NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90)

Final scope

Remit/Appraisal objective

To review and update if necessary the Institute's guidance on the clinical and cost-effectiveness of clopidogrel and modified-release dipyridamole, within their licensed indications, for the prevention of occlusive vascular events in individuals with established peripheral arterial disease, or with a history of myocardial infarction, ischaemic stroke, or transient ischaemic attacks.[1]

Background

Occlusive vascular events are the result of a reduction in blood flow related to the narrowing or blocking of an artery which is usually caused by atherosclerosis and atherothrombosis. Occlusive vascular events include transient ischaemic attack (TIA), ischaemic stroke and myocardial infarction (MI). Peripheral arterial disease (PAD) is also caused by narrowing of arteries. PAD may be asymptomatic but commonly presents with leg pain on walking (intermittent claudication). People with PAD are at high risk of occlusive vascular events, including MI, stroke or TIA.

Annually, between 94,000 and 117,000 people experience a stroke episode in England and Wales and a further 20,000 people have a TIA. Stroke accounts for 11% of deaths in England. Stroke is also the leading cause of disability in adults. In the UK, annually, around 259,500 people experience an acute MI. MI is associated with high morbidity and mortality; around 30% of people die from their first MI. Approximately 20% of people from 55 to 75 years of age have evidence of lower extremity PAD. Five percent of this population appears to have symptoms with the most common one being intermittent claudication. Since the UK population above 55 years of age is approximately 17 million, this equates to a prevalence of around 850,000 with intermittent claudication.

NICE guidance (TA90) on clopidogrel and dipyridamole in the prevention of occlusive vascular events makes the following recommendations: For people

[1] The original remit from the Department of Health to the Institute was "To appraise the clinical and cost effectiveness of clopidogrel and modified release dipyridamole, both as monotherapy and in combination with aspirin as appropriate, compared with prophylactic doses of aspirin, for the secondary prevention of myocardial infarction, stroke and vascular death; and if the evidence allows to advise on the selection of patients for whom these treatments would be appropriate."

who have had an ischaemic stroke or a TIA the use of modified-release dipyridamole in combination with aspirin is recommended for a period of two years from the most recent event. Thereafter, or if modified-release dipyridamole is not tolerated, they should revert to standard care which includes the use of long-term, low-dose aspirin. People with occlusive vascular events or PAD and who are intolerant to low-dose aspirin are advised to use clopidogrel alone (within its licensed indications).

The technologies

Dipyridamole is an adenosine reuptake inhibitor and phosphodiesterase inhibitor with both antiplatelet and vasodilating activity. Modified-release dipyridamole (Persantin Retard, Boehringer Ingelheim) is licensed for the secondary prevention of ischaemic stroke and TIAs either alone or in conjunction with aspirin. A combination product containing modified-release dipyridamole and standard release aspirin (Asasantin Retard, Boehringer Ingelheim) is also available for the same indication.

Clopidogrel (Plavix, Bristol-Myers Squibb and Sanofi-Aventis) is a thienopyridine antiplatelet agent. After activation in the liver, clopidogrel irreversibly inhibits the binding of adenosine diphosphate receptor (ADP) to its platelet receptor. The blockade of ADP inhibits platelet aggregation by preventing the activation of the glycoprotein IIb/IIIa complex. Clopidogrel is licensed for the prevention of atherosclerotic events in people with a history of myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. It is also licensed for use in combination with aspirin for acute coronary syndromes; this indication is not included in this appraisal.

Intervention(s)	• Clopidogrel • Modified-release dipyridamole alone or in combination with aspirin
Population(s)	Patients with established peripheral arterial disease or those with history of myocardial infarction, ischaemic stroke or transient ischaemic attacks.
Comparators	The interventions will be compared with aspirin and, where appropriate, with each other.
Outcomes	The outcome measures to be considered include: • myocardial infarction (NSTEMI and STEMI) • unstable angina • stroke • death • vascular death • adverse effects of treatment including bleeding complications • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows, the effectiveness of clopidogrel in people with multi-vascular disease who are considered to be at high risk of recurrent occlusive vascular events, will be considered. If the evidence allows, the duration of treatment with the specified interventions will be considered.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal, No. 152, July 2008, Drug-eluting stents for the treatment of coronary artery disease. Expected review date in July 2009. Technology Appraisal, No. 122, June 2007, Alteplase for the treatment of acute ischaemic stroke. Expected review date in April 2010. Technology Appraisal, No. 94, January 2006, Statins for the prevention of cardiovascular events. In April 2009, following consultation, the Institute decided to make this guidance 'static'. Technology Appraisal, No. 80, July 2004, Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. To be reviewed within the clinical guideline 'Acute coronary syndromes: the management of unstable angina and non-ST segment elevation myocardial infarction.' Technology Appraisal, No. 71, October 2003, Ischaemic heart disease – coronary stents. This guidance has been partially replaced by TA 152. Technology Appraisal, No. 52, October 2002, Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. In January 2006, following consultation, the Institute decided to make this guidance 'static'. Technology Appraisal, No. 47 September 2002, Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. To be reviewed within the clinical guideline 'Acute coronary syndromes: the management of unstable angina and non-ST segment elevation myocardial infarction.' Related Guidelines: Clinical guideline, No. 68, July 2008, Stroke. The diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). Expected review date in 2011. Clinical guideline, No. 48, May 2007, MI: secondary prevention. Secondary prevention in primary and secondary care for patients following myocardial infarction. Expected review date in 2010. Clinical guideline in preparation, Acute coronary syndromes: the management of unstable angina and non-ST segment elevation myocardial infarction. Earliest anticipated date of publication in 2010.