker used in heart failure
6. Explanation: The restriction is a mortality signal rather than a bleeding one: phosphodiesterase inhibitors showed decreased survival compared with placebo in advanced heart failure, so cilostazol is avoided across grades of heart failure. [9]
7. Question: A patient taking ticagrelor reports mild breathlessness a few days after starting. What does this most likely represent?
 1. A recognised and common effect of ticagrelor itself
 2. Certain evidence of new heart failure
 3. An anaphylactic reaction to the tablet excipients
 4. An expected consequence of glycoprotein IIb/IIIa blockade
7. Explanation: Dyspnoea occurred in about a fifth of patients in the THEMIS population, was usually mild to moderate in intensity, and often resolved during continued treatment. It still warrants clinical assessment, but it is a known drug effect rather than an unexplained finding. [10]
8. Question: Which of these is the correct account of reversal for antiplatelet-related major haemorrhage?
 1. Vitamin K reverses all antiplatelet agents
 2. A specific monoclonal antibody fragment reverses the P2Y₁₂ inhibitors
 3. There is no specific antidote for any antiplatelet drug, so care is supportive and may include blood products
 4. Protamine reverses aspirin and clopidogrel equally well
8. Explanation: No specific antidote exists for any antiplatelet medication. Management centres on supportive care, and resuscitation with blood products including packed red blood cells and platelets may be necessary for severe haemorrhage. [3]

Frequently asked questions

1. Question: Why does aspirin's effect last for days when the drug itself disappears in hours?
 1. Answer: Because the inhibition is covalent and the target cell cannot repair it. Aspirin acetylates a serine residue in the cyclooxygenase-1 active site, and a circulating platelet has no nucleus with which to make replacement enzyme. Aggregation therefore stays suppressed until new platelets replace the affected ones, which takes about seven to ten days. [4]
2. Question: What actually distinguishes clopidogrel, prasugrel and ticagrelor?
 2. Answer: Two properties. Clopidogrel and prasugrel are prodrugs needing hepatic bioactivation and they then bind the P2Y₁₂ receptor irreversibly; ticagrelor needs no activation and binds reversibly. Prasugrel achieves greater inhibition than clopidogrel but carries more bleeding risk, and ticagrelor brings dyspnoea and ventricular pauses that the thienopyridines do not. [5][6][10][3]
3. Question: Why is clopidogrel's response so variable between patients?
 3. Answer: Its activation is the bottleneck. Only a minority of an absorbed dose escapes esterase hydrolysis and passes through the two-step cytochrome pathway, so anything that reduces CYP2C19 function - a loss-of-function allele, or an inhibiting proton pump inhibitor - leaves less active metabolite and higher on-treatment platelet reactivity.

[5]

4. Question: Is there a reversal agent for antiplatelet drugs?

4. Answer: No. There is currently no specific antidote for any antiplatelet medication. Management of serious bleeding is supportive, and resuscitation with blood products including packed red blood cells and platelets may be necessary in severe haemorrhage. This is a real point of difference from several anticoagulants, which do have specific reversal agents. [3]

5. Question: Why is cangrelor used at all when oral agents exist?

5. Answer: For control over timing. It reaches maximum platelet inhibition within minutes of administration and normal platelet function returns within about an hour of discontinuation, which suits the procedural window of percutaneous coronary intervention in someone who has not already received a P2Y₁₂ inhibitor. [7]

6. Question: Why does dipyridamole appear both as an antiplatelet drug and as a stress-testing agent?

6. Answer: One mechanism, two applications. Inhibiting phosphodiesterase and adenosine deaminase raises cyclic nucleotide levels, which inhibits aggregation and also produces vasodilation through prostacyclin release. That vasodilation is what makes intravenous dipyridamole useful in thallium nuclear stress testing, and it is also why oral dipyridamole is withheld before adenosine-based testing. [8]

7. Question: Why is cilostazol not simply another option for arterial disease?

7. Answer: Its restriction is unusual for this class. Cilostazol improves walking distance in intermittent claudication, but phosphodiesterase inhibitors as a group showed decreased survival compared with placebo in class III to IV heart failure, so it is contraindicated where heart failure is present, and it also requires care in severe hepatic or renal impairment. [9]

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