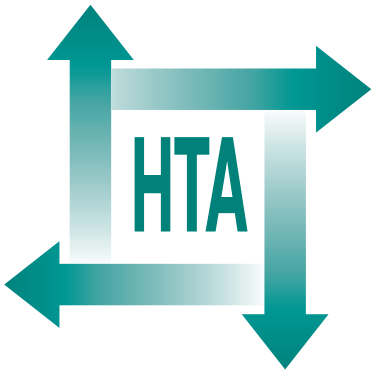
Health Technology Assessment 2004; Vol. 8: No. 40

Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation

C Main, S Palmer, S Griffin, L Jones, V Orton, M Sculpher, R Henderson, C Sudlow, N Hawkins and R Riemsma

October 2004

Health Technology Assessment
NHS R&D HTA Programme



How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation

C Main,[1*] S Palmer,[2] S Griffin,[2] L Jones,[1] V Orton,[1] M Sculpher,[2] R Henderson,[3] C Sudlow,[4] N Hawkins[2] and R Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, UK
[2] Centre for Health Economics, University of York, UK
[3] Nottingham City Hospital, UK
[4] University of Edinburgh, UK

* Corresponding author

Declared competing interests of authors: Cathie Sudlow has previously received an educational grant for presenting a paper at a conference sponsored by Sanofi Synthelabo. Rob Riemsma is a member of the editorial board for *Health Technology Assessment*, although he was not involved in the editorial process for this report.

Published October 2004

This report should be referenced as follows:

Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al*. Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation. *Health Technol Assess* 2004;**8**(40).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned 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 monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 02/24/02. 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, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation

C Main,[1*] S Palmer,[2] S Griffin,[2] L Jones,[1] V Orton,[1] M Sculpher,[2] R Henderson,[3] C Sudlow,[4] N Hawkins[2] and R Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, UK
[2] Centre for Health Economics, University of York, UK
[3] Nottingham City Hospital, UK
[4] University of Edinburgh, UK
* Corresponding author

Objectives: To review systematically the clinical effectiveness and the cost-effectiveness of clopidogrel used in combination with standard therapy including aspirin, compared with standard therapy alone for the treatment of non-ST-segment elevation acute coronary syndromes (ACS).
Data sources: Electronic databases. Manufacturers' submissions.
Review methods: Studies were selected using rigorous criteria. The quality of randomised controlled trials (RCTs) was assessed according to criteria based on NHS CRD Report No. 4, and the quality of systematic reviews was assessed according to the guidelines for the Database of Reviews of Effect (DARE) criteria. The quality of economic evaluations was assessed according to a specifically tailored checklist. The clinical effectiveness and cost-effectiveness of clopidogrel in combination with standard therapy compared with standard therapy alone were synthesised through a narrative review with full tabulation of the results of the included studies. In the economic evaluations, a cost-effectiveness model was constructed using the best available evidence to determine cost-effectiveness in a UK setting.
Results: One RCT (the CURE trial) was a randomised, double-blind, placebo-controlled trial of high quality and showed that clopidogrel in addition to aspirin was significantly more effective than placebo plus aspirin in patients with non-ST-segment elevation ACS for the composite outcome of death from cardiovascular causes, non-fatal mycardial infarction or stroke over the 9-month treatment period. However, clopidogrel was associated with a significantly higher number of episodes of both major and minor bleeding. The results from the five systematic reviews that assessed the adverse events associated with long-term aspirin use showed that aspirin was associated with a significantly higher incidence of haemorrhagic stroke, extracranial haemorrhage and gastrointestinal haemorrhage compared with placebo. Of the cost-effectiveness evidence reviewed, only the manufacturer's submission was considered relevant from the perspective of the 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. This model indicated that clopidogrel appears cost-effective compared with standard care alone in patients with non-ST-elevation ACS as long as the NHS is willing to pay £6078 per quality of life year (QALY). The results were most sensitive to the inclusion of additional strategies that assessed alternative treatment durations with clopidogrel. Although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk.
Conclusions: The results of the CURE trial indicate that clopidogrel in combination with aspirin was significantly more effective than placebo combined with

aspirin in a wide range of patients with ACS. This benefit was largely related to a reduction in Q-wave myocardial infarction. There was no statistically significant benefit in relation to mortality. The trial data suggested that a substantial part of the benefit derived from clopidogrel is achieved by 3 months, with a further small benefit over the remaining 9 months of chronic treatment. The results from the base-case model suggest that treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 12 months, compared with standard therapy alone, is cost-effective in non-ST elevation ACS patients as long as the health service is willing to pay £6078 per additional QALY. However, although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk. To estimate the exact length of time that clopidogrel in addition to standard therapy should be prescribed for patients with non-ST-segment ACS would require a prospective trial that randomised patients to various durations of therapy. This would accurately assess whether a 'rebound' phenomenon occurs in patients if clopidogrel were stopped after 3 months of treatment.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Absolute risk reduction (ARR) The difference between the event rates in two groups; where the adverse event rate is less in the intervention group, this suggests that the intervention is beneficial.

Acetylsalicylic acid (ASA) Also called aspirin.

Acute coronary syndromes (ACS) Severe symptomatic coronary artery disease including unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI).

Agonist A drug that both binds to receptors and has an intrinsic effect; a drug that triggers an action from a cell.

Angina pectoris Pain in the chest due to lack of blood-borne oxygen supplying the heart muscle; it is usually induced by exercise and relieved by rest.

Angioplasty A procedure in which a small balloon on the end of a catheter is inserted into an artery (in coronary heart disease the coronary arteries) and inflated to widen a narrowed artery; also; percutaneous transluminal coronary angioplasty (PTCA).

Ankle brachial pressure index The ratio of ankle to brachial systolic pressure, used to diagnose peripheral arterial disease.

Antagonist A drug that nullifies the effect of another drug.

Antiplatelet agent Type of anticlotting agent that works by inhibiting blood platelets. Antiplatelet drugs include clopidogrel, dipyridamole and ASA.

Atheroma Organised lipids and platelets deposited in the wall of medium and larger-sized arteries, causing a narrowing of the artery.

Atherosclerosis A major disease of the arteries. Deposition of organised lipid and platelets at the arterial wall forming atheromatous plaques. These may narrow the lumen, reducing blood flow and the elasticity of the blood vessels. Hypertension, diabetes, high levels of cholesterol in the blood and cigarette smoking are the major established risk factors for atherosclerosis.

Atherothrombosis Atherothombosis classified by thrombosis superimposed on an atheromatous plaque is the pathophysiological disease process underlying most ischaemic vascular events. It is characterised by a sudden (unpredictable) atherosclerotic plaque disruption (rupture, fissuring or erosion) leading to platelet activation and thrombus formation.

Bias Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth.

Blinding A procedure used in clinical trials to avoid the possible bias that might be introduced if the patient and/or doctor knew which treatment the patient would be receiving. If neither the patient nor the doctor is aware of which treatment has been given, the trial is termed 'double-blind'. If only one of the patient or doctor is aware, the trial is called 'single-blind'.

continued

Glossary *continued*

Cardiac catheterisation A procedure involving the introduction of a catheter into the systemic arterial or venous circulations to study the structure and function of the heart. During the procedure the patency of the coronary artery anatomy can be assessed by selective injection of radiographic dye into the coronary arteries (coronary arteriography).

Cardiovascular Pertaining to the heart and its blood vessels.

Carotid artery Blood vessel taking blood to the brain.

Central tendency The degree of clustering of the values of a statistical distribution that is usually measured by the arithmetic mean, mode or median.

Cerebrovascular Pertaining to the blood vessels of the brain.

Clopidogrel An inhibitor of platelet aggregation which acts by inhibiting adenosine diphosphate (ADP) binding to its receptor and the subsequent activation of the ADP complex.

Co-intervention In a randomised controlled trial, the application of additional diagnostic or therapeutic procedures to members of either the experimental or reference group, or to both groups.

Composite end-point A combination of several different possible outcomes or events associated with individuals in a medical investigation. In vascular medicine the most common composite end-point used is myocardial infarction, stroke or vascular death.

Confidence interval (CI) A measure of precision of statistical estimate.

Confounding (1) The masking of an actual association or (2) false demonstration of an apparent association between the study variables when no real association between them exists.

Coronary arteries The arteries that supply the heart muscle with blood.

Coronary artery bypass graft (CABG) A surgical procedure that involves replacing diseased (narrowed) coronary arteries with veins obtained from the patient's lower extremities (autologous graft).

Coronary artery disease (CAD) Gradual blockage of the coronary arteries, usually by atherosclerosis.

Coronary heart disease (CHD) Narrowing or blockage of the coronary arteries by atheroma, which can lead to angina, coronary thrombosis or heart attack, heart failure and/or sudden death.

Cost–benefit analysis An attempt to give the consequences of the alternative interventions a monetary value. In this way, the consequences can be more easily compared with the costs of the intervention. This involves measuring individuals' 'willingness to pay' for given outcomes, and can be difficult.

Cost-effectiveness The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.

Cost minimisation When two alternatives are found to have equal efficacy or outcomes (consequences). Therefore, the only difference between the two is cost. This is sometimes considered a subtype of cost-effectiveness analysis.

Cost–utility analysis The consequences of alternatives are measured in 'health state preferences', which are given a weighting score. In this type of analysis, different consequences are valued in comparison with each other, and the outcomes (e.g. life-years gained) are adjusted by the weighing assigned. In this way, an attempt is made to value the quality of life associated with the outcome so that life-years gained become quality-adjusted life-years gained.

Creatine kinase myocardial band (CK-MB) A cardiac enzyme, which is a marker of damage to heart muscle and becomes raised in the serum after myocardial infarction.

Creatinine An end-point of protein metabolism found in the blood and urine, which can be used to help assess if the kidneys are working adequately.

Electrocardiogram (ECG) A recording of the electrical signals from the heart.

continued

Glossary *continued*

Embolus Material other than blood (usually a clot) that is carried through the circulation and may lodge in an artery, causing partial or total obstruction of blood flow.

End-point A clearly defined outcome or event associated with an individual in a medical investigation.

External validity The ability to generalise the results from this experiment to a larger population.

Forest plot The way in which results from a meta-analysis are often presented. Results are displayed graphically as horizontal lines representing the 95% or 99% confidence intervals of the effect of each trial (strictly the 95% or 99% CIs of a relative risk of the intervention group compared with the control group). The results of the meta-analysis are also shown in Forest plots.

GI bleeding This describes any bleeding that may occur along the course of the gastrointestinal tract.

GU bleeding This describes any bleeding that may occur as a result of bleeding in the genito-urinary tract.

Haematoma A collection of blood, usually in soft tissues.

Haematuria The finding of blood in the urine.

Haemoptysis The expectoration of blood or of blood-stained sputum.

Haemorrhage The escape of blood from the vessels; bleeding. The massive accumulation of blood within a tissue is called a haematoma.

Haemorrhagic stroke Stroke due to bleeding in the brain.

Hazard ratio Measure of relative risk used in survival studies.

Hypotension The condition of an individual's blood pressure being lower than normal.

Incidence The number of new events (new cases of a disease) in a defined population, within a specified period of time.

Infarction Death of tissue following interruption of the blood supply.

Intention-to-treat analysis method An analysis of a clinical trial where participants are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they dropped out, fully complied with the treatment or crossed over and received the other treatment.

Interim analysis A formal statistical term indicating an analysis of data partway through a study.

Intermittent claudication The most common symptom of peripheral arterial disease, characterised by calf, thigh or buttock pain and weakness brought on by walking. Pain disappears on resting the affected limb.

Internal validity The degree to which a study is logically sound and free of confounding variables.

Intravenous Pertaining to a route into the circulation via a vein.

Ischaemia A low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue.

Ischaemic heart disease (IHD) Also called coronary artery disease and coronary heart disease, this term is applied to heart ailments caused by narrowing of the coronary arteries and therefore characterised by a decreased blood supply to the heart.

Ischaemic stroke (IS) A type of stroke that is caused by blockage in a cerebral blood vessel.

Kaplan–Meier curves (also called product limit method) A non-parametric method of compiling life or survival tables, developed by Kaplan and Meier in 1958. This combines calculated probabilities of survival and estimates to allow for censored observations, which are assumed to occur randomly. The intervals are defined as ending each time an event (e.g. death, withdrawal) occurs and are therefore unequal.

Meta-analysis A quantitative method for combining the results of many studies into one set of conclusions.

continued

Glossary *continued*

Mortality rate The proportion of deaths in a population or in a specific number of the population per unit of time.

Myocardial infarction (MI) An infarction caused by obstruction of circulation (coronary artery) to a region of the heart resulting in permanent damage to an area of the heart muscle. Also called a heart attack.

Nitrates A group of medications that relieve angina pain, relax smooth muscle, dilate veins, lower blood pressure and improve blood flow through the coronary arteries.

Non-ST-segment elevation MI (NSTEMI) A myocardial infarction that is not associated with elevation of the ST segment on the ECG.

Number-needed-to-treat (NNT) In clinical treatment regimens, the number of patients with a specified condition who must follow the specified regimen for a prescribed period in order to prevent occurrence of specified complications or adverse outcomes of the condition. Mathematically equal to 1/(risk difference).

Occlusive vascular event (OVE) An event caused by the blockage of an artery, such as MI, unstable angina, ischaemic stroke, transient ischaemic attack or peripheral arterial disease.

Percutaneous coronary intervention (PCI) Broad term used to describe techniques used to relieve coronary narrowing, including percutaneous transluminal coronary angioplasty, other angioplasty and implantation of intracoronary stents.

Percutaneous revascularisation The restoration of blood supply by a procedure using equipment inserted into an artery through a skin incision.

Percutaneous transluminal cutaneous angioplasty (PTCA) Dilation of a coronary artery narrowing by means of a balloon-tipped catheter. The catheter is inserted into the circulation through the skin and advanced to the heart, where the balloon is inflated to dilate the narrowing.

Peripheral arterial disease (PAD) A condition in which the arteries that carry blood to the arms or legs become narrowed slowing or obstructing the flow of blood. Also known as peripheral vascular disease (PVD).

Phase II trial A study with a small number of patients diagnosed with the disease for which the drug is being studied. In this study, the safety of the new drug is tested. Early effectiveness data are also collected for varying doses of the drug.

Phase III trial A study with a large number of patients diagnosed with the disease for which the drug is being studied and is unlicensed for the indication. In this study, the drug is tested against a placebo or alternative treatment.

Placebo A 'dummy' treatment administered to the reference group in a controlled clinical trial in order to distinguish the specific and non-specific effects of the experimental treatment (i.e. the experimental treatment must produce better results than the placebo in order to be considered effective).

Plaque Plaque in an artery refers to deposits of atheroma in the wall of the artery caused by lipid deposition.

Platelet Platelets promote clotting by forming a plug and promoting coagulation of blood proteins.

Prevalence The measure of the proportion of people in a population who have some attribute or disease at a given point in time or during some time period.

Proportional hazards model Regression method for modelling survival times. The outcome variable is whether or not the event of interest has occurred and, if so, after what period; if not, the duration of follow-up. The model predicts that hazard or risk of the event in question at any given time.

p-Value In the context of significant tests, the *p*-value represents the probability that a given difference is observed in a study sample, when such a difference does not exist in the relevant population. Small *p*-values indicate stronger evidence to reject the null hypothesis of no difference.

Quality-adjusted life-year (QALYs) A term originally developed in cancer studies to balance poor quality of life (possibly with long life expectancy) with good quality of life (possibly with short life expectancy).

continued

Glossary *continued*

Q-wave A negative deflection at the onset of a QRS complex in an ECG. An abnormal Q-wave is one that spans 0.04 seconds or more in duration and reaches more than 25% of the amplitude of the adjacent R-wave. Abnormal Q-waves are a sign of myocardial infarction (heart attack).

Random allocation A method of allocation to ensure that the next treatment assignment is unpredictable.

Randomised controlled trial (RCT) (also randomised clinical trial) These are designed to measure the efficacy and safety of particular types of healthcare interventions, by randomly assigning people to one of two or more treatment groups and, where possible, blinding them and the investigators to the treatment that they are receiving. The outcome of interest is then compared between the treatment groups. Such studies are designed to minimise the possibility of an association due to confounding and remove the many sources of bias present in other study designs.

Refractory angina Angina that persists despite anti-ischaemic medication and/or revascularisation.

Relative risk (RR) The proportion of diseased people among those exposed to the relevant risk factor divided by the proportion of diseased people among those not exposed to the risk factor. This should be used in those cohort studies where those with and without disease are followed to observe which individuals become diseased.

Relative risk reduction (RRR) Alternative way of expressing relative risk. It is calculated as follows: RRR = (1 – RR) × 100%. The RRR can be interpreted as the proportion of the initial or baseline 'risk' which was eliminated by a given treatment or intervention, or by avoidance of exposure to a risk factor.

Revascularisation The restoration of blood supply, either naturally (e.g. after a wound) or surgically (e.g. by means of vascular graft or prosthesis).

Risk difference The difference (absolute) in the proportion with the outcome between the treatment and control groups. If the outcome represents an adverse event and the risk difference is negative (below zero) this suggests that the treatment reduces the risk – referred to as the absolute risk reduction.

Stable angina Term used for angina (pectoris), which is relatively predictable, and the intensity and frequency of which remain stable over time.

ST-elevation Elevation of the ST segment in an ECG.

Stent Metal device inserted into a coronary artery during percutaneous coronary intervention to support the vessel wall and reduce the risk of reocclusion.

Stratification The division of a population into parts known as strata, particularly for the purpose of enhancing comparability.

Stroke The sudden death of brain cells due to a lack of oxygen when the blood flow to the brain is impaired by blockage or rupture of an artery to the brain causing neurological dysfunction.

Thrombocytopenia A decrease in the number of platelets in the blood, resulting in the potential for increased bleeding and decreased ability for clotting.

Thrombolysis The mechanism by which thrombi are dissolved. Thrombolysis also refers to the lysis (dissolution) of thrombolytic agents used in the therapy of myocardial infarction.

Thrombus Blood clot. An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation.

Ticlopidine An inhibitor of platelet aggregation.

Transient ischaemic attack (TIA) A brain disorder caused by temporary disturbance of blood supply to an area of the brain, resulting in a sudden, brief (less than 24 hours, usually less than 1 hour) decrease in brain functions. If the neurological deficit lasts more than 24 hours, it is described as an ischaemic stroke.

continued

Glossary *continued*

Unstable angina Angina pectoris in which the cardiac pain has changed in pattern or is more severe or which occurs at rest.

Vascular disease Any disease of the circulatory system.

List of abbreviations

ACS	acute coronary syndromes
ADP	adenosine diphosphate
AMI	acute myocardial infarction
AR	absolute risk
ARR	absolute risk reduction
ASA	acetylsalicylic acid; also called aspirin
ATT	Antithrombotic Trialists
BNF	British National Formulary
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCU	coronary care unit
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CHDP	Coronary Heart Disease Policy
CI	confidence interval
CK-MB	creatine kinase myocardial band
CREDO	Clopidogrel for Reduction of Events During Observation
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators
CV	cardiovascular
CVD	cardiovascular disease
DARE	Database of Reviews of Effect
ECG	electrocardiogram
GI	gastrointestinal
GPA	glycoprotein IIb/IIIa inhibitor
HUI	Health Utilities Index
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease
IS	ischaemic stroke
ITT	intention-to-treat
LYG	life-years gained
MI	myocardial infarction
NHAR	Nottingham Heart Attack Register
NICE	National Institute for Clinical Excellence
NNT	number-needed-to-treat
NSAID	non-steroidal anti-inflammatory drug
NSF	National Service Framework
NSTEMI	non-ST-segment elevation myocardial infarction
OR	odds ratio
OVE	occlusive vascular event
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention

continued

List of abbreviations *continued*

PRAIS-UK	Prospective Registry of Acute Ischaemic Syndromes in the UK
PTCA	percutaneous transluminal coronary angioplasty
PVD	peripheral vascular disease
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RI	refractory ischaemia
RR	relative risk
RRR	relative risk reduction
SD	standard deviation
SLSR	South London Stroke Register
TIA	transient ischaemic attack
TIMI	Thrombosis in Myocardial Infarction
TTP	thrombotic thrombocytopenic purpura
UAP	unstable angina pectoris
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Most of the mortality and morbidity associated with non-ST-segment elevation acute coronary syndromes (ACS) arises from disruption of atheromatous plaques, followed by platelet aggregation and thrombus formation. Aspirin is the most commonly prescribed antiplatelet agent, which is known to reduce the risk of fatal and non-fatal myocardial infarction in patients with unstable angina. Clopidogrel, a different antiplatelet agent, inhibits platelet aggregation induced by adenosine diphosphate, thereby reducing ischaemic events. Combining clopidogrel with aspirin may therefore have an additive effect as each acts via a different inhibitory pathway.

Aim of the review

To review systematically the clinical effectiveness and the cost-effectiveness of clopidogrel used in combination with standard therapy including aspirin, compared with standard therapy alone for the treatment of non-ST-segment elevation ACS.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

Eleven electronic databases were searched from inception to April 2003 for the clinical effectiveness and cost-effectiveness sections. In addition, the manufacturers' submissions to the National Institute for Clinical Excellence were reviewed.

Study selection

Studies were included if they fulfilled the following criteria:

- Intervention: studies in which clopidogrel was used in combination with standard therapy (including aspirin) compared with standard therapy alone.
- Participants: individuals with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). Trials that only included participants with ACS who had undergone angioplasty were excluded.
- Outcome measures: studies that reported on cardiovascular death, myocardial infarction, stroke, refractory ischaemia, severe ischaemia, heart failure, revascularisation, unstable angina, other vascular events and death were included. Bleeding complications and haematological parameters were the adverse events assessed. Studies that reported on the quality of life and costs from all reported perspectives were also included.
- Design: randomised controlled trials (RCTs) that compared clopidogrel in combination with standard therapy, including aspirin, with standard therapy 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 considered both costs and consequences (including cost-effectiveness, cost–utility and cost–benefit analyses) were included.

Data extraction and quality assessment

Both data extraction and quality assessment were undertaken by one reviewer and independently checked by a second reviewer, with any disagreements being resolved through discussion. The quality of RCTs was assessed according to criteria based on NHS CRD Report No. 4, and the quality of systematic reviews was assessed according to the guidelines for the Database of Reviews of Effect (DARE) criteria. The quality of economic evaluations was assessed according to a checklist updated from one developed by Drummond and colleagues.

Data synthesis

The clinical effectiveness and cost-effectiveness of clopidogrel in combination with standard therapy compared with standard therapy alone were synthesised through a narrative review with full tabulation of the results of the included studies. In the economic evaluations, a cost-effectiveness model was constructed using the best available evidence to determine cost-effectiveness in a UK setting.

Results

Clinical effectiveness

One RCT (the CURE trial) was included in the review of the clinical effectiveness of clopidogrel in combination with aspirin. 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. The results of the trial showed that clopidogrel in addition to aspirin was significantly more effective than placebo plus aspirin in patients with non-ST-segment elevation ACS for the composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or stroke over the 9-month treatment period. However, clopidogrel was associated with a significantly higher number of episodes of both major and minor bleeding. The results from the systematic reviews that assessed the adverse events associated with long-term aspirin use showed that aspirin was associated with a significantly higher incidence of haemorrhagic stroke, extracranial haemorrhage and gastrointestinal haemorrhage compared with placebo.

Cost-effectiveness

The systematic literature search identified only one study that met the criteria for inclusion in the cost-effectiveness review. A separate cost-effectiveness model and accompanying report were submitted by the manufacturers (Sanofi-Synthelabo Ltd and Bristol-Myers Squibb).

Of the cost-effectiveness evidence reviewed, only the manufacturer's submission was considered relevant from the perspective of the 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. This model indicated that clopidogrel appears cost-effective compared with standard care alone in patients with non-ST-elevation ACS as long as the NHS is willing to pay £6078 per quality-adjusted life-year (QALY). The results were most sensitive to the inclusion of additional strategies which assessed alternative treatment durations with clopidogrel. Although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk.

Conclusions

Clinical effectiveness

The results of the CURE trial indicate that clopidogrel in combination with aspirin was significantly more effective than placebo combined with aspirin in a wide range of patients with ACS. This benefit was largely related to a reduction in Q-wave mycardial infarction. There was no statistically significant benefit in relation to mortality. The trial data suggested that a substantial part of the benefit derived from clopidogrel is achieved by 3 months, with a further small benefit over the remaining 9 months of chronic treatment.

Cost-effectiveness

The results from the base-case model suggest that treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 12 months, compared with standard therapy alone, is cost-effective in non-ST elevation ACS patients as long as the health service is willing to pay £6078 per additional QALY. However, although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk.

Recommendations for future research

To estimate the exact length of time that clopidogrel in addition to standard therapy should be prescribed for patients with non-ST-segment ACS would require a prospective trial that randomised patients to various durations of therapy. This would accurately assess whether a 'rebound' phenomenon occurs in patients if clopidogrel were stopped after 3 months of treatment.

Chapter 1

Aim of the review

The main aim in the short-term treatment of non-ST-segment-elevation acute coronary syndromes (ACS) is to prevent progression to full-thickness myocardial infarction (MI) or cardiovascular (CV) death. Long-term management after an episode of ACS involves management of the risk factors for further events and includes treatment with antiplatelet therapy. The most widely prescribed antiplatelet agent is aspirin [or acetylsalicylic acid (ASA)], which has been shown to reduce the risk of both fatal and non-fatal MI in patients with unstable angina.[1] This review examined the clinical and the cost-effectiveness of clopidogrel used in combination with aspirin relative to aspirin alone for the treatment of non-ST-segment elevation ACS. The review assessed clopidogrel used in combination with aspirin for both the short- and long-term treatment of ACS.

Chapter 2
Background

Description of underlying health problem

The indication covered in this report is non-ST-segment elevation ACS, which includes a range of patient groups with a broadly similar underlying pathology. Non-ST-segment elevation is distinguished from ST-segment elevation ACS by the absence of ST-segment elevation on the 12-lead electrocardiogram at presentation. Patients who are initially diagnosed as having non-ST-segment elevation ACS may, after further investigation, be labelled as having either unstable angina or non-ST-segment elevation MI (NSTEMI). NSTEMI is diagnosed when the serum level of a cardiac enzyme is elevated to a range indicating that myocardial necrosis has occurred. Patients with unstable angina or NSTEMI are at substantial risk of death or non-fatal myocardial (re-) infarction of approximately 10% within 30 days, despite the use of standard antiplatelet and antithrombotic therapy. Intravenous thrombolytic therapy which is used in the care of patients with ST-elevation ACS is not effective for non-ST-elevation cases.

At the time of presentation, it is difficult to distinguish between patients with unstable angina and those with NSTEMI, and these can usually only be differentiated after 4–16 hours when biochemical markers can be tested. A definite diagnosis is often not possible until 2–3 days after the event when the full pattern of enzyme elevation has been clarified. Most patients with non-ST-segment elevation ACS and elevated serum markers of myocardial necrosis do not develop abnormal Q-waves on the ECG, but a minority progress to non-Q-wave MI.[2] Q-wave MIs and non-Q-wave MIs differ in the extent of myocardial necrosis that they cause, with the former considered more severe than the latter.[3]

The risk of death or ischaemic complications from unstable angina is significant. One study of men aged 51–59 years showed that the 16-year survival rate was 34% for those with a history of MI, 53% for those with a history of angina and 72% for those with no history of coronary disease.[4] Although MI patients with ST-segment depression have a better early survival (5 days) than those with ST-segment elevation, their longer term mortality (6 months) may be worse.[5] In the short term, patients are routinely investigated to assess whether myocardial injury has occurred and are stratified on particular risk factors as being at high, intermediate or low risk of acute ischaemia (*Table 1*).[5,6] The 30-day risk of fatal or non-fatal MI is 12–30% in the first group, 4–8% in the second and <2% in the third group.[5] However, it has also been shown that approximately only one-third of subsequent adverse cardiovascular events occur during initial hospitalisation,[7] and the total

TABLE 1 *Risk stratification of unstable angina*

High-risk features
Prolonged (>10 minutes) ongoing chest pain/discomfort. ST elevation or depression (>0.5 mm) or deep T-wave inversion in three or more leads
Elevated serum markers of myocardial injury (especially cardiac troponin I or T)
Associated syncope
Associated heart failure, mitral regurgitation or gallop rhythm
Associated haemodynamic instability (systolic blood pressure <90 mmHg, cool peripheries, diaphoresis)
Intermediate-risk features
Prolonged but resolved chest pain/discomfort
Nocturnal pain
New onset grade III or IV chest pain in the previous 2 weeks[a]
Age >65 years
History of MI or revascularisation
ECG normal or pathological Q-waves
No significant (>0.5 mm) ST deviation, or minor T-wave inversion in fewer than three leads
Low-risk features
Increased angina frequency or severity
Angina provoked at a lower threshold
New onset angina more than 2 weeks before presentation
Normal ECG and negative serum troponin
No high or intermediate risk factors

[a] Grade III: marked limitation of ordinary physical activity. Grade IV: inability to carry out any physical activity without discomfort.

TABLE 2 *Prevalence of angina, myocardial infarction and stroke (ever and currently) by age and sex in 1998*

		Age (years)							
Sex	**CVD conditions**	**16–24 (%)**	**25–34 (%)**	**35–44 (%)**	**45–54 (%)**	**55–64 (%)**	**65–74 (%)**	**75+ (%)**	**Total (%)**
Men	**Angina**								
	Ever	–	0.1	0.7	2.8	10.5	15.6	18.3	5.3
	Currently	–	0.1	0.5	1.9	7.1	8.2	11.3	3.2
	Heart attack								
	Ever	0.1	0.2	0.5	2.7	8.4	11.6	13.5	4.2
	Currently	0.1	–	0.2	0.5	0.8	1.8	1.2	0.6
	Stroke								
	Ever	0.1	–	0.4	1.2	3.3	6.2	10.3	2.3
	Currently	–	–	–	0.2	0.8	1.4	3.4	0.6
Women	**Angina**								
	Ever	–	0.2	0.4	1.4	5.5	9.9	17.0	3.9
	Currently	–	–	0.3	1.0	3.7	6.7	10.3	2.5
	Heart attack								
	Ever	–	0.1	0.3	0.8	2.4	5.5	6.5	1.8
	Currently	–	–	–	0.1	0.7	1.0	0.8	0.3
	Stroke								
	Ever	0.4	0.4	0.6	0.7	2..2	5.0	8.8	2.1
	Currently	–	0.1	–	0.1	0.7	0.5	1.7	0.4

event rate after 8 months of observation can be as high as 57%.[8] Therefore, there is an obvious need also to reduce late cardiac events within these patient groups. This is particularly pertinent as patients with symptomatic disease in one vascular bed are also likely to have diffuse disease, placing them at risk of subsequent events in additional vascular territories.[9] The longer term management of patients therefore focuses on the modification of risk factors including diet, cigarette smoking, physical activity, blood pressure, cholesterol level, diabetes and weight control.[10] Concomitant early management can also include percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) particularly in high-risk patients, alongside additional pharmacological interventions such as antithrombin therapy, antiplatelet therapy, beta-blockers, glycoprotein IIb/IIIa antagonists or calcium channel blockers.

Epidemiology of coronary heart disease (CHD)

Statistics on the incidence and prevalence of occlusive vascular disease are difficult to collate, as the majority of sources only provide data on one or two manifestations of the disease. It is acknowledged that although cardiovascular disease (CVD) age-standardised mortality rates have been falling by about 4% per annum in the UK, these reductions are lower than in other Western countries. Approximately 10% of people in the UK have diseases of the heart and circulatory system, and this increases with age, affecting 27% of men and women aged 65–74 years and 30% of those aged ≥ 75 years.[11] Across all ages, the prevalence of ischaemic heart disease (IHD) or ischaemic stroke (IS) combined is 8–9% in men and 6% in women in England.[12] Data are given in *Table 2*

In spite of overall improvements in the mortality rate, it is apparent that these have not been experienced systematically across the social classes or ethnic groups. Death rates from heart disease among unskilled men are now three times greater than those among professional men. However, this trend is less marked for women.[13] Likewise, there are also ethnic variations in the death rate from heart disease, with this being 38% higher for men and 43% higher for women born in the Indian subcontinent than the rates for the country as a whole.[13] However, the dearth of routine data on CHD does not allow for differences in health related behaviour, such as early presentation to services and local service provision to be examined separately from the mortality rate. It is apparent that there is a geographic disparity across the regions in the prevalence of treated CHD and stroke.[14] The age-standardised rate (as a

percentage of the rate for England and Wales) for treated CHD in both males and females is highest (>110) in the North West, Yorkshire and Wales and lowest in the South East (<90). The pattern for the age-standardised rate (as a percentage of the rate for England and Wales) for treated stroke also shows a regional variation, with the rates being highest in the North West and Yorkshire (>110) and again lowest in the South East (<90).

Significance in terms of ill-health

The surveys that have examined morbidity most reliably and most frequently (the Health Survey for England, the General Household Survey and the Survey of General Practitioners) suggest that whereas mortality from CHD is falling, morbidity is not and in older age groups has risen by over one-third in the past 10 years.[11] Within Europe it has been estimated that CHD is the leading single cause of disability, accounting for 10% of total disability-adjusted life-years. The figures for England and Wales can be expected to be even higher owing to the high incidence of CHD in this region relative to the rest of Europe.[15]

Stroke has a major impact on people's lives and is the leading cause of disability in the UK and other developed countries. Recovery from stroke occurs over varying time spans; only 30% of survivors will be fully independent within 3 weeks, rising to nearly 50% by 6 months.[16] A significant proportion do not regain their independence and will require long-term care. Among stroke survivors, about 31% will require help in walking and 71% will have impairments that affect their ability to work in their previous capacity.[17]

The economic burden from CHD in terms of both direct healthcare costs and indirect costs (including informal care costs and loss of productivity) is high. It has been estimated that in 1999 CHD cost £1.73 billion to the UK health care system, £2.42 billion in 'informal care' and £2.91 billion in friction period adjusted productivity loss, with 24.1% of production losses being attributable to mortality and 75.9% to morbidity.[18] Overall, therefore, the total annual cost of all CHD-related burdens equated to £7.06 billion in 1999.

Current service provision

Estimating the current service provision and the current costs in the area of CHD and IS is difficult owing to the lack of routine data and the lack of differentiation between disease subgroups. In relation to the treatment of ACS, the International Classification of Diseases (9th revision) does not differentiate between stable and unstable angina. The number of people coded as having an AMI, but who are in fact admitted to hospital with unstable angina, is also not known. In addition to this, deaths due to ACS will often be classified as AMI. The incidence of new cases of ACS has been estimated to be about 22,600 patients per annum.[19] The 1999 NHS Executive data showed that at least 129,458 cases of angina were seen by consultants, with cost per 'finished consultant episode' ranging from £156 to £1123.[20] In terms of hospital admissions, there was one admission for unstable angina per 1000 total population per year according to the Hospital Episode Statistics.[21] However, other estimates from the UK and the USA have reported rates two to three times greater, similar to those reported for AMI.

In the UK, evidence-based treatment guidelines recommend early treatment with antiplatelet therapy, generally aspirin, for the secondary prevention of vascular events in patients with confirmed non-ST-segment elevation ACS, prior history of stroke or transient ischaemic attack (TIA), prior history of MI, stable angina, intermittent claudication, diabetes and in patients who have undergone percutaneous transluminal coronary angioplasty (PTCA) or CABG. The UK guidelines/standards for current antiplatelet therapy are summarised in Appendix 1.

The National Service Framework (NSF) for Coronary Heart Disease was introduced in 2000 to inform service provision, practice and patient management in the area of CHD.[13] The only antiplatelet drug recommended by the NSF is aspirin, which accounts for 91% of all prescribed antiplatelet drugs.[22] However, despite its wide use, aspirin is still perceived to be under-prescribed, although over-the-counter purchase may well account for a proportion of this apparent shortfall. Clopidogrel, a thienopyridine antiplatelet drug, is unrelated to aspirin and therefore can be used in patients who show a genuine intolerance or who have contraindications to aspirin. Furthermore, as the action of aspirin and clopidogrel is mediated by different inhibitory mechanisms, combining the two drugs may also have an additive effect.

Within the last 5 years, the prescribing of antiplatelet drugs has doubled, reaching 5.1 million prescription items for the quarter to December 2001. At the same time, their cost has increased 10-fold to £15.9 million.[22] Aspirin is by far the most frequently prescribed antiplatelet

drug (91% of items and 25% of cost, quarter to December 2001). Clopidogrel is used much less frequently (approximately 4% of prescription items) but accounts for 57% of antiplatelet drug costs. However, there are large variations in total spending on antiplatelet drugs across the health authorities, in particular on clopidogrel. Health authorities spending the most on antiplatelet drugs are nearly all in the North of England and have high rates of CHD.

Description of clopidogrel

It is widely accepted that atherothrombosis is a cause of occlusive vascular events (OVEs). The aims of antiplatelet therapy are therefore twofold: first, to prevent the occurrence of ischaemic events through inhibition of platelet thrombus formation, and second, to protect distal tissues through inhibition of microembolisation.[23] The clinical manifestations of atherothrombosis include TIA, IS, unstable angina, MI and intermittent claudication.[23] The importance of long-term secondary prevention is clear. For example, after a first attack of unstable angina or NSTEMI, the long-term risk of events is substantial, at about 6–8% per year for the 2 years after the index event.[24] Similarly, after a first stroke the risk of a recurrent stroke is highest in the first 6 months, but patients may remain at a greater risk of stroke than the general population for a number of years.[25] Aspirin and other oral antiplatelet agents have been shown to be protective in patients at increased risks of ischaemic vascular events.[26] Patients with symptomatic disease in one vascular bed are also likely to have diffuse disease, placing them at risk of subsequent events in additional vascular territories.[9] This is demonstrated in individuals with asymptomatic peripheral arterial disease (PAD), who are twice as likely as healthy individuals to suffer from concomitant coronary artery disease (CAD).[27] Secondary prevention of an ischaemic event in the index territory will provide primary prevention for other arterial territories that are still clinically silent.

Atherothrombosis involves the formation of a platelet-rich thrombus at the site of a disrupted atherosclerotic plaque, which can lead to local occlusion or distal embolism. Atherosclerotic plaque formation occurs as a result of damage to vascular endothelium. When a plaque ruptures, platelets circulating in the blood are exposed to a variety of thrombogenic factors. *Figure 1* shows the various pathways which mediate thrombus formation. The oral antiplatelet agents currently available target one or more of these pathways

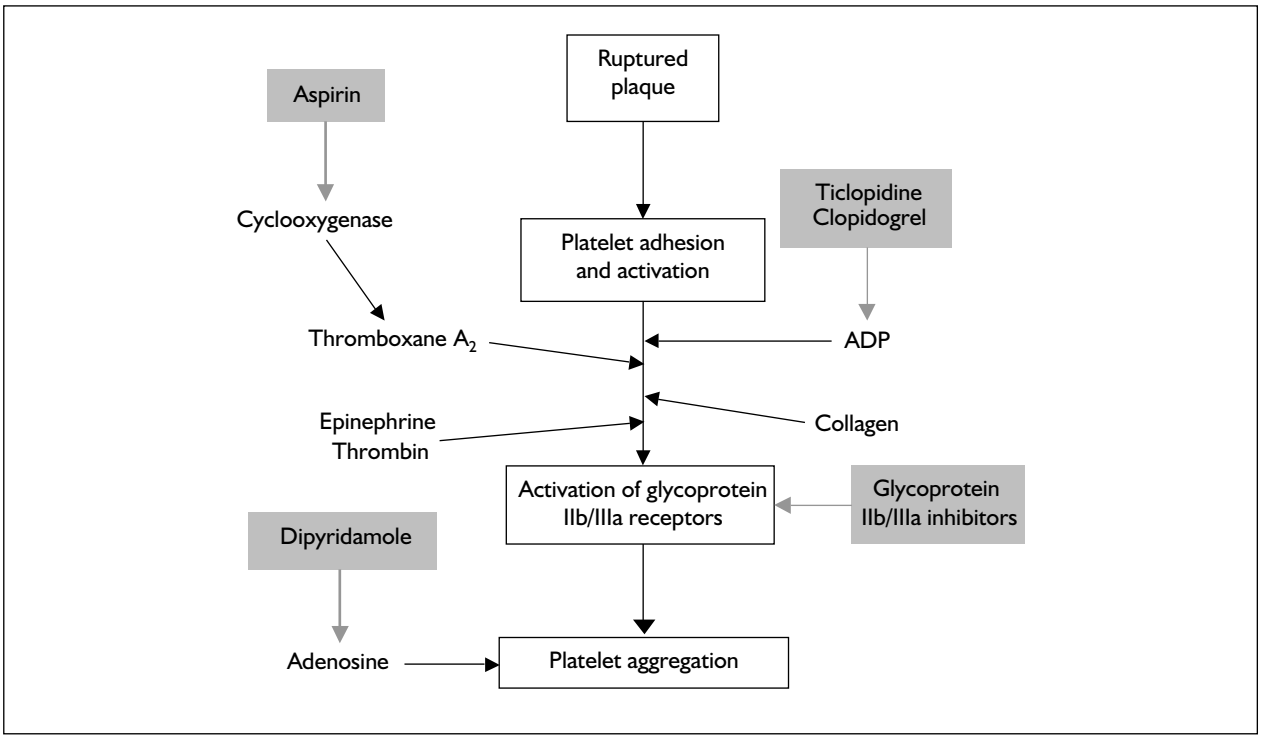


FIGURE 1 *Simplified flow diagram showing thrombus formation. Aspirin inhibits platelet aggregation by inactivating the enzyme cyclooxygenase, which in turn blocks the formation of thromboxane A_2. Ticlopidine and clopidogrel selectively inhibit the binding of adenosine diphosphate (ADP) to its platelet receptor.*

(also shown in *Figure 1*). Aspirin is the 'gold standard' for the long-term treatment and secondary prevention of ischaemic vascular events. Currently available alternatives to aspirin are the thienopyridines ticlopidine and clopidogrel, which may be administered alone or in combination with aspirin.

The addition of clopidogrel to standard aspirin therapy may therefore provide an additional mechanism of action for increased platelet inhibition. The potential interest in this dual antiplatelet approach had previously been confirmed by the synergistic antiplatelet pharmacological effects observed in animal models,[28–30] and *ex vivo* studies in healthy volunteers[31] and in post-MI patients.[32]

Clopidogrel

The following section of the report summarises the product characteristics for clopidogrel available from the electronic Medicine Compendium (www.emc.vhn.net).

Clopidogrel (Plavix®, Bristol-Myers Squibb, Sanofi Synthelabo) is available in 75-mg film-coated tablets.

The recommended dose of clopidogrel is 75 mg as a single daily dose, with or without food. Safety and efficacy have not been established in patients below the age of 18 years.

Clopidogrel is indicated for the secondary prevention of atherothrombotic events in patients suffering from MI (from a few days until <35 days), IS (from 7 days until <6 months) or established PAD, and in patients suffering from non-ST segment elevation ACS (unstable angina or non-Q-wave MI) in combination with aspirin.

Contraindications as reported by the manufacturer

- 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.

Special warnings and special indications for use as reported by the manufacturer

- Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment.
- As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with aspirin, non-steroidal anti-inflammatory drugs (NAIDs), heparin, glycoprotein IIb/IIIa inhibitors or thrombolytics. Patients should be followed carefully for any signs of bleeding, including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery.
- The concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleeding. If a patient is to undergo elective surgery and an antiplatelet effect is not necessary, clopidogrel should be discontinued 7 days prior to surgery.
- Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed [particularly gastrointestinal (CI) and intraocular].
- Patients should be told that it may take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with aspirin), and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.
- Thrombotic thrombocytopenic purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a condition requiring prompt treatment, including plasmapheresis.
- In view of the lack of data on patients with acute myocardial infarction (AMI) with ST-segment elevation, clopidogrel therapy should not be initiated within the first few days following MI.
- In view of the lack of data, clopidogrel cannot be recommended in acute IS (<7 days).
- Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, clopidogrel should be used with caution in these patients.
- Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.

Chapter 3
Methods

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–July 2003)
HEED (CD-ROM, 1995–May 2003)
HTA (http://www.york.ac.uk/inst/crd/), searched 27 May 2003
Inside Conferences (Dialog, 1993–May 2003)
JICST (Dialog, 1985–May 2003)
MEDLINE (Ovid, 1966–April 2003)
NHSEED (http://www.york.ac.uk/inst/crd/) searched 27 May 2003
National Research Register (CD-ROM, February 2003)
PASCAL (Dialog, 1973–May 2003)
SciSearch (Datastar, 1990–May, 2003).

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–July 2003)
HEED (CD-ROM, September 2003)
MEDLINE (Ovid, 1966–August 2003)
NHSEED (http://www.york.ac.uk/inst.crd), searched 10 September 2003.

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.

Inclusion and exclusion criteria

Two reviewers independently screened the titles and abstracts of the studies identified from all searches and sources. A full 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.

Interventions

Clopidogrel (Plavix®, Bristol-Myers Squibb, 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 ACS (e.g. anti-thrombin therapy, nitrates, beta-blockers, glycoprotein IIb/IIIa antagonists or calcium channel blockers) were included.

Participants

Patients with unstable angina or NSTEMI were included. Participants with established PAD or those with a history of MI, IS or TIA were the subject of a parallel appraisal.

Study design

- Randomised controlled trials (RCTs) that compared clopidogrel in combination with aspirin with 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 considered both costs and consequences (including cost–effectiveness, cost–utility and cost-benefit analyses) were included.

Outcome measures

The following outcome measures were included in the review:

- CV death
- MI (non-fatal)
- stroke (identified as ischaemic and haemorrhagic where reported separately)
- refractory ischaemia (RI)
- severe ischaemia
- heart failure
- revascularisation
- unstable angina
- other vascular events
- death
- bleeding complications (major and minor)
- other adverse events (nausea, vomiting, diarrhoea, gastric and duodenal ulceration, headache, dizziness, vertigo, paraesthesia, rash, pruritis, hepatic and biliary disorders, neutropenia and thrombocytopenia)
- quality of life (QoL)
- costs from all reported perspectives.

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 were 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 NHS CRD Report No. 4.[33] The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond and colleagues[34] This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Clinical Excellence (NICE). 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.

Chapter 4

Results

Quantity and quality of research available

Assessment of clinical effectiveness and cost-effectiveness

A total of 2906 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness. Of the titles and abstracts screened, 441 studies were ordered as full papers and assessed in detail. Six studies were not received or were unavailable at the time of the assessment. For the assessment of the clinical effectiveness of clopidogrel alone or in combination with aspirin, one RCT was identified. The RCT by the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators (CURE)[35] assessed clopidogrel in combination with aspirin compared with placebo combined with aspirin in both the acute and longer term management of patients with ACS without ST-segment elevation. No phase IV post-marketing studies of clopidogrel were identified. A summary of the included RCT is presented in *Table 3* and full data extraction tables are presented in Appendix 5.

Seven different reports of the CURE Trial were identified. In addition to the main publication of the trial,[35] a further publication reported a temporal analysis of the main results, assessing both the early and late effects of clopidogrel.[36] Two further papers reported *post hoc* subgroup analysis of the trial results. The first examined the benefit of clopidogrel in patients with ACS without ST-segment elevation in various risk groups[37] and the second reported on the effects of aspirin dose when used alone or in combination with clopidogrel in patients with ACS.[38] The further three publications identified reported the results of the prespecified subgroup analysis of patients undergoing PCI within the CURE trial. The main report of the PCI-CURE examined the effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing PCI.[39] One of the further two identified publications reported the results for the subgroup of patients who had undergone CABG[40] and the other discussed the results of the subgroup analyses in relation to all patients with ACS.[41]

TABLE 3 *Summary of included RCT*

Study	Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators[35]
Study design	Double-blind, randomised, placebo-controlled trial
Participants	12,562 patients with ACS without ST-segment elevation
Intervention	Clopidogrel (75 mg/day) plus aspirin versus placebo plus aspirin. The aspirin dose varied between 75 and 325 mg/day

Systematic reviews/meta-analyses

In addition to the primary studies, one systematic review was identified which investigated clopidogrel therapy in patients with non-ST-segment elevation ACS.[42] This review was a critical appraisal of the CURE trial. A further three related systematic reviews by the Antithrombotic Trialists' Collaboration were identified that included evaluations of clopidogrel for the secondary prevention OVEs.[26,43,54] However, none of these included data from the CURE trial.

Cost-effectiveness

All economic evaluations (including accompanying models) included in the company submission were assessed. This includes a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models were to changes in key assumptions. Following this analysis, if the existing models (company or published) were not sufficient, modified versions of the models were developed.

Excluded studies

A total of 385 studies were excluded. Of these, 100 papers were used as background articles for the review. The majority of the other excluded articles were non-systematic reviews, commentaries and letters to the editor. A flow diagram showing the process of study identification is presented in *Figure 2*. A full list of the excluded studies with reasons for exclusions are presented in Appendix 3.

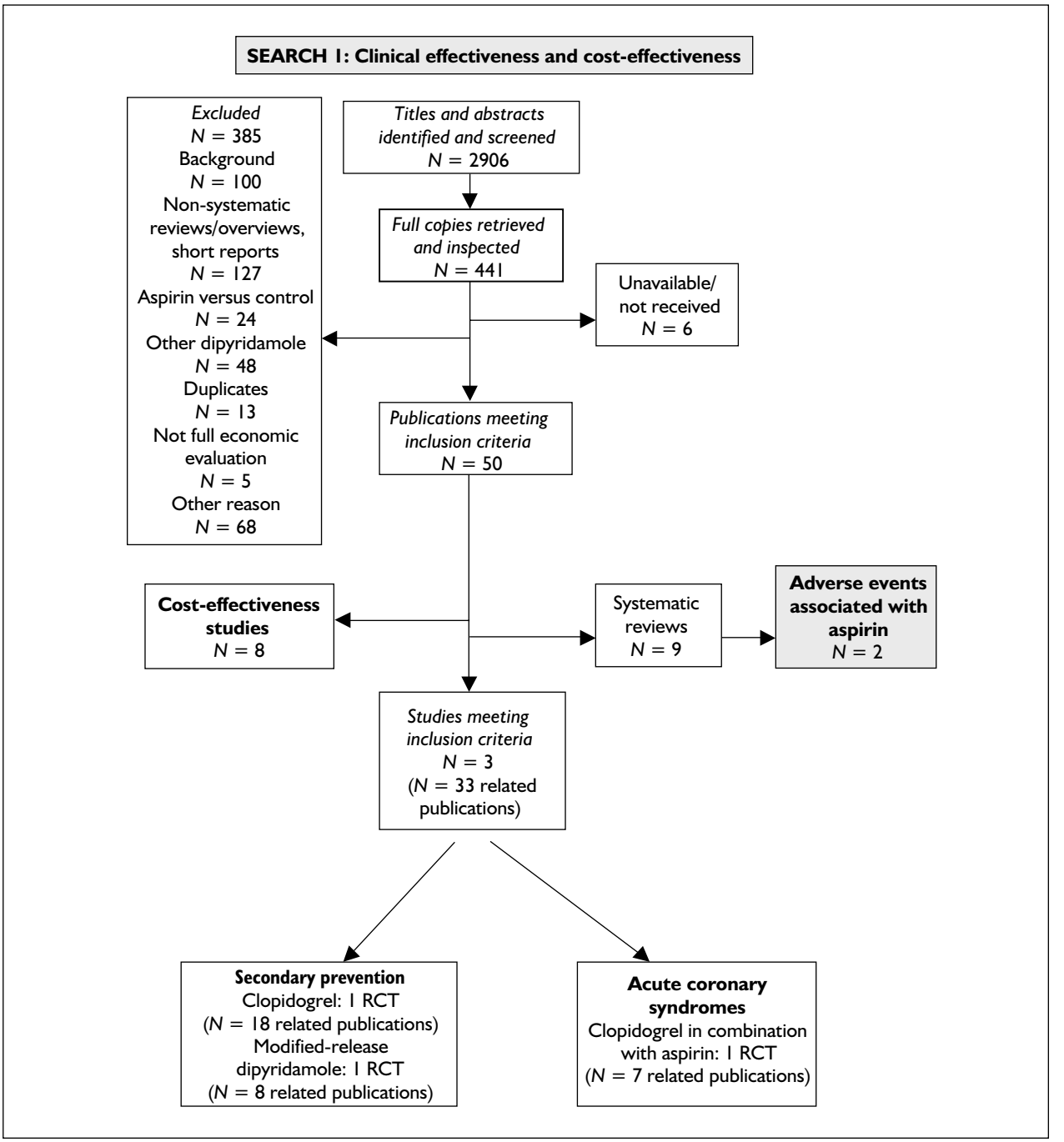


FIGURE 2 *Process of study identification*

A total of 5449 titles and abstracts were screened following the searches for adverse event studies. Of these, 147 were ordered as full papers and assessed in detail. Five of these studies were not received and one study was unavailable. Four systematic reviews that investigated adverse events associated with long-term aspirin use[45–48] were identified. Two additional reviews were identified from the searches for the assessment of clinical effectiveness and cost-effectiveness.[47,49] The process of study identification for the adverse event associated with aspirin use is displayed in *Figure 3*.

Excluded studies: search for adverse events

A total of 137 studies were excluded. Of these, 18 studies were used as background articles. Of the remaining studies, most were non-systematic reviews and general overviews of aspirin for indications other than prevention of ischaemic events. Three studies were duplicates. A full list of

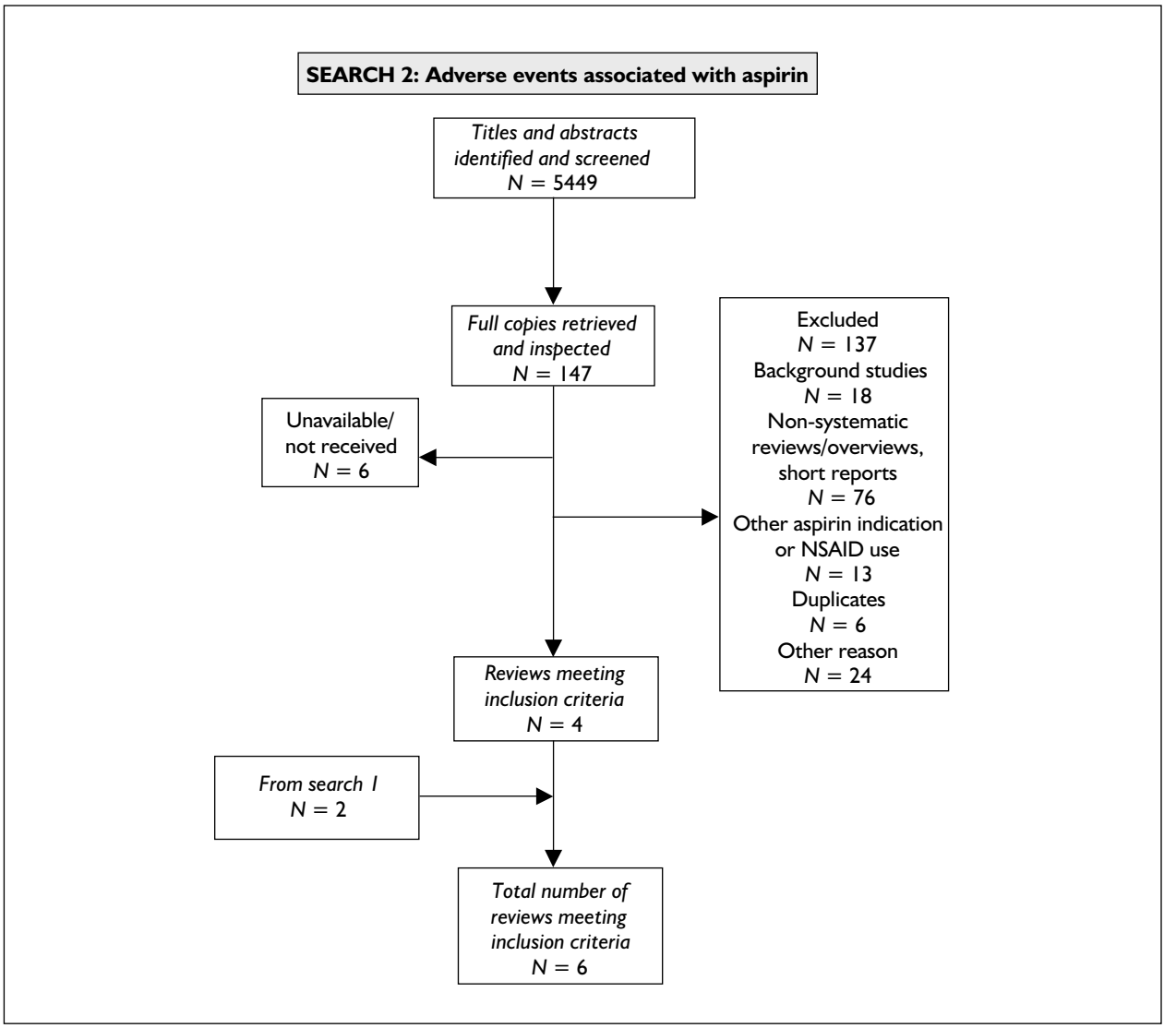


FIGURE 3 *Process of study identification for adverse events*

the excluded studies with reasons for exclusions is presented in Appendix 3.

Other relevant trials

The screening of the initial searches identified the Clopidogrel for Reduction of Events During Observation (CREDO) trial, which evaluated clopidogrel as an adjunct to standard therapy in patients who were to undergo urgent or elective PCI.[50] Approximately 50% of the study population had unstable angina as the indication for PCI and clopidogrel therapy, with other indications including stable angina and recent MI. This study was therefore outside the scope of the present review, but relevant to the interpretation of the results from PCI-CURE.[39]

The CREDO trial was a randomised, double-blind, placebo-controlled trial that prospectively evaluated 2116 patients who were to undergo urgent or elective PCI or who were deemed highly likely to require PCI.[50] Following randomisation, and 3–24 hours prior to PCI, patients either received a 300-mg loading dose of clopidogrel (n = 1053) or matching placebo (n = 1063). All patients also received 325 mg aspirin. Immediately after the PCI procedure, all patients received 75 mg/day clopidogrel (in addition to 325 mg/day aspirin) until day 28. From day 29 until 12 months, patients in the loading dose group received 75 mg/day clopidogrel and the no-pretreatment group received placebo. Both groups continued to receive standard therapy including aspirin (81–325 mg/day) until the end of the 12-month follow-up.

At baseline, both treatment groups were well matched for age, sex and cardiovascular risk

factors, although there was less use of statins and calcium channel blockers in the clopidogrel group. Indications for PCI included recent MI (clopidogrel group 14.3% versus placebo group 13.1%), unstable angina (clopidogrel group 52.5% versus placebo group 53.1%) and stable angina and other (clopidogrel group 32.8% versus placebo group 32.8%). The majority of patients enrolled underwent PCI following an initial angiogram (86% in both groups). In total 1 year of treatment was completed in 63% of the patients in the clopidogrel group and 61% in the placebo group.

The one-year primary outcome was a composite of death, MI or stroke in the intention-to-treat (ITT) population. At 28 days, the primary outcome was a composite of death, MI or urgent target vessel revascularisation in the per protocol population (all randomised patients who underwent PCI). Prespecified secondary analyses included the individual components of the composite end-points, administration of clopidogrel less than 6 hours or more than 6 hours before the PCI procedure and the need for target vessel revascularisation or any revascularisation at 1-year follow-up.

The results of the trial showed that the continuation of clopidogrel therapy (in addition to aspirin) for 1 year was associated with a 26.9% relative risk reduction (RRR) in the combined risk of death, MI or stroke at 1 year (95% confidence interval CI: 3.9 to 44.4%), absolute risk reduction (ARR) = 3%. A similar level of benefit was found in the individual components of this composite end-point, although these were not significant. Further analysis of the data showed that in the group randomised to a clopidogrel loading dose, an RRR of 19.7% (95% CI: 13.3 to 43.1%) was achieved by 28 days for the composite end-point of death, MI or stroke compared with placebo. However, this reduction was not statistically significant ($p = 0.21$). Continued treatment with clopidogrel beyond 28 days to 12 months was associated with a further significant benefit with an RRR of 37.4% in the primary end-point (95% CI: 1.8 to 60.1%).

Ongoing trials

The MATCH is a trial to determine whether clopidogrel plus aspirin is superior to clopidogrel alone in preventing atherothrombotic events in patients at high risk of recurrences after recent TIA or IS. The trial is a randomised, double-blind, prospective study in patients with recent TIA or IS who have at least one additional risk factor (prior IS, MI, angina pectoris, diabetes or PAD). Patients are randomly allocated to aspirin 75 mg/day or placebo and both receive clopidogrel 75 mg/day. A total of 7601 patients have been enrolled and will be followed up for a maximum of 18 months. The primary efficacy end-point is the first occurrence of an event in the composite of IS, MI, vascular death or rehospitalisation for an acute ischaemic event. The secondary end-points are IS, MI, vascular death (combined or separately); IS or vascular death (combined); any stroke; any death; non-fatal IS; non-fatal MI or rehospitalisation for an ischaemic event. The trial is due to be completed by 2004. The MATCH trial addresses a different clinical question to that of the present report (clopidogrel plus aspirin versus clopidogrel alone rather than clopidogrel plus aspirin versus aspirin alone), but the results may have implications for the indications for which clopidogrel is currently licensed.

Clopidogrel

Description of the included RCT

Main trial publication

The CURE Trial[35] was a randomised, double-blind, placebo-controlled trial that evaluated the efficacy and safety of the early and longer term use of clopidogrel (in addition to standard therapy including aspirin) versus placebo (in addition to standard therapy including aspirin) in patients with ACS without ST-segment elevation. The *a priori* inclusion criteria were patients >60 years of age with no ECG changes but with a history of CAD. These criteria were extended following the enrolment of 3000 participants to include patients admitted to hospital within 24 hours of the onset of symptoms suggestive of an ACS without ST-segment elevation greater than 1 mm, but with either ECG changes compatible with new ischaemia or elevated cardiac enzymes, or trophin I or T, to at least twice the upper limit of normal.[35] The study included 12,562 patients, 6259 who were randomised to clopidogrel combined with aspirin and 6303 to aspirin combined with placebo. Immediately after randomisation, a loading dose of clopidogrel (300 mg orally) or matching placebo was administered, followed by clopidogrel (75 mg/day) or matching placebo for 3–12 months (mean duration of treatment, 9 months). Aspirin (recommended dose 75–325 mg/day) was started or continued simultaneously with the blinded study drug. Patients also received standard therapy regardless of their group of randomisation. These concomitant treatments included heparin,

angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, lipid-lowering agents, intravenous nitrates and revascularisation procedures. Follow-up assessments were conducted at hospital discharge and at 1 and 3 months for all patients, with additional follow-up visits at 6, 9 and 12 months for patients randomised early in the study. The CURE trial had two co-primary end-points and the trial was designed to detect a statistically significant difference in these composite end-points:

- A composite of death from CVD, non-fatal MI or stroke.
- A combination of death from CV causes, non-fatal MI, stroke (end-point 1) or refractory ischaemia.
- Secondary outcomes were time to severe ischaemia, heart failure and the need for revascularisation.
- The main safety-related outcome was bleeding complications, which were categorised as life-threatening, major or minor. The haematological parameters also monitored during the trial were thrombocytopenia and neutropenia.

The co-primary end-points were assessed using log-rank statistics and further subgroup analyses were also conducted with the use of tests for interactions in the Cox regression model.

The CURE trial also incorporated a non-randomised *a priori* subgroup analysis of the effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing PCI (the PCI-CURE study).[39] The aim of the study was to examine whether, in addition to aspirin, pre-treatment with clopidogrel followed by long-term therapy after PCI is superior to a strategy of no pre-treatment and short-term therapy of only 4 weeks after PCI. The subgroup study included 2658 patients undergoing PCI in the CURE trial who were assigned treatment with clopidogrel (n = 1313) or placebo (n = 1345). PCI was undertaken at the discretion of the local investigator. Patients were pretreated with aspirin and study drug for a median of 6 days before PCI during the initial hospital admission and for a median of 10 days overall. After PCI, most patients (>80%) in both groups received open-label thienopyridine (either clopidogrel or ticlopidine) for about 4 weeks, after which study drug was restarted for a mean duration of 8 months. The primary outcome of the study was the composite of CV death, MI, or urgent target-vessel revascularisation within 30 days of PCI. Cardiovascular death or MI from the time of PCI to the scheduled end of follow-up was also assessed to determine the effects of continuing clopidogrel long term after PCI. The safety-related outcomes were the same as those monitored for the main CURE trial. An ITT analysis was used as the primary analysis, with all analyses of primary, secondary and other outcomes being compared by use of the log-rank statistic.

The study profile is shown in *Figure 4*.

Quality of the included study

CURE was a high-quality, randomised, double-blind, placebo-controlled trial. The evaluation of the CURE trial in relation to study quality is shown in *Table 4*. Full details of the quality checklist are available in Appendix 4.

TABLE 4 *Quality checklist for CURE*

Was the method used to assign participants to the treatment groups really random?	Yes
What method of assignment was used?	Computer generated
Was the allocation of treatment concealed?	Yes
What method was used to conceal treatment allocation?	Computer generated
Was the number of participants who were randomised stated?	Yes
Were details of baseline comparability presented in terms of MI, stroke, heart failure, hypertension, diabetes and current or former smoker?	Yes
Was baseline comparability achieved in terms of MI, stroke, heart failure, hypertension, diabetes and current or former smoker?	Yes
Were the eligibility criteria for study entry specified?	Yes
Were any co-interventions identified that may influence the outcomes for each group?	Yes
Were the outcome assessors blinded to the treatment allocation?	Yes
Were the participants who received the intervention blinded to the treatment allocation?	Yes
Was the success of the blinding procedure assessed?	Not stated
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Yes
Were the reasons for withdrawal stated?	Not stated
Was an ITT analysis included?	Yes

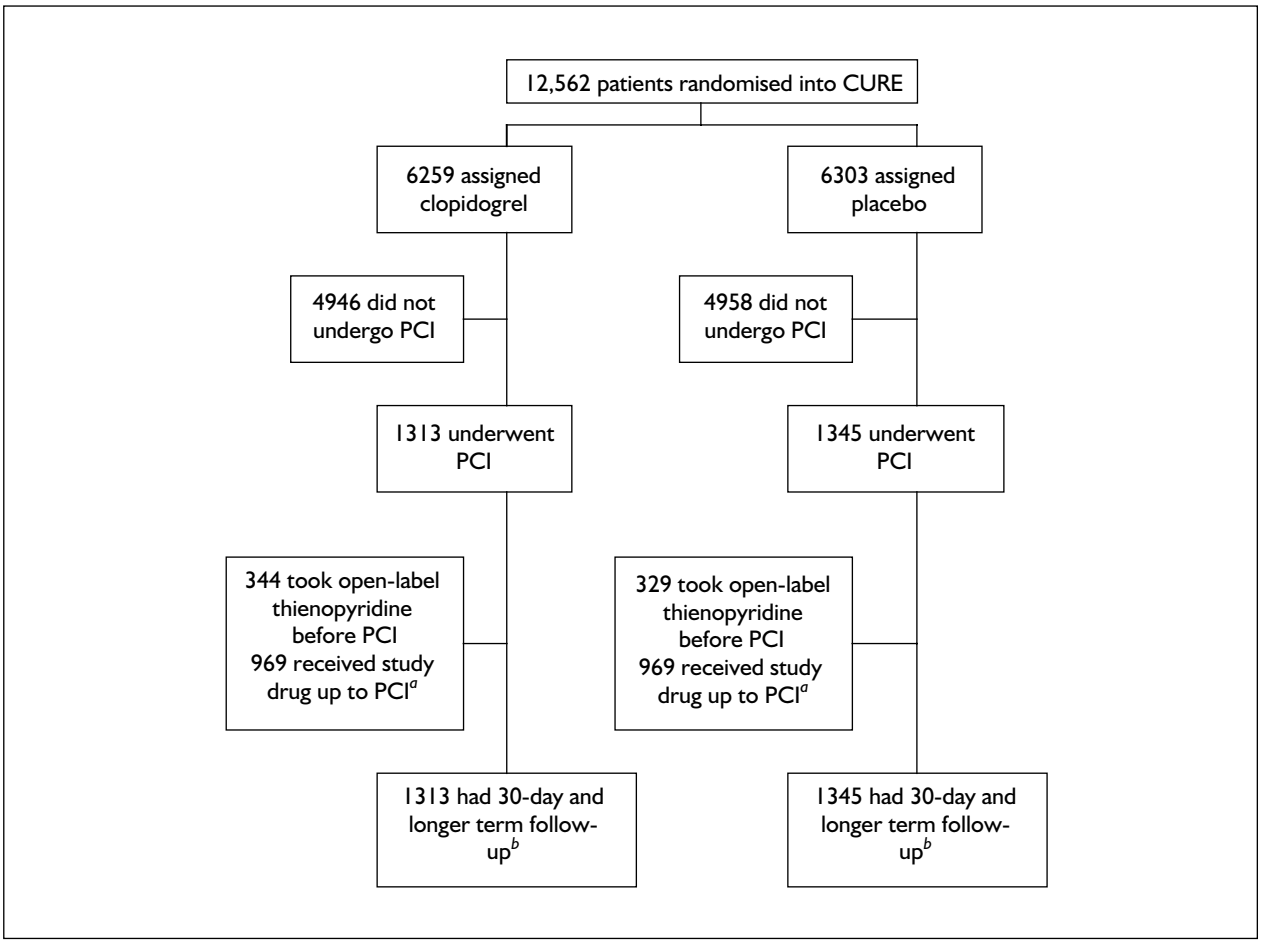


FIGURE 4 *Study profile.* [a] *Per-protocol analysis.* [b] *ITT analysis.*

Effectiveness of clopidogrel used in combination with aspirin in the treatment of non-ST-segment ACS

The following section of the report summarises the CURE trial[35] and the further analysis of the early and late effects of clopidogrel by Yusuf and colleagues.[36]

The baseline demographic characteristics, CV risk factors, ECG changes, medication use and clinical diagnosis at the time of admission were well balanced between the clopidogrel and placebo groups. During initial hospitalisation, 99% of the patients in both groups were taking aspirin, 96% were taking it at 3 months and 94% at the final follow-up visit.

Co-primary outcomes

The primary outcome was a composite of the first occurrence of an event in the outcome cluster of death from CV causes, non-fatal MI or stroke. This outcome occurred in 582 of the patients in the clopidogrel group (9.3%) compared with 719 of the patients randomised to placebo (11.4%). This showed an RRR 20%, relative risk (RR) = 0.80 (95% CI: 0.72 to 0.90) in favour of clopidogrel. This corresponds to an ARR of 2.1% and to a number-needed-to-treat (NNT) to prevent a life-threatening event of 48, over an average of a 9-month treatment period. The rate of the second co-primary outcome, death from CV causes, non-fatal MI, stroke or RI was also lower in the clopidogrel group (1035 patients; 16.5%) than in the placebo group (1187 patients; 18.8%). This showed an RRR of 14%, RR = 0.86 (95% CI: 0.79 to 0.94) in favour of clopidogrel. The results of the co-primary outcomes are summarised in *Table 5*.

Secondary outcomes

Significantly fewer patients in the clopidogrel group than the placebo group had severe ischaemia (176 patients, 2.8% versus 237, 3.8%, respectively); RR = 0.74 (95% CI: 0.61 to 0.90). Likewise, there was a significant reduction in the number of patients suffering from recurrent angina within the clopidogrel group compared with the patients on placebo (1307 patients, 20.9% versus 1442, 22.9%); RR = 0.91 (95% CI: 0.85 to

TABLE 5 *Incidence of co-primary end-points over a mean of 9-month follow-up*

Randomised group *n* (%)				
Clopidogrel	**Placebo**	**RR (95% CI)**	**ARR (%)[a]**	**NNT[a]**
First co-primary outcome: composite of death from CV causes, non-fatal MI, or stroke				
582 (9.3)	719 (11.4)	0.80 (0.72 to 0.90) $p < 0.001$	2.1	48
Second co-primary outcome: first primary outcome or refractory ischaemia				
1035 (16.5)	1187 (18.8)	0.86 (0.79 to 0.94) $p < 0.001$	2.3	44

[a] Values calculated, not reported in original report.

TABLE 6 *Relative risk of the secondary outcomes in CURE*

Outcome	RRR (%)	RR	95% CI
Severe ischaemia	26	0.74	0.61 to 0.90
Recurrent angina	9	0.91	0.85 to 0.98
Revascularisation procedure whilst in hospital	8	0.92	
Radiological evidence of heart failure	18	0.82	0.69 to 0.98

0.98). Slightly fewer of the patients in the clopidogrel group underwent coronary revascularisation during the study (36.0% versus 36.9%), but this difference was accounted for entirely by a difference in the rate of revascularisation during the initial period of hospitalisation (20.8% in the clopidogrel group versus 22.7% in the placebo group). Radiological evidence of heart failure was also found in fewer patients in the clopidogrel group (229 patients, 3.7% versus 280, 4.4%) than in the placebo group; RR = 0.82 (95% CI to 0.69 to 0.98). The results of the secondary outcomes in the trial are displayed in *Table 6*.

Components of the composite end-point

The results of the incidence of components of the composite end-point showed that the clearest difference between the clopidogrel and placebo group was observed in the rates of MI. Within the clopidogrel group 116 patients (1.9%) versus 193 (3.1%) in the placebo group experienced a Q-wave MI; RR = 0.60 (95% CI: 0.48 to 0.76). However, the difference between the groups for the rates of non-Q-wave MI was not significantly different. The rates of RI were also significantly different between the clopidogrel and placebo group. However, this difference was observed primarily in first events that occurred during the initial hospitalisation period, 85 in the clopidogrel group compared with 126 in the placebo group, RR = 0.68 (95% CI: 0.52 to 0.90) with little difference in the rate of rehospitalisation for unstable angina. There were no differences between the groups in the rate of death from CV causes, RR = 0.93 (95% CI: 0.79 to 1.18) or stroke, RR = 0.86 (95% CI: 0.63 to 1.18). Death from non-CV causes was not included as one of the components of the composite outcome measure, but no differences were seen between the groups for this outcome, RR = 0.91 (95% CI: 0.60 to 1.39). *Table 7* shows the incidence of the components of the composite end-points at a mean of 9-month follow-up and *Table 8* the incidence of death from non-cardiovascular causes.

Post-hoc *subgroup analysis*

The consistency of the beneficial effects of clopidogrel therapy in a number of key subgroups of patients over the 9 months of therapy are displayed in *Table 9*. This benefit was also consistent among subgroups receiving or not receiving lipid-lowering drugs, beta-blockers, heparin or angiotensin-converting-enzyme inhibitors at the time of randomisation. A tendency was also observed towards a greater benefit among patients who had previously undergone revascularisation [RR for the first primary outcome = 0.56 (95% CI: 0.43 to 0.72)] than among those who had not [RR = 0.88 (95% CI: 0.78 to 0.99)]. However, given the large number of subgroup analyses that were performed, these results could be spurious and should therefore be interpreted with caution.

A further *post hoc* subgroup analysis by Budaj and colleagues[37] showed that clopidogrel therapy conferred a consistent benefit in low-,

TABLE 7 *Incidence of components of composite end-points at 9-month follow-up*

Outcome: components of composite end-points	Randomised group, *n* (%)		RR (95% CI)
	Clopidogrel	Placebo	
Death from CV causes	318 (5.1)	345 (5.5)	0.93 (0.79 to 1.08)
MI[a]	324 (5.2)	419 (6.7)	0.77 (0.67 to 0.89)
Q-wave MI	116 (1.9)	193 (3.1)	0.60 (0.48 to 0.76)
Non-Q-wave MI	216 (3.5)	242 (3.8)	0.89 (0.63 to 1.18)
Stroke	75 (1.2)	87 (1.4)	0.86 (0.63 to 1.18)
RT[b]	544 (8.7)	587 (9.3)	0.93 (0.82 to 1.04)
During initial hospitalisation	85 (1.4)	126 (2.0)	0.68 (0.52 to 0.90)
After discharge	459 (7.6)	461 (7.6)	0.99 (0.87 to 1.13)

[a]Some patients had both a Q-wave MI and non-Q-wave MI.
[b]Only the first ischaemic event was counted for each patient.

TABLE 8 *Death from non-cardiovascular causes*

Outcome	Clopidogrel	Placebo	RR (95% CI)
Death from non-cardiovascular causes	41 (0.7%)	45 (0.7%)	0.91 (0.60 to 1.39)

TABLE 9 *Rates and relative risk of the first primary outcome in various subgroups*

Characteristic	No. of patients	Patients with event (%)	
		Clopidogrel	Placebo
Overall	12,562	9.3	11.4
Associated MI	3,283	11.3	13.7
No associated MI	9,279	8.6	10.6.
Male sex	7,726	9.1	11.9
Female sex	4,836	9.5	10.7
≤ 65 years old	6,354	5.4	7.6
>65 years old	6,208	13.3	15.3
ST-segment deviation	6,275	11.5	14.3
No ST-segment deviation	6,287	7.0	8.6
Enzymes elevated at entry	3,176	10.7	13.0
Enzymes not elevated at entry	9,386	8.8	10.9
Diabetes	2,840	14.2	16.7
No diabetes	9,722	7.9	9.9
Low risk	4,187	5.1	6.7
Intermediate risk	4,185	6.5	9.4
High risk	4,184	16.3	18.0
History of revascularisation	2,246	8.4	14.4
No history of revascularisation	10,316	9.5	10.7
Revascularisation after randomisation	4,577	11.5	13.9
No revascularisation after randomisation	7,985	8.1	10.0

intermediate- and high-risk patients with ACS, stratified by their risk for future atherothrombotic events (MI, stroke or vascular death) according to the Thrombolysis in Myocardial Infarction (TIMI) risk score.[51] As shown in *Table 10*, all risk groups received a consistent benefit in the clopidogrel treatment arm; however, the absolute benefit was greatest in patients with the highest TIMI risk scores. Although more high-risk patients went on to suffer an event, the difference between the clopidogrel and placebo groups was greatest in the high-risk subgroup.

A subgroup analysis by Peters and colleagues[38] examined the benefits and risk of adding clopidogrel to different doses of aspirin within the

TABLE 10 *Effectiveness of clopidogrel therapy in low-, intermediate- and high-risk patients with ACS stratified by the TIMI risk score at 12 months*

Risk group	Clopidogrel (%)	Placebo (%)	RR	95% CI	NNT
Low (n = 1674)	4.1	5.7	0.71	0.52 to 0.97	63
Intermediate (n = 3626)	9.8	11.4	0.85	0.74 to 0.98	63
High (n = 1003)	15.9	20.7	0.73	0.60 to 0.90	21

TABLE 11 *Effectiveness of clopidogrel therapy stratified by aspirin dose*

Aspirin dose (mg)	Clopidogrel (%)	Placebo (%)	RR	95% CI
≤ 100	8.6	10.5	0.81	0.68 to 0.97
101–199	9.5	9.8	0.97	0.77 to 1.22
≥ 200	9.8	13.6	0.71	0.59 to 0.85

trial. The patients were divided into three aspirin dose groups of ≤ 100 mg, 101–199 and ≥ 200 mg. The results in *Table 11* indicate that clopidogrel was significantly more beneficial than placebo in the groups of patients receiving either ≤ 100 mg or ≥ 200 mg of aspirin daily.

Temporal trends in the CURE trial[36]

Early effects of clopidogrel (0 to 30 days after randomisation)

To explore the effectiveness of clopidogrel relative to placebo in both acute and longer term phases of ACS, Yusuf and colleagues[36] reported the results during the various periods of the trial. The data for the first 30 days were provided for a composite that included the primary outcomes plus refractory and severe ischaemia in order to maintain the power to detect differences in rapidity of onset. The results from randomisation to 30 days showed that 270 patients (4.3%) in the clopidogrel group developed cardiovascular (CV) death, MI or stroke compared with 343 (5.4%) in the placebo group, RR = 0.79 (95% CI: 0.67 to 0.92); $p < 0.004$. A significant reduction in the composite that included CV death, MI, stroke or RI was also observed: 480 patients (7.7%) in the clopidogrel group versus 580 (9.2%) in the placebo group, RR = 0.83% (95% CI: 0.73 to 0.93). The addition of severe ischaemia to this composite also showed further beneficial effects in favour of clopidogrel with 602 (9.6%) of patients in the clopidogrel group experiencing this outcome versus 740 (11.7%) of patients in the placebo group, RR = 0.81 (95% CI: 0.73 to 0.90).

An exploration of the rapidity of the onset of effects indicated a benefit for the clopidogrel group both within the first 7 days and between days 8 and 30 (see Appendix 5 for data extraction tables). An examination of the data during the first 24 hours after randomisation indicated a 34% RRR in the expanded composite outcome (CV death, MI, stroke, refractory or severe ischaemia). However, no significant differences between the groups were observed on the composites of CV death, stroke, MI or CV death, stroke, MI or RI at 24-hours post-randomisation.

Late effects of clopidogrel (31 days to 12 months)

To examine the longer term effectiveness of clopidogrel therapy, the data from 31 days to 12 months of follow-up were analysed. When the data were analysed over this period together, there was an 18% reduction in the primary outcome of CV death, MI or stroke, RR = 0.82 (95% CI: 0.70 to 0.95) (*Table 12*). However, this benefit was not consistent over the different trial intervals, with a RRR of 22% (95% CI: 8.6 to 33.4), 32% (95% CI: 12.8 to 46.4), 4% (95% CI: –26.9 to 26.7), 6% (95% CI: –33.5 to 34.3) and 14% (95% CI: –31.6 to 44.2) being observed during the 0–1, 1–3, 3–6, 6–9 and 9–12 month study intervals, respectively. Hence the greatest differences in events rates between the clopidogrel and placebo group were observed within the first 3 months of treatment. These results should be treated with caution, however, given that the trial was not adequately powered to detect temporal differences between the groups in response to treatment.

Adverse events

The incidence of major bleeding was significantly more common in the clopidogrel group (3.7%) than the placebo group (2.7%) over the duration of the trial, RR = 1.38 (95% CI: 1.13 to 1.67) (*Table 13*). In total 135 patients (2.2%) in the

TABLE 12 *Effects of clopidogrel compared with placebo by time periods*

	Events (%)					
	0 to 30 days			>30 days to 1 year		
	Clopidogrel	Placebo	RR (95% CI)	Clopidogrel	Placebo	RR (95% CI)
CV death/MI/stroke	4.3	5.4	0.79 (0.67 to 0.92)	5.2	6.3	0.82 (0.70 to 0.95)
RI	3.7	4.3	0.86 (0.72 to 1.03)[a]	5.3	5.4	0.98 (0.84 to 1.15)
Severe ischaemia[b]	3.8	5.0	0.75 (0.63 to 0.88)	NA	NA	NA
CV death/MI/stroke/RI	7.7	9.2	0.83 (0.73 to 0.93)	9.6	10.6	0.90 (0.80 to 1.10)
CV death/MI/stroke/in-hospital severe ischaemia	9.6	11.7	0.81 (0.73 to 0.90)	NA	NA	NA

NA, Outcome not applicable within this time period.
[a] The entire difference in RI was due to a difference in events occurring in hospital, with little effect later. Note that the definitions for RI during the initial hospitalisation and after discharge are dissimilar.
[b] Severe ischaemia includes RI.

TABLE 13 *Summary of bleeding complications*[a]

	Randomised group, *n* (%)		
Outcomes	**Clopidogrel**	**Placebo**	**RR (95%CI)**
Major bleeding[b]	231 (3.7)	169 (2.7)	1.38 (1.13 to 1.67)
Requiring blood transfusion of 2 or more units of blood	177 (2.8)	137 (2.2)	1.30 (1.04 to 1.62)
Life threatening	135 (2.2)	112 (1.8)	1.21 (0.95 to 1.56)
Fatal	11 (0.2)	15 (0.2)	1.01 (0.75 to 1.31)
Causing 5 g/dl drop in haemoglobin level	58 (0.9)	57 (0.9)	1.01 (0.94 to 1.07)
Requiring surgical intervention	45 (0.7)	43 (0.7)	1.06 (0.92 to 1.09)
Causing haemorrhagic stroke	7 (0.1)	5 (0.1)	1.02 (0.60 to 1.74)
Requiring inotropic agents	34 (0.5)	34 (0.5)	1.00 (0.90 to 1.12)
Requiring blood transfusion of 4 or more units of blood	74 (1.2)	60 (1.0)	1.00 (0.95 to 1.06)
Non-life-threatening	96 (1.5)	57 (0.9)	1.70 (1.22 to 2.35)
Major bleeding by TIMI definition[51]	68 (1.1)	73 (1.2)	0.94 (0.68 to 1.30)
Major bleeding by GUSTO definition[52]	78 (1.2)	70 (1.1)	1.12 (0.81 to 1.55)
Site of major bleeding			
Gastrointestinal	83 (1.3)	47 (0.7)	1.01 (0.94 to 1.07)
Retroperitoneal	8 (0.1)	5 (0.1)	1.03 (0.62 to 1.71)
Urinary (haematuria)	4 (0.1)	5 (0.1)	0.98 (0.51 to 1.90)
Arterial puncture site	36 (0.6)	22 (0.3)	1.01 (0.88 to 1.15)
Surgical site	56 (0.9)	53 (0.8)	1.00 (0.93 to 1.07)
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75 to 2.56)
Total with bleeding complications	533 (8.5)	317 (5.0)	1.69 (1.48 to 1.94)

[a] Some patients had more than one bleeding episode.
[b] Major bleeding defined as substantially disabling bleeding, intraocular bleeding leading to loss of vision or bleeding necessitating blood transfusion of 2 or more units of blood. Major bleeding was classified as life-threatening if the bleeding episode was fatal or led to a reduction in the haemoglobin level of at least 5 g/dl, significant hypotension with need for inotropes, requiring surgical intervention, symptomatic intracranial haemorrhage or requiring blood transfusion of 4 or more units. Minor bleeding included any other bleeding requiring permanent or temporary discontinuation of the study drug.

clopidogrel and 112 (1.8%) in the placebo group experienced life-threatening bleeds, RR = 1.21 (95% CI: 0.95 to 1.56). The number of patients who required transfusion of two or more units of blood was also higher in the clopidogrel group, 177 (2.8%), than the placebo group, 137 (2.2%); RR = 1.30 (95% CI: 1.04 to 1.62). There was no difference in the number of fatal bleeding episodes, bleeding requiring surgical intervention or haemorrhagic stroke between the two groups. The excess of major bleeding episodes that were observed was attributable to GI haemorrhages and bleeding at the sites of arterial punctures. The rate of major bleeding episodes was higher both early, within 30 days of randomisation [2.0% versus 1.5; RR = 1.31 (95% CI: 1.01 to 1.70] and late, more than 30 days post-randomisation [1.7% versus 1.1%; RR = 1.48 (95% CI: 1.10 to 1.99).

An examination of the risk of experiencing any bleeding complication over the length of the trial by different time periods indicated that in both groups the risk decreased steadily throughout the trial duration. However, the risk still remained higher in the clopidogrel group at each time period (*Table 14*).

A further *sub-hoc* analysis by Peters and colleagues[38] assessed the bleeding risks associated with adding clopidogrel to different doses of aspirin, stratified according to aspirin doses of ≤ 100, 101–199 and ≥ 200 mg. The results in *Table 15* show that there was an incremental increase in the rate of major bleeding with increasing doses of aspirin. These differences were observed in the bleeding rates associated with different aspirin doses in both the clopidogrel (3.0, 3.4 and 4.9%) and the placebo group (1.9, 2.8 and 3.7%). The excess risk of bleeding with clopidogrel was 1.1, 0.6 and 1.2% for doses ≤ 100, 101–199 and ≥ 200 mg, respectively, indicating that the excess risk of bleeding observed with clopidogrel remains constant regardless of the aspirin dose.

Overall there was no significant excess of major bleeding episodes after CABG observed in the clopidogrel group compared with the placebo group (1.3% versus 1.1%, respectively), RR = 1.26 (95% CI: 0.93 to 1.71). However, the study medication was discontinued before the procedure for most patients scheduled to undergo CABG surgery at a median time of 5 days. Within the 910

TABLE 14 *Temporal trends in bleeding risk*

	Risk of bleeding (life-threatening, major, minor, other) (%)	
Months of therapy	**Clopidogrel**	**Placebo**
0–1	599/6259 (9.6)	413/6303 (6.6)
1–3	276/6123 9 (4.5)	144/6168 (2.3)
3–6	228/6037 (3.8)	99/6048 (1.6)
6–9	162/5005 (3.2)	74/4972 (1.5)
9–12	73/3841 (1.9)	40/3844 (1.0)

TABLE 15 *Major and life-threatening bleeding by various doses of aspirin*

	ASA	Clopidogrel	All patients
Major bleeding complications			
ASA ≤ 100 mg (%)	1.86	2.97	2.41
ASA 101–199 mg (%)	2.82	3.41	3.12
ASA ≥ 200 mg (%)	3.67	4.86	4.26
p-value for trend	<0.0001	<0.001	<0.0001
Adjusted[a] OR (95% CI) for 101–199 vs ≤ 100 mg	1.52 (1.00 to 2.31)	1.20 (0.84 to 1.73)	1.33 (1.01 to 1.74)
Adjusted[a] OR (95% CI) for ≥ 200 vs ≤ 100 mg	1.7 (1.22 to 2.59)	1.63 (1.19 to 2.23)	1.70 (1.33 to 2.16)
Life-threatening bleeding complications			
ASA ≤ 100 mg (%)	1.26	1.75	1.50
ASA 101–199 mg (%)	1.90	1.39	1.64
ASA ≥ 200 mg (%)	2.37	3.29	2.82
p-value for trend	0.004	0.0006	<0.0001
Adjusted[a] OR (95% CI) for 101–199 vs ≤ 100 mg	1.48 (0.89 to 2.46)	0.79 (0.47 to 1.32)	1.06 (0.74 to 1.52)
Adjusted[a] OR (95% CI) for ≥ 200 vs ≤ 100 mg	1.64 (1.04 to 2.59)	1.82 (1.22 to 2.71)	1.72 (1.27 to 2.32)

[a] Adjusted for gender, weight, hypertension, components of the TIMI risk score, rates of angiography, PCI and CABG, the use of NSAIDs, heparin, glycoprotein IIb/IIIa inhibitors, oral anticoagulants, open-label ticlopidine or clopidogrel at any time during the study period.

patients in whom the study medication was discontinued more than 5 days before the procedure, there was no excess of major bleeding within 7 days after surgery (4.4% of patients in the clopidogrel group versus 5.3% of those in the placebo group). In the 912 patients who ceased taking medication within 5 days before CABG surgery, the rate of major bleeding was 9.6% in the clopidogrel group compared with 6.3% in the placebo group (RR = 1.53).

The number of patients with thrombocytopenia (26 in the clopidogrel group and 28 in the placebo group) or neutropenia (five in the clopidogrel group and eight in the placebo group) was similar in the two treatment groups. Significantly more patients reported experiencing either a rash (6.02% versus 4.6%) or diarrhoea (4.46% versus 3.36%) in the clopidogrel group compared with the placebo group. Severe rash was also reported more frequently in the clopidogrel group than the placebo arm (0.26% versus 0.10%). Conversely, the incidence of indigestion/nausea/vomiting (15.01% in the clopidogrel group versus 17.6% in the placebo group) and abnormal liver function (2.97% in the clopidogrel group versus 3.15% in the placebo group) was reported significantly more frequently by patients in the placebo arm.

PCI-CURE

The following section of the report summarises the prespecified subgroup analysis of the treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing PCI (the PCI-CURE study).[39]

Overall, 2658 patients in the CURE trial underwent PCI, of whom 1313 were assigned to clopidogrel and 1345 placebo. In this group 1730 PCIs were undertaken in the initial hospital stay and 928 after discharge. During the initial hospital stay the median time before PCI was 6 days in both groups and 10 days overall. In both groups the average duration of follow-up after PCI was 8 months. No patients were lost to follow-up. The baseline characteristics of the participants assigned to clopidogrel and those assigned to placebo were well matched and a propensity analysis was undertaken to adjust for possible selection bias.

Effectiveness

The primary outcome was a composite of the first occurrence of an event in the outcome cluster of death from CV causes, non-fatal MI or urgent revascularisation. This outcome occurred in 59 of the patients in the clopidogrel group (4.5%) compared with 86 of the patients randomised to placebo (6.4%) in the first 30 days after PCI, a RRR of 30% in favour of clopidogrel; RR = 0.70 (95% CI: 0.50 to 0.97). The composite of CV death or MI was also lower in the clopidogrel group; RR = 0.66 (95% CI: 0.44 to 0.99). All deaths within the first 30 days were CV deaths and were similar between the groups (14 versus 13). Individually patients on clopidogrel had significantly fewer MIs and Q-wave MIs than patients on placebo.

From the time of PCI until the end of follow-up (mean 8 months after PCI) there were significantly fewer occurrences of the primary outcome in the patients on clopidogrel than placebo. Likewise, there were also significantly fewer occurrences of the end-point of CV death, MI, or any revascularisation procedures within the clopidogrel group. There were also significantly fewer MIs in the clopidogrel group than the placebo group. However, this difference in the number of MIs was mainly due to a difference in Q-wave MIs. The total number of CV deaths was similar between the groups at follow-up (32 versus 31). Overall, including events before and after PCI, patients treated with clopidogrel experienced a RRR of 31% in CV deaths or MI compared with patients receiving placebo; RR = 0.69 (95% CI: 0.54 to 0.87). This equates to an ARR of 3.8% with an NNT of 26. Significantly fewer patients (20.9%) within the clopidogrel group received treatment with intravenous glycoprotein IIb/IIIa inhibitors during PCI than those assigned to placebo (26.6%), RR = 0.79 (95% CI: 0.69 to 0.90); $p = 0.001$. The need for a second revascularisation was also lower in the clopidogrel group than the placebo group [186 (14.2%) versus 230 (17.1%); RR = 0.82 (95% CI: 0.68 to 1.00)], although this was mainly due to fewer repeat PCI [141 (10.7%) versus 174 (12.9%); RR = 0.83 (95% CI: 0.66 to 1.03)].

Table 16 show the major outcome events in the PCI-CURE and *Table 17* the bleeding events after PCI.

Adverse events

Within the first 30 days after PCI, there were no significant differences between the two treatment groups in minor or major (life-threatening and non-life-threatening) bleeding episodes. At the end of follow-up, similar non-significant differences were found for major bleeding. However there were significantly more minor bleeding episodes in the clopidogrel group (3.5%) than the placebo (2.1%) group, RR = 1.68 (95%

TABLE 16 *Major outcome events*

	Clopidogrel, *n* (%)	Placebo, *n* (%)	RR (95% CI)
Events before PCI			
MI or RI	159 (12.1)	206 (15.3)	0.76 (0.62 to 0.93)
MI	47 (3.6)	68 (5.1)	0.68 (0.47 to 0.99)
Events from PCI to 30 days			
CV death, MI, urgent revascularisation	59 (4.5)	86 (6.4)	0.70 (0.50 to 0.97)
CV death, MI	38 (2.9)	59 (4.4)	0.66 (0.44 to 0.99)
CV death	14 (1.1)	13 (1.0)	1.10 (0.52 to 2.35)
MI	28 (2.1)	51 (3.8)	0.56 (0.35 to 0.89)
Q-wave MI	11 (0.8)	32 (2.4)	0.35 (0.18 to 0.70)
Urgent revascularisation	25 (1.9)	38 (2.8)	0.67 (0.41 to 1.11)
Events from PCI to end of follow-up			
CV death, MI	79 (6.0)	108 (8.0)	0.75 (0.56 to 1.00)
CV death, MI, any revascularisation	240 (18.3)	292 (21.7)	0.83 (0.70 to 0.99)
CV death	32 (2.4)	31 (2.3)	1.07 (0.65 to 1.75)
MI	59 (4.5)	85 (6.4)	0.71 (0.51 to 0.99)
Q-wave MI	20 (1.5)	47 (3.5)	0.43 (0.26 to 0.73)
Overall revascularisation	186 (14.2)	230 (17.1)	0.82 (0.68 to 1.00)
Overall results: events before and after PCI			
CV death, MI	116 (8.8)	169 (12.6)	0.69 (0.54 to 0.87)

TABLE 17 *Bleeding events after PCI*

	Clopidogrel, *n* (%)	Placebo, *n* (%)	RR (95% CI)
From PCI to 30 days			
Major	21 (1.6)	19 (1.4)	1.13 (0.61 to 2.1)
Life-threatening	9 (0.7)	10 (0.7)	0.92 (0.38 to 2.26)
Non-life-threatening	12 (0.9)	9 (0.7)	1.37 (0.58 to 3.23)
Minor	13 (1.0)	10 (0.7)	1.33 (0.59 to 3.03)
Blood transfusion of 2 or more units	14 (1.1)	15 (1.1)	0.96 (0.46 to 1.97)
From PCI to follow-up			
Major	36 (2.7)	33 (2.5)	1.12 (0.70 to 1.78)
Life-threatening	16 (1.2)	18 (1.3)	0.91 (0.47 to 1.78)
Non-life-threatening	20 (1.5)	15 (1.1)	1.37 (0.70 to 2.66)
Minor	46 (3.5)	28 (2.1)	1.68 (1.06 to 2.68)
Blood transfusion of 2 or more units	28 (2.1)	27 (2.0)	1.06 (0.63 to 1.79)

CI: 1.06 to 2.68). In those patients who had received a glycoprotein IIb/IIIa inhibitor there was no significant difference in the rate of either life-threatening or non-life-threatening bleeding at 30 days. No haematological adverse events for the patients undergoing PCI were reported in the subgroup analysis.

Comparator: aspirin

The effects of aspirin therapy for patients at high risk of occlusive events has been most extensively studied by the Antithrombotic Trialists' (ATT) Collaboration and the Antiplatelets Trialists' Collaboration.[26,43] The most recent meta-analysis[26] included data from 197 randomised trials that compared antiplatelet therapy versus control and 90 that compared different antiplatelet regimens. The primary outcome was a 'serious vascular event', defined as non-fatal MI, non-fatal stroke, or death from a vascular cause (including death from an unknown cause). Aspirin was the most widely studied antiplatelet drug. In patients at high-risk of occlusive events (excluding those with acute stroke) compared with control, aspirin at any dose reduced the odds of a serious vascular event by 25% [odds ratio (OR 0.77; 95% CI: 0.73 to 0.81].

Effects of different doses of aspirin

The ATT meta-analysis[26] also investigated the effect of different daily aspirin doses. Data from trials directly comparing aspirin doses ≥ 75 mg/day with doses <75 mg/day showed that there was no significant difference between the different aspirin regimens, but could not preclude a clinically important difference. The authors reported that as doses <75 mg/day have been less widely studied there remains uncertainty about whether they are as effective as higher doses. Indirect comparisons between trials of higher doses of aspirin (≥ 75 mg/day) versus no aspirin suggested that no particular range of dose was preferable, but doses of <75 mg/day seemed to have a smaller proportional effect than higher doses.

Adverse events

This section of the report provides an overview of the results of systematic reviews that have primarily examined the adverse events associated with long-term aspirin use. Five systematic reviews were identified.[45–47,49,53] in addition to the ATT meta-analysis. Further study details and the results of the quality assessment are presented in Appendix 6.

Haemorrhagic stroke

One systematic review[53] of aspirin versus control (placebo or no treatment) for at least 1 month duration found that aspirin treatment was associated with an increased absolute risk (AR) of haemorrhagic stroke (an increase in AR of 12 events per 10,000 persons). The authors found no difference in the risk when different doses of aspirin were used. A second review[45] that examined the incidence of haemorrhagic stroke as a secondary outcome found an excess risk in patients allocated to low-dose aspirin compared with placebo.

Extracranial haemorrhage

The systematic review by the ATT[26] found that aspirin increased the risk of major extracranial haemorrhage by about half compared with placebo or no treatment (OR 1.6; 95% CI: 1.4 to 1.8). Approximately 20% of the cases of extracranial haemorrhage caused death. The review found that there was no evidence of a difference in the risk of extracranial haemorrhage with different daily doses.

Gastrointestinal haemorrhage

One systematic review[49] of aspirin versus control (placebo or no treatment) found that the risk of GI haemorrhage was higher in patients treated with aspirin (OR 1.68; 95% CI: 1.51 to 1.88). The risk of haemorrhage did not appear to differ between doses or formulations. A review of 17 observational studies[47] (including over 10,000 cases of upper GI track haemorrhage or perforation which resulted in admission to hospital) found that the risk of GI haemorrhage more than doubled in aspirin users compared with non-users (RR 2.6; 95% CI: 2.4 to 2.7). However, the risk decreased when the analysis was restricted to prospective studies (RR 2.2; 95% CI: 2.8 to 3.3). A third review[45] of low-dose aspirin versus placebo reported an increased risk of GI haemorrhage with aspirin (RR 2.5; 95% CI: 1.4 to 4.7). There were no reported deaths related to GI haemorrhage and almost no association with permanent morbidity. The last systematic review[53] of low-dose aspirin versus placebo also found an increased risk of bleeding in the aspirin treatment group (OR 1.52; 95% CI: 1.32 to 1.75).

Chapter 5

Economic review

Summary of studies included in the cost-effectiveness review

The systematic literature search detailed in Chapter 3 identified only one study which met the criteria for inclusion in the cost-effectiveness review.[54] 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.

The following sections provide a detailed overview of the cost-effectiveness evidence from each of these sources and an assessment of the quality and relevance of the data from the perspective of the UK NHS. A quality checklist for each study is reported in Appendix 7. An overall summary of the cost-effectiveness evidence is provided at the end of the chapter.

Review of Gaspoz *et al*. (2003). Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease[54]

Overview

The following review refers to the corrected version of this paper.[54]

This study was designed to estimate the cost-effectiveness of five treatment strategies in comparison with no treatment for the treatment of CHD and non-coronary disease. The five treatment strategies were (1) aspirin for all eligible patients, (2) aspirin for all eligible patients and clopidogrel for those patients ineligible for aspirin, (3) clopidogrel for all patients and (4) and (5) two options for the combination of aspirin for all eligible patients and clopidogrel for all patients. Strategy (4) employs the most optimistic estimate of the RRR associated with the combination of clopidogrel and aspirin whereas strategy (5) uses the trial data from CURE[35] and assumes that patients receive clopidogrel for only 1 year. The model also estimates the costs and effects of current aspirin use. The main outcome measure was cost per quality-adjusted life-year (QALY) gained. The model also calculated the expected number of deaths from coronary disease, deaths from non-coronary disease and MIs. Non-coronary disease is defined to include stroke. The study is based on a deterministic, decision-analytic model of CHD in a US population aged between 35 and 84 years, evaluated over a period of 25 years. A US payer perspective can be assumed.

The model determines the expected costs and outcomes for patients who survive the first 30 days following a coronary event which may be cardiac arrest, acute MI or angina. Those patients face a yearly risk of cardiac arrest, acute MI, coronary revascularisation or any combination of these events, in addition to death from other causes. Patients on treatment face the risk of adverse events, but compliance was not modelled as the relevant model parameters were based on ITT analyses. Each event is potentially fatal. The risks of events differ between the first and subsequent years following the initial event and according to the number of previous events in the patients' histories. The model records both coronary and non-coronary costs. Non-coronary events include strokes. Data used in the model were sourced from published trials, US national statistics and published pricing lists. The model was originally designed to assess the cost-effectiveness of statins in CHD and this influenced the structure and the type of events modelled.

Summary of effectiveness data

The percentage reductions in odds of CHD events and non-coronary mortality for aspirin were taken from the Antiplatelet Trialists' Collaboration overview (ATT).[44] The percentage reduction in odds of CHD events for clopidogrel and the combination of clopidogrel and aspirin were obtained from the CAPRIE[55] and CURE[35] trials, respectively. The percentage reduction in odds of non-coronary events for clopidogrel compared with aspirin was also taken from CAPRIE and this appears to have been applied to the combination of clopidogrel and aspirin also. The reduction in the rate of CHD events (MI, cardiac arrest and death from CHD) for aspirin, clopidogrel and the combination of aspirin and clopidogrel was 31, 33.7 and 37.2%, respectively. The corresponding

reductions in the rate of non-coronary disease, which includes stroke, were 2.8, 2.9 and 2.9%, respectively.

The model includes the risk of GI adverse events and rash, and the rates for these are taken from CAPRIE for both clopidogrel and the combination of clopidogrel with aspirin. The baseline risk of (non-haemorrhagic) stroke is taken from an overview of secondary statin trials, and the relative risk reduction associated with aspirin for stroke appears to be taken from the ATT.

The baseline risks of events in the model are based on the Framingham Heart Study and have been updated using more recent published data concerning trends in cardiac disease. The current usage of aspirin among patients eligible for treatment was estimated from a profile of Medicare beneficiaries, and the potential usage was calculated from a population-based study of aspirin intolerance. In the base case, only 85% of patients are assumed to take aspirin. It is assumed that 94.3% are eligible or able to take aspirin.

Summary of resource utilisation and cost data

The prices of aspirin and clopidogrel were obtained from published price lists and the price of the combination of drugs was assumed to be the sum of the separate prices as a preparation containing both was not available. The costs associated with cardiac events, strokes and adverse events associated with treatment were taken from previously published studies. The cost of non-coronary care was a yearly estimate from a national survey. Costs were discounted at an annual rate of 3% and were reported in US dollars for the year 2000. Productivity costs and personal or informal care were not included in the analysis. The total cost associated with no treatment was estimated to be $1,797,000 million (mn) dollars for the whole US population. The corresponding cost associated with strategies (1)–(5) was estimated to be $1,874,000mn, $1,888,000mn, $2,054,000mn, $2,090,000mn and $1,898,000mn, respectively. The estimated cost of current usage of aspirin was $1,867,000mn.

The cost of coronary disease is initially lower with the interventions than with no treatment. However, the costs of non-coronary disease and later coronary disease soon become higher with the interventions as patients who would have died in the absence of treatment survive, thereby increasing the number of people alive with coronary disease and who may incur further costs.

Summary of cost-effectiveness data

Quality of life (QoL) for non-coronary events was obtained from an observational population-based study which presented preference-based QoL estimates for general stroke or brain haemorrhage. The precise values extracted from the study are not presented. QoL estimates for coronary disease are based on whether patients have angina, heart failure or both and are taken from a published study.

The current use of aspirin is estimated to be cost-effective, with a ratio of $11,000 per QALY gained. Extending the use to all eligible patients is also estimated to be cost-effective, with a ratio of $11,000 per QALY gained when compared with the current use of aspirin. The corresponding cost-effectiveness ratio for strategy 2 (aspirin for all eligible patients and clopidogrel for those patients ineligible for aspirin) can be calculated from the information given in the paper as being $19,000 per QALY gained relative to current use of aspirin. Strategy 3 (clopidogrel for all patients) and strategy 5 (clopidogrel for all patients plus aspirin for all eligible patients using data from CURE) have cost-effectiveness ratios of more than $100,000 per QALY gained compared with the current use of aspirin. This is driven largely by the additional acquisition cost of clopidogrel. The cost-effectiveness ratio of strategy 4 (clopidogrel for all patients plus aspirin for all eligible patients using the most optimistic estimates of relative risk reductions) compared with the current use of aspirin is $57,000 per QALY gained. This strategy employs the most favourable estimate of the RRR associated with aspirin plus clopidogrel from the early period of treatment (the actual period is not stated) and assumes that this reduction is maintained over the lifetime of the cohort. This contradicts the evidence from CURE which shows that the assumed risk reduction of 20% in coronary events is not reflected over 1 year of treatment. As such, the result should be interpreted with caution. Use of clopidogrel can only be considered cost-effective in this study when it is restricted to those patients ineligible for aspirin.

A series of univariate sensitivity analyses were performed which indicated that the outcome was sensitive to the effect of the interventions on revascularisation, which was zero in the base-case analysis. The study also explored the price of clopidogrel required to bring the estimated cost per QALY ratio below the posited threshold of $50,000. The results of the sensitivity analyses are not reported here as they do not change the decision about the cost-effectiveness of strategies

3 and 5. The sensitivity analysis may change the decision regarding strategy 4 but this strategy would have been more suitable as a sensitivity analysis itself.

Comments

This study appears to be comprehensive and well conducted, although is deficient in the presentation of model parameters. The study focuses on the general disease area of CHD rather than focusing on a particular aspect. As such, its relevance to ACS is clearly limited. Due to the potential heterogeneity in the different patient groups considered in the model, it would be inappropriate to conclude that the overall estimate of cost-effectiveness provides a reliable estimate for each of the specific groups. The existence of differences in the baseline event rates and costs of each of these groups may lead to different conclusions concerning the relative cost-effectiveness of the alternative strategies.

The specific transitions allowed in the model are not illustrated but may be assessed in previous papers that make use of the Coronary Heart Disease Policy (CHDP)[56] model. However, there is a potential concern that the CHDP model is largely derived from data assembled in 1987 and hence may not adequately reflect current treatment practices. Although the authors state that the model has been updated with revised estimates, it is difficult to assess the impact of these revisions due to the lack of transparency in the baseline event data. Furthermore, the model only includes patients who have survived 30 days following their acute event. In ACS patients, the first 30 days is a particularly high-risk period and it is also the period during which the greatest benefit from treatment may be attained. Failure to consider the impact of clopidogrel in this acute period will lead to an underestimate of the cost-effectiveness of the use of clopidogrel in combination with aspirin in patients with ACS.

In addition, from a UK NHS perspective, the study has a number of important limitations. First, the baseline data were sourced from a variety of sources including published studies, US national statistics and the Framingham Heart Study. The lack of clarity in these inputs means that insufficient detail is provided to assess the generalisability and transferability of these data to non-US settings. The costs are specific to the USA, as are the QoL estimates. As such, the results may not be generalisable to a UK setting where the pattern of care is likely to be different. The QoL estimates are not quoted and so the comparability with estimates from the UK cannot be assessed.

Review of the submission by Sanofi Synthelabo Ltd and Bristol-Myers Squibb

Overview

This model is designed to assess the long-term cost-effectiveness of 12 months of treatment with clopidogrel in addition to aspirin, compared with aspirin alone, for patients with non-ST-segment elevation ACS in the UK. The model is probabilistic, and is based on the cost-effectiveness model used in a previous NICE technology assessment report on glycoprotein IIb/IIIa antagonists.[57] The model consists of a short-term component which considers costs and effects over a 12-month period mirroring the period of follow-up of CURE, and a longer term element which extends the analysis over a longer term time horizon.

For the baseline analysis the expected costs and outcomes of a cohort of non-ST elevation ACS patients (of starting age 60 years) are evaluated over a time horizon of 40 years. The assumed treatment duration for clopidogrel in the model is based on the follow-up period in the CURE trial (9 months). For convenience, durations were rounded up and costed for the nearest full year. After 1 year, all patients were assumed to be treated with aspirin alone for the remainder of their life.

Baseline event rates applied in the model were obtained from UK observational data used in the glycoprotein IIb/IIIa model report. Baseline event data for the first 6 months were based on data from the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK)[58] and an audit of all non-ST-segment elevation ACS patients undergoing acute PCI at Leeds General Infirmary in 2000.[59] The use of UK-specific data to model baseline data was justified on the basis that the multinational trial evidence from CURE may differ from UK practice. Consequently, the use of baseline event rates (i.e. those relating to use of aspirin alone) observed in the control group of CURE trials may not provide reliable estimates for UK practice.

The short-term model is structured as a decision tree as shown in *Figure 5*.

Table 18 details the combined probabilities taken from PRAIS-UK and the Leeds PCI audit reported

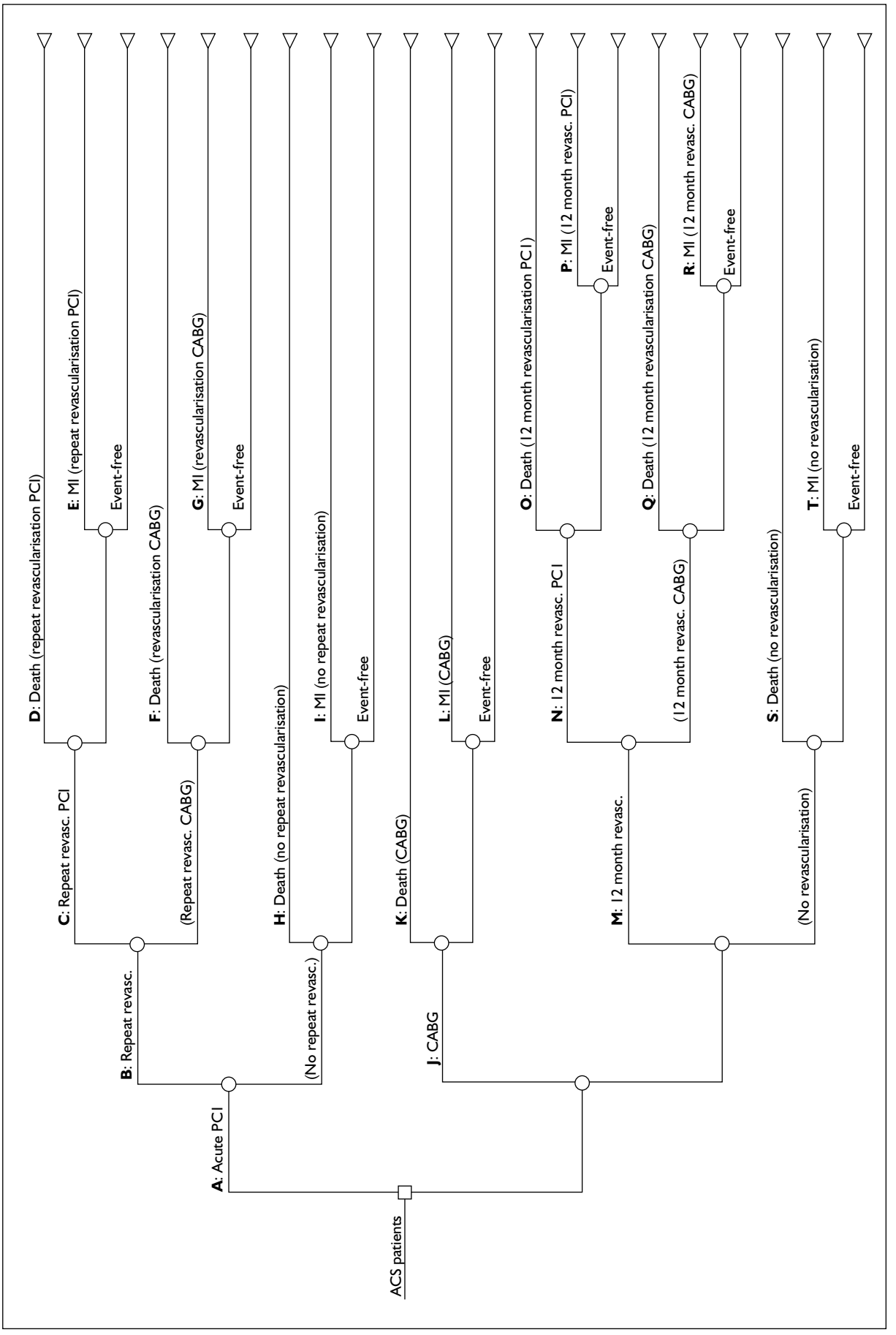


FIGURE 5 *Decision tree used in manufacturer's submission (reproduced from Sanofi submission)*

TABLE 18 *Baseline probabilities used in the short-term model taken from PRAIS-UK and the Leeds audit*

Node in *Figure 1*	Description	Probability	Parameters of the beta distribution[a]	
			α	β
A	Acute PCI	0.05	53	980
B	Repeat revascularisation	0.048	8	157
C	Repeat revascularisation PCI	1.00	–	–
D	Death (revascularisation PCI)	0.00	0.01	7.99
E	MI (revascularisation PCI)	0.13	1	7
F	Death (revascularisation CABG)	0.00	–	–
G	MI (revascularisation CABG)	0.00	–	–
H	Death (no repeat revascularisation)	0.03	5	152
I	MI (no repeat revascularisation)	0.03	5	147
J	CABG	0.05	47	933
K	Death (CABG)	0.11	5	42
L	MI (CABG)	0.07	3	39
M	6-month revascularisation	0.05	48	885
N	6-month revascularisation PCI	0.48	23	25
O	Death (6-month revascularisation PCI)	0.09	2	21
P	MI (6-month revascularisation PCI)	0.10	2	19
Q	Death (6-month revascularisation CABG)	0.00	0.01	24.99
R	MI (6-month revascularisation CABG)	0.16	4	21
S	Death (no revascularisation)	0.08	68	817
T	MI (no revascularisation)	0.05	40	777
	Baseline risk of GI bleeding:			
	(i) Undergoing PCI in acute period	0.00	0.01	52.99
	(ii) Undergoing CABG in acute period	0.02	1	46
	(iii) No initial revascularisation	0.01	12	921

[a] The parameter α represents the number of patients in the sample who experienced the event and β represents the number that did not (i.e. $\alpha + \beta$ = total sample).

by Palmer and colleagues.[57] that were used to construct a UK-specific baseline. This data, based on a 6-month period, were then extrapolated to 12 months (details are reported in the summary of effectiveness section).

Node labels relate to the decision tree in *Figure 5*. For each strategy, the initial chance node (node A) reflects uncertainty in whether a patient receives a PCI during the acute phase (30 days). For those who do not receive this 'acute PCI', there is uncertainty regarding whether they undergo a CABG instead during the acute period (node J); and for those who do not undergo CABG, there is uncertainty regarding whether any revascularisation is undertaken during the follow-up period (node M). For patients who receive an acute PCI, there is uncertainty regarding the need for repeat revascularisation (node B), which might be a further PCI or CABG (node C). For all patients, there is uncertainty regarding the final health-related outcomes of the short-term model over the initial 12-month period (nodes D–G, H–L and O–T). Three mutually exclusive outcomes are modelled: non-fatal MI, death and event-free during the 12-month period.

After this first year, patients entered a long-term model. Two long-term models were provided, although the results were only presented for one of these models. The base-case analysis was based on the long-term model reported in Palmer and colleagues[57] – see *Figure 6*. Depending on progress through the short-term model, patients enter the long-term model either in the event-free (IHD) state or the MI state. Patients entering the IHD state can experience a non-fatal MI, in which case they move to the MI state for 1 year, after which they can die or move to the post-MI state. Patients experiencing any subsequent non-fatal MIs remain in the post-MI state, although the costs of these recurrent events are incorporated in the model. Probability data determining how patients move between the states in *Figure 6* and the costs of the alternative health states were based on the analysis of two cohorts from the Nottingham Heart Attack Register (NHAR) reported in detail in Palmer and colleagues.[57]

Since the long-term data used in the base-case analysis data did not include stroke events, a secondary analysis using alternative baseline data sources was also undertaken to incorporate the

risk of stroke in ACS patients. The model in this secondary analysis used a combination of observational data sources that were used in a separate model developed to assess the cost-effectiveness of clopidogrel in the secondary prevention of OVEs. Patients begin the model in one of four health states: event-free, the first year following MI, the first year following stroke or vascular death. Patients face the risk of recurrent MI, recurrent stroke (only in the secondary analysis), vascular death, or death from other causes, or they may remain event-free. All patients experiencing MI or stroke enter a health state describing the first year after each event wherein the risk of experiencing a further event is greater than in the subsequent years. In the base-case analysis, patients may only move from MI to death and may not experience a recurrent MI. The first year following MI corresponds to an increased risk of death in the model. In the secondary analysis, patients may experience recurrent events. Patients who survive their first year following an initial or recurrent event without experiencing a subsequent event enter a post-stroke or post-MI health state where the risk of further events is lower.

Summary of effectiveness data

The RRR data for clopidogrel combined with aspirin compared with aspirin alone are taken from CURE. The RRR is for first events only. Clopidogrel combined with aspirin is associated with an RRR for non-fatal MI, non-fatal stroke, vascular death and PCI of 29, 27, 7, and 2.4%, respectively. The RRR for CABG was assumed to be the same as that for PCI. The combination is associated with an RR increase for bleeding events of 38%. In the model, the baseline event data for bleeding are modelled by applying separate estimates from PRAIS-UK for the probability of major bleeding in patients undergoing acute revascularisation (PCI and CABG) and patients with no initial revascularisation. No attempt is made to uprate the baseline bleed data reported at 6 months in PRAIS-UK to 1 year, despite the potential for a continued risk of a major bleed over the course of treatment with clopidogrel.

For the first year of the model, the baseline annual rate of strokes was taken from PRAIS-UK but, as this only presented information up to 6 months, these were extrapolated to annual rates by multiplying them by the proportion of events that occurred in the second 6 months of the CURE trial. The baseline annual rates of MI and vascular death were taken from NHAR and calculated by adding the rate in the first 6-months to half the annual rate for the subsequent years. The risk of PCI or CABG was not uprated and, therefore, the 6-month risk is applied without alteration. The baseline risk of non-vascular death is calculated from published national statistics. All baseline risks are implicitly assumed to be those associated with aspirin monotherapy.

The base-case long-term risk of events was taken from the study by Palmer and colleagues,[57] which calculated the risk of all future events for the cohort using standard survival analytic techniques.

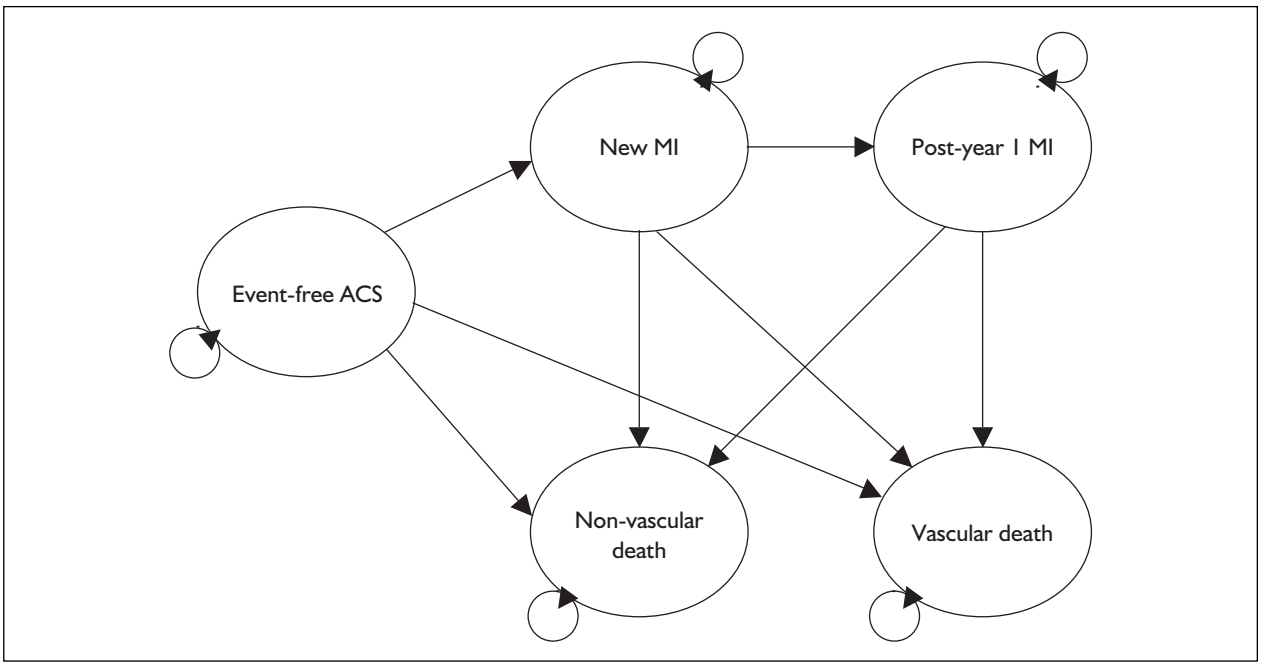


FIGURE 6 *Base case long-term model submitted by Sanofi Sythelabo Ltd and Bristol-Myers Squibb*

TABLE 19 *Annual transition probabilities used in the long-term model (95% CIs) based on data taken from the NHAR*

	To state			
From state	**IHD**	**Non-fatal MI**	**Post-MI**	**All-cause death**
IHD	0.9049 (0.8896 to 0.9186)	0.0186 (0.0133 to 0.0254)	–	0.0765 (0.0643 to 0.0904)
Non-fatal MI	–	–	0.7900 (0.7177 to 0.8471)	0.2100 (0.1529 to 0.2822)
Post-MI	–	–	0.9266 (0.9024 to 0.9466)	0.0734 (0.0534 to 0.0976)
Dead	–	–	–	1

The probabilities used are shown in *Table 19*. However, an error was made in the calculation of the baseline risk of vascular death in this model. The risk of vascular death applied in the model was based on the estimate of all-cause mortality reported in Palmer and colleagues derived from PRAIS-UK/Leeds (short-term model) and the NHAR (long-term model). Consequently, the model overestimates the risk of death faced by patients by including an additional risk of non-vascular mortality which had already been incorporated.

The long-term baseline probability of any event in the secondary analysis was calculated using a logistic regression to model the risk of any event at each age from 60 to 90 years old from two observational cohort studies. The NHAR was used to predict outcomes for MI patients, and the South London Stroke Register (SLSR)[60] was used to calculate probabilities for stroke patients. The initial probability of a stroke in ACS event-free patients was assumed to be 0.01. The type of event was calculated by employing a multinomial regression to predict the ratio of MIs, strokes and vascular deaths occurring at each age from 60 to 90 years old, with the exception of the SLSR as no data were available on MIs in this dataset. The risk of MI for stroke patients in the SLSR was assumed to be the risk of MI following stroke in CAPRIE. The probabilities of MI, stroke and vascular death can be calculated from these ratios. The probability of these events were modelled as log-normal distributions. As this distribution is not bounded at one, the probability of stroke, vascular death and either stroke or vascular death could exceed one in some simulations. Where this was the case, the probability of an MI was less than zero in order to maintain the correct number of patients in the cohort. This problem can be overcome by instead modelling the ratios directly in a distribution, as when they are converted into probabilities they automatically sum to one.

The baseline probability of non-vascular death was calculated from published national statistics which presented the number of deaths in England and Wales by International Classification of Diseases (ICD) code. The proportion assumed to be vascular with ICD codes corresponding to diseases of the circulatory system were removed in order not to double count the number of vascular deaths.

Summary of resource utilisation and cost data

The costs associated with stroke are taken from the study by Chambers and colleagues[61] and inflated to the current price year. The costs in the Chambers study were largely derived from expert clinical opinion. The costs include long-term care but not informal, personal or indirect costs. The costs associated with MI and ACS are taken from the glycoproteins model,[57] which calculated them from the subgroup of ACS patients in NHAR. The costs of revascularisation procedures are taken from NHS reference costs and the costs of bleeding events are taken from a published study.[62,63] The costs of revascularisation differed from the estimates reported by Palmer and colleagues,[57] which were based on fully-allocated costs according to the observed length of hospitalisation and interventions reported in PRAIS-UK. The costs of ACS and MI were modelled as normal distributions truncated at a minimum of £500. The cost of stroke, PCI, CABG and bleeding events were modelled as triangular distributions. The costs used in the model are give in *Table 20*.

Summary of cost-effectiveness data

Costs are discounted at 6% and heath benefits are discounted at 1.5%. The model calculates the total cost, total number of events and presents cost per QALY or cost per life-year gained. QALYs were calculated by applying utility values taken from published studies to six health states: ACS event-free year 1, ACS event-free year 2, MI year 1,

MI post-year 1 and stroke (combined disabled and non-disabled).

The utilities of ACS patients were estimated from combination of different sources including estimates associated with stroke, MI and angina. The utilities for MI were taken from the same studies as the utilities for ACS health states. The utility for stroke was estimated from a meta-analysis of utilities for stroke. The utilities for each health state are given in *Table 21*.

The utility values were assigned triangular distributions. Three utility values were obtained for the MI and ACS states and the lowest of these was assumed to be the minimum, the highest the maximum and the central estimate the most likely. The bounds for the stroke utility scores were calculated in part from the standard errors in the meta-regression.

In the ACS model base case, the deterministic estimate of cost per QALY associated with clopidogrel as compared to aspirin is £5668.

TABLE 20 *Cost parameters used in model submitted by Sanofi Synthelabo Ltd and Bristol-Myers Squibb: £ sterling 2002*

Cost parameter	Cost per year (range) (£)
ACS event-free	1421.00 (1316–1526)
MI year 1	3966.00 (3209–4723)
MI post-year 1	1587.00 (840–2334)
Stroke year 1	7465.80 (5599–11199)
Stroke post-year 1	4532.80 (3400–6799)
PCI intervention	2445.00 (1504–2520)
CABG intervention	6275.00 (5144–7034)
Bleed intervention	2377.24 (1783–3566)
Aspirin	3.47
Clopidogrel plus aspirin	463.76
Clopidogrel day 1 loading dose	5.04

TABLE 21 *Utility estimates used in model submitted by Sanofi Synthelabo Ltd and Bristol-Myers Squibb*

Heath state	Utility (range)
ACS event-free, year 1	0.80 (0.70–0.90)
ACS event-free, post-year 1	0.93 (0.88–0.98)
Independent stroke	0.74 (0.69–0.79)
Dependent stroke	0.38 (0.29–0.47)
New MI, year 1	0.80 (0.70–0.90)
New MI, post-year 1	0.93 (0.88–0.98)

Deterministic sensitivity analyses

Several univariate and multivariate sensitivity analyses were conducted for a 40-year time horizon (treatment with clopidogrel for 1 year only). The results of these are presented in *Table 22*.

Clopidogrel with aspirin appears cost-effective in most of the analyses except numbers 10 and 11. The relative risks of stroke and death both constitute relative risk increases when they are set to the upper 95% CI. When the health state costs are increased, the cost-effectiveness of clopidogrel with aspirin becomes more favourable. This is a combination of competing effects. When the cost of the initial states increases, the treatment will become less cost-effective as the reduction in risk of recurrent events means proportionally more patients remain in these initial states on treatment. In contrast, if the cost of new events increases, treatment with clopidogrel becomes more cost-effective as the value of preventing events is increased. The treatment looks more effective when compliance is set to the rates seen in the CURE trial as it is assumed that the RRRs taken from the ITT analyses remain the same, but the

TABLE 22 *Deterministic sensitivity analyses provided in report submitted by Sanofi Synthelabo Ltd and Bristol-Myers Squibb*

Assumption	Cost per QALY (clopidogrel vs aspirin) (£)
Base case	5668
1. Health state costs set to upper 95% CI	5000
2. Health state costs set to lower 95% CI	6332
3. Trial compliance rates	4545
4. RRRs set to 80%	7006
5. Utilities set to upper 95% CI	5446
6. Utilities set to lower 95% CI	5909
7. Risk and cost of bleeding events set to upper 95% CI	5909
8. RR for MI set to upper 95% CI	6373
9. RR for stroke set to upper 95% CI	5949
10. RR for death set to upper 95% CI	More costly, less effective
11. RR for MI, stroke and death set to upper 95% CI	More costly, less effective
12. Equal 6% discount rate for costs and effects	7521

cost of supplying the drug is reduced. Sensitivity analysis number 4 is more realistic as 100% of the drug costs are incurred as they are all prescribed to patients but reduced compliance means that the effectiveness is reduced, which is modelled by reducing the RRRs to 80% of those observed in the trial. When the utilities are increased the treatment looks less cost-effective because the health cost of each event is lower, and the converse is true when the utilities associated with each state are reduced. When the risk and cost of bleed events increases, the treatment appears less cost-effective as it is associated with an RR increase for bleeds. When the same discount rate is used for health benefits as for costs, the cost-effectiveness is reduced as the net present value of the health gains associated with treatment is reduced.

Additional sensitivity analyses were performed in which the baseline risk of events were varied. Only when the baseline risk of total events falls to 2% and the risk of vascular death falls to 1% does the cost-effectiveness of treatment exceed £30,000.

Probabilistic sensitivity analysis

In the probabilistic analysis, all of the parameters in the model are allowed to vary simultaneously according to their distribution. This provides a more comprehensive estimate of the uncertainty about the cost-effectiveness of the treatment compared with the univariate sensitivity analyses by accounting for the full range of possible values in each (uncertain) input. The probabilistic analysis indicates that the probability that treatment with clopidogrel and aspirin is more cost-effective than treatment with aspirin alone increases as the willingness to pay for an additional QALY increases. If society is willing to pay £10,000 for an additional QALY, the probability that treatment with clopidogrel and aspirin is cost-effective is around 0.72; if society is willing to pay £30,000 it rises to 0.85, and if society is willing to pay £50,000 it is 0.87.

Comments

The model appears comprehensive and well presented. The model structure is flexible enabling a range of sensitivity analysis to be reported. The treatment duration considered is 1 year. Data from the CURE trial suggest that a large proportion of events occur in the first 30 days to 3 months following diagnosis and there is also a suggestion of a temporal element to the treatment effect. As such, it may be useful to consider alternative treatment strategies involving shorter durations of treatment. In the base case, only MIs and not strokes are considered. This seems reasonable given that the main risk faced by these patients is of recurrent MI.

The only adverse event considered in the model is bleeding, and this is assumed to be a proportion of those patients undergoing PCI. Antiplatelet therapy alone in the absence of PCI is associated with an increased risk of bleeding events and as such it may be more realistic to attribute bleed events as a proportion of all patients in the cohort. This would also enable bleeding events to be modelled over the long-term model rather than confined to the first year. An associated issue is that the use of PCI in ACS patients is increasing over time.[64] The rate of PCI in PRAIS-UK may be lower than that in current practice. The source of the cost estimate for bleeding events included fatal bleeds, which may overestimate the cost of bleeding events. As treatment is associated with more bleeding events then this may be a conservative assumption.

In the secondary analysis, only age was used as a covariate for predicting vascular events in the logistic and multinomial regression equations. There are potentially many more risk factors which are important predictors of vascular events. It is particularly important to consider these when using data from separate cohort studies which may have been conducted on very different patient groups. A further problem arises in the secondary analysis when patients are allowed to experience stroke and then experience MI. The utility associated with stroke is lower than the utility associated with MI, and as such this allows patients' utility to increase following an MI event. Their costs also fall as the long-term care cost for MI patients is lower than that for stroke patients. This is counter-intuitive and can be remedied by not allowing patients to experience any rise in utility or fall in long-term care costs once they have experienced a stroke. The costs associated with stroke are based solely on expert opinion and as such their validity is uncertain.

Summary of the cost-effectiveness evidence

Of the cost-effectiveness evidence reviewed, only the manufacturers' submission was relevant to the current review and assessed from the perspective of the UK NHS. This review has highlighted the potential limitations within this submission in its use of data and in the model structure used. This has led to the development of a new model with the aim of providing more reliable estimates of the cost-effectiveness from the perspective of the UK NHS.

Chapter 6
Economic model

Introduction

The review of economic evidence from the literature and manufacturers' submissions, reported in Chapter 5, has highlighted a number of potential limitations in existing studies assessing the cost-effectiveness of clopidogrel from a UK NHS perspective. First, the only study identified in the systematic literature search used data from the non-UK sources to derive estimates of baseline event data, resource utilisation and costs. The generalisability of these estimates to the UK NHS is potentially unreliable. This is particularly important since the cost-effectiveness of clopidogrel obtained in a UK population may be very different to those found in patients randomised to the control group in CURE or observational data from US sources. This might reflect differences in the epidemiology of the disease or, more probably, differences in overall management in the UK.

The issue of generalising the results from CURE to a UK setting was directly addressed in the manufacturers' submission by Sanofi-Synthelabo Ltd and Bristol-Myers Squibb, by sourcing relevant baseline data from UK-specific sources. Despite the potential merit of this approach in the context of informing the cost-effectiveness estimates from a UK NHS perspective, there were a number of potential inaccuracies in the analysis and concern was noted related to several assumptions underlying the analysis. These limitations meant that it was not possible to make a reliable comparison of the relative cost-effectiveness of clopidogrel in combination with standard treatment, compared with standard treatment alone, on the basis of existing evaluations. To overcome these limitations and to assist the decision-making process in the context of the NHS, a new model was developed. The following sections outline the structure of the model in detail and provide an overview of the key assumptions and data sources used to populate the model.

Methods

Overview

The model has been developed to estimate costs from the perspective of the UK NHS, and health outcomes in terms of life-years and QALYs. For the main analysis, a lifetime time horizon was used, that is, the model considers the costs and outcomes of a hypothetical cohort of patients with non-ST-segment elevation ACS over a period of 40 years. As a secondary analysis, cost and outcomes are also reported over a 5-year time horizon (representing the maximum period of follow-up data available from the observational data used). The model is made up of two parts: a short-term element, which relates to a period of 12 months after a patient presents with non-ST-segment elevation ACS, and a long-term element, which extrapolates a patient's lifetime costs and outcomes conditional on surviving the first 12 months after the acute episode.

The model has been adapted from the decision model recently undertaken to evaluate the cost-effectiveness of glycoprotein IIb/IIIa inhibitors (GPAs) in patients with non-ST-segment elevation ACS.[57] Details of the methodology and data inputs are reported in full in the earlier assessment report.[57] To avoid excessive duplication, only a brief overview of the data sources and input parameters is reported here. By utilising the previous GPA model reported by Palmer and colleagues,[57] both the model structure and data share a common basis with the cost-effectiveness model submitted as part of the manufacturers' submission. However, access to the full-range of data sources reported by Palmer and colleagues,[57] (including patient-level data on resource utilisation) has enabled a more comprehensive approach to be undertaken in comparison with the manufacturers' submission. Where there were differences between our modelling approach and that undertaken as part of the manufacturers' submission, these are reported in each section. Justification for the use of alternative data or assumptions is also provided. Where uncertainties remain regarding the most appropriate assumption, these are addressed using sensitivity analysis to explore the robustness of the model to alternative assumptions proposed in the manufacturers' submission.

The model is probabilistic in that all input parameters are entered as probability distributions to reflect their imprecision, and Monte Carlo

simulation is used to reflect this uncertainty in the model's results.[65,66] A 2001–02 price base is used and annual discount rates of 6% for costs and 1.5% for benefits are adopted in the base-case analysis.[67]

Treatment strategies under comparison

In the base-case analysis, two strategies are considered:

- strategy 1: treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 12 months, followed by standard therapy for the remainder of a patient's lifetime
- strategy 2: lifetime treatment with standard therapy (including aspirin) alone.

Although patients with ACS remain at continued risk of death, MI or recurrent ischaemia, the majority of these events occur early after the acute event. Evidence from observational sources indicates that the highest risk of cardiac death is at the time of presentation, and after 2 months this risk declines to the same level as for patients with chronic stable angina.[67] Similar reductions in the rate for non-fatal cardiac events (myocardial infarction, recurrent angina) have been also been reported after the initial hospitalisation.[68,69] This relationship was also evident in the CURE trial. Of the total number of CV deaths reported up to 1 year (placebo group), approximately 37% were incurred during the first 30 days, 65% by 3 months and 81% by 6 months (data provided by manufacturer).[35]

Although there does not appear to be adequate statistical support for a reduction in the relative treatment effect of clopidogrel over the course of the follow-up period reported in the CURE trial, the benefit of treatment with clopidogrel will clearly be greatest when the absolute baseline risk is highest. From an efficiency perspective, this may have important implications concerning the optimal duration of treatment with clopidogrel. Treatment with clopidogrel for shorter durations may therefore be considered alternative strategies to those included in the base-case analysis and their relative cost-effectiveness should be considered. A series of sensitivity analyses were therefore undertaken to explore the relative cost-effectiveness of alternative durations of treatment with clopidogrel. Three alternative strategies (representing treatment with clopidogrel over a 1, 3 or 6-month duration) were considered alongside the two main strategies included in the base-case analysis. This series of analyses is reported in detail in later sections (pp. 47 and 51). The following sections report the structure, data inputs and results for the base-case analysis.

Short-term model

Structure

The short-term model is structured using the same decision tree as shown in the section 'Overview' (p. 27) (*Figure 5*) and characterises the period up to 12 months following an episode of ACS. Baseline probabilities of death, non-fatal MI and revascularisation, and also resource utilisation and costs, are incorporated to reflect standard therapy (strategy 2). Three mutually exclusive outcomes are modelled: MI, death (CV and non-CV) and IHD without non-fatal MI during the 12-month period. These outcomes also represent the starting health states for the long-term model. Full details on the methodology and data sources used to populate the short-term model are reported in the following sections.

Baseline probabilities in the short-term model

Patients in the CURE trial were recruited from 482 centres in 28 countries, of which patients from the UK accounted for approximately 6% of the total sample. The largest single recruiting centres were Poland (16%) and Canada (14%). In many respects, treatment patterns and resource use in the UK can be expected to differ from those in other centres involved in the CURE trial. For example, the rate of PCI in patients with ACS, and in IHD generally, is lower than in most developed countries.[64] One implication of these differences in UK practice is that the baseline event rates observed in the control group of the CURE trial are unlikely to provide reliable estimates for UK practice. A similar justification for using UK specific sources of baseline event data was provided in the industry submission by Sanofi-Synthelabo Ltd and Bristol-Myers Squibb.

For this reason, we constructed baseline event rates, specific for UK practice, from an alternative data source.[70] This is an observational cohort registry of 1046 patients admitted to 56 UK hospitals with ACS between 23 May 1998 and 3 February 1999. Patients were followed up for 6 months after their index hospital admission. Patients were eligible if they were admitted to hospital with a primary clinical diagnosis of ACS without ST elevation on the admission ECG. The hospitals included in PRAIS-UK served 24% of the UK population. For the purposes of this model, patients who received glycoprotein IIb/IIIa

antagonists in PRAIS-UK (n = 13; 1%) were excluded from the analysis.

The parameter estimates from PRAIS-UK relating to patients who received a PCI during the acute phase of their ACS were based on a relatively small number of patients (n = 53). For this reason, supplementary data from an audit of ACS patients undergoing acute PCI at a large UK cardiac centre (Leeds) were included.[59] All acute PCIs (n = 213) performed in the calendar year 2000 were identified from the angiography suite database. Case-notes were obtained from medical records for 211 (99%) patients (two patients were excluded owing to a lack of case-note data). Absolute numbers of Leeds patients in each baseline category were then added to the equivalent numbers from PRAIS-UK and the totals entered into the model.

Table 23 details the combined probabilities taken from PRAIS-UK and the Leeds PCI audit, that were used to construct a UK-specific baseline. Uncertainty in these probabilities is characterised using the beta distribution with the α parameter being the number of patients who experienced the event of interest in the relevant subsample and β the number of patients who did not experience the event.

The baseline event data are used to represent standard therapy in the UK (including treatment with aspirin), that is, strategy 2. Evidence from PRAIS-UK demonstrated that aspirin was actually only used in 87% of patients in hospital and 78% at 6 months follow-up.[70] This contrasts with data from CURE which reported aspirin use in 99% of patients in hospital, 96% at 3 months and 94% at the final follow-up.[35] Consequently, the baseline data from PRAIS-UK may overestimate the risks of the primary outcomes compared to use of aspirin in all patients (in the absence on contraindications).

A comparison of the outcomes in PRAIS-UK at 6 months with the main study outcomes reported in CURE at 9 months demonstrated that patients in PRAIS-UK had a higher incidence of the major outcomes. Both the rate for all-cause mortality (7.4% vs 6.2%) and a composite measure based on death, MI and stroke (14.8% vs 11.4%) were higher in PRAIS-UK than the aspirin group in CURE. These data provide potential support for the aforementioned caveat concerning the

TABLE 23 *Baseline probabilities used in the short-term model taken from PRAIS-UK[69] and Leeds audit[59]*

Node in *Figure 5*	Description	Probability	Parameters of the beta distribution	
			α	β
A	Acute PCI	0.05	53	980
B	Repeat revascularisation	0.048	8	157
C	Repeat revascularisation PCI	1.00	–	–
D	Death (revascularisation PCI)	0.00	0.01	7.99
E	MI (revascularisation PCI)	0.13	1	7
F	Death (revascularisation CABG)	0.00	–	–
G	MI (revascularisation CABG)	0.00	–	–
H	Death (no repeat revascularisation)	0.03	5	152
I	MI (no repeat revascularisation)	0.03	5	147
J	CABG	0.05	47	933
K	Death (CABG)	0.11	5	42
L	MI (CABG)	0.07	3	39
M	6-month revascularisation	0.05	48	885
N	6-month revascularisation PCI	0.48	23	25
O	Death (6-month revascularisation PCI)	0.09	2	21
P	MI (6-month revascularisation PCI)	0.10	2	19
Q	Death (6-month revascularisation CABG)	0.00	0.01	24.99
R	MI (6-month revascularisation CABG)	0.16	4	21
S	Death (no revascularisation)	0.08	68	817
T	MI (no revascularisation)	0.05	40	777
	Baseline risk of GI bleeding: All patients	0.01	13	1020
	Baseline risk of stroke: All patients	0.01	15	1018

Node labels relate to the decision tree in *Figure 5*.

potential elevated risk compared with a true baseline of treatment with aspirin in all patients. However, these differences also have to be considered in relation to the characteristics of the samples (patients in PRAIS-UK were about 2 years older than patients recruited in CURE, 66 vs 64 years) and the different inclusion and exclusion criteria applied in the studies. In particular, patients with the following characteristics were excluded from the CURE trial: contraindications to antithrombotic or antiplatelet therapies; at high risk for bleeding or severe heart failure; those taking oral anticoagulants and those who had undergone coronary revascularisation in the previous 3 months; and the use of intravenous GPAs in the previous 3 days. In contrast, patients recruited in PRAIS-UK were not subject to these exclusion criteria and hence it may be argued that these patients are more representative of those faced in actual clinical practice than the sample of patients recruited in CURE. The apparent differences in the utilisation of aspirin between PRAIS-UK and CURE may also be due, in part, to the inclusion of patients in PRAIS-UK in whom aspirin was contraindicated. On balance, the use of PRAIS-UK data appears to be more generalisable to routine clinical practice in the UK compared with the aspirin group in CURE.

Baseline resource use and cost data

Within the short-term model, baseline resource use data are taken from PRAIS-UK, and these data are detailed in *Table 24*. In part, resource use relates directly to the clinical events shown in the short-term model structure, specifically to revascularisation using PCI or CABG. In addition, mean length of inpatient hospital stay is taken from PRAIS-UK. This is entered separately into the model according to whether or not revascularisation was undertaken during the acute period and, if so, whether it was PCI or CABG. For patients who undergo (repeat or initial) revascularisation within the initial 6 months, but outside of the acute period, length of stay data were not collected in PRAIS-UK. For PCI undertaken outside the acute period, a fully allocated cost for the procedure was applied from published estimates,[71] whereas for CABG it was assumed that these parameters take on the same value as the length of stay observed in the study for acute revascularisation. Uncertainty in the level of resource use has been incorporated by assigning distributions to each input parameter. The probability of a particular item of resource use is characterised by a beta distribution and lengths of inpatient stay in hospital are characterised as log-normal distributions.

This costing approach outlined above for data from PRAIS-UK differs from the approach applied in the model submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squibb. In the absence of patient-level data on resource utilisation, the company applied estimates of the costs of

TABLE 24 *Resource use associated with the short-term model taken from PRAIS-UK*[57]

		Parameters of the beta distribution	
Item of resource use	**Probability**	α	β
Angiography when:			
(i) Undergoing PCI in acute period	0.96	51	2
(ii) Undergoing CABG in acute period	0.81	38	9
(iii) No initial revascularisation	0.21	193	740
CCU stay when:			
(i) Undergoing PCI in acute period	0.38	20	33
(ii) Undergoing CABG in acute period	0.61	28	18
(iii) No initial revascularisation	0.41	375	543
	Mean value	**Standard deviation**	
Length of inpatient stay:			
(i) Undergoing PCI in acute period	10.30	8.04	
(ii) Undergoing CABG in acute period	15.28	12.32	
(iii) No initial revascularisation	5.45	4.78	
Length of CCU stay:			
(i) Undergoing PCI in acute period	3.70	4.12	
(ii) Undergoing CABG in acute period	4.71	6.61	
(iii) No initial revascularisation	2.11	1.95	

hospitalisations and procedural costs taken from national sources. The generalisability of these estimates (in particular the procedural costs which are based on a variety of patient groups from NHS Reference Costs) to non-ST-segment elevation ACS patients is unclear.

Three other areas of resource use are modelled explicitly within the baseline model: non-fatal MI, adverse events (stroke and major bleeds) and resources associated with death. For patients who experience a non-fatal MI during the 6-month period, resource use and cost are incorporated into the model based on costs estimated in NHS hospitals in England.[62] Costs associated with death are based on the likelihood of dying in hospital and the associated length of hospital stay, as reported in the NHAR.

Adverse events related to major bleeding and stroke are also incorporated into the short-term model. These events do not formally comprise separate health states in the model and as such only the costs of these events are included. Baseline data on the probability of a major bleed (1.3%) or stroke (1.5%) were based on data from PRAIS-UK. All other costs in the short-term model (e.g. the costs of pharmaceuticals other than clopidogrel and aspirin) are assumed to be equivalent in the various strategies.

All unit cost data used in the analysis to value resource use are shown in *Table 25*, together with the sources of those data. The acquisition costs of clopidogrel and aspirin are based on undiscounted prices from the BNF.[72] For clopidogrel, the total drug costs per patient are based on an initial loading dose (300 mg, day 1) followed by 75 mg daily (364 days). For aspirin, the total costs are based on a daily dose of 300 mg. The overall costs for the drugs in strategy 1 are £467.54 (£464.07 for clopidogrel plus £3.47 for aspirin) and in strategy 2 are £3.47. These unit costs are used, together with the resource use data, to generate an overall mean cost (and standard deviation) of each of the pathways in the short-term model.

Extrapolation of 6-month baseline data to 12 months

Baseline data reported in PRAIS-UK were only reported at 6 months follow-up. In order to provide input parameters into the short-term model it was necessary to extrapolate these data to 12 months to reflect the follow-up period reported in the CURE trial. For the major outcomes (all-cause mortality, non-fatal MI and event-free) this was undertaken using the annual transition probabilities applied in the long-term model from the NHAR (full details of the long-term data are reported in the section 'Transition probabilities' (p. 41)]. The annual probabilities applied from the NHAR were converted to 6-monthly probabilities by calculating the underlying hazard rate over the 12-month period. In contrast to probabilities, the annual hazard rate can be divided by a factor of 2 to convert to a 6-monthly hazard, and the 6-monthly probability can then be easily obtained. This approach differed from the manufacturers' submission which estimated the 6-monthly probabilities by simply applying half the annual

TABLE 25 *Unit costs used in the analysis*

Unit cost	Unit	Base-case value (£)	Source reference
PCI	Procedure	1410.04	71
CABG	Procedure	4902.22	71
Repeat PCI	Per day	2976.00	71
Angiogram	Procedure	748.25	71
Cardiac ward	Day	157.47	71
Non-cardiac ward	Day	244.00	71
Coronary care unit	Day	459.04	71
Outpatient	Visit	59.70	71
Cardiac day case	Visit	108.58	71
Non-cardiac day case	Visit	182.00	71
Guidewire	Item	61.75	71
Stent	Item	599.01	71
Guiding catheter	Item	37.05	71
Blood	Unit	85.00	Specific NHS trust
Full blood count	Item	4.00	Specific NHS trust
Endoscopy	Item	246.00	71
Clopidogrel	28-tablet pack, 75 mg	35.31	72
Aspirin	20-tablet pack, 300 mg	0.19	72

probability. The industry approach will not correctly estimate the transitions between particular health states; however, this is unlikely to impact significantly upon the final results since the size of the error in this instance is not large.

Costs incurred in the 6-month extrapolation were based on half the mean annual cost derived from the NHAR data for the IHD, non-fatal MI and post-MI states. In addition to these costs, the additional costs of major bleeding and stroke were also included. In the absence of data on either of these events from the NHAR registry, the bleed data from PRAIS-UK were uprated from 6 months to 12 months assuming a constant hazard over this period. The observed probability at 6 months from PRAIS-UK was 1.3%, and extrapolating these data to 12 months increased the rate to 2.5%. This approach differed from the industry submission, which did not uprate the bleed data beyond the initial 6-month period. The incidence of stroke at 6-months reported in PRAIS-UK was 1.5%. This was uprated to 12 months using the same approach applied in the manufacturers' submission by using the proportion of additional strokes observed between 6 and 12 months in CURE.

Effectiveness of clopidogrel and aspirin compared with aspirin alone

The RRs taken from the CURE are shown in *Table 26* for the use of clopidogrel in addition to aspirin compared with aspirin alone. Separate RRs for each of the major end-points in the short-term model are provided. To account for uncertainty in these estimates, the logRRs are modelled as normal distributions. These results are then exponentiated to provide estimates of the RRs applied in the probabilistic analysis. The RR reductions are only applied to the initial 12-month period; in other words, the duration of the treatment effect of clopidogrel is 1 year only, which is the same assumption as made in the manufacturers' model.

TABLE 26 *Relative risks of outcomes applied in decision model: clopidogrel plus aspirin vs aspirin alone*[35]

Outcome	Relative risk	
	Mean (95% CI)	LogRR (SE)
All-cause mortality	0.93 (0.81 to 1.07)	–0.08 (0.07)
Non-fatal MI	0.71 (0.60 to 0.84)	–0.34 (0.09)
Non-fatal stroke	0.73 (0.50 to 1.09)	–0.31 (0.20)
Major bleed	1.38 (1.13 to 1.67)	0.32 (0.10)
Revascularisation	0.98 (0.93 to 1.02)	–0.02 (0.02)

Long-term model

Rationale

Any assessment of the cost-effectiveness of clopidogrel in combination with standard therapy should allow for the long-term cost and outcome implications of the short-term effects of the drug. In order to provide a realistic estimate of the QALY impact of clopidogrel, the long-term implications for survival and health-related QoL of the short-term effects for clopidogrel reported during the the first 12 months need to be modelled.

The long-term (extrapolation) model estimates a future prognosis for patients who finish the short-term (12 months) model in one of two disease states: those having experienced a non-fatal MI and those who have not (IHD). That prognosis will include the possibility of patients experiencing further non-fatal MIs and also dying (from both CV and non-CV reasons). Hence the extent to which the use of clopidogrel reduces the risk of death and non-fatal MI, relative to baseline, during the initial 12-month period will be translated into differences in long-term costs and QALYs on the basis of the long-term model.

Structure

The long-term model takes the form of a four-state Markov process as illustrated in *Figure 7*. Depending on progress through the short-term model, patients enter the model either in the IHD state or the non-fatal MI state. Patients entering the IHD state can experience a non-fatal MI, in which case they move to the non-fatal MI state for 1 year, after which they can die or move to the post-MI state. Patients experiencing any subsequent non-fatal MIs remain in the post-MI state, although the costs of such events are reflected in the model. The transitions from the

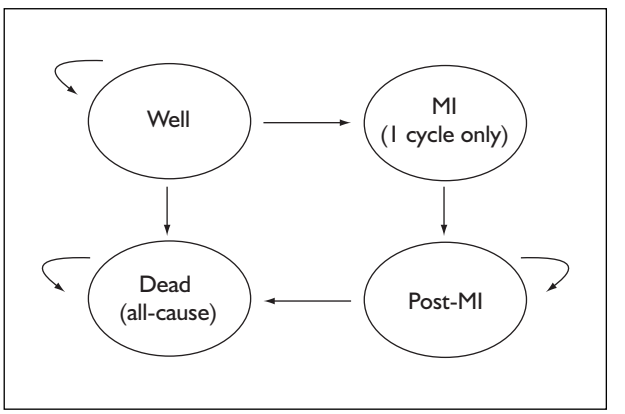


FIGURE 7 *Structure of the long-term model*

TABLE 27 *Annual transition probabilities used in the long-term model (95%)*

	To state			
From state	**IHD**	**MI**	**Post-MI**	**Dead**
IHD	0.9096 (0.8976, 0.9198)	0.0181 (0.0139, 0.0239)	–	0.0723 (0.0634, 0.0829)
MI	–	–	0.8123 (0.7613, 0.8510)	0.1877 (0.1489, 0.2385)
Post-MI	–	–	0.9303 (0.9121, 0.9451)	0.0697 (0.0549, 0.0879)
Dead	–	–	–	1

Data are based on 2.5 and 97.5 percentiles from the Monte Carlo simulation.

IHD, non-fatal MI and post-MI states to the dead state reflect the all-cause mortality risk (including both cardiovascular and non-cardiovascular mortality) estimated from the NHAR data (see the next section).

The structure of this model is similar to that used in the manufacturers' submission. However, rather than modelling death as a single state, the manufacturers separated the dead state into two separate states: vascular death and non-vascular death. The transition probabilities applied in the manufacturers' model for the transition to vascular death (from IHD, non-fatal MI and post-MI) mistakenly utilised the 'all-cause' mortality risk reported by Palmer and colleagues.[57] Consequently, by incorporating an additional transition to non-vascular death, the manufacturers over-estimated the risk of mortality in the long-term model. The estimates of life-years and QALYS gained with the combination of clopidogrel and standard therapy are therefore likely to be conservative estimates.

Transition probabilities

The transition probabilities used in the long-term model are shown in *Table 27* and are based on a cycle length of 1 year. Probability data determining how patients move between the states in *Figure 7* are based on the analysis of two cohorts from the NHAR. These cohorts [from 1992 (n = 979) and 1998 (n = 300)] were chosen because extensive additional follow-up had already been conducted. The subgroup of patients used had an initial working diagnosis of either typical ischaemic pain/angina on cardiac presentation (rule out MI), or patients who were suspected of having had an MI but which was later ruled out.

Transition probabilities were calculated from the NHAR data using survival analysis techniques.[57] These methods allowed for both censoring and differential follow-up between the two NHAR cohorts. In undertaking the revised analysis a minor error was noted in the calculations for the transitions applied in the previous GPA model report.[57] By applying the reported transitions probabilities directly from the GPA model report, the manufacturers' submission also included this error. However, the magnitude of the error was minimal. All data and analyses reported in the following section have rectified the error and are based on the correct probability estimates for each of the transitions in the long-term model.

Based on a cycle length of 1 year, the annual percentage probability of non-fatal MI and death were estimated to be 1.8% and 7.2%, respectively, for IHD patients. The probability of death in the first year following non-fatal MI was 19% and for subsequent years was 7%. These probabilities are assumed to be fixed with respect to time; in other words, the probabilities remain the same no matter how many cycles have elapsed. The validity of this assumption has been justified previously in this dataset.[57] The uncertainty associated with each transition probability was characterised by assigning a normal distribution to the log (hazard). The estimates of the log (hazard) were then exponentiated and converted to probabilities.

Costs in the long-term model

Costs were incorporated into the Markov model by attaching a mean annual cost to the IHD, non-fatal MI and post-MI states. An additional transition cost is also added when a patient dies, based on data from the NHAR. These state and transition costs relate to hospital resource use only, and are based on data collected as part of the 1998 cohort of the NHAR. Average annual health state costs were calculated by aggregating the resources consumed by each patient in the 1998

NHAR cohort according to whether they would have fallen into the three non-dead states in the model: IHD, non-fatal MI or post-MI. The resource use and costs used in the long-term model are detailed in Appendix 8. As for the short-term model, the uncertainty in resource use in the long-term model is characterised by beta distributions (to reflect the proportion of patients utilising a particular resource item) and log-normal distributions (to reflect the intensity of use).

Quality adjustment

In order to estimate QALYs, it is necessary to quality-adjust the period of time the average patient is alive within the model using an appropriate utility or preference score. Ideally, utility data are required which differentiate between the health status of patients in the IHD, non-fatal MI and post-MI states of the long-term model. A number of data sources were identified which provided estimates of utilities associated with IHD and non-fatal MI. However, none of these sources provides separate estimates of the three non-dead states in the long-term model based on consistent valuation methods. In the base-case analysis, it was assumed that the health states of all patients who are alive are valued, on average, at the same utility regardless of which health state they are in. For the base-case analysis, this is assumed to be 0.8 with a standard deviation of 0.09, based on the approach used in the original GPA model.[57] Additional sensitivity analyses were undertaken using alternative sources, including the manufacturers' estimates.

Analytical methods

The overall model is run for a period of 40 cycles (equivalent to 40 years), after which most of the patients will have died in the model. Therefore, the mean life-years and QALYs per patient can be calculated for each strategy, and also the mean lifetime costs. The age of the patients in the model is not incorporated as an explicit parameter, so the age to which the analysis relates will reflect that of the patients in the cohorts used to populate the model. In PRAIS-UK, the mean age of patients was 66 years; in the NHAR the mean age of the two cohorts was 68 years. In the CURE trial the mean age of patients at baseline was 64 years.[35]

The results of the model are presented in two ways. First, mean lifetime costs and QALYs of the strategies are presented and their cost-effectiveness compared, estimating incremental cost-effectiveness ratios (ICERs) as appropriate, using standard decision rules.[73] To present the uncertainty in the cost-effectiveness of the alternative strategies, cost-effectiveness acceptability curves (CEACs) are used.[74,75] These show the probability that combination treatment of clopidogrel plus standard therapy (strategy 1) is more cost-effective than treatment with standard therapy alone (strategy 2) using alternative values for the maximum (or threshold) value the health service is willing to pay for an additional QALY in these patients.

The model was developed in Excel with the Crystal Ball 'add-on'. The Monte Carlo simulation was run for 1000 iterations. The model was run several times, once for a base-case analysis and then for a number of alternative sensitivity analyses. The sensitivity analyses were divided into related sections to assess the robustness of the results of the base-case model to the use of alternative assumptions in the following areas:

1. time horizon of the model (constrained to 5 years to represent maximum follow-up period in observational data sources)
2. variation in the sources of baseline data used to populate the base-case model
3. risk stratification, to explore the impact of heterogeneity in baseline event data between high-risk (defined as presence of one or more of the following characteristics: age ≥ 70 years, ST-depression and diabetes) and low-risk patients (absence of all of these)
4. alternative utility estimates to those applied in the base-case analysis to estimate QALYs
5. alternative unit cost data for input parameters in the model
6. alternative discount rates applied to both costs and outcomes (3.5% discount rate applied to both).

Results

Results of the short-term model

Table 28 details the results of the short-term model. Treatment with clopidogrel reduces the probability of leaving the short-term model in either the non-fatal MI or the death (all-cause) state. Consequently, a higher number of patients start the long-term model in the event-free state (IHD) following treatment with clopidogrel (86%) compared with treatment with aspirin alone (83.6%). Treatment with clopidogrel is the more expensive option, costing an average of £2538 per patient in the initial 12 months, including all components of costs, as opposed to standard treatment alone, which costs approximately £2206.

TABLE 28 *Results of the short-term model: probabilities (95% CI) of leaving short-term model in one of three health states and expected costs for each strategy (95% CI)*

Health state	Strategy 1: clopidogrel plus aspirin	Strategy 2: aspirin alone
IHD	0.860 (0.834 to 0.882)	0.836 (0.816 to 0.856)
Non-fatal MI	0.041 (0.030 to 0.054)	0.057 (0.045 to 0.072)
Dead	0.099 (0.083 to 0.122)	0.107 (0.091 to 0.0124)
Expected cost per patient (£)	2,538 (1,769 to 4,317)	2,206 (1,389 to 4,182)
Expected cost per patient (drug acquisition costs only) (£)	445.91 (441.82 to 449.51)	3.28 (3.25 to 3.31)

Data are based on mean and 2.5 and 97.5 percentiles from the Monte Carlo simulation.

TABLE 29 *Base-case estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis*

				Probability cost-effective for maximum WTP[b]		
Strategy	Cost (£)	QALY	ICER[a] (£)	£10,000	£30,000	£50,000
1. Clopidogrel	12,695	8.2795	6078	0.68	0.79	0.81
2. Standard therapy	12,225	8.2022		0.32	0.21	0.19

[a] ICER: clopidogrel and standard therapy compared with standard therapy alone.
[b] The probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay (WTP) for an additional QALY.

Despite a reduction in the costs of revascularisation over this period and a reduction in the costs of non-fatal MI in patients treated with clopidogrel, these savings were not sufficient to offset the additional drug acquisition costs of clopidogrel. The average drug costs, incurred during the short-term model, for combined treatment with clopidogrel and standard therapy was £446, compared with only £3 for treatment with standard therapy alone.

Base-case analysis

Table 29 presents the lifetime analysis of the ICER for the base-case analysis. The ICER examines the additional costs that one strategy incurs over another and compares this with the additional benefits. The ICER of clopidogrel plus standard therapy (strategy 1) compared with treatment with standard therapy alone (strategy 2) is £6078 per QALY gained. Hence the results of the base-case analysis indicate that strategy 1 is the optimal decision provided that the NHS is prepared to pay at least this amount per additional QALY.

Although the results of the ICER can be used to determine the optimal decision based on a comparison of mean costs and QALYs, they do not incorporate the uncertainty surrounding this decision *Figure 8* presents the base-case results in the form of CEACs for each strategy. The results of the CEACs incorporate the uncertainty within the model in relation to both the estimates of mean costs and QALYs, and in the maximum willingness to pay for an additional QALY. The CEACs demonstrate that the probability that strategy 1 is cost-effective increases as the maximum willingness to pay increases: if society is prepared to pay £10,000 for an additional QALY, the probability that strategy 1 is cost-effective is around 0.68, increasing to 0.81 if the maximum willingness to pay is £30,000. Consequently, the results from the base-case analysis demonstrate that, provided the health service is prepared to pay over £6078 per QALY, then strategy 1 is always the optimal decision.

Results of the sensitivity analyses to explore the impact of alternative assumptions relating to the sources of data used in the base-case model

Table 30 details the results of each individual sensitivity analysis undertaken to assess the robustness of the base-case model to alternative assumptions. Reducing the time horizon of the model to 5 years resulted in an increase in the ICER for strategy 1 to £14,844 (compared with £6078 in the base-case analysis) and reduced the probability that this strategy is cost-effective from

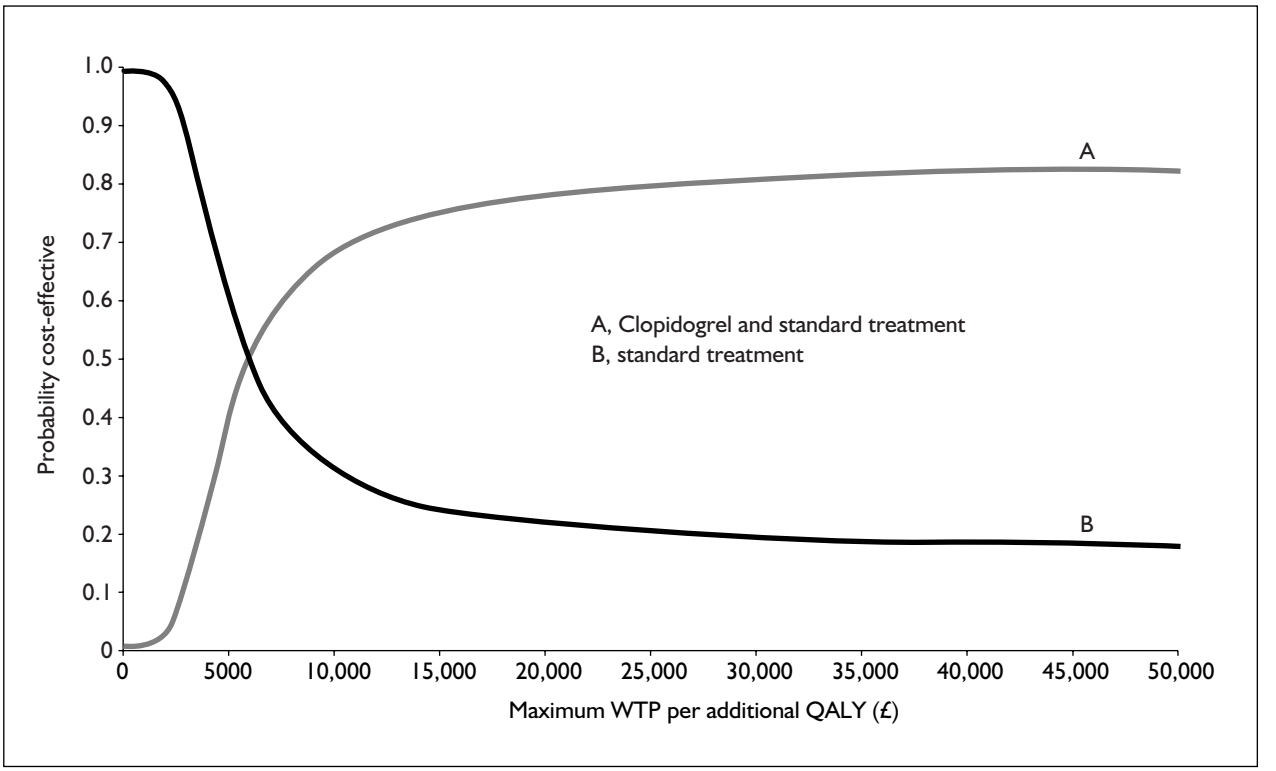


FIGURE 8 *Base-case results in the form of a cost-effectiveness acceptability curve. This shows the probability that each strategy is more cost-effective than the others conditional on a different maximum willingness to pay (WTP) for an additional QALY.*

0.68 to 0.27 at a maximum willingness to pay of £10,000 per QALY. At a maximum willingness to pay of £30,000 the probability values for the 5-year analysis were close to the base-case analysis estimate (0.74 and 0.81, respectively) .

The results of the base-case model were based on the baseline risks derived by combining two separate data sources (PRAIS-UK and the Leeds PCI audit). Although PRAIS-UK was designed to be representative of UK practice, the inclusion of the Leeds PCI audit may affect the generalisability of these findings. A separate sensitivity analysis was therefore undertaken to explore the impact of only using baseline event data from PRAIS-UK. This separate analysis had minimal impact and reduced the ICER from £6078 to £6070. The analysis demonstrated the robustness of the results to the decision to include data from the Leeds PCI audit in the base-case analysis.

The impact of patient heterogeneity was explored in detail in a separate analysis using risk stratification. This approach was undertaken to examine the cost-effectiveness of clopidogrel in particular subgroups of patients. In the absence of clinical measures of high risk (e.g. troponin measurements) reported in PRAIS-UK, a pragmatic decision was made to use other non-troponin-based markers of high risk to define a high- and low-risk population using data from PRAIS-UK. This classification was based on discussion with clinical collaborators in the previous report on glycoprotein IIb/IIIa antagonists[57] and the results of a published analysis of the relationship between prognostic indicators and outcomes based on the PRAIS-UK data. In that study, patients over 70 years of age had a threefold risk of death or new MI compared with those aged less than 60 years ($p < 0{\cdot}01$), and those with ST depression or bundle branch block on the ECG had a five-fold greater risk than those with normal ECG ($p < <0{\cdot}001$).[69] Using data from PRAIS-UK, high-risk status was determined by the presence of at least one of the following characteristics: age 70 years or more, ST depression (or bundle branch block) or diabetes. Using these risk markers, approximately 58% ($n = 597$) of patients were classified as being at high risk. Due to the lack of reported data on the RRRs for specific risk groups in CURE, the same RRs were applied to both the high- and low-risk groups as applied in the base-case analysis (although the absolute risk reductions would clearly differ according to the different baseline event rates in each group).

TABLE 30 *Results of sensitivity analyses using alternative assumptions to the base-case analysis*

Element	Sensitivity analysis	Strategy	Cost (£)	QALY	ICER (£)	Probability cost effective for maximum WTP		
						£10,000	£20,000	£30,000
Time horizon of the model	5 cycles	1	7,190	3.2839	14,844	0.27	0.64	0.74
		2	6,774	3.2559		0.73	0.36	0.26
Source of baseline data	PRAIS-UK data only	1	12,807	8.3012	6,070	0.67	0.79	0.82
		2	12,339	8.2242		0.33	0.21	0.18
Risk stratification	PRAIS-UK (High-risk)	1	12,724	8.0614	4,939	0.73	0.82	0.84
		2	12,240	7.9634		0.27	0.18	0.16
	PRAIS-UK (Low-risk)	1	13,440	8.7350	8,734	0.56	0.76	0.80
		2	12,972	8.6815		0.44	0.24	0.20
Utilities used to calculate QALYs	(a) Life-year analysis	1	12,695	10.3933	4,811	0.76	0.82	0.85
		2	12,225	10.3016		0.24	0.18	0.15
	(b) Utilities altered to industry estimates	1	12,925	9.5936	5,113	0.75	0.83	0.85
		2	12,448	9.4463		0.25	0.17	0.15
	(c) Utilities from ACS trial	1	12,925	7.4531	6,567	0.71	0.81	0.84
		2	12,448	7.3804		0.29	0.19	0.16
Discounting	3.5% costs, 3.5% outcomes	1	15,034	7.0181	7,728	0.62	0.78	0.82
		2	14,537	6.9538		0.38	0.22	0.18
Cost inputs								
	(a) Excluding cost of stroke	1	12,644	8.2795	6,303	0.67	0.78	0.80
		2	12,156	8.2022		0.33	0.22	0.20
	(b) Alternative stroke cost	1	12,703	8.2795	6,044	0.68	0.79	0.81
		2	12,235	8.2022		0.32	0.21	0.19
	(c) Increase bleed cost to literature estimate	1	12,714	8.2795	6,146	0.68	0.79	0.81
		2	12,238	8.2022		0.32	0.22	0.19
	(d) Increase bleed cost to industry estimate	1	12,763	8.2795	6,324	0.67	0.78	0.80
		2	12,274	8.2022		0.33	0.22	0.20

WTP, willingness to pay.

In the high-risk subgroup analysis, the ICER of clopidogrel compared with standard therapy alone resulted in a reduction in the ICER to £4939 per QALY. The application of lower baseline event data in the low-risk subgroup resulted in a less favourable ICER of £8734 per QALY. Although differences in the baseline event data in the two risk groups resulted in different estimates of the ICER, the use of clopidogrel appeared cost-effective in both groups as long as the NHS is willing to pay at least £8734 per QALY gained. Despite these findings, care should be exercised in the interpretation of these results owing to the lack of differential RR data from the CURE trial for these specific risk groups. However, the results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender) were reported to be consistent with the results of the primary analysis reported in the industry submission. This provides additional support for the approach outlined here in which the same relative risks were applied to different baseline event data.

Although a separate search of utility studies was conducted, none of these sources provided separate estimates of the three non-dead states in the long-term model based on consistent valuation methods. In the absence of any more appropriate data, the base-case analysis used the same utility estimates originally applied in the previous model of the cost-effectiveness of glycoproteins in non-ST elevation ACS patients.[57] In that analysis, the same utility was applied to all living patients throughout the course of the model [0.8, standard deviation (SD) 0.09]. The impact of using alternative estimates was explored in a series of separate analyses. The effect of using life-years gained as an outcome measure (equivalent to assuming utility of 1 for the IHD and non-fatal MI states) reduced the ICER for clopidogrel to £4811. The cost-effectiveness model submitted by Sanofi-Synthelabo Ltd and Bristol–Myers Squibb applied separate utility estimates for the first-year event-free (IHD) and non-fatal MI states and the post-year 1 states based on a range of estimates reported in published studies. Patients in the IHD and non-fatal MI states were assigned the same utilities (year 1 = 0.80, range 0.7–0.9; post-year 1 = 0.93, range 0.88–0.98). Applying these estimates resulted in a reduction in the ICER to £5113. The use of higher utility estimates in the post-year 1 states resulted in an ICER which was closer to the analysis based on life-years gained than that derived from the base-case analysis which applied a constant estimate throughout a patient's remaining life regardless of subsequent events.

A separate search of utility studies identified estimates based on the Health Utilities Index (HUI) reported in a trial of invasive versus conservative management in non-ST-segment elevation ACS patients. These estimates were reported at baseline and at 6-months follow-up for both groups. There were minimal differences between groups and for the purposes of this analysis the estimates were averaged across the groups for the two separate time points. Estimates at baseline (0.64) and 6-month follow-up (0.73) were applied as a proxy to the year 1 and post-year 1 health states for both IHD and non-fatal MI. No formal estimates of uncertainty in these figures was reported, so a uniform distribution was assigned based on the high and low estimates reported for each of the invasive and conservative groups. Application of these utility estimates resulted in a more conservative estimate of the ICER (£6567) than either the base-case analysis (£6078) or the analysis using the utility estimates proposed in the industry submission (£5113). The decision resulting from the base-case analysis was therefore likely to be robust to the alternative estimates of utility applied in the sensitivity analysis.

The impact of alternative discount rates to those applied in the base-case analysis (6% costs, 1.5% outcomes) was explored by using a common rate of 3.5% for both costs and outcomes that has been recently proposed in the draft of the NICE methodological guidance for manufacturers. The use of a common discount rate increased the ICER of clopidogrel to £7728 per QALY.

A further series of additional analyses was undertaken to explore the impact of alternative assumptions related to the cost data applied in the base-case analysis. The cost of stroke applied in the base-case analysis for the first 12 months was based on the estimate used in the company submission (£7466 per annum), which, in turn, was based on the weighted long-term costs of independent and dependent stroke survivors reported by Chambers and colleagues.[61] These data were derived from expert opinion and the robustness of this figure is difficult to ascertain. An estimate of the cost of stroke was also identified in a separate search undertaken to identify UK cost studies in stroke patients, from a study reporting estimates obtained from a patient-level trial analysis (£8620 per annum).[76] Application of this estimate in the model reduced the ICER

marginally to £6044. The results of the base-case analysis were therefore likely to be robust to alternative assumptions concerning the costs of non-fatal strokes in the initial 12-month period. It is unclear what impact the inclusion of stroke (on both costs and QALYs), beyond the initial 12-month perspective covered by the short-term model, would have on the base-case ICER. However, the results of the base-case analysis are likely to provide a conservative estimate of the ICER of clopidogrel owing to the favourable relative risk reduction reported in CURE for non-fatal stroke (RRR 0.73; 95% CI: 0.5 to 1.09).

The cost of bleeding incorporated in the base-case model was based on expert clinical opinion on the resource requirements of a GI bleed and comprised the cost of two-units of blood, an endoscopy and a full blood count. The total cost applied was estimated at £424. The figure applied in the manufacturers' submission was significantly higher and was based on an estimate of the average cost of a fatal or non-fatal bleed (£2377). In addition, a further estimate was identified from the systematic review which was based on the cost of a GI bleed (£963). The use of these alternative estimates increased the ICER to £6324 and £6146, respectively. Again, the results of base-case analysis were robust to this source of uncertainty.

Sensitivity analysis to explore the cost-effectiveness of alternative durations of treatment with clopidogrel

As discussed in the section 'Treatment strategies under comparison' (p. 36), the cost-effectiveness of clopidogrel compared with standard treatment is related both to the relative treatment effect and the absolute risk (baseline). If the relative treatment effect (e.g. RRR) remains constant while the absolute risk associated with the major endpoints (e.g. CV death, non-fatal MI) decrease during the course of the first 12-months, then the incremental costs and benefits of continuing treatment beyond a particular duration (e.g. initial 30 days, 3 months) should also be considered. As the absolute benefit of clopidogrel, relative to standard care, declines over the course of the initial 12-month period, the incremental cost per QALY of providing clopidogrel for successively longer durations may increase.

Although the base-case analysis has demonstrated that clopidogrel used for 12-months appears cost-effective compared with standard therapy alone as long as the health service is willing to pay at least £6078 per QALY gained, the incremental cost-effectiveness of using clopidogrel for 12-months as compared to shorter treatment durations has not yet been established. A series of three separate strategies, representing alternative treatment durations with clopidogrel, was considered in addition to the main strategies included in the base-case analysis. The five strategies evaluated in this sensitivity analysis are as follows:

- strategy 1: treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 12 months
- strategy 2: treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 6 months
- strategy 3: treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 3 months
- strategy 4: treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 1-month
- strategy 5: lifetime treatment with standard therapy (including aspirin) alone.

The model used for this sensitivity analysis follows a similar approach to that applied in base-case model and includes a short-term element (representing the first year after a patient presents with non-ST-segment elevation ACS); and a long-term element which extrapolates a patient's lifetime costs and outcomes, conditional on surviving the first 12 months after the acute episode. Although the long-term element in both models is identical, the model structure applied in the first 12-month period differs between the two models.

In order to model the use of clopidogrel for alternative durations during the initial 12-month period, a revised structure was used to represent the baseline probabilities of death, non-fatal MI and revascularisation, and also resource costs. In the base-case model, both resource utilisation (e.g. revascularisation) and health outcomes (death, non-fatal MI, IHD) were incorporated within the same decision-tree structure. The probabilities of each of the separate health outcomes were then conditioned according to the probability of various resource events (e.g. acute PCI/acute CABG/no-acute revascularisation). In the revised model, health outcomes and resource utilisation were modelled separately. This approach was necessary owing to the problems of replicating the previous short-term decision tree for multiple time periods which would be difficult to propagate owing to the large number of potential nodes which would not have sufficient (or any) data.

TABLE 31 *Distribution of events in PRAIS-UK across separate periods during the 6-month follow-up period*

	Period			
Event	**0–1 month**	**1–3 months**	**3–6 months**	**Total (0–6 months)**
Death (all-cause)	33 (43.4)	21 (27.6)	22 (28.9)	76
Non-fatal MI	41 (74.5)	4 (7.3)	10 (18.2)	55
PTCA	55 (71.4)	11 (14.3)	11 (14.3)	77
CABG	38 (52.1)	22 (30.1)	13 (17.8)	73
Stroke	8 (53.3)	3 (20)	4 (26.7)	15
Major bleed	9 (69.2)	2 (15.4)	2 (15.4)	13
MI (fatal and non-fatal)	54 (71.1)	8 (10.5)	12 (15.8)	76

Data from PRAIS-UK were used to model the baseline probabilities for the revised short-term model. Rather than calculating the probability of each outcome and resource events over the entire 6-month follow-up period, the number of major events occurring over discrete time intervals over the 6-month follow-up were modelled. Data for the main events considered in the short-term model are reported in *Table 31* over three separate intervals (0–1 month, 1–3 months, 3–6 months). Categorising the events according to these discrete intervals clearly demonstrates the decline in AR after the initial acute period. Between 43 and 75% of the total number of events reported at 6 months occurred during the first 30 days. By 3 months this had risen to between 70 and 80%.

The probabilities of death, non-fatal MI and IHD (i.e. no event) occurring during each interval were modelled using the Dirichlet distribution.[77] The Dirichlet distribution is the multidimensional generalisation of the beta distribution and can be used to represent polychotomous (i.e. more than two events) transition probabilities to ensure that the sum of probabilities across multiple events equals one. During the first 30 days in PRAIS-UK, a total of 33 patients died, 41 patients had a non-fatal MI and the remainder (959) were classified as IHD. The probabilities of each event were thus modelled using a Dirichlet (33,41,959) distribution. Of the 959 patients with IHD at 1 month, the probabilities of death, non-fatal MI or remaining in the IHD state during the next interval (1–3 months) were then modelled using a Dirichlet (21,4,934) distribution, reflecting the number of observed events in PRAIS-UK during this interval. A similar process was then used to determine the probabilities between 3 and 6 months. These probabilities were used to represent the transition probabilities for standard care alone (i.e. strategy 5) across each separate period.

The use of clopidogrel over alternative durations was then modelled by applying the relative risks reported in *Table 26* to the baseline probabilities estimated for strategy 5 across each separate period. The RRs for clopidogrel were only applied to those periods where treatment with clopidogrel was continued. For treatment periods of less than 6 months duration (strategies 3 and 4), patients were assumed to revert back to the transition probabilities associated with standard care after the initial treatment period. Consequently, for strategy 4 (clopidogrel for 30 days only), the RRs were only applied to the first 30 days; patients were then assumed to follow the same transition probabilities as standard care for the periods between 1 and 3 and 3 and 6 months. For strategy 3 (clopidogrel for 3 months), the RRs were applied to both the first 30 days and the period between 1 and 3 months.

The data at 6 months were then extrapolated to 12 months using the annual transition probabilities applied in the long-term model from the NHAR (see the section 'Extrapolation of 6-month baseline data to 12 months', p. 39). For strategy 1, the impact of continuing treatment for this additional period was modelled by also applying the RRs to these transitions. Patients in strategies 2–5 followed the same set of transition probabilities.

The probabilities for the (resource- and cost-generating) events PTCA, CABG, fatal and non-fatal MIs, stroke and major bleeds were modelled using beta distributions for each separate period. The same unit costs as applied in the base-case model were used. The RRs for these events reported for clopidogrel were then applied to each period in which treatment with clopidogrel was continued.

Table 32 presents the analysis of the ICER for this analysis. When more than two programmes are

TABLE 32 *Base-case estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis*

				Probability cost-effective for maximum WTP		
Strategy	**Cost (£)**	**QALY**	**ICER (£)**	**£10,000**	**£30,000**	**£50,000**
1. Clopidogrel, 12 months	13,044	8.3848	5,159	0.74	0.83	0.84
2. Clopidogrel, 6 months	12,762	8.3216	ED	0	0	0.01
3. Clopidogrel, 3 months	12,647	8.3060	ED	0	0	0
4. Clopidogrel, 1 month	12,570	8.2929	824	0.15	0.06	0.04
5. Standard therapy	12,549	8.2685		0.11	0.11	0.11

ED, option ruled out by extended dominance.

being compared, the ICERs are calculated using the following process:[73]

1. The strategies are ranked in terms of cost (from the least expensive to the most costly).
2. If a strategy is more expensive and less effective than the previous strategy, then this strategy is said to be dominant and is excluded from the calculation of the ICERs.
3. The ICERs are calculated for each successive alternative, from the cheapest to the most costly. If the ICER for a given strategy is higher than that of the next more effective strategy, then this strategy is ruled out on the basis of extended dominance.
4. Finally, the ICERs are recalculated excluding any strategies that are ruled out using the notions of dominance and extended dominance.

Applying this process to the base-case results, strategies 2 (6-month treatment with clopidogrel) and 3 (3-month treatment with clopidogrel) are ruled out by extended dominance, because the ICER of the next most effective strategy (strategy 1: 12-month treatment with clopidogrel) is lower than the ICER of these strategies.

The options under consideration are, therefore, strategies 1, 4 and 5. The ICER of strategy 4 (1-month treatment with clopidogrel) compared with strategy 5 (standard care alone) is £824 per QALY. The ICER of strategy 1 compared with strategy 4 is £5159. Hence the results of the base-case analysis indicate that optimal decision concerning the duration of treatment with clopidogrel is dependent on the amount the NHS is prepared to pay per additional QALY. If the NHS is prepared to pay more than £5159 per QALY then treatment with clopidogrel for 12 months is cost-effective. If the decision-maker is prepared to pay less than this amount (but more than £824 per QALY), then the optimal treatment would be to use clopidogrel for 1 month. *Figure 9* presents the uncertainty in these results in the form of multiple CEACs. The CEACs demonstrate that the probability that strategy 1 is cost-effective increases as the maximum willingness to pay increases: if society is prepared to pay £30,000 for an additional QALY, the probability that strategy 1 is cost-effective is around 74%, increasing to 84% if the maximum willingness to pay is £50,000.

Sensitivity analysis to explore the cost-effectiveness of alternative durations of treatment with clopidogrel and alternative assumptions related to the extrapolation period

The results of the sensitivity analysis reported in the previous section highlighted a potential area of uncertainty associated with the use of the NHAR data for the extrapolation of PRAIS-UK data in the short-term model. In both the revised model and the base-case model, data from PRAIS-UK (6 months follow-up) were extrapolated to 12-months using data from a separate cohort from the NHAR. When comparing the alternative strategies based on separate treatment durations with clopidogrel, a potential inconsistency was revealed between the probabilities of major events (death, non-fatal MI) estimated from the two separate sources. The rate of decline in the AR of these events during the first 6 months in PRAIS-UK was not maintained when these data were extrapolated to 12 months using the NHAR data. Consequently, the probabilities of death and non-fatal MI for the period between 6 and 12 months were higher than would be expected if the risk of

TABLE 33 *Estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis*

Strategy	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP		
				£10,000	£30,000	£50,000
1. Clopidogrel, 12 months	13,090	8.3972	13,988	0.28	0.74	0.81
2. Clopidogrel, 6 months	12,869	8.3814	6,951	0.36	0.09	0.04
3. Clopidogrel, 3 months	12,752	8.3645	5,625	0.07	0.01	0
4. Clopidogrel, 1 month	12,673	8.3506	895	0.21	0.08	0.06
5. Standard therapy	12,648	8.3222		0.08	0.09	0.09

these events continued to decline at a similar rate to that observed during the previous intervals in PRAIS-UK. The relationship between the period covering 6–12 months and that of previous periods is a key source of uncertainty in the model. In the absence of longer term follow-up from PRAIS-UK, it is unclear whether the use of data from the NHAR for this period will result in potential bias in the results for treatment with clopidogrel for a 12-month period. To address this uncertainty in more detail, a separate analysis was undertaken whereby the data reported at 6 months from PRAIS-UK were extrapolated to 12 months using the observed relationship between these periods reported in the CURE study. Separate transition probabilities of death and non-fatal MI, between 6 and 12 months, were calculated and applied to the revised model reported in the previous section.

Applying this alternative method of extrapolation provided results which were more consistent with a continued decline in the absolute risk of major events in the period between 6 and 12 months. The expected costs and QALYS and the ICER of the alternative strategies based on this approach are reported in *Table 33*. In this scenario, none of the five strategies are ruled out on the grounds of dominance/extended dominance. The use of clopidogrel over longer periods is associated with both increased costs and QALYs compared with shorter durations, such that ICER rises as the duration of treatment with clopidogrel increases. The ICER of strategy 4 (1-month treatment with clopidogrel) compared with strategy 5 (standard care alone) is £895 per QALY. The ICER of strategy 3 compared with strategy 4 is £5625. The ICER of strategy 2 compared with strategy 3 is £6951. The ICER of strategy 1 compared with strategy 2 is £13,988. Hence the results of this analysis indicate that the decision concerning the optimal duration of treatment with clopidogrel is dependent on the amount the NHS is prepared to pay per additional QALY. As the amount the NHS is prepared to pay increases, the more cost-effective treatment with clopidogrel for longer durations becomes.

Figure 10 presents the uncertainty in these results in the form of multiple CEACs. The CEACs demonstrate that the probability that strategy 1 is cost-effective increases as the maximum willingness to pay increases: if society is prepared to pay £10,000 for an additional QALY, the probability that strategy 1 is cost-effective is only around 28%, increasing to 81% if the maximum willingness to pay is £50,000. These results demonstrate that the implementation decision is potentially sensitive to the methods used to extrapolate the baseline data.

Although the CEAC provides a useful graphical representation of the uncertainty associated with the probability that individual strategies are cost-effective over a range of threshold values, the results of the CEAC can only be used to identify the optimal implementation decision under a restrictive set of assumptions. This is because the strategy with the highest probability of being cost-effective does not necessarily have the highest expected pay-off (i.e. net benefit), and will only do so when the distributions of these pay-offs are symmetrical. This limitation can be overcome by using a cost-effectiveness frontier to indicate which strategy is optimal (and the associated probability that this strategy is the most cost-effective) across the range of values representing the maximum amount the NHS is prepared to pay for an additional QALY.[75] The frontier for this analysis is provided in *Figure 11*. The discontinuities that exist in the frontier reflect the significant skew in the distributions of net benefit for particular strategies (strategy 3).

We conducted a final sensitivity analysis using the method outlined above for the extrapolation of

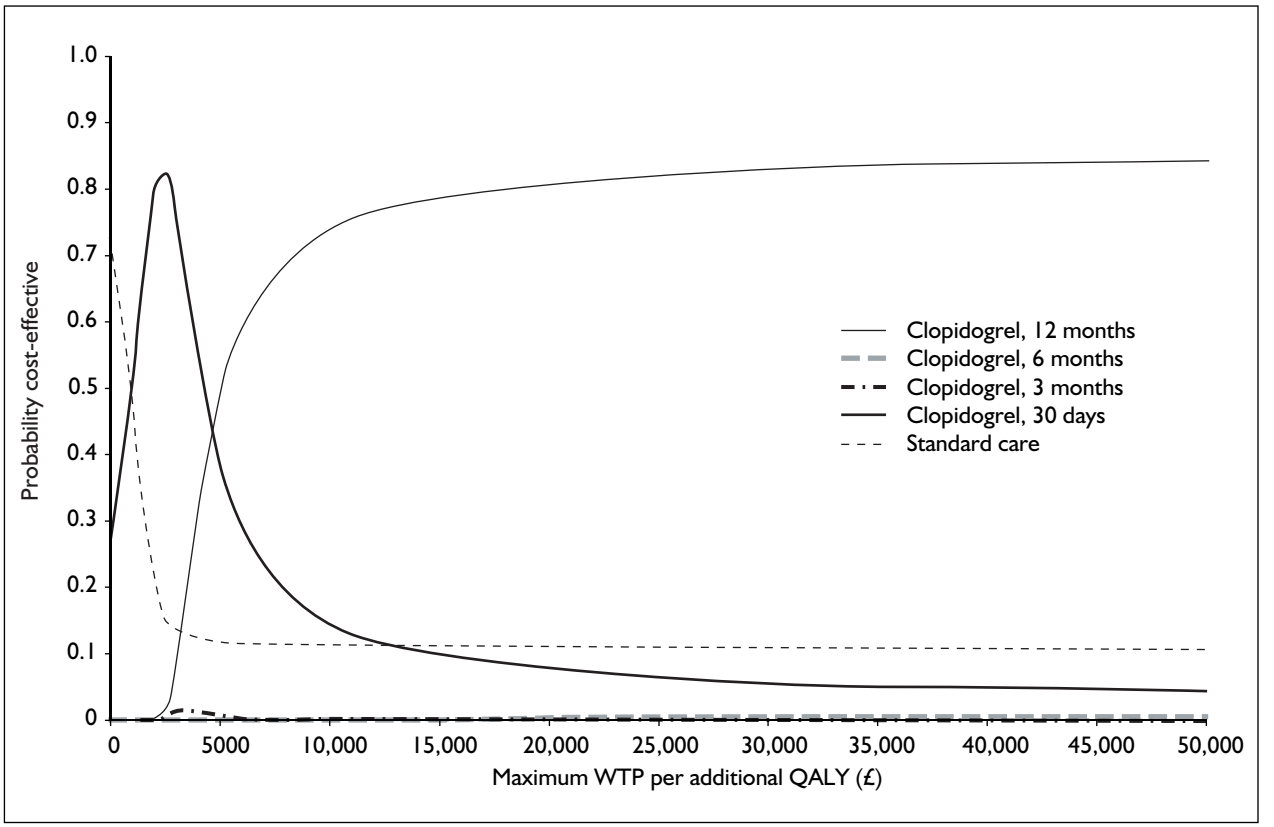


FIGURE 9 *Cost-effectiveness acceptability curves for alternative durations of treatment with clopidogrel*

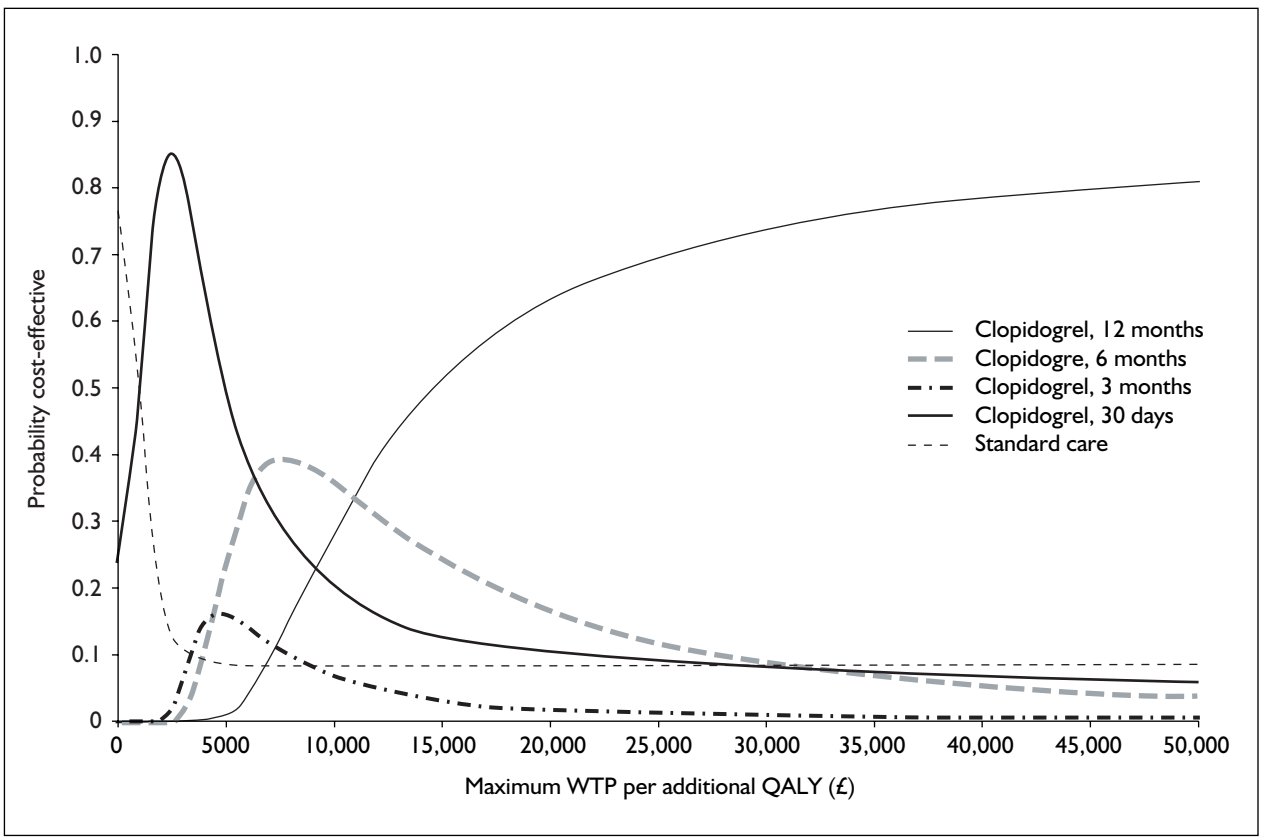


FIGURE 10 *Cost-effectiveness acceptability curves for alternative durations of treatment with clopidogrel using separate method of extrapolation*

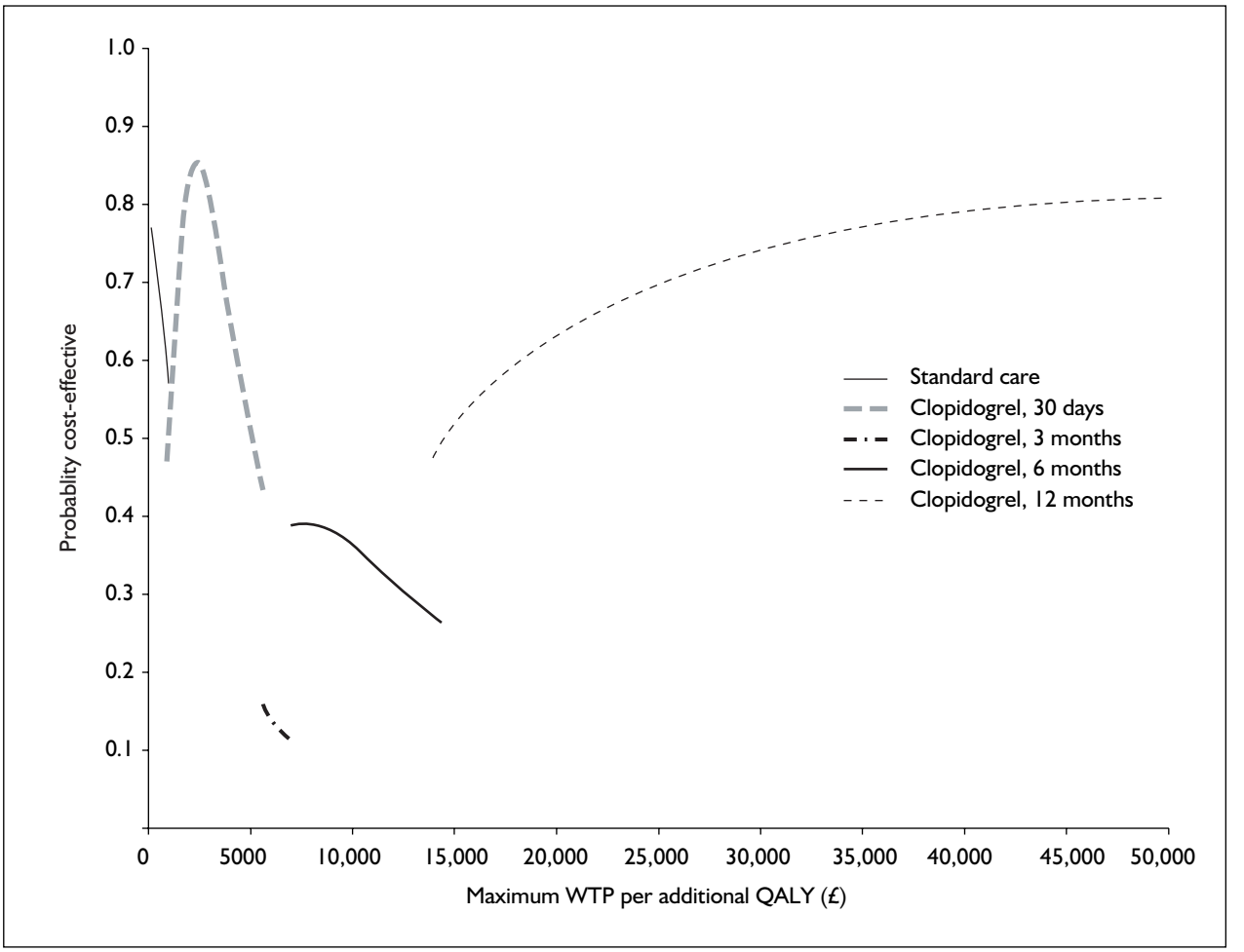


FIGURE 11 *Cost-effectiveness frontier for alternative durations of treatment with clopidogrel*

PRAIS-UK data to 12 months using the CURE trial. The impact of patient heterogeneity explored in the base-case model using risk stratification was repeated to assess the potential impact this heterogeneity had on the relative cost-effectiveness of alternative treatment durations with clopidogrel. The expected costs and QALYs and the ICER of the alternative strategies based on this approach for the high-risk and low-risk groups are reported in *Tables 34* and *35*, respectively. In both risk groups, none of the five strategies was ruled out on the grounds of dominance/extended dominance. As before, the use of clopidogrel over longer-periods was associated with both increased costs and QALYs compared with shorter durations. However, the ICERs between the various strategies were markedly different between the two risk groups.

In the high-risk group, the ICER of strategy 4 (1-month treatment with clopidogrel) compared with strategy 5 (standard care alone) was £588 per QALY, the ICER of strategy 3 compared with strategy 4 was 4281, the ICER of strategy 2 compared with strategy 3 was £4852 and the ICER of strategy 1 compared with strategy 2 was £8756. For the low-risk group, the ICER between each strategy was considerably higher. The ICER of strategy 4 compared with strategy 5 was £1732. The ICER increased to £11,816 between strategy 3 and strategy 4. The most marked difference between the separate risk groups was seen in the ICER for continuing treatment with clopidogrel beyond 3 months. The ICER for strategy 2 compared with strategy 3 rose to £30,786. The ICER for strategy 1 compared with strategy 2 increased to £34,629.

The differences between the high- and low-risk groups was also evident in the probability that each strategy was cost-effective at various threshold willingness to pay values. At £10,000 per QALY, the probability that clopidogrel was cost-effective was 55% in the high-risk group and

TABLE 34 *Estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis (high-risk patients)*

				Probability cost-effective for maximum WTP		
Strategy	**Cost (£)**	**QALY**	**ICER (£)**	**£10,000**	**£30,000**	**£50,000**
1. Clopidogrel,12 months	12,637	7.9972	8,756	0.55	0.80	0.83
2. Clopidogrel, 6 months	12,418	7.9723	4,852	0.19	0.03	0.02
3. Clopidogrel, 3 months	12,301	7.9479	4,281	0.03	0.01	0
4. Clopidogrel, 1 month	12,213	7.9275	588	0.15	0.07	0.06
5. Standard therapy	12,189	7.8864		0.09	0.09	0.09

TABLE 35 *Estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis (low-risk patients)*

				Probability cost-effective for maximum WTP		
Strategy	**Cost (£)**	**QALY**	**ICER (£)**	**£10,000**	**£30,000**	**£50,000**
1. Clopidogrel, 12 months	13,928	8.9964	34,629	0.01	0.31	0.57
2. Clopidogrel, 6 months	13,705	8.9899	30,786	0.03	0.16	0.13
3. Clopidogrel, 3 months	13,597	8.9864	11,816	0.31	0.30	0.15
4. Clopidogrel, 1 month	13,528	8.9805	1,732	0.54	0.14	0.07
5. Standard therapy	13,506	8.9680		0.11	0.08	0.08

only 1% in the low-risk group. At £30,000 per QALY, the probabilities were 80% and 31%, respectively. At a threshold of £50,000 per QALY, the use of clopidogrel was cost-effective in both risk groups.

Discussion

Summary of results

The results from the base-case model suggest that treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 12 months, compared with standard therapy alone, is cost-effective in non-ST-segment elevation ACS patients as long as the health service is willing to pay £6078 per additional QALY. The base-case model estimates that this will result in a (mean per patient) gain of 0.08 QALYs at an additional cost of £470, compared with standard therapy alone. The resulting cost per QALY gained for clopidogrel is therefore about £6078. This finding appears robust to a range of potential uncertainties in parameter estimates used to populate the base-case model. The maximum cost per QALY gained arising from the sensitivity analyses applied to base-case model was £12,313, based on an analysis of the cost and outcomes at 5 years. For the approaches using a more appropriate lifetime perspective, the maximum ICER was £7981 per QALY gained, based on the subgroup of patients classified as low-risk (aged less than 70 years, no ST depression and no diabetes).

The base-case results appear to be most sensitive to the inclusion of additional comparators, the use of shorter treatment durations of clopidogrel and the methods used to extrapolate the baseline observational data from PRAIS-UK from 6 to 12 months. In the base-case model (and also in the manufacturers' submission), data from PRAIS-UK reported at 6 months were uprated to 12 months using observational data from a separate cohort of ACS patients from the NHAR. An alternative approach using data from the CURE trial demonstrated that the method of extrapolation used in this period was a potentially important source of uncertainty. The ICER of clopidogrel for 12 months duration ranged between £5159 and £13,988 using the different approaches. The difference in these estimates was due mainly to the impact that the alternative approaches had on the relative cost-effectiveness of the separate clopidogrel strategies. The rate of decline in the absolute risk of the major events (e.g. non-fatal MI, death) observed during the first 6 months in PRAIS-UK was not maintained when

data from NHAR were used. Consequently, the estimates based on the use of clopidogrel over the 12-month period may overestimate the cost-effectiveness of this strategy using this approach. The use of data from the CURE trial for the period between 6 and 12 months may be considered a more conservative approach in this instance.

When the more conservative approach was used, the impact of heterogeneity in the overall ACS population was potentially important in determining the optimal duration of treatment with clopidogrel. For high-risk patients, the ICER of using clopidogrel for 12 months remained favourable compared with shorter treatment durations. However, in low-risk patients the cost-effectiveness of providing treatment with clopidogrel for successively longer durations became less clear. For low-risk patients, the ICER of providing treatment with clopidogrel for 6 months compared with only 3 months was approximately £30,786. The ICER of providing clopidogrel for 12 months compared with only 6 months was £34,629. Although these results indicate that the optimal duration of clopidogrel is sensitive to the risk stratification applied, it is important to treat them with caution. In the absence of appropriate RR data for these separate groups and the separate periods, a common RR was applied throughout the model.

Comparison with the results of the manufacturers' submissions

Table 36 provides a comparison of probabilistic results from the model submitted by the manufacturers and the alternative models developed by the University of York TAR group for the two base-case strategies. In their submission, the manufacturers' reported the overall cost-effectiveness of clopidogrel for 12 months at £5668 per QALY gained, compared with standard care alone. However, these figures are based on the deterministic estimates from the manufacturers' model. When input parameters are assigned distributions to characterise their uncertainty, a more appropriate estimate of the cost per QALY gained is obtained from the mean (or expected) costs and QALYs obtained from the simulated outputs. Using this approach, the ICER based on the manufacturers' submission increases to £5902 per QALY gained.

The base-case model that we developed for this appraisal estimated the ICER to be £6078 per QALY gained. Although the separate models do not appear to provide conflicting results based on a comparison of the ICERs, there are several important differences between the models. These differences result in a marked discrepancy between the estimates of mean costs and QALYs reported in the separate models. The estimates of the mean costs in the two strategies were about £2000 lower in the industry submission compared with our own estimates. Similarly, the estimates of QALYs in the two strategies were also significantly lower (approximately 0.5 QALY difference in both strategies between the two models). These differences are due, in part, to the different resource costs and utility estimates applied in the separate models. However, a comparison of the life-years gained (LYG) between the two models indicates that there were more fundamental differences between the models. The estimates of LYG in the industry submission for clopidogrel (9.01) and standard care (8.93) were approximately 1.3 lower than our own estimates (10.39 and 10.30, respectively). As outlined in the sections 'Structure' (p. 40) and 'Transition probabilities' (p. 41), these differences are primarily due to the manufacturers overestimating the mortality rate and using the incorrect transition rates in their long-term model. Both of these errors will underestimate the LYG in both strategies. Similarly, the higher costs in our model are primarily attributable to the additional costs incurred by patients due to their higher life expectancy. However, despite these errors, the resulting difference in the ICERs of the alternative models was minimal and did not significantly affect the decision based on the different estimates.

Earlier it was highlighted that the method of extrapolation between 6 and 12 months was a key source of uncertainty. Although the impact of this was explored in relation to the alternative strategies based on different treatment durations, a direct comparison of how the alternative extrapolation impacted on the base-case strategies was not reported. To facilitate a comparison between the alternative models outlined in this section, the results of this additional analysis are also reported in *Table 36*. The use of the CURE trial data in this period resulted in a slight increase in estimates of both mean costs and QALYs compared with the base-case model. However, the ICER was only marginally affected, resulting in a reduction from £6078 to £5898.

Despite the differences between the alternative models, the estimate of the ICER appeared remarkably robust. The estimate of the ICER across the alternative models ranged from £5898 to £6078.

TABLE 36 *Comparison of probabilistic results from the alternative base-case models (manufacturers and TAR group)*

					Probability cost effective for maximum WTP		
Approach	**Strategy**	**Cost (£)**	**QALY**	**ICER(£)**	**£10,000**	**£30,000**	**£50,000**
Manufacturers' submission	1. Clopidogrel	10,763	7.7362	5,902	0.72	0.85	0.87
	2. Standard therapy	10,299	7.6576		0.28	0.15	0.13
Base-case model	1. Clopidogrel	12,695	8.2795	6,078	0.68	0.79	0.81
	2. Standard therapy	12,225	8.2022		0.32	0.21	0.19
Revised model using alternative extrapolation	1. Clopidogrel	13,090	8.3972	5,898	0.71	0.85	0.87
	2. Standard therapy	12,648	8.3222		0.29	0.15	0.13

Conclusions

The models presented here indicate that clopidogrel appears cost-effective compared with standard care alone in patients with non-ST-segment elevation ACS as long as the NHS is willing to pay £6078 per QALY. A comparison of the cost-effectiveness of treatment with clopidogrel for 12 months (in addition to standard care) compared with standard care alone indicates that the incremental cost per QALY gained is between £4299 and £12,313 (the range for the analyses using a lifetime extrapolation is £4229–7981). Despite differences between the alternative models proposed, the estimate of the ICER remained robust.

The results were most sensitive to the inclusion of additional strategies which assessed alternative treatment durations with clopidogrel. Although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk.

Chapter 7

Discussion

The CURE trial[35] was a randomised, double blind, placebo-controlled trial that evaluated the efficacy and safety of the early and longer term use of clopidogrel (in addition to standard therapy) versus placebo (in addition to standard therapy) in patients with ACS without ST-segment elevation. The trial compared 75 mg/day clopidogrel in combination with aspirin versus placebo plus aspirin. The aspirin dose varied between 75 and 325 mg/day in both groups. The trial included 12,562 patients with ACS without ST-segment elevation; 6259 were randomised to clopidogrel and 6303 to placebo. The quality of the trial was good, although it is not clear from the trial reports whether the success of blinding was established and the reasons for withdrawals from the trial were not reported. However, all other aspects of the trial are clearly reported, including the two protocol modifications that occurred. The first modification involved a recalculation of the sample size due to lower than expected event rates. This led to a larger sample size, which should add validity to the results of the trial. The second protocol modification involved a tightening of the initial entry criteria after the first 3000 patients (24% of the total study population) had been enrolled. It is possible that some patients who were initially enrolled did not have ACS. This ultimately could have two different impacts upon the interpretation of the trial results. The first of these would be that the change in the inclusion criteria could have increased the clinical heterogeneity of the trial population. This would in turn reduce the internal validity of the results. In contrast, it is possible that the enrolled patients without ACS were exposed to a similar risk as those with ACS while deriving less benefit from the intervention. This in turn would have led to an underestimation of the treatment effect. The second protocol modification also led to the inclusion of more high-risk patients. This patient group may therefore not be a representative sample of hospitalised patients with ACS and may limit the external validity of the trial.

Summary of clinical effectiveness data

Co-primary outcomes

The results from the CURE trial demonstrated that clopidogrel (in addition to standard therapy including aspirin) was significantly more effective than placebo plus aspirin in patients with non-ST-segment elevation ACS for the composite outcome of death from CV causes, non-fatal MI or stroke, reducing the RR by 20% over the 9-month treatment period. This equated to an ARR of 2.1% and an NNT of 48. In addition, when the second co-primary outcome (the first composite outcome plus RI) was considered, a benefit of comparable magnitude was observed in favour of the clopidogrel group, with a 14% RRR being observed. This equated to an ARR of 2.3% and an NNT of 44. The CURE trial was not powered to detect an effect on single components of the primary outcomes, there were no statistically significant differences in the incidence of stroke or CV death and neither was a statistically significant difference observed in the rates of non-CV death. Whereas the rate of each component of the composite outcomes tended to be lower in the clopidogrel group, the 20% RRR for the composite outcome was largely driven by a 23% relative reduction in the rate of MI in the clopidogrel group. This reduction in MI was due to a statistically significant reduction in the incidence of Q-wave MI. No statistically significant reduction in non-Q-wave MI was shown. Accordingly, based on the trial data, the overall morbidity benefit associated with clopidogrel consists of a reduction in the number of non-fatal MIs within this patient population. In relation to RI, the beneficial effects seen within the clopidogrel group were largely due to a reduction in the number of first events that occurred during the initial hospitalisation period. No further statistically significant differences were seen between patients in the two treatment regimens in terms of a difference in the rate of rehospitalisation for unstable angina.

Secondary outcomes

There was a significant trend in favour of clopidogrel for the secondary outcomes of severe ischaemia, recurrent angina and heart failure over the 9-month treatment period. Slightly fewer of the patients in the clopidogrel group underwent coronary revascularisation during the study, but this difference was accounted for entirely by differences in the rate of revascularisation during

the initial period of hospitalisation. No statistically significant differences in terms of the rates of revascularisation procedures were observed post-hospitalisation between the two treatment groups.

Effects within subgroups

The consistency of the beneficial effects of clopidogrel therapy in a number of key sub-groups of patients over the 9 months of therapy was demonstrated through a number of *post-hoc* subgroup analyses. These effects were consistent in patients at low, intermediate and high risk for future atherothrombotic events, stratified according to the TIMI risk score.[51] Although these benefits were consistent across the different groups, the greatest absolute benefit was observed in patients with the highest TIMI risk scores. Clopidogrel therefore was shown to be of most benefit in patients at high risk of further atherothrombotic events. Analysis of the results stratified according to aspirin dose indicated that clopidogrel further reduced the incidence of the first co-primary outcome (CV death, MI or stroke) regardless of the concomitant aspirin dose administered. Further examination of the effects of clopidogrel by subgroup indicated a tendency towards a greater benefit among patients who had previously undergone revascularisation compared with those who had not.

Temporal trends of therapy

Analysis of the data during the first month post-randomisation indicated that clopidogrel therapy had a rapid beneficial effect, with statistically significant differences between the groups emerging as early as 24 hours after the administration of the loading dose. These beneficial effects in terms of the co-primary outcomes were still observed at 30 days follow-up with an RRR of 21%, although there was no statistically significant difference between the groups in terms of the rates of RI post-hospital discharge. However, although clopidogrel was clearly beneficial in the acute and early chronic phases of treatment, it did not have an equal beneficial effect (month-by-month) throughout the trials' chronic treatment period (from 1 month to 1 year). Analysis of the data by treatment period indicated that significant differences in favour of clopidogrel treatment were observed for the periods of 0–1 and 1–3 months. However, for the treatment periods of 3–6, 6–9 and 9–12 months no statistically significant differences between the groups were observed.

PCI-CURE

In the 21% of patients who underwent PCI, the group that had been randomised to receive clopidogrel experienced an absolute reduction in the rate of CV death, MI or urgent revascularisation of 1.9% (4.5% versus 6.4%) [RR = 0.70 (95% CI: 0.50 to 0.97)] in the 30-day period following PCI. As more than 80% in each group undergoing PCI received open-label treatment with either clopidogrel or ticlopidine for a median of 30 days after PCI, the results suggest that the benefit observed in the 30-day period after PCI required treatment with clopidogrel prior to the procedure. Overall, it appears that patients undergoing PCI have a higher benefit from clopidogrel therapy than those who are managed conservatively.

Adverse events

The incidence of major and minor bleeding complications was significantly more common in the clopidogrel group than the placebo group throughout the duration of the trial. These differences were due to a greater number of patients requiring a transfusion of two or more units of blood and an excess of GI haemorrhages, bleeding at the sites of arterial punctures and minor bleeding episodes. However, no significant differences were observed in terms of the number of fatal bleeding episodes, bleeding requiring surgical intervention or haemorrhagic stroke. An examination of the risk of experiencing any bleeding complication over the length of the trial indicated that the risk of bleeding decreased steadily throughout the trial duration in both groups. It did, however, remain higher in the clopidogrel group in every period. A further subgroup analysis that assessed the bleeding risk associated with adding clopidogrel to different doses of aspirin showed that there was an incremental increase in the rate of major bleeding with increasing doses of aspirin. The excess risk with clopidogrel was 1.1, 1.2 and 1.2% for aspirin doses ≤ 100, 101–199 and ≥ 200 mg, respectively. This subgroup analysis indicated that the use of lower doses of aspirin in combination with clopidogrel may result in a lower incidence of both major and minor bleeding episodes.

In relation to the haematological parameters monitored in the trial, there were no significant differences in the number of patients with thrombocytopenia or neutropenia in the two treatment groups. However, severe rash and diarrhoea were significantly more frequent in the clopidogrel treatment group than the placebo group. Conversely, the incidence of indigestion, nausea, vomiting and abnormal liver function was reported more frequently in the placebo arm relative to the treatment group.

Summary of cost-effectiveness data

The models presented here indicate that clopidogrel appears cost-effective, compared with standard care alone, in patients with non-ST-segment elevation ACS provided that the NHS is willing to pay £6078 per QALY. A series of sensitivity analyses were undertaken to determine the robustness of this result to alternative assumptions. The sensitivity analysis indicated that the incremental cost per QALY gained is between £4299 and £12,313 (the range for the analyses using a lifetime extrapolation is £4229–7981). Despite differences between the alternative models proposed by the TAR group and the manufacturers, the base-case estimate of the ICER appeared robust.

The base-case results were most sensitive to the following factors: (1) the use of shorter-treatment durations of clopidogrel and (2) the methods used to extrapolate the baseline observational data. Alternative approaches to extrapolating the baseline data demonstrated that this was a potentially important source of uncertainty. The ICER of clopidogrel for 12 months duration ranged between £5159 and £13,988 using the different approaches. When a more conservative approach was used to extrapolate the data, the impact of heterogeneity in the overall ACS population was potentially important in determining the optimal duration of treatment with clopidogrel. For high-risk patients, the ICER of using clopidogrel for 12 months remained favourable compared with shorter treatment durations. However, in low-risk patients the cost-effectiveness of providing treatment with clopidogrel for successively longer durations became less clear. For low-risk patients, the ICER of providing treatment with clopidogrel for 6 months compared with only 3 months was approximately £30,786. The ICER of providing clopidogrel for 12 months compared with only 6 months was £34,629.

Assumptions, limitations and uncertainties

The results of the CURE trial showed that patients who received clopidogrel therapy derived a greater benefit than those who received placebo over a 9-month treatment period. This benefit was observed across a number of subgroups of patients including patients undergoing PCI and revascularisation procedures, and also in those classified as being at low, intermediate and high risk of further atherothrombotic events. However, when extrapolating the results of the trial to patients with ACS treated within the UK, a number of points should be considered.

The entry criteria to the CURE trial were strict and required patients to have abnormal ECGs or elevated serum markers. The participants in the study were therefore at higher risk of MI, stroke or death than the general population of hospital patients with ischaemic chest pain and the study results cannot be generalised to all patients with non-ST-segment elevation ACS. Furthermore, the greatest absolute benefit of clopidogrel was observed in patients identified to be at high risk of further atherothrombotic events by the TIMI risk score. This suggests that the main benefit from clopidogrel therapy was derived by a smaller group of high-risk patients.

With 12,562 patients, the CURE trial was not powered to detect a realistic difference in individual components of the primary outcomes, and there were no statistically significant differences in the incidence of stroke, CV death or non-CV death between the two treatment groups. Although there was a significant reduction in the incidence of the first co-primary outcome (MI, stroke or CV death) in the treatment arm, this was driven by a reduction in the incidence of non-fatal Q-wave MI. MI was over four times more frequent than stroke in the trial population, confirming that the population of ACS patients are at higher risk of sustaining a future MI than having a subsequent stroke. Clopidogrel may therefore be of major clinical benefit in the prevention of non-fatal Q-wave MI within this population. Clopidogrel had no statistically significant effect on the rate of death from non-CV causes.

The analysis of the effects of clopidogrel therapy over the duration of the trial suggests that the beneficial effects of treatment are not observed consistently month-by-month in the chronic phase of treatment. The temporal trends suggest that whereas the benefit of clopidogrel is apparent even at 12-month follow-up, between 3 and 6 months these benefits are no longer significantly greater than those derived from aspirin therapy alone. Furthermore, despite exclusion of patients judged at 'high risk of bleeding' from the trial, the addition of clopidogrel significantly increased the absolute rate of major bleeding, with the rate being higher both during the 30 days after randomisation and from 31 days until the end of the trial. Although the bleeding rates in both

groups were shown to decrease throughout the duration of the trial, both major and minor bleeding rates remained higher in the clopidogrel group. Any treatment advantage of clopidogrel should therefore be weighed against the higher risk of bleeding. As clopidogrel was not statistically significantly more beneficial than aspirin alone in the latter half of the trial, it may be that there is a better benefit–harm ratio from a shorter duration of treatment. In relation to practice within the UK, it should be noted that the results of the *post-hoc* subgroup analysis conducted by Peters and colleagues[38] indicate that there was an incremental increase in the rate of major bleeding with increasing doses of aspirin. Data from Intercontinental Marketing Services (derived from British Pharmaceutical Index and Hospital Index and Hospital Pharmacy Audit) demonstrate that the most common UK aspirin dosage is 75 mg/day, comprising 80% of aspirin doses prescribed. However, 80% of patients in the CURE trial were prescribed doses of aspirin above 100 mg/day. This suggests that aspirin doses commonly used in the UK today are associated with a much lower risk of major bleeding than was seen overall in the CURE study. There was no dose–response relationship shown between aspirin and the incidence of minor bleeding observed in the trial. So-called minor or 'nuisance bleeding' can affect patient medication compliance. However, as the reasons for withdrawal from the trial were not reported, it is not possible to assess the extent to which this may be related to withdrawals or dropouts.

Implications for further research

To estimate the exact length of time that clopidogrel in addition to standard therapy should be prescribed for inpatients with non-ST-segment elevation ACS a prospective trial that randomised patients to various durations of therapy would need to be conducted. This would accurately assess whether a 'rebound' phenomenon occurs in patients if clopidogrel were stopped after 3 months of treatment. However, such a trial would have to be considerably larger than the CURE trial to be sufficiently powered.

Chapter 8
Conclusions

Clinical effectiveness

The results of the CURE trial indicate that clopidogrel in combination with aspirin was significantly more effective than placebo combined with aspirin in a wide range of patients with ACS. This benefit was largely related to a reduction in Q-wave MI, but there was no statistically significant benefit in relation to mortality. The trial demonstrated that a substantial part of the benefit derived from clopidogrel is achieved by 3 months, with a further small benefit over the remaining 9 months of chronic treatment.

Cost-effectiveness

The results from the base-case model suggest that treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 12 months, compared with standard therapy alone, is cost-effective in non-ST-segment elevation ACS patients as long as the health service is willing to pay £6078 per additional QALY. The base-case model estimates that this will result in a (mean per patient) gain of 0.08 QALYs at an additional cost of £470, compared with standard therapy alone. This finding appears robust to a range of potential uncertainties in parameter estimates used to populate the base-case model. The results were most sensitive to the inclusion of additional strategies which assessed alternative treatment durations with clopidogrel. Although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low-risk.

Acknowledgements

We thank the expert advisory panel for their useful advice and constructive comments on the draft protocol and report and also Nerys Woolacott for her input at the beginning of the review.

This report was commissioned by the NHS R&D HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D Programme. Any errors are the responsibility of the authors.

Contributions of authors

Caroline Main (Research Fellow, Systematic Reviews) was the lead reviewer responsible for writing the protocol, study selection, data extraction, validity assessment and writing the final report. Stephen Palmer (Senior Research Fellow, Health Economics) was involved in the cost-effectiveness section, as well as writing the protocol, study selection, data extraction, development of the economic model and report writing. Susan Griffin (Research Fellow, Health Economics) was involved in the cost-effectiveness section, as well as writing the protocol, study selection, data extraction, development of the economic model and report writing. Lisa Jones (Research Fellow, Health Economics) was second reviewer involved in writing the protocol, study selection, data extraction, validity assessment and writing the final report. Vickie Orton (Information Officer) devised the search strategies and carried out the literature searches; she also wrote the search methodology sections of the report. Mark Sculpher (Professor of Health Economics) provided input at all stages, commented on various drafts of the report; Mark also had overall responsibility for cost-effectiveness section of the report. Rob Henderson (Consultant Cardiologist) provided input at all stages, commented on various drafts of the report and contributed to the discussion section of the report. Cathie Sudlow (Wellcome Clinician Scientist) provided input at all stages, commented on various drafts of the report and contributed to the discussion section of the report. Neil Hawkins (Research Fellow, Health Economics) was involved in the cost-effectiveness section; advised on the development of the economic model. Rob Riemsma (Reviews Manager, Systematic Reviews) provided input at all stages, commented on various drafts of the report; Rob also had overall responsibility for the clinical effectiveness section of the report and supervised overall process.

References

1. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, *et al*. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988; **319**:1105–11.
2. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, *et al*. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. *Circulation* 2000;**102**:1193–209.
3. Antman E, Braunwald E. Acute myocardial infarction. In Braunwald E, Fauci A, Kasper D, Hauser S, Longo D, Jameson J, editors. *Harrison's principles of internal medicine*. New York: McGraw-Hill; 2001. pp. 1386–99.
4. Rosengren A, Wilhelmsen L, Hagman M, Wedel H. Natural history of myocardial infarction and angina pectoris in a general population sample of middle-aged men: a 16-year follow-up of the Primary Prevention Study, Goteborg, Sweden. *J Intern Med* 1998;**244**:495–505.
5. Fitchett D, Goodman SG, Langer A. New advances in the management of acute coronary syndromes: matching treatment to risk. *Can Med Assoc J* 2001; **164**:1309–16.
6. Braunwald E. Unstable angina: a classification. *Circulation* 1989;**80**:410–14.
7. Zimmerman J, Fromm R, Meyer D. Diagnostic marker, cooperative study for the diagnosis of myocardial infarction. *Circulation* 1999;**99**:1671–7.
8. Sabia P, Abbott R, Afrookteh A. Importance of two-dimensional echocardiographic assessment of left ventricular systolic function in patients presenting to the emergency room with cardiac related syndromes. *Circulation* 1991;**84**:1615–24.
9. Easton JD. Evidence with antiplatelet therapy and ADP-receptor Antagonists. *Cerebrovasc Dis* 2003; **16**:20–6.
10. British Heart Foundation. *Coronary heart disease statistics*. London: British Heart Foundation; 1999.
11. Petersen S, Rayner M. *Coronary heart disease statistics: heart failure supplement*. London: British Heart Foundation; 2002.
12. Department of Health. *Health survey for England 1998*. London: The Stationery Office; 1999.
13. Hobbs R. The National Service Framework on coronary heart disease. *Br J Cardiol* 1999; **6**:455–8.
14. Office for National Statistics. *Key health statistics from general practice*. Report No: MB6 No1. London: HMSO; 1996.
15. Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C. Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review. *Health Technol Assess* 2000;**4**(23).
16. Scottish Intercollegiate Guidelines Network (SIGN). *Management of patients with stroke – Rehabilitation, prevention and management of complications, and discharge planning*. Report No. 64. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2002.
17. Gresham GE, Fitzpatrick TE, Wolf PA, McNamara PM, Kannel WB, Dawber TR. Residual disability in survivors of stroke – the Framingham Study. *N Engl J Med* 1975;**293**:954–6.
18. Liu JL, Maniadakis N, Gray A, Rayner M. The economic burden of coronary heart disease in the UK. *Heart* 2002; **88**:597–603.
19. Gandhi MM, Lampe FC, Wood DA. Incidence, clinical characteristics, and short-term prognosis of angina pectoris. *Br Heart J* 1995;**73**:193–8.
20. Purcell H. The epidemiology of unstable angina. *Br J Cardiol* 1998;**5**:S3–S4.
21. British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary 42*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2001.
22. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, *et al*. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**:995–1003.
23. Drouet L. Atherothrombosis as a systemic disease. *Cerebrovasc Dis* 2002;**1**:1–6.
24. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988;**260**:2088–93.
25. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project [published erratum appears in *Stroke* 1994;**25**:1887]. *Stroke* 1994; 25:333–7.

26. Baigent C, Sudlow C, Collins R, Peto R. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.

27. Fowkes F. Epidemiology of peripheral vascular disease. *Atherosclerosis* 1997;**131**:529–31

28. Makkar RR, Eigler NL, Kaul S, Frimerman A, Nakamura M, Shah PK, *et al*. Effects of clopidogrel, aspirin and combined therapy in a porcine *ex vivo* model of high-shear induced stent thrombosis. *Eur Heart J* 1998;**18**:1538–46.

29. Harker LA, Marzee UM, Kelly AB, Chronos NRF, Sundell IB, Hanson SR, *et al*. Clopidogrel inhibition of stent, graft, and vascular thrombogenesis with antithrombotic enhancement by aspirin in nonhuman primates. *Circulation* 1998;**98**:2461–9.

30. Herbert JM, Dol F, Bernat A, Folotico R, Lale A, Savi P. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. *Thromb Haemos* 1998;**80**:512–18.

31. Cadroy Y, Bossavy JP, Thalamus C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. *Circulation* 2000;**101**:2823–8.

32. Moshfegh K, Redondo M, Julmy F, Wuillemin WA, Gebauer MU, Haeberli A, *et al*. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy. *J Am Coll Cardiol* 2000; **36**:699–705.

33. NHS Centre for Reviews and Dissemination. *Report 4: undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews*. York: University of York; 2001.

34. Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford Medical Publications; 1997.

35. Yusuf S, Zhao F, Mehta S, Chrolavicius S, Tognoni G, Fox K. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.

36. Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, *et al*. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation* 2003;**107**:966–72.

37. Budaj A, Yusuf S, Mehta SR, Fox KA, Tognoni G, Zhao F, *et al*. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups [comment]. *Circulation* 2002;**106**:1622–6.

38. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, *et al*. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes. Observations from the clopidogrel in unstable angina to prevent recurrent events (CURE) study. *Circulation* 2003;**108**:1682–7.

39. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, *et al*. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study [comment]. *Lancet* 2001;**358**:527–33.

40. Mehta SR, Ellis S, Rapaport E, Mehta S, Cannon C. Aspirin and clopidogrel in patients with ACS undergoing PCI: CURE and PCI-CURE. *J Invas Cardiol* 2003;**15**(Suppl B):17B–20B.

41. Mehta SR, Yusuf S, Boden WE, Pepine CJ. Short- and long-term oral antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention. Optimizing management of non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2003;**41**:79–88.

42. Boucher M, Armstrong P, Pharand C, Skidmore B, Canadian Coordinating Office for Health Technology Assessment. *The role of clopidogrel in the secondary prevention of recurrent ischemic vascular events after acute myocardial ischemia: a critical appraisal of the CURE trial*. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2002.

43. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *BMJ* 1988;**296**:320–31.

44. Altman R, Carreras L, Diaz R, Figueroa E, Paolasso E, Parodi JC, *et al*. Collaborative overview of randomised trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81–106.

45. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Arch Intern Med* 2002; **162**:2197–202.

46. Stalnikowicz-Darvasi R. Gastrointestinal bleeding during low-dose aspirin administration for prevention of arterial occlusive events. A critical analysis. *J Clin Gastroenterol* 1995;**21**:13–6.

47. Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. *Br J Clin Pharmacol* 2001;**52**:563–71.

48. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials [comment]. *JAMA* 1998;**280**:1930–5.

49. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000;**321**:1183–7.

50. Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, *et al*. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial [published erratum appears in *JAMA* 2003;**289**:98]. *JAMA* 2002;**288**:2411–20.

51. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, T.L. S. Thrombolysis in Myocardial Infarction (TIMI) Trial: phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;**11**:1–11.

52. Berkowitz S, Granger C, Pieper K, Lee K, Gore J, Simons M, *et al*. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation* 1997; **95**:2508–16.

53. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke. A meta-analysis of randomized controlled trials. *JAMA* 1998;**280**:1930–5.

54. Gaspoz J-M, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink MGM, *et al*. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 2003;**348**:560–1.

55. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.

56. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. *Am J Public Health* 1987;**77**:1417–26.

57. Palmer S, Sculpher M, Philips Z, Robinson M, Ginnelly L, Bakhai A, *et al*. A cost-effectiveness model comparing alternative management strategies for the use of glycoprotein IIb/IIIa antagonists in non-ST-elevation acute coronary syndrome. Report to the National Institute for Clinical Excellence. URL: http://www.nice.org.uk/Docref.asp?d=32030. Accessed 2002.

58. Collinson J, Flather MD, Fox KAA, Findlay I, Rodrigues E, Dooley P, *et al*. Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK). *Eur Heart J* 2000;**21**:1450–7.

59. Alfakih K, Robinson MB, Hall AS, McLenechan J. Outcomes of percutaneous intervention in acute coronary syndromes: from clinical trials to clinical practice. *Br J Cardiol* 2003;**10**:56–8.

60. Wolfe CD, Rudd AG, Howard R, Coshall C, Stewart J, Lawrence E, *et al*. Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London Stroke Register. *J Neurol Neurosurg Psychiatry* 2002;**72**:211–16.

61. Chambers M, Hutton J, Gladman J. Cost-effectiveness analysis of antiplatelet therapy in the prevention of recurrent stroke in the UK. Aspirin, dipyridamole and aspirin–dipyridamole. [published erratum appears in *Pharmacoeconomics* 2000;**17**:69]. *Pharmacoeconomics* 1999;**16**:577–93.

62. Department of Health. *NHS reference costs*. London: Department of Health; 2002.

63. Lightowlers S, McGuire A. Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. *Stroke* 1998;**29**:1827–32.

64. British Cardiovascular Intervention Society. BCIS audit returns of interventional procedures 2000. URL: (http://www.bcis.org.uk/audit/oct01.html). Accessed 2001.

65. Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000; **17**:479–500.

66. Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Making* 2002;**22**:290–308.

67. Department of Health. *Policy appraisal and health*. London: Department of Health; 1995.

68. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, *et al*. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – 2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation* 2002;**106**:1893–900.

69. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with Eptifibatide in patients with acute coronary syndromes. *N Eng J Med* 1998;**339**:436–43.

70. Collinson J, Flather MD, Fox KA, Findlay I, Rodrigues E, Dooley P, *et al*. Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST

elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK)[comment]. *Eur Heart J* 2000;**21**:1450–7.

71. Sculpher MJ, Smith DH, Clayton T, Henderson RA, Buxton MJ, Pocock SJ, *et al*. Coronary angioplasty versus medical therapy for angina: health service costs based on the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Eur Heart J* 2002;**23**:1291–300.

72. British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary 44*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2002.

73. Johannesson M, Weinstein S. On the decision rules of cost-effectiveness analysis. *J Health Econ* 1993;**12**:459–67.

74. Van Hout BA, Al MJ, Gordon GS, Rutten FFH. Costs, effects and c/e-ratios alongside a clinical trial. *Health Econ* 1994;**3**:309–19.

75. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–89.

76. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003;**21**:43–50.

77. Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Medical Decis Making* 2003;**23**:341–50.

78. *National Service Framework for Older People*. London: Department of Health; 2001.

79. Stroke TIWPf. *National clinical guidelines for stroke Update*. London: Royal College of Physicians; Update 2002.

80. Scottish Intercollegiate Guidelines Network (SIGN). *Drug therapy for peripheral arterial disease*. Report No. 27. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 1998.

81. Group Padac. Antiplatelet therapy in peripheral arterial disease. Consensus statement. *Eur J Vasc Endovasc Surgery* 2003;**26**:1–16.

82. Scottish Intercollegiate Guidelines Network (SIGN). *Secondary prevention of coronary heart disease following myocardial infarction*. Report No. 41. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2000.

83. Acheson J, Danta G, Hutchinson E. Controlled trial of dipyridamole in cerebral vascular disease. *BMJ* 1969;**1**:614–15.

84. Adams HP, Davis PH. Management of transient ischemic attacks. *Compr Ther* 1995;**21**:355–61.

85. Vázquez R, Esteban J, García M. Effects of the dipyridamole and the association of dipiridamole and dihydroergotoxine methanesulphonate on the mean cerebral passage time in patients with stroke. *Medicina Clínica* 1978;**71**:172–6.

86. Alberts MJ, Easton JD. Clopidogrel plus aspirin for stroke prevention [comment]. *Stroke* 2002;**33**:2546–7.

87. Algra A, van Gijn J, Kappelle LJ, Koudstaal PJ, Stam J, Vermeulen M. Creative mathematics with clopidogrel; exaggeration of the preventive effect by manufacturer [comment] [in Dutch]. *Ned Tijdschr Geneeskd* 1999;**143**:2479.

88. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, *et al*. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Available at http//: www.acc.org.clinical/guidelines

89. American–Canadian Co-operative Study Group. Persantine Aspirin Trial in cerebral ischemia. Part II: endpoint results. The American–Canadian Co-operative Study Group. *Stroke* 1985;**16**:406–15.

90. Anonymous. Trials of drugs for prevention of 'secondary' MIs indecisive. *Hosp Pract* 1980; **15**:49–54.

91. Anonymous. Dipyridamole/acetylsalicylic acid (Asasantin™) – a new fixed combination [in Dutch]. *Geneesmiddelenbulletin* 1999;**33**:19–20.

92. Anonymous. Clopidogrel. *Prescrire Int* 1999; **8**:163–4.

93. Anonymous. Clopidogrel cuts risk of vascular events in patients with acute coronary syndromes. *Hosp Formulary* 2001;**36**:367–8.

94. Anonymous. Early therapy with clopidogrel in acute coronary syndrome is useful [in German]. *Dtsch Apoth Ztg* 2001;**141**:42.

95. Anonymous. Clopidogrel also for the treatment of acute coronary syndrome [in German]. *Dtsch Apoth Ztg* 2002;**142**:50–2.

96. Anonymous. Clopidogrel of benefit in coronary intervention. *Pharma J* 2002;**269**:722–5.

97. Aronow WS. Antiplatelet agents in the prevention of cardiovascular morbidity and mortality in older patients with vascular disease. *Drugs Aging* 1999; **15**:91–101.

98. Aspirin Myocardial Infarction Study (AMIS) Research Group. AMIS: a randomized controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980;**243**:661–9.

99. Bachman F. Rapid platelet inhibition of clopidogrel 375 mg loading dose. *Eur Heart J* 1996;**17** (Suppl):263.

100. Benavente O, Hart RG, Diener HC, Lowenthal A. Antiplatelet therapy to prevent stroke: risk of brain haemorrhage and efficacy in atrial fibrillation [1] (multiple letters). *J Neurol Sci* 1997;**153**:110.

101. Bennett CL, Connors JM, Carwile JM, Moake JL, Bell WR, Tarantolo SR, *et al*. Thrombotic thrombocytopenic purpura associated with clopidogrel [comment]. *N Engl J Med* 2000; **342**:1773–7.

102. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**:624–9.

103. Bhatt DL, Hirsch AT, Hacke W, Topol EJ. A new endpoint for antiplatelet therapy for atherosclerosis: repeat hospitalization for ischemic or bleeding events. *Circulation* 1999;**100**:3747A.

104. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001;**103**:368–8.

105. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001;**103**:363–8.

106. Bogousslavsky J. Benefit of ADP receptor antagonists in atherothrombotic patients: new evidence. *Cerebrovasc Dis* 2001;**2**: 5–10.

107. Bollinger A, Brunner U. Antiplatelet drugs improve the patency rates after femoro-popliteal endarterectomy. *Vasa* 1985;**14**:272–9.

108. Born GV, Collins R. Aspirin versus clopidogrel: the wrong question? [comment]. *Lancet* 1997;**349**:806–7.

109. Bousser MG, Eschwege E, Haguenau M, Lefauconnier JM, Touboul D, Touboul PJ. 'A.I.C.L.A.' controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. Part I: protocol [author's translation; in French]. *Rev Neurol (Paris)* 1981;**137**:333–41.

110. Bousser MG, Eschwege E, Haguenau M, Lefauconnier JM, Thibult N, Touboul D, Touboul PJ. 'A.I.C.L.A.' controlled trial of aspirin and dipyridamole in the secondary prevention of atherosclerotic cerebral ischemia. Part II: baseline studies [in French]. *Rev Neurol* (*Paris*) 1982;**138**:1–15.

111. Bousser MG, Eschwege E, Haguenau M, Lefauconnier JM, Thibult N, Touboul D, Touboul PJ. Controlled trial of aspirin and dipyridamole in the secondary prevention of atherothrombotic cerebral ischemic accidents [in French]. *Presse Med* 1983:**12**:3049–57.

112. Bousser MG, Eschwege E, Haguenau M, Lefaucconnier JM, Thibult N, Touboul D, *et al*. 'AICLA' controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. *Stroke* 1983; **14**:5–14.

113. Boysen G, Soelberg-Sørensen P, Juhler M, Andersen A, Boas J, Olsen J, *et al*. Danish very-low-dose aspirin after carotid endarterectomy trial. *Stroke* 1988;**19**:1211–15.

114. Boysen G. Bleeding complications in secondary stroke prevention by antiplatelet therapy: a benefit–risk analysis. *J Intern Med* 1999; **246**:239–45.

115. Anonymous. Significant reduction of reinfarction risk by dipyridamole plus acetylsalicylic acid. *Therapiewoche* 1985;**35**:2527–34.

116. Brechter C, Backlund H, Krook H, Muller R, Nitelius E, Olsson JE, *et al*. Comparison between anticoagulant treatment and anti-platelet therapy in order to prevent cerebral infarction in patients with TIA/RIND. *Lakartidningen* 1980;**77**:4947–56.

117. Breddin K, Loew D, Lechner K, Uberla K, Walter E. Secondary prevention of myocardial infarction: a comparison of acetylsalicylic acid, placebo and henprocoumon. *Haemostasis* 1980;**9**:325–44.

118. Breddin HK. Pharmaceutical prevention of recurrence of myocardial infarction [in German]. *Verh Dtsch Ges Innere Med***87**:305–14.

119. Britton M, Helmers C, Samuelsson K. High-dose acetylsalicylic acid after cerebral infarction. A Swedish co-operative study. *Stroke* 1987;**18**:325–34.

120. Brown DL, Topol EJ. Stroke complicating percutaneous coronary revascularization. *Am J Cardiol* 1993;**72**:1207–9.

121. Cairns JA, Theroux P, Lewis HD, Ezekowitz M, Meade TW. Antithrombotic agents in coronary artery disease. *Chest* 2001;**119**: 228–52.

122. Calverley DC, Jacobs LG. Antiplatelet therapy in the elderly: aspirin, ticlopidine, clopidogrel and GPIIb/GPIIIa antagonists: thromboembolic disease and anticoagulation in the elderly. *Clin Geriatr Med* 2001;**17**:31–48.

123. Campbell N, Grimshaw J, Ritchie L. Outpatient cardiac rehabilitation: are the potential benefits being realised? *J R Coll Physicians London* 1996; **30**:514–19.

124. Canadian Co-operative Study Group. A randomised trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med* 1978;**299**:53–9.

125. Gent M. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.

126. Second Chinese Cardiac Study Collaborative Group. Rationale, design and organization of the Second Chinese Cardiac Study (CCS-2): a randomized trial of clopidogrel plus aspirin, and of metoprolol, among patients with suspected acute myocardial infarction. Second Chinese Cardiac Study (CCS-2) Collaborative Group. *J Cardiovasc Risk* 2000;**7**:435–41.

127. Chapman T, Bowley D, Lambert A, Walker A, Ashley S, Wilkins D. Haemorrhage associated with combined clopidogrel and aspirin therapy. *Eur J Vasc Endovasc Surg* 2001;**22**:478–9.

128. Cheung R. Clopidogreal and thrombotic thrombocytopenic purpura. *N Engl J Med* 2000; **343**:1192.

129. Cohen SN. Dipyridamole plus aspirin in cerebrovascular disease [comment]. *Arch Neurol* 2000;**57**:1086–7.

130. Colwell J, Bingham S, Abraira C, Anderson J, Comstock J, Kwaan H, *et al*. Veterans Administration Cooperative Study of antiplatelet agents in diabetic patients after amputation for gangrene: unobserved, sudden, and unexpected deaths. *J Diabetes Complications* 1989;**3**:191–7.

131. Coronary Drug Project (CDP) Research Group. Aspirin in coronary heart disease. *Circulation* 1980;**62**:59–62.

132. Coukell AJ, Markham A, Gent M, Schroer K. Clopidogrel. Commentaries. *Drugs*1997;**54**:745–51.

133. Coukell AJ, Markham A. Clopidogrel. *Drugs* 1997; **54**:745–50.

134. Crassard I, Niclot P, Bousser MG. Aspirin and cerebral ischemic accidents [in French]. *Rev Med Interne* 2000;**21**:41s–49s.

135. Crawford KM, Talbert RL. Antiplatelet therapy in secondary stroke prevention. *Expert Opin Pharmacother* 2001;**2**:1609–13.

136. Creager MA. Results of the CAPRIE trial: efficacy and safety of clopidogrel. Clopidogrel versus aspirin in patients at risk of ischaemic events. *Vasc Med* 1998;**3**:257–60.

137. Cristallini P, Capitelli M, Cianti C, Galloni C. Pharmacologic prevention of cerebral vascular accidents [in Italian]. *Arch Med Interna* 1979; **31**:133–9.

138. Culliton BJ, Waterfall WK. Studies of myocardial infarction. *BMJ* 1980;**280**:1370–1.

139. Yusuf S, Mehta S, Anand S, Avezum A, Awan N, Bertrand M, *et al*. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme: rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J* 2000;**21**:2033–41.

140. D'Addato M, Curti T, Bertinia D, Donini I, Ferrero R, Fioranit P. Indobufen versus acetylsalicyclic acid plus dipyridamole in long-term patency afer femoropopliteal bypass. *Int Angiol* 1992;**11**:106–12.

141. D'Agostino RB, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. *Stat Med* 2003;**22**:169–86.

142. Dale S. *Stroke*. London: Office of Health Economics; 1989.

143. de Boer AC, Han P, Turpie AG, Butt R, Gent M, Genton E. Platelet tests and antiplatelet drugs in coronary artery disease. *Circulation* 1983;**67**:500–4.

144. De Schryver EL, Gorter JW, Algra A, van Gijn J. Prevention of vascular complications after cerebral ischemia of arterial origin. European Stroke and Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT): moderated coagulation, aspirin–dipyridamole combination or aspirin alone? *Rev Med Interne* 1999;**20**:397–9.

145. De Schryver E. ESPRIT: protocol change. *Cerebrovasc Dis* 2001;**11**:286.

146. De Schryver EL, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. In *The Cochrane Library* Issue 3, 2004.

147. Degeorges M, Boissel JP, Guermonprez JL, Sultan Y, Weber S. Secondary prevention of myocardial infarction. *Sem Hop* 1981;**57**:1623–5.

148. Department of Health. *Hospital episode statistics, vol. 1. Finished consultant episodes by diagnosis, operation and specialty, England 2000–2001*. London: Department of Health; 2001.

149. Dalton B, Papoushek C, Evans MF. Is acetylsalicylic acid plus dipyridamole superior to ASA alone for secondary prevention of stroke? *Can Fam Physician* 2001;**47**:2235–9.

150. Diener HC, Dyken ML. Aspirin dose in secondary prevention of stroke. *Cerebrovasc Dis* 1998;**8**:360–2.

151. Diener HC. Dipyridamole trials in stroke prevention. *Neurology* 1998;**51**:S17–19.

152. Diener H, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European stroke prevention study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *Nervenheilkunde* 1999;**18**:380–90.

153. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;**143**:1–13.

154. Diener HC. Aspirin in the prevention of strokes. *Biom Pharmacother* 1999;**53**:309–11.

155. Diener HC. Stroke prevention: antiplatelet and antithrombolytic therapy. *Haemostasis* 2000;**3**:14–26.

156. Diener HC, Darius H, Bertrand-Hardy JM, Humphreys M. Does early high dosage dipyridamole in prevention of secondary stroke induce cardiac events? *Z Kardiol* 2001;**90**:348–51.

157. Diener HC, Darius H, Bertrand-Hardy JM, Humphreys M, European Stroke Prevention Study. Cardiac safety in the European Stroke Prevention Study 2 (ESPS2). *Int J Clin Pract* 2001;**55**:162–3.

158. Diener HC. Aspirin therapy should be first-line treatment in secondary prevention of stroke – against [comment]. *Stroke* 2002;**33**:2138–9.

159. Doggrell SA. Clopidogrel: a CURE in acute coronary syndromes? *Expert Opin Pharmacother* 2002;**3**:351–3.

160. Donaldson D, Salter M, Kester R, Rajah S, Hall T, Sreeharan N. The influence of platelet inhibition on the patency of femoro-popliteal Cacron bypass grafts. *Vasc Surg* 1985;**19**:224–30.

161. Donnan GA, Davis SM. Aspirin therapy should be first line: probably, but watch this space [comment]. *Stroke* 2002;**33**:2139–40.

162. Du X, Sourbutts J, Cruickshant K, Summers A, Roberts N, Walton E. A community based stroke register in a high risk area for stroke in north west England. *J Epidemiol Commun Health* 1997;**51**:472–8.

163. Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med* 1991;**325**:1261–6.

164. Duval S, Tweedie R. Nonparametric 'trim and fill' method for accounting for publication bias in meta-analysis. *J Am Stat Assoc* 2000;**95**:89–98.

165. Dyken ML. Antiplatelet agents and stroke prevention. *Semin Neurol* 1998;**18**:441–50.

166. Easton JD. Antiplatelet therapy in the prevention of stroke. *Drugs* 1991;**5**:39–50.

167. Easton JD. What have we learned from recent antiplatelet trials? *Neurology* 1998;**51**:S36–8.

168. Easton JD, Diener HC, Bornstein NM, Einhaupl K, Gent M, Kaste M, *et al*. Antiplatelet therapy: views from the experts. *Neurology* 1999;**53**:S32–7.

169. Easton JD. Future perspectives for optimizing oral antiplatelet therapy. *Cerebrovasc Dis* 2001;**2**:23–8.

170. Ehresmann U, Alemany J, Loew D. Prophylaxe von rezidivverschlussen nach revaskularisationseingreffen mit acetysalicylsaure. *Med Welt* 1977;**28**:1157–62.

171. Elmi F, Peacock T, Schiavone J. Isolated profound thrombocytopenia associated with clopidogrel [comment]. *J Invas Cardiol* 2000;**12**:532–5.

172. Elwood P, Cochrane A, Burr M, Sweetnam P, Williams G, Welsby E, *et al*. A randomised controlled trial of acetylsalicylic acid in the secondary prevention of mortality from myocardial infarction. *BMJ* 1974;**i**:436–40.

173. Elwood P, Sweetnam P. Aspirin and secondary mortality after myocardial infarction. *Lancet* 1979;**ii**:1313–15.

174. Elwood PC, Stillings MR. Use of aspirin in cardiovascular prophylaxis. *Cardiovasc J S Afr* 2000;**11**:155–60.

175. Escolar G, Heras M. Clopidogrel: a selective inhibitor of platelet ADP receptors. *Drugs Today* 2000;**36**:187–99.

176. European Stroke Prevention Study Working Group. Secondary stroke prevention: aspirin/dipyridamole combination is superior to either agent alone and to placebo. *Stroke* 1996;**27**:195.

177. Dom L, Moens E, Franck G, Doyen P, Marquardsen J, Callaghan N, *et al*. The European Stroke Prevention Study (ESPS). *Lancet* 1987; **2**:1351–4.

178. Lowenthal A, Dom L, Moens E, Franck G, Doyen P, Laterre C, *et al*. European Stroke Prevention Study. *Stroke* 1990;**21**:1122–30.

179. ESPS Group, Lowenthal A, Dom L, Moens E, Franck G, Doyen P, *et al*. European Stroke Prevention Study. ESPS Group. *Stroke* 1990;**21**:1122–30.

180. ESPS Working Group. European Stroke Prevention Study 2. A study of low-dose acetylsalicylic acid and of high dose dipyridamole in secondary prevention of cerebrovascular accidents. *Eur J Neurol* 1995;**2**:416–24.

181. Lowenthal A, Dom L, Moens E, Franck G, Doyen P, Laterre C, *et al*. The European Stroke Prevention Study (ESPS). *Rev Bras Clin Ter* 1988; **17**:300–4.

182. Lowenthal A. Second European Stroke Prevention Study. ESPS-2 Working Group. *J Neurol* 1992; **239**:299–301.

183. Evans AE. Secondary prevention after myocardial infarction. *Lancet* 1986;**2**:150–1.

184. Ferguson JJ. Research news: Second European Stroke Prevention Study. *Circulation* 1996;**93**:399.

185. Ferguson JJ. Second European Stroke Prevention Study. *Circulation* 1996;**93**:399.

186. Fields W, Lemak N, Frankowski R, Hardy R. Controlled trial of aspirin in cerebral ischemia. *Stroke* 1977;**8**:301–14.

187. Fields W, Lemak N, Frankowski R, Hardy R. Controlled trial of aspirin in cerebral ischemia. Part II: surgical group. *Stroke* 1978;**9**:309–18.

188. Fields WS. Role of antiplatelet agents in cerebrovascular disease. *Curr Ther* 1979; **20**:103–111.

189. Forbes CD. Secondary prevention of stroke – new trials. *Scott Med J* 1998;**43**:5–6.

190. Forbes CD. Secondary prevention of stroke – an update. *J R Soc Health* 1998;**118**:15–17.

191. Forbes CD. Secondary stroke prevention with low-dose aspirin, sustained release dipyridamole alone and in combination. ESPS Investigators. European Stroke Prevention Study. *Thromb Res* 1998;**92**:S1–6.

192. Forbes CD. Antiplatelet therapy for secondary stroke prevention [comment]. *Scott Med J* 1999; **44**:54–9.

193. Franck G. 2nd European Study on Secondary Prevention of Stroke (ESPS 2). Respective roles of acetylsalicylic acid, dipyridamole and their combination. *Rev Med Liege* 1995;**50**:491.

194. Friedewald WT, Furberg CD, May GS. Aspirin and myocardial infarction. *Cardiovasc Rev Rep* 1984; **5**:1285–9.

195. Fragmin during instability in coronary artery disease (FRISC) study group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996;**347**:561–8.

196. Frison I, Pocock S. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. *Stat Med* 1992; **2**:1685–704.

197. Furberg CD, May GS. Clinical trials of platelet-active drugs in coronary heart disease: summary of design features. *Circulation* 1980;**62**:V-49–52.

198. Furberg CD, May GS. Effect of long-term prophylactic treatment on survival after myocardial infarction. *Am J Med* 1984;**76**:76–83.

199. Gent M, Barnett H, Sackett D, Taylor D. A randomized trial of aspirin and sulfinpyrazone in patients with threatened stroke. Results and methodologic issues. *Circulation* 1980;**62**:97–105.

200. Gent M, Hampton JR, Roberts RS, Verstraete M. CAPRIE trial – reply. *Lancet* 1997;**349**:356.

201. Gent M. Clopidogrel, a new potent adenosine diphosphate (ADP)-receptor antagonist for the prevention of myocardial infarction and ischemic stroke. *Today's Ther Trends* 1998;**16**:237–54.

202. Gent M. The CAPRIE trial: culmination of the pre-registration program for clopidogrel. Clopidogrel versus aspirin in patients at risk of ischaemic events. Clopidogrel versus aspirin in patients at risk of ischaemic events. *Semin Thromb Hemost* 1999;**2**:1–2.

203. Gentile R, Laganà B, Calcagni S, Borgia M, Baratta L. Efficacy of platelet inhibiting agents in the prevention of reinfarction in smoker patients. In *Proceedings of X World Congress of Cardiology; 1986; Washington*. 1986. p. 302 (Abstract 1724).

204. Gerschutz GP, Bhatt DL. The CURE trial: using clopidogrel in acute coronary syndromes without ST-segment elevation. *Cleve Clin J Med* 2002; **69**:377–8.

205. Giansante C, Calabrese S, Fisicaro M, Fiotti N, Mitri E. Treatment of intermittent claudication with antiplatelet agents. *J Int Med Res* 1990; **18**:400–7.

206. Gibbs CR, Lip GYH. Do we still need dipyridamole? *Br J Clin Pharmacol* 1998;**45**:323–8.

207. Gibbs CR, Li-Saw-Hee FL, Lip GY. Up to date review of the secondary preventive measures for recurrent ischaemic stroke and transient ischaemic episodes. *Scott Med J* 1998;**43**:6.

208. Goldman M, McCollum C. A prospective randomised study to examine the effect of aspirin plus diyridamole on the patency of prosthetic femoro-popliteal grafts. *Vasc Surg* 1984;**18**:217–21.

209. Goodnight SH, Coull BM, McAnulty JH, Taylor LM. Antiplatelet therapy – Part I. *West J Med* 1993;**158**:385–92.

210. Goodnight SH, Coull BM, McAnulty JH, Taylor LM. Antiplatelet therapy – Part II. *West J Med* 1993;**158**:506–14.

211. Goodnight SH. Antiplatelet therapy with aspirin: from clinical trials to practice. *Thromb Haemost* 1995;**74**:401–5.

212. Gorelick PB, Hanley DF. Clopidogrel and its use in stroke patients. *Stroke* 1998;**29**:1737.

213. Gorelick PB, Born GV, D'Agostino RB, Hanley DF, Moye L, Pepine CJ. Therapeutic benefit: aspirin revisited in light of the introduction of clopidogrel. *Stroke* 1999;**30**:1716–21.

214. Gorter JW, De Schryver E, Algra A. Prevention of vascular complications following cerebral ischemia of arterial origin; the ESPRIT trial: mild anticoagulant therapy, combination treatment with acetylsalicylic acid plus dipyridamole or treatment with acetylsalicylic acid alone? *Ned Tijdschr Geneeskd* 1998;**142**:316–18.

215. Gorter JW, De Schryver E, Algra A. Prevention of vascular complications after cerebral ischaemia of arterial origin; the ESPRIT study: mild anticoagulant therapy, combination treatment with acetylsalicylic acid and dipyridamole, or treatment with acetylsalicylic acid alone? *Nervenarzt* 1999;**70**:368–70.

216. Grau AJ, Reiners S, Lichy C, Buggle F, Ruf A. Platelet function under aspirin, clopidogrel, and both after ischemic stroke: a case-crossover study [comment]. *Stroke* 2003;**34**:849–54.

217. Green R, Roedersheimer L, DeWeese J. Effects of aspirin and dipyridamole on expanded polytetrafluroethylene graft patency. *Surgery* 1982;**92**:1016–26.

218. Guiraud-Chaumeil B, Rascol A, David J, Boneu B, Clanet M, Bierme R. A 3-year trial of antiplatelet drugs in secondary prevention of cerebral ischemic accidents. *Rev Neurol (Paris)* 1982;**138**:367–85.

219. Guiraud-Chaumeil B, Rascol A, David J, Boneu B, Clanet M, Bierme R. Prévention des récidives des accidents vasculaires cérébraux ischémiques par les anti-agrégants plaquettaires. *Rev Neurol (Paris)* 1982;**138**:367–85.

220. Matias-Guiu J, Davalos A, Pico M, Monasterio J, Vilaseca J, Codina A. Low-dose acetylsalicylic acid (ASA) plus dipyridamole versus dipyridamole alone in the prevention of stroke in patients with reversible ischemic attacks. *Acta Neurol Scand* 1987;**76**:413–1.

221. Hacke W. Advances in stroke management: update 1998. *Neurology* 1999;**53**:S1–2.

222. Hankey GJ. Clopidogrel: a new safe and effective antiplatelet agent. But unanswered questions remain. *Med J Aust* 1997;**167**:120–1.

223. Hankey GJ, Sudlow CLM, Dunbabin DW, Ernst ME. Regular or 'super-aspirins'? A review of thienopyridines or aspirin to prevent stroke. *J Am Geriatr Soc* 2001;**49**:487–9.

224. Hankey GJ, Sudlow CLM, Dunbabin DW, Ernst ME. Regular or 'super-aspirins'? A review of thienopyridines or aspirin to prevent stroke. *J Am Geriatr Soc* 2001;**49**:487–9.

225. Hanssen C, Williams E. Severe transmural myocardial ischemia after dipyridamole administration implicating coronary steal. *Clin Cardiol* 1998;**21**:293–6.

226. Harjola P, Meurala H, Frick M. Prevention of early reocclusion by dipyridamole and ASA in arterial reconstructive surgery. *J Cardiovasc Surg (Torino)* 1981;**22**:141–4.

227. Harrington RA. Trials of novel antiplatelet agents. *J Myocardial Ischemia* 1994;**6**:20–4.

228. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**:145–53.

229. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.

230. Heiss H, Just H, Middleton D, Deichsel G. Reocclusion prophylaxis with dipyridamole combined with acetylsalkicylic acid following PTA. *Angiology* 1990;**41**:263–9.

231. Hennekens CH. Aspirin in chronic cardiovascular disease and acute myocardial infarction. *Clin Cardiol* 1990;**13**:62–6.

232. Hennekens CH. Treatment and prevention of cardiovascular disease by aspirin. *Drug Saf* 1991;**6**:166–70.

233. Hennekens CH. Aspirin in the treatment and prevention of cardiovascular disease. *Ann Rev Pub Health* 1997;**18**:37–49.

234. Hennekens CH. Update on aspirin in the treatment and prevention of cardiovascular disease. *Am J Managed Care* 2002;**8**:S691–700.

235. Heptinstall S. Efficacy of dipyridamole as prophylaxis for stroke and the added value of dipyridamole in combination with aspirin. *Platelets* 1996;**7**:7–8.

236. Hervey PS, Goa KL. Extended-release dipyridamole/aspirin. *Drugs* 1999;**58**:469–75.

237. Hess H, Keil-Kuri E. Theoretische grundlagen der prophylaxe obliterierender arteriopathien mit aggregationshemmern und ergebnisse einer langzeitstudie mit ASS (Colfarit). In: Marx R, Breddin H, editors. *Colfarit Symposium III; 1975*; Cologne: Bayer; 1975. pp. 307–15.

238. Hess H, Mietaschk A, Deichsel G. Drug-induced inhibition of platelet function delays progression of peripheral occlusive arterial disease. A prospective double-blind arteriographically controlled trial. *Lancet* 1985;**1**:415–19.

239. Hess H, Muller-Fasbender H, Ingrisch H, Mietaschk A. Verhutung von wiederverschlussen nach rekanalisation obliterierter arterian mit der kathetermoethode. *Dtsch Med Wochenschr* 1978;**103**:1994–7.

240. Hillis GS, Jennings KP. Dipyridamole: An unfulfilled promise? *Cardiovasc Surg* 1997; **5**:350–3.

241. Hirsh J. The role of aspirin and antithrombotic agents in cardiovascular disease. *Cardiovasc Rev Rep* 1984;**5**:1003–13.

242. Hodara M, Samama M. Platelet inhibitors in the secondary prevention of myocardial infarction. *Gaz Med* 1984;**91**:35–42.

243. Huber K. Current study: update on CURE study. *J Kardiol* 2001;**8**:472–3.

244. Ishikawa K, Kanamasa K, Hama J, Ogawa I, Takenaka T, Naito T, *et al*. Aspirin plus either dipyridamole or ticlopidine is effective in preventing recurrent myocardial infarction. Secondary Prevention Group. *Jpn Circ J* 1997; **61**:38–45.

245. Jackson G. CURE – clopidogrel's major advance. *Intern J Clin Pract* 2001;**55**:155.

246. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis [published erratum appears in *Drugs* 2001;**61**:52]. *Drugs* 2000;**60**:347–77.

247. Jonas S, Zeleniuch-Jacquotte A. The effect of antiplatelet agents on survival free of new stroke: a meta-analysis. *Stroke: Clinical Updates* 1998;**8**:1–4.

248. Jonas S, Barnett HJM, Algra A. Aggrenox (aspirin + extended-release dipyridamole) and plavix (clopidogrel) in secondary stroke prevention: efficacy and drug costs. *J Neurosurg* 2001;**187**(Suppl 1).

249. Kerins DM, FitzGerald GA. The current role of platelet-active drugs in ischaemic heart disease. *Drugs* 1991;**41**:665–71.

250. Gallus AS. Aspirin and other platelet-aggregation inhibiting drugs. *Med J Australia* 1985;**142**:41–7.

251. Klimt CR, Knatterud GL, Stamler J, Meier P. Persantine–Aspirin Reinfarction Study. Part II. Secondary coronary prevention with persantine and aspirin. *J Am Coll Cardiol* 1986;**7**:251–69.

252. Kohler T, Kaufman J, Kacoyanis G, Clowes A, Donaldson M, Kelly E. Effect of aspirin and dipyridamole on the patency of lower extremity bypass grafts. *Surgery* 1984;**96**:462–6.

253. Kubler W. Secondary and primary prevention of coronary heart disease: platelet aggregation inhibitors and anticoagulants. *Z Kardiol* 2002; **2**:40–8.

254. Kurz X, Annemans L, Dresse A, Kulbertus H. Association AAS–dypiridamole ((Asasantine (R)) dans la prevention des recidives d'AVC (analyse cout-efficacite) (la pharmaco-economie). Cost-effectiveness analysis of an association of acetylsalicylic acid and sustained-release dipyridamole in the prevention of recurrent stroke in Belgium. *Rev Med Liege* 1998;**53**:265–9.

255. Kurz X, Annemans L, Dresse A. An acetylsalicylic acid–dypiridamole combination (Asasantine) in the prevention of the recurrence of cerebrovascular accidents (a cost-effectiveness analysis). *Rev Med Liege* 1998;**53**:265–9.

256. Lee TK, Lien IN, Ryu SJ, Lee KY, Hu HH, Tchen PH, *et al*. Secondary prevention of ischemic stroke with low dose acetylsalicylic acid. *J Formos Med Assoc* 1990;**89**:635–44.

257. Lenz TL, Hilleman DE. Aggrenox: a fixed-dose combination of aspirin and dipyridamole. *Ann Pharmacother* 2000;**34**:1283–90.

258. Libretti A, Catalano M. Treatment of claudication with dipyridamole and aspirin. *Int J Clin Pharmacol Res* 1986;**6**:59–60.

259. Lowe GDO. Clopidogrel in prevention of cardiovascular events. *Rev Contemp Pharmacother* 2003;**12**:265–98.

260. Lowenthal A, Buyse M. Secondary prevention of stroke: does dipyridamole add to aspirin? *Acta Neurol Belg* 1994;**94**:24–34.

261. Lubsen J. Notes on results of the 'Aspirin myocardial infarction study' and the 'Persantine–aspirin reinfarction study' in the United States. *Ned Tijdschr Geneeskd* 1981; **125**:1606–9.

262. Lucas C. Secondary prevention of stroke: the PROGRESS study. *Rev Med Interne* 2002;**23**:341–8.

263. MacWalter RS. Secondary prevention of stroke. *Thromb Haemost* 1999;**82**:95–103.

264. MacWalter RS, Shirley CP. A benefit–risk assessment of agents used in the secondary prevention of stroke. *Drug Saf* 2002;**25**:943–63.

265. Malinin AI, O'Connor CM, Dzhanashvili AI, Sane DC, Serebruany VL. Platelet activation in patients with congestive heart failure: do we have enough evidence to consider clopidogrel? *Am Heart J* 2003;**145**:397–403.

266. Malinin AI, Eisert RM, Atar D, Barkagan Z, Serebruany VL. Aggrenox (extended-release dipyridamole and low-dose aspirin in combination): protecting platelets from excessive activation in patients with vascular events. *Heartdrug* 2002;**2**:93–104.

267. Marx JL. AMIS negative on aspirin and heart attacks. A large clinical trial shows that aspirin does not prevent cardiac deaths in patients who have already had a heart attack. But questions remain. *Science* 1980;**207**:859–60.

268. Matsagas MI, Jagroop IA, Mikhailidis DP, Geroulakos G. Is aspirin still the antiplatelet drug of choice for patients with peripheral arterial disease? *Eur J Vasc Endovasc Surg* 2003;**25**:281–2.

269. McCollum C, Alexander C, Kenchington G, Franks P, Gennhalgh R. Antiplatelet drugs in femoropopliteal vein bypass: a multicenter trial. *J Vasc Surg* 1991;**13**:150–62.

270. Shukla V. Clopidogrel(TM): an alternative to acetylsalicylic acid and ticlopidine in antiplatelet therapy? *Issues Emerging Health Technol* 1999; **6**:1–4.

271. Mehta P. Aspirin in the prophylaxis of coronary artery disease. *Curr Opin Cardiol* 2002;**17**:552–8.

272. Millan-Guerrero R, Isais-Cardenas M. Intravenous dipyridamole acute cerebral infarction. Is it efficient? *Gac Med de Mex* 1999;**135**:391–6.

273. Minar E, Ahmadi A, Koppensteiner R, Maca T, Stumpflen A, Ugurluoglu A. Comparison of effects of high-dose and low-dose aspirin on restenosis after femoropopliteal percutaneous transluminal angioplasty. *Circulation* 1995;**91**:2167–73.

274. Misson J, Clark W, Kendall MJ. Clopidogrel: secondary prevention of vascular ischaemic events. *J Clin Pharm Ther* 1998;**23**:91–5.

275. Mueller T, Haltmayer M, Poelz W, Haidinger D. Monitoring aspirin 100 mg and clopidogrel 75 mg therapy with the PFA-100 device in patients with

peripheral arterial disease. *Vasc Endovasc Surg* 2003;**37**:117–23.

276. Muhlestein JB. Antiplatelet agents in clinical practice: an economic perspective. *Fibrinol Proteol* 1997;**11**:133–6.

277. Muller TH, Binder K, Guth BD. Pharmacology of current and future antithrombotic therapies. *Cardiol Clin* 1994;**12**:411–42.

278. Muller TH. Inhibition of thrombus formation by low-dose acetylsalicylic acid, dipyridamole, and their combination in a model of platelet-vessel wall interaction. *Neurology* 2001;**57**:S8–11.

279. Mustard JF, Kinlough-Rathbone RL, Packham MA. Aspirin in the treatment of cardiovascular disease: a review. *Am J Med* 1983;**74**:43–9.

280. Nappi J, Talbert R. Dual antiplatelet therapy for prevention of recurrent ischemic events. *Am J Health Syst Pharm* 2002;**59**:1723–35.

281. Nenci GG, Gresele P. The clinical use of antiplatelet agents in coronary artery disease: established results and new perspectives. *Ospedale Maggiore* 1996;**90**:375–87.

282. Noble S, Goa KL. Ticlopidine. A review of its pharmacology, clinical efficacy and tolerability in the prevention of cerebral ischaemia and stroke [published erratum appears in *Drugs Aging* 1996;**8**:444]. *Drugs Aging* 1996;**8**:214–32.

283. Paradiso-Hardy FL, Papastergiou J, Lanctot KL, Cohen EA. Thrombotic thrombocytopenic purpura associated with clopidogrel: further evaluation. *Can J Cardiol* 2002;**18**:771–3.

284. Patrono C. Prevention of myocardial infarction and stroke by aspirin: different mechanisms? Different dosage? *Thromb Res* 1998;**92**:S7–12.

285. Pechlaner C, Wiedermann CJ, Melandri G, Moller BH, Dronfield MW, Morice AH, *et al*. The RITA 3 trial (multiple letters). *Lancet* 2002;**360**:1971–4.

286. Krol WF, Klimt CR, Morledge J, *et al*. Persantine – aspirin reinfarction study. Design, methods and baseline results. *Circulation* 1980;**62**:11–42.

287. Persantine–aspirin Reinfarction Study Research Group. Persantine–aspirin reinfarction study. Design, methods and baseline results. *Circulation* 1980;**62**:II 1–42.

288. Petrucci E, Mainardi LT, Balian V, Ghiringhelli S, Bianchi AM, Bertinelli M, *et al*. Assessment of heart-rate-variability changes during dipyridamole infusion and dipyridamole-induced myocardial-ischemia – a time-variant spectral approach. *J Am Coll Cardiol* 1996;**28**:924–34.

289. Picano E, Abbracchio MP. European Stroke Prevention Study-2 results: serendipitous demonstration of neuroprotection induced by endogenous adenosine accumulation? *Trends Pharmacol Sci* 1998;**19**:14–16.

290. Prandoni P, Milani L, Barbiero M, Cardaioli P, Sanson A, Barbaresi F, *et al*. A combination of dipyridamole with low-dose aspirin in the treatment of unstable angina. A multicenter pilot double-blind study. *Minerva Cardioangiol* 1991; **39**:267–73.

291. Puranen J, Laakso M, Riekkinen P Sr., Sivenius J. Risk factors and antiplatelet therapy in TIA and stroke patients. *J Neurol Sci* 1998;**154**:200–4.

292. Puranen J, Laakso M, Riekkinen PJ, Sivenius J. Efficacy of antiplatelet treatment in hypertensive patients with TIA or stroke. *J Cardiovas Pharmacol* 1998;**32**:291–4.

293. Rajah S, Penny A, Crow M, Watson P. The interaction of varying doses of dipyridamole and acetylsalicyclic acid on the inhibition of platelet functions and their effect on bleeding time. *Br J Clin Pharmacol* 1979;**8**:483–9.

294. Ranke C, Creutzig A, Luska G, Wagner H, Galanski M, Bode-Boger S. Controlled trial of high- versus low-dose aspirin treatment after percutaneous transluminal angioplasty in patients with peripheral vascular disease. *Clin Invest Med* 1994;**72**:673–80.

295. Regensteiner JG, Hiatt WR. Current medical therapies for patients with peripheral arterial disease: a critical review. *Am J Med* 2002; **112**:49–57.

296. Reuther R, Dorndorf W. Aspirin in patients with cerebral ischaemia and normal angiograms or non-surgical lesions. In Breddin H, Dorndorf W, Loew D, Marx R, editors. *Acetylsalicylic acid in cerebral ischaemia and coronary heart disease*. Stuttgart: Schattauer; 1978. pp. 97–106.

297. Reyero JB, Segura VV. Clopidogrel in acute coronary syndromes with non-ST elevation (multiple letters). *Rev Esp Cardiol* 2002;**55**:452–4.

298. Richardson D, Chen S. Data quality assurance and quality control measures in large multicenter stroke trials: the African–American Antiplatelet Stroke Prevention Study (AAASPS) experience. *Cur Control Trials Cardiovascr Med* 2001;**2**:115–17.

299. Riekkinen P, Sivenius J, Kilpeläinen H. Acetylsalicylic acid and dipyridamole in the treatment of TIA and stroke prevention. *Suomen Lääkärilehti* 1988;**43**:1348–52.

300. Ringleb PA, Hacke W. Antiplatelet therapy in stroke prevention. *Cerebrovasc Dis* 2003;**15**:43–8.

301. Robinson L, Jewell N. Some surprising results about covariate adjustments in logistic regression. *Int Stat Rev* 1991;**58**:227–40.

302. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. *Br J Surg* 2001;**88**:787–800.

303. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *Br J Clin Pharmacol* 1993;**35**:219–26.

304. Ruhle H. Anticoagulants and thrombocyte aggregation inhibitors in or following myocardial infarct. *Z Arztl Fortbild* 1985;**79**:463–6.

305. Rumboldt Z, Bozic I, Sardelic S. Secondary prevention of myocardial infarction: impact of clinical trials on clinical practice. *Eur J Clin Pharmacol* 1995;**48**:311–12.

306. Sakai M, Kuboki K, Maeda S, Ueda S, Kuwajima I, Okawa S, *et al*. Effect of antiplatelet and anticoagulant therapy on secondary prevention and long-term prognosis after acute myocardial infarction in aged patients. *Jpn J Geriatr* 1992;**29**:29–34.

307. SALT Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet* 1991;**338**:1345–9.

308. Saniabadi AR, Fisher TC, McLaren M, Belch JF, Forbes CD. Effect of dipyridamole alone and in combination with aspirin on whole-blood platelet-aggregation, Pgi2 generation, and red-cell deformability ex-vivo in man. *Cardiovasc Res* 1991;**25**:177–83.

309. Schellinger PD, Orberk E, Hacke W. Antithrombotic therapy after cerebral ischemia. *Fortschr Neurol Psychiatr* 1997;**65**:425–34.

310. Schoop W, Levy H. Prevention of peripheral arterial occlusive disease with antiaggregants. *Thromb Haemost* 1983;**50**:137 (abstract 0416).

311. Schoop W, Levy H, Schoop B, Gaentzsch A. *Experimentelle und klinische Studien zu der sekundaren Pravention der peripheren Arterisklerose*. Stuttgart: Thieme; 1983.

312. Schror K. Antiplatelet drugs. A comparative review. *Drugs* 1995;**50**:7–28.

313. Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ, *et al*. Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions. *Health Technol Assess* 1998;**2**(10).

314. Sempere AP, Ferrero M, Tahoces ML, Duarte J, Tabernero C, Cabezas C, *et al*. Side effects of antithrombotic treatment in the secondary prevention of cerebrovascular disease. *Rev Neurol* 2000;**30**:5–7.

315. Sherry S. Results of the anturane reinfarction trial. *Hamostaseologie* 1982;**2**:31–37.

316. Sivenius J, Riekkinen PJ, Kilpelainen H, Laakso M, Penttila I. Antiplatelet therapy is effective in the prevention of stroke or death in women: subgroup analysis of the European Stroke Prevention Study (ESPS). *Acta Neurol Scand* 1991; **84**:286–90.

317. Sivenius J, Riekkinen PJ, Smets P, Laakso M, Lowenthal A. The European Stroke Prevention Study (ESPS): results by arterial distribution. *Ann Neurol* 1991;**29**:596–600.

318. Sivenius J, Laakso M, Penttila IM, Smets P, Lowenthal A, Riekkinen PJ. The European Stroke Prevention Study: results according to sex. *Neurology* 1991;**41**:1189–92.

319. Sivenius J, Riekkinen PJ, Laakso M, Smets P, Lowenthal A. European Stroke Prevention Study (ESPS): antithrombotic therapy is also effective in the elderly. *Acta Neurol Scand* 1993;**87**:111–4.

320. Sivenius J, Laakso M, Riekkinen P Sr, Smets P, Lowenthal A. European Stroke Prevention Study: effectiveness of antiplatelet therapy in diabetic patients in secondary prevention of stroke. *Stroke* 1992;**23**:851–4.

321. Sivenius J, Riekkinen PJ Sr, Laakso M. Antiplatelet treatment in elderly people with transient ischaemic attacks or ischaemic strokes. *BMJ* 1995;**310**:25–6.

322. Sivenius J, Diener HC, Bendixen BH, Adams HP, Barnett HJM, Meldrum HE, *et al*. Upcoming alternatives to aspirin for antiaggregant therapy in stroke prevention. *Eur Neurol* 1996;**36**:253–9.

323. Sivenius J, Diener HC. The role of dipyridamole in stroke prevention. *Eur Neurol* 1996;**36**:253–6.

324. Sivenius J, Riekkinen P. The Second European Stroke Prevention Study (ESPS-2): Satellite Symposium at the Meeting of the European Federation of Neurological Societies on Secondary Prevention of Stroke and TIA, Prague, 5 June 1997. *Int J Clin Pract Suppl Issue* 1997;91.

325. Sorensen P, Pedersen H, Marquardsen J, Petersson H, Heltberg A, Simonsen N, *et al*. Acetylsalicylic acid in the prevention of stroke in patients with reversible cerebral ischemic attacks. A Danish cooperative study. *Stroke* 1983;**14**:15–22.

326. Stachenko SJ, Bravo G, Cote R, Boucher J, Battista RN. Aspirin in transient ischemic attacks and minor stroke: a meta-analysis. *Fam Pract Res J* 1991;**11**:179–91.

327. Study group on pharmacological treatment after PTA. Platelet inhibition with ASA/dipyridamole after percutaneous balloon angioplasty in patients with symptomatic lower limb arterial disease. A prospective double-blind trial. *Eur J Vasc Dis* 1994;**8**:83–8.

328. Taddei S, Arzili F, Arrighi P, Salvetti A. Dipyridamole decreases circulating renin–angotensin system activity in hypertensive patients. *Hypertension* 1992;**5**:29–31.

329. Diez Tejedor E, Barreiro Tella P, Acosta Varo J, Arpa Gutierrez J. Long term therapy in cerebral ischemic attacks. *Arch Neurobiol* 1980;**43**:29–44.

330. Fields WS. Persantine aspirin trial in cerebral ischemia. *Stroke* 1983;**14**:99–103.

331. American-Canadian Co-operative Study Group. Persantine aspirin trial in cerebral ischemia – Part III: risk factors for stroke. *Stroke* 1986; **17**:12–8.

332. European Stroke Prevention Study (ESPS). Principal end-points. The ESPS Group. *Lancet* 1987;**2**:1351–4.

333. Chalmers TC. The persantine–aspirin reinfarction study. *Circulation* 1980;**62**(6 Pt 2):V85–8.

334. Group P-ARSR. Persantine and aspirin in coronary heart disease. *Circulation* 1980;**62**:449–61.

335. Klimt CR. Persantine and ASS in coronary heart disease. The Persantine/ASS Reinfarction Study Group – Paris. *Munch Med Wochenschr* 1980; **22**:1761–71.

336. WASH study Steering Committee and Investigators. The WASH study (Warfarin/Aspirin Study in Heart failure): rationale, design and end-points. *Eur J Heart Fail* 1999;**1**:95–9.

337. Theis JG, Deichsel G, Marshall S. Rapid development of tolerance to dipyridamole-associated headaches. *Br J Clin Pharmacol* 1999; **48**:750–5.

338. Theiss W, Bloemer H. Platelet suppressant therapy and oral anticoagulants in the secondary prevention of acute myocardial infarction. *Herz* 1979;**4**:419–27.

339. Thizon-de-Gaulle I. Antiplatelet drugs in secondary prevention after acute myocardial infarction. *Rev Port Cardiol* 1998;**17**:993–7.

340. Thommen A. Secondary prophylaxis of myocardial infarction. *Therapiewoche Schweiz* 1990;**6**:680–1.

341. Tijssen JGP. Dipyridamole and acetylsalicylic acid (ASA) in the secondary prevention of vascular events after stroke or TIA. *Int J Clin Prac Suppl Issue* 1997;91.

342. Tijssen JG. Low-dose and high-dose acetylsalicylic acid, with and without dipyridamole: a review of clinical trial results. *Neurology* 1998;**51**:S15–16.

343. Uchiyama SI. Clopidogrel. Mainly on results of CAPRIE and indications to practice. *Ther Res* 1998;**19**:1418–23.

344. Uchiyama S. Secondary prevention of occlusive cerebrovascular diseases: medical treatment. *Jpn J Neurosurg* 2002;**11**:402–9.

345. Ufkes JGR. Hopeful medication in secondary prevention of heart infarction with dipyridamole. *Pharm Weekbl* 2001;**133**:1298–300.

346. UK-TIA Study Group. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991; **54**:1044–54.

347. Valentin V. Clopidogrel in acute coronary syndromes with non-ST elevation. Clinical implications of the CURE trial. *Rev Esp Cardiol* 2001;**54**:1127–34.

348. Verheugt FWA. Bleeding risk of combined oral anticoagulant and antiplatelet therapy in cardiovascular disease. *J Cardiovas Risk* 1996; **3**:229–32.

349. Violi F. CAPRIE trial. *Lancet* 1997;**349**:356.

350. Vogel G, Fischer C, Huyke R. Prevention of reinfarction with acetylsalicylic acid. In: Breddin H, Loew D, Uberla K, editors. *Prophylaxis of venous peripheral cardiac and cerebral vascular diseases with acetylsalicylic acid*. Stuttgart: Schattauer; 1981. pp. 123–8.

351. Wahlgren NG. Critical analysis of the combination of dipyridamole plus acetylsalicylic acid versus acetylsalicylic acid alone in the secondary prevention of stroke. *Int J Clin Pract Suppl Issue* 1998;87.

352. Warlow C. Aspirin should be first-line antiplatelet therapy in the secondary prevention of stroke [comment]. *Stroke* 2002;**33**:2137–8.

353. Weichert W, Meents H, Abt K, Lieb H, Hach W, Krywabnek J. Acetylsalicyclic acid re-occlusion prophylaxis after angioplasty (ARPA-study). A randomised double-blind trial of two different dosages of ASA in patients with peripheral occlusive arterial disease. *Vasa* 1994;**23**:57–65.

354. White HD, French JK, Hamer AW, Brown MA, Williams BF, Ormiston JA, *et al*. Frequent re-occlusion of patent infarct-related arteries between 4 weeks and 1 year: effects of antiplatelet therapy. *J Am Coll Cardiol* 1995;**25**:218–23.

355. Wilterdink JL, Easton JD. Dipyridamole plus aspirin in cerebrovascular disease. *Arch Neurol* 2000;**56**:1087–1092.

356. Yusuf S. Clopidogrel in unstable angina to prevent recurrent ischaemic events (CURE). Presented at the Annual Meeting of the American College of Cardiology, Orlando, FL, March 2001.

357. Auer J. Clopidogrel in unstable angina to prevent recurrent ischemic events (CURE). *J Kardiol* 2001;**8**:201–2.

358. Zekert F. Klinische anwendung von aggregationshemmern bei arterieller verschuskrankheit. In Zekert F, editor. *Thrombosen, Embolien und Aggregationshemmer in der Chirurgie*. Stuttgart: Schattauer; 1975. pp. 68–72.

359. Zielinski R, French L. Aspirin and dipyridamole for the secondary prevention of stroke. *J Fam Pract* 1999;**48**:92.

360. Abrishami MA, Thomas J. Aspirin intolerance – a review. *Ann Allergy* 1977;**39**:28–37.

361. Almony GT, Lefkovits J, Topol EJ. Antiplatelet and anticoagulant use after myocardial infarction. *Clin Cardiol* 1996;**19**:357–65.

362. Anonymous. Antiplatelet drugs in cardiovascular prevention. *Prescrire Int* 2000;**9**:81–91.

363. Anonymous. Aspirin: real benefits, but real risks, too. *Harvard Heart Lett* 1999;**9**:1–3.

364. Anonymous. Clopidogrel: alternative to acetylsalicylic acid. *Can Fam Physician* 2000;46.

365. Anonymous. Meta-analysis of antiplatelet trials. *Pharm J* 2002;268.

366. Arnau JM, Agusti A. Is aspirin underused in myocardial infarction? *Pharmacoeconomics* 1997; **12**:524–32.

367. Awtry EH, Loscalzo J. Aspirin. *Circulation* 2000; **101**:1206–18.

368. Baker H, Moore-Robinson M. Cutaneous responses to aspirin and its derivatives. *Br J Dermatol* 1970;**82**:319–20.

369. Barnett HJ. Aspirin in stroke prevention. An overview. *Stroke* 1990;**21**(Suppl.):IV40–3.

370. Baume P. Aspirin is good for you. *Med J Aust* 1992; **157**:511–13.

371. Bennett JS, Mousa S. Platelet function inhibitors in the year 2000. *Thromb Haemost* 2001; **85**:395–400.

372. Berger PB. The thienopyridines in coronary artery disease. *Curr Cardiol Rep*1999;**1**:192–8.

373. Berkes EA. Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. *Clin Rev Allergy Immunol* 2003;**24**:137–47.

374. Bertele V. Primary and secondary prevention of thrombosis and arteriosclerosis. *G Arteriosclerosi* 1993;**18**:61–71.

375. Bhatt DL, Topol EJ. Antiplatelet and anticoagulant therapy in the secondary prevention of ischemic heart disease. *Cardiol Clin* 2001; **19**:253–65.

376. Bjarnason I, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology* 1993;**104**:1832–47.

377. Bjorkman D. Nonsteroidal anti-inflammatory drug-associated toxicity of the liver, lower gastrointestinal tract, and esophagus. *Am J Med* 1998;**105**:17S–21S.

378. Black C, Paterson KR. New antiplatelet agents: ticlopidine and clopidogrel. Antiplatelet therapy but at what cost? *Adverse Drug React Toxicol Rev* 2001;**20**:277–303.

379. Borg KT, Pancioli AM. Transient ischemic attacks: an emergency medicine approach. *Emerg Med Clin North Am* 2002;**20**:597–608.

380. Born GV. Anti-thrombotic drugs in the treatment of coronary heart disease: the present situation with aspirin. *Z Kardiol* 1990;**79**:147–50.

381. Borsch G, Schmidt G. Drug-induced lesions in the upper gastrointestinal tract. *Med Monatsschr Pharm* 1984;**7**:227–32.

382. Cairns JA. Antithrombotic therapy in cardiac disease: management of unstable angina and acute MI. *Prim Cardiol* 1991;17.

383. Carson JL, Rees Willett L. Toxicity of nonsteroidal anti-inflammatory drugs: an overview of the epidemiological evidence. *Drugs* 1993;**46**:243–8.

384. Catella-Lawson F, FitzGerald GA. Long-term aspirin in the prevention of cardiovascular disorders. Recent developments and variations on a theme. *Drug Saf* 1995;**13**:69–75.

385. Cavusoglu E, Cheng J, Bhatt R, Kunamneni PB, Marmur JD, Eng C. Clopidogrel in the management of ischemic heart disease. *Heart Dis* 2003;**5**:144–52.

386. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001; **23**:1296–310.

387. Cleland JGF. Anti-thrombotic agents in ischaemic heart disease: a clinical A–Z. *Care Crit Ill* 1992; **8**:168–71.

388. Cooke AR. Aspirin, ethanol and the stomach. *Austr Ann Med* 1970;**19**:269–74.

389. Dammann HG. Gastroduodenal tolerability profile of low-dose enteric-coated ASA. *Gastroenterol Int* 1998;**11**:205–16.

390. Del Zoppo GJ. Antithrombotic treatments in acute ischemic stroke. *Curr Opin Hematol* 2000;**7**:309–15.

391. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis [comment] *BMJ* 2000;**321**:1183–7.

392. Derry S, Kong Loke Y. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000;**321**:1183–7.

393. Di Pasquale G, Ottani F, Cere E, Biancoli S, Sassone B, Lombardi A. Antiplatelet agents or anticoagulants in the secondary prevention after myocardial infarction. *Recenti Prog Med* 1998; **89**:514–19.

394. Dickinson JP, Prentice CR. Aspirin: benefit and risk in thromboprophylaxis. *QJM* 1998;**91**:523–38.

395. Dippel DWJ. The results of CAPRIE, IST and CAST. *Thromb Res* 1998;**92**:S13–16.

396. Dobrilla G, Benvenuti S, de Guelmi A. The epidemiology of the gastroduodenal damage induced by aspirin and other nonsteroidal anti-inflammatory drugs. *Recenti Prog Med* 1997; **88**:202–11.

397. Duggan JM. Gastrointestinal toxicity of minor analgesics. *Br J Clin Pharmacol* 1980;**10**:407S–10S.

398. Eichenberger A, Pontiggia L, Beer JH. Antiaggregation: aspirin. *Ther Umsch* 2003; **60**:15–18.

399. Elwood PC, Hughes C, O'Brien JR. Platelets, aspirin, and cardiovascular disease. *Postgrad Med J* 1998;**74**:587–91.

400. Feret B. Clopidogrel: a new antiplatelet agent. *Conn Med* 1999;**63**:331–3.

401. Fiorucci S, Antonelli E, Morelli A. Mechanism of non-steroidal anti-inflammatory drug-gastropathy. *Dig Liver Dis* 2001;**33**:S35–43.

402. Fisher M. Antithrombotic and thrombolytic therapy for ischemic stroke. *J Thromb Thrombol* 1999;**7**:165–9.

403. Fitzmaurice DA, Blann AD, Lip GY. ABC of antithrombotic therapy: bleeding risks of antithrombotic therapy. *BMJ* 2002;**325**:828–31.

404. Fitzmaurice DA, Blann AD, Lip GY. Bleeding risks of antithrombotic therapy. *BMJ* 2002;**325**:828–31.

405. Forster W. Myocardial reinfarction prophylaxis with low-dose ASA. *Munch Med Wochenschr* 1993;135.

406. Fowler PD. Aspirin, paracetamol and non-steroidal anti-inflammatory drugs. A comparative review of side effects. *Med Toxicol* 1987;**2**:338–66.

407. Friend DG. Aspirin: the unique drug. *Arch Surg* 1974;**108**:765–9.

408. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Ann Intern Med* 1991;**115**:787–96.

409. Rodriguez LAG. Nonsteroidal antiinflammatory drugs, ulcers and risk: a collaborative meta-analysis. *Semin Arthritis Rheum* 1997;**26**:11–15.

410. Gaziano JM, Skerrett PJ, Buring JE. Aspirin in the treatment and prevention of cardiovascular disease. *Haemostasis* 2000;**30**:1–13.

411. Giri AK. The genetic toxicology of paracetamol and aspirin: a review. *Mutation Res Rev Genet Toxicol* 1993;**296**:199–210.

412. Girolami B, Bernardi E, Prins MH, Ten Cate JW, Prandoni P, Hettiarachchi R, *et al*. Antithrombotic drugs in the primary medical management of intermittent claudication: a meta-analysis. *Thromb Haemost* 1999;**81**:715–22.

413. Gonzalez ER. Antiplatelet therapy in the prevention of atherothrombotic events. *Pharmacy and Therapeutics* 2000;**25**:42–52.

414. Gore RM, Levine MS, Ghahremani GG. Drug-induced disorders of the stomach and duodenum. *Abdom Imaging* 1999;**24**:9–16.

415. Graham DY. NSAID-induced gastric injury. *Practitioner* 1998;**5**:92–6.

416. Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. *Lancet* 1999;**354**:1457–63.

417. Harding SA, Fox KAA. Clopidogrel in coronary artery disease. *Br J Cardiol* 2002;**9**:S8–12.

418. Hartmann A. High dosage acetylsalicylic acid administration for prevention of acute cerebral ischemia. *Nervenarzt* 1995;**66**:886–9; discussion 885.

419. Hassan M, Amonkar M. Aspirin use for primary and secondary prophylaxis of cardiovascular disease. *Curr Ther Res Clin Exp* 2001;**62**:676–90.

420. Hawkey CJ. Review article: aspirin and gastrointestinal bleeding. *Aliment Pharmacol Ther* 1994;**8**:141–6.

421. Hawkey CJ. Non-steroidal anti-inflammatory drug gastropathy: causes and treatment. *Scand J Gastroenterol* 1996;**220** (Suppl):124–7.

422. Hawkey CJ. Management of gastroduodenal ulcers caused by non-steroidal anti-inflammatory drugs. *Best Pract Res Clin Gastroenterol* 2000;**14**:173–92.

423. Hawkins C, Hanks GW. The gastroduodenal toxicity of nonsteroidal anti-inflammatory drugs. A review of the literature. *J Pain Symptom Manage* 2000;**20**:140–51.

424. Heller CA, Ingelfinger JA, Goldman P. Nonsteroidal antiinflammatory drugs and aspirin – analyzing the scores. *Pharmacotherapy* 1985; **5**:30–8.

425. Hennekens CH. Update on aspirin in the treatment and prevention of cardiovascular disease. *Am Heart J* 1999;**137**:S9–13.

426. Henry DA, Johnston A, Dobson A, Duggan J. Fatal peptic ulcer complications and the use of non-steroidal anti-inflammatory drugs, aspirin, and corticosteroids. *BMJ* 1987;**295**:1227–9.

427. Henry DA. Side-effects of non-steroidal anti-inflammatory drugs. *Baillière's Clin Rheumatol* 1988;**2**:425–54.

428. Henry D, Lim LY, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, *et al*. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; **312**:1563–6.

429. Heras M, Sionis A. Clopidogrel in acute coronary syndromes (unstable angina and non-Q-wave myocardial infarction). *Drugs Today* 2003; **39**:249–64.

430. Herbert JM. Clopidogrel and antiplatelet therapy. *Expert Opin Investig Drugs* 1994;**3**:449–55.

431. Hirschowitz BI, Hawkey CJ. Questions regarding future research on aspirin and the gastrointestinal tract. *Am J Med* 2001;**110**:74S–8S.

432. Hirsh J. Progress review: the relationship between dose of aspirin, side-effects and antithrombotic effectiveness. *Stroke* 1985;**16**:1–4.

433. Hirsh J, Salzman EW, Harker L, Fuster V, Dalen JE, Cairns JA, *et al*. Aspirin and other platelet active drugs. Relationship among dose, effectiveness, and side effects. *Chest* 1989; **95**:12S–18S.

434. Hudson N, Hawkey CJ. Non-steroidal anti-inflammatory drug-associated upper gastrointestinal ulceration and complications. *Eur J Gastroenterol Hepatol* 1993;**5**:412–19.

435. Joseph JE, Machin SJ. New antiplatelet drugs. *Blood Reviews* 1997;**11**:178–90.

436. Kelton JG, Hirsh J. Bleeding associated with antithrombotic therapy. *Semin Hematol* 1980; **17**:259–91.

437. Klijn CJM, Kappelle LJ, Algra A, Van Gijn J. Outcome in patients with symptomatic occlusion of the internal carotid artery or intracranial arterial lesions: a meta-analysis of the role of baseline characteristics and type of antithrombotic treatment. *Cerebrovascr Dis* 2001;**12**:228–34.

438. Knodel LC. NSAID adverse effects and interactions: who is at risk? *Am Pharm* 1992; **32**:39–47.

439. Kolts BE, Achem SR. Gastrointestinal side effects of nonsteroidal anti-inflammatory drug use. *Hosp Formulary* 1992;27.

440. Lanas A. Non-steroidal anti-inflammatory drugs and gastrointestinal bleeding. *Ital J Gastroenterol Hepatol* 1999;**31**:S37–42.

441. Lavie CJ, Milani RV. Multifactorial approach to the primary and secondary prevention at atherosclerosis. *Ochsner J* 2003;**5**:12–17.

442. Leschke M, Schoebel FC, Stiegler H, Fischer Y, Schannwell CM, Strauer BE. Antithrombotic therapy in chronic coronary syndromes – a comparative review of antiplatelet drugs, anticoagulation, and chronic thrombolysis. *Z Kardiol* 1998;**87**:145–51.

443. Lewis JH, Zimmerman HJ. NSAID hepatotoxicity. *Intern Med* 1996;**17**:45–68.

444. Lichtenstein DR, Syngal S, Wolfe MM. Nonsteroidal antiinflammatory drugs and the gastrointestinal tract: the double-edged sword. *Arthritis Rheum* 1995;**38**:5–18.

445. Lockhart L, McMeeken K, Mark J, Cross S, Tait G, Isles C. Secondary prevention after myocardial infarction: Reducing the risk of further cardiovascular events. *Coron Health Care* 2000; **4**:82–91.

446. Lubbe DF, Berger PB. The thienopyridines. *J Interv Cardiol* 2002;**15**:85–93.

447. Majhail NS, Lichtin AE. Clopidogrel and thrombotic thrombocytopenic purpura: no clear case for causality. *Cleve Clin J Med* 2003;**70**:466–70.

448. Maynard SJ, Scott GO, Riddell JW, Adgey AAJ. Management of acute coronary syndromes. *BMJ* 2000;**321**:220–3.

449. McCabe DJH, Brown MM. Prevention of ischaemic stroke – antiplatelets. *Br Med Bull* 2000;**56**:510–25.

450. Michaels AD, O'Rourke RA. The secondary prevention of myocardial infarction. *Curr Prob Cardiol* 1999;**24**:620–77.

451. Mikhailidis DP, Jagroop IA. Is clopidogrel markedly superior to aspirin in patients with peripheral vascular disease? *Platelets* 1998;**9**:273–8.

452. Mohr JP. Prevention of recurrent ischemic stroke: recent clinical trial results. *Neurologia* 2002; **17**:378–82.

453. Morassut P, Yang W, Karsh J. Aspirin intolerance. *Semin Arthritis Rheum* 1989;**19**:22–30.

454. Namazy JA, Simon RA. Sensitivity to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2002;**89**:542–50; quiz 550, 605.

455. Orford JL, Fasseas P, Brosh D, Berger PB. Clopidogrel. *Indian Heart J* 2001;**53**:788–91.

456. Patrono C, Coller B, Dalen JE, FitzGerald GA, Fuster V, Gent M, *et al*. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. *Chest* 2001;**119**:39S–63S.

457. Pepine CJ. Aspirin and newer orally active antiplatelet agents in the treatment of the post-myocardial infarction patient. *J Am Coll Cardiol* 1998;**32**:1126–8.

458. Picano E. Dipyridamole in chronic stable angina pectoris: a randomized, double blind, placebo-controlled, parallel group study. *Eur Heart J* 2001;**22**:1785–93.

459. Pueyo G, Elosua R, Marrugat J. Meta-analysis of the scientific evidence on the usefulness of sporadic intake of acetylsalicylic acid in the prevention of coronary heart disease. *Med Clin (Barc)* 2002;**118**:166–9.

460. Quiralte J, Blanco C. New trends in aspirin sensitivity. *Clin Exp Allergy* 1998;**28**:55–6.

461. Rahman A, Khan AK, Siddique MI. Non-steroidal anti-inflammatory drugs. *J Inst Postgrad Med Res* 1996;**11**:61–6.

462. Righini M, De Moerloose P. New antiplatelet agents: the end of the monopoly of aspirin? *Med Hyg* 2000;**58**:21–4.

463. Rodgers A, MacMahon S. Antiplatelet therapy and the prevention of thrombosis. *Aust NZ J Med* 1996;**26**:210–15.

464. Garcia Rodriguez LA. Variability in risk of gastrointestinal complications with different nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;**104**:30S–34S.

465. Rodvein R, Cooke AR. Aspirin revisited. *Ser Haematol* 1975;**8**:141–50.

466. Sainte-Laudy J. Acetylsalicylic acid: hypersensitivity, intolerance, or allergy? *Aller Immunol (Paris)* 2001;**33**:120–6.

467. Salter RH. Aspirin and gastrointestinal bleeding. *Am J Dig Dis* 1968;**13**:38–58.

468. Sandercock P, Keir S. Antiplatelet therapy for stroke. *Continued Professional Development Bull Neurol* 2000;**2**:7–9.

469. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Review: aspirin reduces the incidence of coronary artery disease in people at risk. *Evid Based Med* 2001;**6**(6):15–21.

470. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet* 2002;**359**:781–5.

471. Sheridan PJ, Crossman DC. Critical review of unstable angina and non-ST elevation myocardial infarction. *Postgrad Med J* 2002;**78**: 717–26.

472. Steinhubl SR. Antiplatelet therapy: aspirin. *J Invas Cardiol* 2003;**15**:11B–16B; discussion 16B.

473. Szczeklik A. Adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. *Ann Allergy* 1987;**59**:113–8.

474. Tramer MR. Aspirin, like all other drugs, is a poison. *BMJ* 2000;**321**:1170–1.

475. Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000;**85**:169–82.

476. Van De Graaff E, Steinhubl SR. Complications of oral antiplatelet medications. *Curr Cardiol Rep* 2001;**3**:371–9.

477. Weber AA, Schror K. Pharmacology of ticlopidine and clopidogrel in comparison with acetylsalicylic acid. *Internist* 1997;**38**:1115–20; discussion 1120.

Appendix 1

Summary of UK guidelines/standards for antiplatelet therapy

Antiplatelet therapy recommendations/standards	Source
Stroke	
To improve the chances of survival and minimise complication risk, all patients with stroke should have a brain scan within 48 hours and be given ASA if a diagnosis of haemorrhage is unlikely.	NSF Older People, 2001[78]
In patients who have sustained an ischaemic cerebrovascular event, antiplatelet therapy, normally ASA (75–325 mg daily) should be prescribed immediately for the secondary prevention of recurrent stroke and other vascular events.	SIGN, 1997[16]
"All patients with ischaemic stroke who are not on anticoagulations should be taking an antiplatelet agent, i.e. ASA (75–325 mg) daily or clopidogrel, or a combination of low-dose ASA and dipyridamole MR. Where patients are ASA intolerant an alternative antiplatelet agent (clopidogrel 75 mg daily or dipyridamole MR 200 mg twice daily) should be used."	National Stroke Guideline, RCP, 2002[79]
PAD	
Patients with intermittent claudication should receive ASA (75–300 mg/day) long-term as prophylaxis against cardiovascular events. Patients with intermittent claudication undergoing angioplasty or surgical graft therapy should also receive ASA therapy as long-term prophylaxis against restenosis and graft failure.	SIGN, 1998[80]
Patients with intermittent claudication, critical limb ischaemia or who have had a previous vascular intervention should be considered for long-term antiplatelet therapy with either ASA (75–325 mg/day) or clopidogrel (75 mg/day). For patients who are intolerant to ASA, clopidogrel is recommended as an alternative antiplatelet agent. Stopping clopidogrel 5 days prior to elective surgery should be considered.	PAD Antiplatelet Consensus Group, 2003[81]
Non-ST-segment elevation ACS	
Patients with confirmed non-ST-segment elevation ACS without persistent ECG ST-segment elevation (unstable angina or NSTEMI) should receive ASA, as soon as the diagnosis is made. Subsequently, low-dose ASA should be continued once daily, unless contraindicated.	British Cardiac Society and Medical Practice Committee and Royal College of Physicians, London, 2001
Patients with unstable angina should receive 300 mg ASA if not already given, then 150 mg/day.	NSF CHD, 2000[13]
MI	
People with acute MI should receive at least 300 mg ASA orally with continuing care with low-dose ASA (75 mg daily).	NSF CHD, 2000[13]
Following MI, low-dose ASA (75–150 mg daily) should be given routinely and continued indefinitely in patients with CHD. Clopidogrel therapy (75 mg daily) is recommended as an effective alternative in patients with contraindications to ASA, or who are intolerant of ASA.	SIGN, 2000[82]

Appendix 2

Search strategies

The search strategies used to identify clinical and cost-effectiveness studies in MEDLINE are presented below.

MEDLINE search for clinical effectiveness of clopidogrel

1 randomized controlled trial.pt.
2 randomized controlled trials/
3 randomi?ed controlled trial$.ti,ab.
4 random allocation/
5 double-blind method/
6 single-blind method/
7 (clin$ adj2 trial$).ti,ab.
8 ((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).ti,ab.
9 placebos/
10 placebo$.ti,ab.
11 random.ti,ab.
12 exp RESEARCH DESIGN/
13 comparative study/
14 exp evaluation studies/
15 follow-up studies/
16 prospective studies/
17 (control or controls or controlled).ti,ab.
18 clinical trials, phase iv/
19 phase iv.ti,ab.
20 phase four.ti,ab.
21 phase 4.ti,ab.
22 post market$ surveillance.ti,ab.
23 or/1-22
24 Ticlopidine/
25 clopidogrel.ti,ab.
26 plavix.ti,ab.
27 90055-48-4.rn.
28 asasantin retard.ti,ab.
29 persantin retard.ti,ab.
30 dipyridamole.ti,ab.
31 dipyridamole/
32 58-32-2.rn.
33 or/24-32 (9392)
34 exp MYOCARDIAL INFARCTION/
35 (myocard$ infarc$ or MI).ti.
36 NSTEMI.ti,ab.
37 non ST segment elevation myocardial infarction.ti,ab.
38 stroke.ti.
39 CEREBROVASCULAR ACCIDENT/
40 (cerebrovascular accident$ or CVA).ti.
41 ISCHEMIC ATTACK, TRANSIENT/
42 (isch?emic stroke or transient isch?emic attack$).ti,ab.
43 ANGINA, UNSTABLE/
44 unstable angina.ti,ab.
45 peripheral arterial disease.ti,ab.
46 (TIA or TIAS).ti.
47 or/34-46
48 23 and 33
49 47 and 48

MEDLINE search for cost-effectiveness studies

1 economics/
2 exp "costs and cost analysis"/
3 economic value of life.sh.
4 economics, dental/ (1454)
5 exp "economics, hospital"/
6 economics, medical/
7 economics, nursing/
8 economics, pharmaceutical/
9 or/1-8
10 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
11 (expenditure$ not energy).tw.
12 (value adj1 money).tw.
13 budget$.tw.
14 or/10-13
15 9 or 14
16 letter.pt.
17 editorial.pt.
18 historical article.pt.
19 or/16-18
20 15 not 19
21 animal/
22 human/
23 21 not (21 and 22)
24 20 not 23
25 (metabolic adj cost).ti,ab,sh.
26 ((energy or oxygen) adj cost).ti,ab,sh.
27 24 not (25 or 26)
28 aspirin/
29 acetylsalicylic acid.ti,ab.
30 aspirin.ab,ti.
31 50-78-2.rn.
32 or/28-31
33 economics/
34 exp "costs and cost analysis"/

35 economic value of life.sh.
36 economics, dental/
37 exp "economics, hospital"/
38 economics, medical/
39 economics, nursing/
40 economics, pharmaceutical/
41 or/33-40
42 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
43 (expenditure$ not energy).tw.
44 (value adj1 money).tw.
45 budget$.tw.
46 or/42-45
47 41 or 46
48 letter.pt.
49 editorial.pt.
50 historical article.pt.
51 or/48-50
52 47 not 51
53 animal/
54 human/
55 53 not (53 and 54)
56 52 not 55
57 (metabolic adj cost).ti,ab,sh.
58 ((energy or oxygen) adj cost).ti,ab,sh.
59 56 not (57 or 58)
60 clopidogrel.ti,ab,hw.
61 plavix.ti,ab.
62 90055-48-4.rn.
63 asasantin retard.ti,ab.
64 persantin retard.ti,ab.
65 dipyridamole.ti,ab.
66 dipyridamole/
67 58-32-2.rn.
68 or/60-67
69 59 and 68

A further MEDLINE search was carried out to identify economic costs related to heart disease in the UK:

1 review.ab.
2 review.pt.
3 meta-analysis.ab.
4 meta-analysis.pt.
5 meta-analysis.ti.
6 or/1-5
7 letter.pt.
8 comment.pt.
9 editorial.pt.
10 or/7-9
11 aspirin/
12 aspirin.ti,ab.
13 acetylsalicylic acid.ti,ab.
14 50-78-2.rn.
15 or/11-14
16 6 not 10
17 15 and 16
18 adverse event$.ti,ab.
19 side effect$.ti,ab.
20 18 or 19
21 17 and 20
22 aspirin/ae
23 16 and 22
24 21 not 23

The full search strategies used to identify studies are listed below.

1. The Cochrane Database of Systematic Reviews

#1. TICLOPIDINE single term (MeSH)
#2. clopidogrel
#3. plavix
#4. (asasantin next retard)
#5. (persantin next retard)
#6. DIPYRIDAMOLE single term (MeSH)
#7. dipyridamole
#8. (#1 or #2 or #3 or #6 or #7)
#9. MYOCARDIAL INFARCTION explode all trees (MeSH)
#10. (myocard*:ti next infarc*:ti)
#11. (myocard*:ab next infarc*:ab)
#12. mi:ti
#13. nstemi:ti
#14. nstemi:ab
#15. (non:ti next st:ti next segment:ti next elevation:ti next myocardial:ti next infarction:ti)
#16. (non:ab next st:ab next segment:ab next elevation:ab next myocardial:ab next infarction:ab)
#17. stroke:ti
#18. stroke:ab
#19. (cerebrovascular:ti next accident*:ti)
#20. (cerebrovascular:ab next accident*:ab)
#21. CEREBROVASCULAR ACCIDENT single term (MeSH)
#22. ISCHEMIC ATTACK TRANSIENT single term (MeSH)
#23. (ischemic:ti next transient:ti next attack*:ti)
#24. (ischemic:ti next transient:ti next stroke:ti)
#25. (ischemic:ab next transient:ab next attack:ab)
#26. (ischemic:ab next transient:ab next stroke:ab)
#27. (ischaemic:ti next transient:ti next attack*:ti)
#28. (ischaemic:ti next transient:ti next stroke:ti)
#29. (ischaemic:ab next transient:ab next stroke:ab)
#30. ANGINA UNSTABLE single term (MeSH)

#31. (unstable:ti next angina:ti)
#32. (unstable:ab next angina:ab)
#33. (peripheral:ti next arterial:ti next disease:ti)
#34. (peripheral:ab next arterial:ab next disease:ab)
#35. (# 9 or #10 or (#11 and #12) or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #30 or #31 or #32 or #33 or #34)
#36. (#8 and #35)

2. EMBASE (Ovid)

1 randomi?ed controlled trial$.ti,ab.
2 randomization/
3 random allocation.ti,ab.
4 double blind procedure/
5 single blind procedure/
6 ((singl$ or doubl$ or trebl$ or tripl$) adj2 (method or blind$ or mask$)).ti,ab.
7 (clin$ adj2 trial$).ti,ab.
8 Placebo/
9 placebo$.ti,ab.
10 random.ti,ab.
11 methodology/
12 research design.ti,ab.
13 comparative study/
14 prospective study/
15 follow up/
16 evaluation/
17 (control or controls or controlled).ti,ab.
18 phase 4 clinical trial/
19 phase 4.ti,ab.
20 phase four.ti,ab.
21 phase iv.ti,ab.
22 postmarketing surveillance/
23 post market$ surveillance.ti,ab.
24 or/1-23
25 Ticlopidine/
26 Clopidogrel/
27 clopidogrel.ti,ab.
28 plavix.ti,ab.
29 90055-48-4.rn.
30 asasantin retard.ti,ab.
31 persantin retard.ti,ab.
32 DIPYRIDAMOLE/
33 dipyridamole.ti,ab.
34 58-32-2.rn.
35 or/25-34
36 exp Heart Infarction/
37 (myocard$ infarc$ or MI).ti.
38 NSTEMI.ti,ab.
39 non ST segment elevation myocardial infarction.ti,ab.
40 stroke.ti.
41 Cerebrovascular Accident/
42 (cerebrovascular accident$ or CVA).ti.
43 Transient Ischemic Attack/
44 (isch?emic stroke or transient isch?emic attack$).ti,ab.
45 Unstable Angina Pectoris/
46 unstable angina.ti,ab.
47 peripheral arterial disease.ti,ab.
48 (TIA or TIAS).ti.
49 or/36-48
50 24 and 35
51 49 and 50

This search identified 1335 records.

3. HEED

DN= 'CLOPIDOGREL'
DN= 'DIPYRIDAMOLE'
DN='TICLOPIDINE'
AB='CLOPIDOGREL'
AB= 'DIPYRIDAMOLE'
AB='TICLOPIDINE'
CS= 1+2 +3 +4+5+6

This search identified 37 records.

4. HTA/NHSEED Database

The CRD databases were searched on the CRD website. The databases were searched simultaneously using the following strategy (truncation is automatic)
1. Clopidogrel or Dipyridamole or plavix or asantin or persantin

This search identified 26 records.

5. Inside Conferences (Dialog)

s (randomi?ed(w)controlled(w)trial?)
s randomization
s (clinical(2w)trial?)
s ((singl? or doubl? or trebl? or tripl?)(2w)(blind? or mask?))
s placebo?
s random
s methodology
s comparative(w)study
s evaluation
s follow(w)up
s prospective(w)study
s (control or controls or controlled)
s phase(w)iv
s phase(w)four

s phase(w)4
s post(w)market?(w)surveillance
s S1:16
s clopidogrel
s plavix
s asasantin(w)retard
s persantin(w)retard
s dipyridamole
s ACETYLSALICYLIC(w)ACID(w)PLUS(w)DIPYRIDAMOLE
s s18:s23
s s17 and 24
s heart(w)infarction
s myocard?(w)infarc?
s NSTEMI
s non(w)ST(w)segment(w)elevation(w)myocardial(w)infarction
s stroke
S (cerebrovascular(w)accident or CVA)
s (TIA or TIAS)
s (isch?emic(w)stroke or transient(w)isch?emic(w)attack?)
s unstable(w)angina
s peripheral(w)arterial(w)disease
s S25:S35
s S25 and S36

This search identified three records.

6. JICST (Dialog)

S1 8093(RANDOMI?ED(W)CONTROLLED(W)TRIAL?)
S2 15360RANDOMIZATION
S3 117525(CLINICAL(2W)TRIAL?)
S4 45104((SINGL? OR DOUBL? OR TREBL? OR TRIPL?)(2W)(BLIND? OR MASK?))
S5 42073PLACEBO?
S6 125100RANDOM
S7 116854METHODOLOGY
S8 381345COMPARATIVE(W)STUDY
S9 733337EVALUATION
S10 152450FOLLOW(W)UP
S11 22572PROSPECTIVE(W)STUDY
S12 1535990(CONTROL OR CONTROLS OR CONTROLLED)
S13 673PHASE(W)IV
S14 160PHASE(W)FOUR
S15 448PHASE(W)4
S16 292POST(W)MARKET?(W)SURVEILLANCE
S17 2887580S1:S16
S18 395CLOPIDOGREL
S19 10PLAVIX
S20 1ASASANTIN(W)RETARD
S21 0PERSANTIN(W)RETARD
S22 3539DIPYRIDAMOLE
S23 3887S18:S22
S24 1309S17 AND S23
S25 15HEART(W)INFARCTION
S26 49283MYOCARD?(W)INFARC?
S27 31NSTEMI/TI,AB
S28 58NON(W)ST(W)SEGMENT(W)ELEVATION(W)MYOCARDIAL(W)INFARCTION
S29 36956STROKE
S30 1182(CEREBROVASCULAR(W)ACCIDENT OR CVA)/TI,AB
S31 1430(TIA OR TIAS)/TI,AB
S32 629(ISCH?EMIC(W)STROKE OR TRANSIENT(W)ISCH?EMIC(W)ATTACK?)
S33 4183UNSTABLE(W)ANGINA
S34 637PERIPHERAL(W)ARTERIAL(W)DISEASE1088381NON
S35 88437S25:S34
S36 289S24 AND S35

This search identified 47 records.

7. MEDLINE (Ovid)

1 randomized controlled trial.pt.
2 randomized controlled trials/
3 randomi?ed controlled trial$.ti,ab.
4 random allocation/
5 double-blind method/
6 single-blind method/
7 (clin$ adj2 trial$).ti,ab.
8 ((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).ti,ab.
9 placebos/
10 placebo$.ti,ab.
11 random.ti,ab.
12 exp RESEARCH DESIGN/
13 comparative study/
14 exp evaluation studies/
15 follow-up studies/
16 prospective studies/
17 (control or controls or controlled).ti,ab.
18 clinical trials, phase iv/
19 phase iv.ti,ab.
20 phase four.ti,ab.
21 phase 4.ti,ab.
22 post market$ surveillance.ti,ab.
23 or/1-22
24 Ticlopidine/
25 clopidogrel.ti,ab.
26 plavix.ti,ab.
27 90055-48-4.rn.
28 asasantin retard.ti,ab.
29 persantin retard.ti,ab.
30 dipyridamole.ti,ab.
31 dipyridamole/
32 58-32-2.rn.

33 or/24-32
34 exp MYOCARDIAL INFARCTION/
35 (myocard$ infarc$ or MI).ti.
36 NSTEMI.ti,ab.
37 non ST segment elevation myocardial infarction.ti,ab.
38 stroke.ti.
39 CEREBROVASCULAR ACCIDENT/
40 (cerebrovascular accident$ or CVA).ti.
41 ISCHEMIC ATTACK, TRANSIENT/
42 (isch?emic stroke or transient isch?emic attack$).ti,ab.
43 ANGINA, UNSTABLE/
44 unstable angina.ti,ab.
45 peripheral arterial disease.ti,ab.
46 (TIA or TIAS).ti.
47 or/34-46
48 23 and 33
49 47 and 48

This search identified 841 records.

A second MEDLINE search was carried out to identify economic studies:

1 economics/
2 exp "costs and cost analysis"/
3 economic value of life.sh.
4 economics, dental/
5 exp "economics, hospital"/
6 economics, medical/
7 economics, nursing/
8 economics, pharmaceutical/
9 or/1-8
10 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
11 (expenditure$ not energy).tw.
12 (value adj1 money).tw.
13 budget$.tw.
14 or/10-13
15 9 or 14
16 letter.pt.
17 editorial.pt.
18 historical article.pt.
19 or/16-18
20 15 not 19
21 animal/
22 human/
23 21 not (21 and 22)
24 20 not 23
25 (metabolic adj cost).ti,ab,sh.
26 ((energy or oxygen) adj cost).ti,ab,sh.
27 24 not (25 or 26)
28 aspirin/
29 acetylsalicylic acid.ti,ab.
30 aspirin.ab,ti.
31 50-78-2.rn.
32 or/28-31
33 economics/
34 exp "costs and cost analysis"/
35 economic value of life.sh.
36 economics, dental/
37 exp "economics, hospital"/
38 economics, medical/
39 economics, nursing/
40 economics, pharmaceutical/
41 or/33-40
42 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
43 (expenditure$ not energy).tw.
44 (value adj1 money).tw.
45 budget$.tw.
46 or/42-45
47 41 or 46
48 letter.pt.
49 editorial.pt.
50 historical article.pt.
51 or/48-50
52 47 not 51
53 animal/
54 human/
55 53 not (53 and 54)
56 52 not 55
57 (metabolic adj cost).ti,ab,sh.
58 ((energy or oxygen) adj cost).ti,ab,sh.
59 56 not (57 or 58)
60 clopidogrel.ti,ab,hw.
61 plavix.ti,ab.
62 90055-48-4.rn.
63 asasantin retard.ti,ab.
64 persantin retard.ti,ab.
65 dipyridamole.ti,ab.
66 dipyridamole/
67 58-32-2.rn.
68 or/60-67
69 59 and 68

This search identified 166 records.

8. NRR

#1 Clopidogrel
#2 Dipyridamole
#3 plavix
#4 asantin
#5 persantin
#6 (#1 or #2 or #3 or #4 or #5)

This search identified 121 studies.

9. PASCAL and Social SciSearch (Dialog)

These databases were searched simultaneously using the following strategy:

1 (RANDOMI?ED(W)CONTROLLED(W) TRIAL?)
2 RANDOMIZATION
3 (CLINICAL(2W)TRIAL?)
4 ((SINGL? OR DOUBL? OR TREBL? OR TRIPL?)(2W)(BLIND? OR MASK?))
5 PLACEBO?
6 RANDOM
7 METHODOLOGY
8 COMPARATIVE(W)STUDY
9 EVALUATION
10 FOLLOW(W)UP
11 PROSPECTIVE(W)STUDY
12 (CONTROL OR CONTROLS OR CONTROLLED)
13 PHASE(W)IV
14 PHASE(W)FOUR
15 PHASE(W)4
16 POST(W)MARKET?(W)SURVEILLANCE
17 S1:S16
18 CLOPIDOGREL
19 PLAVIX
20 ASASANTIN(W)RETARD
21 PERSANTIN(W)RETARD
22 DIPYRIDAMOLE
23 S18:S22
24 S17 AND S23
25 HEART(W)INFARCTION
26 MYOCARD?(W)INFARC?
27 NSTEMI/TI,AB
28 82 NON(W)ST(W)SEGMENT(W)ELEVATION(W) MYOCARDIAL(W)INFARCTION
29 STROKE
30 (CEREBROVASCULAR(W)ACCIDENT OR CVA)
31 (TIA OR TIAS)/TI,AB
32 ISCH?EMIC(W)STROKE OR TRANSIENT(W)ISCH?EMIC(W)ATTACK?)
33 UNSTABLE(W)ANGINA
34 PERIPHERAL(W)ARTERIAL(W)DISEASE
35 S25:S34
36 S24 AND S35

This research identified 916 records.

The strategies used to identify studies of the side-effects of aspirin are presented below.

1. The Cochrane Library

#1. ASPIRIN single term (MeSH)
#2. (acetylsalicylic:ti next acid:ti)
#3. (acetylsalicylic:ab next acid:ab)
#4. aspirin:ti
#5. aspirin:ab
#6. (#1 or #2 or #3 or #4 or #5)
#7. (side:ti next effect:ti)
#8. (side:ti next effects:ti)
#9. (side:ab next effect:ab)
#10. (side:ab next effects:ab)
#11. (adverse:ti next event:ti)
#12. (adverse:ti next events:ti)
#13. (adverse:ab next events:ab)
#14. (adverse:ab next event:ab)
#15. (#7 or #8 or #9 or #10 or #11 or #12 or #13. or #14)
#16. (#6 and #15)

This research identified eight records.

2. Embase (Ovid)

1 review.ab.
2 review.pt.
3 meta-analysis.ab.
4 meta-analysis.ti.
5 or/1-4
6 letter.pt.
7 editorial.pt.
8 6 or 7
9 5 not 8
10 aspirin.ti,ab.
11 acetylsalicylic acid.ti,ab.
12 acetylsalicylic acid/
13 63781-77-1.rn.
14 or/10-13
15 aspirin/ae
16 9 and 14
17 16 not 15
18 or/2-4
19 18 not 8
20 19 and 14
21 20 not 15

This research identified 6517 records.

3. HEED

DN=aspirin
AB=aspirin
DN=acetylsalicylic acid
AB=acetylsalicylic acid
CS=1 or 2 or 3 or 4

This research identified 133 records.

4. MEDLINE (Ovid)

1 review.ab.
2 review.pt.
3 meta-analysis.ab.
4 meta-analysis.pt.
5 meta-analysis.ti.
6 or/1-5
7 letter.pt.
8 comment.pt.
9 editorial.pt.
10 or/7-9
11 aspirin/
12 aspirin.ti,ab.
13 acetylsalicylic acid.ti,ab.
14 50-78-2.rn.
15 or/11-14
16 6 not 10
17 15 and 16
18 adverse event$.ti,ab.
19 side effect$.ti,ab.
20 18 or 19
21 17 and 20
22 aspirin/ae
23 16 and 22
24 21 not 23

This research identified 317 records.

A further MEDLINE search was carried out to identify economic costs related to heart disease in the UK:

1 economics/
2 exp "costs and cost analysis"/
3 economic value of life.sh.
4 economics, dental/
5 exp "economics, hospital"/
6 economics, medical/
7 economics, nursing/
8 economics, pharmaceutical/
9 or/1-8
10 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
11 (expenditure$ not energy).tw.
12 (value adj1 money).tw.
13 budget$.tw.
14 or/10-13
15 9 or 14
16 letter.pt.
17 editorial.pt.
18 historical article.pt.
19 or/16-18
20 15 not 19
21 animal/
22 human/
23 21 not (21 and 22)
24 20 not 23
25 (metabolic adj cost).ti,ab,sh.
26 ((energy or oxygen) adj cost).ti,ab,sh.
27 24 not (25 or 26)
28 exp heart diseases/
29 heart attack$.ti,ab.
30 heart failure.ti,ab.
31 exp cardiovascular diseases/ or peripheral vascular diseases/
32 Myocardial Infarction/
33 myocardial infarction.ti,ab.
34 exp Cerebrovascular Accident/
35 stroke.ti,ab.
36 Ischemic Attack, Transient/
37 or/28-36
38 37 and 27
39 limit 38 to yr=1990-2003
40 (hospital and (stay or bed$)).ti,ab.
41 exp Patient Care/
42 (patient adj3 level adj3 cost$).ti,ab.
43 (drug adj treatment$).ti,ab.
44 Drug Costs/
45 or/40-44
46 45 and 39
47 limit 46 to yr=1990-2003
48 exp Great Britain/
49 ((Great Britain or United Kingdom or Scotland or Ireland or England or Wales) not (New South Wales or New England)).ti,ab,in.
50 48 or 49
51 47 and 50
52 limit 51 to yr=1990-2003

This research identified 133 records.

5. NHSEED

1.aspirin or acetylsalicylic acid

This research identified 79 records.

6. NRR

#1 ASPIRIN
#2 (Acetylsalicylic and ACID)
#3 ASPIRIN*:ME
#4 (#1 or #2 or #3)
#5 (ADVERSE and EVENT*)
#6 (SIDE and EFFECT*)
#7 (#5 or #6)
#8 (#4 and #7)

This research identified 34 records.

Appendix 3

Excluded studies

Clinical and cost-effectiveness searches

Study details	Reason for exclusion
Acheson, 1969[83]	Controlled trial of standard-release dipyridamole versus placebo
Adams, 1995[84]	Article about the management of TIA
Alberts, 2002[86]	Letter to the editor about clopidogrel in combination with aspirin for stroke prevention
Algra, 1999[87]	Letter to the editor about miscounting in reports of the CURE trial
American Heart Association Task Force, 2002[88]	Guideline update for the management of ACS
American-Canadian Cooperative Study Group, 1985[89]	Standard-release dipyridamole and aspirin versus aspirin; not licensed indication
Anonymous, 1980[90]	Comment on PARIS (standard-release dipyridamole versus aspirin)
Anonymous, 1985[115]	Report on PARIS-II trial (standard-release dipyridamole) (in German)
Anonymous, 1999[91]	Comment on ESPS-2 (in Dutch)
Anonymous, 1999[92]	Short news report about the CAPRIE trial (clopidogrel)
Anonymous, 2001[93]	Comment on the CURE trial
Anonymous, 2001[94]	Commentary on clopidogrel trials (in German)
Anonymous, 2002[95]	Article on use of clopidogrel in ACS (in German)
Anonymous, 2002[96]	News report of use of clopidogrel in patients undergoing PCI
Aronow, 1999[97]	General article about antiplatelet agents in older patients with vascular disease; not a systematic review
Aspirin MI Study Research, Group, 1980[98]	RCT of aspirin versus placebo (AMIS study)
Bachmann, 1996[99]	Pilot study of clopidogrel. Studied anti-aggregatory effect in human volunteers
Benavente, 1997[100]	Letter to the editor on ESPS-2
Bennett, 2000[101]	Case reports of TTP associated with clopidogrel – patients not all taking clopidogrel for secondary prevention and not all patients were in RCTs
Bertrand, 2000[102]	CLASSICS study; clopidogrel with and without a loading dose in combination with aspirin versus ticlopidine in combination with aspirin after coronary stenting
Bhatt, 1999[103]	CAPRIE – repeat hospitalisation (abstract). Available as full report[123]
Bhatt, 2000[104]	Subgroup analyses of patients in CAPRIE with history of cardiac surgery (abstract). Full publication available[105]
Bogousslavsky, 2001[106]	Review of ADP receptor antagonists; not a systematic review
Bollinger, 1985[107]	Not secondary prevention. Patients had undergone femoro-popliteal endarterectomy
Born, 1997[108]	Letter to the editor; comment on the CAPRIE trial
Bousser, 1981[109]	Protocol of AICLA (standard-release dipyridamole and aspirin versus aspirin)
Bousser, 1982[110]	Report on AICLA (standard-release dipyridamole)
Bousser, 1983[111]	Results of AICLA (standard-release dipyridamole)
Bousser, 1983[112]	Standard-release dipyridamole and aspirin versus aspirin (AICLA); not licensed indication
Boysen, 1988[113]	Low-dose aspirin versus placebo. Patients had undergone carotid endarterectomy
Boysen, 1999[114]	Review of antiplatelet drugs in secondary stroke prevention; not a systematic review
Brechter, 1980[116]	Trial of anticoagulants in TIA (in German)
Breddin, 1980[117]	RCT of aspirin versus placebo for the secondary prevention of MI
Breddin, 1981[118]	General discussion of secondary prevention of MI (in German)
Britton, 1987[119]	RCT of aspirin versus placebo for the secondary prevention of stroke (Swedish Co-operative study)
Brown, 1993[120]	Study on the incidence of strokes following PCI
Cairns, 2001[121]	General overview of antithrombotic agents; not a systematic review
Calverley, 2001[122]	General article on antiplatelet therapy in the elderly. Not a systematic review
Campbell, 1996[123]	Observational study about outpatient cardiac rehabilitation
Canadian Cooperative Study Group, 1978[124]	Aspirin alone and in combination with sulfinpyrazone versus placebo

continued

Study details	Reason for exclusion
CAPRIE steering committee, 1996[125]	Duplicate copy of CAPRIE Steering Committee[55]
CCS-2 Collaborative Group, 2000[126]	Chinese Cardiac Study (CCS-2): patients with acute MI; not licensed indication
CCS-2 Collaborative Group, 2000[126]	Not secondary prevention. Patients have suspected acute MI
Chapman, 2001[127]	Letter to the editor on use of clopidogrel (case study)
Cheung, 2000[128]	Letter to the editor regarding TTP
Cohen, 2000[129]	Letter to the editor: comment on the dipyridamole trials
Colwell, 1989[130]	Not licensed indication; standard-release dipyridamole and aspirin (VA co-operative study)
Coronary Drug Project Research Group, 1980[131]	Early aspirin study
Coukell, 1997[132]	Duplicate copy of Coukell, 1997[133]
Coukell, 1997[133]	Short article about the pharmacology of clopidogrel
Crassard, 2000[134]	Overview of aspirin in CHD (in French)
Crawford, 2001[135]	Short article about antiplatelet therapy in secondary stroke prevention; not a systematic review
Creager, 1998[136]	Overview of results from the CAPRIE trial
Cristallini, 1979[137]	General discussion of primary prevention of MI (in Italian)
Culliton, 1980[138]	Commentary on PARIS and AMIS trials (standard-release dipridamole)
CURE Study Investigators, 2000[139]	Duplicate copy of CURE 2000[35]
D'Addato, 1992[140]	Comparator is not aspirin (indobufen). Patients had undergone grafting
D'Agostino, 2002[141]	Trial design (methodology article)
Dale, 1989[142]	Background on stroke; incidence and prevalence (data from 1980s)
Dalton, 2001[149]	Comment on ESPS-2
De Boer, 1983[143]	Study of platelet survival time in patients with CAD
De Schryver, 1999[144]	Comment on the design and rationale of ESPRIT (in French)
De Schryver, 2001[145]	Protocol change to ESPRIT
De Schryver, 2003[146]	Cochrane review – systematic review examining dipyridamole (no extra data reported)
Degeorges, 1981[147]	Commentary on secondary prevention of MI (in French)
Department of Health, 2001[148]	Hospital episode statistics
Diener, 1998[150]	Letter to the editor; aspirin dose in secondary prevention of stroke
Diener, 1998[151]	Comment on secondary prevention dipyridamole trials
Diener, 1999[152]	Report of ESPS-2; same as Diener *et al*. 1996[153](in German)
Diener, 1999[154]	Discussion article about aspirin in the prevention of stroke
Diener, 2000[155]	Discussion article about stroke prevention with antiplatelet therapy
Diener, 2001[156]	Report on *post-hoc* analysis of ESPS-2; same as Diener *et al*. 2001[157] (in German)
Diener, 2002[158]	Discussion article about aspirin for secondary prevention of stroke
Doggrell, 2002[159]	Comment on the CURE trial
Donaldson, 1985[160]	Versus placebo. Patients had undergone grafting
Donnan, 2002[161]	Discussion article about aspirin for secondary prevention of stroke
Du, 1997[162]	Background on incidence of stroke in a high-risk area
Dutch TIA Trial Study Group, 1991[163]	Low-dose versus high-dose aspirin
Duval, 2000[164]	Background on trial methodology
Dyken, 1998[165]	Article about antiplatelet agents and stroke prevention; not a systematic review
Easton, 1991[166]	Overview of antiplatelet therapy in the prevention of stroke; not a systematic review
Easton, 1998[167]	Discussion article about recent antiplatelet trials
Easton, 1999[168]	Discussion article about antiplatelet therapy
Easton, 2001[169]	General overview of antiplatelet therapy; not a systematic review
Ehresmann, 1977[170]	Aspirin versus placebo
Elmi, 2000[171]	Case report of TTP with clopidogrel use
Elwood, 1974[172]	Aspirin versus placebo
Elwood, 1979[173]	Aspirin versus placebo
Elwood, 2000[174]	Review article on the use of aspirin in cardiovascular prophylaxis; not a systematic review
Escolar, 2000[175]	Overview of clopidogrel: pharmacodynamics, phamacokinetics and clinical studies

continued

Study details	Reason for exclusion
ESPS-2 Working Group, 1996[176]	Early-report of ESPS-2 (abstract)
ESPS Group, 1987[177]	Standard-release dipyridamole and aspirin versus placebo (ESPS-1); not licensed indication
ESPS Group, 1990[178]	Duplicate of ESPS Group, 1990[179]
ESPS Working Group, 1995[180]	Early report on the rationale for ESPS-2; includes baseline data
ESPS-1 investigators, 1988[181]	Report of ESPS-1 (standard-release dipyridamole) (in Spanish)
ESPS-2 working group, 1992[182]	Interim report of ESPS-2
Evans, 1986[183]	Commentary on secondary preventative measures after acute MI
Ferguson, 1996[184]	Duplicate copy of Ferguson, 1996[185]
Ferguson, 1996[185]	News report of the results of ESPS-2
Fields, 1977[186]	Aspirin versus placebo (cerebral ischaemia)
Fields, 1978[187]	Aspirin versus placebo
Fields, 1979[188]	General background article on the antiplatelet agents
Fields, 1983[330]	Early report of the American–Canadian Persantine–Aspirin trial (standard-release dipyridamole)
Forbes, 1998[189]	Letter about ESPS-2 and CAPRIE
Forbes, 1998[190]	Background on stroke, includes brief discussion of ESPS-2 and CAPRIE
Forbes, 1998[191]	Summary of ESPS-2 trial; same as Diener *et al*. 1996[153]
Forbes, 1999[192]	Review article of antiplatelet therapy for stroke prevention; not a systematic review
Franck, 1995[193]	Report of ESPS-2 (in French)
Friedewald, 1984[194]	Overview of aspirin trials; not a systematic review
FRISC study group, 1996[195]	FRISC study; low-molecular-weight heparin (dalteparin) versus placebo for patients with CAD
Frison, 1992[196]	Background article on trial design
Furberg, 1980[197]	Commentary on the design of antiplatelet trials
Furberg, 1984[198]	Overview of treatments for AMI
Gallus, 1985[250]	General overview of antiplatelet agents. Not a systematic review
Gent, 1980[199]	Aspirin and sulfinpyrazone versus placebo
Gent, 1997[200]	Letter to the editor on behalf of the CAPRIE Steering Committee
Gent, 1998[201]	Overview of the CAPRIE trial
Gent, 1999[202]	Article describes the preregistration programme for CAPRIE
Gentile, 1986[203]	Abstract. Dipyridamole versus isosorbide dinitrate
Gerschutz, 2002[204]	Comment on the CURE trial
Giansante, 1990[205]	Not licensed indications. Study examines ticlopidine, aspirin–dipyridamole and xanthinol nicotinate in patients with PAD
Gibbs, 1998[206]	Discussion article about dipyridamole
Gibbs, 1998[207]	Letter to the editor – comment on review of secondary prevention for recurrent ischaemic stroke and TIAs
Goldman, 1984[208]	Aspirin plus dipyridamole for patients with vascular grafts
Goodnight, 1993[209]	Article about the antiplatelet agents; not a systematic review
Goodnight, 1993[210]	Article about the antiplatelets agents; not a systematic review
Goodnight, 1995[211]	Article about aspirin for patients with vascular disease and the influence of clinical trials. Not a systematic review
Gorelick, 1998[212]	Letter to the editor on the results of the CAPRIE trial
Gorelick, 1999[213]	Discussion article about aspirin and clopidogrel
Gorter, 1998[214]	Report of the ESPRIT trial (in Dutch)
Gorter, 1999[215]	Comment on ESPRIT (in German)
Grau, 2003[216]	Case-crossover study investigating platelet function under aspirin, clopidogrel or both
Green, 1982[217]	Study examined aspirin–dipyridamole, aspirin and placebo in patients who had undergone PTFE grafting
Guiraud-Chaumeil, 1982[218]	Duplicate copy of Guiraud-Chaumeil[219]
Guiraud-Chaumeil, 1982[219]	Standard release dipyridamole and aspirin versus aspirin (Toulouse-TIA); not licensed indication
Guiu, 1987[220]	Standard-release dipyridamole + ASA versus ASA. Not an RCT
Hacke, 1998[221]	Background article on acute stroke
Hankey, 1997[222]	Comment on the CAPRIE trial
Hankey, 2001[223]	Duplicate report of Hankey *et al*.[224]
Hankey, 2001[224]	Systematic review of the thienopyridines. Based on Cochrane Review by the same authors

continued

Study details	Reason for exclusion
Hanssen, 1998[225]	Case report – dipyridamole used as a vasodilator
Harjola, 1981[226]	Not secondary prevention. Patients had undergone arterial reconstructive surgery
Harrington, 1994[227]	Overview of antiplatelet trials (no results reported)
Heart outcomes prevention evaluation investigators, 2000[228]	HOPE study; ramipril versus placebo in high risk patients
Heart Protection Study Collaborative Group, 2002[229]	MRC/BHF Heart Protection Study; simvastatin versus placebo
Heiss, 1990[230]	Not licensed indication. Patients had had PTA
Hennekens, 1990[231]	Overview of the aspirin trials; not a systematic review
Hennekens, 1991[232]	Overview of aspirin trials; not a systematic review
Hennekens, 1997[233]	Discussion on the aspirin trials. Not a systematic review
Hennekens, 2002[234]	Background on ASA; general article, not a systematic review
Heptinstall, 1996[235]	Editorial article about ESPS-2
Hervey, 1999[236]	Overview of extended-release dipyridamole–aspirin; not a systematic review
Hess, 1975[237]	Abstract; theoretical background to antiplatelet treatment (in German)
Hess, 1985[238]	Not licensed indication (standard-release dipyridamole)
Hess, 1994[239]	Not licensed indication (standard-release dipyridamole) (in German)
Hillis, 1997[240]	Comment on dipyridamole as an antiplatelet agent
Hirsh, 1984[241]	Overview article reporting on standard release dipyridamole; not a systematic review
Hodara, 1984[242]	Article on the secondary prevention of MI (in French)
Huber, 2001[243]	News report on the CURE trial (in German)
Ishikawa, 1997[244]	Not licensed indication (standard-release dipyridamole)
Jackson, 2001[245]	Editorial on use of clopidogrel, based on the results of the CURE trial
Jarvis, 2000[246]	Review of the role of clopidogrel in the prevention of atherothrombosis; not a systematic review
Jonas, 1998[247]	Summary of meta-analysis of antiplatelets versus placebo. No search reported
Jonas, 2001[248]	Comment on ESPS-2 and CAPRIE (abstract)
Kerins, 1991[249]	Commentary on the role of antiplatelet drugs in ischaemic heart disease; not a systematic review
Klimt 1986[251]	Standard-release dipyridamole and aspirin for the long-term therapy of CHD after MI (Persantine–Aspirin Reinfarction Study); not licensed indication
Kohler, 1984[252]	Patients had undergone PTFE grafts. Not licensed indication
Kubler, 2002[253]	Overview of antiplatelet therapy (in German)
Kurz, 1998[254]	Duplicate copy of Kurz, 1998[255]
Lee, 1990[256]	Dipyridamole (standard-release). Not an RCT
Lenz, 2000[257]	Overview of dipyridamole trials; not a systematic review
Libretti, 1986[258]	Not licensed indication. Treatment of claudication with dipyridamole and aspirin
Lowe, 2003[259]	Overview of the role of clopidogrel as an antiplatelet agent
Lowenthal, 1994[260]	Meta-analysis on ASA and standard-release dipyridamole; search is not reported (would not pass DARE criteria)
Lubsen, 1981[261]	Commentary on the PARIS trial (in Dutch)
Lucas, 2002[262]	Comment on the PROGRESS trial (in French)
MacWalter, 1999[263]	General overview of secondary prevention of stroke; not a systematic review
MacWalter, 2002[264]	Benefit–risk assessment of agents used in secondary stroke prevention; not a systematic review
Malinin, 2002[266]	Background on pharmacological action of aspirin and dipyridamole; not a systematic review
Malinin, 2003[265]	Background review on clopidogrel for congestive heart failure
Marx, 1980[267]	Commentary on the AMIS trial
Matsagas, 2003[268]	Comment on CAPRIE and CURE trials for patients with PAD
McCollum, 1991[269]	Not licensed indication (standard-release dipyridamole following bypass)
Mehta, 2002[271]	Overview of aspirin for the prophylaxis of CAD; not a systematic review
Millan-Guerrero, 1999[272]	Article about intravenous dipyridamole for acute stroke (in Spanish)
Minar, 1995[273]	High-dose versus low-dose aspirin after angioplasty
Misson, 1998[274]	Non-systematic review of clopidogrel. No new data reported
Mueller, 2003[275]	Use of new device for monitoring ASA and clopidogrel intake
Muhlestein, 1997[276]	Economic evaluation on abciximab and ticlopidine
Muller, 1994[277]	General overview of the pharmacology of current and future antithrombotic therapies
Muller, 2001[278]	Trial in healthy subjects to investigate the inhibition of thrombus formation by low-dose aspirin and dypridamole

continued

Study details	Reason for exclusion
Mustard, 1983[279]	Review of aspirin trials; not a systematic review
Nappi, 2002[280]	Overview of antiplatelet therapy; not a systematic review
Nenci, 1996[281]	General review article on the antiplatelet agents. Not a systematic review
Noble, 1996[282]	Overview of ticlopidine; not a systematic review
Paradiso-Hardy, 2002[283]	Bayesian analysis of TTP associated with clopidogrel therapy
Patrono, 1998[284]	Discussion article about aspirin doses and mechanisms of action
Pechlaner, 2002[285]	Letters to the editor regarding RITA 3 trial (early angiography)
Persantine-Aspirin Reinfarction Study Group, 1980[286]	Duplicate copy of PARIS, 1980[287]
Petrucci, 1996[288]	Assessment of dipyridamole for stress testing using echocardiographic test results
Picano, 1998[289]	Article about the potential pharmacological actions of dipyridamole
Prandoni, 1991[290]	Dipyridamole + ASA in unstable angina (in Italian)
Puranen, 1998[291]	Subgroup analysis of ESPS-1
Puranen, 1998[292]	Subgroup analysis of patients with TIA or stroke from ESPS 1
Rajah, 1979[293]	Effect of dipyridamole on bleeding time; study conducted on healthy participants
Ranke, 1994[294]	High-dose versus low-dose aspirin. Patients had undergone PTA
Regensteiner, 2002[295]	Meta-analysis of current medical therapies for patients with peripheral vascular disease
Reuther, 1978[296]	Aspirin versus placebo
Reyero, 2002[297]	Letter to the editor on the CURE trial (in Spanish)
Richardson, 2001[298]	Discussion on data quality assurance and control in stroke trials
Riekkinen, 1988[299]	Discussion article about aspirin and dipyridamole (in Swedish)
Ringleb, 2003[300]	Overview of antiplatelet therapy for stroke; not a systematic review
Robinson, 1991[301]	Background on trial methodology
Robless, 2001[302]	No adverse events data from the aspirin trials is included and no extra information on CAPRIE
Roderick, 1993[303]	Review using only the trial reported in the first ATT meta-analysis; not systematic review as no search is performed
Ruhle, 1985[304]	Background article on antiplatelets (in German)
Rumboldt, 1995[305]	Letter regarding impact of clinical trial on clinical practice
Sakai, 1992[306]	Retrospective study on warfarin, ticlopidine and aspirin (in Japanese)
SALT collaborative group, 1991[307]	Low-dose aspirin versus placebo
Saniabadi, 1991[308]	Study of the effect of dipyridamole on antiplatelet aggregation in whole blood ($n = 16$)
Schellinger, 1997[309]	General discussion on antithrombotic therapy (in German)
Schoop, 1983[310]	Abstract. Not licensed indication (standard-release dipyridamole)
Schoop, 1983[311]	Not licensed indication (standard-release dipyridamole) (in German)
Schror, 1995[312]	Comparative review of antiplatelet agents; not a systematic review
Sculpher, 1998[313]	Systematic review of effectiveness, costs and cost-effectiveness of interventions for stable angina
Sempere, 2000[314]	Not an RCT (community based observational study) (in Spanish)
Sherry, 1982[315]	Comment on the persantin–aspirin reinfarction study (standard release dipyridamole) (in German)
Shukla, 1999[270]	Comment on the CAPRIE trial
Sivenius, 1991[316]	ESPS-1: subgroup analysis of stroke or death in women
Sivenius, 1991[317]	ESPS-1 (placebo control): results stratified by arterial distribution
Sivenius, 1991[318]	ESPS-1 (comparator is placebo): results stratified by sex
Sivenius, 1993[319]	ESPS-1: subgroup analysis of elderly patients
Sivenius, 1992[320]	ESPS 1: placebo controlled
Sivenius, 1995[321]	Subgroup analysis of ESPS-1
Sivenius, 1996[322]	Article about the role of dipyridamole in stroke prevention; not a systematic review
Sivenius, 1996[323]	Overview of dipyridamole in stroke prevention; not a systematic review
Sivenius, 1997[324]	Article about ESPS-2
Sorensen, 1983[325]	Aspirin versus placebo; Danish Co-operative Study
Stachenko, 1991[326]	Meta-analysis on ASA but no adverse events data reported
Steinhubl, 2002[50]	CREDO study – included patients who were to undergo elective PCI
Study group on pharmacological treatment after PTA 1994[327]	Versus placebo. Patients had undergone percutaneous balloon angioplasty
Taddei, 1992[328]	Study of the effect of dipyridamole on adenosine renin release

continued

Study details	Reason for exclusion
Tejedor, 1980[329]	Anticoagulant (cumarin drugs) in combination with antiplatelet drugs (ASA and dipyridamole) (in Spanish)
The American–Canadian Co-operative study group, 1986[331]	RCT comparing standard-release dipyridamole in combination with aspirin with aspirin; not licensed indication
The ESPS Group, 1987[332]	Duplicate copy of first ESPS article[177]
The Persantine–Aspirin Reinfaction Study Group, 1980[333]	Report on the PARIS trial (standard-release dipyridamole)
The Persantine–Aspirin Reinfarction Study Group, 1980[334]	Report on the PARIS trial (standard-release dipyridamole)
The Persantine–Aspirin Reinfarction Study Group, 1980[335]	Standard release dipyridamole (in German)
The WASH Study Steering Committee 1999[336]	Pilot study on effectiveness of warfarin, aspirin and placebo
Theis, 1999[337]	Bioequivalence trial on diypridamole and aspirin
Theiss, 1979[338]	Overview of antiplatelet therapy; not a systematic report (in German)
Thizon-de-Gaulle, 1998[339]	Background and secondary report of CAPRIE
Thommen, 1990[340]	General comment on secondary prevention of MI (in German)
Tijssen, 1997[341]	Comment of dipyridamole versus ASA trials
Tijssen, 1998[342]	Review of ESPS-2 and other dipyridamole studies; not a systematic review
Uchiyama, 1998[343]	Comment of the results of the CAPRIE trial (in Japanese)
Uchiyama, 2002[344]	Overview on antiplatelet therapy (in Japanese)
Ufkes, 1998[345]	Background on dipyridamole (in Dutch)
UK-TIA study, 1991[346]	Aspirin versus placebo
Valentin, 2001[347]	Clinical implications of the results of the CURE trial (in Spanish)
Vázquez, 1978[85]	Study on the effects of dipyridamole and dipridamole plus dihydroergotoxine methanesulphonate on cerebral circulation
Verheugt, 1996[348]	Systematic review of studies that combine aspirin or dipyridamole with warfarin versus aspirin or placebo
Violi, 1997[349]	Letter to the editor; comment on the CAPRIE trial
Vogel, 1981[350]	Aspirin versus placebo
Wahlgren, 1998[351]	Overview of standard-release and modified-release dipyridamole trials for the secondary prevention of stroke
Warlow, 2002[352]	Discussion article about aspirin for secondary prevention of stroke
Weichert, 1994[353]	Low-dose versus high-dose aspirin after angioplasty
White, 1995[354]	Study examined the effect of aspirin–dipyridamole on the patency of infarct-related artery versus placebo
Wilterdink, 1999[355]	Meta-analysis of data from Antiplatelet Trialists' Collaboration and ESPS-2. No search reported (would not meet DARE criteria)
Yusuf, 2001[356]	Early conference report of CURE (abstract)
Yusuf, 2001[357]	Conference report on the CURE trial (in German)
Zekert, 1975[358]	Aspirin versus placebo (in German)
Zielinski, 1999[359]	Letter to editor; summary of ESPS-2 trial results

Aspirin/adverse event searches

Study details	Reason for exclusion
Abrishami, 1977[360]	Overview of literature on aspirin intolerance from 1970s; not a systematic review
Almony, 1996[361]	General article about antiplatelet and anticoagulant use after MI; not a systematic review
Anonymous, 2000[362]	Background on the use of antiplatelet drugs in secondary prevention; not a systematic review
Anonymous, 1999[363]	Short article about the benefits and risks of prophylactic aspirin
Anonymous, 2000[364]	Commentry on the use of clopidogrel and CAPRIE (no new data reported)
Anonymous, 2002[365]	Comment on publication of ATTmeta-analysis in *BMJ*
Arnau, 1997[366]	Overview of the use of aspirin in MI (not systematic)
Awtry, 2000[367]	Overview of aspirin in the treatment of CVD; not a systematic review
Baker, 1970[368]	Short report about cutaneous responses to aspirin; not a systematic review
Barnett, 1990[369]	Overview of aspirin in stroke prevention; not a systematic review
Baume, 1992[370]	Short article giving a general overview of aspirin therapy; not a systematic review
Bennett, 2001[371]	Overview of platelet function inhibitors; not a systematic review
Berger, 1999[372]	Overview of clopidogrel and ticlopidine (no new data on CAPRIE represented)
Berkes, 2003[373]	Overview of anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs; not a systematic review
Bertele, 1993[374]	Article about the primary and secondary prevention of atherosclerosis; not a systematic review (in Italian)
Bhatt, 2001[375]	Overview of use of antiplatelets in secondary prevention (not systematic)
Bjarnason, 1993[376]	SR on adverse effects of NSAIDs on the large and small intestine (not aspirin specific)
Bjorkman, 1998[377]	Overview of adverse events associated with NSAIDs (not systematic review)
Black, 2001[378]	Overview of ticlopidine and clopidogrel; not a systematic review
Borg, 2002[379]	General article about the emergency treatment of transient ischaemic attacks; not a systematic review
Born, 1990[380]	Overview of aspirin trials – both primary and secondary prevention (not systematic review)
Borsch, 1984[381]	Report about drug-induced lesion in the upper GI tract; not a systematic review
Cairns, 1991[382]	Overview of antithrombotic trials (not systematic review)
Carson, 1993[383]	Overview of the toxicity associated with NSAIDs; not a systematic review
Catella-Lawson, 1995[384]	Overview of aspirin trials (not systematic)
Cavusoglu, 2003[385]	General article about clopidogrel; not a systematic review
Claxton, 2001[386]	Systematic review of medication compliance and dose regimens
Cleland, 1992[387]	Discusses the uses of aspirin and warfarin in ischaemic heart disease; not a systematic review
Cooke, 1970[388]	Brief review of effects of aspirin and ethanol on the stomach; not a systematic review
Dammann, 1998[389]	Overview of gastroduodenal tolerability of low-dose aspirin (not systematic review)
del Zoppo 2000[390]	Article about antithrombotic treatments in acute ischaemic stroke
Derry, 2000[49]	Duplicate copy of Derry, 2000[391]
Derry, 2000[391]	Duplicate article[392]
Di Pasquale, 1998[393]	Editorial about antiplatelet agents and anticoagulants in the secondary prevention of MI; not a systematic review (in Italian)
Dickinson, 1998[394]	Overview of benefits and risks of aspirin use; not systematic review
Dippel, 1998[395]	Duplicate record[439]
Dobrilla, 1997[396]	Article reviews gastroduodenal damage induced by aspirin and other NSAIDs; not a systematic review
Duggan, 1980[397]	Overview of GI toxicity associated with minor analgesics; not a systematic review
Eichenberger, 2003[398]	Brief overview of the pharmacological actions of aspirin
Elwood, 1998[399]	Overview of the use of aspirin in CVD; not a systematic review
Feret, 1999[400]	Brief report about clopidogrel
Fiorucci, 2001[401]	Article about the mechanisms of NSAID associated gastropathy
Fisher, 1999[402]	Article about antithrombotic therapy for ischaemic stroke; not a systematic review
Fitzmaurice, 2002[403]	General review of bleeding risks with antithrombotic therapy
Fitzmaurice, 2002[404]	Duplicate article[403]
Forster, 1993[405]	Pharmacological action of aspirin (in German)
Fowler, 1987[406]	Comparative review of aspirin, paracetamol and NSAIDS; not a systematic review
Friend, 1974[407]	General article about aspirin; not a systematic review
Gabriel, 1991[408]	Meta-analysis investigated the risk of serious GI complications associated with non-aspirin NSAIDs
Garcia Rodriguez, 1997[409]	Systematic review of risk of development of ulcers with NSAID use; data from aspirin not reported separately
Gaziano, 2000[410]	Overview of aspirin use in the treatment and prevention of CVD; not a systematic review

continued

Study details	Reason for exclusion
Giri, 1993[411]	Article on genetic toxicology of aspirin (animal models)
Girolami 1999[412]	Meta-analysis investigating antithrombotic drugs in the primary medical management of intermittent claudication
Gonzalez, 2000[413]	General article about antiplatelet therapy; not a systematic review
Gore, 1999[414]	Article about drug-induced disorders of the stomach and duodenum (NSAIDs); not a systematic review
Graham, 1998[415]	Overview of NSAIDs and gastric injury (not systematic and not aspirin specific)
Hankey, 1999[416]	Duplicate of record[135]
Harding, 2002[417]	Commentary on all the clopidogrel trials including CAPRIE and CURE (no new data reported)
Hartmann, 1995[418]	Article investigates the administration of high-dose aspirin for the prevention of acute cerebral ischaemia; not a systematic review and no adverse events reported
Hassan, 2001[419]	Report of the prevalence of aspirin use for both primary and secondary prevention
Hawkey, 1994[420]	Review article on aspirin and bleeding (not systematic)
Hawkey, 1996[421]	General article about gastropathy associated with NSAIDs; not a systematic review
Hawkey, 2000[422]	Overview of the management of NSAID induced gastroduodenal ulcers
Hawkins, 2000[423]	Literature review on NSAIDs (does not include aspirin)
He, 1998[53]	Duplicate article[48]
Heller, 1985[424]	Review of antiarthritic efficacy of NSAIDs (not systematic)
Hennekens, 1999[425]	Overview of the use of aspirin in the treatment and prevention of CVD; not a systematic review
Henry, 1987[426]	Case–control study investigating fatal peptic ulcer complications and the use of NSAIDs
Henry, 1988[427]	Overview of side-effects associated with NSAIDs; not a systematic review
Henry, 1996[428]	Meta-analysis investigating the risk of GI complications with NSAIDs; not secondary prevention or ACS
Heras, 2003[429]	Article about the use of clopidogrel in ACS
Herbert, 1994[430]	Pharmacological action of clopidogrel
Hirschowitz, 2001[431]	Consensus report on adverse events associated with aspirin; not based on a systematic review
Hirsh, 1985[432]	Review of the relationship between aspirin dose and side-effects; not a systematic review
Hirsh, 1989[433]	Article about the association of aspirin dose, effectiveness and side-effects; not a systematic review
Hudson, 1993[434]	Article about GI ulceration and complications associated with NSAIDs
Joseph, 1997[435]	Article about antiplatelet drugs; not a systematic review
Kelton, 1980[436]	Overview of bleeding associated with antithrombotic therapy; not a systematic review
Klijn, 2001[437]	Meta-analysis investigating outcome in patients with symptomatic occlusion of the internal carotid artery or intracranial arterial lesions
Knodel, 1992[438]	Overview of adverse events of NSAIDs (not systematic)
Kolts, 1992[439]	General article about the GI side-effects associated with NSAIDs; not a systematic review
Lanas, 1999[440]	Review of association between NSAID use and GI bleeding (not aspirin specific); not a systematic review
Lavie, 2003[441]	Article discusses a multifactorial approach to the primary and secondary prevention of atherosclerosis; not a systematic review
Leschke, 1998[442]	Article includes a comparative review of antiplatelet drugs but is not a systematic review (in German)
Lewis, 1996[443]	Overview of hepatotoxicity associated with NSAIDs; not a systematic review
Lichtenstein, 1995[444]	Overview of NSAID-mediated GI injury; not a systematic review
Lockhart, 2000[445]	Review of literature on secondary prevention after an MI (not systematic)
Lubbe, 2002[446]	General article about the thienopyridines (clopidogrel and ticlopidine); not a systematic review
Majhail, 2003[447]	Case reports of TTP associated with clopidogrel use
Maynard, 2000[448]	Background on the management of ACS (risk stratification)
McCabe, 2000[449]	Article about the prevention of ischaemic stroke using antiplatelet therapy; not a systematic review
Michaels, 1999[450]	Article about the secondary prevention of MI. Discusses pharmacological and non-pharmacological interventions; not a systematic review
Mikhailidis, 1998[451]	Discussion article about PVD subgroup results from the CAPRIE trial
Mohr, 2002[452]	Overview of trials investigating prevention of recurrent ischaemic stroke; not a systematic review
Morassut, 1989[453]	Article about aspirin intolerance; not a systematic review

continued

Study details	Reason for exclusion
Namazy, 2002[454]	Overview of sensitivity to NSAIDS; not a systematic review
Orford, 2001[455]	Commentary on CAPRIE, CURE and PCI-CURE (no new data reported)
Patrono, 2001[456]	Overview of aspirin dose and its relation to effectiveness and side-effects; not a systematic review
Pepine, 1998[457]	Editorial on CAPRIE trial
Picano, 2001[458]	RCT of dipyridamole in chronic stable angina
Pueyo, 2002[459]	Meta-analysis of the use of aspirin in primary prevention (in Spanish)
Quiralte, 1998[460]	Article about aspirin sensitivity; not a systematic review
Rahman, 1996[461]	General article about NSAIDs; not a systematic review
Righini, 2000[462]	Article about alternative antiplatelets agents to aspirin; not a systematic review (in French)
Rodgers, 1996[463]	Review of antiplatelet therapy; not a systematic review
Rodriguez, 1998[464]	Systematic review of GI complications of NSAIDs (not aspirin specific)
Rodvein, 1976[465]	Overview of aspirin from the 1970s; not a systematic review
Sainte-Laudy, 2001[466]	Article on mechanism of action of aspirin (in French)
Salter, 1968[467]	General article about aspirin and GI bleeding; not a systematic review
Sandercock, 2000[468]	Overview of aspirin trials in stroke (not systematic); the only adverse events data represented are from CAST and IST (acute stroke)
Sanmuganathan, 2001[469]	Systematic review of aspirin use in primary prevention
Schulz, 2002[470]	Comment on trial methodology in ACS
Sheridan, 2002[471]	Review of unstable angina and STEMI; not a systematic review
Steinhubl, 2003[472]	Review on aspirin as an antiplatelet agent; not a systematic review
Szczeklik, 1987[473]	Overview of adverse reactions to aspirin and NSAIDs; not a systematic review
Tramer, 2000[474]	Commentary on systematic review of aspirin[391]
Tramer, 2000[475]	Quantitative estimation of rare adverse events associated with NSAIDs; not aspirin specific
Van De Graaff, 2001[476]	Overview of complication associated with oral antiplatelet medications; not a systematic review
Weber, 1997[477]	Article discusses the pharmacology of ticlopidine and clopidogrel compared with aspirin

Appendix 4

Details of quality assessment

Clinical effectiveness studies were assessed using the following criteria based on CRD Report 4[33]

1. Was the method used to assign participants to the treatment groups really random? (*Computer-generated random numbers and random number tables were accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week*.)
2. Was the allocation of treatment concealed? (*Concealment was deemed adequate where randomisation is centralised or pharmacy controlled, or where the following are used: serially numbered identical containers, on-site computer-based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque*.)
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of MI, stroke, heart failure, hypertension, diabetes and current or former smoker?
5. Was baseline comparability achieved in terms of MI, stroke, heart failure, hypertension, diabetes and current or former smoker?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
13. Were the reasons for withdrawals stated?
14. Was an intention to treat analysis included?

Items were graded in terms of yes (item properly addressed), no (item not properly addressed), partially addressed (item partially addressed), unclear or not enough information or NA (not applicable).

Studies of cost-effectiveness were assessed using the following criteria, which is an updated version of the checklist developed by Drummond and colleagues[34]

Study question

1. Costs and effects examined.
2. Alternatives compared.
3. The viewpoint(s)/perspective of the analysis is clearly stated (*e.g. NHS, society*).

Selection of alternatives

4. All relevant alternatives are compared (*including do nothing if applicable*).
5. The alternatives being compared are clearly described (*who did what, to whom, where and how often*).
6. The rationale for choosing the alternative programmes or interventions compared is stated.

Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?

Effectiveness data

9. The source(s) of effectiveness estimates used are stated (*e.g. single study, selection of studies, systematic review, expert opinion*).
10. Effectiveness data from RCT or review of RCTs.
11. Potential biases identified (especially if data not from RCTs).
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).

Costs

13. All the important and relevant resource use included.

14. All the important and relevant resource use measured accurately (with methodology).
15. Appropriate unit costs estimated (with methodology).
16. Unit costs reported separately from resource use data.
17. Productivity costs treated separately from other costs.
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion.

Benefit measurement and valuation

19. The primary outcome measure(s) for the economic evaluation are clearly stated (*cases detected, life-years, QALYs, etc*.).
20. Methods to value health states and other benefits are stated (*e.g. time trade-off*).
21. Details of the individuals from whom valuations were obtained are given (*patients, members of the public, healthcare professionals, etc*.).

Decision modelling

22. Details of any decision model used are given (*e.g. decision tree, Markov model*).
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified.
24. All model outputs described adequately.

Discounting

25. Discount rate used for both costs and benefits.
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?

Allowance for uncertainty

Stochastic analysis of patient-level data

27. Details of statistical tests and CIs are given for stochastic data.
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs).
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Stochastic analysis of decision models

30. Are all appropriate input parameters included with uncertainty?
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?
32. Are the probability distributions adequately detailed and appropriate?
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Deterministic analysis

34. The approach to sensitivity analysis is given (*e.g. univariate, threshold analysis*).
35. The choice of variables for sensitivity analysis is justified.
36. The ranges over which the variables are varied are stated.

Presentation of results

37. Incremental analysis is reported using appropriate decision rules.
38. Major outcomes are presented in a disaggregated as well as aggregated form.
39. Applicable to the NHS setting.

All items were graded as either ✓, yes (item adequately addressed); ×, no (item not adequately addressed); ?, unclear or not enough information; NA, not applicable; or NS, not stated.

Systematic reviews and meta-analyses were assessed using the criteria for DARE, as illustrated in the table.

Criteria	Components	Not applicable	Poor	Fair	Good
1. Are inclusion/exclusion criteria reported that address the review question?	1. Study design 2. Participants 3. Healthcare intervention 4. Outcomes	Not addressed	1/4 components addressed	At least 2/4 components addressed	3/4 components addressed, criteria applied by more than one reviewer
2. Is there evidence of a substantial effort to search for all relevant research literature?	Prospective meta-analyses that restrict search to trials within database can also be included. If authors' expertise and confidence that all trials included without further searches reported in paper then this can also be included	Not mentioned	One named database searched, minimal description of dates and terms	Either one named database searched with dates and terms reported with following up references/contacting researches, or more than one named database searched	More than one database searched, description of dates and terms and other retrieval methods reported: handsearching, unpublished literature, experts in field, Internet searches, citation searches
3. Is the validity of included studies adequately assessed?		Not assessed/reported	Not assessed systematically	Assessed systematically by one reviewer (or number of reviewers not clear)	Assessed systematically by more than one reviewer
4. Is sufficient detail of the individual studies presented?	Design Participants Sample size Intervention Outcomes	Details not available	Some detail in text or studies inadequately presented in tables	Details presented in tables but one or more important characteristics not included, or details of studies well described in text. Review may state that owing to space limitations study details are presented elsewhere	Details presented in tables and text. Tables include almost all or all relevant information. Enough information to judge whether authors' summary and conclusions are appropriate
5. Are the primary studies summarised appropriately?		No effort to combine or summarise evidence	Evidence summarised but not synthesised and not adequately weighted according to sample size and/or quality of design. Methods used to pool data are not adequate and/or heterogeneity is not addressed	Studies synthesised with appropriate techniques, but heterogeneity is not addressed	Included studies are synthesised appropriately. Heterogeneity between studies is investigated adequately

Appendix 5

Details of data extraction for clinical effectiveness studies

Data extraction tables for the CURE trial

Study details	Inclusion criteria	Intervention details
Authors Yusuf *et al.*, 2003[36] *(1) Data extracted from CURE Study Investigators, (2000)[35] *(2) Data extracted from Budaj *et al.*, (2002)[37] *(3) Data extracted from Mehta *et al.*, (2003)[41] *(4) Data extracted from Mehta *et al.*, (2001)[39] *(5) Data extracted from Mehta. *et al.* (2003)[40] *(6) Data extracted from Sponsor Submission to NICE *(7) Data extracted from Peters *et al.*, (2002)[38] **Study Design** Randomised, double-blind, placebo-controlled trial	**Definition high risk** See inclusion criteria **Inclusion/exclusion criteria** Clinical evaluation had to establish the diagnosis of acute coronary syndromes and no ST-segment elevation. Patients were eligible for the study if they had been hospitalised within 24 hours after the onset of symptoms. Initially patients > 60 years of age with no new ECG changes but with a history of CAD were included. After enrolment of the first 3000 patients, only patients with either ECG or an elevation in the serum level of cardiac enzymes or markers at entry were included. Patients with contraindications to antithrombotic or antiplatelet therapy, those at high risk for bleeding or severe heart failure, those taking oral anticoagulants, or patients who had undergone coronary revascularisation in the previous 3 months or who had received intravenous glycoprotein IIb/IIIa receptor inhibitors in the previous 3 days were excluded.	**Intervention 1** Clopidogrel + aspirin (ASA) 75 mg daily plus 75–325 mg daily ASA **Intervention 2** Aspirin + placebo 75–325 mg daily ASA + placebo **Further information** A loading dose of clopidogrel (300 mg orally) or matching placebo was administered immediately after randomisation

Intervention	No. of patients	No. of patients lost to follow-up	Mean ages (SD) (years)	Qualifying event	Prognostic indicators, *n* (%)						
					MI	Stroke	Heart failure	Hyper-tension	Current/ former smoker	Diabetes	Other
Clopidogrel + aspirin (ASA)	6259	6	64.2 (11.3)	Unstable angina: 4690 (74.9) Suspected MI: 1569 (25.1) Associated MI[a]: 1624 (25.9)	2029 (32.4)	274 (4.4)	462 (7.4)	3750 (59.9)	3790 (60.6)	1405 (22.4)	CABG or PTCA: 1107 (17.7) ECG abnormality: Any: 5863 (93.7) ST segment: Depression ≥ 1 mm: 2642 (42.2) Elevation ≥ 1 mm: 203 (3.2) Transient elevation >2 mm: 38 (0.6) T-wave inversion: Major (≥ 2 mm): 1589 (25.4) Other (<2 mm): 721 (11.5) Other: 670 (10.7)
Aspirin + placebo	6303	7	64.2 (11.3)	Unstable angina: 4724 (74.9) Suspected MI: 1579 (25.1) Associated MI[a]: 1659 (26.3)	2015 (32.0)	232 (3.7)	492 (7.8)	3642 (57.8)	3841 (60.9)	1435 (22.8)	CABG or PTCA: 1139 (18.1) ECG abnormality: Any: 5921 (93.9) ST segment: Depression ≥ 1 mm: 2646 (42.0) Elevation ≤ 1 mm: 199 (3.2) Transient elevation >2 mm: 37 (0.6) T-wave inversion: Major (≥ 2 mm): 1635 (25.9) Other (<2 mm): 713 (11.3) Other: 690 (10.9) *(2) Median TIMI risk score for the total CURE population and for the clopidogrel and placebo groups was 3

[a] Defined as an MI associated with an episode of pain that occurred before randomisation.

* (1) Medications at time of randomisation and during initial hospitalisation (all patients) (N = 12,563)

	At randomisation (%)	In hospital (%)
Aspirin	66.50	99.10
Heparin	37.90	46.00
Low-molecular-weight heparin	32.20	54.00
I.V. glycoprotein IIb/IIIa inhibitors	0.10	3.20
ACE inhibitors	36.00	48.90
Beta-blockers	57.50	77.50
Calcium channel blockers	27.80	35.00
Lipid-lowering agents	24.90	45.60
Intravenous nitrates	44.40	52.90

*(3) Additional procedures: of the 12,652 patients recruited, 5491 (44%) underwent angiography, 2072 (16.5%) had CABG surgery (the study medication was temporarily interrupted for more than 5 days in 84.9% of the patients who underwent CABG surgery. In these patients, the study medication was restarted after a median of 11 days) and 2658 (21.2%) underwent PCI (the use of study medication was temporarily interrupted for more than 5 days in 85.8% of patients who underwent PCI, and in addition a vast majority of patients received theinopyridine for about 2–4 weeks).

* (2) Distribution of thrombolysis in myocardial infarction (TIMI) risk factors in placebo and clopidogrel groups

Factor	Overall (n = 12,562)	Placebo (n = 6303)	Clopidogrel (n = 6259)
Age≥ 65	6565 (52.3)	3287 (52.1)	3278 (52.4)
≥ CAD risk factors	1831 (14.6)	886 (14.1)	945 (15.1)
Known CAD (>50% stenosis)	3155 (25.1)	1602 (25.4)	1553 (24.8)
Aspirin use in past 7 days	8302 (66.1)	4134 (65.6)	4168 (66.6)
Severe angina within 24 hours	12317 (98)	6184 (98.1)	6133 (98.0)
ST deviation ≥ 0.5 mm	6275 (50.0)	3127 (49.6)	3148 (50.3)
Elevated cardiac markers	3176 (26.3)	1592 (25.3)	1584 (25.3)

Values are number of patients (%).
TIMI risk score is based on seven independent risk predictors: (1) age ≥ 65 years, (2) ≥ 3 CAD risk factors (family history of CAD, hypertension, hypercholesterolaemia, diabetes, and/or current smoking), (3) documented CAD (≥ 50% stenosis on coronary angiography), (4) aspirin use 7 days before hospitalisation, (5) at least two episodes of angina within 24 hours before hospitalisation, (6) ST-segment deviation ≥ 0.5 mm and (7) elevated cardiac markers.

*(7) Regional distribution and baseline characteristics by aspirin dose group

	≤ 100 mg	101–199 mg	≥ 200 mg
N (%)	5320 (42.2)	3109 (24.8)	4110 (32.8)
Canada/United States, *n* (%)	232 (10.5)	78 (3.5)	1906 (86.0)
Latin America, *n* (%)	187 (13.8)	144 (10.7)	1019 (75.5)
Australia/New Zealand/South Africa, *n* (%)	209 (18.4)	832 (73.4)	93 (8.2)
Western Europe, *n* (%)	3096 (61.6)	954 (19.0)	979 (19.5)
Eastern Europe, *n* (%)	1596 (56.8)	1101 (39.2)	113 (4.0)
Weight, mean (kg)	77.3	77.3	78.2
Male (%)	58.8	61.1	65.4
Body mass index, mean	27.3	27.4	27.6
Current smokers (%)	20.8	24.2	25.1
Previous MI (%)	32	31.1	33.2
Diabetes (%)	21	19.8	26.2
Hypertension (%)	58.8	56.6	60.5
History of PCI (%)	9.2	7.1	12.8
History of CABG (%)	10	8.9	13.8
TIMI risk score, mean	3.3	3.1	3.5

*(7) Additional medications and procedures during the entire study period stratified by aspirin dose

	≤ 100 mg	101–199 mg	≥ 200 mg	*p*-value
N	5320	3109	4110	–
Heparin (%)	89.7	93.6	95.1	<0.0001
NSAIDs (%)	14.1	14.9	13.2	0.13
Glycoprotein IIb/IIIa inhibitors (%)	5.6	3.7	10	<0.0001
Other antiplatelet agents combined[a] (%)	19	17.5	25.4	<0.0001
Oral anticoagulants (%)	5	5.1	5.2	0.95
PCI (%)	19.9	17.3	25.9	<0.0001
CABG (%)	15.6	16.5	17.7	0.02

[a] Open-label ticlopidine or clopidogrel.

Definition of primary outcomes	Definition of secondary outcomes	Definition of bleeding complications
The first primary outcome was the composite of death from CV causes, non-fatal MI or stroke. The second primary outcome was the composite of the first primary outcome or RI. The classification of death from CV causes was defined as any death from which there was no clearly documented non-vascular cause. MI was defined by the presence of at least two of the following: ischaemic chest pain; elevation of the serum levels of cardiac markers or enzymes (troponin, creatine kinase, CK-MB isoenzyme or other cardiac enzymes) to at least twice the upper limit of the normal reference range or three times the upper limit of normal within 48 hours after PCI (or to a level 20% higher than the previous value if the level had already been elevated because of an early MI); and ECG changes compatible with infarction. Stroke was defined as a new focal neurological deficit of vascular origin lasting more than 24 hours. Stroke was further classified as the result of intracranial haemorrhage, ischaemia (if a computed tomographic or magnetic resonance imaging scan was available) or uncertain cause. RI in the hospital was defined as recurrent chest pain lasting >5 minutes with new ischaemic ECG changes while the patient was receiving optimal medical therapy (two antianginal agents, one of which was intravenous nitrate unless such therapy was contraindicated) and leading to additional interventions (such as thrombolytic therapy, cardiac catheterisation, the insertion of an intra-aortic balloon pump, coronary revascularisation or transfer to a referral hospital for an invasive procedure) by midnight of the next calendar day. RI after discharge was defined by rehospitalisation lasting at least 24 hours for unstable angina, with ischaemic ECG changes	The secondary outcomes were severe ischaemia, heart failure and the need for revascularisation. Severe ischaemia (in the hospital) was defined as ischemia that was similar to in-hospital RI but for which no urgent intervention was performed. Recurrent angina (in the hospital) was defined similarly, but ECG changes were not required	Bleeding complications were categorised as life-threatening, major or minor. Major bleeding episodes were defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision or bleeding necessitating the transfusion of at least 2 units of blood. Major bleeding was classified as life-threatening if the bleeding episode was fatal or led to a reduction in the haemoglobin level of at least 5 g/dl or to substantial hypotension requiring the use of intravenous inotropic agents, if it necessitated a surgical intervention, if it was symptomatic intracranial haemorrhage, or if it necessitated the transfusion of 4 or more units of blood. Minor bleeding episodes included other haemorrhages that led to the interruption of the study medication. Bleeding episodes were also classified using the TIMI criteria for major bleeds and the GUSTO (Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria for severe bleeds

Outcome 1: clopidogrel versus ASA in first 24 hours after randomisation	Outcome 2: clopidogrel versus ASA on days 1, 2 and 3	Outcome 3: clopidogrel versus ASA within the first 7 days
CV death, MI or stroke Clopidogrel: 27/6259 (event rate 0.4%) ASA: 34/6303 (event rate 0.5%) RR (95% CI) 0.80 (0.48 to 1.32)	No. of events, placebo versus clopidogrel (RR) **CV death, MI or stroke** Day 1: 34 versus 27 (0.80) Day 2: 67 versus 54 (0.81) Day 3: 89 versus 75 (0.85)	**CV death, MI or stroke** Clopidogrel: event rate 2.1% ASA: event rate 2.5% RR (95% CI) 0.82 (0.65 to 1.04)
CV death, MI, stroke, or refractory ischaemia Clopidogrel: 53/6259 (event rate 0.8%) ASA: 70/6303 (event rate: 1.1%) RR (95% CI) 0.76 (0.53 to 1.09)	**CV death, MI, stroke, or severe ischaemia** Day 1: 135 versus 89 (0.66), $p < 0.01$ Day 2: 233 versus 162 (0.70), $p < 0.001$ Day 3: 288 versus 217 (0.75), $p < 0.001$	**CV death, MI, stroke, refractory ischaemia:** Clopidogrel: event rate 3.5% ASA: event rate 4.2% RR (95% CI) 0.82 (0.69, 0.98)
CV death, MI, stroke, severe ischaemia[a] Clopidogrel: 89/6259 (event rate 1.4%) ASA: 135/6303 (event rate 2.1%) RR (95% CI) 0.66 (0.51 to 0.86) $p < 0.003$		**CV death, MI, stroke, severe ischaemia** Clopidogrel: event rate 5.2% ASA, event rate 6.7% RR (95% CI) 0.77 (0.67 to 0.89)

[a] Includes RI.

Outcome 4: clopidogrel versus ASA days 8–30	Outcome 5: clopidogrel versus ASA days 0–30	Outcome 6: clopidogrel versus ASA >30 days–1 year
CV death, MI or stroke Clopidogrel: event rate 2.3% ASA: event rate 3.0% RR (95% CI) 0.76 (0.61 to 0.94)	**CV death, MI, stroke** Clopidogrel: event rate 4.3% ASA: event rate 5.4% RR (95% CI) 0.79 (0.67 to 0.92)	**CV death, MI, stroke** Clopidogrel: event rate 5.2% ASA: event rate 6.3% RR (95% CI) 0.82 (0.70 to 0.95)
CV death, MI, stroke, refractory ischaemia Clopidogrel: event rate 4.4% ASA: event rate 5.2% RR (95% CI) 0.83 (0.71 to 0.98)	**Refractory ischaemia** Clopidogrel: event rate 3.7% ASA: event rate 4.3% RR (95% CI) 0.86 (0.72 to 1.03)	**Refractory ischaemia** Clopidogrel: event rate 5.3% ASA: event rate 5.4% RR (95% CI) 0.98 (0.84 to 1.15)
CV death, MI, stroke, severe ischaemia Clopidogrel: event rate 4.6% ASA: event rate 5.4% RR (95% CI) 0.86 (0.73 to 1.01)	**Severe ischaemia**[a] Clopidogrel: event rate 3.8% ASA: event rate 5.0% RR (95% CI) 0.75 (0.63 to 0.88)	**Severe ischaemia** Not applicable
	CV death, MI, stroke, refractory ischaemia Clopidogrel: event rate 7.7% ASA: event rate 9.2% RR (95% CI) 0.83 (0.73 to 0.93)	**CV death, MI, stroke, refractory ischaemia** Clopidogrel: event rate 9.6% ASA: event rate 10.6% RR (95% CI) 0.90 (0.80 to 1.01)
	CV death, MI, stroke, in-hospital ischaemia Clopidogrel: event rate 9.6% ASA: event rate 11.7% RR (95% CI) 0.81 (0.73 to 0.90)	**CV death, MI, stroke, in-hospital severe ischaemia** Not applicable

[a] Severe ischaemia includes RI.

Overall outcomes from randomisation to 1 year follow-up (mean 9 months)

Outcome 7: death (CV causes, non-fatal MI or stroke	**Outcome 8: death (CV causes, non-fatal MI, stroke or RI**	**Outcome 9: Severe ischaemia**		**Other outcome**
Clopidogrel: 582/6259 (9.3%) ASA: 719/6303 (11.4%) RR (95% CI) 0.80 (0.72 to 0.90), $p < 0.001$	Clopidogrel: 1035/6259 (16.5%) ASA: 1187/6303 (18.8%) RR (95% CI) 0.86 (0.79 to 0.94), $p < 0.001$	Clopidogrel: 176/6259 (2.8%) ASA: 237/6303 (3.8%) RR (95% CI) 0.74 (0.61 to 0.90), $p = 0.003$		The proportion of patients receiving blinded medication was 88.4% in the clopidogrel group and 87.0% in the placebo group at hospital discharge, 82.9% and 82.1% at 30 days and 92.2% and 92.1% by study end, respectively. The use of open-label thienopyridines/clopidogrel was 10.7% in the clopidogrel group and 12.1% in the placebo group at hospital discharge, 13.0% and 13.7% at 30 days and 2.9% and 3.1% at study end
Outcome 10: recurrent angina	**Outcome 11: coronary revascularisation**	**Outcome 12: main study outcomes alone**		
Clopidogrel: 1307/ 6259 (20.9%) ASA: 1442/6303 (22.9) RR (95% CI) 0.91 (0.85 to 0.98), $p = 0.01$	Clopidogrel: 2253/6259 (36%) ASA: 2326/6303 (36.9%) Radiological evidence of heart failure: Clopidogrel: 229/6259 (3.7%) ASA: 280/6303 (4.4%) RR (95% CI) 0.82 (0.69 to 0.98), $p = 0.03$	Death from CV causes Clopidogrel: 318/6259 (5.1%) ASA: 345/6303 (5.5%) RR (95% CI) 0.93 (0.79 to 1.08) MI (some patients had both a Q-wave and a non-Q-wave MI): Clopidogrel: 324/6259 (5.2%) ASA: 419/6303 (6.7%) RR (95% CI) 0.77 (0.67 to 0.89) Q-wave MI: Clopidogrel: 116/6259 (1.9%) ASA: 193/6303 (3.1%) RR (95% CI) 0.60 (0.48 to 0.76) Non-Q-wave MI: Clopidogrel: 216/ 6259 (3.5%) ASA: 242/6303 (3.8%) RR (95% CI) 0.89 (0.74 to 1.07) Stroke: Clopidogrel: 75/6259 (1.2%) ASA: 87/6303 (1.4%) RR (95% CI) 0.86 (0.63 to 1.18)	RI (only the first ischaemic event was counted for each patient): Clopidogrel: 544/6259 (8.7%) ASA: 587/6303 (9.3%) RR (95% CI) 0.93 (0.82 to 1.04) RI during hospitalisation: Clopidogrel: 85/6259 (1.4%) ASA: 126/6303 (2.0%) RR (95% CI) 0.68 (0.52 to 0.90) RI after discharge: Clopidogrel: 459/6259 (7.6%) ASA: 461/6303 (7.6%) RR (95% CI) 0.99 (0.87 to 1.13) Death from non-CV: Clopidogrel: 41/6259 (0.7%) ASA: 45/6303 (0.7%) RR (95% CI) 0.91 (0.60 to 1.39)	

*(2) Validation of TIMI risk score/event rate in various risk groups at 9 months: *n* (%)

Events	0–1 (*n* = 752)	2 (*n* = 2524)	3 (*n* = 3730)	4 (*n* = 3567)	5 (*n* = 1593)	6–7 (*n* = 398)	*p* χ^2 for trend
CV death, MI or stroke	26 (3.5)	136 (5.4)	326 (8.7)	448 (12.6)	275 (17.3)	90 (22.7)	<0.0001
CV death, MI, stroke or RI	85 (11.3)	274 (10.9)	593 (15.9)	732 (20.6)	420 (26.4)	118 (29.8)	< 0.0001
CV death	10 (1.3)	45 (1.8)	167 (4.5)	245 (6.9)	150 (9.4)	46 (11.6)	<0.0001
MI	13 (1.7)	87 (3.5)	179 (4.8)	251 (7.0)	158 (9.9)	55 (13.9)	<0.0001
Stroke	4 (0.5)	20 (0.8)	40 (1.1)	57 (1.6)	32 (2.0)	9 (2.3)	<0.0001
RI	61 (8.1)	152 (6.0)	321 (8.6)	357 (10.0)	1 98 (12.4)	42 (10.6)	<0.0001
Major bleeding	14 (1.9)	59 (2.3)	109 (2.9)	127 (3.6)	73 (4.6)	18 (4.6)	<0.0001

Outcome 1: clopidogrel versus ASA by TIMI risk-group stratification at 9 months follow-up: CV death, MI or stroke

Low-risk group (TIMI score 0–2):
Clopidogrel: event rate 4.1%
ASA: event rate 5.7%
RR (95% CI) 0.71 (0.52 to 0.97)
NNT: 63

Intermediate-risk group (TIMI score 3–4):
Clopidogrel: event rate 9.8%
ASA: event rate 11.4%
RR (95% CI) 0.85 (0.74 to 0.98)
NNT: 63

High-risk group (TIMI score 5–7):
Clopidogrel: event rate 15.9%
ASA: event rate 20.7%
RR (95% CI) 0.73 (0.60 to 0.90)
NNT: 21

*(7) Incidence of the first co-primary end-point by various doses of aspirin

	Aspirin alone	Aspirin + clopidogrel	All patients	Hazard ratio aspirin + clopidogrel vs aspirin alone[a]	95% CI
ASA dose ≤ 100 mg	10.5%	8.6%	9.6%	0.81	0.68 to 0.97
ASA 101–199 mg	9.8%	9.5%	9.7%	0.97	0.77 to 1.22
ASA ≥ 200 mg	13.6%	9.8%	11.7%	0.71	0.59 to 0.85
p-value for trend	0.0016	0.17	0.0011	–	–
Adjusted HR for 101–199 vs ≤ 100 mg	1.0 (0.82 to 1.23)	1.2 (0.98 to 1.48)	1.09 (0.95 to 1.26)	–	–
Adjusted HR for ≥ 200 mg vs ≤ 100 mg[b]	1.3 (1.08 to 1.52)	1.2 (0.95 to 1.40)	1.23 (1.08 to 1.39)	–	–

[a] Test for heterogeneity, p = NS.
[b] Adjusted for gender, weight, hypertensions, components of the TIMI risk score and rates of angiography, PCI and CABG.

Bleeding complications and other adverse events

Bleeding complications

Clopidogrel versus ASA in first 24 hour after randomisation	Clopidogrel versus ASA within the first 7 days	Clopidogrel versus ASA days 8–30	Clopidogrel versus ASA days 0–30	Clopidogrel versus ASA >30 days – 1 year
Life-threatening/major Clopidogrel: 5/6259 (event rate 0.08%) ASA: 6/6303 (event rate 0.10%) RR (95% CI) 0.84 (0.26 to 2.75)	**Major bleeds** Clopidogrel, event rate 0.86% ASA, event rate 0.73% RR (95% CI) 1.18 (0.80 to 1.75)	**Major bleeds** Clopidogrel, event rate: 1.17% ASA, event rate: 0.82% RR (95% CI) 1.43 (1.00 to 2.04)	**Any major bleeds** Clopidogrel: event rate 2.01% ASA: event rate 1.54% RR (95% CI) 1.31 (1.01 to 1.70)	**Any major bleeds** Clopidogrel: event rate 1.75% ASA: event rate 1.18% RR (95% CI) 1.48 (1.10 to 1.99)
TIMI major bleeds Clopidogrel: 1/6259 (event rate 0.02%) ASA: 0/6303 (event rate 0%)	**Life-threatening bleeds** Clopidogrel, event rate 0.48% ASA, event rate 0.44% RR (95% CI) 1.08 (0.65 to 1.80)	**Life-threatening bleeds** Clopidogrel, event rate: 0.81% ASA, event rate: 0.53 % RR (95% CI) 1.53 (0.99 to 2.37)	**Life-threatening bleeds** Clopidogrel: event rate 1.28% ASA: event rate 0.97% RR (95% CI) 1.32 (0.95 to 1.84)	**Life-threatening bleeds** Clopidogrel: event rate 0.91% ASA: event rate 0.83% RR (95% CI) 1.09 (0.75 to 1.59)
GUSTO severe/life-threatening bleeds Clopidogrel: 0/6259 (event rate 0%) ASA: 2/6303 (event rate 0.03%)	**TIMI major bleeds** Clopidogrel, event rate 0.19 ASA, event rate 0.17 RR (95% CI) 1.10 (0.49 to 2.49)	**TIMI major bleeds** Clopidogrel, event rate: 0.39% ASA, event rate: 0.40% RR (95% CI) 0.97 (0.55 to 1.69)	**TIMI major bleeds** Clopidogrel: event rate 0.58% ASA: event rate 0.57% RR (95% CI) 1.01 (0.64 to 1.60)	**TIMI major bleeds** Clopidogrel: event rate 0.53% ASA: event rate 0.60% RR (95% CI) 0.87 (0.54 to 1.40)
	GUSTO severe/life-threatening bleeds Clopidogrel, event rate 0.21 ASA, event rate 0.21 RR (95% CI) 1.01 (0.47 to 2.17)	**GUSTO severe/life-threatening bleeds** Clopidogrel, event rate: 0.50% ASA, event rate: 0.37% RR (95% CI) 1.36 (0.79 to 2.33)	**GUSTO severe/life-threatening bleeds** Clopidogrel: event rate 0.70% ASA: event rate 0.57% RR (95% CI) 1.23 (0.79 to 1.91)	**GUSTO severe/life-threatening bleeds** Clopidogrel: event rate 0.56% ASA: event rate 0.55% RR (95% CI) 1.01 (0.63 to 1.62)

* (2) Major bleeding complications in placebo and clopidrogel groups stratified by TIMI risk factors

Low-risk group (TIMI score 0 –2)
Clopidrogrel, event rate 41/1602 (2.6)
ASA, event rate 32/1674 (1.9)
RR (95% CI) 1.34 (0.83 to 1.86), $p = 0.21$

Intermediate-risk group (TIMI score 3–4)
Clopidogrel, event rate 140/3671 (3.8)
ASA, event rate 96/3626 (2.6)
RR (95% CI) 1.44 (1.12 to 1.86), $p = 0.005$

High-risk group (TIMI score 5–7)
Clopidogrel, event rate50/986 (5.1)
ASA, event rate 41/1003 (4.1)
RR (95% CI) 1.25 (0.83 to 1.86), $p = 0.30$

Trends

The RR of the primary outcome in the first 30 days after randomisation was 0.79 (95% CI: 0.67 to 0.92). RR of primary outcome between 30 days to the end of treatment to 0.82 (95% CI: 0.70 to 0.95).

Adherence to study medication and aspirin

Temporary discontinuation of study medication (for more than 5 days): clopidogrel 46.2%; ASA 45.4%

Discontinuation due to revascularisation/surgical procedure: total for both groups = 84%

Permanent study medication discontinuation: clopidogrel 21.1%; ASA 18.8%

Percentage of patients taking aspirin in both group: 99% of patients whilst in hospital; 96% at 3 months; 94% at the final follow-up visit

	Bleeding complications		
	Clopidogrel	**ASA**	**RR (95% CI)**
Major bleeding	231/6259 (3.7%)	169/6303 (2.7%)	1.38 (1.13 to 1.67) $p = 0.001$
Necessitating transfusion of ≥ 2 units of blood	117/6259 (2.8%)	137/6303 (2.2%)	1.30 (1.04 to 1.62) $p = 0.02$
Life threatening	135/6259 (2.2%)	112/6303 (1.8%)	1.21 (0.95 to 1.56) $p = 0.13$
Fatal	11/6259 (0.2%)	15/6303 (0.2%)	
Causing 5 g/dl drop in haemoglobin level	58/6259 (0.9%)	57/6303 (0.9%)	
Requiring surgical intervention	45/6259 (0.7%)	43 /6303 (0.7%)	
Causing hemorrhagic stroke	7/6259 (0.1%)	5/6303 (0.1%)	
Requiring inotropic agents	34/6259 (0.1%)	34/6303 (0.5%)	
Necessitating transfusion of ≥ 4 units of blood	34/6259 (0.5%))	60/6303 (1.0%)	
Non-life threatening	96/6259 (1.5%)	57/6303 (0.9%)	1.70 (1.22 to 2.35) $p = 0.002$
Minor bleeding	322/6259 (8.5%)	153/6303 (2.4%)	2.12 (1.75 to 2.56) $p < 0.001$
Total with bleeding complications	533/6259 (8.5%)	317/6303 (5.0%)	1.69 (1.48 to 1.94) $p < 0.001$
Site of major bleeding			
GI	83/6259 (1.3%)	47/6303 (0.7%)	
Retroperiotoneal	8.6259 (0.1%)	5/6303 (0.1%)	
Urinary (haematuria)	4/6259 (0.1%)	5/6303 (0.1%)	
Arterial puncture site	36/6259 (0.6%)	22/6303 (0.3.%)	
Surgical site	56/6259 (0.9%)	53/6303 (0.8%)	
Other adverse events			
Patients with thrombocytopenia	26/6259 (0.4%)	28/6303 (0.4%)	
Patients with neutropenia	8/6259 (0.1%)	5/6303 (0.1%)	

Other adverse events

*(6) Data extracted from Sanofi-Sythelabo Ltd and Bristol-Myers Squibb: sponsors, submission to NICE

	Clopidogrel (n = 6259)	ASA (n = 6303)
Central and peripheral nervous system disorders:		
Any events (e.g. headache, dizziness, vertigo, paraesthesia)	7.8	7.8
GI disorders:[a]		
Any events (e.g. abnormal pain, dyspepsia, diarrhoea, nausea):[b]	11.7	12.5
Resulting in early permanent discontinuation	0.9	0.8
Clinically severe	0.8	0.9
Diarrhoea:		
Severe diarrhoea[b]	2.1	2.2
Peptic, gastric, duodenal ulcers	0.1	0.1
Hepatic and biliary disorders:		
Any events	1	0.8
Skin and appendage disorders:		
Any events[b]	4	3.5
Severe events[b]	0.3	0.1
Rash	1.3	1.1
Pruritus	0.5	0.5

[a] Including less frequently reported events: constipation, tooth disorder, vomiting, flatulence and gastritis
[b] Statistically significant differences between treatments ($p \leq 0.05$).

*(7) Major and life-threatening bleeding by various doses of aspirin

Major bleeding complications	Aspirin alone	Aspirin + clopidogrel	All patients
ASA ≤ 100 mg (%)	1.86	2.97	2.41
ASA 101–199 mg (%)	2.86	3.41	3.12
ASA ≥ 200 mg (%)	3.67	4.86	4.26
p-value for trend	<0.0001	<0.001	<0.0001
Adjusted[a] OR for 101–199 vs ≤ 100 mg	1.52 (1.00 to 2.31)	1.20 (0.84 to 1.73)	1.33 (1.01 to 1.74)
Adjusted[a] OR for ≥ 200 vs ≤ 100 mg	1.7 (1.22 to 2.59)	1.63 (1.19 to 2.23)	1.70 (1.33 to 2.16)
Life-threatening bleeding complications			
ASA ≤ 100 mg (%)	1.26	1.75	1.50
ASA 101–199 mg (%)	1.90	1.39	1.64
ASA ≥ 200 mg (%)	2.37	3.29	2.82
p-value for trend	0.004		<0.0001
Adjusted[a] OR for 101–199 vs ≤ 100 mg	1.48 (0.89 to 2.46)	0.0006	1.06 (0.74 to 1.52)
Adjusted[a] OR for ≥ 200 vs ≤ 100 mg	1.64 (1.04 to 2.59)	0.79 (0.47 to 1.32)	1.72 (1.27 to 2.32)

[a] Adjusted for gender, weight, hypertension, components of the TIMI risk score,1.64 (1.04 to 2.59) rates of angiography, PCI and CABG, and the use of NSAIDs, heparin, glycoproteinIIa/IIIa inhibitors, oral anticoagulanats, open-label ticlopdine, or clopidogrel at any time during the study period

*(7) Risk of major bleeding by aspirin dose in various patient subgroups

	≤ 100 mg, % (n)	101–199 mg, % (n)	≥ 200 mg, % (n)	p for trend
PCI alone	1.9 (997)	2.4 (508)	3.9 (1000)	0.0068
CABG	6.9 (829)	7.6 (514)	11.1 (728)	0.0030
No revascularisation	1.5 (3494)	2.2 (2987)	2.3 (2382)	0.019
Heparin	2.6 (4774)	3.2 (2909)	4.4 (3910)	<0.0001
No heparin	0.9 (546)	2.0 (200)	1.5 (200)	0.39
GP IIb/IIIa	5.4 (298)	1.7 (115)	5.1 (410)	0.96
No glycoprotein IIb/IIIa	2.2 (5022)	3.2 (2994)	4.2 (3700)	<0.0001

PCI-CURE

*(4) Study details	Inclusion criteria	Intervention details
Authors Mehta *et al.*, 2001[39] **Study design** Subgroup of patients undergoing PCI from CURE	Inclusion/exclusion criteria as for CURE trial	**Intervention 1** Clopidogrel + aspirin (ASA) 75 mg daily plus 75 mg daily ASA **Intervention 2** Aspirin + placebo 75–325 mg daily ASA + placebo **Further information** A loading dose of clopidogrel (300 mg orally) or matching placebo was administered immediately after randomisation. Patients were pretreated with aspirin and study drug for a median of 6 days before PCI during the initial hospital admission, and for a median of 10 days overall. After PCI, most patients (>80%) in both groups received open-label thienopyridine (either clopidogrel or ticlopidine) in combination with aspirin for 2–4 weeks (median 30 days; inter-quartile range 19–33), after which administration of the study medication was resumed until the end of follow-up 3–12 months after randomisation (mean 8 months)
***(4) Definition of primary outcome**	**Definition of secondary outcome**	**Definition of bleeding complications**
The primary outcome was the composite of CV death, MI or urgent target-vessel revascularisation within 30 days of PCI. All deaths were classified as CV (including deaths that were sudden, or unknown cause or secondary to complications of a cardiac procedure) unless there was documented evidence of a clear non-cardiovascular cause. MI was defined as the presence of at least two of the three following criteria: ischaemic symptoms; cardiac enzyme concentration at least three times the upper limit of normal within 48 hours of PCI and two times the upper limit of normal thereafter; or new ECG changes compatible with MI. Periprocedural increases in cardiac enzyme concentrations were not routinely screened for; MI was reported when it was clinically apparent. Urgent target-vessel revascularisation within 30 days of PCI was defined as either a second PCI or any coronary-artery bypass procedure done on a non-elective basis in the target vessel because of recurrent myocardial ischaemia	CV or MI from the time of PCI to the scheduled end of the trial was also assessed	Major bleeding was defined as bleeding that was significantly disabling, intraocular or requiring at least 2 units of blood. Major bleeding was subclassified as life threatening if it was fatal, if it led to a decrease in haemoglobin concentration of 50 g/l, if it caused significant hypotension requiring intravenous inotropes of surgical intervention, if it resulted in symptomatic intracranial haemorrhage or if it necessitated transfusion of 4 or more units of blood. Minor bleeding was defined as other bleeding that led to interruption of study medication

*(4) Baseline characteristics, day of PCI and use of open-label thienopyridine

	ASA (*n* = 1345)	Clopidogrel (*n* = 1313)
Patients' characteristics		
Mean age (SD) (years)	61.4 (10.9%)	61.6 (11.2%)
Women	405 (30.1%)	399 (30.3%)
Diabetes	255 (19.0%)	249 (19.0%)
Previous MI	349 (26.0%)	359 (27.3%)
Previous PCI	185 (13.8%)	176 (13.4%)
Previous CABG	175 (13.0%)	157 (12.0%)
Smokers	396 (29.5%)	406 (30.9%)
ST depression	571 (42.4%)	567 (43.2%)
ST elevation	59 (4.4%)	65 (5.1%)
Stent use	1092 (81.3%)	1080 (82.4%)
Median days (IQR) after randomisation on which PCI done		
All PCI	10 (5–25)	10 (5–30)
PCI during initial hospital stay	6 (4–10)	6 (3–10)
PCI after initial hospital stay	49 (24–106)	49 (23–89)
Open-label thienopyridine use		
Before PCI	329 (24.7%)	344 (26.4%)
Overall	1131 (84.1%)	1089 (82.9%)
Target vessels for PCI		
Left main	24 (1.8%)	23 (1.8%)
Proximal	351 (26.1%)	374 (28.5%)
Mid/distal	300 (22.3%)	308 (23.5%)
Left anterior descending, circumflex	393 (29.3%)	380 (29.0%)
Right coronary	440 (32.8%)	419 (31.9%)
Saphenous vein graft	32 (2.4%)	43 (3.3%)
Unfractionated heparin was used during the procedure in 2313 (87%) of patients and low-molecular-weight heparin in about 309 (12%).		

*(4) Outcome 1: clopidogrel versus ASA in first 30 days post-PCI	Outcome 2: clopidogrel versus ASA from PCI to end of follow-up	Outcome 3: clopidogrel versus ASA – overall results including events before and after PCI	Outcome 4: clopidogrel versus ASA – events before PCI
CV death, MI, urgent revascularision Clopidogrel: 59/1313 (event rate 4.5%) ASA: 86/1345 (event rate 6.4%) RR (95% CI) 0.70 (0.50 to 0.97), $p = 0.03$ CV death, MI Clopidogrel: 38/1313 (event rate 2.9%) ASA: 59/1345 (event rate 59/1345 (event rate 4.4%) RR (95% CI) 0.66 (0.44 to 0.99), $p = 0.04$ CV death Clopidogrel: 14/1313 (event rate 1.1%) ASA: 13/1345 (event rate 1.0%) RR (95% CI) 1.10 (0.52 to 2.35) MI Clopidogrel: 28/1313 (event rate 2.1%) ASA: 51/1345 (event rate 3.8%) RR (95% CI) 0.56 (0.35 to 0.89) Q-wave MI Clopidogrel: 11/1313 (event rate 0.8%) ASA: 32/1345 (2.4%) RR (95% CI) 0.35 (0.18 to 0.70) Urgent revascularisation Clopidogrel: 25/1313 (event rate 1.9%) ASA: 38/1345 (event rate 2.8%) RR (95% CI) 0.67 (0.41 to 1.11)	CV death, MI Clopidogrel: 79/1313 (event rate 6.0%) ASA: 108/1345 (event rate 8.0%) RR (95% CI) 0.75 (0.56 to 1.00), $p = 0.047$ CV death, MI, any revascularisation Clopidogrel: 240/1313 (event rate 18.3%) ASA: 292/1345 (event rate 21.7%) RR (95% CI) 0.83 (0.70 to 0.99) $p = 0.03$ CV death Clopidogrel: 32/1313 (event rate 2.4%) ASA: 31/1345 (event rate 2.3%) RR (95% CI) 1.07 (0.65 to 1.75) MI Clopidogrel: 59/1313 (event rate 4.5%) ASA: 85/1345 (event rate 6.4%) RR (95% CI) 0.71 (0.51 to 0.99) Q-wave MI Clopidogrel: 20/1313 (event rate 1.5%) ASA: 47/1345 (event rate 3.5%) RR (95% CI) 0.43 (0.26 to 0.73) Any revascularisation Clopidogrel: 186/1313 (event rate 14.2%) ASA: 230/1345 (event rate 17.1%) RR (95% CI) 0.82 (0.68 to 1.00)	CV death, MI Clopidogrel: 116/1313 (event rate 8.8%) ASA: 169/1345 (event rate 12.6%) RR (95% CI) 0.69 (0.54 to 0.87) $p = 0.002$	MI or RI Clopidogrel: 159/1313 (event rate 12.1%) ASA: 206/1345 (event rate 15.3%) RR (95% CI) 0.76 (0.62 to 0.93), $p = 0.008$ MI Clopidogrel: 47/1313 (event rate 3.6%) ASA: 68/1345 (event rate 5.1%) RR (95% CI) 0.68 (0.47 to 0.99), $p = 0.04$

*(4) Primary outcome (CV death, MI, urgent revascularisation) events prevented at various time points within 30 days of PCI (ITT analysis)

No. of days after PCI	ASA (*n* = 1345)	Clopidogrel (*n* = 1313)	Absolute risk (%)	RR (95% CI)
2	41 (3.0%)	32 (2.4%)	–0.60	0.80 (0.50 to 1.27)
7	59 (4.4%)	40 (3.0%)	–1.40	0.69 (0.46 to 1.03)
14	73 (5.4%)	48 (3.7%)	–1.70	0.67 (0.47 to 0.96)
30	86 (6.4%)	59 (4.5%)	–1.90	0.70 (0.50 to 0.97)

*(4) CC death or MI from randomisation to study end in key subgroups

	ASA	Clopidogrel	RR (95% CI)
Overall	169 (12.6%)	116 (8.8%)	0.69 (0.54 to 0.87)
Stent	128 (11.7%)	94 (8.7%)	0.73 (0.56 to 0.95)
No stent	41 (16.2%)	22 (9.4%)	0.56 (0.34 to 0.95)
Age ≤ 65 years	80 (9.8%)	47 (5.9%)	0.59 (0.41 to 0.84)
Age >65 years	89 (16.9%)	69 (13.4%)	0.79 (0.57 to 1.08)
Male	112 (11.9%)	72 (7.9%)	0.65 (0.48 to 0.87)
Female	57 (14.1%)	44 (11.0%)	0.77 (0.52 to 1.15)
Diabetes	42 (16.5%)	32 (12.9%)	0.77 (0.48 to 1.22)
No diabetes	127 (11.7%)	84 (7.9%)	0.66 (0.50 to 0.87)
PCI during initial hospital stay	109 (12.0%)	68 (8.3%)	0.68 (0.50 to 0.92)
PCI after initial hospital stay	60 (13.8%)	48 (9.8%)	0.70 (0.48 to 1.02)
Prior CABG	38 (21.7%)	15 (9.6%)	0.42 (0.23 to 0.76)
No prior CABG	131 (11.2%)	101 (8.7%)	0.77 (0.59 to 0.99)
PCI ≤ 72 hours of randomisation	37 (13.5%)	23 (8.5%)	0.62 (0.37 to 1.05)
PCI >72 hours of randomisation	132 (12.3%)	93 (8.9%)	0.71 (0.54 to 0.92)

*(4) Main outcomes adjusted for covariates that influence likelihood of undergoing PCI (propensity score)

Outcome	Adjusted RR (95% CI)[a]	*p*-Value
PCI to 30 days		
CV death, MI, urgent revascularisation	0.65 (0.46 to 0.92)	0.01
CV death, MI	0.60 (0.39 to 0.92)	0.02
PCI to end of follow-up – CV death, MI	0.72 (0.53 to 0.96)	0.03

To minimise PCI selection bias, a propensity-score model using logistic regression to identify baseline factors (including treatment allocation) that was predictive of having a PCI in a randomly selected sample of half the patients from the CURE database was developed and then validated in the remaining half. The validated propensity score was included in Cox's regression model that compared the effect of clopidogrel and ASA in patients undergoing PCI. This allowed the effect of treatment allocation on clinical outcomes in patients undergoing PCI, after adjustment for selection bias to be assessed.
[a] Clopidrogrel versus ASA.

*(4) Bleeding after PCI

	ASA (*n* = 1345)	Clopidogrel (*n* = 1313)	RR (95% CI)	*p*-Value
From PCI to 30 days				
Major	19 (1.4%)	21 (1.6%)	1.13 (0.61 to 2.10)	0.69
Life-threatening	10 (0.7%)	9 (0.7%)	0.92 (0.38 to 2.26)	0.86
Non-life-threatening	9 (0.7%)	12 (0.9%)	1.37 (0.58 to 3.23)	0.48
Minor	10 (0.7%)	13 (1.0%)	1.33 (0.59 to 3.03)	0.49
Blood transfusion of 2 or more units	15 (1.1%)	14 (1.1%)	0.96 (0.46 to 1.97)	0.9
From PCI to follow-up				
Major	33 (2.5%)	36 (2.7%)	1.12 (0.70 to 1.78)	0.64
Life-threatening	18 (1.3%)	16 (1.2%)	0.91 (0.47 to 1.78)	0.78
Non-life-threatening	15 (1.1%)	20 (1.5%)	1.37 (0.70 to 2.66)	0.36
Minor	28 (2.1%)	46 (3.5%)	1.68 (1.06 to 2.68)	0.03
Blood transfusion of 2 or more units	27 (2.0%)	28 (2.1%)	1.06 (0.63 to 1.79)	0.82

Subgroup analysis: CABG patients

*(5) Outcomes by CABG in initial hospitalisation

	ASA	Clopidogrel	RR	95% CI
CABG during initial hospitalisation:				
No. of patients	528	485		
CV death/MI/stroke (%)	16.7	13.2	0.78	0.57 to 1.08
No CABG:				
No. of patients	5775	5774		
CV death/MI/stroke (%)	11	8.9	0.8	0.71 to 0.89

*(5) Bleeding outcomes of patients undergoing CABG surgery after randomisation in CURE

	ASA (%)	Clopidogrel (%)	RR	95% CI
No. of patients	1061	1011	0.83	
TIMI major	3.1	2.6	1.26	0.50 to 1.37
CURE major	6.6	8.3	1.26	0.93 to 1.71
Life-threatening	5	6.4	1.29	0.90 to 1.83
Other major	1.6	1.9	1.17	0.61 to 2.24
GUSTO severe	3.6	4.5	1.24	0.81 to 1.90

Appendix 6

Details of systematic reviews

Antithrombotic Trialists' Collaboration

Author (year)
Baigent *et al.*, 2002[26] (Antithrombotic Trialists' Collaboration)

Objective
To determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events.

Inclusion/exclusion criteria
Study designs
RCTs that used a randomisation method that precluded prior knowledge of the next treatment to be allocated and that were 'unconfounded' (i.e. contained two randomised groups that differed only with respect to the antiplatelet comparison of interest) were included. Trials that used an alternation or odd/even date method of randomisation were excluded. Trials of oral antiplatelet regimens were included if they had assessed more than one day of treatment, but trials of parenteral antiplatelet regimens of any duration were included.

Participants
Participants at high risk (>3% per year) of vascular events because of evidence of pre-existing disease (previous occlusive event or predisposing condition). Trials among patients with dementia or occluded retinal veins were excluded.

Intervention
Trials that compared an antiplatelet regimen with a control or one antiplatelet regime with another were included. An antiplatelet drug was defined as one whose primary effect on the vascular system is to inhibit platelet adhesion, platelet aggregation or both.

Outcomes measure
The primary outcome measure was 'serious vascular event' (i.e. non-fatal MI, non-fatal stroke or death from a vascular cause and also including any death from an unknown cause). An event was considered non-fatal only if the patient survived to the end of the scheduled follow-up period or died of a definitely non-vascular cause. Deaths were divided into those with a vascular cause (defined as cardiac, CV, venous thromboembolic, haemorrhagic, other vascular or unknown cause) and non-vascular. Strokes were subdivided into intracranical haemorrhages (including intracerebral, subdural, subarachnoid and extradural haemorrhages) and strokes of ischaemic or unknown aetiology; TIAs were not included. Major extracranial bleeds were defined as those occurring outside the cranial cavity that were considered by the trialist to be serious (in general this meant that the patient required admission to hospital or blood transfusion). If during the trial a patient experienced more than one type of non-fatal outcome, both events were recorded but the patient contributed only once to the composite outcome of serious vascular events. If during the trial a patient experienced more than one non-fatal event of the same type or more than one pathological type of stroke, only the first was recorded.

Results
Number of included studies
289 RCTs (overall total $n = 78,956$); 197 RCTs compared antiplatelet therapy versus control, 195 with data on vascular events) and 90 compared different antiplatelet regimens, 9 with data on vascular events).

Participant baseline characteristics
Previous stroke/TIA ($n = 18,270$); Acute stroke ($n = 40,821$); stable angina ($n = 2920$); atrial fibrillation ($n = 2770$); PAD ($n = 9214$); diabetes ($n = 4961$).

Serious vascular events (195 trials of antiplatelet treatment versus control; $n = 135,640$): 7705 (10.7%) serious vascular events were recorded among 71,912 patients allocated antiplatelet therapy versus an adjusted total of 9502 (13.2%) among 72,139 allocated control ($p < 0.0001$). Division of the trials into five subcategories of patients, indicated evidence of differences in the proportional reductions in serious vascular events among them (χ^2 for heterogeneity between categories = 2.14; df = 4; $p = 0.0003$). A smaller effect was observed in patients treated during acute stroke (χ^2 for heterogeneity between acute stroke and other categories = 18.0; df = 1; $p = 0.00002$). The overall net benefit was highly significant both among patients with acute stroke ($p = 0.0009$) and separately among patients in each of the other categories ($p < 0.0001$).

Non-fatal MI (2774 non-fatal MIs in 150 trials and 48,428 deaths attributed to CHD): overall, antiplatelet treatment produced a 34% (3%) proportional reduction in non-fatal MI ($p < 0.001$) and a 26% (2%) reduction in non-fatal MI or death from CHD ($p < 0.001$).

continued

Stroke (3522 non-fatal strokes in 158 trials and 1424 fatal strokes): antiplatelet therapy produced a 25% (3%) proportional reduction in non-fatal stroke ($p < 0.0001$) with no significant heterogeneity between the proportional reductions in the five high risk categories of patients ($\chi^2 = 5.8$, df = 4; NS). Among the trials that recorded at least one haemorrhagic stroke, subdivision of all strokes (fatal or not) according to aetiology indicated that there was a proportional increase in fatal or non-fatal haemorrhagic stroke of 22% (95% CI: 3 to 35%) $p < 0.01$ and a proportional decrease in fatal or non-fatal ischaemic stroke of 30% (95% CI: 4% to 35%) $p < 0.0001$. There was no significant heterogeneity between the proportional effects on each of these types of stroke in the five high-risk categories studied ($\chi^2 = 2.5$ and 3.3, respectively; both NS).

Vascular and non-vascular deaths (9605 deaths attributed to vascular (or unknown) causes in 193 trials and 1414 deaths attributed to non-vascular causes): antiplatelet therapy produced a significant 15% (2%) proportional reduction in vascular deaths ($p < 0.0001$). There was no significant heterogeneity between the proportional reductions in each of the five high-risk categories of patient ($\chi^2 = 7.7$, df = 4; NS). There was no excess of non-vascular deaths (785/71,656) (1.1%) antiplatelet vs (872/71,876) (1.2%) adjusted control; OR 0.92 (95% CI: 0.82 to 1.03; NS).

Pulmonary embolism: 32 trials had recorded at least one non-fatal pulmonary embolism event and among these antiplatelet therapy significantly reduced the risk of fatal or non-fatal pulmonary embolism (150/32,777 (0.46%) antiplatelet vs 200/32,758 [0.61% adjusted control; OR = 25% (10%); $p < 0.01$].

Major extracranial bleeds (787 major extracranial bleeds in 60 trials): 159 (20%) of the bleeds caused death. Overall, the proportional increase in risk of a major extracranial bleed with antiplatelet therapy was about half (OR = 1.6; 95% CI: 1.4 to 1.8) with no significant difference between the proportional increases observed in each of the five high-risk categories of patient ($\chi^2 = 2.6$, df = 4; NS). The proportional increase in fatal bleeds was not significantly different from that for non-fatal bleeds, only the excess of non-fatal bleeds was significant. There were too few fatal and non-fatal bleeds in any particular category for the ARs to be estimated directly.

Effects in different categories of patients

Patients with a history of MI: in 18,788 patients with a history of MI in 12 trials, allocation to a mean duration of 27 months of antiplatelet therapy resulted in 36 (SE 5) fewer vascular events per 1000 patients. The benefit reflects large and highly significant reductions in non-fatal reinfarction [18 (3) fewer per 1000; $p < 0.0001$] and vascular death [14 (4) fewer 1000; $p = 0.0006$) in addition to a small but still significant reduction in non-fatal stroke.

Patients with acute AMI: data on 19,288 patients with suspected AMI in 15 trials showed that allocation to a mean duration of 1 month of antiplatelet therapy resulted in 38 (5) fewer serious vascular events per 1000 treated patients. This reflects a large and highly significant reduction in non-fatal reinfarction [13 (2) fewer per 1000; $p < 0.0001$] and in vascular death [23 (4) fewer per 1000; $p < 0.0001$], together with a small but significant reduction in non-fatal stroke [2 (1) fewer per 1000; $p = 0.02$].

Patients with a history of stroke or TIA: the results from 18,270 patients in 21 trials allocated to a mean duration of 29 months of antiplatelet therapy resulted in 36 (6) fewer serious vascular events per 1000 patients. This reflects a large and highly significant reduction in non-fatal stroke [25 (5) fewer per 1000; $p < 0.0001$] along with a smaller but still significant reduction in non-fatal MI [6 (2) fewer per 1000; p = 0.0009].

Patients with acute ischaemic stroke: the results from 40,821 patients in 7 trials allocated to a mean duration of 3 weeks of antiplatelet therapy produced an 11% (3%) proportional reduction in vascular events. This results in an absolute risk reduction of 9 (3) fewer serious vascular events per 1000 patients, a significant reduction in non-fatal stroke [4 (2) fewer per 1000 patients; $p = 0.003$] and a reduction of 5 (2) fewer vascular deaths per 1000 patients.

For 40,428 patients in 4 of the trials, data were separated into outcomes considered to be due to haemorrhage and those that were due to ischaemic (or unknown) causes. Antiplatelet therapy produced an absolute excess of 1.9 (SE 1.0) haemorrhagic strokes per 1000 patients, and an absolute reduction of 6.9 (1.4) fewer ischaemic strokes per 1000, yielding an overall reduction in the risk of any further stroke (including those of unknown cause) of 5.4 (1.9) per 1000.

Patients with CAD (unstable angina, CABG, coronary angioplasty, stable angina and heart failure): among 15,828 patients in 55 trials there was a significant 37% (5%) proportional reduction in serious vascular events ($p < 0.0001$). There were independently significant benefits among patients with unstable angina [46% (7%) reduction, $p < 0.0001$], those undergoing coronary angioplasty [53% (14%) reduction, $p < 0.0002$] and those with stable angina [33% (9%) reduction, $p = 0.0004$]. The proportional RR among patients who had had a CABG was smaller [4% (14%)].

Patients at high risk of embolism (non-rheumatic atrial fibrillation, cardiac valve disease and cardiac valve surgery): among 5162 patients at high-risk of embolism in 14 trials, there was a significant 26% (7%) proportional reduction in serious vascular events ($p = 0.0003$). Overall, among 2770 patients with atrial fibrillation in 4 trials there was a proportional reduction of 24% (9%) in serious vascular events or 23% (10%) if one small trial of indobufen vs placebo that included some patients without atrial fibrillation is excluded.

Patients with PAD (intermittent claudication, peripheral grafting and peripheral angioplasty): among 9214 patients with PAD in 42 trials there was a proportional reduction of 23% (8%) in serious vascular events ($p = 0.004$). Similar benefits among patients with intermittent claudication, those having peripheral grafting and those undergoing peripheral angioplasty were observed [heterogeneity test ($\chi^2 = 3.8$, df = 3; NS)].

continued

Effects of different doses of aspirin: among 3570 patients in 3 trials directly comparing aspirin ≥ 75 mg daily vs aspirin <75 mg daily there was no significant difference between the different aspirin regimens. However, aspirin doses of < 75 mg have been less widely assessed than doses of 75–150 mg daily, so there remains uncertainty about whether such low doses are as effective as daily doses of ≥ 75 mg. Among the trials of higher daily doses of aspirin vs no aspirin, no particular range of aspirin dose was preferable for the prevention of serious vascular events. The proportional reduction in vascular events was 19% (3%) with 500–1500 mg daily, 26% (3%) with 160–325 mg daily and 32% (6%) with 75–150 mg daily. However, daily doses <75 mg seemed to have a smaller effect [proportional reduction 13% (8%); $\chi^2 = 7.7$, df = 3; $p = 0.05$].

The results showed no evidence that aspirin doses of ≥ 1000 mg daily were preferable for the prevention of serious vascular events among patients at high risk of stroke.

In trials comparing aspirin with control, the proportional increase in the risk of a major extracranial bleed was similar with all daily aspirin doses <325 mg, OR = 1.7 (95% CI: 0.8 to 3.3) for <75 mg; OR = 1.5 (95% CI: 1.0 to 2.3) for 75–150 mg; and OR = 1.4 (95% CI: 1.0 to 2.0) for 160–325 mg. Two trials that compared 75–325 mg aspirin daily with <75 mg daily also found no significant difference in major extracranial bleeds [39/1576 (2.5%) with 75–325 mg vs 28/2555 (1.8%) with <75 mg; NS].

Authors' conclusions

Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an AMI or ischaemic stroke, unstable or stable angina, previous MI, stroke or cerebral ischaemia, PAD or atrial fibrillation. Low-dose aspirin (75–150 mg daily) is an effective antiplatelet regimen for long-term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be required. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, but more research into this strategy is needed.

df, degrees of freedom; SE, standard error.

Systematic reviews/meta-analysis investigating the safety of aspirin

Review details	Inclusion/exclusion criteria	Results
Author (year) Derry and Loke, 2000[49] **Objective** To assess the incidence of GI haemorrhage associated with long-term aspirin therapy and to determine the effect of dose reduction and formulation on the incidence of haemorrhage	**Study designs** Full journal publications of RCTs of aspirin used as an antiplatelet agent with >50 patients in each arm were included. Trials that used an inadequate method of randomisation such as date of birth were excluded. Abstracts, review articles, case reports, clinical observations and unpublished data were not included. Studies designed to assess the effects of aspirin in special groups were also excluded. **Participants** Indications for aspirin extended from primary prevention in 'healthy' individuals to secondary prophylaxis after stroke. In all trials patients were excluded if they had a history of peptic ulcer, previous GI haemorrhage or any other contraindication to aspirin. **Intervention** Oral aspirin alone versus placebo or no treatment Treatment duration was for a minimum of 12 months (mean 28 months). Crossover studies and those in which aspirin was used in conjunction with other antiplatelet agents or anticoagulants were excluded. Trials that compared aspirin at different doses or with other antiplatelet agents or anticoagulants without a placebo or 'no treatment' control arm were also excluded. **Outcomes measure** Only trials that provided numerical data on all GI haemorrhages in both the treatment and the control groups were included. Where specific terms were used to describe bleeding complications, data on patients with 'haematemesis' or 'melaena' or with both of these, but not with 'proctorrhagia', were accepted. Data from trials that reported only on selected categories of gastrointestinal haemorrhage were excluded. **Participant baseline characteristics** Specific indications for aspirin: TIA or stroke: 5540 (ASA 2729; placebo 2711) Hypertension 9790 (ASA 9399; placebo 9391) Atrial fibrillation: 672 (ASA 336; placebo 336) CV risk factors: 2540 (ASA 1268; placebo 1272) Unstable angina: 796 (ASA 399; placebo 397) Primary prevention: 22471 (ASA 11237; placebo 11234) MI: 8821 (ASA 4236; placebo 4585) TIA: 1473 (ASA 2083; placebo 1265) CABG: 237 (ASA 127; placebo 110) Breast cancer: 186 (ASA 93; placebo 93) PVD 516 (ASA 223; placebo 293) Stroke 466 (ASA 253; placebo 213) Male: 74% Female: 26% Participants were predominantly middle-aged (no age definition or range provided)	**Number of included studies** 24 RCTs (overall total $n = 65,987$) Aspirin $n = 33\,622$; control $n = 32,365$ 8 RCTS assessed aspirin 50–162.5 mg/day ($n = 49,927$) and 16 RCTs assessed aspirin 162.5–1500 mg/day ($n = 16,060$) GI haemorrhage occurred in 2.47% of the patients taking aspirin compared with 1.42% of those taking placebo. The pooled OR for GI haemorrhage with aspirin was 1.68 (95% CI: 1.51 to 1.88), $p < 0.0001$, and the NNT based on an average of 28 months of aspirin was 106 (95% CI: 82 to 140). Aspirin dose 50–162.5 mg/day: GI haemorrhage occurred in 2.30% of those taking aspirin compared with 1.45% taking placebo. The pooled OR for GI haemorrhage within the aspirin group compared with placebo was 1.59 (95% CI: 1.40 to 1.81), $p < 0.0001$. The results of a meta-regression to test for a linear relationship between daily dose of aspirin and risk of GI haemorrhage gave a pooled OR of 1.015 (95% CI: 0.984 to 1.047) per 100-mg dose reduction. This gave an estimated RR in the incidence of GI haemorrhage of 1.5% per 100-mg reduction of dose ($p = 0.3$). Modified release formulations of aspirin: five trials ($n = 4298$) specifically stated that a modified release formulation of aspirin was used with daily doses of 75–1500 mg. The OR for GI haemorrhage in these five trials was 1.93 (95% CI: 1.15 to 3.23). **Authors' conclusions** Long-term therapy with aspirin is associated with a significant increase in the incidence of GI haemorrhage. No evidence exists that reducing the dose or using modified release formulations would reduce the incidence of GI haemorrhage.

continued

Review details	Inclusion/exclusion criteria	Results
Author (year) Weisman and Graham, 2002[45] **Objective** To compare the benefit and GI risk of aspirin use for the secondary prevention of thromboembolic events	**Study designs** Randomised, placebo controlled interventions with an aspirin-only arm were included. Trials were excluded if aspirin was (1) administered for less than 3 months; (2) prescribed short-term for thrombophylaxis in procedures such as angioplasty or CABG; (3) used for non-prevention indications such as pain, headache or arthritis; (4) co-administered with another agent; or (5) used to prevent CV events in otherwise healthy individuals (primary prevention). **Participants** Participants who had experienced a previous stroke, MI or TIA or who had a history of angina were included. **Intervention** Low-dose aspirin (daily dose 50–325 mg). **Outcome measure** Outcome measures consisted of MI, stroke, vascular death, vascular event (i.e. any stroke, MI or other vascular events defined as possibly or definitely of cardiac, cerebral, embolic, haemorrhagic or unknown cause) and all-cause mortality. In addition, data on serious adverse events related to bleeding were included. Bleeding events were abstracted regardless of their severity. Subjective tolerability was not evaluated **Participant baseline characteristics** Specific indications for aspirin: Previous MI: 2427 Previous stroke or TIA: 1757 Weighted mean age: 59.5 years Weighted mean % male: 83.8 Weighted mean % female: 16.2	**Number of included studies** 6 RCTs (overall total $n = 6300$) Aspirin $n = 3127$; placebo $n = 3173$ 1 RCT assessed aspirin 50 mg/day ($n = 427$), 2 assessed aspirin 75 mg/day ($n = 1748$), 2 assessed aspirin 300 mg/day ($n = 2859$) and 1 assessed aspirin 324 mg/day ($n = 1266$) **Efficacy** All-cause mortality: in the aspirin and placebo groups there were 241 and 291 deaths, respectively. The common RR across studies was 18%. There was no significant heterogeneity observed between studies on this outcome measure ($p = 0.5$). Total vascular events: the RR for total vascular events was 0.7 (95% CI: 0.6 to 0.8), $p < 0.001$ (RR = 30%). However, significant heterogeneity was observed between the studies ($p < 0.001$) MI: the RR for MI was 0.7 (95% CI: 0.6 to 0.8); $p < 0.001$ (RR = 30%). However, significant heterogeneity was observed between the studies on this outcome measure ($p < 0.001$) Stroke: the RR of stroke was 0.8 (95% CI: 1.4 to 4.7); $p = 0.07$ (RR = 20%). No significant heterogeneity between studies was observed for this outcome measure ($p > 0.99$). **Adverse events** GI tract bleeding: there were 58 reports of GI bleeding across the six studies (41 in the aspirin groups, 17 in the placebo groups). Only about half of the cases of GI bleeding were deemed severe enough to require withdrawal. There were no reported deaths related to GI bleeding and bleeding led to almost no permanent morbidity. Only 1 report (UK-TIA) demonstrated a statistically significant increased risk of GI bleeding as a result of aspirin intake. Overall, the RR for GI tract bleeding was 2.5 (95% CI: 1.4 to 4.7); $p = 0.001$. This gave an RR of –150. AR increases ranged from less than 0% to 2.0%, mean = 1.4% (52-month follow-up). No significant heterogeneity between studies on this outcome measure was observed ($p = 0.5$). Cerebral haemorrhage: only 2/6 of the trials reported cases of hemorrhagic stroke (UK-TIA and SALT) and in both trials CV ischaemic events were the qualifying events for study inclusion. However, the findings of these 2 studies indicate an excess risk of haemorrhagic stroke in those allocated to aspirin (18 versus 6). To evaluate the relative benefit and risk of aspirin in the secondary prevention of MI and stroke, the benefits observed in reducing the risk of death and GI bleeding were compared. The results showed that all-cause mortality occurred in 9.2% of the placebo group and 7.7% of the aspirin group. Conversely, 1.6% of the aspirin group had a GI haemorrhage compared with 0.6% in the control group. Based on the differences between the rates of the aspirin and placebo treated patients, it was determined that 1.5 deaths could be prevented for every non-fatal GI bleed attributed to the use of aspirin. **Authors' conclusions** Aspirin use for the secondary prevention of thromboembolic events has a favourable benefit-to-risk profile and should be encouraged in those at high risk.

continued

Review details	Inclusion/exclusion criteria	Results
Author (year) Stalnikowicz-Darvasi, 1995[46] **Objective** To assess the risk of low-dose aspirin induced GI bleeding in the prevention of thromboembolic events	**Study designs** Placebo-controlled studies were eligible for inclusion. No further details on whether the trials were randomised were presented in the paper. Abstracts, letters to the editor and case series were excluded. **Participants** Seven of the nine studies were conducted among patients with established CV or cerebrovascular conditions and two studies used participants without clinically apparent cerebrovascular disease. Four studies included only male patients and in all other studies there was a preponderance of men. The mean age of the patients was between 55 and 75 years. Most of the studies stated that patients with a history of peptic ulcer disease were excluded. **Intervention** Aspirin 75–325 mg. In one study, 325 mg aspirin every other day was given and in another study buffered aspirin was used. Follow-up varied between 3 and 72 months. **Outcome measure** Studies that reported GI effects of treatment were eligible for inclusion. Detection of GI bleeding by means of a questionnaire or occult blood in stools was applied in three studies and changes in blood hematocrit levels during the study were analysed in three. **Participant baseline characteristics** Reported use of aspirin: Primary prevention, 2 studies (n = 2207) TIA, 2 studies (n = 2980) Secondary preventions, 2 studies (n = 1654) CABG, 2 studies (n = 297) Prevention of emboli in atrial fibrillation, 1 study (n = 627)	**Number of included studies** 9 controlled clinical trials (overall total n = 29,513) Aspirin n = 14,732 Placebo n = 14,781 4 studies assessed aspirin 75 mg/day (n = 4259), 1 assessed aspirin 100 mg/day (n = 60), 1 assessed aspirin 300 mg/day (n = 1620), 2 assessed aspirin 324 mg/day (n = 1503) and 1 assessed aspirin 325 mg/day (n = 22,071) 485 patients (3.3%) and 322 patients (2.2%) bled from the GI tract in the low-dose aspirin and placebo groups, respectively ($p < 0.001$). The overall OR for GI bleeding was 1.52 (95% CI: 1.32 to 1.75). The monthly probability of GI bleeding per 1000 patients treated with aspirin ranged between 0 and 2.1. The number of episodes of major bleeding was 28 (5.8%) and 10 (3.1%) among the aspirin- and placebo-treated patients, respectively (not significant). There was no correlation between the probability of bleeding and the length of treatment. There was one fatality from GI bleeding in the low-dose aspirin group, which was related to drug administration, and none in the placebo group. **Author's conclusions** Low-dose aspirin carries a certain risk of GI bleeding, but in general it is not life-threatening.

continued

Review details	Inclusion/exclusion criteria	Results
Author (year) Garcia Rodriguez *et al.*,2001[47] **Objective** To assess the RR of serious upper GI complications associated with aspirin exposure in general and with specific aspirin doses and formulations in particular	**Study designs** Case–control and cohort studies that reported valid RR estimates or adequate data for the RR comparing aspirin users with non-users were included. **Participants** No specific inclusion criteria related to participants were reported. Three of the 17 included studies restricted their sample to elderly populations. Studies often had the following exclusion criteria: cancer (n = 10), oesophageal varices (n = 10), Mallory-Weiss disease (n = 10), alcoholism (n = 7), chronic liver disease (n = 7) or/and coagulophathies (n = 6). **Intervention** Aspirin 75–>600 mg/day (specific doses not reported). These were plain, buffered or coated. Aspirin exposure was defined as use during the last week in nine studies, use in the last month in three studies and use reaching the index date or prescriptions that would cover the index date in the other five studies. **Outcome measure** Serious upper GI complications (UGIC) defined as bleeding, perforation or other serious upper GI events resulting in hospitalisation or visit to specialist. Studies in which the outcome was identification of GI bleeding with endoscopy rather than the presence of serious GI complications, or where the combined outcome of upper and lower GI bleeding was reported were excluded. **Exclusion criteria** Studies in which there were methodological concerns regarding both the design (i.e. patients with ulcer history excluded only from cases) and the analysis (i.e. unclear interpretation of discordant pairs for McNemar's test) were excluded. **Participant baseline characteristics** No participant baseline characteristics were reported	**Number of included studies** Seventeen studies (overall total n = 67,722) cases n = 121,40; controls n = 55,582 Three cohort studies (n = 1159) Fourteen case-control studies (n = 66,563) of which three were nested within a well-defined cohort (n = 46,487) The overall RR of UGIC associated with aspirin use was 2.6 (95% CI: 2.4 to 2.7). However, the individual RR estimates were heterogeneous ($p < 0.01$) and varied from 1.4 to 11.2. For cohort studies and nested case–control studies the RR associated with aspirin use was 2.2 (95% CI: 2.1 to 2.4). For non-nested case–control studies the RR was 3.1 (95% CI: 2.8 to 3.3). The summary RR was 2.6 (95% CI: 2.3 to 2.9) for plain, 5.3 (95% CI: 3.0 to 9.2) for buffered and 2.4 (95% CI: 1.9 to 2.9) for enteric-coated aspirin formulations. The original studies found a dose–response relationship between UGIC and aspirin, although the risk was still elevated for doses lower or up to 300 mg/day. **Authors' conclusions** Aspirin was associated with UGIC even when used at low doses or in buffered or enteric-coated formulations. The latter findings may be partially explained by channelling of susceptible patients to these formulations.

continued

Review details	Inclusion/exclusion criteria	Results
Author (year) He *et al.*, 1998[48] **Objective** To estimate the risk of hemorrhagic stroke associated with aspirin treatment	**Study designs** Trials that had (1) a random allocation procedure, (2) a concurrent control group, (3) no differences other than the intervention between the treatment and control group and (4) intervention duration of at least 1 month were included. Trials that had a non-randomised treatment allocation were excluded. **Participants** No specific inclusion criteria related to participants were reported. Two of the 16 trials included healthy participants only, whereas the others all included participants with pre-existing disease. The mean age of participants was 59 years; 86% were male, 99% were white and 24% had hypertension (range 10–64%). Participants with acute complete stroke were excluded. **Intervention** Oral aspirin alone versus placebo or no treatment. Treatment duration was for a minimum of 1 month. The specific aspirin doses are not reported. Trials which compared (1) aspirin treatment with treatment using other antiplatelet or anticoagulant agents, (2) higher versus lower dosages of aspirin or (3) aspirin treatment combined with other antiplatelet or anticoagulent agent compared with a control or (4) used different anticoagulation therapies in the treatment and control groups were excluded. **Outcomes measure** Only trials that provided information on the occurrence of stroke subtype during follow-up were included. The primary outcome was the incidence of stroke subtype and the secondary outcome measures the incidence of total stroke, MI, CV mortality and all-cause mortality. **Participant baseline characteristics** Specific indications for aspirin: TIA: 2135 (ASA 1069; placebo 1066) MI: 19,069 (ASA 9419; placebo 9650) Cerebral ischemia: 402 (ASA 198; placebo 204) Cerebral infarction: 505 (ASA 253; placebo 252) Healthy: 27,210 (ASA 14,466; placebo 11,034; control 1710) Atrial fibrillation: 1792 (ASA 888; placebo 904) TIA or minor ischaemic stroke: 1360 (ASA 676; placebo 684) Stable angina: 2035 (ASA 1009; placebo 1026) Atrial fibrillation and TIA or minor ischaemic stroke: 782 (ASA 404; placebo 378) Carotid stenosis: 372 (ASA 188; placebo 184)	**Number of included studies** 16 RCTs (overall total $n = 55,462$) Aspirin $n = 33,622$; control $n = 32,365$ Five trials were conducted in patients with a history of TIA or minor ischaemic stroke, 2 in patients with a previous ischaemic stroke, 2 in patients with atrial fibrillation, 2 in patients with a history of MI, 2 in patients with stable angina, 1 in patients with carotid stenosis and 1 in patients with atrial fibrillation and a TIA or minor ischaemic stroke. Overall, aspirin use was associated with a 15% proportional reduction in all-cause mortality, RR = 0.85 (95% CI: 0.80 to 0.90; $p < 0.001$) and a 16% reduction in cardiovascular mortality, RR = 0.84 (95% CI: 0.79 to 0.90; $p < 0.001$). Aspirin therapy was also associated with a 32% proportional reduction in total MI, RR = 0.68 (95% CI: 0.62 to 0.74); $p < 0.001$) and a 22% reduction in fatal MI, RR = 0.78 (95% CI: 0.68 to 0.90; $p < 0.001$). Aspirin treatment was also associated with a 12% proportional reduction in total stroke, RR = 0.88 (95% CI: 0.76 to 1.02; $p = 0.08$) but not in fatal stroke, RR = 1.07 (95% CI: 0.85 to 1.35; $p = 0.60$). 108 haemorrhagic strokes occurred in 13/16 trials. In the remaining 3 trials no cases of haemorrhagic stroke were reported. In 11/13 trials reporting hemorrhagic stroke, aspirin treatment was associated with an increased AR of haemorrhagic stroke. However, none of the ARs reached the level of statistical significance. The RR of hemorrhagic stroke was also increased in the 11 trials, varying from 1.08 to 4.09. There was no significant heterogeneity in AR or RR among these studies ($p = 0.99$). **Effect on stroke subtype** Treatment with aspirin was associated with an increase of 12 (95% CI: 5 to 20) haemorrhagic strokes per 10,000 persons and a reduction of 39 (95% CI: 17 to 61) ischaemic strokes per 10,000 persons. Regarding RR, aspirin use was associated with an 84% increase in the risk of hemorrhagic stroke, RR = 1.84 (95% CI: 1.24 to 2.74; $p < 0.001$). In contrast, aspirin use was associated with an 18% decrease in the risk of ischaemic stroke, RR = 0.82 (95% CI: 0.73 to 0.92). The NNT to prevent 1 event was 73 for total MI, 278 for fatal MI and 256 for ischaemic stroke. The NNT to cause 1 event was 833 for haemorrhagic stroke. ARs of hemorrhagic stroke did not vary significantly by type of trial participant or characteristics of the study design. **Authors' conclusions** Aspirin therapy increases the risk of haemorrhagic stroke. However, the overall benefit of aspirin use on MI and ischaemic stroke may outweigh its adverse effects on risk of haemorrhagic stroke in most populations.

PVD, peripheral vascular disease.

Quality assessment of the systematic reviews

Author (year)	Quality assessment
Antithrombotic Trialists' Collaboration, 2002[26]	1: Good 2: Good 3: Good 4: Fair 5: Good
Derry and Loke, 2000[49]	1: Good 2: Fair/good 3: Good 4: Fair 5: Good
Weisman and Graham, 2002[45]	1: Good 2: Fair/good 3: NA 4: Fair 5: Fair
Stalnikowicz-Darvasi, 1995[46]	1: Fair 2: Poor/fair 3: Fair 4: Fair 5: Fair
Garcia Rodriguez, *et al.*, 2001[47]	1: Good 2: Fair 3: Fair 4: Fair 5: Fair/good
He *et al.*, 1998[48]	1: Good 2: Fair 3: NA 4: Fair 5: Fair

Reviews assessed according to the DARE criteria: refer to quality assessment in Appendix 4. NA, not applicable.

Appendix 7

Details of quality assessment for economic studies

All items will be graded as either ✓ (item adequately addressed), × (item not adequately addressed), ? (unclear or not enough information), NA (not applicable) or NS (not stated).

Review of Gaspoz *et al.*[54] Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease

Study question		Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	×	Can be assumed to be US third party payer
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	×	Dipyridamole preparation not included as alternative treatment strategies
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	×	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	×	Did discussed unconfirmed dose–response effect of aspirin
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	?	Resource use data not presented
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	×	Secondary source for utility unclear

continued

Study question		Comments
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	?	Based on previously used model so some parameters may be available from previous sources
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	×	Only costs discounted
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	×	3% for costs and 0% for health benefits.
Allowance for uncertainty		
Stochastic analysis of patient-level data	×	
27. Details of statistical tests and CIs are given for stochastic data	NA	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	NA	
30. Are all appropriate input parameters included with uncertainty?	NA	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	NA	
Deterministic analysis	✓	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	Univariate
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	×	US based and not relevant in UK setting. Medicare costs included

Review of submission by Sanofi Synthelabo Ltd and Bristol-Myers Squibb

Study question		Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	×	Dipyridamole preparations not included as alternative treatment strategies
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	NA	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	?	Resource use data not presented
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	×	Secondary source for utility unclear
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals etc.)	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	✓	

continued

Study question		Comments
Allowance for uncertainty		
Stochastic analysis of patient-level data	✓	
27. Details of statistical tests and CIs are given for stochastic data	✓	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	✓	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	NA	
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	×	Model makes use of some inappropriate distributions such as log-normal for probabilities and triangular for costs
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
Deterministic analysis	✓	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	Univariate
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Appendix 8

Resources use and costs for the long-term model based on data from the NHAR[57]

Hospital stays	IHD[a]			MI[b]			Post-MI[c]		
	No. of patients	Average total LOS/ no. of visits	SD	No. of patients	Average total LOS/ no. of visits	SD	No. of patients	Average total LOS/ no. of visits	SD
Cardiac									
Day-case	1								
Non-coronary care unit	76	8.87	9.58	5	10.80	7.82	5	5.95	6.05
Inc. coronary care unit	17	6.82	6.82	10	8.80	6.44	1	2.00	–
Outpatient visit	115	3.44	2.50	21	3.43	3.06	8	2.88	1.73
Non-cardiac									
Day-case	1								
Non-coronary care unit	67	10.39	17.81	7	12.00	13.60	3	7.00	7.94
Inc. coronary care unit									
Outpatient visit	138	4.86	4.91	15	3.27	3.45	9	2.33	1.32
Interventions									
Angiography	20			5					
PTCA	2			3					
CABG	7			1					
Average health state cost (SD)[a]		£1421 (£944)			£3966 (£1722)			£1587 (£1091)	

[a] 252 patients, 113,222 patient days follow-up
[b] 27 patients, 7248 patient days follow-up
[c] 15 patients, 2993 patient days follow-up

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine

Dr Jeffrey Aronson
Reader in Clinical Pharmacology, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London

Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University

Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen

Professor Stuart Logan, Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter & Plymouth

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Professor Mark Sculpher, Professor of Health Economics, Centre for Health Economics, Institute for Research in the Social Services, University of York

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Birmingham

Ms Kate Thomas, Deputy Director, Medical Care Research Unit, University of Sheffield

Professor Simon G Thompson, Director, MRC Biostatistics Unit, Institute of Public Health, Cambridge

Ms Sue Ziebland, Senior Research Fellow, Cancer Research UK, University of Oxford

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre

Professor Imti Choonara, Professor in Child Health, University of Nottingham, Derbyshire Children's Hospital

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Stan Kaye, Professor of Medical Oncology, Consultant in Medical Oncology/Drug Development, The Royal Marsden Hospital

Ms Barbara Meredith, Project Manager Clinical Guidelines, Patient Involvement Unit, NICE

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Dr Aileen Clarke,
Reader in Health Services Research, Public Health & Policy Research Unit,
Barts & the London School of Medicine & Dentistry,
Institute of Community Health Sciences, Queen Mary,
University of London

Mr Matthew William Cooke,
Senior Clinical Lecturer and Honorary Consultant,
Emergency Department,
University of Warwick, Coventry & Warwickshire NHS Trust,
Division of Health in the Community, Centre for Primary Health Care Studies, Coventry

Dr Carl E Counsell, Senior Lecturer in Neurology,
University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Professor Paul Gregg,
Professor of Orthopaedic Surgical Science, Department of Orthopaedic Surgery,
South Tees Hospital NHS Trust

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint

Ms Maryann L. Hardy,
Lecturer,
Division of Radiography,
University of Bradford

Professor Alan Horwich,
Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Dr Simon de Lusignan,
Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences,
St George's Hospital Medical School, London

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Professor James Neilson,
Professor of Obstetrics and Gynaecology, Dept of Obstetrics and Gynaecology,
University of Liverpool,
Liverpool Women's Hospital

Dr John C Pounsford,
Consultant Physician, North Bristol NHS Trust

Dr Vimal Sharma,
Consultant Psychiatrist & Hon Snr Lecturer,
Mental Health Resource Centre,
Victoria Central Hospital,
Wirrall

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh,
Professor of Public Health,
University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Mary Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry, University Mental Health Group, Royal South Hants Hospital, Southampton

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278