Complete Summary

GUIDELINE TITLE

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

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events. London (UK): National Institute for Health and Clinical Excellence (NICE); 2005 May. 34 p. (Technology appraisal; no. 90).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

- Occlusive vascular events (OVEs) including transient ischaemic attack (TIA), ischaemic stroke, and myocardial infarction (MI)
- Symptomatic peripheral arterial disease (PAD)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Neurology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole relative to prophylactic doses of aspirin for the secondary prevention of occlusive vascular events

TARGET POPULATION

People who have had an occlusive vascular event, or who have symptomatic peripheral arterial disease

Note: This guidance does not apply to people who have had, or are at risk of, a stroke associated with atrial fibrillation, or who require treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Modified-release (MR) dipyridamole (Asasantin Retard®, Persantin Retard®) alone or in combination with aspirin
2. Clopidogrel (Plavix®)

MAJOR OUTCOMES CONSIDERED

- Vascular events, including myocardial infarction, stroke (divided into ischaemic and haemorrhagic where possible), and other vascular events (including unstable angina)
- Vascular death
- Death
- Adverse events, including bleeding complications (major and minor as defined by trial investigators) and other adverse events (nausea, vomiting, diarrhoea, constipation, gastric and duodenal ulceration, headache, dizziness, vertigo, paraesthesia, rash, pruritis, urticaria, hepatic and biliary disorders, neutropenia, thrombotic thrombocytopenia purpura, thrombocytopenia; myalgia, hypotension, hot flushes and tachycardia, severe bronchospasm and angioedema)
- 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 and Centre for Health Economics (see the "Companion Documents" field).

Search Strategy

The following databases were searched for trials and reviews of clopidogrel and modified release (MR) dipyridamole:

- Cochrane Databases of Systematic Reviews (CD ROM, issue 2003/02)
- 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)

The results were entered into an Endnote Library and deduplicated.

The full details of the search strategies are given in Appendix 1 of the systematic review companion document.

Additional searches were conducted for reviews of the side effects of aspirin in the following databases:

- Cochrane Databases of Systematic Reviews (CD ROM, 2003/02)
- 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

The full strategies are presented in Appendix 1 of the systematic review companion document.

A further MEDLINE search was carried out to identify economic costs related to heart disease in the UK. The strategy is also presented in Appendix 1 of the systematic review companion document.

Inclusion and Exclusion Criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed according to the criteria set out below. Studies that did not meet all of the criteria were excluded and their bibliographic details listed with reasons for exclusion. Any discrepancies were resolved by consensus and if necessary a third reviewer was consulted.

Interventions

This review covered the effectiveness of the following two alternative antiplatelet agents, used within their respective licensed indications:

- Clopidogrel (Plavix®, Bristol-Myers Squib, Sanofi Synthelabo).
- MR-dipyridamole used alone or in combination with aspirin (Asasantin Retard®, Persantin Retard®, Boehringer Ingelheim).

Studies in which clopidogrel or dipyridamole were administered with concomitant medications commonly prescribed in patients with atherothrombotic disease (e.g., diuretics, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, hormone replacement) were included.

Participants

- For clopidogrel, participants with established peripheral arterial disease or those with a history of myocardial infarction, ischaemic stroke, or transient ischaemic attacks were included. Participants with unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) are the subject of a parallel appraisal and were not considered in this review. Studies evaluating clopidogrel as an adjunct to percutaneous coronary intervention were also excluded.
- For dipyridamole, participants with a history of ischaemic stroke or transient ischaemic attacks were included.

Study Design

- Randomised controlled trials (RCTs) that compared clopidogrel alone or dipyridamole, alone or in combination with aspirin, to aspirin were included in the assessment of clinical effectiveness.
- For the evaluation of adverse events associated with clopidogrel and dipyridamole therapy, RCTs and post-marketing surveillance studies included.

Outcomes

See "Major Outcomes Considered" field.

Data Extraction Strategy

Data relating to both study design and quality were extracted by one reviewer into an Access database and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus and if necessary a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Quality Assessment Strategy

The quality of the individual studies was assessed by one reviewer, and independently checked for agreement by a second, into an Access database. Disagreements were resolved through consensus and if necessary a third reviewer was consulted. The quality of the clinical effectiveness studies was assessed according to criteria based on NHS CRD Report No. 4.19 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 Abstracts of Reviews of Effect (DARE) criteria. This information was tabulated and summarised within the text of the report. Full details of the quality assessment strategy are reported in Appendix 5 of the systematic review companion document.

NUMBER OF SOURCE DOCUMENTS

- In the review of clinical effectiveness, two randomized controlled trials were identified.
- For the assessment of the cost-effectiveness of clopidogrel and MR-dipyridamole, eight cost-effectiveness reviews were included.
- Five systematic reviews that primarily 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

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 and Centre for Health Economics (see the "Companion Documents" field).

Methods of Analysis/Synthesis

The results of the data extraction and quality assessment for each study of clinical effectiveness were presented in structured tables and as a narrative summary.

For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality were presented in structured tables. This covered studies based on patient-level data and decision models and included any studies provided by manufacturers. For analyses based on patient-level data, the validity of the studies was assessed for the source of resource use and effectiveness data, the valuation methods used to cost the resource use and value patient benefits, the methods of analysis and generalisability of results. Studies were classified as follows:

I. Prospective resource use and patient outcome data.
II. Mixed prospective and retrospective data.
III. Retrospective data.

For analyses based on decision models, the critical appraisal was based on a range of questions including:

i. Structure of model
ii. Time horizon
iii. Details of key input parameters and their sources
iv. Methods of analysis (e.g. handling uncertainty).

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

Cost Effectiveness

The York model assessed the cost effectiveness of differing combinations of treatment strategies in four patient subgroups, under a number of different

scenarios. The results of the model were sensitive to the assumptions made in the alternate scenarios, in particular the impact of therapy on non-vascular deaths.

Conclusions

- The following conclusions are possible assuming the National Health Service (NHS) is willing to pay up to 20,000 to 40,000 pounds sterling per additional quality-adjusted life year (QALY).
- For the stroke and transient ischaemic attack (TIA) sub-groups, acetylsalicylic acid-modified release dipyridamole (ASA-MR-dipyridamole) would be the most cost-effective therapy given a 2-year treatment duration as long as all patients were not left disabled by their initial (qualifying) stroke. For a lifetime treatment duration, ASA-MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke. In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy. Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.
- For the myocardial infarction (MI) and peripheral arterial disease (PAD) sub-groups, clopidogrel would be considered cost-effective for treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

See Section 4.2 of the original guideline document and Section 5 of the systematic review companion document for a detailed economic 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

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

- As part of the prevention of occlusive vascular events:
    - The combination of modified-release (MR) dipyridamole and aspirin is recommended for people who have had an ischaemic stroke or a transient ischaemic attack for a period of 2 years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy should revert to standard care (including long-term treatment with low-dose aspirin)
    - Clopidogrel alone (within its licensed indications) is recommended for people who are intolerant of low-dose aspirin and either have experienced an occlusive vascular event or have symptomatic peripheral arterial disease.
- For the purposes of this guidance, aspirin intolerance is defined as either of the following:
    - Proven hypersensitivity to aspirin-containing medicines
    - History of severe dyspepsia induced by low-dose aspirin.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of the combination of modified-release (MR) dipyridamole and aspirin or clopidogrel alone for the prevention of further occlusive vascular events

POTENTIAL HARMS

Adverse events associated with therapy including bleeding complications, nausea, vomiting, diarrhoea, constipation, gastric and duodenal ulceration, headache, dizziness, vertigo, paraesthesia, rash, pruritis, urticaria, hepatic and biliary disorders, neutropenia, thrombotic thrombocytopenia purpura, thrombocytopenia, myalgia, hypotension, hot flushes and tachycardia, severe bronchospasm, and angioedema.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to clopidogrel include:

- Hypersensitivity to the active substance or any component of the medicinal product
- Severe liver impairment
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage
- Breast-feeding

Contraindications to modified-release dipyridamole and aspirin include:

- Hypersensitivity to any component of the product or salicylates
- Patients with active gastric or duodenal ulcers or with bleeding disorders
- Patients in the last trimester of pregnancy

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 who have had an occlusive vascular event (OVE), that is, an ischaemic stroke, a transient ischaemic attack (TIA), or a myocardial infarction (MI), or people who have symptomatic peripheral arterial disease (PAD), should review their current practice and policies to take account of the guidance set out in Section 1 of the original guideline document and in the "Major Recommendations" section of this summary.
- Local guidelines or care pathways for people with an OVE or symptomatic PAD 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.
- As part of the prevention of OVEs:
    - For a person who has had an ischaemic stroke or a TIA, the combination of MR dipyridamole and aspirin is prescribed for 2 years

from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy reverts to standard care.
- For a person who is intolerant of low-dose aspirin and who either has experienced an OVE or has symptomatic PAD, clopidogrel alone is prescribed within its licensed indications.

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 Health and Clinical Excellence (NICE). Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events. London (UK): National Institute for Health and Clinical Excellence (NICE); 2005 May. 34 p. (Technology appraisal; no. 90).

ADAPTATION

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

DATE RELEASED

2005 May

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

Appraisal Committee Members: Dr Sunil Angris, General Practitioner, Waterhouses Medical Practice, Staffordshire; Dr Jane Adam, Radiologist, St George's Hospital, London; Professor David Barnett (*Chair*) Professor of Clinical Pharmacology, University of Leicester; Professor Stirling Bryan, Professor of Health Economics, Health Economics Facility, Health Services Management Centre, University of Birmingham; Professor John Cairns, Professor of Health Economics, Health Economics Research Unit, University of Aberdeen; Professor David Chadwick, Professor of Neurology, Department of Neurological Science, Walton Centre for Neurology & Neurosurgery, Liverpool; Dr Lorna Duggan, Consultant Forensic Psychiatrist in Developmental Disabilities, St Andrew's Hospital, Northampton; Mrs Fiona Duncan, Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool; Dr Paul Ewings, Statistician, Taunton & Somerset NHS Trust, Taunton; Dr Trevor Gibbs, Industry Representative, Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford; Mr Sanjay Gupta, Stroke Services Manager, Basildon & Thurrock University Hospitals NHS Trust; Professor Philip Home (*Vice-Chair*) Professor of Diabetes Medicine, Department of Medicine, University of Newcastle upon Tyne; Dr Peter Jackson, Clinical Pharmacologist, Molecular & Clinical Pharmacology, University of Sheffield; Dr Terry John, General Practitioner, The Firs, London; Dr Mike Laker, Medical Director, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary, Newcastle-Upon-Tyne; Dr George Levvy, Lay Representative, Chief Executive, Motor Neurone Disease Association, Northampton; Professor Richard Lilford, Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham; Professor John Lumley, Honorary Consultant, The Ernest Cooke Clinic Microvascular Unit, Great Ormond Street, Bart's and the Royal London NHS Trust, Barbican, London; Dr Simon Mitchell, Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester; Dr Virginia Pearson, Chief Executive, South Petherton Hospital, South Somerset PCT; Dr Christa Roberts, Industry Representative, UK Manager Vascular Intervention, Guidant Ltd.; Dr Stephen Saltissi, Consultant Cardiologist, Royal Liverpool University Hospital; Dr Lindsay Smith, General Practitioner, Westlake Surgery, Somerset; Mr Mike Spencer, General Manager, Clinical Support Services, Cardiff and Vale NHS Trust; Dr Rod Taylor, Senior Lecturer, Department of Public Health & Epidemiology, University of Birmingham; Professor Mary Watkins, Professor of Nursing, University of Plymouth; Dr Norman Waugh, Department of Public Health, University of Aberdeen; Mrs Miranda Wheatley-Price, Lay Representative, Director of Service Development, Colon Cancer Concern, London

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 and modified-release dipyridamole in the prevention of occlusive vascular events. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2005 May. 2 p. (Technology appraisal 90). 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 and modified-release dipyridamole in the secondary prevention of occlusive vascular events. Assessment report. York (UK): Centre for Reviews and Dissemination and Centre for Health Economics; 2004 Nov. 248 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: N0838. 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 and modified-release dipyridamole in the prevention of occlusive vascular events. Understanding NICE guidance - information for people who have had an occlusive vascular event, or who have symptomatic peripheral arterial disease, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2005 May. 7 p. (Technology appraisal 90).

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: N0754. 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 summary was completed by ECRI on December 1, 2005.

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