

# DRUG UPDATE

No.55

June 2007

## CLOPIDOGREL IN ST-ELEVATION MYOCARDIAL INFARCTION

Clopidogrel in combination with aspirin is now indicated for use in patients suffering from ST-segment elevation myocardial infarction who are medically treated and eligible for thrombolytic therapy. Recently conducted clinical trials suggest benefit from the addition of clopidogrel to standard antiplatelet treatment with aspirin, at the time of presentation for up to one month thereafter. There is no evidence to suggest benefit from clopidogrel in combination with aspirin beyond this time. Discharge documentation should clearly indicate the intended duration of clopidogrel therapy.

### What is it?

Clopidogrel (Plavix® Sanofi-Aventis/Bristol-Myers Squibb) is an antiplatelet agent which inhibits the adenosine diphosphate (ADP)-mediated platelet aggregation pathway. In July 2006 the European Medicines Agency extended its licence to cover the treatment of patients experiencing an ST-segment elevated myocardial infarction (STEMI). The recommended dose in STEMI is 75 mg once daily for one month (with an initial loading dose of 300 mg for patients  $\leq$  75 years old).<sup>1</sup>

Clopidogrel is also licensed as monotherapy for the prevention of atherothrombotic events in patients suffering from myocardial infarction (MI), ischaemic stroke or established peripheral arterial disease and in combination with aspirin in patients with non-ST-segment elevated myocardial infarction (NSTEMI).<sup>1</sup>

### What is the rationale for use?

Two recent large, well conducted clinical trials support the short-term addition of clopidogrel to aspirin therapy for patients with a STEMI. The CLARITY study involved 3,491 patients 18 to 75 years old who were randomised to clopidogrel (300 mg loading dose followed by 75 mg once daily) or placebo within 12 hours of the onset of a STEMI.<sup>2</sup> Patients also received standard therapy including fibrinolytic treatment, aspirin and where appropriate, heparin. Treatment was continued until the day of follow-up coronary angiography, and for patients who did not undergo coronary angiography, up to and including day 8 or hospital discharge (whichever came first). The composite primary outcome was the incidence of an occluded infarct-related artery, death from any cause or recurrent MI before angiography. An absolute reduction of 6.7% in the group assigned to clopidogrel

plus standard treatment was demonstrated (21.7% vs. 15.0%,  $p < 0.001$  compared with placebo). Patients were followed up 30 days after the onset of STEMI, at which point treatment with clopidogrel was associated with a 2.5% absolute reduction in the incidence of the primary endpoint (11.6% compared with 14.1% in the placebo group,  $p = 0.03$ ). Assessment of the individual end points demonstrated no significant differences in death or stroke associated with clopidogrel treatment. However, a reduction in recurrent MI was seen with clopidogrel treatment compared with placebo (1.8% absolute risk reduction,  $p = 0.02$ ). This study was not powered to demonstrate statistically significant reductions in overall mortality.

The PCI-CLARITY study was a planned sub-analysis ( $n = 1,863$ ) of the CLARITY study which evaluated the effects of pre-treatment with aspirin plus clopidogrel, compared with aspirin plus placebo, in patients who went on to have coronary artery stenting.<sup>3</sup> Again there was a reduction in the incidence of cardiovascular death, MI or stroke following percutaneous coronary intervention (PCI) (3.6% vs. 6.2%,  $p = 0.008$ ) in those receiving aspirin plus clopidogrel. Pre-treatment with aspirin plus clopidogrel also reduced the incidence of recurrent MI or stroke prior to PCI (4.0% vs. 6.2%,  $p = 0.03$ ).

The COMMIT study ( $n = 45,852$ ) evaluated the effects of adding clopidogrel (75 mg) or placebo to aspirin therapy (162 mg) in patients presenting within 24 hours of a suspected MI.<sup>4</sup> Treatment was administered up to and including the date of the patient's repeat angioplasty (mean treatment duration = 14.9 days). This was a large, well designed, randomised, placebo-controlled study conducted in a Chinese population, with statistical power to evaluate improvements in overall mortality in contrast to the smaller CLARITY study.<sup>2</sup>

Treatment with clopidogrel was associated with a reduction in the incidence of death, re-infarction or stroke (composite primary outcome) compared with placebo (9.2% and 10.1% respectively,  $p = 0.002$ ). Death from any cause was reported for 7.5% of patients in the clopidogrel group compared with 8.1% in the placebo group ( $p = 0.03$ ). Allocation to clopidogrel produced a modest 0.3% absolute reduction in the reinfarction risk ( $p = 0.02$ ). Compared with placebo, clopidogrel treatment was associated with a non-significant 0.2% absolute reduction in the risk of stroke. However, these events were relatively infrequent within the follow-up period (1.1% vs. 0.9%,  $p = 0.11$ ).

### How safe is it?

In the CLARITY study, short duration treatment with clopidogrel and aspirin did not appear to be associated with a significantly increased risk of major bleeding.<sup>2</sup>

In the COMMIT study there was no excess in severe haemorrhage including haemorrhagic stroke but there was an increase in minor bleeding including dental and skin bruising (3.6% vs. 3.1%,  $p = 0.005$ ).<sup>4</sup> However, the relatively low incidence of brain imaging carried out in patients with fatal stroke may have resulted in a lower detection rate of fatal intracranial haemorrhage.

Studies which have treated patients with combinations of aspirin and clopidogrel longer-term have demonstrated a significant excess of bleeding events compared with aspirin alone.<sup>5,6</sup>

### How much does it cost?

A single treatment course of clopidogrel 75 mg for 28 days costs £35.31 (Drug Tariff June 2007).

### When should it be used?

There is now evidence to support the use of the combination of aspirin plus clopidogrel for one month following STEMI. Treatment with aspirin plus clopidogrel beyond one month has not been demonstrated. After this treatment period, therapy should resume with aspirin alone (antiplatelet therapy). This is in contrast to the evidence in patients with NSTEMI for whom longer term treatment is recommended (3-12 months).<sup>7,8</sup> Short-term treatment with aspirin plus clopidogrel has not been associated with an increased risk of bleeding.<sup>2-4</sup> However this risk is increased with longer-term use; therefore patients should not be continued on combination therapy for any longer than indicated and arrangements should be made for review and appropriate discontinuation of clopidogrel. The duration of treatment with clopidogrel should be clearly indicated on discharge communication.

### Points for practice in primary care

- This is a single, one-month treatment course of clopidogrel (in addition to aspirin daily) which ideally should be supplied on discharge from hospital. After this, continuation of aspirin therapy is usually devolved to primary care.
- Repeat prescriptions for clopidogrel (in addition to aspirin) for patients after a STEMI are not normally required and should be queried.
- The need for continuing treatment with clopidogrel and aspirin should be clearly indicated on discharge documentation and the reasons for extending treatment should be recorded.
- The additional bleeding risks associated with aspirin plus clopidogrel treatment become significant at 12 months. Clopidogrel treatment beyond 12 months in any patient is not routinely required.

## REFERENCES

1. Sanofi Pharma Bristol-Myers Squibb SNC. Summary of product characteristics: Plavix® 75mg film coated tablets (Clopidogrel). September 2006. [www.medicines.org.uk](http://www.medicines.org.uk)
2. Sabatine MS et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction. *N Engl J Med* 2005;352:1179-89. (RCT)
3. Sabatine MS et al. Effect of clopidogrel pre-treatment before percutaneous coronary intervention in patient with ST-elevation myocardial infarction treated with fibrinolytics. *JAMA* 2005;294:1224-32. (RCT)
4. COMMIT Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607-21. (RCT)
5. The CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. (RCT)
6. CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; 354:1706-17. (RCT)
7. Scottish Intercollegiate Guidelines Network (SIGN). Acute coronary syndromes: a national clinical guideline. Guideline 93; February 2007. (G)
8. National Institute of health and Clinical Excellence. Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. Technology Appraisal Guidance 80. July 2004. (G)

KEY RCT - randomised controlled trial, G- guideline

## Regional Drug and Therapeutics Centre

Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH

Tel: 0191 232 1525 Fax 0191 260 6192

E-mail: [nyrdtc.di@ncl.ac.uk](mailto:nyrdtc.di@ncl.ac.uk) Website: [www.nyrdtc.nhs.uk](http://www.nyrdtc.nhs.uk)

Not to be used for commercial purposes