Guideline for the use of clopidogrel in combination with aspirin in Coronary Heart Disease (CHD)

This guideline sets out Bedfordshire & Hertfordshire Cardiac Network’s recommendations for the use of clopidogrel in combination with low dose aspirin in CHD with the aim of promoting consistent, high quality, safe, prescribing across the network. When implementing the guideline prescribing clinicians will need to consider the balance of benefits and risks in individual patients.

Summary of recommendations for the duration of clopidogrel use in combination with low dose aspirin

<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ST elevation acute coronary syndrome – moderate to high risk patients only (as defined overleaf)</td>
<td>12 months (NICE recommendation)</td>
</tr>
<tr>
<td>ST elevation myocardial infarction (STEMI)</td>
<td>Consider use in hospitals only (if used, to be discontinued on discharge or after 1 month whichever is sooner)</td>
</tr>
<tr>
<td>Elective percutaneous coronary intervention (PCI) with:</td>
<td></td>
</tr>
<tr>
<td>• Bare metal stent (BMS)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>• Drug eluting stent (DES)</td>
<td>12 months</td>
</tr>
<tr>
<td>Stable angina</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Key issues in the use of clopidogrel in CHD:

- Where clopidogrel use is indicated in combination with aspirin, clopidogrel will usually be initiated in secondary/tertiary care. The indication and duration of use will be clearly stated. After clopidogrel has been discontinued, low-dose aspirin (75mg) should be continued indefinitely.
- Clopidogrel is a suitable alternative to aspirin only where aspirin is contraindicated or genuinely not tolerated i.e. proven hypersensitivity to aspirin-containing medicines or history of severe dyspepsia induced by low-dose aspirin that does not respond to the addition of a PPI.
- The recommended dose of clopidogrel is 75 mg for all indications. Details of in-hospital use, including loading doses are given on page 4 of this guideline.
ACUTE CORONARY SYNDROME

Acute coronary syndrome is a term used to refer to any group of clinical symptoms associated with acute myocardial ischaemia. It encompasses a spectrum of disorders including:

- Troponin +ve ACS
- Troponin -ve ACS
- ST elevation myocardial infarction (STEMI)

Non-ST elevation acute coronary syndrome

Clopidogrel in combination with aspirin is recommended for use in the treatment of non-ST segment elevation acute coronary syndrome in patients at moderate to high risk of MI or death. For the purposes of this guidance, moderate to high risk is defined as at least one of:

- The presence of elevated blood markers of myocardial damage e.g. troponin (NSTEMI)
- Symptoms of ischaemia, accompanied by the results of clinical investigations indicating ongoing myocardial ischaemia, such as new ECG changes (especially dynamic or unstable patterns).

_Troponin –ve patients should only receive clopidogrel if they meet the definition above._

Clopidogrel in combination with aspirin should be continued for 12 months after the most recent acute episode of non-ST elevation acute coronary syndrome, as defined above. Thereafter standard care, including treatment with low-dose aspirin, is recommended.

When considering the addition of clopidogrel to aspirin, the increased benefit obtained by reducing the risk of CV events must be balanced against the increased risk of harm resulting from major side effects, notably bleeding. Combination therapy of aspirin and clopidogrel is associated with a 2.1% absolute reduction in risk of death from CV causes, non-fatal MI or stroke. In other words, for every 100 patients treated for nine months, two deaths, non-fatal MIs or strokes are prevented. However, this is at the expense of one further patient suffering a major bleed. NICE considered this benefit to harm ratio sufficient to recommend the use of clopidogrel in combination with aspirin in moderate to high-risk patients with non-ST elevation acute coronary syndrome for 12 months. Subgroup analysis of the CURE study has shown that the greatest benefits occurred within the first three months of treatment. However, the trial was not powered to detect temporal differences between the sub-groups, so the analysis should be interpreted with caution.

ST elevation myocardial infarction (STEMI)

The use of clopidogrel in combination with aspirin for STEMI is currently unlicensed although the manufacturer is seeking a licence for this indication. The evidence from CLARITY and COMMIT is not robust enough to recommend the routine unlicensed use of clopidogrel in combination with aspirin for STEMI. This recommendation will be reviewed as further evidence is published.

There is currently no evidence to support the continuation of clopidogrel in combination with aspirin following discharge from hospital with STEMI. Further studies are required to demonstrate long-term safety and efficacy.

In the COMMIT trial the addition of clopidogrel to aspirin is associated with a 0.9% reduction in the absolute risk of a composite outcome of death, reinfarction and stroke. This corresponds to 9 fewer events for every 1,000 patients treated for a mean of 15 days. In the CLARITY-TIMI trial the addition of clopidogrel to standard thrombolytic regimes yields a 6.7% reduction in the absolute risk of a composite of occlusion of the infarct related artery on angiography or death or recurrent MI before angiography. This result was driven primarily by the reduction in the rate of infarct related artery occlusion. Clopidogrel was given for up to 8 days or until discharge whichever came first (median 3.5 days).

ELECTIVE PERCUTANEOUS CORONARY INTERVENTION (PCI)

Clopidogrel given in combination with aspirin before a PCI reduces the risk of major ischaemic events. In PCI-CURE, combination therapy of aspirin and clopidogrel is associated with a 1.9% absolute reduction in risk of a composite end point of cardiovascular death, MI or urgent target vessel revascularisation within 30 days of PCI with no significant risk of adverse events. The available evidence of effectiveness and
safety supports different durations of clopidogrel use in combination with aspirin depending on the type of stent deployed.

The Bedfordshire & Hertfordshire Cardiac Network recommends that clopidogrel should be used in combination with aspirin for 4 weeks where a bare metal stent has been deployed and for 12 months where a drug-eluting stent has been deployed. This is consistent with the recommendations of the European Society of Cardiology. Shorter or longer use of clopidogrel may be recommended by the interventionist for specific individual circumstances.

ANGINA
There is currently no evidence to support the use of clopidogrel in combination with aspirin in angina.

SPECIAL CONSIDERATIONS
Patients awaiting non-cardiac surgery or patients at high risk of bleeding
Pending or previous percutaneous coronary intervention (PCI)
Wherever possible a bare metal stent (BMS) should be deployed at PCI if either non-cardiac surgery is anticipated imminently or if the bleeding risk is deemed to be high, in order to enable a shorter duration of clopidogrel treatment (4 weeks).

In patients with a drug eluting stent (DES) there is an increased risk of late stent thrombosis. If either bleeding occurs or unforeseen surgery is required, the risks and benefits of stopping clopidogrel use prior to the recommended treatment duration should be considered on an individual basis, as the coronary lesion anatomy will influence the decision. It is recommended that all such cases should be discussed with the interventional cardiologist.

Non-ST elevation ACS patients who have not undergone PCI
Clopidogrel prolongs bleeding time and should be used with caution in patients who have conditions with a propensity to bleed (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is undesirable, clopidogrel should be discontinued 7 days prior to surgery.

Complex patients
In exceptional circumstances, where the PCI procedure is complex, the interventional cardiologist may recommend that clopidogrel should be continued in combination with aspirin for up to 12 months following PCI. In these cases the indication and recommended duration of treatment will be clearly stated on discharge and on the patient-held record.

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References
3. Clarification of recommendation 1.3 National Institute for Clinical Excellence, website accessed Feb 2006
Use of Clopidogrel and Aspirin in non ST elevation ACS, ST elevation MI and elective coronary stenting

Non ST elevation ACS

Moderate / High Risk Only
(ECG change and/or Enzyme Rise)
Aspirin 300mg od loading dose then 75mg od
Clopidogrel 300mg loading dose then 75mg od

Elective PCI

Preload
Aspirin 300mg
Clopidogrel 600mg > 2hrs prior
or 300mg > 6hrs prior

- If already on both, no need to preload.
  Give 75mg of both on day of procedure
- No need to reload if procedure delayed
- If absolute CI to aspirin, clopidogrel 300mg
  > 6hrs prior +/- GPIIb/IIIa inhibitor

Clopidogrel 600mg > 2hrs prior
or 300mg > 6hrs prior

PCI

Aspirin 75mg od indefinitely
Clopidogrel:-
- Bare Metal Stent (BMS) :
  75mg od 4 weeks
- Drug Eluting Stent (DES) :
  75mg od 12 months

ST elevation MI

Thrombolysis
Aspirin 300mg loading dose then 75mg od

Aspirin 75mg od indefinitely
Clopidogrel – consider in-hospital use only, for maximum 1 month. Further guidance awaited

Interventional Cardiologist may recommend longer treatment
For patients with true aspirin allergy, clopidogrel must be continued indefinitely

Based on document prepared by Clopidogrel Guidelines Working Group for Anglia Cardiac Network May 2006