



## Complete Summary

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### GUIDELINE TITLE

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

### BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. London (UK): National Institute for Clinical Excellence (NICE); 2004 Jul. 24 p. (Technology appraisal; no. 80).

### GUIDELINE STATUS

This is the current release of the guideline.

## \*\* REGULATORY ALERT \*\*

### FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse:** This guideline references a drug(s)/intervention(s) for which important revised regulatory and/or warning information has been released.

- [June 8, 2007, Troponin-I Immunoassay](#): Class I Recall of all lots of the Architect Stat Troponin-I Immunoassay. The assay may report falsely elevated or falsely decreased results at and near a low level, which may impact patient treatment.

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## SCOPE

### **DISEASE/CONDITION(S)**

Non-ST-segment-elevation acute coronary syndrome (including unstable angina and non-ST-segment-elevation myocardial infarction)

### **GUIDELINE CATEGORY**

Assessment of Therapeutic Effectiveness  
Treatment

### **CLINICAL SPECIALTY**

Cardiology  
Family Practice  
Internal Medicine

### **INTENDED USERS**

Advanced Practice Nurses  
Physician Assistants  
Physicians

### **GUIDELINE OBJECTIVE(S)**

To assess the effectiveness and cost-effectiveness of clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome

### **TARGET POPULATION**

People who have non-ST-segment-elevation acute coronary syndrome (including unstable angina and non-ST-segment-elevation myocardial infarction)

### **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Clopidogrel (Plavix<sup>®</sup>) in combination with low-dose aspirin
2. Assessment of risk for myocardial infarction or death through clinical investigations (e.g., electrocardiography) and measurement of blood levels of cardiac markers

### **MAJOR OUTCOMES CONSIDERED**

- Cardiovascular death
- Myocardial infarction
- Stroke
- Refractory ischemia
- Severe ischemia
- Heart failure
- Revascularisation

- Unstable angina
- Other vascular events and death
- Adverse events including bleeding complications and haematological parameters
- Quality of life
- Costs from all reported perspectives

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases  
 Searches of Unpublished Data

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

**Note from the National Guideline Clearinghouse (NGC):** The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination, University of York (see the "Companion Documents" field).

#### Search Strategy

The searches were conducted for both the present report and the parallel appraisal on the clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events in conjunction.

The following databases were searched for the clinical and cost-effectiveness studies on clopidogrel and dipyridamole treatment.

- The CDSR (Cochrane Database of Systematic Reviews)
- Embase (Ovid, 1980 - 2003/07)
- HEED (CD ROM, 1995 - 2003/05)
- HTA (<http://www.york.ac.uk/inst/crd/>) searched 27/05/03
- Inside Conferences (Dialog, 1993 - 2003/05)
- JICST (Dialog, 1985 - 2003/05)
- MEDLINE (Ovid, 1966 - 2003/04)
- NHSEED (<http://www.york.ac.uk/inst/crd/>) searched 27/05/03
- National Research Register (CD ROM, 2003/02)
- PASCAL (Dialog, 1973 - 2003/05)
- SciSearch (Datastar, 1990 - 2003/05)

For the additional searches that were conducted for reviews of the adverse events associated with aspirin use the following databases were searched:

- The CDSR (Cochrane Database of Systematic Reviews)
- Embase (Ovid, 1980-2003/07)
- HEED (CD ROM, 2003/09)

- MEDLINE (Ovid, 1966 - 2003/08)
- NHSEED (<http://www.york.ac.uk/inst/crd/>) Searched 10/09/03

A further MEDLINE search was carried out to identify economic costs related to heart disease in the UK. The results from all the searches were entered into an Endnote Library and de-duplicated.

The full strategies are presented in Appendix 2 of the assessment report.

## **Inclusion and Exclusion Criteria**

Two reviewers independently screened the titles and abstracts of the studies identified from all searches and sources. A full paper copy of any study judged to be relevant by either reviewer was obtained where possible. The full copy of the study was assessed for inclusion by one reviewer and checked for accuracy by a second, using the criteria set out below. Any discrepancies were resolved by discussion and if necessary through consultation with a third reviewer. Studies that did not meet the inclusion criteria were excluded. The bibliographic details of the excluded studies along with the reasons for exclusion are presented in Appendix 3 of the assessment report.

### **a. Interventions**

- Clopidogrel (Plavix®, Bristol-Myers Squib, Sanofi Synthelabo) in combination with aspirin.

Studies in which the combination of clopidogrel and aspirin were administered with concomitant medications commonly prescribed as standard therapy in patients with non-ST-segment elevation acute coronary syndrome (ACS) (e.g. anti-thrombin therapy, nitrates, beta-blockers, glycoprotein IIb / IIIa antagonists, or calcium channel blockers) were included.

### **b. Participants**

- Patients with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI) were included. Participants with established peripheral arterial disease or those with a history of myocardial infarction, ischaemic stroke or transient ischaemic attacks were the subject of a parallel appraisal.

### **c. Study design**

- Randomised controlled trials (RCTs) that compared clopidogrel in combination with aspirin to aspirin alone were included in the assessment of clinical effectiveness.
- For the evaluation of adverse events associated with combined aspirin and clopidogrel therapy, RCTs and post-marketing surveillance studies with a clearly defined protocol and denominator were included. For aspirin therapy, as its safety profile is well established, only systematic reviews and meta-analyses were included.
- A broader range of studies were considered in the assessment of cost effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included.

d. Outcome measures

See "Major Outcomes Considered" field.

#### **NUMBER OF SOURCE DOCUMENTS**

- In the review of clinical effectiveness, one randomized controlled trial was identified.
- For the assessment of the cost-effectiveness, only one study met the criteria for inclusion in the cost-effectiveness review. In addition, economic evidence was also provided by the manufacturers. A separate cost effectiveness model and accompanying report was submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squibb.
- Six reviews that examined adverse events associated with long-term aspirin use were identified.

#### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus

#### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

#### **METHODS USED TO ANALYZE THE EVIDENCE**

Systematic Review with Evidence Tables

#### **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

##### **Data Extraction Strategy**

Data relating to both study design and quality were extracted by one reviewer and independently checked for accuracy by a second. Data from multiple publications was extracted and reported as a single study. Any disagreements were resolved by discussion, or if necessary through consultation with a third reviewer.

##### **Quality Assessment Strategy**

The quality of the individual studies was assessed by one reviewer and independently checked for agreement by a second. Any disagreements were resolved through consensus, or if necessary through consultation with a third reviewer. The quality of the clinical effectiveness studies was assessed according to criteria based on National Health Service Centre for Reviews and Dissemination (NHS CRD) Report No. 4. The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond et al. This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Clinical Excellence. The quality of the systematic reviews was assessed according to the

guidelines for the Database of Reviews of Effect (DARE) criteria. Full details of the quality assessment strategy are reported in appendix 4 of the assessment report.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

### **Considerations**

Technology appraisal recommendations are based on a review of clinical and economic evidence.

### **Technology Appraisal Process**

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients, and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

## **Who is on the Appraisal Committee?**

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

Of the cost-effectiveness evidence reviewed, only the manufacturer's submission was considered relevant from the perspective of the National Health Service (NHS). The review of this evidence highlighted potential limitations within the submission in its use of data and in the model structure used. These limitations led to the development of a new model with the aim of providing a more reliable estimate of the cost-effectiveness from the perspective of the UK NHS.

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

## **RECOMMENDATIONS**

### **MAJOR RECOMMENDATIONS**

- Clopidogrel, in combination with low-dose aspirin, is recommended for use in the management of non-ST segment-elevation acute coronary syndrome

- (ACS) in people who are at moderate to high risk of myocardial infarction (MI) or death.
- 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:
    - the results of clinical investigations, such as new electrocardiogram (ECG) changes (other than persistent ST-segment-elevation), indicating ongoing myocardial ischaemia, particularly dynamic or unstable patterns
    - the presence of raised blood levels of markers of cardiac cell damage such as troponin.
  - 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 above). Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended.

### **CLINICAL ALGORITHM(S)**

None provided

## **EVIDENCE SUPPORTING THE RECOMMENDATIONS**

### **TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

For the assessment of the clinical effectiveness of clopidogrel alone or in combination with aspirin one randomised controlled trial (RCT) was identified (the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators [CURE]). The study was a randomised, double-blind, placebo controlled trial of high quality. A further five systematic reviews of varying quality examined the adverse events associated with long-term aspirin use.

Of the cost-effectiveness evidence reviewed, only the manufacturer's submission was considered relevant from the perspective of the National Health Service (NHS). The review of this evidence highlighted potential limitations within the submission in its use of data and in the model structure used. These limitations led to the development of a new model with the aim of providing a more reliable estimate of the cost-effectiveness from the perspective of the UK NHS.

## **BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**

### **POTENTIAL BENEFITS**

Appropriate use of clopidogrel for the prevention of further occlusive vascular events

### **POTENTIAL HARMS**

- Adverse events associated with clopidogrel and aspirin therapy including bleeding complications.

- 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.
- There is particular need for caution in patients who need to undergo surgery (such as urgent coronary artery bypass surgery) while being treated with clopidogrel. For elective procedures, in which 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, available at <http://emc.medicines.org.uk/>.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

- As with other antiplatelet agents, clopidogrel should be used with caution in people receiving treatment with other drugs that interfere with clotting.(e.g. warfarin)
- There is particular need for caution in patients who need to undergo surgery (such as urgent coronary artery bypass surgery) while being treated with clopidogrel. For elective procedures, in which 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, available at <http://emc.medicines.org.uk/>.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

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

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

#### Implementation and Audit

- Clinicians who care for people with acute coronary syndrome (ACS) should review their current practice and policies to take account of the guidance.
- Local guidelines or care pathways for people with ACS should incorporate the guidance.

- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
  - 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 myocardial infarction (MI) or death.
  - 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.
- Local clinical audits on the care of patients with ACS could also include criteria relating to the management of ACS based on the national standards, including standards in the National Service Framework.

## **IMPLEMENTATION TOOLS**

Audit Criteria/Indicators

Patient Resources

Quick Reference Guides/Physician Guides

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## **INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES**

### **IOM CARE NEED**

Living with Illness

Staying Healthy

### **IOM DOMAIN**

Effectiveness

Patient-centeredness

## **IDENTIFYING INFORMATION AND AVAILABILITY**

### **BIBLIOGRAPHIC SOURCE(S)**

National Institute for Clinical Excellence (NICE). Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. London (UK): National Institute for Clinical Excellence (NICE); 2004 Jul. 24 p. (Technology appraisal; no. 80).

### **ADAPTATION**

Not applicable: The guideline was not adapted from another source.

### **DATE RELEASED**

2004 Jul

### **GUIDELINE DEVELOPER(S)**

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

### **SOURCE(S) OF FUNDING**

National Institute for Health and Clinical Excellence (NICE)

### **GUIDELINE COMMITTEE**

Appraisal Committee

### **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

*Committee Members:* Dr Jane Adam, Radiologist, St George's Hospital, London; Dr Sunil Angris, General Practitioner, Waterhouses Medical Practice, Staffordshire; 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 Mike Laker, Medical Director, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary, Newcastle- Upon-Tyne; Dr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton; Professor Richard Lilford, Professor of Clinical Epidemiology, Department of Public Health & 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

## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

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.

## **GUIDELINE STATUS**

This is the current release of the guideline.

## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- Clopidogrel in the treatment of non-ST segment-elevation acute coronary syndrome. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Jul. 2 p. (Technology appraisal 80). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- A rapid and systematic review of the clinical effectiveness and cost-effectiveness of clopidogrel used in combination with aspirin compared to aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes (ACS). Assessment report. Centre for Reviews and Dissemination, University of York; 2003 Nov. 180 p. Available in Portable Document Format (PDF) from the [NICE Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0613. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the [original guideline document](#).

## **PATIENT RESOURCES**

The following is available:

- Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. Understanding NICE guidance - information for people with non-ST-segment-elevation acute coronary syndrome, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Jul. 10 p. (Technology appraisal 80).

Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0614. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## **NGC STATUS**

This NGC summary was completed by ECRI on March 10, 2006. This summary was updated by ECRI Institute on July 12, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Troponin-1 Immunoassay.

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