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Antiplatelet drugs

What are antiplatelet drugs?

Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation in the arterial circulation. In faster-flowing vessels, thrombi are composed mainly of platelets with little fibrin.[1] Antiplatelet drugs are used for:[2]

- Primary prevention of atherothrombotic events, but only in people who are at high risk.
- Secondary prevention of atherothrombotic events in people with acute coronary syndrome, angina, peripheral arterial disease, and atrial fibrillation (although anticoagulants are usually used for people with atrial fibrillation).
- Secondary prevention of cardiovascular events in people after myocardial infarction, stent implantation, stroke or transient ischaemic attack.
- The prevention of atherothrombotic events in people undergoing percutaneous coronary intervention (PCI).

Aspirin[1] [2]

- Aspirin irreversibly inhibits cyclo-oxygenase, which catalyses the production of thromboxane and prostaglandins.
- Antithrombotic action derives from reduction in thromboxane A2.
- Aspirin also has analgesic, anti-inflammatory and antioxidant properties.
- Long-term use of low-dose aspirin is recommended in patients with established cardiovascular disease (secondary prevention). High blood pressure should be controlled before aspirin is given.

- The use of aspirin in primary prevention of cardiovascular disease, in patients with or without diabetes, or hypertension, is not recommended.
- Aspirin is given following coronary bypass surgery. It is also used for intermittent claudication, for stable angina and acute coronary syndromes, for use following placement of coronary stents and for use in stroke.
- Following transcatheter aortic valve implantation (TAVI), aspirin monotherapy is considered rather than dual antiplatelet therapy. If aspirin is not tolerated, clopidogrel should be considered as an alternative.
- If there is a high risk of gastro-intestinal bleeding, a proton pump inhibitor can be added.

Clopidogrel[1] [3]

- Clopidogrel is a thienopyridine. It inhibits the binding of adenosine diphosphate to its platelet receptor, preventing ADP-mediated up-regulation of glycoprotein (GP) IIb/IIIa receptor, again blocking amplification of platelet aggregation.
- Clopidogrel is used for the prevention of atherothrombotic events in patients with a history of symptomatic ischaemic disease (eg, ischaemic stroke).
- Clopidogrel is also used, in combination with low-dose aspirin, for the prevention of atherothrombotic and thromboembolic events in patients with atrial fibrillation (and at least one risk factor for a vascular event), and for whom warfarin is unsuitable.
- The use of clopidogrel with aspirin increases the risk of bleeding.
- Clopidogrel monotherapy may be an alternative when aspirin is contra-indicated, for example in patients with aspirin hypersensitivity, or when aspirin is not tolerated despite the addition of a proton pump inhibitor.

- The National Institute for Health and Care Excellence (NICE) recommends clopidogrel as an option to prevent occlusive vascular events:
    - For people who have had an ischaemic stroke or who have peripheral arterial disease or multivascular disease; or
    - For people who have had a myocardial infarction, only if aspirin is contra-indicated or not tolerated.

Prasugrel[1] [4]

- Prasugrel is a thienopyridine. It inhibits the binding of adenosine diphosphate to its platelet receptor, preventing ADP-mediated up-regulation of glycoprotein (GP) IIb/IIIa receptor, again blocking amplification of platelet aggregation..
- Prasugrel, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention.
- NICE guidance recommends prasugrel in combination with aspirin in ACS patients undergoing primary PCI when:
    - Immediate PCI is necessary for ST-segment elevation myocardial infarction (STEMI); or
    - Stent thrombosis occurred during treatment with clopidogrel; or
    - The patient has diabetes mellitus.
- The combination is recommended for 12 months only - beyond which there is doubtful clinical benefit.

Dipyridamole[1] [3]

- The mechanism is not fully understood but it is thought to act by inhibiting adenosine uptake into platelets and reducing ADP-induced aggregation.
- Dipyridamole also has vasodilating properties that can make it unsuitable for use in those with severe coronary artery disease, unstable angina, recent myocardial infarction or left ventricular outflow obstruction.

- Dipyridamole is licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks.
- NICE recommends modified-release dipyridamole in combination with aspirin as an option to prevent occlusive vascular events:
    - For people who have had a transient ischaemic attack; or
    - For people who have had an ischaemic stroke, only if clopidogrel is contra-indicated or not tolerated.
- NICE recommends modified-release dipyridamole alone as an option to prevent occlusive vascular events:
    - For people who have had an ischaemic stroke, only if aspirin and clopidogrel are contra-indicated or not tolerated; or
    - For people who have had a transient ischaemic attack, only if aspirin is contra-indicated or not tolerated.

Ticagrelor[1]

- Ticagrelor is a $P2Y_{12}$ receptor antagonist that prevents ADP-mediated $P2Y_{12}$ dependent platelet activation and aggregation.
- Ticagrelor, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome. The combination is usually given for up to 12 months, and can be used for both medical management or where further coronary intervention is planned. If it needs to be continued beyond 12 months then the diagnosis should be confirmed by a cardiology specialist.[5]

Cangrelor[1]

- Cangrelor is a direct $P2Y_{12}$ platelet receptor antagonist that blocks adenosine diphosphate induced platelet activation and aggregation.
- Cangrelor, in combination with aspirin, is licensed for the reduction of thrombotic cardiovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received treatment with oral clopidogrel, prasugrel or ticagrelor prior to the procedure and in whom oral therapy with these drugs is not suitable.

- Cangrelor is to be used under expert supervision only.

Glycoprotein IIb/IIIa antagonists[1]

- Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets.
- All require intravenous administration under specialist supervision. Patients receiving these drugs require very close monitoring, usually on coronary care units (CCUs).
- Thromboxane A2 and ADP are just two of over 90 known platelet agonists. Blockade by aspirin and clopidogrel will not affect the platelet's ability to be stimulated by other agonists whilst use of a GP IIb/IIIa antagonist should inhibit aggregate formation whatever agonist influences the platelet.
- Abciximab is a monoclonal antibody which binds to glycoprotein IIb/IIIa receptors and to other related sites. It is licensed as an adjunct to heparin (unfractionated) and aspirin for the prevention of ischaemic complications in high-risk patients undergoing percutaneous transluminal coronary intervention. Abciximab should be used once only (to avoid additional risk of thrombocytopenia).
- Eptifibatide (in combination with heparin (unfractionated) and aspirin) and tirofiban (in combination with heparin (unfractionated), aspirin, and clopidogrel) also inhibit glycoprotein IIb/IIIa receptors. They are licensed for use to prevent early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction.
- Tirofiban is also licensed for use in combination with heparin (unfractionated), aspirin, and clopidogrel, for the reduction of major cardiovascular events in patients with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention.
- GP IIb/IIIa antagonists can cause severe bleeding, most often from the site of femoral puncture for percutaneous transluminal coronary angioplasty (PTCA). It can take over 12 hours for platelet function to be restored after stopping an infusion.

Indications[1] [2]

Secondary prevention of CVD

- Angina: aspirin 75 mg. Clopidogrel 75 mg daily should be considered for people unable to take aspirin.
- Atrial fibrillation: dual antiplatelet therapy with aspirin 75 mg daily plus clopidogrel 75 mg daily may be suitable for people who are unable or unwilling to take anticoagulants.
- Acute coronary syndrome (ACS):
    - Which is medically managed: aspirin 75 mg daily plus ticagrelor 90 mg twice a day for 12 months.
    - Who are undergoing coronary artery bypass grafting (CABG): aspirin 75 mg in combination with ticagrelor 90 mg twice a day, or prasugrel 10 mg daily. Clopidogrel 75 mg daily should be prescribed if prasugrel or ticagrelor are not suitable.
- Percutaneous coronary intervention (PCI):
    - For people with ACS: aspirin 75 mg in combination with either ticagrelor 90 mg twice a day, or prasugrel 10 mg daily. Clopidogrel 75 mg daily should be prescribed if prasugrel or ticagrelor are unsuitable.
    - For people with stable coronary artery disease: aspirin 75 mg daily plus clopidogrel 75 mg daily. Ticagrelor or prasugrel may be considered instead of clopidogrel where appropriate.
- Stroke, or transient ischaemic attack: clopidogrel 75 mg daily is the preferred antiplatelet. Modified-release dipyridamole should be prescribed combined with aspirin if clopidogrel is unsuitable.[6]
- Peripheral arterial disease, or multivascular disease: clopidogrel 75 mg daily is the preferred antiplatelet. Aspirin 75 mg alone should be prescribed if clopidogrel is unsuitable.

Primary prevention of CVD

- Previously, aspirin was recommended for those without apparent CVD in whom the total CVD risk over 10 years is >20%, and for almost all patients with diabetes aged over 50. The evidence to support this unlicensed indication is not robust and thus current guidance is that aspirin should not be used in primary prevention (including in those with diabetes mellitus or hypertension).
- However, antiplatelet treatment may be considered for people with a high risk of stroke or myocardial infarction.
- Clopidogrel and dipyridamole are neither indicated nor licensed for primary prevention of cardiovascular events.

Atrial fibrillation (AF)

AF carries a high risk of stroke and other thromboembolic events. Oral anticoagulants are more efficacious than aspirin at preventing stroke (particularly in those at highest risk) but carry a greater risk of major haemorrhage.

The NICE guidance on AF and the prevention of stroke no longer recommends the use of aspirin monotherapy for thromboprophylaxis.[7]

See the separate Atrial Fibrillation article for more details.

Antiplatelet drugs and coronary stents[1]

- Patients selected for percutaneous coronary intervention (PCI), with the placement of a coronary stent, require dual antiplatelet therapy with aspirin and either cangrelor, clopidogrel, prasugrel, or ticagrelor. Aspirin therapy should continue indefinitely.
- Following PCI in patients with stable angina, clopidogrel is recommended in addition to aspirin for at least one month after placement of a bare-metal stent, and for at least six months if a drug-eluting stent is used.
- Clopidogrel should not be discontinued prematurely in patients with a drug-eluting stent as there is an increased risk of stent thrombosis as a result of the eluted drug slowing the re-endothelialisation process.

- Patients considered to be at high-risk of developing late stent thrombosis with a drug-eluting stent may require a longer duration of treatment with clopidogrel combined with aspirin.
- Prasugrel or ticagrelor are alternatives to clopidogrel in certain patients undergoing PCI.

Pre-eclampsia

Pre-eclampsia is associated with excessive production of thromboxane so antiplatelet agents have been proposed as possible therapy to prevent or delay the development of pre-eclampsia.

A Cochrane review found that low-dose aspirin given to pregnant women led to small-to-moderate benefits, including reductions in pre-eclampsia, preterm birth, the baby being born small-for-gestational age and fetal or neonatal death. Overall, administering antiplatelet agents to 1,000 women led to 20 fewer pregnancies with serious adverse outcomes. Aspirin probably slightly increased the risk of postpartum haemorrhage of more than 500 mL. Overall, antiplatelet agents improved outcomes. As almost all the women in this review were recruited to the trials after 12 weeks of gestation, it is unclear whether starting treatment before 12 weeks of gestation would have additional benefits without any increase in adverse effects.[8] .

Primary prevention of cancers[9]

Platelets have been hypothesised to promote certain neoplastic malignancies. Thrombocytosis remains a marker of poor prognosis in patients with solid tumours. Experimental data suggest that lowering of platelet count may reduce tumour growth and metastasis. Therefore platelets could contribute to cancer growth and metastasis, and drugs reducing platelet count or platelet activation might attenuate cancer progression and improve outcomes. However, antiplatelet drugs are still not part of routine pharmacological cancer prevention and treatment protocols.

Cautions and contra-indications[1]

See individual antiplatelet drug profiles; however, some general or important points are:

- All antiplatelet drugs can cause bleeding. Avoid in patients who are at a high risk of bleeding or where the consequences of bleeding would be severe - for example, active peptic ulcer disease, uncontrolled hypertension.
- Hypersensitivity and allergy. NICE guidance suggests that true hypersensitivity to aspirin (characterised by rash, urticaria and angio-oedema) is rare.[10]
- Aspirin can cause bronchospasm and worsen pre-existing asthma. A systematic review estimated the prevalence of aspirin-exacerbated asthma in adults with pre-existing asthma as 21% (from oral provocation testing). From this, it suggests that approximately 80% of asthmatics can take aspirin safely but caution should be exercised. Always check about previous experiences with aspirin and other NSAIDs and warn to stop aspirin if their asthma deteriorates. High-risk features for developing aspirin-induced asthma include severe asthma, nasal polyps, urticaria and rhinitis.
- Hypertension should be controlled (blood pressure <150/90 mm Hg) before commencing treatment.

Side-effects of antiplatelet drugs[1]

See individual drug profiles. All antiplatelet drugs can cause gastrointestinal (GI) disturbance and bleeding - dipyridamole is the least risky (but is rarely used alone) to the high risk associated with the GP IIb/IIIa antagonists.

Interactions[1]

Check the individual antiplatelet drug profile. Be wary of co-prescribing with other drugs that increase risk of bleeding (ie anticoagulants and heparin, other antiplatelet drugs, corticosteroids, iloprost). Adding clopidogrel to aspirin increases the antiplatelet effect but also increases the risk of bleeding so is only justified where the risk is outweighed by the potential benefit.

Elective surgery - stopping antiplatelet drugs[11]

- The balance between reducing the risk of bleeding complications and losing the protection and even a rebound increased risk of ischaemic event is uncertain.
- A Cochrane review found low-certainty evidence that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery may make little or no difference to mortality, bleeding requiring surgical intervention, or ischaemic events.
- The review found moderate-certainty evidence that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery probably makes little or no difference to bleeding requiring transfusion.
- Evidence was limited to few studies with few participants, and with few events.
- Therefore the individual's relative risk needs to be evaluated, including the individual patient's risk of ischaemic events and haemorrhage as well as the nature of the surgery.

Further reading

- Cardiovascular disease: risk assessment and reduction, including lipid modification; NICE Guidance (July 2014 - last updated February 2023)
- Acute coronary syndromes; NICE Guidance (November 2020)

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