SHEFFIELD GUIDANCE FOR CLOPIDOGREL AND PRASUGREL▼ USE IN PRIMARY AND SECONDARY CARE

This document provides a basis for patient selection where clopidogrel or prasugrel therapy is being considered. Category A is defined in terms of situations where there is a supporting body of good quality evidence. Clopidogrel should not be considered for patients who come under Category B.

Category A: Clopidogrel Recommended

1.1 For people who have had an ischaemic stroke or who have peripheral arterial disease or multivascular disease (life long)

1.2 For TIA where aspirin or dipyridamole are contra indicated or not tolerated (unlicensed indication) (life long)

1.3 Used alone for people who have had a myocardial infarction or stable angina only if aspirin is contraindicated or not tolerated[1] (see also 1.4) (life long)

1.4 In combination with aspirin for patients with STEMI or non-STE acute coronary syndrome **(12 months of therapy)** where cardiac markers are elevated or there are relevant ECG changes.
The duration of treatment must be clearly specified on the prescription kardex or patient notes and on discharge

1.5 In combination with aspirin for patients undergoing coronary or carotid stent procedures (unlicensed indications). Treatment is for **4 weeks (bare metal stents in patients with chronic stable angina and carotid stents in vascular disease)** or **12 months (drug-eluting stents in patients with chronic stable angina or stenting in patients with acute coronary syndromes, as for 1.2)** but must be specified. Patients who have undergone coronary brachytherapy (irradiation) or insertion of a left main stent receive clopidogrel indefinitely. The secondary care trust provides the medication for 4 weeks and continuing courses are supplied by primary care.
The duration of treatment must be clearly specified on the prescription kardex or patient notes and on discharge.

Clopidogrel should be given as a single daily dose of 75 mg (with a loading dose where appropriate).

[1] Clopidogrel 75mg has only been shown to be superior to the 325mg dose of aspirin with respect to GI adverse events. One study has shown a combination of low-dose aspirin and PPI to be safer than clopidogrel alone in patients treated for aspirin-induced bleeding ulcers. (NEJM 2005;352:238-44).

Category B: Avoid Clopidogrel

2.1 Patients who have not had a previous event i.e. avoid use in primary prevention.

2.2 Patients in whom clopidogrel is contraindicated: severe liver disease, active peptic ulceration, intracranial haemorrhage and breast-feeding.

2.4 Concurrent use with aspirin (except as described above) or use in combination with dipyridamole.

2.5 Do not co-prescribe aspirin and clopidogrel for atrial fibrillation or stroke/TIA except following carotid stenting. For a limited number of patients with AF co-prescription of aspirin and clopidogrel may be appropriate, noting that the combination is unlicensed and the Active A trial[2] showed the decrease in cardiovascular events is matched almost exactly by an increased risk of severe bleeds. In these patients the combination should be initiated by a specialist.

[2] Active A trial NEJM 2009;306:2066-2078

Category C: Consider Prasugrel▼

Prasugrel in combination with aspirin, within its marketing authorisation, is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when:

- Immediate primary percutaneous coronary intervention for STEMI is necessary, or
- Stent thrombosis has occurred during clopidogrel treatment. or
- The patient has diabetes mellitus

Prasugrel should be given as a maintenance daily dose of 10mg for up to 12 months, give a reduced maintenance dose of 5mg if over 75 years or weight less than 60kg (noting that no clinical data exists on the safety or effectiveness of the 5mg dose).

The duration of treatment must be clearly specified on the prescription kardex or patient notes and on discharge.

Clopidogrel interaction with omeprazole and esomeprazole

Omeprazole has been shown to inhibit the conversion of clopidogrel to its active form by the enzyme CYP2C19 thus significantly reducing the antiplatelet effect of clopidogrel. The European Medicines Agency and MHRA have stated the concomitant use of clopidogrel and omeprazole or esomeprazole should be discouraged unless considered essential They have concluded there is no solid ground to extend the warning to other proton pump inhibitors (PPIs) however the MHRA still say that it is not possible to completely exclude a possible interaction with other PPIs and therefore potential risk of reduction in efficacy of clopidogrel should be weighed against the GI benefit of PPI.

For patients who are prescribed clopidogrel and omeprazole or esomeprazole in combination, consider the following at their next review:

- If prescribed clopidogrel and omeprazole or esomeprazole but no aspirin, review whether clopidogrel can be switched to aspirin or alternatively review continued need for a PPI*
- If clopidogrel and aspirin are prescribed together in line with Sheffield Guidelines and omeprazole or esomeprazole are also prescribed review the continued need for a PPI*
- Check whether patients who are taking clopidogrel are buying over-the-counter omeprazole and consider whether another gastrointestinal therapy would be more suitable

The current evidence does not support extending this advice to other PPIs.

*Where concomitant use of clopidogrel and a PPI is required an alternative PPI to omeprazole / esomeprazole should be prescribed. Lansoprazole is the Sheffield formulary choice.

[3] http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm. April 2010.
[4] http://www.cks.nhs.uk/antiplatelet_treatment/management/quick_answers/scenario_antiplatelet_treatment/clinical_summary_managing_gi_adverse_effects/managing_antiplatelet_induced_dyspepsia

Generic Clopidogrel

Generic clopidogrel tablets are now available in the UK. The generic preparations contain different salts to that in branded clopidogrel (Plavix). The licensing authorities are satisfied that available generic clopidogrel products (clopidogrel hydrochloride and clopidogrel besilate) are bioequivalent to the reference product, Plavix (clopidogrel hydrogen sulphate) however there is some variation in licensed indications due to patent protection issues.

All clopidogrel preparations are licensed for the prevention of atherothrombotic events in adults suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

Plavix is additionally licensed for patients suffering from acute coronary syndrome (ACS):

Non-ST acute coronary syndrome, including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).

STEMI, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

As the clopidogrel preparations are deemed to be bioequivalent NHS Sheffield / Sheffield Teaching Hospitals recommends prescribers should continue to prescribe generically for all indications and prescribe the most cost effective salt once the option is available on the prescribing system.

http://www.npci.org.uk/blog/?p=456

Compliance devices, e.g. Nomad or Venalink

The hydrochloride salt of clopidogrel and the clopidogrel besilate manufactured by Arrow Generics are not suitable for compliance devices. When a patient requires a compliance device please consider:

Relevant NICE guidance:

NICE TA1TA 210 December 2010. Clopidogrel and modified release dipyridamole for the prevention of occlusive vascular events
http://guidance.nice.org.uk/TA210

NICE TA182 October 2009 Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary interventions
http://www.nice.org.uk/nicemedia/pdf/TA182Guidance.pdf