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Prescribing clopidogrel

Clopidogrel is an inhibitor of platelet aggregation. Unlike aspirin, which inhibits platelet cyclo-oxygenase, clopidogrel acts by inhibiting adenosine diphosphate receptors on platelets. It is licensed, as an alternative to aspirin, for the secondary prevention of atherothrombotic events, such as myocardial infarction (MI) and stroke. It is also licensed in combination with aspirin for use in patients with acute coronary syndrome (ACS) at high risk of thrombotic vascular events. Guidance on the use of clopidogrel in these conditions is being prepared by the National Institute of Clinical Excellence.

Clopidogrel was first marketed in 1998 and its use has grown rapidly over the last few years. In Wales during the year up to November 2003, approximately £7 million was spent on 190,000 dispensed items, a growth of £2.2 million over the previous year.[1] This usage has sparked controversy as to whether the extra associated cost is justified. Clopidogrel 75 mg costs £35.31 per 28-day supply compared with dispersible aspirin 75 mg which costs around 18 pence.[2]

In order to address these concerns a number of questions need to be considered:

- What are the licensed indications?
- What is the evidence that it is effective, or that it is more effective than aspirin?
- What is the evidence that it is safe, or that it is safer than aspirin?
- Is there evidence that it should be used in those who cannot take aspirin?
- Does combining clopidogrel with aspirin confer additional benefits, and what are the risks?
- When used in combination with aspirin, for how long should it be prescribed?

This bulletin also considers:

- Further uses for clopidogrel? Percutaneous coronary intervention (PCI) and stents.
- Prescribing across primary and secondary care.

Summary

- Clopidogrel has become widely used over the last few years as an alternative to aspirin to prevent atherothrombotic events in those at high risk. Also, increasing use has occurred as add-on therapy to aspirin.
- Clopidogrel is licensed for use in patients with myocardial infarction, ischaemic stroke or in those who suffer peripheral arterial disease. Use in combination with aspirin is specifically for those with acute coronary syndrome. Prescribers should be wary about use of clopidogrel outside these indications (i.e. “off-label” use).
- Like aspirin, clopidogrel is an antiplatelet agent and can cause bleeding. It should not be thought of as a safer alternative to aspirin, and in combination with aspirin it is associated with additional risks.
- One reasonable place for use of clopidogrel is where aspirin is indicated for secondary prevention of atherothrombotic events but where there is a clear allergy or a serious gastro-intestinal adverse reaction to aspirin. However, it should be noted that clopidogrel can also be associated with such events.
- There is controversy over the appropriate place and duration of treatment when combining clopidogrel with aspirin for acute coronary syndrome; trial evidence suggests that treatment of high-risk cases for three months gives the best balance risk and benefit, but use for up to 12 months is licensed.
- There is a need to agree policies regarding the prescribing of clopidogrel between primary and secondary care, and to develop audit criteria in order to manage the use of this medicine appropriately.

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What are the licensed indications for clopidogrel?

Despite widespread use of clopidogrel, the licensed indications for its use are very specific.[3]

1. As single antiplatelet therapy for the prevention of atherothrombotic events in patients with:
- myocardial infarction (from a few days until less than 35 days after the event)
- ischaemic stroke (from seven days until less than six months after the event)
- established peripheral arterial disease (PAD).

2. In combination with aspirin for the prevention of atherothrombotic events in patients suffering from non-ST-segment-elevation ACS (unstable angina or non-Q-wave MI). For this use the Summary of Product Characteristics (SPC) advises that:
- clopidogrel treatment should be initiated with a single 300 mg loading dose and then continued at 75 mg once a day
- since higher doses of aspirin are associated with higher bleeding risk, the maximum dose of aspirin used should be 100 mg
- the optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months; the maximum benefit was seen at three months.

There seems to be confusion over the use of clopidogrel with a belief that it is an all-purpose substitute for aspirin and that combination with aspirin is risk-free. Clopidogrel is being used for primary prevention of vascular events in people who are allergic to aspirin, and in combination with aspirin in stroke patients. Use of clopidogrel in such cases or for longer than recommended is outside its licensed indications or "off-label" and has specific medico-legal implications.[4]

What is the evidence that clopidogrel is effective, or that it is more effective than aspirin?

The main study to address this question was the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial.[5] This was an international, randomised, double-blind study which compared aspirin 325 mg daily with clopidogrel 75 mg daily in 19,185 patients who had suffered a recent ischaemic stroke [not transient ischaemic attack (TIA)], a recent MI, or symptomatic PAD. After just under two years of follow-up, the risk of reaching the combined primary endpoint of ischaemic stroke, MI or vascular death was slightly lower with clopidogrel than with aspirin (annual rate 5.32% vs. 5.83%, P=0.043). Thus, 196 patients would have to be treated with clopidogrel instead of aspirin to prevent one event over one year; the number need to treat (NNT) is 196. Subgroup analysis of the data suggest that most of the benefit in favour of clopidogrel was seen in those patients who had PAD at entry to the study.

The marginal benefit seen in this study is not considered sufficient to support the use of clopidogrel as a direct substitute for aspirin. It is important to recognise when comparing clopidogrel to aspirin that aspirin has an immense body of evidence supporting its use over a long period of time.[6] It is generally agreed that clopidogrel should be reserved for patients with vascular disease who are unable to take aspirin because of allergy (bronchospasm or angio-oedema or rash).

What is the evidence that clopidogrel is safe, or that it is safer than aspirin?

In the CAPRIE study, the absolute difference in most adverse effects was small and overall the rates of adverse events were similar.[7] Fewer people had severe gastro-intestinal (GI) haemorrhage with clopidogrel than with aspirin (0.49% vs. 0.71%, P<0.05). Also, fewer people taking clopidogrel reported indigestion, nausea or vomiting (15.0% vs. 17.6%, P<0.05), but rashes and diarrhoea were more common with clopidogrel (rash 6.0% vs. 4.6%, diarrhoea 4.5% vs. 3.4%; P<0.05 for both). In assessing overall GI tolerability, 27.1% of patients reported GI events whilst taking clopidogrel and 3.2% discontinued treatment because of GI events.[8] The corresponding rates for aspirin were 29.8% and 4.0%, respectively. When equating these results to UK practice it is important to realise that the aspirin dose used in this study (325 mg daily) was relatively high. It is not clear how clopidogrel use compares with use of lower aspirin doses.

Is there evidence that clopidogrel should be used in those who cannot take aspirin?

Evidence for use of clopidogrel in those allergic to, or intolerant of aspirin is lacking, as these people were excluded from the aspirin and clopidogrel studies. In the CAPRIE study, between 3% and 4% of patients stopped taking either aspirin or clopidogrel because of GI intolerance.

If the problem with aspirin is GI disturbance, or a history of ulcer, one option to consider is prescribing a gastroprotective agent such as a proton-pump inhibitor (PPI). Evidence supporting this approach is also lacking, but it is a generally

accepted strategy if there are problems with a nonsteroidal anti-inflammatory drug.[9] Clopidogrel is contra-indicated in patients with active peptic ulcer, and the use of clopidogrel provides no price advantage over adding a low-cost PPI to aspirin. In patients taking a PPI there is no good reason to use clopidogrel first-line, except where there is allergy to aspirin.

If clopidogrel is used after an ischaemic stroke it should not be started until seven days have elapsed. Dipyridamole is an alternative for those who have had a stroke or TIA and who cannot take aspirin.[10]

Does combining clopidogrel with aspirin confer additional benefits, and what are the risks?

The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial (CURE) study,[11] compared the combination of clopidogrel with aspirin to aspirin given alone in patients admitted with ACS. It received considerable media attention, but behind the headlines this study raises important questions about the balance of risk and benefit for antiplatelet therapy. This international, randomised, double-blind study involved 12,562 patients admitted to hospital with symptoms suggestive of ACS. Most were at particular high risk with troponin and/or electrocardiogram (ECG) changes but without ST-segment-elevation on ECG. Exclusion criteria included contra-indications to antithrombotic or antiplatelet therapy, a high risk of bleeding, and severe heart failure.

All patients received standard therapy and aspirin (75 mg to 325 mg daily, according to local practice), and either clopidogrel (300 mg loading dose then 75 mg daily) or placebo for three to 12 months (about nine months, on average). The main measure used to assess efficacy was a composite endpoint of death from cardiovascular causes, non-fatal MI or stroke. Clopidogrel was associated with a 2.1% absolute reduction in this outcome (9.3% vs. 11.4%, P<0.001). This means that of 48 patients treated with clopidogrel plus aspirin, instead of aspirin alone, for about nine months, one was prevented from either dying from cardiovascular causes, or having a non-fatal MI or a stroke (NNT 48). However, subgroup analysis suggest this benefit was mostly driven by a 1.5% absolute reduction in the incidence of MI. There was little effect on stroke or cardiovascular death taken individually.

The clinical significance of the CURE study is dependent on the criteria used for MI diagnosis,[12] which is currently a subject of debate. The study endpoints for an MI included patients with changes in troponin concentrations that reflect levels of myocardial damage which may not previously have been classified as a confirmed MI. This alters the interpretation and clinical application of the CURE study when weighing up the benefits of treatment against potential harm.

Despite exclusion of patients judged at "high risk of bleeding", the addition of clopidogrel significantly increased the absolute rate of major bleeding (defined as substantially disabling bleeding, intra-ocular bleeding leading to the loss of vision, or bleeding necessitating transfusion of at least two units of blood) by 1% (from 2.7% to 3.7%, P=0.001).[11] That is, of 100 people treated for about nine months, one would suffer severe harm associated with the addition of clopidogrel; the number needed to harm (NNH) is 100. The rate of harm was similarly manifest both during the 30 days after randomisation (2% vs. 1.5%) and from 30 days after randomisation until the end of the trial (1.7% vs. 1.1%). There is insufficient information to determine what proportion of major bleeding occurred within the first three months, when most of the benefit was seen.

When used in combination with aspirin, for how long should clopidogrel be prescribed?

Duration of therapy after an ACS event has become controversial. A subgroup analysis of the CURE results divides the data into early effects (those occurring in the first month) and late effects (those occurring after one month and up to the 12 months that some subjects remained in the study).[13] The authors concluded that the benefit of combination therapy over aspirin was the same in the early and late phases (same difference in event rate of 1.1%, NNT 90), and therefore, use of the combination is beneficial throughout 12 months. However, another analysis of the event rates shows that most of the late effect actually occurred between 30 days and three months (difference in event rate 0.9%, NNT 111), and thereafter (from three months to 12 months) little additional benefit over aspirin alone is seen (0.2% difference in event rate, NNT 500).[14]

The risk of major haemorrhage (NNH 100 over about nine months, and not confined to the first month of use) needs to be weighed against the composite primary outcome of reduction in cardiovascular death, non-fatal MI or stroke (NNT 48, nine months). As previously stated, this

endpoint was largely derived from non-fatal MIs defined by parameters that may have different clinical implications. From the trial evidence, treatment for three months appears to best balance risk and benefit. However, in patients with ACS, clopidogrel in combination with aspirin is licensed for use for up to one year and many clinical guidelines support such use for nine to 12 months.

Further uses for clopidogrel? Percutaneous coronary intervention (PCI) and stents

An analysis of observational data from the CURE study relating to patients who underwent PCI (for example stenting or angioplasty) is available[15] but is difficult to interpret alongside current practice. Subsequently, the Clopidogrel for the Reduction of Events During Observation (CREDO) study has been published.[16] Estimates of efficacy from the CREDO study (2,116 patients) show that a loading dose of clopidogrel followed by a sustained course over 12 months of aspirin plus clopidogrel instead of aspirin alone, reduced the incidence of death, MI or stroke (P=0.02, NNT 33). However, CREDO also suggests an increase, although not statistically significant (p=0.07), in the risk of a major bleed (a drop in haemoglobin of 5g); NNH 48.

Clopidogrel in combination with aspirin has been specifically studied in patients following insertion of stents. There may be local guidelines advising on such use; policies may vary, but they typically advise that clopidogrel is continued for one month in patients with bare metal stents and for longer (e.g. three to six months) in patients following insertion of drug-eluting stents.

Use for PCI and for stents is "off-label" and it is important that local protocols are agreed and prescribing responsibilities established. There should be a clear statement about appropriate shared-care.

Prescribing across primary and secondary care

There is a need for clear guidelines to be agreed between primary and secondary care on the appropriate use of clopidogrel. Alongside prescribing arrangements, regular audits are appropriate to ensure adherence to local policies. Direction on these matters, which are important safety and clinical governance issues, is expected from the All Wales Medicines Strategy Group.

Preliminary audit results indicate that the following issues are important:

- Any reason for using clopidogrel instead of aspirin should be clearly identified, documented and shared between primary and secondary care.
- Partnership committees should have clear guidelines on the use of clopidogrel in combination with aspirin that include the duration of treatment. Consideration should be given to prescribing of this combination by hospitals only.

This bulletin is based on work prepared by Dr Martin Duerden, Medical Director of Conwy Local Health Board and university lecturer in therapeutics.

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The Summary of Product Characteristics should be consulted for full prescribing information.