National Institute for Health and Clinical Excellence

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Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events

Technology Appraisal 90

Technology Appraisal Guidance 90
Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events

Ordering information

You can download the following documents from www.nice.org.uk/TA090

- The full guidance for this technology appraisal (this document).
- A quick reference guide, which has been distributed to health professionals working in the NHS in England.
- Information for people with people who have had an occlusive vascular event, or who have symptomatic peripheral arterial disease, their families and carers, and the public.
- The assessment report – details of all the studies that were looked at.

For printed copies of the quick reference guide or information for the public, phone the NHS Response Line on 0870 1555 455 and quote:

- N0838 (quick reference guide)
- N0754 (information for the public).

This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Health professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of health professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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1 Guidance

This guidance applies to people who have had an occlusive vascular event, or who have symptomatic peripheral arterial disease. This guidance does not apply to people who have had, or are at risk of, a stroke associated with atrial fibrillation, or who require treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures.

1.1 As part of the prevention of occlusive vascular events:

1.1.1 the combination of modified-release (MR) dipyridamole and aspirin is recommended for people who have had an ischaemic stroke or a transient ischaemic attack for a period of 2 years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy should revert to standard care (including long-term treatment with low-dose aspirin)

1.1.2 clopidogrel alone (within its licensed indications) is recommended for people who are intolerant of low-dose aspirin and either have experienced an occlusive vascular event or have symptomatic peripheral arterial disease.

1.2 For the purposes of this guidance, aspirin intolerance is defined as either of the following:

- proven hypersensitivity to aspirin-containing medicines
- history of severe dyspepsia induced by low-dose aspirin.

2 Clinical need and practice

2.1 Occlusive vascular events (OVEs) are the result of a reduction in blood flow related to the narrowing or blocking of an artery. Examples of such events include transient ischaemic attack (TIA), ischaemic stroke and myocardial infarction (MI).

2.2 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 OVEs, including MI, stroke or TIA.

2.3 Narrowing or blocking of an artery is usually caused by atherosclerosis and atherothrombosis. Atherosclerotic plaque formation within artery walls results from damage to the vascular endothelium caused by several insults working together over a long period. These include factors such as elevated low-density lipoproteins, cigarette smoking, hypertension and diabetes mellitus. Atherothrombosis is characterised by sudden atherosclerotic plaque disruption leading to platelet activation and thrombus (clot) formation. Such a thrombus may then block an artery, either locally or more distally by embolisation.

2.4 In England and Wales, 110,000 new cases of stroke and 30,000 TIAs are estimated to occur every year and 102,000 people are diagnosed with PAD every year. The annual number of MIs has been estimated to be approximately 237,000, and approximately 76,500 hospital admissions for MI were recorded in England and Wales for the financial year 2002/03.

2.5 Ischaemic stroke and MI are associated with a high morbidity and mortality; 30% of people die from their first MI. After a stroke, approximately 23% of people die within 30 days, and of the initial stroke survivors, only 30–40% are alive after 3 years. Stroke is also the leading cause of disability in the UK and other Western countries, with about 25−30% of stroke survivors remaining permanently disabled. People who have had an OVE are at increased risk of recurrent events, and people with symptomatic atherosclerosis in one vascular bed are also at higher risk of subsequent events in other vascular beds. However, people who have had an MI are more likely to experience a recurrent MI than a stroke. People who have had a stroke are initially more likely to experience a recurrent stroke than to experience an MI. Within 1–5

years after a stroke, the risk of dying from a recurrent stroke becomes smaller than the risk of dying as a result of non-stroke cardiovascular events.

2.6 The economic burden from coronary artery disease in terms of direct healthcare costs and indirect costs (including informal care costs and loss of productivity) was estimated in 1999 at more than £7 billion. The annual cost of stroke in the UK has been quoted as £1.7–2.3 billion (NHS and Social Services expenditure, 1999 and 2000/01 estimates), one third of which was for the care of new stroke patients and two thirds for acute recurrent strokes and long-term care costs of stroke survivors.

2.7 Antiplatelet agents have been shown to be effective in the prevention of recurrent OVEs. Aspirin is an antiplatelet agent and has been recommended by national clinical guidelines both for patients with coronary artery disease (including people who have survived an MI) and for people who have had an ischaemic stroke. For the prevention of cardiovascular events, daily doses of 75–150 mg aspirin have been recommended in national and international guidelines. For the prevention of ischaemic stroke, daily doses of 75-325 mg or 50–325 mg aspirin have been recommended (Royal College of Physicians guideline and European Stroke Initiative, respectively). The adverse effects of aspirin are related to bleeding complications and include haemorrhagic stroke and gastrointestinal haemorrhage. However, the benefits of antiplatelet treatment in people at moderate to high risk are considered to outweigh the risk of major bleeding.

3 The technologies

3.1 *Clopidogrel*

3.1.1 Clopidogrel (Plavix, Sanofi-Synthelabo, Bristol-Myers Squibb [SSBMS]) is a thienopyridine antiplatelet drug and selectively inhibits the binding of adenosine phosphate to its platelet receptor. Clopidogrel is licensed for the prevention of atherothrombotic events in people who have had an MI (from a

few days until less than 35 days), have had an ischaemic stroke (from 7 days until less than 6 months) or have established PAD.

3.1.2 Contraindications include severe liver impairment, active pathological bleeding and breastfeeding. Because of its antiplatelet activities, clopidogrel increases the risk of bleeding. For full details of side effects and contraindications, see the Summary of Product Characteristics.

3.1.3 The cost of treatment for 1 year at a dose of 75 mg daily is £460.29 (excluding VAT; *British National Formulary*, 46th edition). Costs may vary in different settings because of negotiated procurement discounts.

3.2 *Dipyridamole*

3.2.1 Dipyridamole (Boehringer Ingelheim) has both antiplatelet and vasodilating properties and is thought to inhibit the uptake of adenosine (a potent inhibitor of platelet activation and aggregation) into blood and vascular cells. Dipyridamole may also inhibit the breakdown of cyclic guanosine monophosphate. This guidance refers to the modified-release (MR) formulation of dipyridamole only, which is licensed for the secondary prevention of ischaemic stroke and TIAs, either alone (Persantin Retard, 200 mg dipyridamole twice daily) or in combination with aspirin (Asasantin Retard, 200 mg dipyridamole plus 25 mg aspirin twice daily).

3.2.2 Because of dipyridamole's activity as a vasodilator, it should be used with caution in people with severe coronary artery disease, including unstable angina and/or recent MI, left ventricular outflow obstruction or haemodynamic instability (for example, decompensated heart failure). Contraindications and special warnings for the combination of MR dipyridamole with aspirin are associated with the product's aspirin component and include active gastric or duodenal ulcers or bleeding disorders. For full details of side effects and contraindications, see the Summary of Product Characteristics.

3.2.3 The cost of treatment with MR dipyridamole (alone or in combination with aspirin) for 1 year is £118.63 (excluding VAT; *British National Formulary*, 46th

edition). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (see Appendix B).

4.1 *Clinical effectiveness*

4.1.1 Clopidogrel

4.1.1.1 One RCT was identified that investigated the use of clopidogrel compared with aspirin in the prevention of OVEs. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study included 19,185 patients with a diagnosis of ischaemic stroke, MI or symptomatic atherosclerotic PAD randomised to receive clopidogrel (75 mg/day) or aspirin (325 mg/day). The duration of follow-up ranged from 1 to 3 years (mean 1.9 years). The mean ages were similar in all groups, and all groups appeared to be well matched in terms of other prognostic indicators. The primary outcome was a composite endpoint of the first occurrence of ischaemic stroke, MI or vascular death.

4.1.1.2 The main analysis across the whole CAPRIE cohort found a lower incidence of the primary outcome with clopidogrel (9.8% over the whole study period) compared with aspirin (10.7%) (relative risk [RR] 0.92, 95% confidence interval [CI]: 0.85 to 1.00). There was statistically significant heterogeneity across the three qualifying subgroups (ischaemic stroke, MI and symptomatic PAD). When the results for each of the subgroups were analysed, there was a statistically significant effect only in patients with PAD (6.7% with clopidogrel, 8.6% with aspirin; RR 0.78, 95% CI: 0.66 to 0.92). The incidence of the primary outcome in people with ischaemic stroke was 13.4% with clopidogrel and 14.4% with aspirin (RR 0.93, 95% CI: 0.82 to 1.05) and for people with MI 9.3% with clopidogrel and 9% with

aspirin (RR 1.03, 95% CI: 0.88 to 1.21). However, the data for these subgroups should be interpreted with caution because the trial was not powered to detect differences in treatment effects between the subgroups.

4.1.1.3 A further analysis determined the effect of treatment on the individual outcomes of the trial (preventing ischaemic stroke, MI or vascular death) across the whole CAPRIE cohort. Clopidogrel reduced the number of patients progressing to an MI (RR 0.81, 95% CI: 0.69 to 0.95). No statistically significant difference was found between clopidogrel and aspirin for ischaemic stroke (RR 0.95, 95% CI: 0.83 to 1.08) and vascular death (RR 0.92, 95% CI: 0.80 to 1.07) (incidence rates not available).

4.1.1.4 For the secondary outcomes (ischaemic stroke, MI, amputation or vascular death; vascular death; any stroke, MI or death from any cause; death from any cause), no statistically significant differences were found between clopidogrel and aspirin, despite point estimates favouring clopidogrel.

4.1.1.5 Overall, clopidogrel did not affect the number of bleeding disorders compared with aspirin. However, gastrointestinal haemorrhage rates were statistically significantly lower with clopidogrel than with aspirin. The incidences of rash and diarrhoea were higher in the clopidogrel group compared with the aspirin group, and the incidence of indigestion/nausea/vomiting was higher in the aspirin group.

4.1.1.6 The authors of the Antithrombotic Trialists' Collaboration (ATTC) meta-analysis and the authors of a Cochrane Review concluded that clopidogrel may be slightly more effective than aspirin in the prevention of OVEs. However, because of the confidence limits, it was commented that the true size of any difference between clopidogrel and aspirin could not be reliably estimated.

4.1.2 MR dipyridamole

4.1.2.1 The European Stroke Prevention Study 2 (ESPS-2) was the only randomised controlled trial (RCT) identified that evaluated MR dipyridamole, aspirin, and MR dipyridamole combined with aspirin (aspirin/MR dipyridamole) compared with placebo. Patients included in the trial had experienced a TIA or an ischaemic stroke within the preceding 3 months. The study included 6602 patients randomised to aspirin (50 mg/day), aspirin/MR dipyridamole (50 mg/day plus 400 mg/day, respectively), MR dipyridamole (400 mg/day) or placebo. Patients were followed on treatment for 2 years. The mean ages of these four groups were similar and patients appeared to be well matched in terms of prognostic indicators. The primary outcomes were stroke, stroke and/or death, and death.

4.1.2.2 In the ESPS-2 study, aspirin (50 mg/day) alone was more effective than placebo, with an 18.1% reduction in the outcome of stroke compared with placebo. Compared with aspirin, MR dipyridamole treatment alone did not cause a reduction in the outcomes of stroke, death or any of the secondary outcomes. For the secondary outcome of MI, there was a small but statistically insignificant increase with MR dipyridamole compared with aspirin.

4.1.2.3 The ESPS-2 study found a lower incidence of stroke with aspirin/MR dipyridamole (9.5%) compared with aspirin alone (12.5%) (RR 0.76, 95% CI: 0.63 to 0.93). The effect on the outcome 'stroke and/or death' was considered uncertain, with incidence rates of 17.3% with aspirin/MR dipyridamole and 20% with aspirin alone (RR 0.87, 95% CI: 0.75 to 1.00). There was no difference between the two treatments for the outcome of death (RR 1.02, 95% CI: 0.84 to 1.23). Among the secondary outcomes, the following were statistically significantly reduced for the aspirin/MR dipyridamole combination compared with aspirin alone: stroke

or TIA (18.1% with aspirin/MR dipyridamole, 22.6% with aspirin alone; RR 0.80, 95% CI: 0.70 to 0.92), other vascular event (1.3% with aspirin/MR dipyridamole, 2.3% with aspirin alone; RR 0.55, 95% CI: 0.33 to 0.94), fatal and non-fatal ischaemic events (12.5% with aspirin/MR dipyridamole, 16.1% with aspirin alone; RR 0.77, 95% CI: 0.65 to 0.92), and vascular events (14.9% with aspirin/MR dipyridamole, 19% with aspirin alone; RR 0.78, 95% CI: 0.67 to 0.91). Point estimates suggested a reduction in the secondary outcomes TIA, MI and vascular death, but these effects were not statistically significant.

4.1.2.4 The frequency of bleeding complications was significantly lower with MR dipyridamole (4.7%) than with aspirin (8.2%), and similar in the aspirin/MR dipyridamole (8.7%) and the aspirin (8.2%) groups. The frequencies of headache, diarrhoea, nausea and vomiting were significantly higher in both the aspirin/MR dipyridamole and MR dipyridamole groups compared with aspirin.

4.1.2.5 The ATTC reviewed 25 studies of aspirin in combination with dipyridamole. The authors of the ATTC meta-analysis and of a Cochrane Review concluded that the addition of dipyridamole to aspirin failed to clearly demonstrate additional reductions in serious vascular events. This assessment by the ATTC and the Cochrane Group relates mainly to studies conducted with the standard-release preparation of dipyridamole and not MR dipyridamole, which has a significantly different absorption profile compared with the standard-release preparation.

4.2 *Cost effectiveness*

4.2.1 None of the previously published studies of cost effectiveness for MR dipyridamole or clopidogrel could be generalised to the UK setting and the NHS. The manufacturers (Boehringer Ingelheim and SSBMS, respectively) submitted new or updated models. The Assessment Group developed a new model based on the SSBMS model.

4.2.2 The model submitted by Boehringer Ingelheim compared MR dipyridamole (with or without aspirin) and aspirin against placebo for the prevention of stroke. The model separated the stroke-survivor cohort into disabled (30.9%) and non-disabled (69.1%), and treatment was for each individual's lifetime, including withdrawal rates seen in the relevant trial. The model considered only the first recurrent stroke. In this model, MR dipyridamole (alone) was less effective and more costly than aspirin. For the combination of aspirin and MR dipyridamole, the cost per quality-adjusted life year (QALY) gained compared with aspirin alone was £4207 for people with stroke and £9448 for people with TIA (5-year analysis). When the time horizon was extended to 30 years, the cost per additional QALY was £3655 for people with stroke and £2038 for people with TIA.

4.2.3 The model submitted by SSBMS compared clopidogrel with aspirin for the prevention of OVEs. Treatment was for 2 years, followed by lifetime treatment with aspirin. The time horizon of the model was 40 years. Adverse events associated with treatment were not modelled, and all stroke-qualifying patients began the model as non-disabled. This model resulted in a cost per QALY gained for clopidogrel of £14,525 compared with aspirin. In an additional analysis for each qualifying subgroup, the costs per additional QALY were £12,527 for the MI group, £15,896 for the stroke group and £17,218 for the PAD group.

4.2.4 The Assessment Group compared clopidogrel and MR dipyridamole (with or without aspirin) with aspirin in the prevention of OVEs. The analysis included both the cost effectiveness of lifetime treatment as well as 2-year treatment followed by lifetime treatment with aspirin (as in the SSBMS model). The cost effectiveness in each relevant qualifying subgroup (stroke, TIA, MI and PAD) was estimated separately, but the RRs for the outcomes were based on the overall results of the trials. The model used RRs for the progression to the individual outcomes (non-fatal stroke, non-fatal MI, vascular or non-vascular death) derived from ESPS-2 and CAPRIE. The time horizon of the analysis was 40 years. Because of the different licensed indications for clopidogrel and

MR dipyridamole (with or without aspirin), different combinations of treatments were compared in each subgroup by qualifying event.

- Stroke: aspirin, clopidogrel, aspirin/MR dipyridamole and MR dipyridamole (alone).
- TIA: aspirin, aspirin/MR dipyridamole and MR dipyridamole (alone).
- MI or PAD: aspirin and clopidogrel.

4.2.5 In the Assessment Group analysis for people with stroke or TIA, lifetime treatment with aspirin/MR dipyridamole resulted in a cost per additional QALY of £26,432 and £12,458 for stroke or TIA, respectively, relative to treatment with aspirin. When treatment duration was reduced to 2 years (followed by treatment with aspirin alone for the remainder of the individual's lifetime), these figures fell to £5500 and £2241. This analysis excluded the relative effects of antiplatelet therapies on non-vascular death. When the RR for non-vascular death was included in the modelling, aspirin/MR dipyridamole was dominated by aspirin alone in the lifetime treatment scenario, and for the 2-year treatment duration, the cost per additional QALY was £7968 for people with stroke and £4266 for people with TIA. Treatment with clopidogrel (stroke subgroup only) resulted in high cost per QALY figures compared with aspirin/MR dipyridamole (which was the next more cost-effective comparator) or was less effective and more costly than the other treatments (lifetime and 2-year treatment duration analysis). MR dipyridamole (alone) was less effective and more costly than aspirin (lifetime and 2-year treatment analysis).

4.2.6 In the original analysis undertaken by the Assessment Group, the transition from stroke to non-fatal MI was excluded to avoid an inconsistency in the sponsor's model, in which the utility applied to people experiencing an MI (after a stroke) was higher in comparison with the utility in those who did not have an MI. After consultee comments on this issue, the occurrence of non-fatal MI in this group of patients was reconsidered and, in order to explore the effect of including this transition, a recalculation was performed using a

relative utility decrement and a fixed additional cost in the first year after an MI. This re-analysis resulted in less favourable estimates of cost effectiveness for MR dipyridamole in combination with aspirin, and more favourable estimates for clopidogrel than the initial model. However, in all four of the scenarios presented (lifetime treatment or 2 years' treatment, RR of non-vascular death included or excluded), either the treatment with clopidogrel was dominated or the incremental cost-effectiveness ratio (ICER) remained greater than £40,000 per QALY in people who have had an ischaemic stroke.

4.2.7 For people with MI or with PAD, the cost per additional QALY for treatment with clopidogrel was between £31,000 and £36,000 compared with aspirin, depending on assumptions made about the annual cost of PAD (lifetime analysis, excluding RR for non-vascular death). For the 2-year treatment duration, the cost per additional QALY was £17,081 for people who have had an MI and £20,733 for people who have PAD (excluding RR for non-vascular death). When effects on non-vascular death were included in the lifetime treatment analysis, the cost per QALY for clopidogrel was £94,446 (people with MI) or clopidogrel was dominated (people with PAD). For 2-year treatment duration (including the RR for non-vascular death), the cost per additional QALY was £21,448 for the MI group and £31,300 for the PAD group.

4.2.8 In order to assess the cost effectiveness of MR dipyridamole (alone) and clopidogrel in aspirin-intolerant people who have had an ischaemic stroke the Assessment Group carried out an additional analysis. The baseline risk of events in this model was estimated using data from a prospective, population-based register of stroke cases. It was assumed that the probabilities derived from this register represented the risk of further events while taking aspirin on the basis that it is considered standard therapy after a stroke and it would be reasonable to expect that most of the people included in the register would be taking aspirin. In order to derive a 'no antiplatelet therapy' baseline, the risk of each event was adjusted by the corresponding relative risk for placebo versus aspirin from the ESPS-2 study. The cost effectiveness of MR dipyridamole

(alone) and clopidogrel was then assessed in relation to this calculated baseline. For the base case analysis, the relative effects of antiplatelet therapies on non-vascular death were excluded. This analysis concluded that, relative to no treatment, lifetime treatment with clopidogrel was associated with a lower cost per additional QALY than MR dipyridamole. The ICERs for lifetime treatment with clopidogrel and MR dipyridamole relative to no treatment were £26,773 and £66,471 per QALY, respectively. However, when the relative effects of antiplatelet therapies on non-vascular death were included, MR dipyridamole was associated with a lower cost per additional QALY relative to no treatment than clopidogrel. The ICER for treatment with MR dipyridamole relative to no treatment was £4,404 per QALY, and the ICER for treatment with clopidogrel relative to no treatment was £13,748 per QALY.

4.3 *Consideration of the evidence*

4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of clopidogrel and MR dipyridamole in the prevention of OVEs, having considered evidence on the nature of the condition and the value placed by users on the benefits of clopidogrel and MR dipyridamole from people who have had OVEs, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the effective use of NHS resources.

4.3.2 The Committee recognised that atherothrombosis is the critical initiating process for OVEs and that people with an OVE in one vascular bed are likely to be at increased risk of OVEs in other vascular beds. However, the Committee agreed that the magnitude of the risk of recurrent OVEs in any vascular bed is dependent on the site of the first event or the mode of presentation of the disease. For this reason, and also because clopidogrel and MR dipyridamole have different licensed indications, the Committee took account of the evidence relating to people with ischaemic cerebrovascular events, MI or PAD separately.

4.3.3 The Committee heard from the experts that treatment with low-dose aspirin has now been widely accepted as effective in the prevention of recurrent OVEs. The Committee were additionally persuaded that although a lifetime effect of the use of antiplatelet treatment is not proven, lifetime treatment with aspirin is now accepted in clinical practice. The important effect of aspirin is in addition to the effects of other medications currently used to reduce the risk of OVEs, including antihypertensives and HMG-CoA reductase inhibitors (statins).

4.3.4 The Committee considered the evidence from the RCTs for clopidogrel (CAPRIE) and MR dipyridamole (ESPS-2) and heard the view of the clinical experts on the outcomes of these trials. Overall, the Committee was persuaded that while both of these antiplatelet agents were effective in reducing the risk of further OVEs, neither drug had a proven effect on mortality over and above that seen with aspirin as sole antiplatelet agent.

4.3.5 The Committee considered the evidence presented in the Assessment Report, which was principally derived from the CAPRIE study, and concluded that clopidogrel was likely to be at least as effective as aspirin for preventing OVEs. The CAPRIE study showed primary outcome rates (ischaemic stroke, MI or vascular death) of 9.8% for clopidogrel and 10.7% for aspirin. An analysis of the CAPRIE data indicated heterogeneity between the prespecified qualifying subgroups, with a more favourable effect in people with PAD and a less favourable effect in people with stroke or MI. However, the Committee was persuaded that undue reliance on subgroup analysis was inadvisable principally because of insufficient study power. Consequently, it was considered inappropriate to rely on post-hoc analyses in other patient subgroups.

4.3.6 The Committee considered the ESPS-2 study and the effectiveness of MR dipyridamole in combination with aspirin, MR dipyridamole (alone), and aspirin compared with placebo. The Committee noted that the dosing regimen used for aspirin in ESPS-2 (25 mg twice daily) was not current clinical

practice. However, the Committee was satisfied that this aspirin regimen resulted in a significant reduction in OVEs compared with placebo in the ESPS-2 study which was similar to that seen in other studies of prevention using aspirin. The experts expressed concern that ESPS-2 was the only available study that showed a beneficial effect of dipyridamole in combination with aspirin compared with aspirin alone in this patient group (TIA or an ischaemic stroke within the preceding 3 months). However, it was acknowledged that ESPS-2 was the only study that used the MR formulation of the drug rather than the conventional standard-release formulation. Therefore, the Committee concluded that MR dipyridamole in combination with aspirin was more effective than aspirin alone in the prevention of stroke. However, MR dipyridamole alone was not more effective than aspirin alone.

4.3.7 The Committee concluded that the analysis carried out by the Assessment Group gave the most reliable estimates of cost effectiveness because it used current UK estimates for costs and treatment populations, included the cost of adverse effects and comprehensively modelled mortality data. The Committee discussed the appropriateness of including both vascular and non-vascular mortality rates in the cost-effectiveness modelling. The Committee noted that in analyses that considered lifetime treatment, differences in the relative effects of different antiplatelet drugs on non-vascular mortality would be compounded as the treatment effects were extrapolated. Consequently, the impact that the RR for non-vascular mortality has on the analysis increases as the duration of treatment is extended to lifetime in the model. Given that any differences in the effects of clopidogrel and MR dipyridamole on non-vascular mortality seen in clinical trials are small, uncertain and based on indirect comparisons, the Committee concluded that the exclusion of the RR for non-vascular death is advisable for the modelling of lifetime treatment.

4.3.8 The Committee considered the evidence for the clinical and cost effectiveness of clopidogrel. It accepted the Assessment Group's approach to using the RR for the individual outcomes based on the results of the whole study cohort. The Committee was not persuaded of the validity of exploring the

effectiveness of clopidogrel in any additional subgroups that had not been prospectively defined. The Committee took into account the magnitude of the absolute effect of clopidogrel in preventing OVEs when compared with aspirin, the uncertainty around this effect, and the opinion of the clinical experts, and concluded that a recommendation for clopidogrel to replace lifetime treatment with aspirin for the prevention of OVEs was not justified. Similarly, the Committee concluded that for shorter periods of treatment, the balance of evidence on clinical effectiveness and cost effectiveness also did not justify a recommendation for clopidogrel to replace aspirin for the prevention of OVEs.

4.3.9 On the basis of the 2-year trial evidence available for the combination of MR dipyridamole with aspirin, the time course for the risk of further events and the Assessment Group's analysis of its cost effectiveness, the Committee concluded that 2 years of treatment with the combination of MR dipyridamole with aspirin should be recommended for the prevention of recurrent stroke in people who have had a stroke or TIA. Thereafter, or if MR dipyridamole is not tolerated, management should revert to standard care, including lifetime low-dose aspirin monotherapy.

4.3.10 The Committee considered the treatment options available for people who are unable to tolerate aspirin. It considered that for this group of people, the appropriate comparator is placebo or no antiplatelet treatment. Although no comparison of clopidogrel with placebo is available, as the CAPRIE study was initiated when aspirin treatment was already used in standard care, the Committee concluded that clopidogrel was likely to be at least as effective as aspirin. Therefore, for people with recent MI or symptomatic PAD who are intolerant of aspirin, clopidogrel was an appropriate alternative. However, people presenting with stroke or TIA who are intolerant of aspirin have the additional option of treatment with MR dipyridamole alone. Therefore, the Committee considered it important to examine the relative cost effectiveness of MR dipyridamole and clopidogrel in this group. The Committee were persuaded that for this group, treatment would be needed for the remainder of

the person's life. Having decided that the most appropriate analysis for this situation was the one that excluded the RR of non-vascular death and based on the additional analysis conducted by the Assessment Group (see Section 4.2.8), the Committee concluded that, compared with MR dipyridamole, clopidogrel was the more cost-effective option for patients with stroke who are intolerant of aspirin.

4.3.11 The Committee considered the issue of patients in whom aspirin is contraindicated because of a history of peptic ulcer. However they were unable to make a recommendation in this group of patients as no evidence on this situation was presented in the CAPRIE study and the relative safety of alternative approaches to antiplatelet therapy in this group of patients had not been appraised.

4.3.12 The experts advised the Committee that the risk of recurrent OVEs after TIA is similar to that seen after ischaemic stroke, and that clopidogrel was likely to be at least as effective as aspirin in people who have had a TIA as it is in people who have had an ischaemic stroke. The Committee accepted that this was also biologically plausible from consideration of the mode of action of the antiplatelet agents. The Committee was aware that TIA is an indication not covered by the current UK marketing authorisation for clopidogrel, and therefore was not in a position to make a recommendation on it.

4.3.13 Following discussion with the clinical experts and review of the evidence, the members of the Committee concluded that they were unable to recommend the use of MR dipyridamole alone in aspirin-intolerant people with TIA, because they were not persuaded that there was sufficient evidence to suggest that this drug would provide adequate protection against cardiac events.

4.3.14 The Committee heard from the experts that the number of people who are genuinely intolerant to aspirin is believed to be small, and low-dose aspirin (75 mg/day) is tolerated by most people. Genuine aspirin intolerance, defined by hypersensitivity reactions or severe dyspepsia, should be differentiated

from mild dyspeptic symptoms, which are common. People who have previously not tolerated high doses of aspirin may be able to tolerate low-dose aspirin.

4.3.15 The Committee discussed the options for continuing antiplatelet therapy in people who suffer a further OVE while on recommended treatment. It was unable to find strong evidence on the best course of action, and in particular that changing antiplatelet therapy when a recurrent event occurred was likely to alter longer-term outcomes. It was persuaded by the evidence presented that the current guidance recommendations were appropriate and that further research was necessary to determine the precise course of action for recurrent OVEs.

5 Recommendations for further research

5.1 Ongoing clinical trials related to this guidance are:

- CHARISMA (clopidogrel versus placebo in vascular disease and high risk factors) – 3 years; 15,200 patients; planned completion 2006.
- MATCH (clopidogrel plus aspirin versus clopidogrel in high-risk patients with stroke and TIA) – 18 months; 7601 patients; completed May 2004.
- WATCH (clopidogrel versus aspirin versus open label warfarin in chronic heart failure patients) – 2 years; 1588 patients; planned completion 2004.
- CASPAR (clopidogrel and aspirin in PAD) – 1 year; 1460 patients; planned completion 2006.
- PROFESS (MR dipyridamole/aspirin versus clopidogrel plus aspirin in recurrent stroke) – 15,500 patients; planned completion 2007/8. Note: following the results of the MATCH study, the investigators of PROFESS have discontinued aspirin from the clopidogrel plus aspirin arm.

- ESPRIT (aspirin versus MR dipyridamole/aspirin versus open label warfarin in ischaemic stroke) – 4500 patients; planned completion 2008.

5.2 Further research is recommended on the effectiveness of clopidogrel compared with MR dipyridamole in aspirin-intolerant people who have had an ischaemic stroke.

5.3 Further research is also recommended on the effectiveness of clopidogrel in people who are at high risk of recurrent OVEs, have diabetes or have had coronary surgery, and in people who have recurrent events while taking recommended antiplatelet therapy.

6 Implications for the NHS

6.1 According to Prescription Cost Analysis from 2003 for England and Wales, £2.6 million was spent on MR dipyridamole in combination with aspirin, £7.7 million on MR dipyridamole and £86.8 million on clopidogrel. Clopidogrel is licensed for more than one indication. The proportion of this spending that is attributable to the use in the prevention of OVEs is not known.

6.2 The budget impact of the current guidance depends on both the use of the antiplatelet drugs in the incident population and the rate of aspirin intolerance, which has been estimated to lie between 6% and 20%. Thus, if it is assumed that 6% of people are aspirin-intolerant, the cost of treating all new aspirin-tolerant stroke survivors and people with TIA with MR dipyridamole in combination with aspirin would be approximately £11.9 million for the first year. This is based on an estimated 77,000 new cases of non-fatal stroke and 30,000 new cases of TIA in England and Wales. The cost of prescribing clopidogrel for new cases of OVEs or symptomatic PAD in aspirin-intolerant people would be £7.6 million in the first year. This is based on 76,479 hospital admissions for MI with an estimated initial survival rate of 85%, 102,000 new cases of PAD and 77,000 non-fatal strokes. If the rate of aspirin intolerance is as high as 20% then the cost of MR dipyridamole falls to £10.1 million and the

cost of clopidogrel rises to £25.2 million. As treatment continues for more than 1 year, these estimated costs would increase on an annual basis until a steady state is reached; for MR dipyridamole in combination with aspirin this is expected after approximately 2 years; for clopidogrel this is expected when new cases are balanced by deaths.

7 Implementation and audit

7.1 Clinicians who care for people who have had an OVE, that is, an ischaemic stroke, a TIA or an MI, or people who have symptomatic PAD, should review their current practice and policies to take account of the guidance set out in Section 1.

7.2 Local guidelines or care pathways for people with an OVE or symptomatic PAD should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.

7.3.1 As part of the prevention of OVEs:

7.3.1.1 For a person who has had an ischaemic stroke or a TIA, the combination of MR dipyridamole and aspirin is prescribed for 2 years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy reverts to standard care.

7.3.1.2 For a person who is intolerant of low-dose aspirin and who either has experienced an OVE or has symptomatic PAD, clopidogrel alone is prescribed within its licensed indications.

8 Related guidance

8.1 The Institute has issued a clinical guideline on prophylaxis for patients who have experienced an MI:

> National Institute for Clinical Excellence (2001) Prophylaxis for patients who have experienced a myocardial infarction. *NICE Inherited Clinical Guideline A*. London: National Institute for Clinical Excellence. All documents and further details are available from www.nice.org.uk/page.aspx?o=20266

8.2 The Institute has issued guidance on clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome:

> National Institute for Clinical Excellence (2004) Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. London: National Institute for Clinical Excellence. All documents and further details are available from www.nice.org.uk/TA080

8.3 There is an ongoing appraisal of statins for the prevention of coronary events in patients at increased risk of developing CHD or those with established CHD; expected date of issue November 2005.

8.4 The Institute has issued a clinical guideline on the management of hypertension in adults in primary care:

> National Institute for Clinical Excellence (2004) Hypertension – management of hypertension in adults in primary care. London: National Institute for Clinical Excellence. All documents and further details are available from www.nice.org.uk/CG018

8.5 The Institute has commissioned a clinical guideline on the identification and management of hyperlipidaemia as part of cardiovascular risk assessment in primary care; expected date of issue September 2007.

9 Proposed date for review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

9.2 It is proposed that the guidance on this technology is reviewed in April 2008.

Andrew Dillon
Chief Executive
May 2005

A version of this guidance written for people who have had an occlusive vascular event, or who have symptomatic peripheral arterial disease, their families and carers, and the public is available from the NHS Response Line (telephone 0870 1555 455 and quote reference number N0754). It is also available from the NICE website (www.nice.org.uk/TA090publicinfo).

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice, Staffordshire

Dr Jane Adam
Radiologist, St George's Hospital, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Professor Stirling Bryan
Professor of Health Economics, Health Economics Facility, Health Services Management Centre, University of Birmingham

Professor John Cairns

Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor David Chadwick

Professor of Neurology, Department of Neurological Science, Walton Centre for Neurology & Neurosurgery, Liverpool

Dr Lorna Duggan

Consultant Forensic Psychiatrist in Developmental Disabilities, St Andrew's Hospital, Northampton

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Dr Trevor Gibbs

Industry Representative, Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford

Mr Sanjay Gupta

Stroke Services Manager, Basildon & Thurrock University Hospitals NHS Trust

Professor Philip Home (Vice-Chair)

Professor of Diabetes Medicine, Department of Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, Molecular & Clinical Pharmacology, University of Sheffield

Dr Terry John

General Practitioner, The Firs, London

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary, Newcastle-Upon-Tyne

Dr George Levvy

Lay Representative, Chief Executive, Motor Neurone Disease Association, Northampton

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Professor John Lumley

Honorary Consultant, The Ernest Cooke Clinic Microvascular Unit, Great Ormond Street, Bart's and the Royal London NHS Trust, Barbican, London

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Virginia Pearson

Chief Executive, South Petherton Hospital, South Somerset PCT

Dr Christa Roberts

Industry Representative, UK Manager Vascular Intervention, Guidant Ltd.

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, Westlake Surgery, Somerset

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Rod Taylor

Senior Lecturer, Department of Public Health & Epidemiology, University of Birmingham

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Norman Waugh

Department of Public Health, University of Aberdeen

Mrs Miranda Wheatley-Price

Lay Representative, Director of Service Development, Colon Cancer Concern, London

B. NICE Project Team

Each appraisal of a technology is assigned to one or more Health Technology Analysts and a Technology Appraisal Project Manager within the Institute.

Dr Elisabeth George and Janet Robertson

Technical Leads, NICE project team

Nina Pinwill

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A The Assessment Report for this appraisal was prepared by Centre for Reviews and Dissemination and Centre for Health Economics, University of York.

I Jones L, Griffin S, Palmer S, et al. *A rapid and systematic review of the clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events*, November 2003.

II Palmer S, *The cost-effectiveness of clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (addendum)*, April 2004.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturers/sponsors:

- Boehringer Ingelheim
- Bristol-Myers Squibb
- Sanofi Synthelabo

II Professional/specialist and patient/carer groups:

- Action Heart
- Association of British Neurologists
- British Association for Nursing in Cardiac Care
- British Association of Stroke Physicians
- British Cardiac Society

- British Geriatrics Society
- British Heart Foundation
- Department of Health
- Different Strokes
- Heart UK
- Long Term Medical Conditions Alliance
- Primary Care Cardiovascular Society
- Royal College of General Practitioners
- Royal College of Physicians
- Royal College of Physicians' Cardiology Committee
- Royal College of Physicians: Intercollegiate Stroke Working Party Group
- Southampton City PCT
- South Somerset PCT
- Stroke Association
- Vascular Surgical Society of GB and Ireland
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- British Stroke Research Group
- Cochrane Heart Group
- Cochrane Stroke Group
- Cochrane Peripheral Vascular Diseases Group
- NHS Purchasing and Supplies Agency

- NHS Quality Improvement Scotland

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD:

- Dr Alan Begg, General Practitioner, Primary Care Cardiovascular Society
- Dr Marcus Flather, Consultant Cardiologist and Director of the Clinical Trial Evaluation Unit, Royal Brompton and Harefield NHS Trust
- Mr Keith Wood, Patient Advocate
- Professor Peter Sandercock, Professor of Medical Neurology, British Association of Stroke Physicians, Department of Clinical Neurosciences, Western General Hospital, Edinburgh

Appendix C. Detail on criteria for audit of the use of clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events

Possible objective for an audit

An audit could be carried out to ensure that clopidogrel and MR dipyridamole are used appropriately in the prevention of occlusive vascular events.

Possible patients to be included in the audit

An audit could be carried out on people who have had an OVE – that is, an ischaemic stroke, a TIA or an MI – or who have symptomatic PAD, and who are seen in a reasonable period for audit, for example, 3 or 6 months. Because the audit measures refer to care over a 2-year period, the data collection strategy may need to be concurrent or prospective. People who have had or who are at risk of having a stroke associated with atrial fibrillation or who require treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures should be excluded from this audit.

Alternatively, an audit could be carried out on prescriptions for clopidogrel or the combination of MR dipyridamole and aspirin for the prevention of OVEs to ensure that the drugs are prescribed only in the circumstances specified.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of care of people who have had an OVE to ensure that clopidogrel and the combination of MR dipyridamole and aspirin are used appropriately are as follows.

Criterion	Standard	Exception	Definition of terms
1. For a person who has had an ischaemic stroke or a TIA: a. the combination of MR dipyridamole and aspirin is prescribed for 2 years following the most recent event **and** b. **thereafter** standard care is provided	100% of people who have had an ischaemic stroke or a TIA	A. The individual does not tolerate or has a contraindication to MR dipyridamole, in which case standard care is provided B. The individual has had an ischaemic stroke and is intolerant of aspirin in which case clopidogrel is prescribed unless clopidogrel is contraindicated (see 2)	'Standard care' includes long-term treatment with low-dose aspirin Clinicians will need to agree locally on the accepted dose for low-dose aspirin Clinicians will need to agree locally on how the period of 2 years is defined for audit purposes For a list of contraindications to and side effects of MR dipyridamole, see Summary of Product Characteristics 'Intolerant of aspirin' is defined as either of the following: proven hypersensitivity to aspirin-containing medicines, or a history of severe dyspepsia induced by low-dose aspirin For a list of contraindications to clopidogrel, see Summary of Product Characteristics
2. For a person who has had an OVE or who has symptomatic PAD, **and** who is intolerant of low-dose aspirin, clopidogrel is prescribed within its licensed indications	100% of people who have had an OVE or who have symptomatic PAD, **and** are intolerant of low-dose aspirin	A. The individual has a contraindication to or experiences a serious side effect of clopidogrel	See above for an explanation of intolerance to aspirin and contraindications to clopidogrel Clinicians will need to agree locally on how patients with symptomatic PAD are documented for audit purposes

The measures that could be used in an audit of prescriptions of clopidogrel and MR dipyridamole for the prevention of OVEs are as follows.

Criterion	Standard	Exception	Definition of terms
1. The combination of MR dipyridamole and aspirin is prescribed over 2 years following the most recent ischaemic stroke or TIA	100% of prescriptions for MR dipyridamole	A. The individual does not tolerate or has a contraindication to or experiences a serious side effect of MR dipyridamole	See above for definitions of key terms
2. Clopidogrel is prescribed for the prevention of OVEs within its licensed indications	0% of prescriptions for clopidogrel	A. An individual is intolerant of low-dose aspirin and has had an OVE or has symptomatic PAD	See above for definitions of key terms

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the } \textbf{criterion} \textit{ plus } \text{number of patients who meet any } \textbf{exception} \text{ listed}}{\text{Number of patients to whom the } \textbf{measure} \text{ applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.