VASCULAR DISEASE - CLOPIDOGREL AND DIPYRIDAMOLE

HMMC Recommendation:

- Following the publication of NICE TA 210 and the advice of local Stroke physicians a flowchart outlining NICE TA 210, with local interpretation is enclosed (Appendix 1).

- After Transient Ischaemic Attack (TIA) clopidogrel is recommended as 1st line option. This is in line with the advice of local specialists and is the approach contained in the London Cardiac and Stroke Networks' document agreed by the Pan London Clinical Advisory Group (Appendix 2). Please note that clopidogrel is not licensed for this indication.

Specialist Advice for treatment of stable patients with prior Stroke or TIA

- Patients currently stable on combination aspirin and dipyridamole following stroke or TIA should be considered for a switch to clopidogrel monotherapy. This will reduce daily pill burden and achieve significant financial savings for the NHS. The decision to switch therapy should be discussed at the next medication review and a switch should only be made with the agreement of the patient.

- Patients stabilised on aspirin monotherapy who have not had a subsequent occlusive vascular event after 2 years are considered low risk and aspirin monotherapy is considered sufficient treatment.

Why was this taken to HMMC?

- NICE TA 210: clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (Review of TA 90) has been published (available at http://guidance.nice.org.uk/TA210)

- Key driver to changes from previous TA is the availability of cheaper generic clopidogrel.

- Clopidogrel is not licensed for the treatment of TIA's and was not considered by NICE post-TIA. However, local specialists supported a similar approach to that contained in the London Cardiac and Stroke Networks' document for the use of clopidogrel as 1st line option after TIA's for the following reasons:
  - to simplify treatment so that Ischaemic Stroke and TIA are treated in the same manner;
  - to reduce daily pill burden;
  - to use a once daily regime rather than a twice daily regime;
  - as dipyridamole is poorly tolerated and better tolerance is anticipated with clopidogrel;
  - as combination aspirin and MR dipyridamole costs more than clopidogrel (£8-10/month vs £2/month);
  - there have been recent availability issues with dipyridamole containing products.

- Since the publication of TA 90, the ESPRIT trial has been published. This provided evidence of a continued treatment effect for aspirin plus MR dipyridamole beyond the two years recommended in TA 90.
After an Ischaemic Stroke or Transient Ischaemic Attack

- Clopidogrel
  - Clopidogrel CI or not tolerated
    - Modified-release Dipyridamole in combination with Aspirin

Dipyridamole CI or not tolerated
- Aspirin

Aspirin CI or not tolerated
- Modified-release Dipyridamole

- Aspirin
  - Clopidogrel CI or not tolerated

- Dipyridamole
  - Aspirin CI or not tolerated

- Aspirin
  - Modified-release Dipyridamole

- Clopidogrel CI or not tolerated

- Aspirin
  - Clopidogrel

- Clopidogrel CI or not tolerated

- Aspirin

- Clopidogrel

- Aspirin

CI - Contraindicated.
- Aspirin intolerance - proven hypersensitivity to aspirin-containing medicines or a history of severe dyspepsia induced by aspirin that does not respond to the addition of a PPI.
- Clopidogrel is not licensed to prevent occlusive vascular events in people who have had a transient ischaemic attack (TIA).
- Dipyridamole Standard Release (including oral suspension) is not licensed to prevent occlusive vascular events in people who have had a TIA or an ischaemic stroke.
- This guidance does not apply to people who have had, or are at risk of, a stroke associated with atrial fibrillation (refer to CG36), or who need treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures (refer to Bedfordshire & Hertfordshire Cardiac Network recommendations).
Appendix 2- London Cardiac and Stroke Networks Prescribing Anti-Platelet Agents Following Stroke and Transient Ischaemic Attack (TIA) recommendations - Agreed by the Pan London Clinical Advisory Group on: 5th March 2011 (adopted by Cardiovascular and Stroke Network North East London and agreed with the PCTs in this area)

The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. Wherever appropriate, these patients should also be considered for recruitment into clinical trials.

Acute Phase of Ischaemic Stroke
- All patients should be prescribed aspirin 300mg daily, initiated within 48 hours of acute ischaemic stroke and continued for up to 14 days (after which clopidogrel or alternative therapy should be initiated as below)
- Aspirin should be avoided within 24 hours of the administration of intravenous or intra-arterial thrombolytic therapy.
- Consider use of a PPI in patients with a history of aspirin-induced GI dyspepsia or ulceration

Secondary Prevention of Ischaemic Stroke and Transient Ischaemic Attack (TIA)
Preferred Option
- Clopidogrel monotherapy is the preferred secondary prevention strategy following stroke or TIA¹
- Clopidogrel therapy should be started when the initial course of aspirin therapy finishes
- The routine maintenance dose of clopidogrel is 75mg daily
- Once initiated, clopidogrel monotherapy should be continued indefinitely
- There is no evidence to support the use of aspirin and clopidogrel combination therapy for routine secondary prevention [however, combination therapy is used for other indications, for example, acute coronary syndromes (ACS)].
- Recent advice from the MHRA recommends that omeprazole and esomeprazole should be avoided in patients taking clopidogrel. For patients requiring a PPI whilst taking clopidogrel use an alternative PPI in line with local guidelines

Alternative Strategies
- Low dose aspirin (75mg daily) and dipyridamole (200mg modified release twice daily) should be considered in patients unable to tolerate clopidogrel first-line
- Dose titration of dipyridamole may help to reduce the incidence and severity of headaches – initiate at a lower dose of dipyridamole (e.g. 25mg three times daily or 200mg MR once daily) and increase to the standard maintenance dose of 200mg MR twice daily after one week.
- Patients unable to tolerate clopidogrel monotherapy or aspirin and dipyridamole combination therapy should receive treatment with aspirin monotherapy. There is no evidence to support the use of dipyridamole monotherapy – therefore it should ONLY be considered for patients unable to tolerate all other options.

Stable Patients with Prior Stroke or TIA
Patients currently stable on aspirin and dipyridamole following stroke or TIA should be considered for a switch to clopidogrel monotherapy. This will reduce their daily pill burden and achieve significant financial savings for the NHS. The decision to switch therapy should only be made with the agreement of the patient.

¹ TIA is currently an unlicensed indication for clopidogrel