



Antiplatelet medicines

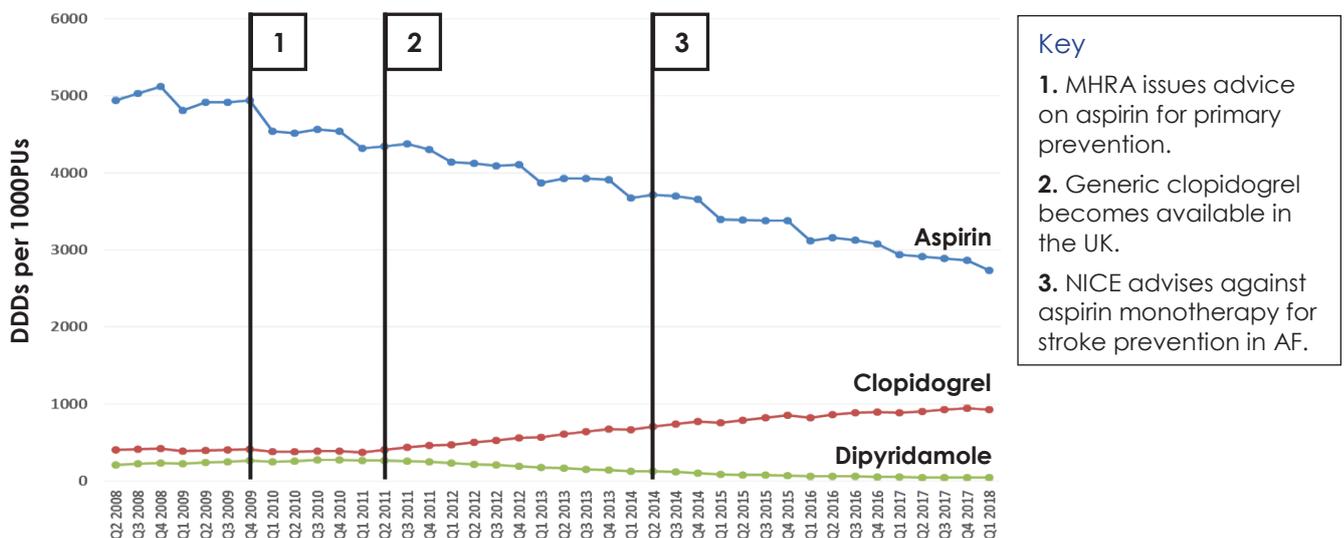
The prescribing patterns of antiplatelet medicines in primary care in Wales have significantly changed in the last decade. In the 10 years to the end of Q1 2018, the use of aspirin (as measured by the defined daily dose per 1000 prescribing units [DDD per 1000PUs]) has declined in absolute terms by 45% and the use of clopidogrel has more than doubled. However, almost three times more aspirin is still prescribed compared with clopidogrel (2736 vs 929 DDDs/1000PUs in Q1 2018). The use of dipyridamole decreased by 79% (to 45 DDDs/1000PUs) during the same period. Interestingly, ticagrelor prescribing accounts for only one item per 1000PUs per quarter, but represents the second highest spend on antiplatelet medicines in primary care – some 42% more is spent on ticagrelor than on clopidogrel, even though 30 times more clopidogrel is prescribed.¹

The fluctuations in prescribing trends appear to reflect changing guidelines covering use for various indications, the availability of generic clopidogrel, and the introduction to market of newer antiplatelet medicines (see Graph 1). This bulletin will explore the use of antiplatelet medicines for some common indications, alone and in combinations with each other and with certain other relevant agents.

Summary

- ◆ Antiplatelet medicines should not be routinely prescribed for the primary prevention of cardiovascular events, including in people with diabetes; any such prescribing is 'off-label'.
- ◆ Primary prevention of cardiovascular events relies on the appropriate management of risk.
- ◆ Aspirin (clopidogrel if aspirin contraindicated) should be considered life-long for patients with an acute coronary syndrome (ACS).
- ◆ Dual antiplatelet therapy with life-long aspirin and another time-limited antiplatelet is required if a patient has an acute coronary event. Choice and duration of the second agent will depend on other interventions received.
- ◆ Clopidogrel is recommended as the first-line antiplatelet medicine in ischaemic stroke or transient ischaemic attack (TIA), and in peripheral arterial disease (PAD).
- ◆ Antiplatelet therapy (specifically aspirin or clopidogrel) and anticoagulation may be considered concomitantly, where there is an indication for both, especially within 12 months of a myocardial infarction (MI).

Graph 1. Prescribing patterns of the most common antiplatelet medicines in Wales.¹



Effects of antiplatelet medicines

Aspirin is the most commonly prescribed antiplatelet in Wales. When given in low doses, it is a cyclo-oxygenase 1 (COX-1) inhibitor, which exerts its antithrombotic effect by inhibiting the generation of thromboxane-A2 by platelets. The effects are irreversible, and are only overcome following the generation of new platelets.²

Clopidogrel, prasugrel, and ticagrelor are all inhibitors of the P2Y₁₂ receptor, which is a mediator of platelet aggregation. Clopidogrel and prasugrel are pro-drugs and require activation by hepatic enzymes. The antagonism of the activation process is postulated as one of the pathways of genetic variability of effect and of antagonistic drug-drug interactions. There appear to be fewer interactions preventing the activation of prasugrel compared with clopidogrel, although experience with this agent is much more limited. Prasugrel and ticagrelor have been shown to produce more rapid platelet inhibition than clopidogrel and are less susceptible to genetic variation.³ They are both currently many times more expensive than clopidogrel.

Dipyridamole inhibits phosphodiesterase, leading to an elevation in the levels of cyclic adenosine monophosphate (cAMP). It may also block the uptake of adenosine by erythrocytes and other cells.⁴ Its indications are limited compared with those of aspirin and clopidogrel and adverse effects can be troublesome; prescribing levels are low and declining.^{1,5}

Primary prevention

There is a broad consensus, based on high quality evidence, that aspirin and other antiplatelets should no longer be **routinely** prescribed for the primary prevention of cardiovascular events, i.e. for a person who does not have prior cardiovascular disease (CVD).^{6,7,8} This includes use in patients with type 1 and type 2 diabetes without established CVD.^{9,10}

Evidence supporting the use of antiplatelets (specifically aspirin) only for secondary prevention comes from a number of trials and meta-analyses suggesting that the risk of harm, particularly haemorrhage, outweighs the risk of benefit in primary prevention.^{7,11} Several further trials of antiplatelets for primary prevention are under way, and are expected to report in the coming years; two involve people with diabetes mellitus, one includes older age people, and another looks at those with moderate cardiovascular risk.⁷

Practitioners are also reminded that no antiplatelet (including low-dose aspirin) has a marketing authorisation (MA) for use in primary prevention.¹¹ Many patients purchase aspirin for this purpose and will require advice on its use. It should be borne in mind that if aspirin is to be used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for CVD (including conditions such as diabetes) and the risk of bleeding.¹¹ Healthcare professionals may assume more responsibility when providing an unlicensed or an off-label medicine than when they use a medicine within the terms of its MA. Also see, *Things to know... about licensed, off-label, and unlicensed use* (available via www.wemerec.org).

Estimation and management of cardiovascular risk remains crucial, whether or not a person has established CVD. Those at the highest risk are likely to gain most benefit from sometimes simple preventative measures, as detailed in Table 1 (adapted from European Society of Cardiology [ESC] and National Institute for Health and Care Excellence [NICE] guidance).^{5,7,9,10,12,13,14,15,16}

Table 1. Goals and targets for important cardiovascular risk factors	
Smoking	No tobacco exposure in any form.
Diet	Total fat 30% or less of total energy intake (saturated fat <7%). Increase mono-unsaturated fats. Choose wholegrain starches, reduce refined sugars, and eat at least five portions of fruit and vegetables per day, two portions of fish (one oily) per week, and 4-5 portions of unsalted nuts, seeds, and legumes per week.
Alcohol	Stick to weekly maximum of 14 units, spread over three or more days. Take several alcohol-free days each week. Avoid binge drinking.
Physical activity	Increase regular physical activity as safe for the person. Aim for at least 150 minutes moderate or 75 minutes vigorous activity per week. Do strengthening exercises on the major muscles on two or more days per week.
Blood pressure	<140/90mmHg if 80yrs or younger <150/90mmHg if over 80yrs (<135/85mmHg and <145/85mmHg respectively if using ABPM or HBPM)
Lipids	Offer appropriate pharmacological lipid-modification for primary prevention in adult patients: 85yrs and over; younger than 85yrs with 10-year CVD risk 10% or more; with type 1 diabetes; or with CKD.
HbA1c	Usually 48 mmol/mol or lower in both type 1 and 2 diabetes.

Secondary prevention

Antiplatelet treatment should usually be advised in all patients with angina, a previous MI, stroke or TIA, and PAD.⁶

Acute coronary syndromes

The term ‘acute coronary syndrome encompasses a range of conditions, including unstable angina, non-ST-segment-elevation MI (NSTEMI) and ST-segment-elevation MI (STEMI).¹⁶ Patients with different ACSs may present similarly; definitive diagnosis is made on the basis of clinical presentation, ECG changes, and measurement of biochemical cardiac markers.⁵ A STEMI is generally caused by complete and persisting blockage of the artery and an NSTEMI reflects partial or intermittent blockage of the artery.¹⁷

A ruptured or eroded coronary atherosclerotic plaque is the primary underlying cause of the arterial blockage in ACS. The formation of a thrombus is principally driven by platelet aggregation under conditions of high stress. The domination of platelet aggregation in such an ACS explains the positive effects of antiplatelets on clinical outcomes. The use of aspirin results in a halving of subsequent event rates in patients with an ACS.¹⁸ The use of antiplatelets in a patient with angina is considered to be secondary prevention, even if the patient has not yet had a cardiovascular ‘event’ per se, because they have established CVD.

In the absence of contraindications, **aspirin** should be given life-long to all patients with stable angina or unstable angina and following an MI (NSTEMI or STEMI).^{5,17,19} Aspirin is first line for monotherapy, but for those with true hypersensitivity, **clopidogrel** may be an alternative.¹⁷ People with a history of dyspepsia or who have had appropriate treatment for an aspirin-induced ulcer, which has healed, and are negative for *H pylori*, may be considered for an antiplatelet with a proton pump inhibitor (PPI).¹⁷

Dual antiplatelet therapy (DAPT), or more rarely an antiplatelet and an anticoagulant, is indicated following an ‘event’ in ACS (a STEMI or NSTEMI). The recommendations for DAPT differ according to the intervention: coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) and type of PCI, or none. The bleeding risk is substantially increased with DAPT compared with monotherapy and so modifiable risk factors should be addressed and the patient closely monitored.

Following **NSTEMI**, it is recommended that, in addition to life-long aspirin:

- clopidogrel or ticagrelor are used for up to 12 months, regardless of intervention.
- prasugrel can be used for up to 12 months for patients having primary or delayed PCI.^{17,20}

Following **STEMI**, it is recommended that, in addition to life-long aspirin:

- clopidogrel is an option for 12 months for patients receiving a bare metal or drug-eluting stent
- clopidogrel can also be used for at least one and up to 12 months for patients undergoing medical management with or without reperfusion treatment with a fibrinolytic agent
- ticagrelor is an option for up to 12 months, if cardiologists intend to treat with PCI
- prasugrel can be used for up to 12 months for patients having primary or delayed PCI.^{17,20}

Choice and duration of use of the secondary antiplatelet will vary depending on the exact intervention and the initiating consultant.

Stroke, TIA, and PAD

Following an **ischaemic stroke** or **TIA**, clopidogrel is now the preferred first-line antiplatelet.⁶ If clopidogrel is unsuitable, dipyridamole m/r plus aspirin is recommended. If dipyridamole cannot be tolerated, then aspirin alone should be considered. If clopidogrel or aspirin are unsuitable, then dipyridamole m/r alone is an appropriate choice.⁶

In **peripheral arterial disease**, clopidogrel is again recommended first-line, with aspirin as the alternative.⁶

Atrial fibrillation

Antiplatelet monotherapy is no longer advised for the prevention of cardiovascular events for people with AF, due to the marginal benefits being negated by a moderate increase in bleeding risk.⁷ If the risk of stroke does not reach the threshold for consideration of anticoagulation, no ‘blood thinning’ therapy is recommended. Where the risk does reach the threshold for anticoagulation, but this is contraindicated or not tolerated, it is recommended that left atrial appendage occlusion be considered.²¹ DAPT may be an alternative where no anticoagulant is suitable and if the patient has a very low risk of bleeding, but this is not a formal NICE recommendation as the potential number of patients fulfilling these criteria is low.²²

Where a patient with an indication for an antiplatelet also develops an indication for anticoagulation (or vice versa), both therapies may be required. There is most experience with antiplatelets and warfarin. Rivaroxaban is now also licensed for use in such circumstances, but experience is limited and this is not recommended by NICE. Other directly-acting oral anticoagulants (DOACs) are not recommended in combination with antiplatelets.¹⁷ The bleeding risk, thromboembolic risk, cardiovascular risk, and the person's wishes should all be taken into account if concomitant therapy is to be considered.¹⁷

Within 12 months of an MI, and unless there is a high risk of bleeding, anticoagulation may be considered together with aspirin or clopidogrel (this is not recommended with prasugrel or ticagrelor).¹⁷ If the MI was more than 12 months ago, the person should be anticoagulated and consideration given to the ongoing need for an antiplatelet.¹⁷ The ESC offer a useful resource to determine the optimum duration of antiplatelet therapy, which may be useful in these circumstances.²³

Bleeding risk scoring tools

Evaluating the risk of bleeding with antiplatelet medicines can be difficult. Commonly used tools, such as HAS-BLED, are validated and applicable only to those who have AF and are to commence warfarin. Its use in other contexts is controversial, but probably widespread. Some of the guiding principles may be of use to estimate bleeding risk in other circumstances, but these, and the risk scores produced, are not validated. Modifiable factors should be addressed where possible before commencing the antiplatelet.

Relevant risk factors for bleeding with antiplatelets from HAS-BLED may include:

- hypertension (>160mmHg systolic)
- abnormal renal or hepatic function
- previous or disposition to bleeding
- older age (>65yrs)
- medication increasing bleeding risk (see below)
- alcohol use.

More formal risk scoring is usually undertaken in secondary care. For example, the ACUITY and CRUSADE tools are frequently used to stratify patients with ACS and predict the risk of bleeding, to guide whether or not to pursue a DAPT strategy, and its duration. PRECISE-DAPT and DAPT are validated tools that also incorporate the risk of bleeding to calculate best duration of therapy.²³

However, none of these scores is perfect and decisions should not be based solely upon them. As none of them measure pre-morbid function, frailty, or the safety of invasive management, decisions can be difficult and often rely predominantly on the experience of the decision-maker.

Important drug-drug interactions

Increased risk of bleeding

The deliberate or 'accidental' use of multiple medicines that increase the risk of bleeding has been highlighted by NICE as a cause for concern.²⁴ People may be at an increased risk of bleeding where antiplatelets are co-prescribed with anticoagulants – including vitamin-K antagonists, such as warfarin, and DOACs, such as apixaban, dabigatran, edoxaban, and rivaroxaban. An analysis of reports to the National Recording and Learning System (NRLS) suggests that the problem can be compounded due to a failure by prescribers to recognise DOACs as anticoagulants.²⁴

In certain circumstances the benefits of the concurrent use of an antiplatelet and an anticoagulant will outweigh the risk. However, the risks should still be borne in mind and the patient should be closely monitored. Concomitant use of antiplatelet medicines with NSAIDs and/or SSRIs also increases the risk of bleeding.⁵ Ticagrelor levels, and therefore the risk of bleeding, are increased where 'strong' CYP3A4 inhibitors are co-prescribed. Co-administration of ticagrelor with ritonavir, ketoconazole, clarithromycin, nefazodone, or atazanavir is contraindicated.⁵

Decreased efficacy

There is some evidence that the effect of clopidogrel is decreased by the concomitant administration of omeprazole or esomeprazole. An alternative PPI should be used if needed in combination with clopidogrel.²⁵ Upon the same basis, it may be prudent to avoid other inhibitors of CYP2C19 with clopidogrel; these include (but are not limited to) fluoxetine, fluvoxamine, moclobemide, fluconazole, ciprofloxacin, cimetidine, and carbamazepine.²⁵ Studies also indicate that grapefruit juice reduces the effectiveness of clopidogrel and the combination should be avoided.⁵ In addition to the increased risk of bleeding, the use of NSAIDs with antiplatelets (specifically with aspirin) may antagonise the antiplatelet effect. Due to the increased cardiovascular risk involved with most NSAID and specific COX-2 inhibitor use, the net cardiovascular benefit of antiplatelet medicines may also be diminished or negated.²⁶

Summaries of Product Characteristics (SPCs) should be consulted for full prescribing information.

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