

Prasugrel (Efient®) with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182): systematic review and economic analysis

Janette Greenhalgh,^{1*} Adrian Bagust,¹
Angela Boland,¹ Kerry Dwan,¹ Sophie Beale,¹
Nigel Fleeman,¹ Joanne McEntee,² Yenel Dundar,¹
Marty Richardson¹ and Michael Fisher³

¹Liverpool Reviews and Implementation Group, University of Liverpool, Liverpool, UK

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

³The Institute for Cardiovascular Medicine and Science, Liverpool Heart and Chest Hospital, Liverpool, UK

*Corresponding author

Declared competing interests of authors: Michael Fisher has received consultancy fees from Daiichi Sankyo Company Ltd.

Published April 2015

DOI: 10.3310/hta19290

Scientific summary

Prasugrel (Efient®) with PCI for ACSs (review of TA182)

Health Technology Assessment 2015; Vol. 19: No. 29

DOI: 10.3310/hta19290

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Acute coronary syndromes (ACSs) are life-threatening conditions associated with acute myocardial ischaemia with or without infarction. These conditions usually result from a reduction in blood flow associated with a coronary artery becoming narrow or blocked through atherosclerosis (an accumulation of plaque containing fatty deposits or, less commonly, erosion of the endothelium) and atherothrombosis (a blood clot formed following the rupture of plaque).

There are three main types of ACS diagnosed by clinical history, electrocardiograph (ECG) and levels of cardiac enzymes: (1) ST segment elevation myocardial infarction (STEMI), (2) non-ST segment elevation myocardial infarction (NSTEMI) and (3) unstable angina (UA). A diagnosis of STEMI indicates that the affected artery is completely occluded, resulting in progressive necrosis of the area of heart muscle dependent on its blood supply. The most common cause of a STEMI is complete and persistent occlusion of a coronary artery by a blood clot (thrombus). A diagnosis of NSTEMI indicates partial or temporary blocking of an artery with limited tissue damage. In the case of UA, the clinical history suggests cardiac ischaemia, but without tissue death.

One treatment for ACS is percutaneous coronary intervention (PCI), also known as coronary angioplasty. Antiplatelet therapy is an established adjunct to PCI both before and for up to 12 months after the procedure. All PCI procedures include adjunctive treatment with antiplatelet drugs. The purpose of antiplatelet treatment is to inhibit the aggregation of platelets that can lead to thrombus formation and further vascular events. Dual therapy [aspirin plus either prasugrel (Efient®, Daiichi Sankyo Company Ltd UK/Eli Lilly and Company Ltd), clopidogrel or ticagrelor (Brilique®, AstraZeneca)] is the standard antiplatelet treatment in clinical practice in the UK. The antiplatelet drug prasugrel is the focus of this review.

Objectives

The remit of this update is to appraise the clinical effectiveness and cost-effectiveness of prasugrel within its licensed indication for the treatment of ACS with PCI and is a review of National Institute for Health and Care Excellence (NICE) technology appraisal TA182.

Methods

Four electronic databases were searched for randomised controlled trials (RCTs) and economic evaluations. Studies that compared prasugrel with clopidogrel or ticagrelor were considered in order to identify patients with ACS who were to be treated with PCI. Outcomes for clinical effectiveness included non-fatal and fatal cardiovascular (CV) events, mortality from any cause, atherothrombotic events, incidence of revascularisation procedures, adverse effects of treatment (including bleeding events) and health-related quality of life (HRQoL). For the assessment of cost-effectiveness, outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts, applied inclusion criteria to relevant publications and quality assessed the included studies. The results of the data extraction and quality assessment were summarised in structured tables and as a narrative description. No meta-analysis or network meta-analyses were undertaken.

Results

One good-quality RCT was identified for inclusion in the clinical review. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial compared prasugrel with clopidogrel in patients with ACS who were scheduled for PCI. No relevant economic evaluations were identified.

Summary of risks and benefits

This review focused on the health outcomes of the subgroup of patients discussed in TA182 and for whom the full dose of prasugrel is licensed, namely the core clinical cohort [i.e. patients without a history of transient ischaemic attack (TIA) or stroke, those with body weight of > 60 kg or those aged < 75 years]. For the primary composite end point of death from CV causes, non-fatal MI or non-fatal stroke, statistically significantly fewer events were recorded in the prasugrel arm (8.3%) than in the clopidogrel arm (11%) [hazard ratio (HR) = 0.74, 95% confidence interval (CI) 0.66 to 0.84; $p < 0.0001$]. No statistically significant difference in non-coronary artery bypass grafting (CABG)-related TIMI (thrombolysis in myocardial infarction) major bleeding was noted between the patients in the prasugrel and clopidogrel arms. However, there was a significant difference in favour of clopidogrel when major and minor bleeding events were combined (3.0% vs. 3.9%) (HR = 1.26, 95% CI 1.02 to 1.57; $p = 0.03$). The analysis of the net clinical benefit outcome (death from any cause, non-fatal MI, non-fatal stroke or non-CABG-related non-fatal TIMI major bleeding) favoured the use of prasugrel (12.5% in the clopidogrel group vs. 10.2% in the prasugrel group; HR = 0.80, 95% CI 0.71 to 0.89; $p < 0.001$). No conclusions could be drawn about the HRQoL of patients treated with prasugrel or clopidogrel owing to small numbers of trial respondents. In the absence of any direct trial evidence, no conclusions could be drawn about the comparative efficacy or safety of prasugrel and ticagrelor.

Summary of the assessment group's cost-effectiveness results

The economic evaluation submitted by the manufacturer met the NICE reference case criteria. However, the assessment group (AG) developed its own economic model for the following reasons: (1) the long-term model phase in the manufacturer's submitted economic model was considered to be unsatisfactory and potentially not sufficiently reliable to generate a realistic representation of 39 years of follow-up; (2) the manufacturer's decision model projects long-term (2–40 years) costs and outcomes solely in terms of mortality hazard rates fixed after 1 year, and takes no account of the effects of accumulating experience of CV events and disability; (3) the AG considered it appropriate to develop an economic model using the most reliable clinical evidence available and, therefore, preferred to use 3-year clinical data from the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial instead of 15-month data from the TRITON-TIMI 38 trial; and (4) to fulfil the remit stated by NICE and to review fully the guidance for prasugrel issued in TA182, the AG was required to compare four patient subgroups. The structure of the decision model submitted by the manufacturer did not readily facilitate modelling these four subgroups in terms of cost-effectiveness.

Independent economic model

The AG's decision model assessed four mutually exclusive subgroups of the core clinical cohort:

- ACS patients treated with PCI for STEMI and with diagnosed diabetes mellitus
- ACS patients treated with PCI for STEMI and without diagnosed diabetes mellitus
- ACS patients treated with PCI for UA or NSTEMI and with diagnosed diabetes mellitus
- ACS patients treated with PCI for UA or NSTEMI and without diagnosed diabetes mellitus.

The results of both the deterministic and probabilistic analyses confirmed that it appears likely that, for all four subgroups, within 5–10 years, prasugrel is a cost-effective treatment option when compared with clopidogrel at a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained. At the full 40-year time horizon, all estimated incremental cost-effectiveness ratios (ICERs) are less than £10,000 per QALY gained, indicating confidence in this interpretation of the available evidence.

Discussion

The remit of this review was to update the evidence underpinning TA182 NICE guidance for the use of prasugrel in the NHS. In TA182, only one RCT (TRITON-TIMI 38) compared prasugrel with clopidogrel in patients presenting with ACS who were intended to undergo treatment with PCI. No new trials were identified for inclusion in this update since the appraisal of prasugrel in 2009; this means that the present review is largely based on the clinical evidence available for TA182.

Clinical effectiveness

This review focused on the health outcomes of the subgroup of patients discussed in TA182 and for whom the full dose of prasugrel is licensed. In the core clinical cohort, all non-bleeding clinical outcomes of the TRITON-TIMI 38 trial favoured the use of prasugrel compared with clopidogrel. These findings held for the 15 months of trial follow-up and across subgroups of patients including those with STEMI and UANSTEMI. There was a statistically significant difference in event rates in favour of clopidogrel when major and minor bleeding rates were combined.

A clinical comparison of prasugrel with ticagrelor was not carried out by the AG (or the manufacturer of prasugrel). There were two reasons for this. First, there was no direct RCT evidence comparing prasugrel with ticagrelor; and, second, it was not possible to conduct an indirect comparison as there were irreconcilable differences between the two pivotal trials [including timing and dosing of clopidogrel and assessment of myocardial infarction (MI)]. Thus, the effectiveness and safety of prasugrel compared with ticagrelor remains unknown.

Cost-effectiveness

In the AG's independent economic model, the outcomes of the TRITON-TIMI 38 trial population were simulated as four mutually exclusive subgroups: (1) STEMI without diabetes mellitus, (2) STEMI with diabetes mellitus, (3) NSTEMI without diabetes mellitus and (4) NSTEMI with diabetes mellitus. This approach has allowed the AG to reconsider the strength of evidence underlying the previous NICE guidance, which excluded patients from treatment with prasugrel if they had not suffered a STEMI event, or had not been diagnosed with diabetes. The new model confirmed that, using a £20,000 to £30,000 per QALY gained threshold, within 5–10 years, it appears likely that prasugrel is a cost-effective treatment option when compared with clopidogrel for all four subgroups.

Strengths and limitations of the assessment

The main strength of this review is that, despite some remaining areas of uncertainty, the case for prasugrel compared with clopidogrel appears to have been strengthened. The results of the AG's independent economic model confirm the cost-effectiveness of prasugrel compared with clopidogrel, at a threshold of £20,000 to £30,000 per QALY gained, for key groups of patients with ACS who are to be treated with PCI. The structure of the AG's model differs from the model developed by the manufacturer in that it uses the most up-to-date clinical evidence available (from the CAPRIE trial) and compares four key patient subgroups. A particular strength of the AG's economic model is that it provides assessments at specific time periods within the modelled time horizon of 40 years.

Both the AG and the manufacturer demonstrate the cost-effectiveness of prasugrel compared with clopidogrel at a threshold of £20,000 to £30,000 per QALY gained. However, the AG acknowledges that any long-term modelling exercise is vulnerable to major assumptions about the continuation of early health outcome gains and it is noted that both the manufacturer's and the AG's models rely on extrapolating relatively short-term results from beyond the end of the trial to a further 40 years.

A key strength of the review is that the AG has been able to reassess the cost-effectiveness of prasugrel compared with clopidogrel using the generic price of clopidogrel in an independent economic model.

Uncertainties

The three areas of uncertainty noted by the Appraisal Committee for TA182 were reconsidered in this review. These centred on the generalisability of the TRITON-TIMI 38 trial results to patients in clinical practice in the UK. The AG is of the opinion that the clinical evidence for the equivalence of a 300-mg loading dose of clopidogrel (administered in TRITON-TIMI 38) with a 600-mg loading dose (often given in clinical practice in the UK) remains uncertain. Similarly, the AG considers that the importance of timing of the administration of the loading dose of clopidogrel on patient outcomes remains unresolved and differs between the TRITON-TIMI 38 trial and clinical practice in the NHS in England and Wales. The AG considers that the case for the effectiveness of prasugrel compared with clopidogrel in preventing MIs of all types and sizes appears to be robust.

A clinical comparison of prasugrel with ticagrelor was not carried out by the AG (or the manufacturer of prasugrel, Daiichi Sankyo Company Ltd UK/Eli Lilly and Company Ltd). Thus, the comparative effectiveness and safety of prasugrel compared with ticagrelor remain unknown.

Conclusions

Suggested research priorities

It would be most valuable to have well-audited data on defined ACS patient groups from a long-term clinical registry of all UK patients receiving prasugrel, ticagrelor and clopidogrel and who are treated with a PCI. Such a data source could provide a basis for research and audit to inform future assessments of these antiplatelet treatments.

It is suggested that any future trials in this area should focus on the comparison of prasugrel with ticagrelor and recruit patients with ACS who are to be treated with a PCI. It is anticipated that the results of the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial, if it is conducted well, could fill the current gap in evidence related to the comparative efficacy and safety of prasugrel compared with ticagrelor.

Study registration

This study is registered as PROSPERO CRD42013005047.

Funding

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

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

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

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) 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 reviewers 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.

HTA programme

The 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 journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: <http://www.nets.nihr.ac.uk/programmes/hta>

This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 12/62/01. The protocol was agreed in June 2013. The assessment report began editorial review in January 2014 and was accepted for publication in May 2014. 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 reviewers 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.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

© Queen's Printer and Controller of HMSO 2015. This work was produced by Greenhalgh *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) 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: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Editor-in-Chief of *Health Technology Assessment* and NIHR Journals Library

Professor Tom Walley Director, NIHR Evaluation, Trials and Studies and Director of the HTA Programme, UK

NIHR Journals Library Editors

Professor Ken Stein Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Professor Aileen Clarke Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson Director of NETSCC, HTA, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Professor Elaine McColl Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Health Sciences Research, Faculty of Education, University of Winchester, UK

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Please visit the website for a list of members of the NIHR Journals Library Board:
www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: nihredit@southampton.ac.uk