

# DRUG UPDATE

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## CLOPIDOGREL

Clopidogrel is an antiplatelet agent used for the secondary prevention of vascular events. Based on current evidence, cost-effective use is justified for the following: (a) Patients with vascular disease who have true aspirin hypersensitivity or those unable to tolerate aspirin despite acid suppressant therapy, (b) as a single agent (or occasionally in combination with aspirin) in patients at particularly high risk of further cardiovascular events on the advice of a consultant vascular specialist, (c) in acute coronary syndromes without ST-segment elevation in addition to aspirin for 3-9 months only and (d) following percutaneous coronary intervention when it should be given for 1-12 months in combination with aspirin. In each case the initiating specialist should specify the planned duration of therapy.

### What is it?

Clopidogrel (Plavix<sup>®</sup>, Sanofi-Synthelabo/BMS) is an antiplatelet agent licensed for the reduction of atherosclerotic events in patients with symptomatic atherosclerotic disease and in acute coronary syndrome (ACS) without ST-segment elevation.<sup>1</sup> The recommended dose is 75 mg once daily (initially 300 mg in ACS). This bulletin provides recommendations for its current place in therapy.

### Generalised Vascular Disease

The comparative, double-blind, CAPRIE study evaluated the efficacy of clopidogrel for vascular disease over almost 2 years (n=19,185).<sup>2</sup> The annual risk of ischaemic stroke, MI or vascular death was 5.32% and 5.83% in the clopidogrel (75 mg/day) and aspirin (325 mg/day) groups respectively (p=0.043).

### Acute Coronary Syndromes

In the CURE study 12,562 hospitalised patients with ACS without ST-segment elevation were randomised to receive clopidogrel (300 mg loading dose followed by 75 mg/day) or placebo in addition to aspirin (75-325 mg/day) for a mean duration of 9 months.<sup>3</sup> Cardiovascular (CV) death, non-fatal MI or stroke occurred in 9.3% and 11.4% of patients in the clopidogrel and placebo group respectively (p<0.001), largely due to an absolute risk reduction (ARR) in MI of 1.5%. There were a significantly smaller number of CV events between 30 days and the end of follow up in the clopidogrel group (5.2% vs. 6.3%, p<0.01).<sup>4</sup> The benefits of combined therapy were offset by a 1% absolute increased risk of major bleeding (see below).<sup>3</sup> Current guidelines for the management of unstable angina and non-ST-segment elevation MI suggest the addition of clopidogrel to aspirin (75-100mg) for 9-12 months.<sup>5-7</sup>

### Percutaneous coronary intervention (PCI)

A CURE trial sub-study (PCI-CURE) examined outcomes for the 2658 patients undergoing PCI.<sup>8</sup> Clopidogrel or placebo was continued up until PCI, patients then received open-label clopidogrel or ticlopidine with aspirin for 2-4 weeks, and then resumed their study medication until study end. From the time of PCI to the end of follow-up (mean duration 8 months) there were significantly fewer CV deaths or MIs in the clopidogrel group (8.0% vs. 6.0%, p=0.047). For the period between 30 days and study end this benefit was not statistically significant (3.1% vs. 3.9%).

In the double-blind randomised CREDO study 2116 patients were assigned to receive a 300 mg clopidogrel loading dose or placebo prior to PCI.<sup>9</sup> All patients received clopidogrel 75 mg/day to day 28. From day 29 to study end (mean 1 year) patients received clopidogrel 75 mg/day or placebo. All patients received aspirin throughout. The addition of clopidogrel pre-treatment to aspirin 3-24 hours before PCI was associated with a non-significant reduction in the combined end-point of death, MI or urgent revascularisation at 28 days. At 12 months there was a 3% ARR of death, MI or stroke (p=0.02) although individual outcomes were not significant. There are currently no plans to apply for a licence for clopidogrel in PCI.<sup>10</sup>

### How safe is it?

In the CAPRIE study gastrointestinal events were less common (15% vs. 17.6%, p<0.05) and rash more common (6.0% vs. 4.6%, p<0.05) with clopidogrel 75 mg than aspirin 325 mg daily, although aspirin sensitive patients were excluded.<sup>2</sup> In the CURE study major bleeding was significantly more common with clopidogrel and aspirin than aspirin alone (3.7% vs. 2.7%, p=0.001).<sup>3</sup> Post marketing surveillance has shown bleeding to be the most commonly reported adverse reaction with clopidogrel.<sup>1</sup> Bleeding during

surgery may be increased and many surgeons recommend discontinuing clopidogrel a few days before surgery.

### When should it be used?

The CAPRIE study found only a marginal benefit for clopidogrel over aspirin at significant cost (number needed to treat to prevent one additional event = 196 per annum at a cost of £90,000). On cost-effectiveness grounds the use of clopidogrel is recommended only for the following:

(a) Patients with vascular disease who have true aspirin hypersensitivity or those unable to tolerate aspirin despite acid suppressant therapy.

(b) Patients at particularly high risk, as a single agent (or more rarely in combination with aspirin or warfarin) on the advice of a consultant vascular specialist.

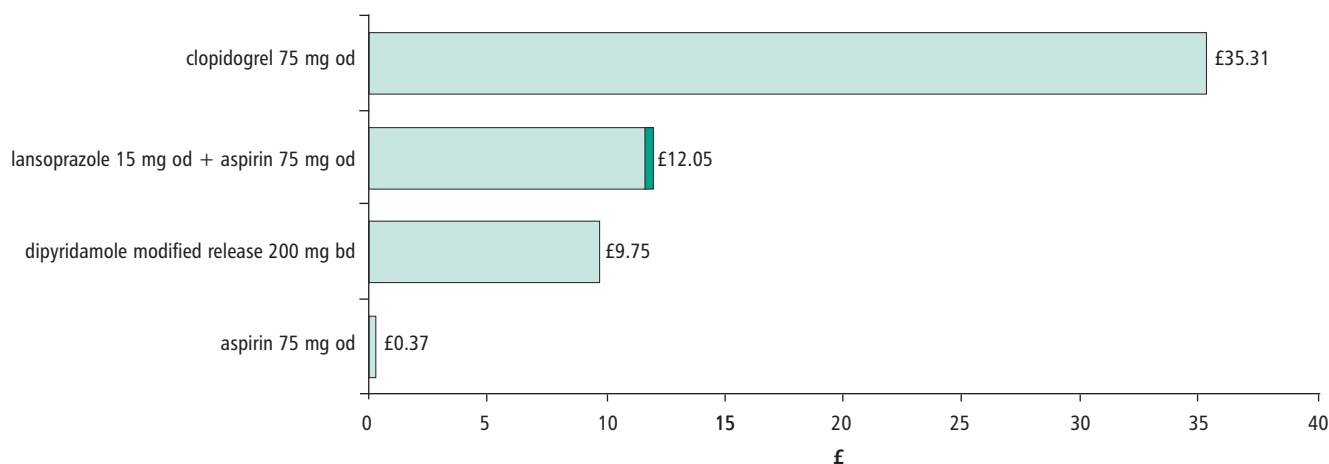
(c) Patients with ACS without ST-segment elevation in combination with aspirin (75-150 mg/day) for 3-9 months only, based on the individual's risk profile for cardiovascular events and bleeding.

(d) After PCI for between 1 and 12 months in combination with aspirin (75-150 mg/day), depending on the type of procedure and the patient's individual risk profile (an unlicensed indication).

In each case the initiating specialist should specify the planned duration of therapy.

### How much does it cost?

Cost for 1 months treatment (prices from MIMS/Drug Tariff February 2004)



NB Doses shown are for general comparison only and do not imply therapeutic equivalence

### REFERENCES

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KEY RCT - randomised controlled trial, CT - controlled trial, MA - meta analysis, R - review, G - guidelines

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