NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome

1 Guidance

1.1 Clopidogrel in combination with low dose aspirin is recommended for use in the management of non-ST-segment-elevation acute coronary syndrome (ACS) in those people who are at moderate to high risk of myocardial infarction (MI) or death.

1.2 For the purposes of this guidance, moderate to high risk of MI or death in people presenting with non-ST-segment-elevation ACS can be determined by clinical signs and symptoms, accompanied by one or both of the following:

(i) The results of clinical investigations such as new ECG changes (other than persistent ST-segment-elevation) indicating ongoing myocardial ischaemia, particularly dynamic or unstable patterns.

(ii) The presence of raised blood levels of markers of cardiac cell damage such as troponin.

1.3 It is recommended that treatment with clopidogrel in combination with low dose aspirin should be continued for up to 12 months after the most recent acute episode of non-ST-segment-elevation ACS (as defined in Sections 1.1 and 1.2). Thereafter, standard care, including treatment with low dose aspirin alone, is recommended.

2 Clinical need and practice

2.1 The term acute coronary syndrome (ACS) is used to refer to any group of clinical symptoms associated with acute myocardial ischaemia. It
encompasses a spectrum of disorders including acute myocardial infarction (MI) and unstable angina pectoris. ACS is usually the result of an acute or subacute primary reduction of myocardial oxygen supply provoked by disruption of an atherosclerotic plaque associated with inflammation, thrombosis, vasoconstriction and microembolisation. The presence of persistent ST-segment-elevation on an ECG usually indicates total occlusion of the affected artery, resulting in necrosis of the tissue supplied by that artery (acute MI).

2.2 ACS without ST-segment-elevation is classified as either unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). Unstable angina and NSTEMI differ primarily in the severity of myocardial ischaemia. In NSTEMI, the ischaemia is severe enough to result in the release of biochemical markers of myocardial injury, such as troponin I or T, into the blood. At the time of presentation, before the results of the blood tests are available, unstable angina and NSTEMI are usually indistinguishable.

2.3 Unstable angina/NSTEMI is associated with a high risk of death or ischaemic complications, particularly in those with signs of ischaemic injury. In one UK-based registry of patients admitted to hospital with non-ST-segment-elevation ACS (the Prospective Registry of Acute Ischaemic Syndromes in the UK, PRAIS-UK), the rate of death was 1.5% in hospital and 7.4% at 6 months. The rate of MI was 3.9% in hospital and 7.3% at 6 months, and the rate for the composite of death or non-fatal MI was 5.0% in hospital and 12.2% at 6 months.

2.4 It is difficult to estimate the incidence of non-ST-segment-elevation ACS in England and Wales. It is thought that there may be variations in the coding of this condition, leading to underestimates of the true incidence. Hospital episode statistics for the financial year 2002–03 show 144,450 finished consultant episodes for angina pectoris in England, of which 83,842 were specified as unstable angina. The corresponding figures for Wales are 8812 episodes of angina pectoris, of which 4421 were specified as unstable angina.
In the same period, there were 105,476 finished consultant episodes for MI in England and 6749 in Wales. It is uncertain how many of these were NSTEMI because this information is not recorded in hospital episode statistics.

2.5 The main aim of the short-term treatment of unstable angina/NSTEMI is to relieve pain and prevent progression to full-thickness MI or death. Acute-phase treatment involves the use of heparin (either unfractionated or low molecular weight), nitrates, beta-blockers or calcium channel blockers, and antiplatelet agents including aspirin and glycoprotein IIb/IIIa inhibitors. Urgent revascularisation procedures (percutaneous coronary intervention [PCI], usually with stent implantation, or coronary artery bypass grafts) may be used in certain high-risk patients (including those with serious ongoing ischaemia, major dysrhythmias or haemodynamic instability).

2.6 Most individuals with ACS have underlying atherosclerosis. They remain at risk of subsequent cardiac events and, because they are also likely to have atherosclerosis in other vascular beds, they are at risk of other occlusive vascular events such as ischaemic stroke. Long-term management after an episode of ACS involves aggressive management of risk factors for further occlusive vascular events. This includes smoking cessation, and the treatment of hypertension and hyperlipidaemia. Aspirin, HMG-CoA inhibitors (statins), beta-blockers and angiotensin-converting enzyme inhibitors may be continued long term in the absence of contraindications.

3 The technology

3.1 Clopidogrel (Plavix, Sanofi-Synthelabo, Bristol-Myers Squibb) is a thienopyridine antiplatelet drug. After activation in the liver, it inhibits platelet aggregation by irreversibly modifying the platelet adenosine diphosphate (ADP) receptor and thus blocking the pro-aggregatory effects of ADP. It is licensed for use in combination with aspirin for the treatment of individuals suffering from unstable angina or NSTEMI.
3.2 Bleeding is the most common reaction reported in the post-marketing experience, usually during the first month of treatment. Thrombotic thrombocytopenic purpura has been reported very rarely following the use of clopidogrel. As with other antiplatelet agents, clopidogrel should be used with caution in people receiving treatment with other drugs that interfere with clotting. The Summary of Product Characteristics advises against use in combination with warfarin. There is particular need for caution in patients who need to undergo surgery while being treated with clopidogrel, for example, urgent coronary artery bypass surgery. For elective procedures, where an antiplatelet effect is not needed, clopidogrel should be discontinued 7 days before surgery. For full details of side effects and contraindications, see the Summary of Product Characteristics.

3.3 In the treatment of non-ST-segment-elevation ACS, clopidogrel is given as an initial 300 mg loading dose, followed by continued treatment at a dose of 75 mg daily in combination with aspirin at a dose of 75–325 mg daily. The Summary of Product Characteristics notes that the optimal duration of treatment has not been formally established, and that clinical trial data support the use of clopidogrel in this indication for up to 12 months, with the maximum benefit being seen at 3 months. The cost of treatment for 1 year (300 mg loading dose then 75 mg daily) is £464.07 (excluding VAT; British National Formulary, 46th edition).

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 The Assessment Group found one randomised controlled trial of clopidogrel in patients with non-ST-segment-elevation ACS that met the inclusion criteria for its review – the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study. CURE was a randomised, double-blind, placebo-controlled
trial in 12,562 people with non-ST-segment-elevation ACS who had presented within 24 hours after the onset of symptoms. At the outset of the study, people with no new ECG changes could be included, provided they were older than 60 years and had a history of coronary artery disease. However, a lower than anticipated event rate in the first 3000 participants prompted a change in the inclusion criteria, in order to recruit a higher-risk population. All new participants, regardless of their age, were required to have either ECG changes indicative of new ischaemia or serum levels of biochemical markers of myocardial damage twice the upper limit of the normal reference range. Participants in the study were randomised to receive either clopidogrel 300 mg immediately followed by 75 mg once daily, or placebo. All participants also received aspirin and other standard therapy, as deemed necessary. Other standard drug treatments included heparin, angiotensin-converting enzyme inhibitors, beta-blockers, nitrates, calcium channel blockers, and lipid-lowering agents. Glycoprotein IIb/IIIa inhibitors were not routinely used and only 6.6% of the trial population received them. Follow-up was for 3-12 months (mean 9 months). The protocol specified two ‘primary’ end-points: the first was a composite of death from cardiovascular causes, non-fatal MI, or stroke; the second was a composite of death from cardiovascular causes, non-fatal MI, stroke, or refractory ischaemia.

4.1.2 The CURE study found a statistically significantly lower incidence of death from cardiovascular causes, non-fatal MI or stroke with clopidogrel plus aspirin therapy compared with placebo plus aspirin: 582 (9.3%) and 719 (11.4%), respectively. This equates to a relative risk reduction in the first composite primary end-point of 20% (95% confidence interval, CI, 10 to 18%, p<0.001) or an absolute risk reduction of 2.1% (95% CI, 1.0 to 3.2%). For the second composite primary end-point, which also included refractory ischaemia, the relative risk reduction with clopidogrel was 14% (95% CI, 6 to 21%, p<0.001) and the absolute risk reduction was 2.3% (95% CI, 1.0 to 3.2%).
4.1.3 The published report presented nine key subgroup analyses (associated MI versus no associated MI, male versus female,  ≤ 65 versus >65 years of age, ST-segment-deviation versus no ST-segment-deviation, elevated cardiac enzymes at entry versus no elevated enzymes at entry, diabetes versus no diabetes, low versus intermediate versus high risk, history of revascularisation versus no history of revascularisation, and revascularisation after randomisation versus no revascularisation after randomisation). These generally showed consistent relative benefits of clopidogrel across the subgroups, with the exception of a tendency towards greater benefit for clopidogrel in those who had previously undergone revascularisation. However, given the number of subgroup analyses, this result may have occurred by chance.

4.1.4 Analysis of the events in different time periods of the trial suggested that the greatest benefits occurred within the first 3 months of treatment. However, the trial was not adequately powered to detect temporal differences between the groups, so these results should be interpreted cautiously.

4.1.5 The rates of both major and minor bleeding episodes were higher in the clopidogrel group compared with the placebo group. Major bleeding (defined as substantially disabling bleeding, intraocular bleeding leading to loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood) occurred in 231 (3.7%) of the clopidogrel group compared with 169 (2.7%) of the placebo group (relative risk, RR, 1.38; 95% CI, 1.13 to 1.67). The rate of major bleeding episodes was highest within 30 days after randomisation. There was no difference in the number of fatal bleeding episodes, bleeding requiring surgical intervention or haemorrhagic stroke between the treatment groups.

4.1.6 A total of 2658 (21.2%) of participants in the CURE study underwent PCI and were included in a pre-designed substudy (PCI-CURE). The objective of this substudy was to determine whether a strategy of pretreatment with clopidogrel followed by long-term use was better than a strategy of no
pretreatment and short-term use of a thienopyridine antiplatelet agent only when a stent has been inserted. More than 80% of the participants in PCI-CURE received a stent and were prescribed open-label clopidogrel or ticlopidine for 2–4 weeks, after which they resumed randomly assigned medication. The primary end-point of PCI-CURE was the composite of death from cardiovascular causes, non-fatal MI or urgent revascularisation of the target vessel within 30 days of PCI. The primary end-point occurred in 59 (4.5%) of the clopidogrel group compared with 86 (6.4%) of the placebo group (RR 0.70; 95% CI, 0.50 to 0.97). Cardiovascular death and MI from the time of PCI to the end of the study were also assessed to determine the effects of long-term continuation of clopidogrel. From the time of PCI to the end of follow-up (mean 8 months), there were significantly fewer cardiovascular deaths and non-fatal MIs in the clopidogrel group compared with the placebo group: 79 (6.0%) and 108 (8.0%), respectively (RR 0.75; 95% CI, 0.56 to 1.00; p = 0.047).

4.1.7 Overall, it appears that adding clopidogrel to standard therapy reduces the risk of adverse vascular events in the first year after an episode of non-ST-segment-elevation ACS, but this was combined with an increase in the incidence of bleeding complications.

4.2 Cost effectiveness

4.2.1 The systematic review of the economic evidence performed by the Assessment Group found only one study published in full that met the inclusion criteria. This was an analysis of five treatment strategies using antiplatelet agents for the treatment of coronary artery disease compared with no treatment over a period of 25 years. However, the analysis was conducted from the perspective of the US healthcare system and the population consisted of patients with recently diagnosed coronary artery disease rather than non-ST-segment-elevation ACS specifically. The Assessment Group therefore concluded that this analysis was of limited value to this appraisal.
4.2.2 The sponsors of clopidogrel (Sanofi-Synthelabo, Bristol-Myers Squibb) submitted an economic analysis from the perspective of the UK NHS. The model was designed to assess the long-term cost effectiveness of treatment with clopidogrel added to standard treatment (including aspirin) compared with standard treatment alone. It was assumed that treatment with clopidogrel was for 12 months (reflecting the follow-up period of the CURE trial rounded up to the nearest full year). After 1 year, it was assumed that all patients received aspirin as their sole antiplatelet agent for the remainder of their lives. The model comprised two components: a short-term decision tree to model the costs and effects over the 12-month treatment period, and a long-term element that extended the analysis over a 40-year time horizon (corresponding to a lifetime of treatment, given that the cohort of patients entered into the model were assumed to be 60 years old). Over the full term of the model, a total of 87 life years and 82 quality-adjusted life years (QALYs) were gained in a hypothetical cohort of 1000 people with ST-segment-elevation ACS. The cost per additional QALY associated with clopidogrel combination therapy for 1 year compared with aspirin alone was £5668.

4.2.3 The Assessment Group developed a model that was similar in structure to that submitted by the sponsors of this product (both were based on a previously published model to evaluate the cost effectiveness of glycoprotein IIb/IIIa inhibitors in non-ST-segment-elevation ACS). The main differences between the Assessment Group’s model and the manufacturer’s model were in the estimation of resource use and the estimates of utility for the different health states. In the Assessment Group’s model, the age of the patients in the model is not incorporated as an explicit parameter. The age to which the analysis relates reflects that of the patients in the cohorts used to populate the model. Two separate observational data sets were used: the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) and the Nottingham Heart Attack Registry (NHAR). In PRAIS-UK, the mean age of patients was 66 years; in the NHAR the mean age of the two cohorts was
68 years. The Assessment Group’s base-case analysis calculated an incremental cost-effectiveness ratio (ICER) of £6078 per QALY for standard therapy plus clopidogrel compared with standard therapy alone. A range of sensitivity analyses was conducted to assess the robustness of the base-case analysis to alternative assumptions. Reducing the time horizon of the model from 40 years to 5 years had the largest effect: the ICER increased to £14,844 per QALY.

4.2.4 The Assessment Group also explored the cost effectiveness of using clopidogrel for periods shorter than 1 year. This was an analysis of five strategies: lifetime treatment with standard therapy (including aspirin) alone, or clopidogrel as an adjunct to standard therapy (including aspirin) for 1 month, 3 months, 6 months or 12 months. The ICER for 1 month of treatment with clopidogrel compared with standard care alone was calculated to be £824 per QALY. The strategies of using clopidogrel for 3 or 6 months were ruled out by extended dominance, and the ICER for 12 months of treatment with clopidogrel compared with 1 month was £5159 per QALY. An alternative method of extrapolation to estimate the transition probabilities between 6 and 12 months gave results more consistent with a continued decline in the absolute risk of events over this period. Using these estimates, none of the five strategies were ruled out on the grounds of dominance/extended dominance. The ICER became less favourable as the duration of treatment with clopidogrel increased:
• 1 month of treatment with clopidogrel compared with standard therapy alone, ICER = £895 per QALY.
• 3 months compared with 1 month of treatment, ICER = £5625 per QALY.
• 6 months compared with 3 months of treatment, ICER = £6591 per QALY.
• 12 months compared with 6 months of treatment, ICER = £13,988 per QALY.

4.2.5 The Assessment Group also explored the cost effectiveness of treatment in people at either ‘higher’ or ‘lower’ risk, as defined within the observational data set, as part of their sensitivity analyses. For the purposes of this analysis, people were considered at higher risk if they had diabetes mellitus, or were over 70 years old, or if they had ST-segment-depression or bundle branch block on ECG, and were considered at lower risk if they had none of these characteristics. This differed from the definitions of high and low risk used in subgroup analyses of the CURE study. In this sensitivity analysis, the ICER for 12 months’ treatment with clopidogrel compared with standard treatment alone was £4939 per QALY in people who were considered at higher risk on the basis of these criteria, and £8734 in people considered at lower risk.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of clopidogrel in non-ST-segment-elevation ACS, having considered evidence on the nature of the condition and the value placed by users on the benefits of clopidogrel from people with coronary artery disease, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.

4.3.2 The Committee considered that the evidence reviewed in the Assessment Report supported the case that clopidogrel, used as an adjunct to standard
therapy with low dose aspirin, was clinically and cost effective in the management of non-ST-segment-elevation ACS. The Committee noted that this conclusion was based on evidence from a single clinical trial, which mainly recruited patients with ACS and a moderate to high risk of suffering a subsequent occlusive vascular event. The Committee heard from the experts that most patients presenting with non-ST-segment-elevation ACS would fulfil the amended and more stringent criteria for entry to the CURE study, but that there is a significant minority of patients who present with no significant ECG changes and no change in biochemical markers of cardiac damage, for whom the value of additional antiplatelet therapy with clopidogrel was unclear. After discussion with the experts, and in the light of the decision made by the CURE investigators to change the inclusion criteria of the study, the Committee concluded that the use of clopidogrel should be directed at those patients for whom there is good evidence of benefit and who have an elevated risk of progressing to MI or death (that is patients who would have fulfilled the more stringent set of criteria for entering the CURE study).

4.3.3 In the CURE trial, clopidogrel treatment was given for 3–12 months (mean duration of treatment 9 months). Although the greatest difference in event rates, and hence the greatest benefit of clopidogrel, occurred in the first 3 months of treatment (see Section 4.1.4), the Committee felt that appreciable benefit still occurred between 3 and 12 months. In the light of the Assessment Group’s cost-effectiveness analysis, the Committee concluded that treatment with clopidogrel for up to 12 months was likely to be cost effective.

4.3.4 Neither the sponsors’ nor the Assessment Group’s cost-effectiveness analysis attempted to model the costs and effects of treatment with clopidogrel beyond the 12-month duration of the clinical trial. In the absence of direct evidence for the clinical and cost effectiveness of clopidogrel for longer periods, and in view of the smaller absolute benefits seen in the later stages of the CURE study, the Committee’s view was that treatment with clopidogrel should continue for no longer than 12 months after the most recent episode of non-ST-segment-elevation ACS. They were not persuaded to recommend
treatment for longer than 12 months after the most recent episode of non-ST-segment-elevation ACS. They concluded that, on the basis of current evidence, after 12 months antiplatelet therapy should revert to standard use of low dose aspirin.

4.3.5 In the light of the sensitivity analyses performed by the Assessment Group (see Section 4.2.5), the Committee saw no reason to base the decision on whether or not to use clopidogrel in an individual on their age (over 70 years or not), whether or not they had diabetes mellitus, or whether or not they had ST-segment-depression or bundle branch block on ECG.

4.3.6 The Committee noted that clopidogrel was associated with an excess risk of bleeding compared with standard therapy in the CURE study. Standard therapy included aspirin and heparin, but most people in CURE did not receive any other drugs that interfere with clotting, for example, only 6.6% of the study population received glycoprotein IIb/IIIa inhibitors. The additional risks and benefits associated with the combined use of clopidogrel and other antithrombotic agents, such as glycoprotein IIb/IIIa inhibitors, in the medical management of ACS are unknown. Therefore, the Committee was unable to make a recommendation on the use of these combinations.

5  Recommendations for further research

5.1 There are several ongoing studies comparing clopidogrel in combination with aspirin with either aspirin alone or clopidogrel in populations known to be at risk of atherothrombosis because of various previous events or predisposing conditions. None of these trials are specifically in people with non-ST-segment-elevation ACS.

5.2 The optimal duration of therapy with clopidogrel in combination with aspirin after an episode of non-ST-segment-elevation ACS has not been established. A study is needed to compare the effect of stopping treatment with clopidogrel within a few months of the acute event with a strategy of continued long-term treatment.
5.3 The indications for which clopidogrel is most commonly used in the NHS are uncertain. Research on current drug utilisation patterns would be useful for determining the likely impact on NHS resources of expanding the use of clopidogrel to additional patient groups such as those with non-ST-segment-elevation ACS.

6 Implications for the NHS

6.1 Since its launch in 1998 (initially for use in the secondary prevention of vascular occlusive events only), the number of prescriptions for clopidogrel has increased continually. In 2002, 1.2 million prescriptions for clopidogrel were dispensed in primary care at a net ingredient cost of £52 million. Given that the CURE study was published in August 2001, and that approval for the ACS indication was granted in September 2002, it is likely that this figure already includes a significant proportion of prescribing for non-ST-segment-elevation ACS. The incidence of non-ST-segment-elevation ACS is uncertain; the extent to which unstable angina is distinguished from other forms of angina in hospital episode statistics is not known and it is also uncertain how many of the events coded as MI are episodes of NSTEMI (see Section 2.4).

6.2 Hospital episode statistics suggest that there are approximately 90,000 episodes of unstable angina in England and Wales in a year (based on figures for the financial year 2002–03). There are also approximately 110,000 finished consultant episodes for MI, an unknown proportion of which are NSTEMI. If it is assumed that half of the episodes coded as MI are NSTEMI, then this suggests there are approximately 145,000 episodes of non-ST-segment-elevation ACS in England and Wales each year. If it is also assumed that 80% of these people would receive treatment with clopidogrel, then the total cost of treatment with clopidogrel would be £54 million per year. However, given that clopidogrel is already prescribed for a significant number of people with non-ST-segment-elevation ACS, the additional cost of implementing this guidance is likely to be substantially less than this figure. For example, if it is assumed that 50% of current prescriptions for clopidogrel
in primary care are for people with non-ST-segment-elevation ACS then the additional cost would be approximately £28 million. However, there is considerable uncertainty about the assumptions used in this estimate.

7 Implementation and audit

7.1 Clinicians who care for people with ACS 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 ACS 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 Clopidogrel in combination with low dose aspirin is prescribed for the management of non-ST-segment-elevation ACS in an individual who is at moderate to high risk of MI or death.

7.3.2 Treatment with clopidogrel in combination with low dose aspirin is continued for up to 12 months after the most recent acute episode of non-ST-segment-elevation ACS.

7.4 Local clinical audits on the care of patients with ACS also could include criteria relating to the management of ACS based on the national standards, including standards in the National Service Framework.

8 Related guidance

8.1 There is an ongoing appraisal of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events.

8.2 The Institute has issued guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of ACS.

All documents and further details available from: www.nice.org.uk.

9 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 any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on this technology will be reviewed in June 2007.

David Barnett
Chair, Appraisal Committee
February 2004
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 three times a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair, vice-chair and a number of other members between them attending meetings of all 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 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  
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 George Levvy  
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  
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  
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.

Janet Robertson and Dr Elisabeth George  
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:


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:

II Manufacturer/sponsors:

- Bristol-Myers Squibb
- Sanofi-Synthelabo

III Professional/specialist and patient/carer groups:

- Action Heart
- Age Concern
- British Association for Nursing in Cardiac Care
- British Cardiac Society
- British Geriatrics Society
- British Heart Foundation
- Department of Health
- Heart UK
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 in the treatment of non-ST-segment-elevation ACS 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
Appendix C. Detail on criteria for audit of the use of clopidogrel in the treatment of non-ST-segment-elevation ACS

Possible objectives for an audit
An audit could be carried out to ensure that clopidogrel is used appropriately in the treatment of non-ST-segment-elevation ACS.

Possible patients to be included in the audit
An audit could be carried out on people being managed for non-ST-segment-elevation ACS, for a reasonable period for audit, for example, 3 or 6 months. For audit purposes, this group could be screened further to identify those patients who are at moderate to high risk of MI or death.

Measures that could be used as a basis for an audit
The measures that could be used in an audit of clopidogrel in the treatment of non-ST-segment-elevation ACS are as follows.
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Standard</th>
<th>Exception</th>
<th>Definition of terms</th>
</tr>
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<tbody>
<tr>
<td>1. Clopidogrel in combination with low dose aspirin is prescribed for an individual who is at moderate to high risk of MI or death</td>
<td>100% of people with non-ST-segment-elevation ACS who are at moderate to high risk of MI or death</td>
<td>A. The individual has a contraindication to clopidogrel</td>
<td>Clinicians will need to agree locally on how to define moderate to high risk of MI or death, for audit purposes, that is, clinical signs and symptoms accompanied by one or both of the following: results of clinical investigations such as new ECG changes (other than persistent ST-segment elevation), including ongoing myocardial ischaemia, particularly dynamic or unstable patterns or the presence of raised blood levels of markers of cardiac cell damage such as troponin. Clinicians also will need to agree locally on what constitutes low dose aspirin for audit purposes. For contraindications, see Summary of Product Characteristics.</td>
</tr>
<tr>
<td>2. Treatment with clopidogrel in combination with low dose aspirin is continued for up to 12 months after the most recent acute episode of non-ST-segment-elevation ACS</td>
<td>100% of people treated with clopidogrel for non-ST-segment-elevation ACS at moderate to high risk of MI or death</td>
<td>None</td>
<td>Clinicians will need to agree locally on how the length of treatment time with clopidogrel in combination with low dose aspirin is counted, for audit purposes.</td>
</tr>
</tbody>
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**Calculation of compliance**

Compliance (%) with each measure described in the table above is calculated as follows.
Number of patients whose care is consistent with the **criterion** 
**plus** number of patients who meet any **exception** listed 
\[ \frac{\text{Number of patients whose care is consistent with the criterion \ plus number of patients who meet any exception listed}}{\text{Number of patients to whom the measure applies}} \times 100 \]

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.