Antiplatelet Drugs

Antiplatelet drug is a generic term, describing agents which decrease platelet aggregation and inhibit thrombus formation. Antiplatelet drugs are most effective for arterial clots that are composed largely of platelets.

Platelets are critical in haemostasis and the development of arterial thrombi. Damaged endothelium activates platelets which respond by adhering and aggregating. Their release of thromboxane A2 and adenosine diphosphate (ADP) amplifies and propagates the process by stimulating surrounding platelets. The production of thrombin via the coagulation cascade is also accelerated, stabilising the thrombus by the conversion of fibrinogen to fibrin. Different classes of antiplatelet drugs act at different junctures in this process.

Aspirin

- Non-selective, irreversible inhibitor of 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. Some of the beneficial actions of aspirin in patients with cardiovascular disease (CVD) may be related to these as well as its antithrombotic effect.\(^1\) However, some of these effects are only apparent at much higher doses.

Clopidogrel\[^2\]

- An ADP receptor antagonist that competitively inhibits ADP from binding to platelet receptors, preventing ADP-mediated up-regulation of glycoprotein (GP) IIb/IIIa receptor, again blocking amplification of platelet aggregation.
- Direct comparison of clopidogrel may indicate that it is a slightly more effective antiplatelet drug than aspirin - for example, when compared head-to-head in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial.\[^3\] However, a high NNT (200) to prevent one additional event and high incremental cost (given aspirin’s low cost) have meant that use of clopidogrel alone is limited to those who cannot tolerate aspirin prophylaxis.\[^4\] More importantly, clopidogrel is routinely used in the treatment of acute coronary syndrome (ACS) and post-percutaneous coronary intervention (PCI) stenting in conjunction with aspirin.

Prasugrel\[^5\]

- Prasugrel is a prodrug from the same family as clopidogrel, with more efficient platelet inhibition.
- National Institute for Health and Care Excellence (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\[^6\]

- The mechanism is not fully understood but it is thought to act by inhibiting adenosine uptake into platelets and reducing ADP-induced aggregation.\[^7\]
- 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.\[^7\]
Glycoprotein IIb/IIIa antagonists\[8, 9, 10\]

- Abciximab was the original GP IIb/IIIa antagonist and is a monoclonal antibody with a much prolonged duration compared to newer agents - eg, eptifibatide which is a non-peptide antagonist.
- These drugs inhibit the final common pathway of platelet aggregation where fibrinogen binds to GP IIb/IIIa receptor.
- 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.\[1\]
- Neutralising antibodies to abciximab form, so it can only be used once.
- 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.

Other agents

- Ticagrelor - licensed for use with aspirin in preventing atherothrombotic events in ACS for 12 months, and can be used for both medical management or where further coronary intervention is planned. If it needs to be continued beyond this then the diagnosis should be confirmed by a cardiology specialist.\[11\]

Indications

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).\[13\] NB: aspirin is increasingly being used in the primary prevention of some cancers - particularly bowel cancer.\[14\]
- Clopidogrel and dipyridamole are neither indicated nor licensed for primary prevention of cardiovascular events.

Secondary prevention of CVD\[15\]

- In those with established atherosclerotic disease, low-dose aspirin (75 mg daily) is recommended indefinitely for long-term secondary prevention. Antithrombotic Trialists' Collaboration (ATTAC) provided evidence that this reduces the risk of any serious vascular event by 25% and vascular mortality by a sixth.\[16\]
- Clopidogrel alone is first-line following an acute ischaemic stroke or in peripheral arterial disease. It is only advised as monotherapy following a myocardial infarction if aspirin is not tolerated\[4, 17\].
- Modified-release dipyridamole 200 mg bd plus low-dose aspirin (50 mg or 75 mg daily) are recommended for secondary prevention following a transient ischaemic attack (TIA). The combination of aspirin and dipyridamole is only recommended after an ischaemic stroke if clopido
grel is not tolerated or contra-indicated.\[18\] This is based on the second European Stroke Prevention (EPS-2) trial.\[19\] EPS-2's findings have been replicated by the more recent European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) study.\[20\] Evidence of long-term benefit was not established by EPS-2, so NICE guidance\[10\] limited treatment duration to two years with preventative treatment reverting to standard treatment (eg, low-dose aspirin) but it should probably continue with no time limit.\[21\]
- There may be a role for triple antiplatelet therapy in the secondary prevention of CVD but this is as yet is unlicensed.

Acute ischaemic events

Myocardial ischaemia

- A single dose of aspirin 300 mg and clopidogrel 300 mg (600 mg - unlicensed in some centres prior to urgent PCI) should be given as soon as possible after an ischaemic event (both non-ST-segment elevation myocardial infarction (NSTEMI) and STEMI), preferably dispersed in water or chewed.\[22\]
- Clopidogrel 75 mg daily is licensed for the treatment of ACS ± ST elevation, in combination with aspirin (usually following loading doses).\[22, 23, 24\]
- Post-PCI clopidogrel 75 mg should continue for one month if a bare metal stent is inserted and 12 months if a drug-eluting stent is inserted. Thereafter, treatment should revert to low-dose aspirin alone.
- Eptifibatide and tirofiban are licensed for use with heparin and aspirin to prevent early myocardial infarction in patients with unstable angina or NSTEMI where early PTCA is desirable but delay is likely.\[25\]
- Eptifibatide: this is also used in NSTEMI where the last episode of chest pain was within 24 hours.
- Rarely, GP IIb/IIIa inhibitors are used in complex patients with unstable angina or an ACS which is not responding to conventional therapy (under specialist supervision).\[21\]

Cerebral ischaemia\[17\]

- Acute ischaemic stroke - thrombolysse if appropriate and follow with aspirin 300 mg once daily for 14 days.\[26\] If not able to be thrombolysed then aspirin alone should be given. A review reported that aspirin caused an excess of about two intracranial and four extracranial haemorrhages per 1,000 people treated, but these small risks were more than offset by the reductions in death and disability from other causes.\[27\]
Long-term management of both TIA or ischaemic stroke - clopidogrel is recommended (see above). Dipyridamole 200 mg bd with aspirin 75 mg once daily is the alternative if clopidogrel is not suitable. Dipyridamole alone is indicated if both aspirin and clopidogrel cannot be given.

Atrial fibrillation (AF)
This carries a high risk of stroke and other thromboembolic events. Warfarin and the newer anticoagulants (eg, dabigatran, rivaroxaban and apixaban) are more efficacious than aspirin at preventing stroke (particularly in those at highest risk) but carry a greater risk of major haemorrhage.

Primary care doctors worry that their patients tend to be older, sicker and with more comorbidities than research patients and thus at higher risk of side-effects.

The latest NICE guidance on AF and the prevention of stroke no longer recommends the use of aspirin monotherapy for thromboprophylaxis. See the separate Atrial Fibrillation article for more details.

Individual decisions to take anticoaguants for thromboprophylaxis with AF remain difficult, and in many cases the use of the novel anticoagulants is superseding warfarin. The CHA\textsubscript{2}DS\textsubscript{2}-VASc score and HAS-BLED scores may help to assess stroke risk:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure (or left ventricular (LV) dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A\textsubscript{2} Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S\textsubscript{2} Prior stroke, TIA or thromboembolic disease</td>
<td>2</td>
</tr>
<tr>
<td>V Vascular disease - eg, presence of peripheral vascular disease, myocardial infarction, aortic atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>A Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sc Sex category (ie female)</td>
<td>1</td>
</tr>
</tbody>
</table>

Anyone with a score of 2 or more should be treated with anticoagulants.\cite{28}

Bleeding risk with warfarin and other anticoagulants is higher where:

- Age is over 75 years.
- There is concurrent treatment with non-steroidal anti-inflammatory drugs (NSAIDs).
- There is a past history of bleeding.
- Polypharmacy.
- Uncontrolled hypertension.

NICE also recommends:

- Start anticoagulant treatment where indicated as soon as possible following diagnosis of AF.
- Treatment decisions should be made in the same way for paroxysmal AF.
- Recent research in AF suggests that patients who are unsuitable for anticoagulants may get additional benefit if aspirin and clopidogrel are combined rather than using aspirin alone - but this is not recommended\cite{31}
- Pre-eclampsia is associated with excessive production of thromboxane so antplatelet agents have been proposed as possible therapy to prevent or delay the development of pre-eclampsia. A Cochrane review found that antiplatelet agents (primarily low-dose aspirin) did indeed have small-to-moderate benefits in the prevention of pre-eclampsia\cite{32} However, research evidence is still required as to which women are most likely to benefit, when to start treatment, suitable dose, etc. Antiplatelet drugs are not licensed for this use.

Cautions and contra-indications\cite{2, 6, 33}

See individual 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. [21]

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. [34]

Hypertension should be controlled (blood pressure <150/90 mm Hg) before commencing treatment.

Side-effects [2, 6]

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 [2, 6]

Check the individual 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.
Treatment issues

Screening, risk assessment and communication

- Appropriate identification of patients remains a challenge:
  - Many of the guidelines advocate case-finding of those at high cardiovascular risk by screening.
  - Asymptomatic adults aged 40 years and over (younger where there is a family history of premature CVD) should receive opportunistic comprehensive cardiovascular risk assessment using Joint British Societies’ (JBS) risk prediction charts. [35]
  - The Scottish Intercollegiate Guidelines Network (SIGN) suggests five-yearly reviews of the same groups. [36]

- By the age of 50, 90% of the UK population are at sufficient cardiovascular risk to require treatment according to current guidelines, and normal symptom-free individuals become 'patients'. [37]
- Screening makes sense from a population perspective where lives are undoubtedly saved but, on an individual basis, a small reduction in cardiovascular risk will lead to very little absolute benefit with all the disadvantages of medicalising lives.
- Communicating balances of risk and benefit to individuals is demanding. Even where figures derived from clinical trials can be applied straightforwardly to a patient’s case, it is impossible to predict whether a particular individual will benefit, be harmed or receive no effect either way from a particular treatment. Sharing this uncertainty is very difficult.
- High-risk individuals for primary and secondary prevention should be identifiable from disease registers. CVD prevention (including the use of antiplatelet drugs) within a practice can be audited against JBS standards. [39]
- The new General Medical Services (nGMS) contract uses antiplatelet therapy as a quality indicator in three domains (CHD 9, STROKE 8 and AF 3) so it is particularly important to consider treatment (where appropriate) and record contra-indications or side-effects to meet targets.

Medicine management

- Routine monitoring of antiplatelet treatment for primary and secondary prevention is not usually required.
- It should be remembered that antiplatelet therapy reduces but does not eliminate the risk of cardiovascular events. Where patients experience a cardiovascular event whilst on antiplatelet medication, it should not be assumed that they are 'resistant' to the drug’s antiplatelet effect or that a switch to another agent would offer any greater protection. True resistance to the antiplatelet action of aspirin or clopidogrel may occur in a small proportion of patients but there are no reliable tests available currently to confirm this. Seek expert advice.
- What dose of aspirin? Antithrombotic Trialists’ Collaboration (ATTC) provided good evidence that lower doses of aspirin (75-150 mg) were no less effective than higher ones, with a reduced rate of bleeding complications. [16] Common practice is to prescribe 75 mg daily for primary and secondary prevention of CVD, although a lot of cardiologists seem to use 150 mg daily.
- GI side-effects are common with aspirin:
  - Advise patients to report any abdominal pain, melaena or rectal bleeding urgently.
  - There is no evidence that enteric coating or dispersible formulations of aspirin lessen the risk.
  - Ensure that it is taken with food.
  - Co-prescription of symptomatic or preventative medication - for example, maintenance dose protein pump inhibitor (PPI) - should be used prior to switching to clopidogrel where similar side-effects may occur.

- Good communication between primary and secondary care is important. For example:
  - Ensuring that where aspirin is given for ACS, it is documented and passed on to the paramedics/admitting team.
  - Discharge plans from CCU/stroke unit should make it clear, to primary care and to the patient, what the long-term plan for medication is and, in particular, when to stop clopidogrel or dipyridamole.

- Ensure mechanisms for stopping clopidogrel and dipyridamole at the correct times through regular medication reviews.
- Auditing prescribing of clopidogrel and dipyridamole will help to ensure that their use falls within the limited indications. [4]

Elective surgery - stopping antiplatelet drugs

- The usual advice is that aspirin should be stopped 5-9 days prior to surgery and clopidogrel stopped seven days before to reduce the risk of bleeding complications. [2, 40]
- However, it has been suggested that stopping aspirin leads to a rapid loss of protection and even rebound increased risk of ischaemic event.
- There also is the risk that the drug may not be restarted.
- This may make us question the wisdom of stopping antiplatelet agents, in high-risk individuals, for minor surgical procedures, such as skin or cataract surgery.
- In general, aspirin should be stopped where the risk of postoperative bleeding is high (eg, during major surgery) or where the consequences of even minor bleeding are significant (eg, retinal and intracranial surgery).
- If concerned, discuss with the surgeon or dentist.

Further reading & references

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- Small daily aspirin dose 'cuts cancer risk'; BBC News Report November 2010

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