Antiplatelet drugs for cardiovascular prevention in people with diabetes

Antiplatelet agents for primary prevention of cardiovascular disease

- Avoid routinely using antiplatelet agents for primary prevention of cardiovascular disease.[1,2]
  - This advice extends to people with diabetes – do not routinely offer antiplatelet therapy to people with type 1 or type 2 diabetes in the absence of cardiovascular disease.[3,4]
- In people at very high risk of myocardial infarction or stroke, antiplatelet agents may be offered if benefits outweigh risks in an individual case.[1] Thus, low-dose aspirin may be considered for primary prevention in people with diabetes with a high degree of cardiovascular risk who are not at increased risk of bleeding.[5]

Although low-dose aspirin does result in a small reduction in risk of serious cardiovascular events (relative reduction 12%), this was negated by a 30% higher incidence of bleeding, principally gastrointestinal.[6]

Antiplatelet agents for secondary prevention of cardiovascular disease[1]

Antiplatelet agents offer clear benefits for cardiovascular protection in those with established atherosclerotic cardiovascular disease – i.e. for secondary prevention.[6]

- Other than an immediate loading dose of antiplatelet therapy for acute coronary syndrome (ACS), treatment will usually be initiated by hospital specialists for ACS, stroke/transient ischaemic attack or percutaneous coronary intervention.
- For stable cardiovascular disease and/or peripheral vascular disease, the combination of aspirin with low-dose rivaroxaban (i.e. antiplatelet plus anticoagulant therapy) may bring added benefits for secondary prevention, and can be considered in those at low bleeding risk.[1,5]
- Anticoagulant agents rather than antiplatelet agents are recommended for management of atrial fibrillation.

Recommended indications for antiplatelet agents for secondary cardiovascular prevention

Indication	Drug/dose	Notes
Stable angina[7]	Aspirin 75 mg *od* if suspected; continue long-term if investigations confirm diagnosis	Avoid enteric-coated aspirin or high-dose aspirin. Less risk of gastrointestinal side effects with low-dose aspirin. Clopidogrel 75 mg *od* if aspirin contraindicated or not tolerated
Acute coronary syndrome (ACS): Unstable angina, NSTEMI or STEMI[8,9]	Aspirin 300 mg *stat* dose if ACS suspected; immediately refer Subsequently, aspirin 75 mg *od* long-term Usually dual therapy with aspirin plus one of clopidogrel 75 mg *od*, prasugrel 5–10 mg *od*, ticagrelor 90 mg *bd* for 12 months	Clopidogrel 300 mg *od* if aspirin hypersensitivity Prasugrel and ticagrelor have a faster onset of action and greater efficacy but higher bleeding risk Dual therapy may be extended in people with high ischaemic risk and reduced in those with high bleeding risk
Stable cerebrovascular disease (previous stroke)[8]	Clopidogrel 75 mg *od* long-term	If clopidogrel not tolerated, aspirin 75 mg *od* or low-dose aspirin plus M/R dipyridamole 200 mg *bd*, or M/R dipyridamole 200 mg *bd* alone
Suspected TIA/stroke seen acutely[8]	Avoid antiplatelet medication until intracranial haemorrhage has been excluded by brain imaging; immediate referral	After investigation, dual therapy with clopidogrel 300 mg *stat* then 75 mg *od*, plus aspirin 300 mg *stat* then 75 mg *od* may be prescribed for 21 days, followed by clopidogrel 75 mg *od* maintenance In selected cases, alternative initial dual therapy with ticagrelor plus aspirin may be prescribed for 30 days
Suspected TIA in last few days (with symptom resolution)[8]	Aspirin or clopidogrel 300 mg *stat* dose; immediate referral	If suspected TIA >1 week ago then aspirin or clopidogrel 75 mg *od* after 300 mg *stat* dose; urgent referral
Stable peripheral arterial disease[1]	Clopidogrel 75 mg *od* long-term	Aspirin 75 mg *od* if clopidogrel contraindicated or not tolerated
Percutaneous coronary intervention[1]	Aspirin 75 mg *od* plus clopidogrel 75 mg *od* for 6 months	Ticagrelor or prasugrel are alternative options to clopidogrel Treatment time may be extended in people with high ischaemic risk and reduced in those with high bleeding risk

ACS=acute coronary syndrome; M/R=modified-release; NSTEMI=non-ST segment elevation myocardial infarction; STEMI=ST segment elevation myocardial infarction; TIA=transient ischaemic attack.

Antiplatelet drugs and dyspepsia[1]

Dyspepsia describes upper gastrointestinal (GI) symptoms including upper abdominal pain, acid reflux, nausea and vomiting. It is a common side effect of antiplatelet agents.

People at high risk of GI side-effects:

- Older age, especially >75 years.
- History of gastroduodenal ulceration/perforation or GI bleeding.
- *Helicobacter pylori* infection.
- Concomitant use of other agents that predispose to GI bleeding: additional antiplatelet medication, warfarin, heparin, DOACs, NSAIDs, corticosteroids, SSRIs, SNRIs.

Managing people taking antiplatelet medication at high risk of GI side-effects

- Add proton pump inhibitor (PPI) for gastroprotection.
  - ➤ Avoid omeprazole and esomeprazole when using clopidogrel, as they can lead to reduced plasma levels of activated clopidogrel. Other PPIs can be used.
- A histamine H2 antagonist (e.g. famotidine) can be used if PPIs are contraindicated or poorly tolerated.

Treating antiplatelet-induced dyspepsia

- If alarm features (e.g. dysphagia, weight loss, jaundice), refer urgently. Refer immediately if active GI bleeding.
- If no alarm features, consider antacid or alginate for symptom relief on an as-required basis.
- Offer PPI for 1 month. Test and treat for *H. pylori* (a 2-week delay after finishing a PPI is required before testing).
  - ➤ Use alternative PPI to omeprazole and esomeprazole if taking clopidogrel.
- Use H2 antagonist if PPIs are contraindicated or poorly tolerated.
- If symptoms recur after initial PPI treatment or *H. pylori* elimination, use maintenance PPI at lowest dose to control symptoms.
- If symptoms persist despite treatment, refer for investigation.

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References are available in the online version of this article.

Contraindications, cautions and side effects of antiplatelet agents

Antiplatelet agent	Contraindications	Cautions	Side effects
Aspirin	Hypersensitivity reactions to aspirin (or other NSAIDs) – bronchospasm, rhinitis, urticaria, angioedema Active bleeding* Bleeding disorders† Severe renal impairment Severe hepatic impairment	Allergic conditions – asthma, hay fever, urticaria Previous peptic ulceration Increased bleeding risk from medical conditions† or other medications‡ Avoid in pregnancy and breastfeeding unless used under specialist advice	Bronchospasm Dyspepsia Bleeding (e.g. gastrointestinal, intracranial or ophthalmological haemorrhage) Hypersensitivity reactions
Clopidogrel	Active bleeding* Severe hepatic impairment Pregnancy and breastfeeding	Renal or hepatic impairment Increased bleeding risk from medical conditions† or other medications‡ Discontinue 7 days before elective surgery	Dyspepsia Haemorrhage Diarrhoea
Prasugrel	Active bleeding* History of stroke/TIA Severe hepatic impairment	Increased bleeding risk from medical conditions† or other medications‡ Renal or hepatic impairment Age >75 years or weight <60 kg: use lower dose Discontinue 7 days before elective surgery Avoid in pregnancy and breastfeeding unless benefit outweighs risk	Haemorrhage
Ticagrelor	Active bleeding* History of intracranial haemorrhage Severe hepatic impairment Avoid if taking strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, HIV protease inhibitors) Pregnancy and breastfeeding	Gout Asthma or COPD Sleep apnoea Increased bleeding risk from medical conditions† or other medications‡ Increased risk of sick sinus syndrome, bradycardia or second- or third-degree AV block Discontinue 5 days before elective surgery	Dyspepsia Haemorrhage Diarrhoea or constipation Hyperuricaemia Headache, dizziness Dyspnoea
Dipyridamole	Active bleeding*	Aortic stenosis Heart failure Unstable angina Hypotension Myasthenia gravis Increased bleeding risk from medical conditions† or other medications‡ Pregnancy and breastfeeding unless benefit > risk	Haemorrhage Angina Tachycardia Diarrhoea Nausea Headache, dizziness

*Active bleeding includes gastrointestinal, intracranial or retinal haemorrhage, and epistaxis.

†Bleeding disorders include haemophilia and thrombocytopaenia.

‡For all antiplatelet agents, the risk of bleeding increases with people taking other antiplatelet agents, warfarin, heparin direct oral anticoagulants (e.g. apixaban, rivaroxaban), NSAIDs (e.g. ibuprofen, naproxen), corticosteroids (e.g. prednisolone, dexamethasone), SSRIs (e.g. paroxetine, citalopram) and SNRIs (e.g. venlafaxine, duloxetine).

AV=atrioventricular; COPD=chronic obstructive pulmonary disease; NSAID=non-steroidal anti-inflammatory drug; TIA=transient ischaemic attack.