

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis

J Greenhalgh,¹ A Bagust,¹ A Boland,¹ C Martin Saborido,¹ J Oyee,¹ M Blundell,¹ Y Dundar,¹ R Dickson,^{1*} C Proudlove² and M Fisher³

¹Liverpool Reviews and Implementation Group (LRiG), University of Liverpool, Liverpool, UK

²North West Medicines Information Centre, Pharmacy Practice Unit, Liverpool, UK

³The Institute for Cardiovascular and Medical Sciences, Liverpool Heart and Chest Hospital, Liverpool, UK

*Corresponding author



Executive summary

Health Technology Assessment 2011; Vol. 15: No. 31
DOI: 10.3310/hta15310

**Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk**



Executive summary

Background

Occlusive vascular events such as myocardial infarction (MI), ischaemic stroke and transient ischaemic attack (TIA) are the result of a reduction in blood flow associated with an artery becoming narrow or blocked through atherosclerosis and atherothrombosis. Peripheral arterial disease is the result of narrowing of the arteries that supply blood to the muscles and other tissues, usually in the lower extremities. Patients with symptomatic peripheral arterial disease (typically intermittent claudication) are at increased risk of experiencing an initial occlusive vascular event. Given the nature of the health problem, some people have multivascular disease, disease in more than one vascular bed, and appear to be at even greater risk of death, MI or stroke than those with disease in a single vascular bed. The primary objective in the treatment of all patients with a history of occlusive vascular events and peripheral arterial disease is to prevent the occurrence of new occlusive vascular events.

Objectives

This review assessed the clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole (MRD) alone or with aspirin (ASA) compared with ASA (and each other, where appropriate) in the prevention of occlusive vascular events in patients with a history of MI or ischaemic stroke/TIA, peripheral arterial disease and multivascular disease.

This review is an update of guidance Technology Appraisal No. 90 (TA90) produced by the National Institute for Health and Clinical Excellence (NICE).

Methods

Four electronic databases (EMBASE, MEDLINE, Web of Science and The Cochrane Library) were searched for randomised controlled trials (RCTs) and economic evaluations. Studies that compared clopidogrel, MRD or MRD + ASA with ASA or with each other were considered; patients with a history of MI or ischaemic stroke/TIA or established peripheral arterial disease were included. Outcomes for clinical effectiveness included MI, stroke, TIA, death and adverse events. Cost-effectiveness outcomes included incremental cost per life-years gained and incremental cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts including economic evaluations, applied inclusion criteria to relevant publications, and quality assessed the included studies. Where multiple publications of the same study were identified, data were extracted and reported as a single study. The results of the data extraction and quality assessment are summarised in structured tables and as a narrative description. For a variety of clinical effectiveness outcomes, indirect analysis (using a mixed-treatment comparison methodology) was performed. Using data provided by the manufacturer of clopidogrel, within-trial time to event rates were explored, as was the clinical effectiveness of clopidogrel compared with ASA for patients with multivascular disease.

Results of the literature review

Four good-quality RCTs were identified. Two were included in the previous guidance [CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) and ESPS-2 (Second European Stroke Prevention Study)] and two were more recently published [ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) and PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes)]. Interventions and patient populations differed: CAPRIE compared clopidogrel with ASA in patients with MI, ischaemic stroke or peripheral arterial disease; ESPS-2 compared MRD + ASA with ASA, MRD alone and placebo in patients with ischaemic stroke/TIA; ESPRIT compared MRD + ASA with ASA in patients with ischaemic stroke/TIA; and PRoFESS compared clopidogrel with MRD + ASA in patients with ischaemic stroke.

Eleven economic evaluations were identified from 34 publications. Four described a UK population.

Summary of benefits and risks

In CAPRIE, statistically significant outcomes in favour of clopidogrel were noted for the primary outcome (first occurrence of ischaemic stroke, MI or vascular death) compared with ASA (overall population). This benefit was small; the boundaries of the confidence intervals (CIs) raise the possibility that clopidogrel is not more beneficial than ASA. In ESPS-2, statistically significant differences in favour of MRD + ASA were observed in comparison with ASA and MRD alone on the primary outcome of stroke. In ESPRIT, for the primary outcome (first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication) the risk of event occurrence was statistically significantly lower in the MRD + ASA arm than in the ASA arm. For PRoFESS (a non-inferiority trial) the null hypothesis that MRD + ASA is inferior to clopidogrel could not be rejected. Across trials, no unexpected adverse events were identified.

The mixed-treatment comparisons for the ischaemic stroke/TIA populations supported the main RCT results and indicated that clopidogrel and MRD + ASA were significantly associated with a lower risk of recurrent stroke than was ASA; the risk of any recurrent stroke was statistically significantly increased for MRD alone compared with clopidogrel and MRD + ASA; and clopidogrel was associated with fewer major bleeding events than ASA. Caveats apply to the mixed-treatment comparisons because of the limited outcomes that were available for selection, the small number of trials and the use of data from subgroups from one trial. These analyses necessarily included a proportion of patients with multivascular disease.

A re-analysis of outcomes from CAPRIE (no data were available for other trials) according to disease status (coronary artery disease/MI only, ischaemic stroke/TIA only, peripheral arterial disease only or multivascular disease) supported the notion of patients with multivascular disease as an important clinical subgroup with elevated single and composite risks of future events.

The results of the literature review of cost-effectiveness evidence indicated that the use of clopidogrel in patients with previous peripheral arterial disease, ischaemic stroke or MI is a cost-effective option compared with ASA in the secondary prevention of occlusive vascular events. The combination of MRD + ASA appeared cost-effective compared with any other treatment in patients with previous ischaemic stroke/TIA in the secondary prevention of occlusive vascular

events. The data are limited as the clinical data have now been superseded by new trial data. The methods used to demonstrate clinical effectiveness in some of the evaluations lacked detail and clarity.

Summary of the Assessment Group's cost-effectiveness results

The two economic evaluations submitted by the manufacturers met the NICE reference case criteria. However, both submitted models used unreliable bases for long-term projection; thus, estimated incidence rates were volatile and could not be relied on to drive the major part of the model calculations. The availability of a lower priced generic clopidogrel renders the estimated incremental cost-effectiveness ratios (ICERs) inapplicable.

The Assessment Group's economic model was designed to explore which treatment strategy is most cost-effective in avoiding future occlusive vascular events in each of the four specified populations, and how the availability of cheaper generic clopidogrel affects the assessment of cost-effectiveness of clopidogrel-containing treatment strategies.

Patients with ischaemic stroke/TIA:

- In all scenarios, the most cost-effective strategy began with generic clopidogrel, followed by MRD + ASA and then ASA.
- In patients who are intolerant of ASA, compared with no treatment, clopidogrel followed by MRD is the most cost-effective approach, independent of both the TA90 guidance and the price of clopidogrel.
- In patients who are intolerant of MRD, the preferred strategy at the branded price is ASA followed by clopidogrel, but, for the generic price, clopidogrel followed by ASA is more cost-effective.
- For patients intolerant to both ASA and MRD, only clopidogrel is available for long-term prevention and is seen to be more cost-effective than no preventive therapy.

Patients with MI:

- In all scenarios, the incremental cost-effectiveness of allowing clopidogrel as a subsequent therapy after failure of ASA therapy compared with ASA treatment alone is < £9000 per QALY gained, suggesting that ASA followed by clopidogrel may be the optimal strategy for this patient group.
- In patients who are intolerant of ASA, clopidogrel is a cost-effective approach independent of both TA90 guidance and the price of clopidogrel (ICERs ranging between £1961 and £12,391 per QALY gained).

Patients with established peripheral arterial disease:

- In all scenarios, the ICER for a strategy of clopidogrel followed by ASA when compared with ASA followed by clopidogrel appeared to be well within the range considered cost-effective (under £13,000 per QALY gained for branded clopidogrel and under £5000 per QALY for generic clopidogrel), suggesting this as the optimal strategy for this patient group.
- In patients who are intolerant to ASA, clopidogrel is a cost-effective approach, independent of both the TA90 guidance and the price of clopidogrel.

Patients with multivascular disease:

- In all scenarios, the incremental cost-effectiveness of clopidogrel followed by ASA is the most cost-effective approach, independent of both the TA90 guidance and the price of clopidogrel.
- In patients who are intolerant to ASA, clopidogrel is a cost-effective approach to occlusive vascular event prevention independent of both the TA90 guidance and the price of clopidogrel.

Sensitivity analyses

The sensitivity analyses undertaken using the de novo economic model allow the most likely sources of influential uncertainty to be identified. First, there is no indication that cost and utility parameters, population characteristics or non-vascular mortality give rise to significant uncertainty in economic results. Second, three types of parameter are implicated in at least one of the sensitivity analyses as likely to be influential on model results – the risk of events occurring, the fatality of such events and the likelihood that patients will cease taking the prescribed preventive medications. Third, model results for the ‘peripheral arterial disease-only’ population appear to be particularly vulnerable to uncertainty in event risks, which were addressed and confirmed probabilistically.

Discussion

This review is based on four trials, two included in the previously published NICE guidance (CAPRIE and ESPS-2) and two more recent and relevant trials (ESPRIT and PRoFESS). The clinical evidence suggests that MRD + ASA is preferred to MRD alone and ASA in patients with a prior history of ischaemic stroke/TIA. There is not enough clinical evidence to make an informed decision regarding the use of MRD + ASA versus clopidogrel in patients with a prior history of ischaemic stroke/TIA.

All trials relevant to the decision problem were of good quality. However, they were disparate in terms of their design, patient populations, interventions and definition/reporting of outcomes (clinical and safety), which means it is difficult to compare outcomes across the trials or to perform evidence synthesis with any confidence.

In an effort to make best use of all of the available clinical information, we undertook a mixed-treatment comparison and investigated outcomes, where possible, for the ischaemic stroke/TIA population, and concluded that there were no major differences in the results of the mixed-treatment comparison and the direct estimates from head-to-head trials.

Additional data provided by the manufacturer allowed the Assessment Group to consider the clinical effectiveness and cost-effectiveness of clopidogrel in patients with multivascular disease. The Assessment Group noted that there are differences in the published definitions of multivascular disease and that these differences may significantly affect the results of clinical and economic analyses.

The results of the Assessment Group’s de novo economic model demonstrate that for patients with ischaemic stroke/TIA, the use of generic clopidogrel, followed by MRD + ASA and ASA, appears to be a cost-effective approach in preventing future occlusive vascular events; for patients with MI, ASA followed by clopidogrel appears to be a cost-effective approach to the prevention

of future occlusive vascular events; for patients with established peripheral arterial disease or multivascular disease, clopidogrel followed by ASA appears to be a cost-effective approach to the prevention of future occlusive vascular events.

Strengths and limitations

We were able to consider the clinical effectiveness and cost-effectiveness of clopidogrel in people with multivascular disease using information provided by the manufacturer. We re-analysed data from the CAPRIE trial and estimated the clinical effectiveness and cost-effectiveness of clopidogrel in this clinically important subgroup of patients. We confirmed the findings of other published clinical papers that patients with multivascular disease are often at high risk of future composite and single clinical events.

Second, we considered the long-term costs and benefits associated with clopidogrel and MRD using treatment scenarios. This approach reflects the real world, as many patients will need to switch between different treatments during their lifetime. Restricting the analysis of costs and benefits of long-term prophylaxis to a few years frequently results in erroneous conclusions.

The structure of the economic model required to address the questions posed in the final scope issued by NICE necessitated careful planning and execution, as well as access to further analyses of clinical data from the manufacturers. We were able to make the best use of limited evidence and estimate relevant ICERs for individual patient populations using an economic model designed to minimise the scope for multiple cumulative bias inherent in long-term projection of multiple competing risks.

The clinical effectiveness and cost-effectiveness findings of the report were limited by the available evidence. For the MI, peripheral arterial disease and multivascular disease patient populations, data were available only from CAPRIE (clopidogrel vs ASA) and the clinical results favoured clopidogrel. Using a single trial to generate clinical evidence for three individual patient populations will attract criticism. It is also important to note that the CAPRIE trial did not distinguish between patients with non-ST-segment elevated MI and those with ST-segment elevated MI, inhibiting the interpretation of the trial results for these subgroups of patients. For the ischaemic stroke/TIA population, the four available studies were all very different in terms of design, patient populations and clinical outcomes, so that even indirect comparisons proved to be fraught with difficulty. The key comparison of interest for patients with ischaemic stroke/TIA was clopidogrel versus MRD + ASA and the results of this trial were inconclusive. In summary, the clinical evidence available, particularly for MI, peripheral arterial disease and multivascular disease populations, to answer the key questions set out in the final scope is limited.

Uncertainties

The findings of this report for the MI, peripheral arterial disease and multivascular disease patient populations rely on several post hoc subgroup analyses from a single trial; this means that there is inevitable uncertainty associated with these findings. The Appraisal Committee that developed the guidance for TA90 considered it inappropriate to rely on post hoc analyses. However, in this case, reliance on the results of post hoc subgroup analyses from a single trial was unavoidable if the questions set out in the final scope issued by NICE were to be adequately addressed in this report. There were clinical data available from PROfESS, ESPS-2 and ESPRIT for the ischaemic stroke/TIA population, but the only clinical data available for patients with prior MI, peripheral arterial disease and multivascular disease were from the CAPRIE trial. Patients with MI, peripheral arterial disease and multivascular disease are not considered to constitute a single homogeneous clinical population; this means that use of subgroup analysis to estimate the clinical effectiveness and cost-effectiveness of clopidogrel for these individual subpopulations, although not ideal, is necessary. It is important to note that the size of each of the

subgroup populations is considerable (MI 5741, peripheral arterial disease 3713, multivascular disease 4991), and proved sufficient to demonstrate important differences in risk profiles between these groups.

In the absence of any universally agreed definition, the multivascular disease subgroup analyses were based on a population defined using the broadest definition described in the published literature. However, any differences in definitions of multivascular disease subgroups could lead to differences in patient numbers and relative risks.

Additionally, the head-to-head trials and the mixed-treatment comparison results will have included subgroups of patients who had disease in more than one vascular bed, as none of the trials distinguished between patients with single and multivascular disease.

Conclusions

A cost-effective approach to the prevention of future occlusive vascular events appears to be as follows:

- for patients with ischaemic stroke/TIA, 'generic clopidogrel, followed by MRD + ASA followed by ASA'
- for patients with MI, 'ASA followed by clopidogrel'
- for patients with established peripheral arterial disease or multivascular disease, 'clopidogrel followed by ASA'

Suggested research

Future trials in this area should distinguish between patients with single and multivascular disease; also, definitions of multivascular disease should be pre-specified (ideally using a common standard) and trialists should ensure that trials are sufficiently powered over an extended follow-up period to allow detection of treatment differences between subgroups of patients. All trial outcomes need to be reported consistently and at key time points.

It would be most valuable to have well audited data on a defined patient group from a long-term clinical registry of all UK patients treated with antiplatelet agents. Such a data source could provide a basis for research and audit to inform future assessments of antiplatelet agents in patients with single and multivascular disease over the long term.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Publication

Greenhalgh J, Bagust A, Boland A, Martin Saborido C, Oyee J, Blundell M, *et al.* Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis. *Health Technol Assess* 2011;15(31).

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 08/97/01. The protocol was agreed in August 2009. The assessment report began editorial review in May 2010 and was accepted for publication in December 2010. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley CBE
Series Editors: Dr Martin Ashton-Key, Professor Aileen Clarke, Dr Tom Marshall, Professor John Powell, Dr Rob Riemsmas and Professor Ken Stein
Associate Editor: Dr Peter Davidson
Editorial Contact: edit@southampton.ac.uk

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

© Queen's Printer and Controller of HMSO 2011. This work was produced by Greenhalgh *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (<http://www.publicationethics.org/>).

This journal may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.