

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

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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This guidance replaces TA90.

1 Guidance

This guidance replaces 'NICE technology appraisal guidance 90' issued in May 2005. For details, see 'About this guidance'.

This guidance applies to people who have had an occlusive vascular event, or who have established peripheral arterial disease. For people who have had a myocardial infarction, this guidance follows on from the recommendations for clopidogrel in combination with low-dose aspirin in [NICE clinical guideline 48](#) and [NICE clinical guideline 94](#). This guidance does not apply to people who have had, or are at risk of, a stroke associated with atrial fibrillation, or who need treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures.

1.1 Clopidogrel is recommended as an option to prevent occlusive vascular events:

- for people who have had an ischaemic stroke or who have peripheral arterial disease or multivascular disease **or**
- for people who have had a myocardial infarction only if aspirin is contraindicated or not tolerated.

1.2 Modified-release dipyridamole in combination with aspirin is recommended as an option to prevent occlusive vascular events:

- for people who have had a transient ischaemic attack **or**
- for people who have had an ischaemic stroke only if clopidogrel is contraindicated or not tolerated.

1.3 Modified-release dipyridamole alone is recommended as an option to prevent occlusive vascular events:

- for people who have had an ischaemic stroke only if aspirin and clopidogrel are contraindicated or not tolerated **or**

- for people who have had a transient ischaemic attack only if aspirin is contraindicated or not tolerated.
- 1.4 Treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.
- 1.5 People currently receiving clopidogrel or modified-release dipyridamole either with or without aspirin outside the criteria in 1.1, 1.2 and 1.3 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

- 2.1 Occlusive vascular events include ischaemic stroke, transient ischaemic attack and myocardial infarction. They occur when blood flow is impeded because an artery is blocked or restricted because of atherosclerosis and atherothrombosis. Atherosclerotic plaques form in artery walls because of damage to the vascular endothelium. Damage is caused by a number of factors working together over a long period, such as elevated low-density lipoproteins, smoking, high blood pressure and diabetes mellitus. If an atherosclerotic plaque is suddenly disrupted, platelet activation and thrombus (clot) formation follows, leading to atherothrombosis. The thrombus can block an artery, either at the original site of the plaque formation or further down the artery. People who have had an occlusive vascular event are at increased risk of another.
- 2.2 Peripheral arterial disease is a condition in which the arteries that carry blood to the arms or legs become narrowed or clogged, slowing or stopping the flow of blood. It occurs most often because of atherosclerosis. People who have peripheral arterial disease are at high risk of having an occlusive vascular event. People with cardiovascular disease who have disease in more than one vascular site are said to have multivascular disease. These people are at increased risk of death, myocardial infarction or stroke, compared with people with disease in a single vascular bed.
- 2.3 Each year in the UK an estimated 98,000 people have a first ischaemic stroke, between 46,000 and 65,000 people have a transient ischaemic attack, and 146,000 have a myocardial infarction. Approximately 2% of the population of England and Wales have had a stroke and about 70% of all strokes are ischaemic. In the UK, in total around 510,000 people have had a transient ischaemic attack and over 1.4 million have had a myocardial infarction. About 20% of the UK population aged 55–75 years have evidence of lower extremity peripheral arterial disease, equating to a prevalence of 850,000 people, of whom 5% have symptoms. An estimated 16% of people with cardiovascular disease have multivascular disease.

- 2.4 Ischaemic stroke and myocardial infarction are associated with high mortality rates. Approximately 23% of people die within 30 days of having a stroke, and of the people who survive, 60% to 70% die within 3 years. Thirty per cent of people die from their first myocardial infarction. In terms of morbidity, an occlusive vascular event can lead to a stay in hospital, reduced health-related quality of life and long-term disability, with a resulting impact on caregivers. Stroke is the leading cause of disability in the UK and it is thought that more than 900,000 people in England are living with the effects of stroke, with about half dependent on others for support with everyday activities.
- 2.5 The aim of treatment is to prevent occlusive vascular events, and their recurrence. This can include pharmacological therapy with one or more antiplatelet agents. Antiplatelet agents include aspirin, clopidogrel and modified-release dipyridamole.
- 2.6 For people who have had a non-ST-segment-elevation myocardial infarction (NSTEMI), 'Unstable angina and NSTEMI' (NICE clinical guideline 94) recommends that aspirin should be started and continued indefinitely, unless contraindicated. In people with predicted 6-month mortality greater than 1.5%, clopidogrel should be considered in addition to aspirin, unless contraindicated, and continued for 12 months. For people who have had an ST-segment-elevation myocardial infarction (STEMI), 'MI: secondary prevention' (NICE clinical guideline 48) recommends that patients treated with a combination of aspirin and clopidogrel during the first 24 hours after the myocardial infarction should continue this treatment for at least 4 weeks. Thereafter, standard treatment including low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy.
- 2.7 The 'National service framework for coronary heart disease' states that GPs and primary care trusts should identify all people with established cardiovascular disease and offer them comprehensive advice and appropriate treatment to reduce their risk of recurrent occlusive vascular events. GP contracts include points for the number of people with coronary heart disease or who have had a stroke and who are taking antiplatelet therapy for secondary prevention.

3 The technologies

- 3.1 Clopidogrel (Plavix, Sanofi-Aventis, Bristol-Myers Squibb) is an irreversible adenosine diphosphate-receptor antagonist with antiplatelet properties. Clopidogrel is available as branded and generic preparations and has a marketing authorisation for 'the prevention of atherothrombotic events in patients suffering from 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'.
- 3.2 Contraindications to clopidogrel include severe liver impairment and active pathological bleeding such as peptic ulcer or intracranial haemorrhage. For full details of side effects and contraindications, see the summary of product characteristics.
- 3.3 The cost of branded clopidogrel for 30 days at a dose of 75 mg daily is £35.64 per person (British national formulary [BNF], edition 60). The cost of generic clopidogrel 75 mg in the NHS Drug Tariff (October 2010) is £3.40 for 30 days. Costs may vary in different settings because of negotiated procurement discounts.
- 3.4 Modified-release dipyridamole (Persantin Retard and Asasantin Retard, Boehringer Ingelheim) has both antiplatelet and vasodilating properties and is thought to inhibit the uptake of adenosine into blood and vascular cells. Dipyridamole may also inhibit the breakdown of cyclic guanosine monophosphate. Modified-release dipyridamole has a marketing authorisation for the 'secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in conjunction with aspirin'. It is available either on its own as Persantin Retard, or in a combination tablet with aspirin as Asasantin Retard.
- 3.5 Dipyridamole has activity as a vasodilator; therefore it should be used with caution in people with severe coronary artery disease, including unstable angina and/or recent myocardial infarction, left ventricular outflow obstruction or haemodynamic instability (for example, decompensated heart failure). For full details of side effects and contraindications, see the summary of product characteristics.

- 3.6 The cost of treatment for 30 days with modified-release dipyridamole alone is £7.50 and modified-release dipyridamole plus aspirin is £7.79 per person (BNF, edition 60). 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 ([appendix B](#)).

4.1 Clinical effectiveness

- 4.1.1 Four randomised controlled trials (RCTs) were identified by the Assessment Group. Two of these were included in NICE technology appraisal guidance 90 (CAPRIE and ESPS-2) and two were published later (ESPRIT and PRoFESS). The RCTs were considered by the Assessment Group to be of good quality. Three of the trials were double blind and one was an open-label study (ESPRIT).
- 4.1.2 CAPRIE (n = 19,185) compared clopidogrel with aspirin and ESPRIT (n = 2736) compared modified-release dipyridamole plus aspirin with aspirin. ESPS-2 (n = 6602) had four groups and compared modified-release dipyridamole with modified-release dipyridamole plus aspirin, and with aspirin and with placebo. PRoFESS (n = 20,332) made a head-to-head comparison of clopidogrel and modified-release dipyridamole plus aspirin. A wide range of dosages of aspirin were used in the trials.
- 4.1.3 All the trials included people who had experienced an ischaemic stroke and two trials included people who had experienced a transient ischaemic attack (ESPS-2 and ESPRIT). CAPRIE was the only trial to include people who had a prior myocardial infarction or who had peripheral arterial disease. The mean length of follow-up in the trials was between 1.91 and 3.5 years. The CAPRIE and ESPRIT trials each used composite endpoints of first occurrence of ischaemic stroke, myocardial infarction, or vascular death (CAPRIE); and first occurrence of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication (ESPRIT). In the ESPS-2 trial, three discrete primary endpoints were reported: stroke, all-cause death, and stroke and/or all-cause death. The PRoFESS trial had a single primary endpoint of recurrent stroke.

Modified-release dipyridamole compared with aspirin

- 4.1.4 The ESPS-2 trial compared modified-release dipyridamole with aspirin. The study reported no statistically significant differences in risk reduction for the primary outcomes of stroke (relative risk [RR] 1.02; 95% confidence interval [CI] 0.85 to 1.22), stroke and/or all-cause death (RR 0.97; 95% CI 0.85 to 1.11), and all-cause death (RR 1.03; 95% CI 0.85 to 1.25). Additionally, no statistically significant differences were reported for secondary outcomes.

Modified-release dipyridamole plus aspirin compared with aspirin

- 4.1.5 Two trials (ESPS-2 and ESPRIT) compared modified-release dipyridamole plus aspirin with aspirin.
- 4.1.6 In the ESPS-2 trial, people receiving modified-release dipyridamole plus aspirin had a reduced risk of stroke (RR 0.76; 95% CI 0.63 to 0.93) compared with the aspirin group. The other primary outcomes in this study did not report statistically significant results for stroke and/or all-cause death (RR 0.87; 95% CI 0.75 to 1.00) and all-cause death (RR 1.02; 95% CI 0.84 to 1.23). For the secondary outcomes, statistically significant results favouring the group receiving modified-release dipyridamole plus aspirin were reported for stroke or transient ischaemic attack (RR 0.80; 95% CI 0.70 to 0.92), other vascular events (RR 0.55; 95% CI 0.33 to 0.94), ischaemic events (RR 0.77; 95% CI 0.65 to 0.92) and vascular events (RR 0.78; 95% CI 0.67 to 0.91). For other outcomes, no statistically significant differences were reported between the treatments.
- 4.1.7 The ESPRIT trial reported a statistically significant result for the primary outcome (that is, first occurrence of non-fatal stroke, non-fatal myocardial infarction, major bleeding complication or death from all vascular causes), favouring people receiving modified-release dipyridamole plus aspirin (hazard ratio [HR] 0.80; 95%CI 0.66 to 0.98). For the secondary outcomes, statistically significant results were reported for death from all vascular causes and non-fatal stroke (HR 0.78; 95% CI 0.62 to 0.97) and all vascular events (HR 0.78; 95% CI 0.63 to 0.97). For other outcomes, no statistically significant differences were

reported between the treatments.

Modified-release dipyridamole plus aspirin compared with modified-release dipyridamole

4.1.8 In the ESPS-2 trial, modified-release dipyridamole plus aspirin compared with modified-release dipyridamole alone reduced the risk of stroke (RR 0.75; 95% CI 0.61 to 0.91). The other primary outcomes in this study did not report statistically significant results. These were stroke and/or all-cause death (RR 0.89; 95% CI 0.77 to 1.03) and all-cause death (RR 0.99; 95% CI 0.81 to 1.19). For the secondary outcomes, statistically significant results were reported for transient ischaemic attack (RR 0.80; 95% CI 0.66 to 0.97), ischaemic events (RR 0.76; 95% CI 0.64 to 0.90) and vascular events (RR 0.76; 95% CI 0.65 to 0.89). For other outcomes, no statistically significant differences were reported between the treatments.

Clopidogrel compared with aspirin

4.1.9 The CAPRIE trial compared clopidogrel with aspirin. For the primary outcome, the trial reported that clopidogrel compared with aspirin reduced the risk of a first occurrence of ischaemic stroke, myocardial infarction or vascular death in two groups. These were the all patients group (8.7% relative risk reduction; 95% CI 0.3 to 16.5) and a subgroup of people with peripheral arterial disease (23.8% relative risk reduction; 95% CI 8.9 to 36.2). No risk reduction was seen between treatments in subgroups defined by prior stroke (7.3% relative risk reduction; 95% CI -5.7 to 18.7) or by prior experience of a myocardial infarction (-3.7% relative risk reduction; 95% CI -22.1 to 12). For other outcomes, no statistically significant differences were reported between the treatments.

4.1.10 Data from the CAPRIE trial also allowed for a post-hoc subgroup analysis of data for people with multivascular disease (defined by the Assessment Group as people with experience of at least two of the following conditions: ischaemic stroke, myocardial infarction and symptomatic peripheral arterial disease). The analysis suggested that clopidogrel (compared with aspirin) reduced the risk of a first occurrence of

ischaemic stroke, myocardial infarction or vascular death (14.9% relative risk reduction; 95% CI 0.3 to 27.3, $p = 0.045$).

Modified-release dipyridamole plus aspirin compared with clopidogrel

- 4.1.11 The PROFESS trial investigated the non-inferiority of modified-release dipyridamole plus aspirin compared with clopidogrel. The trial reported no statistically significant difference in the primary outcome of recurrent stroke of any type (HR 1.01; 95% CI 0.92 to 1.11). For the secondary outcomes, there was a statistically significant reduction in the risk of events in the modified-release dipyridamole group compared with the clopidogrel group for new or worsening congestive heart failure (HR 0.78; 95% CI 0.62 to 0.96) and a statistically significant increase in the risk of events in the modified-release dipyridamole group compared with the clopidogrel group for intracranial haemorrhage (HR 1.42; 95% CI 1.11 to 1.83).

Indirect comparisons

- 4.1.12 The Assessment Group completed an indirect comparison that compared clopidogrel, modified-release dipyridamole plus aspirin, modified-release dipyridamole alone and aspirin using data from the four RCTs. Comparisons were made in a population of people with a history of ischaemic stroke or transient ischaemic attack.
- 4.1.13 The Assessment Group reported that the results from the mixed treatment comparison showed no statistical difference between the pairs of drug interventions, except for the outcomes of 'any recurrent stroke' and major bleeding. Compared with people assigned to treatment with aspirin, there was evidence of a risk reduction for 'any recurrent stroke' in people taking either clopidogrel (RR 0.75; 95% CI 0.60 to 0.93) or modified-release dipyridamole plus aspirin (RR 0.76; 95% CI 0.62 to 0.92). People treated with modified-release dipyridamole alone were at statistically significant higher risk of 'any recurrent stroke' than people treated with either clopidogrel or modified-release dipyridamole plus aspirin. The direct and indirect evidence was consistent.

4.2 Cost effectiveness

Bristol-Myers Squibb and Sanofi-Aventis model (clopidogrel)

- 4.2.1 The Bristol-Myers Squibb and Sanofi-Aventis model estimated the cost effectiveness of four treatments for the secondary prevention of occlusive vascular events. These treatments were aspirin, clopidogrel, modified-release dipyridamole plus aspirin and modified-release dipyridamole alone. In line with the licensed indications for the products, all four treatments were compared for use in people with a prior ischaemic stroke. In people with a history of myocardial infarction, peripheral arterial disease or multivascular disease, clopidogrel was compared with aspirin.
- 4.2.2 The manufacturers submitted a Markov model that comprised six health states: no event in model, history of stroke, history of myocardial infarction, TA80 state (an intermediate state reflecting NICE technology appraisal guidance 80 [now updated in CG94] which recommended clopidogrel plus aspirin for up to 12 months after an NSTEMI event), history of stroke and myocardial infarction, and death (split into vascular and non-vascular death). People entering the model could remain stable, have a myocardial infarction or stroke, or die. The modelled patient population was aged 65 years. The model was run with 3-month cycles for 35 years. The perspective adopted was that of the UK NHS in line with the NICE reference case. Costs and utility values were discounted at a rate of 3.5%.
- 4.2.3 Each patient population was modelled in the same way, with the exception that the baseline risks of vascular events differed by cohort (ischaemic stroke, myocardial infarction, peripheral arterial disease and multivascular disease). Event rates were different for years 1, 2 and 3 of the model. Event rates in year 3 were used to inform the model from year 3 onwards. Relative treatment effects for clopidogrel, modified-release dipyridamole and modified-release dipyridamole plus aspirin were based on either direct evidence or indirect evidence, using a network meta-analysis. The non-treatment costs used in the model were based on information from published burden of illness studies. Treatment costs were sourced from MIMS. All costs were inflated to 2007/08 prices, if

necessary. The model included the branded price of clopidogrel. Utility values were derived from the published literature and were between 0.61 and 0.87. A disutility associated with adverse events of between –0.3 and –0.001 was also applied in the model.

- 4.2.4 In people who have had an ischaemic stroke, modified-release dipyridamole plus aspirin was associated with an additional cost of £107 and an additional quality-adjusted life year (QALY) of 0.45, producing an incremental cost-effectiveness ratio (ICER) of £237 per QALY gained compared with aspirin. Clopidogrel was associated with an additional cost of £2324 and an additional QALY of 0.07, producing an ICER of £31,204 per QALY gained compared with aspirin. Clopidogrel was associated with greater costs and fewer QALYs than modified-release dipyridamole plus aspirin.
- 4.2.5 In people who have had a myocardial infarction, clopidogrel was associated with an additional cost of £2643 and an additional QALY of 0.13, producing an ICER of £20,662 per QALY gained compared with aspirin. For people with peripheral arterial disease, clopidogrel was associated with an additional cost of £2470 and an additional QALY of 0.13, producing an ICER of £18,854 per QALY gained compared with aspirin. For people with multivascular disease, clopidogrel was associated with an additional cost of £1805 and an additional QALY of 0.12, producing an ICER of £15,524 per QALY gained compared with aspirin.

Boehringer Ingelheim model (modified-release dipyridamole)

- 4.2.6 The Boehringer Ingelheim model estimated the cost effectiveness of modified-release dipyridamole plus aspirin compared with aspirin, clopidogrel and no treatment. The manufacturer did not estimate the cost effectiveness of modified-release dipyridamole alone, because no new trial data were available for this treatment since NICE technology appraisal guidance 90. Separate analyses were conducted for people who have had an ischaemic stroke, and for people who have had a transient ischaemic attack. Only people tolerant to aspirin were considered in the analysis.

- 4.2.7 The manufacturer submitted a Markov model based on the Assessment Group model from NICE technology appraisal guidance 90. The model had five health states: no recurrent stroke, haemorrhagic stroke, recurrent ischaemic stroke, vascular death and non-vascular death. People entered the model at the 'no recurrent stroke' state and after each cycle of 6 months could move to any of the other four states, or remain in the current state. After each cycle, transitions could occur to the other states.
- 4.2.8 The baseline age in the model was 66 years, with a time horizon of 50 years. The perspective adopted was that of the NHS and personal social services. Transition probabilities between the states in the model for the first 4 years were taken from the PROFESS, ESPRIT and ESPS-2 trials. Different transition probabilities were calculated for each 6-month period over the 4 years. Transition probabilities in subsequent years for the stroke states were based on the final 6-month period of the 4 years. Transition probabilities to death were estimated based on a factor of 1.5 applied to Office for National Statistics death rate data for the general population.
- 4.2.9 Costs of stroke events were calculated from the literature and varied according to disabled or non-disabled status. Costs of hospital stay following congestive heart failure and other haemorrhagic events were sourced from the 2006/07 National Reference Costs. Drug acquisition costs were based on branded drug costs for modified-release dipyridamole and aspirin, and clopidogrel, and on the generic price for aspirin (2009 prices). Utility data from the PROFESS trial at 1 year were used, which was provided as commercial in confidence. A short-term disutility associated with different events was also included in the model. Costs and utility values were discounted at a rate of 3.5% per year.
- 4.2.10 In people who have had an ischaemic stroke, treatment with modified-release dipyridamole plus aspirin was associated with an additional cost of £704, and 0.131 additional QALYs per person with a corresponding ICER of £5377 per QALY gained, compared with aspirin. Treatment with clopidogrel compared with modified-release dipyridamole plus aspirin was associated with additional costs of £1808 and 0.015 additional QALYs per person with an ICER of £114,628 per QALY gained. The results

were similar in people who have had a transient ischaemic attack. In this population, treatment with modified-release dipyridamole plus aspirin compared with aspirin was associated with an additional cost of £732 and 0.121 additional QALYs per person with an ICER of £6053 per QALY gained. The manufacturer reported that its model suggested that at a cost-effectiveness threshold of £20,000 per QALY gained, modified-release dipyridamole plus aspirin would no longer be cost effective compared with clopidogrel if the price of generic clopidogrel reduced to approximately 50% of that of branded clopidogrel.

Assessment Group model

- 4.2.11 The Assessment Group developed an individual patient sampling model, in which a series of individual profiles were generated whose combined characteristics were representative of the specified population. Analyses were split by population: ischaemic stroke, myocardial infarction, peripheral arterial disease and multivascular disease. The ischaemic stroke and transient ischaemic attack populations were assumed to be equivalent in risk and outcomes and so were modelled together. Within the myocardial infarction group, treatment strategies as described in the clinical guidelines on STEMI and NSTEMI ([NICE clinical guideline 48](#) and [NICE clinical guideline 94](#)) were modelled initially. Once initial treatment was completed according to the guidelines, potential treatment strategies for this appraisal were considered as follow-on treatment.
- 4.2.12 The Assessment Group presented different treatment strategies, depending on the population and intolerances. The Assessment Group considered that this approach reflected the real world, because people may switch between different treatments. For each person in the model, age, sex and disability status was set. According to these variables, estimates of time to first event were applied. These events determined the event history of the person and included a fatal or new non-fatal ischaemic stroke event, a fatal or new non-fatal non-ischaemic stroke event, a fatal or new non-fatal myocardial infarction, death from other vascular causes, death from non-vascular causes and person discontinues current preventive medication for any reason. Only one event could occur at any one time. If the event was non-fatal then the person continued in the model, with an updated age, sex and disability

status and updated risks, with the potential to incur additional events over time, moving through the model over a lifetime. Each person was modelled in the same way. Data provided by the manufacturers from the CAPRIE and PROFESS trials were used to develop risk models for the economic model and to work out event fatality. An exponential survival function was used to model medication continuance over time. Adverse events were incorporated into the model.

- 4.2.13 Resource use was measured in terms of clinical events and time spent in chronic states, and differed by disability status. Drug costs were taken from the BNF58 and from the NHS Drug Tariff (January 2010) for generic clopidogrel, which at that point reported that the price of 30 tablets was £10.90. Unit costs were drawn from various sources, including the manufacturers' submissions, and inflated if necessary to 2009. The costs were £6410 for non-fatal ischaemic or haemorrhagic stroke if the person was not disabled and £13,647 if they were disabled, £8768 for fatal ischaemic or haemorrhagic stroke, £5762 for non-fatal myocardial infarction, £2218 for fatal myocardial infarction and £2225 for other vascular or non-vascular death.
- 4.2.14 Utility values were also drawn from a variety of sources, including the manufacturers' submissions and additional analyses requested from the manufacturer. Mean utility values were assigned to each chronic health state and a specific utility decrement effect was applied for each modelled event. Utility values for the myocardial infarction and peripheral arterial disease groups were 0.87 and 0.80 respectively. Utility values for the ischaemic stroke group and all utility decrements were taken from the Boehringer Ingelheim submission. Discounting at 3.5% was applied to costs and benefits after the first year. A lifetime horizon was used.
- 4.2.15 Deterministic and probabilistic sensitivity analyses were conducted to explore the impact of uncertainty on the cost-effectiveness estimates.

People who have had an ischaemic stroke or transient ischaemic attack

- 4.2.16 For people who have had an ischaemic stroke or transient ischaemic attack, when the branded price for clopidogrel was used, the Assessment Group reported that the optimal treatment strategy was

modified-release dipyridamole plus aspirin, followed by aspirin and finally clopidogrel. This produced an ICER of £16,894 per QALY gained and incremental costs of £354 and 0.021 QALYs compared with treatment with the next best strategy of modified-release dipyridamole plus aspirin, followed by aspirin.

- 4.2.17 When the generic price for clopidogrel was used, the optimal treatment strategy changed so that it began with clopidogrel, followed by modified-release dipyridamole plus aspirin and finally aspirin. This produced an ICER of £13,558 per QALY gained, compared with the next best strategy of clopidogrel, followed by aspirin, followed by modified-release dipyridamole plus aspirin. This strategy was associated with an additional cost of £334 and 0.024 additional QALYs.
- 4.2.18 For people with intolerance to aspirin, clopidogrel followed by modified-release dipyridamole was the optimal treatment strategy with an ICER of £7142 per QALY gained compared with treatment with clopidogrel alone. This strategy was associated with an additional cost of £616 and 0.086 additional QALYs. It could be calculated from the data that for people with intolerance to aspirin and clopidogrel or for whom clopidogrel wasn't licensed, the optimal treatment strategy was modified-release dipyridamole alone with an ICER of £314 per QALY gained compared with no preventive treatment. This strategy was associated with an additional cost of £167 and 0.531 additional QALYs.
- 4.2.19 For people with intolerance to modified-release dipyridamole, the optimal treatment strategy depended on the price of clopidogrel. At the branded price, the preferred strategy was aspirin followed by clopidogrel with an ICER of £6797 per QALY gained, compared with clopidogrel alone. This strategy was associated with an additional cost of £628 and 0.092 additional QALYs. At the generic price, the optimal strategy was clopidogrel followed by aspirin, compared with aspirin followed by clopidogrel, with an ICER of £3970 per QALY gained, an additional cost of £224 and 0.056 additional QALYs. For people with intolerance to both aspirin and modified-release dipyridamole, only clopidogrel is available for long-term prevention. It was considered optimal by the Assessment Group compared with no preventive therapy, with an ICER of £275 per QALY gained. This strategy was associated with an additional cost of

£163 and 0.591 additional QALYs.

- 4.2.20 From the Assessment Group's analysis of the ischaemic stroke data, the ICERs could be calculated for people with intolerance to clopidogrel or for whom treatment with clopidogrel is not licensed, such as people who have had a transient ischaemic attack. Treatment with modified-release dipyridamole plus aspirin followed by aspirin had an ICER of £9145 per QALY gained, compared with treatment with aspirin followed by modified-release dipyridamole. This strategy was associated with an additional cost of £567 and 0.062 additional QALYs.

People who have had a myocardial infarction

- 4.2.21 The Assessment Group reported that for people who have had a myocardial infarction the optimal treatment strategies were the same regardless of the price of clopidogrel. Aspirin followed by clopidogrel, compared with aspirin alone, was the optimal strategy for this population, with an ICER of £1964 per QALY gained (using the price of generic clopidogrel) and a difference in costs of £185 and QALYs of 0.094. For people with intolerance to aspirin, treatment with clopidogrel was likely to be the optimal treatment, compared with no preventive therapy, with an ICER of £2020 per QALY gained (using the price of generic clopidogrel) and a difference in cost of £468 and 0.232 additional QALYs.
- 4.2.22 After consultation on the appraisal consultation document, the Assessment Group provided a reanalysis of the data for people who have had a myocardial infarction. This analysis used a price of clopidogrel of £5.13, reflecting the NHS tariff price for August 2010. The results showed that the lower price had no effect on the optimal treatment strategy: aspirin followed by clopidogrel remained the optimal treatment strategy.

People with established peripheral arterial disease

- 4.2.23 The Assessment Group reported that for people with peripheral arterial disease the optimal treatment strategies were the same regardless of the price of clopidogrel. Clopidogrel followed by aspirin was the optimal strategy for this group, with an ICER of £2815 per QALY gained. It was

associated with an additional cost of £983 and an additional 0.349 QALYs compared with treatment with aspirin alone followed by treatment with clopidogrel. In people with intolerance to aspirin, clopidogrel alone was the optimal treatment strategy. Compared with no preventive therapy, clopidogrel gave an additional 0.773 QALYs at a cost of £557, with an ICER of £721 per QALY gained.

People with multivascular disease

4.2.24 The Assessment Group reported that for people with multivascular disease the optimal treatment strategies were the same regardless of the price of clopidogrel. Clopidogrel followed by aspirin was the optimal strategy for this group, compared with aspirin followed by clopidogrel. For the optimal strategy, treatment was associated with an ICER of £2604 per QALY gained, and incremental costs of £595 and incremental QALYs of 0.228. In people with intolerance to aspirin, clopidogrel alone was the optimal treatment strategy and was associated with lower total costs of –£548 compared with no preventive therapy, 0.723 additional QALYs and a corresponding ICER of –£758 per QALY gained.

4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of clopidogrel and modified-release dipyridamole, having considered evidence on the nature of occlusive vascular events and peripheral arterial disease and the value placed on the benefits of clopidogrel and modified-release dipyridamole by people who have had an occlusive vascular event or are at risk of one, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.3.2 The Committee discussed current clinical management for the prevention of occlusive vascular events. The Committee heard from clinical specialists that they would value clear, straightforward guidance so that treatment could be started at the earliest possible point, when the risk of recurrent events is highest. Patient experts explained that treatment with clopidogrel or modified-release dipyridamole plus aspirin was an important part of treatment for the prevention of occlusive vascular

events but is just one part of a wider programme of management involving both pharmacological and non-pharmacological treatment. The Committee heard from the patient experts that people are often on a number of treatments and would value a reduction in the number of tablets that need to be taken. The Committee heard from the patient experts that they considered that clopidogrel had fewer severe side effects than aspirin or modified-release dipyridamole. The Committee recognised that antiplatelet therapy such as clopidogrel and modified-release dipyridamole was one part of clinical management and that people valued treatments with ease of administration and few side effects.

4.3.3 The Committee discussed the results of the ESPRIT and PROFESS trials, which became available after the publication of NICE technology appraisal guidance 90. The Committee noted that these trials included people who have had an ischaemic stroke or a transient ischaemic attack and there was no new evidence for people with peripheral arterial disease or for people who have had a myocardial infarction. The Committee discussed the results of the PROFESS trial and considered that it had not shown that clopidogrel provided greater benefits than modified-release dipyridamole plus aspirin. But the Committee also considered that the trial had not shown that modified-release dipyridamole plus aspirin provided greater benefits than clopidogrel. The Committee noted comments made in the consultation on the appraisal consultation document about the exclusion of the MATCH and CHARISMA trials, but considered that these trials studied a combination of clopidogrel plus aspirin that was outside the scope of this appraisal. Likewise, it noted comments made about the EARLY trial that compared early and standard initiation of treatment, but considered that this had been appropriately excluded from the Assessment Group's review. The Committee concluded that the data published after NICE technology appraisal guidance 90 supported the conclusions in that guidance.

4.3.4 The Committee specifically discussed the duration of follow-up in the ESPRIT and PROFESS trials, recognising that in NICE technology appraisal guidance 90 the evidence was limited to 2 years' follow-up. It noted that the ESPRIT trial had a mean follow-up of 3.5 years and the PROFESS trial had a mean follow-up of 2.5 years. The Committee heard

from the clinical specialists that in clinical practice the length of time people stayed on treatment varied, but it could be longer than 2 years. The clinical specialists discussed evidence from the ESPRIT trial that showed that Kaplan-Meier curves by treatment group continued to diverge over time. While the clinical specialists recognised that the study and its results have limitations, they considered that this provided evidence of a continued treatment effect beyond the 2 years used in NICE technology appraisal guidance 90. The Committee was persuaded that it was appropriate to examine the Assessment Group's analyses of cost effectiveness without specifying a limit on the duration of treatment.

4.3.5 The Committee considered the subgroup of people with multivascular disease. It noted that there is a range of definitions of multivascular disease, but heard from the clinical specialists that identifying the subgroup of people with multivascular disease was important and clinically meaningful. The Committee discussed the post-hoc analyses from the CAPRIE trial that suggested that this group is at high risk of occlusive vascular events and may need more intensive treatment. The Committee was aware of the limitations of post-hoc analyses but noted that the subgroups were based on large numbers of people. On balance, it considered multivascular disease to be appropriate to consider in the cost-effectiveness analysis.

4.3.6 The Committee recognised that after the publication of NICE technology appraisal guidance 90, clopidogrel became available in a number of generic preparations. The Assessment Group's analyses used both the branded and generic prices. The Committee was aware that after the assessment report was written the price of clopidogrel was reduced further from approximately £10 to approximately £5 per month. It noted that this would affect the cost-effectiveness results, because treatment with generic clopidogrel would cost less than previously stated. The Committee considered that it was appropriate to take account of the generic price of clopidogrel in its considerations and that any treatment with clopidogrel should use the least costly licensed preparation.

4.3.7 The Committee discussed the cost-effectiveness results from the two manufacturers' models. The Committee considered the Boehringer Ingelheim model, which reported that in people who have had an

ischaemic stroke or a transient ischaemic attack, treatment with modified-release dipyridamole plus aspirin was cost effective compared with aspirin, with ICERs of around £5400 and £6100 per QALY gained, respectively. The Committee considered the Bristol-Myers Squibb and Sanofi-Aventis model, which found that in people who have had an ischaemic stroke, treatment with modified-release dipyridamole plus aspirin was cost effective with an ICER of around £240 per QALY gained compared with aspirin. In people who have had a myocardial infarction, or who have peripheral arterial disease and for people with multivascular disease, the ICERs were all below £21,000 per QALY gained, compared with aspirin. The Committee discussed the limitations of the models, noting that in the submissions neither model used the generic price of clopidogrel. However, the Committee was aware that the manufacturer of modified-release dipyridamole had commented that at a cost-effectiveness threshold of £20,000 per QALY gained, if the price of generic clopidogrel was about 50% of that of branded clopidogrel, modified-release dipyridamole plus aspirin would no longer be cost effective compared with clopidogrel. Furthermore, the Committee was aware of comments in response to consultation on the Assessment Report from the manufacturer of clopidogrel that for people who have had an ischaemic stroke, using a price of £10.90 for clopidogrel produced an ICER of under £500 per QALY gained for clopidogrel in comparison with modified-release dipyridamole.

4.3.8 The Committee discussed the results of the Assessment Group's model for the subgroup of people with peripheral arterial disease. It noted that a treatment strategy of clopidogrel followed by aspirin had an ICER of around £2800 per QALY gained, compared with aspirin alone. For people with intolerance to aspirin, treatment with clopidogrel had an ICER of around £720 per QALY gained compared with no preventive therapy. The Committee considered that for people with peripheral arterial disease clopidogrel was a cost-effective use of NHS resources.

4.3.9 The Committee discussed the results of the Assessment Group's model for the subgroup of people with multivascular disease. It noted that a treatment strategy of clopidogrel followed by aspirin had an ICER of around £2600 per QALY gained, compared with aspirin alone. In people with intolerance to aspirin, clopidogrel was a cost-saving strategy,

costing less and producing more benefits than no preventive therapy. The Committee considered that for people with multivascular disease clopidogrel was a cost-effective use of NHS resources.

4.3.10 The Committee discussed the results of the Assessment Group's model for the subgroup of people who have had a myocardial infarction. It recognised that the model had incorporated the current [NICE clinical guideline 48](#) and [NICE clinical guideline 94](#) on the use of clopidogrel plus aspirin for the treatment of people with STEMI and NSTEMI, and modelled the use of clopidogrel monotherapy after its use as a combination therapy for acute coronary syndromes. The treatment strategy of aspirin followed by clopidogrel had an ICER of £2000 per QALY gained, compared with aspirin alone. A treatment strategy of clopidogrel followed by aspirin was associated with greater costs and fewer QALYs than starting with aspirin. In people with intolerance to aspirin, clopidogrel had an ICER of £2000 per QALY gained compared with no preventive therapy. The Committee discussed the re-analysis provided by the Assessment Group after the consultation on the appraisal consultation document, which showed that the further reduction of the price of clopidogrel to £5.13 (the price in July 2010) had no effect on the optimal treatment strategy. The Committee concluded that for people who have had a myocardial infarction, when treatment with combined clopidogrel and aspirin therapy is no longer appropriate, clopidogrel was a cost-effective use of NHS resources only for people who have a contraindication to aspirin or intolerance to it.

4.3.11 The Committee discussed the results of the Assessment Group's model for people who have had an ischaemic stroke. The Committee noted that the optimal treatment strategy changed depending on whether the branded or generic price of clopidogrel was used. When the generic price of clopidogrel was used, the Assessment Group model found that clopidogrel followed by modified-release dipyridamole plus aspirin and then aspirin alone had an ICER of £13,600 per QALY gained, compared with clopidogrel followed by aspirin, followed by modified-release dipyridamole plus aspirin. In people with intolerance to modified-release dipyridamole, clopidogrel followed by aspirin had an ICER of £4000 per QALY gained compared with aspirin alone. In people with intolerance to aspirin, clopidogrel followed by modified-release dipyridamole alone had

an ICER of £7100 per QALY gained, compared with treatment with clopidogrel alone. For people who had intolerance to clopidogrel and aspirin, treatment with modified-release dipyridamole alone had an ICER of £314 per QALY gained in comparison with no preventive treatment. The Committee recognised that the differences in the total costs and QALYs for the different treatment strategies each including clopidogrel, modified-release dipyridamole plus aspirin and aspirin were small. However, it noted that these were consistent in all analyses, and with a further reduction in the price of clopidogrel the differences in costs would be larger. The Committee concluded that using clopidogrel at the generic price was a cost-effective use of NHS resources. Modified-release dipyridamole plus aspirin was a cost-effective use of NHS resources only when it was used for people who had a contraindication or intolerance to clopidogrel. Modified-release dipyridamole alone was a cost-effective use of NHS resources only when it was used in people who had a contraindication or intolerance to aspirin and clopidogrel.

- 4.3.12 The Committee heard from the clinical specialists that people who have had a transient ischaemic attack are sometimes treated with clopidogrel. However, the Committee recognised that recommendations could not be made for the use of clopidogrel for people who have had a transient ischaemic attack because clopidogrel is not licensed for this indication. For people who have had a transient ischaemic attack, treatment with modified-release dipyridamole plus aspirin followed by aspirin had an ICER of £9,100 per QALY gained compared with treatment with aspirin alone. For people who had intolerance to aspirin, treatment with modified-release dipyridamole alone had an ICER of £314 per QALY gained in comparison with no preventive treatment. The Committee considered that for people who have had a transient ischaemic attack, treatment with modified-release dipyridamole plus aspirin could be considered a cost-effective use of NHS resources. Modified-release dipyridamole alone was considered to be a cost-effective use of NHS resources for people who have had a transient ischaemic attack only if aspirin is contraindicated or not tolerated.

Summary of the Appraisal Committee's key conclusions

TA210 (STA)	Appraisal title: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90)	FAD section
Key conclusions		
For people who have had an ischaemic stroke, clopidogrel is recommended as a treatment option. For people who have a contraindication or intolerance to clopidogrel, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to both clopidogrel and aspirin, modified-release dipyridamole alone is recommended as a treatment option.		1.1
For people who have had a transient ischaemic attack, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to aspirin, modified-release dipyridamole alone is recommended as a treatment option.		1.2
For people who have had a myocardial infarction, clopidogrel is recommended only when treatment with aspirin is contraindicated or not tolerated.		1.3
For people with peripheral arterial disease, clopidogrel is recommended as a treatment option.		1.4
For people with multivascular disease, clopidogrel is recommended as a treatment option.		
Treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.		
Current practice		
Clinical need of patients including the availability of alternative treatments	Patients are often on a number of treatments and would value a reduction in the number of tablets that need to be taken.	4.3.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits	This is a review of established technologies.	n/a
What is the position of the treatment in the pathway of care for the condition	Treatment with clopidogrel or modified-release dipyridamole plus aspirin is an important part of treatment for the prevention of occlusive vascular events, but is just one part of a wider programme of management involving both pharmacological and non-pharmacological treatment.	4.3.2
	Clopidogrel is not licensed for the treatment of transient ischaemic attack, and therefore recommendations could not be made about the use of clopidogrel in this patient population.	4.3.12
Adverse effects	The Committee heard from patient experts that they considered that clopidogrel had fewer severe side effects than aspirin or modified-release dipyridamole.	4.3.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	Two trials (ESPRIT and PROFESS) became available since the publication of NICE technology appraisal guidance 90.	4.3.3

Relevance to general clinical practice in the NHS	The clinical specialists cited evidence from the ESPRIT trial that showed that Kaplan-Meier curves by treatment group continued to diverge over time. While the clinical specialists recognised that the study and its results have limitations, they considered that this provided evidence of a continued treatment effect beyond the 2 years recommended in NICE technology appraisal guidance 90.	4.3.4
Uncertainties generated by the evidence	The ESPRIT and PRoFESS trials included people who have had an ischaemic stroke or a transient ischaemic attack, and there was no new evidence relating to people with peripheral arterial disease or people who have had a myocardial infarction.	4.3.3
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness	NICE technology appraisal guidance 90 considered subgroups of people who had experienced ischaemic stroke, transient ischaemic attack or myocardial infarction, or who had peripheral arterial disease.	n/a
	Additionally, the Committee considered multivascular disease to be appropriate to consider in the cost-effectiveness analysis.	4.3.5
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The data published after NICE technology appraisal guidance 90 were supportive of the conclusions in that guidance.	4.3.3
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee discussed the manufacturers' models, noting that neither model used the generic price of clopidogrel.	4.3.7

Uncertainties around and plausibility of assumptions and inputs in the economic model	Since the assessment report was written, the price of clopidogrel has been reduced further from approximately £10 to £5 a month.	4.3.6
Incorporation of health-related quality of life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	This was not an issue in the analyses.	n/a
Are there specific groups of people for whom the technology is particularly cost-effective?	NICE technology appraisal guidance 90 includes subgroups of people who had experienced ischaemic stroke, transient ischaemic attack or myocardial infarction, or who had peripheral arterial disease.	n/a
	Additionally, the Committee considered multivascular disease to be appropriate to consider in the cost-effectiveness analysis because in post-hoc analyses of the CAPRIE trial, people with multivascular disease were found to be at high risk of occlusive vascular events.	4.3.5

What are the key drivers of cost effectiveness?	Since the publication of NICE technology appraisal guidance 90, clopidogrel has become available in a number of generic formulations.	4.3.6
	For people who have had an ischaemic stroke, the optimal strategy for treatment changed depending on whether the branded or generic price of clopidogrel was used.	4.3.11
Most likely cost-effectiveness estimate (given as an ICER)	For the subgroup of people with peripheral arterial disease, a treatment strategy of clopidogrel followed by aspirin had an ICER of around £2800 per QALY gained compared with aspirin alone. In people with intolerance to aspirin, treatment with clopidogrel had an ICER of around £720 per QALY gained compared with no preventive therapy.	4.3.8
	For the subgroup of people with multivascular disease, a treatment strategy of clopidogrel followed by aspirin had an ICER of around £2600 per QALY gained compared with treatment with aspirin alone. In people with intolerance to aspirin, clopidogrel was a cost-saving strategy, costing less and producing more benefits than no preventive therapy.	4.3.9
	For the subgroup of people who have had a myocardial infarction, the treatment strategy of aspirin followed by clopidogrel had an ICER of £2000 per QALY gained, compared with treatment with aspirin alone. In people with intolerance to aspirin, clopidogrel had an ICER of £2000 per QALY gained compared with no preventive therapy	4.3.10

	For people who have had an ischaemic stroke, when the generic price of clopidogrel was used, the treatment strategy of clopidogrel followed by modified-release dipyridamole plus aspirin and then aspirin alone had an ICER of £13,600 per QALY gained compared with treatment with clopidogrel followed by aspirin, followed by modified-release dipyridamole plus aspirin. In people with intolerance to modified-release dipyridamole, the treatment strategy of clopidogrel followed by aspirin had an ICER of £4000 per QALY gained compared with aspirin alone. In people with intolerance to aspirin, the treatment strategy of clopidogrel followed by modified-release dipyridamole alone had an ICER of £7,100 per QALY gained, compared with treatment with clopidogrel alone. For people who had intolerance to clopidogrel and aspirin, treatment with modified-release dipyridamole alone had an ICER of £314 per QALY gained in comparison with no preventive therapy.	4.3.11
	For people who have had a transient ischaemic attack, treatment with modified-release dipyridamole plus aspirin had an ICER of £9,100 per QALY gained compared with treatment with aspirin alone. For people who had intolerance to aspirin, treatment with modified-release dipyridamole alone had an ICER of £314 per QALY gained in comparison with no preventive therapy.	4.3.12
Additional factors taken into account		
Patient Access Schemes (PPRS)	No patient access schemes were submitted.	n/a
End of life considerations	End-of-life considerations were not discussed.	n/a
Equalities considerations, social value judgements	No equalities issues were raised in the submissions.	n/a

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the [NICE website](#). When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if the doctor responsible for the care of a patient thinks that clopidogrel and modified-release dipyridamole is the right treatment for the prevention of occlusive vascular events, it should be available for use, in line with NICE's recommendations.
- 5.3 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- Costing report and costing template to estimate the savings and costs associated with implementation.
 - Audit support for monitoring local practice.

6 Related NICE guidance

- Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE clinical guideline 94 (2010).
- MI: secondary prevention. Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007).

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review by the Guidance Executive in July 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
November 2010

Appendix A: Appraisal Committee members, and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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 Kathryn Abel

Reader and Consultant Psychiatrist / Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden

Consultant in Intensive Care Medicine / Anaesthesia Sheffield Teaching Hospitals NHS Trust

Professor Mike Campbell

Statistician, Institute of Primary Care and General Practice, University of Sheffield

David Chandler

Lay Member

Dr Mary Cooke

Lecturer, School of Nursing, Midwifery & Social Work, University of Manchester

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Professor Peter Crome

Consultant Physician, Bucknall Hospital

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Richard Devereaux-Phillips

Public Affairs and Reimbursement Manager UK & Ireland, Medtronic

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Professor Catherine Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Henry Marsh

Consultant Neurosurgeon, St George's Hospital

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician Belfast City Hospital

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Neil Myers

General Practitioner

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Lay Member

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Dr Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Professor Paul Trueman

Health Economics Research Group, Brunel University

Dr Judith Wardle

Lay Member

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Helen Starkie

Technical Lead

Zoe Garrett

Technical Adviser

Lori Farrar

Project Manager

Appendix B: Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

- Greenhalgh J, Saborido CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90), April 2010
- Greenhalgh J, Saborido CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90) addendum, April 2010
- Greenhalgh J, Saborido CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90) addendum 2, May 2010
- Greenhalgh J, Saborido CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90) addendum 3, June 2010
- Greenhalgh J, Saborido CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90) addendum 4, June 2010

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I) Manufacturers/sponsors:

- Boehringer Ingelheim
- Bristol-Myers Squibb

- Sanofi-Aventis

II) Professional/specialist and patient/carer groups:

- Anticoagulation Europe (ACE)
- Diabetes UK
- Heart Care Partnership (UK)
- HEART UK
- Insulin Dependent Diabetes Trust (IDDT)
- The Stroke Association
- Association of British Neurologists
- British Association of Stroke Physicians
- British Cardiovascular Intervention Society (BCIS)
- British Cardiovascular Society
- British Heart Foundation
- Royal College
- Royal College of Physicians Cardiology Committee
- The Vascular Society

III) Other consultees:

- Department of Health
- Welsh Assembly Government

IV) Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency
- NHS Quality Improvement Scotland

- Bayer (aspirin)
- Galpharm International (aspirin)
- Liverpool Reviews and Implementation Group, University of Liverpool
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. 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 for the prevention of occlusive vascular events (review of technology appraisal guidance 90) by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Russell Smith, Consultant Cardiologist, nominated by British Cardiovascular Society – clinical specialist
- Professor Thompson Robinson, Professor of Stroke Medicine, nominated by British Association of Stroke Physicians – clinical specialist
- David Gerald MBE, Immediate Past President, nominated by Heart Care Partnership UK – patient expert
- Dr Rob Ryckborst, nominated by Insulin Dependent Diabetes Trust – patient expert

D. Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Boehringer Ingelheim
- Bristol-Myers Squibb Pharmaceuticals Ltd
- Sanofi-Aventis

Changes after publication

February 2014: implementation section updated to clarify that clopidogrel and modified-release dipyridamole is recommended as an option for preventing occlusive vascular events. Additional minor maintenance update also carried out.

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [multiple technology appraisal](#) process.

It replaces NICE technology appraisal guidance 90 (published May 2005).

The review and re-appraisal of clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events has resulted in a change in the guidance. Specifically:

- Treatment with modified-release dipyridamole in combination with aspirin for people who have had an ischaemic stroke is now recommended only if clopidogrel is contraindicated or not tolerated.
- Treatment with modified-release dipyridamole in combination with aspirin for people who have had an ischaemic stroke or a transient ischaemic attack is no longer limited to 2 years' duration from the most recent event.
- Clopidogrel is no longer recommended only for people who are intolerant of aspirin and have had an occlusive vascular event or have peripheral arterial disease (see section 1 for new guidance).
- Modified-release dipyridamole alone is now recommended as an option to prevent occlusive vascular events (see sections 1.2 and 1.3).

The recommendations from this guideline have been incorporated into a [NICE Pathway](#). We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not

override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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