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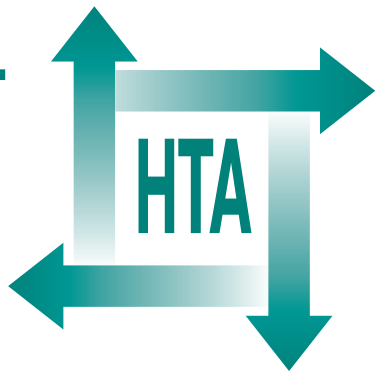

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Abstract

Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation

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

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Objectives: To examine the clinical effectiveness and cost-effectiveness of two alternative antiplatelet agents, clopidogrel and modified-release (MR)-dipyridamole, relative to prophylactic doses of aspirin for the secondary prevention of occlusive vascular events.
Data sources: Electronic databases.
Review methods: A total of 2906 titles and abstracts were rigorously screened and 441 studies were assessed in detail. Two RCTs were identified. For the assessment of cost-effectiveness, eight reviews were identified. The results were presented in structured tables and as a narrative summary. No additional clinical effectiveness data were presented in either of two company submissions. All economic evaluations (including accompanying models) included in the company submissions were assessed. Following this analysis, if the existing models (company or published) were not sufficient, a *de novo* model or modified versions of the models were developed.
Results: In the CAPRIE trial the point estimate for the primary outcome, i.e. ischaemic stroke, myocardial infarction (MI) or vascular death, favoured clopidogrel over aspirin, but the boundaries of the confidence intervals raise the possibility that clopidogrel is not more beneficial than aspirin. In terms of the secondary outcomes reported, there was a non-significant trend in favour of clopidogrel over aspirin but the boundaries of the confidence intervals on the relative risks all crossed unity. There was no difference in the number of patients ever reporting any bleeding disorder in the clopidogrel group compared with the aspirin group. The incidences of rash and diarrhoea were statistically significantly higher in the clopidogrel group than the aspirin group. Patients in the aspirin group had a higher incidence of indigestion/nausea/vomiting than patients in the clopidogrel group. Haematological adverse events were rare in both the clopidogrel and aspirin groups. No cases of thrombotic thrombocytopenic purpura were reported in either group. Treatment with MR-dipyridamole alone did not significantly reduce the risk of any of the primary outcomes reported in ESPS-2 compared with treatment with aspirin. ASA–MR-dipyridamole was significantly more effective than aspirin alone in patients with stroke or transient ischaemic attacks (TIAs) at reducing the outcome of stroke and marginally more effective at reducing stroke and/or death. Treatment with ASA–MR-dipyridamole did not statistically significantly reduce the risk of death compared to treatment with aspirin. The number of strokes was statistically significantly reduced in the ASA–MR-dipyridamole group compared with the MR-dipyridamole group. In terms of the other primary outcomes, stroke and/or death and death, the results favoured treatment with ASA–MR-dipyridamole but the findings were not statistically significant. There was no difference in the number of bleeding complications between the ASA–MR-dipyridamole and aspirin groups. The incidence of bleeding complications was significantly lower in the MR-dipyridamole treatment group. More patients in the MR-dipyridamole treatment groups experienced headaches compared to patients receiving treatment with aspirin alone. The York model assessed the cost-effectiveness of differing combinations of treatment strategies in four patient

subgroups, under a number of different scenarios. The results of the model were sensitive to the assumptions made in the alternative scenarios, in particular the impact of therapy on non-vascular deaths.

Conclusions: Clopidogrel was marginally more effective than aspirin at reducing the risk of ischaemic stroke, MI or vascular death in patients with atherosclerotic vascular disease, however, it did not statistically significantly reduce the risk of vascular death or death from any cause compared with aspirin. There was no statistically significant difference in the number of bleeding complications experienced in the clopidogrel and aspirin groups. MR-dipyridamole in combination with aspirin was superior to aspirin alone at reducing the risk of stroke and marginally more effective at reducing the risk of stroke and/or death. Compared with treatment with MR-dipyridamole alone, MR-dipyridamole in combination with aspirin significantly reduced the risk of stroke. Treatment with MR-dipyridamole in combination with aspirin did not statistically significantly reduce the risk of death compared with aspirin. Compared with treatment with MR-dipyridamole alone, bleeding complications were statistically significantly higher in patients treated with aspirin and MR-dipyridamole in combination with aspirin. Due to the assumptions that have to be made, no conclusions could be drawn about the relative effectiveness of MR-dipyridamole, alone or in combination with aspirin, and clopidogrel from the adjusted indirect comparison. The following would apply for a cost of up to £20,000–40,000 per additional quality-adjusted life-year. For the stroke and TIA subgroups, ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration as long as all patients were not left disabled by their initial (qualifying) stroke. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke. In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy. Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario. For the MI and peripheral arterial disease subgroups, clopidogrel would be considered cost-effective for a treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered. It is suggested that the combination of clopidogrel and aspirin should be evaluated for the secondary prevention of occlusive vascular events. Also randomised, direct comparisons of clopidogrel and MR-dipyridamole in combination with aspirin are required to inform the treatment of patients with a history of stroke and TIA, plus trials that compare treatment with clopidogrel and MR-dipyridamole for the secondary prevention of vascular events in patients who demonstrate a genuine intolerance to aspirin.

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 the intervention is beneficial.

Acute coronary syndrome (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 or a drug.

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; includes percutaneous transluminal angioplasty (PTCA).

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 Fat deposited in the wall of medium- and larger-sized arteries, causing 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, high levels of cholesterol in the blood and cigarette smoking are the major established risk factors for atherosclerosis.

Atherothrombosis 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'.

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.

continued

Glossary *continued*

Cerebrovascular Pertaining to the blood vessels of the brain.

Clopidogrel A thienopyridine, structurally related to ticlopidine and an inhibitor of platelet aggregation.

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 MI, stroke or vascular death.

Confidence interval (CI) A measure of precision of a 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 patients' 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, this often leads 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 fairly 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, marker of damage to heart muscles, which becomes raised in the serum.

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.

Dipyridamole Inhibitor of platelet aggregation, also available in combination with aspirin (Persantin)

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

Embolus A clot (thrombus) that has been dislodged and carried through the circulation.

External validity The ability to generalise the results from an 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 confidence intervals (typically 95% but may be 99%) of the effect of each trial.

Factorial trial A clinical trial with a factorial design enables two (and occasionally more) interventions to be evaluated separately, in combination and against a control. The most

continued

Glossary *continued*

commonly used approach is the 2 × 2 factorial design whereby patients may be randomised to one of four treatment options. The analysis of such trials rests on the assumption that no statistical interaction exists between the interventions (i.e. the effect of one intervention does not depend on the administration of the one of the other interventions).

GI bleeding Any bleeding that may occur along the course of the gastrointestinal (GI) tract.

Haematoma The vomiting of blood.

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. Small haemorrhages are classified according to size as petechiae (very small), purpura (up to 1 cm) and ecchymoses (larger). The massive accumulation of blood within a tissue is called a haematoma.

Haemorrhagic stroke Stroke due to bleeding in the brain.

Heterogeneity Heterogeneity means that there is between-study variation. If heterogeneity exists, the pooled effect size in a meta-analysis has no meaning, as the presence of heterogeneity indicates that there is more than one true effect size in the studies being combined.

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

Infarction Death of tissue following interruption of the blood supply.

Intention-to-treat analysis method A method of data analysis in which all patients are analysed in the group to which they were assigned at randomisation, regardless of treatment adherence.

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

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

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

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) See also 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 A type of stroke that is caused by blockage in a cerebral blood vessel.

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

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

Myocardial infarction (MI) An infarction caused by obstruction of circulation to a region of the heart; results from permanent damage to an area of the heart muscle. Also called a heart attack.

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

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

Occlusive vascular event An event caused by the blockage of an artery, such as myocardial infarction, 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 cutaneous angioplasty, other angioplasty and implantation of intracoronary stents.

continued

Glossary *continued*

Percutaneous revascularisation The surgical restoration of blood supply (e.g. by a procedure, through a skin incision into an artery).

Percutaneous transluminal cutaneous angioplasty (PTCA) Dilation of a coronary vessel by means of a balloon catheter inserted through the skin and through the lumen of the vessel to the site of the narrowing, where the balloon is inflated to flatten plaque against the arterial wall.

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

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).

Quality-adjusted life-years (QALYs) An index of survival that is weighted or adjusted by a patient's quality of life during the survival period. QALYs are calculated by multiplying the number of life-years by an appropriate utility or preference score.

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.

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) An alternative way of expressing relative risk (RR). It is calculated as 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).

Stable angina Term used for angina (pectoris) that is relatively predictable and the intensity and frequency of which remains similar over long periods of time.

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

Stent An artificial structure inserted into a coronary artery following percutaneous transluminal cutaneous angioplasty to support the vessel wall and reduce the risk of reocclusion.

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 by a series of events, the most important of which involves the local

continued

Glossary *continued*

action of plasmin within the substance of the thrombus. Intracoronary thrombolysis refers to the lysis of clots by thrombolytic agents introduced into the coronary arteries, used in therapy of myocardial infarction.

Thrombus An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causes vascular obstruction at the point of its formation. Some authorities thus differentiate thrombus from simple coagulation or clot formation.

Ticlopidine An inhibitor of platelet aggregation; a thienopyridine.

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.

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

Vascular disease Any disease of the circulatory system.

List of abbreviations

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ADP	adenosine diphosphate
AMI	acute myocardial infarction
AR	absolute risk
ARR	absolute risk reduction
ASA	acetylsalicylic acid (aspirin)
ATT	Antithrombotic Trialists' Collaboration
BNF	British National Formulary
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CEAC	cost-effectiveness acceptability curve
cGMP	cyclic guanosine monophosphate
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase myocardial band fraction
COX	cyclooxygenase
CVD	cerebrovascular disease
DARE	Database of Reviews of Abstracts of Effects
DM	diabetes mellitus
DOD	Department of Defense
DP	dipyridamole
DRG	diagnosis-related group
ECG	electrocardiogram
ECS	Edinburgh Claudication Study
EQ	EuroQoL
ESPS-2	Second European Stroke Prevention Study
GI	gastrointestinal
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
LDH	lactate dehydrogenase
LDL	low-density lipoprotein

continued

List of abbreviations *continued*

LSM	least-squares mean
LYG	life-year gained
MI	myocardial infarction
MIMS	Monthly Index of Medical Specialties
MR	modified-release
NHAR	Nottingham Heart Attack Registry
NICE	National Institute for Clinical Excellence
NSF	National Service Framework
NSTEMI	non-ST-segment elevation myocardial infarction
OCSP	Oxfordshire Community Stroke Project
OR	odds ratio
OVE	other vascular event
PAD	peripheral arterial disease
PASBA	Patient Administration Systems and Biostatistics Activity database (maintained by the US Department of Defense)
PCI	percutaneous coronary intervention
PVD	peripheral vascular disease
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
RS	rating scale
SG	standard gamble
SLSR	South London Stroke Register
SSBMS	Sanofi-Synthelabo Ltd/Bristol-Myers Squib
TASS	Ticlopidine Aspirin Stroke Study
TIA	transient ischaemic attack
TTO	time trade-off
TTP	thrombotic thrombocytopenic purpura
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

It is widely accepted that atherothrombosis is the most important cause of occlusive vascular events. The clinical manifestations of atherothrombosis include transient ischaemic attack (TIA), ischaemic stroke, unstable angina, myocardial infarction (MI) and intermittent claudication. The importance of long-term secondary prevention in patients at high risk of recurrent vascular events is clear and aspirin and other oral antiplatelet agents have been shown to be protective in such patients. This review examined the clinical effectiveness and cost-effectiveness of two alternative antiplatelet agents, clopidogrel and modified-release (MR)-dipyridamole, relative to prophylactic doses of aspirin for the secondary prevention of occlusive vascular events.

Methods

Search strategy

Eleven databases were searched for randomised clinical trials (RCTs) and reviews for the assessment of the clinical effectiveness and cost-effectiveness of clopidogrel and MR-dipyridamole. Additional searches were conducted in five databases for systematic reviews of side effects associated with aspirin treatment. A further MEDLINE search was carried out to identify economic costs related to heart disease in the UK.

Inclusion/exclusion criteria

Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full paper of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Disagreements were resolved through discussion. For the assessment of clinical effectiveness, RCTs that compared clopidogrel or dipyridamole alone, or in combination with aspirin, to aspirin were included. For the assessment of cost-effectiveness, a broader range of studies were considered. For the evaluation of adverse events associated with aspirin, only systematic reviews were included.

Data extraction and quality assessment

Data from included studies were extracted by one reviewer and independently checked for accuracy by a second reviewer. Individual studies were assessed for quality by one reviewer and independently checked by a second for accuracy.

Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study of clinical effectiveness were presented in structured tables and as a narrative summary. For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables. For analyses based on patient-level data, the validity of the studies was assessed for the source of resource use and effectiveness data, the valuation methods used to cost the resource use and value patient benefits, the methods of analysis and generalisability of results. For analyses based on decision models, the critical appraisal was based on a range of questions.

Handling the company submission

No additional clinical effectiveness data were presented in either of the two company submissions. All economic evaluations (including accompanying models) included in the company submission were assessed. Following this analysis, if the existing models (company or published) were not sufficient, modified versions of the models were developed.

Results

A total of 2906 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness and 441 studies were ordered as full papers and assessed in detail. Two RCTs were identified. The CAPRIE trial investigated clopidogrel compared with aspirin for the secondary prevention of ischaemic events in patients with MI, ischaemic stroke or peripheral arterial disease (PAD), and ESPS-2 investigated MR-dipyridamole alone and in combination with aspirin compared with aspirin alone and placebo for the secondary prevention of stroke in patients with prior stroke or transient ischaemic attack. For the assessment of the cost-effectiveness of clopidogrel and MR-dipyridamole, eight cost-effectiveness reviews were identified.

A total of 5449 titles and abstracts were screened following the searches for adverse events associated with aspirin and 147 articles were ordered as full papers and assessed in detail. Five systematic reviews that primarily examined adverse events associated with long-term aspirin use were identified.

Clinical effectiveness

Clopidogrel

One RCT, the CAPRIE trial, was identified that investigated the use of clopidogrel for the secondary prevention of occlusive vascular events. In addition, 15 papers reporting on additional aspects of the CAPRIE trial were identified.

The point estimate for the primary outcome (ischaemic stroke, MI or vascular death) favoured clopidogrel over aspirin, but the boundaries of the confidence intervals raise the possibility that clopidogrel is not more beneficial than aspirin. In terms of the secondary outcomes reported, there was a non-significant trend in favour of clopidogrel over aspirin but the boundaries of the confidence intervals on the relative risks all crossed unity.

There was no difference in the number of patients ever reporting any bleeding disorder in the clopidogrel group compared with the aspirin group. The incidences of rash and diarrhoea were statistically significantly higher in the clopidogrel group than the aspirin group. Patients in the aspirin group had a higher incidence of indigestion/nausea/vomiting than patients in the clopidogrel group. Haematological adverse events were rare in both the clopidogrel and aspirin groups. No cases of thrombotic thrombocytopenic purpura were reported in either group.

MR-dipyridamole

One RCT, ESPS-2, was identified which investigated the use of MR-dipyridamole and acetylsalicylic acid (ASA)–MR-dipyridamole for the secondary prevention of occlusive vascular events. In addition, four papers reporting on additional aspects of the trial were identified.

Treatment with MR-dipyridamole alone did not significantly reduce the risk of any of the primary outcomes reported in ESPS-2 compared with treatment with aspirin. ASA–MR-dipyridamole was significantly more effective than aspirin alone in patients with stroke or TIAs at reducing the outcome of stroke and marginally more effective at reducing stroke and/or death. Treatment with ASA–MR-dipyridamole did not statistically significantly reduce the risk of death compared to treatment with aspirin. The number of strokes was statistically significantly reduced in the ASA–MR-dipyridamole group compared with the MR-dipyridamole group. In terms of the other primary outcomes, stroke and/or death and death, the results favoured treatment with ASA–MR-dipyridamole but the findings were not statistically significant.

There was no difference in the number of bleeding complications between the ASA–MR-dipyridamole and aspirin groups. The incidence of bleeding complications (including severe and fatal bleeds) was significantly lower in the MR-dipyridamole treatment group. More patients in the MR-dipyridamole treatment groups experienced headaches compared to patients receiving treatment with aspirin alone.

Cost-effectiveness

The York model assessed the cost-effectiveness of differing combinations of treatment strategies in four patient subgroups, under a number of different scenarios. The results of the model were sensitive to the assumptions made in the alternative scenarios, in particular the impact of therapy on non-vascular deaths.

Summary of cost-effectiveness data in stroke patients

The results from the extended model developed by the University of York TAR team were sensitive to the scenario under consideration. The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional quality-adjusted life-year (QALY). ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration as long as all patients were not left disabled by their initial (qualifying) stroke. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke. In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy. Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.

Summary of cost-effectiveness data in TIA patients

The following conclusions are possible from the York model assuming that the NHS is willing to

pay up to £20,000–40,000 per additional QALY. ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered. Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.

Summary of cost-effectiveness data in MI patients

The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY. Clopidogrel would be considered cost-effective for treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

Summary of cost-effectiveness data in PAD patients

The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY. Clopidogrel would be considered cost-effective for treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

Conclusions

Clinical effectiveness

- Clopidogrel was marginally more effective than aspirin at reducing the risk of ischaemic stroke, MI or vascular death in patients with atherosclerotic vascular disease. That is, the point estimate favoured treatment with clopidogrel but the lower boundary of the 95% confidence intervals suggests that the size of this benefit may be very small.
- Treatment with clopidogrel did not statistically significantly reduce the risk of vascular death or death from any cause compared with aspirin.
- There was no statistically significant difference in the number of bleeding complications experienced in the clopidogrel and aspirin groups.
- Compared with aspirin alone, treatment with MR-dipyridamole alone did not significantly reduce the risk of any of the primary outcomes reported in ESPS-2.
- MR-dipyridamole in combination with aspirin was superior to aspirin alone at reducing the risk of stroke and marginally more effective at reducing the risk of stroke and/or death. Compared with treatment with MR-dipyridamole alone, MR-dipyridamole in combination with aspirin significantly reduced the risk of stroke.
- Treatment with MR-dipyridamole in combination with aspirin did not statistically significantly reduce the risk of death compared with aspirin.
- Compared with treatment with MR-dipyridamole alone, bleeding complications were statistically significantly higher in patients treated with aspirin and MR-dipyridamole in combination with aspirin.
- Due to the assumptions that have to be made, no conclusions could be drawn about the relative effectiveness of MR-dipyridamole, alone or in combination with aspirin, and clopidogrel from the adjusted indirect comparison.

Cost-effectiveness

- The following conclusions are possible assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY.
- For the stroke and TIA subgroups, ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration as long as all patients were not left disabled by their initial (qualifying) stroke. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke. In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy. Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.
- For the MI and PAD subgroups, clopidogrel would be considered cost-effective for a treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

Research recommendations

- The combination of clopidogrel and aspirin should be evaluated for the secondary prevention of occlusive vascular events. Two ongoing studies should provide evidence in this area.

- Randomised, direct comparisons of clopidogrel and MR-dipyridamole in combination with aspirin are required to inform the treatment of patients with a history of stroke and TIA.
- Trials are required which compare treatment with clopidogrel and MR-dipyridamole for the secondary prevention of vascular events in patients who demonstrate a genuine intolerance to aspirin.

Chapter 1

Aim of the review

The most widely prescribed antiplatelet agent is aspirin, which in secondary prevention reduces the risk of myocardial infarction (MI), stroke and vascular death by about 25%. This review examined the clinical effectiveness and cost-effectiveness of two alternative antiplatelet agents, clopidogrel and modified-release (MR)-dipyridamole, relative to prophylactic doses of aspirin for the secondary prevention of occlusive vascular events.

Chapter 2
Background

Description of underlying health problem

Coronary heart disease (CHD) is a term that refers to a narrowing or blockage of the coronary arteries due to the deposition of fat and atherosclerotic plaque development within the artery walls. Collectively, CHD is the leading single cause of death in the UK and one of the most important causes of years of life lost before the age of 65 years.[1,2] In 1998, CHD accounted for over 110,000 deaths in England, including 41,000 individuals under the age of 75 years.[3]

Approximately 10% of people in the UK have diseases of the heart and circulatory system, and this increases with age, affecting around 27% of men and women aged 65–74 years and around 30% of those ≥75 years.[4] Across all ages, the prevalence of ischaemic heart disease or stroke combined in England, is 9% in men and 6% in women. Approximately 30% of individuals aged 55–74 years in the general population are affected by peripheral arterial disease (PAD).[5]

There are approximately 237,000 MIs per year in England and Wales. The annual incidence rate for men aged 30–69 years is around 600 per 100,000 population and for women the equivalent rate is 200 per 100,000 population.[4] Estimates from the National Service Frameworks (NSFs) indicate that there are around 110,000 new cases of stroke in England and Wales each year. The economic burden from CHD in terms of direct healthcare costs and indirect costs (including informal care costs and loss of productivity) is high. Overall, the total annual cost of all CHD-related burdens equated to over £7 billion in 1999, the highest of all diseases in the UK for which comparable analyses have been undertaken.[6]

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. However, it is apparent that geographically there is a disparity across the regions in the prevalence of treated CHD and stroke.[7] The age-standardised rate for treated CHD in both males and females is highest in the North West, Yorkshire and Wales and lowest in the South East. The pattern for the age-standardised rate for treated stroke also shows a regional variation, with the rates being highest in the North West and Yorkshire and again lowest in the South East.

Significance in terms of ill-health

Data from surveys that have examined morbidity most reliably suggest that whereas mortality from CHD is rapidly falling, morbidity is not and may even be rising.[1] In older age groups, morbidity associated with CHD has risen by over one-third in the past decade.[4] Within Europe, it has been estimated that CHD is the leading single cause of disability, accounting for around 10% of disability-adjusted life-years. The figures for England and Wales are expected to be even greater owing to the higher incidence of CHD relative to the rest of Europe.[8] In particular, stroke has a major impact on people's lives and is the leading cause of disability in the UK and other Western countries.

Current service provision

In terms of CHD overall, there were around 378,000 episodes of care (finished consultant episodes, ordinary admissions and daycases combined) for CHD in NHS hospitals in 2000–01. This represents 5% of all inpatient cases in men and 2% in women. The numbers treated for stroke were considerably lower at around 145,000, equating to 1% in each gender.[9] The number of 'days in hospital' more accurately represents the morbidity of each disease subgroup. The figures from 2000–01 indicate there were in total over 1 million days spent in hospital due to CHD (over 0.5 million of these being due to MI) and over 2 million being due to stroke.

The NSF for Coronary Heart Disease was introduced in 2000 to inform service provision and practice in this area.[3] The only antiplatelet drug recommended by the NSF is low-dose aspirin, which accounts for 91% of all prescribed antiplatelet drugs.[10] National Institute for Clinical

Excellence (NICE) clinical guidelines issued in 2001 also recommend that patients who have survived an MI be offered long-term treatment with an antiplatelet drug, namely aspirin.[11] The National Clinical Guidelines for Stroke[12] recommend that all patients who have suffered a stroke should be taking aspirin. However, despite these recommendations, aspirin is still perceived to be under-prescribed, although over-the-counter purchase may well account for a proportion of this apparent shortfall. Two alternative antiplatelet agents, clopidogrel and MR-dipyridamole, are licensed for the secondary prevention of occlusive vascular events. Clopidogrel, a thienopyridine antiplatelet drug, is unrelated to aspirin and therefore can be used in patients who show a genuine intolerance to aspirin. Dipyridamole (DP), an adenosine reuptake inhibitor and phosphodiesterase inhibitor, has both antiplatelet and vasodilating properties. MR-dipyridamole is licensed for the secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in combination with aspirin.

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 to almost £16 million.[10] 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 (~4% of prescription items) but accounts for 57% of antiplatelet drug costs, and MR-dipyridamole accounts for ~4% of prescriptions.[10] There is large variation 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.[10]

Description of clopidogrel and MR-dipyridamole

It is widely accepted that atherothrombosis is the most important cause of occlusive vascular events. The clinical manifestations of atherothrombosis include transient ischaemic attack (TIA), ischaemic stroke, unstable angina, MI and intermittent claudication.[13] The importance of long-term secondary prevention in patients at high risk of recurrent vascular events is clear. For example, 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.[14] Aspirin and other oral antiplatelet agents have been shown to be protective in patients at increased risks of ischaemic vascular events.[15] 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.[16] This is demonstrated in individuals with asymptomatic PAD who are twice as likely as normal subjects to suffer from concomitant coronary artery disease (CAD).[5]

Atherothrombosis involves the formation of a platelet-rich thrombus at the site of a disrupted atherosclerotic plaque that leads to local occlusion or distal embolism. Atherosclerotic plaque formation occurs as a result of damage to vascular endothelium. Possible causes of damage include elevated and modified low-density lipoproteins (LDLs); free radicals caused by cigarette smoking, hypertension and diabetes mellitus (DM); genetic alterations; elevated plasma homocysteine concentrations; infectious microorganisms; and combinations of these and other factors.[17] When a plaque ruptures, platelets circulating in the blood are exposed to a variety of thrombogenic factors. *Figure 1* shows the various pathways that mediate thrombus formation. 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, and DP, which may be administered alone or in combination with aspirin. These antiplatelet agents target one or more of the pathways that mediate thrombus formation (also shown in *Figure 1*).

Aspirin inhibits platelet aggregation by inactivating the enzyme cyclooxygenase (COX), 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. DP is thought to inhibit adenosine (a potent inhibitor of platelet activation and aggregation) uptake into blood and vascular cells.[18] DP may also inhibit the breakdown of cyclic guanosine monophosphate (cGMP).

Clopidogrel

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

Clopidogrel (Plavix®, Bristol-Myers Squib, 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.

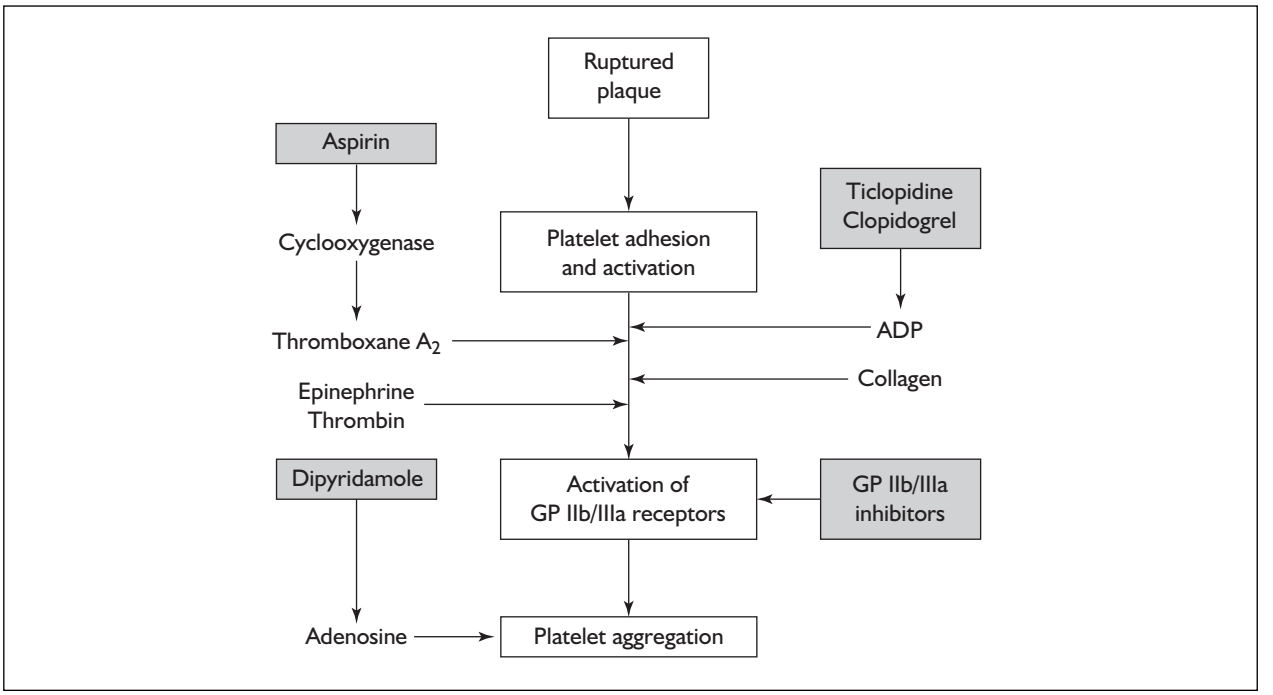

FIGURE 1 *Simplified flow diagram showing thrombus formation. GP, glycoprotein.*

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), ischaemic stroke (from 7 days until <6 months) or established PAD.

Contraindications

- 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

- 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, 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 bleedings. 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 (GI) 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, in 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 ischaemic stroke (<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.

MR-dipyridamole

This section of the report summarises the product characteristics for MR-dipyridamole available from the electronic Medicine Compendium (www.emc.vhn.net).

MR-dipyridamole is available in two preparations:

- Asasantin Retard® (Boehringer Ingelheim Ltd) is available in capsules containing DP 200 mg and aspirin 25 mg.
- Persantin Retard® (Boehringer Ingelheim Ltd) is available in hard gelatine capsules containing DP 200 mg.

The recommended dose of MR-dipyridamole is 200 mg twice daily. Capsules should usually be taken once in the morning and once in the evening, preferably with meals. Capsules should be swallowed whole, without chewing. DP is indicated alone, or in combination with aspirin, for the secondary prevention of transient ischaemic attacks and ischaemic stroke.

Contraindications

Asasantin Retard

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

Persantin Retard

- Hypersensitivity to any component of the product.

Special warnings and precautions for use

Asasantin Retard

- Among other properties, DP acts as a vasodilator. It should be used with caution in patients with severe CAD, including unstable angina and/or recent MI, left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated heart failure).
- Patients being treated with regular oral doses of Asasantin Retard should not receive additional intravenous DP. If pharmacological stress testing with intravenous DP for CAD is considered necessary, then Asasantin Retard should be discontinued 24 hours prior to testing.
- Asasantin Retard should be used with caution in patients with coagulation disorders.
- In patients with myasthenia gravis, readjustment of therapy may be necessary after changes in DP dosage.
- Due to the aspirin component, Asasantin Retard should be used with caution in patients with asthma, allergic rhinitis, nasal polyps, chronic or recurring gastric or duodenal complaints, impaired renal (avoid if severe) or hepatic function or glucose-6-phosphate dehydrogenase deficiency. In addition, caution is advised in patients hypersensitive to other non-steroidal anti-inflammatory drugs.
- Asasantin Retard is not indicated for use in children and young people <16 years of age. There is a risk of Reye's syndrome when children take aspirin.
- The dose of aspirin in Asasantin Retard has not been studied in secondary prevention of MI.

Persantin Retard

- Among other properties, DP acts as a potent vasodilator. It should therefore be used with caution in patients with severe CAD including unstable angina and/or recent MI, left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated heart failure).
- Patients treated with regular oral doses of Persantin should not receive additional intravenous Persantin. If pharmacological stress testing with intravenous Persantin for CAD is considered necessary, then oral Persantin should be discontinued 24 hours prior to testing.
- In patients with myasthenia gravis, readjustment of therapy may be necessary after changes in DP dosage.
- Persantin should be used with caution in patients with coagulation disorders.

Chapter 3
Methods

Search strategy

The following databases were searched for trials and reviews of clopidogrel and MR-dipyridamole:

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

The results were entered into an Endnote Library and deduplicated.

The full details of the search strategies are given in Appendix 1.

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

- Cochrane Databases of Systematic Reviews (CD-ROM, 2003/02)
- EMBASE (Ovid, 1980–2003/07)
- HEED (CD-ROM, 2003/09)
- MEDLINE (Ovid, 1966–2003/08)
- NHSEED (http://www.york.ac.uk/inst.crd), searched 10/09/03.

The full strategies are presented in Appendix 1. A further MEDLINE search was carried out to identify economic costs related to heart disease in the UK. The strategy is also presented in Appendix 1.

Inclusion and exclusion criteria

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

Interventions

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

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

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

Participants

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

Study design

- Randomised controlled trials (RCTs) that compared clopidogrel alone or DP, alone or in combination with aspirin, with aspirin were

included in the assessment of clinical effectiveness.
- For the evaluation of adverse events associated with clopidogrel and DP 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/or meta-analyses that primarily examined adverse events associated with long-term aspirin use were included.
- For the assessment of cost-effectiveness, a broader range of studies were considered, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and consider both costs and consequences (including cost-effectiveness, cost–utility and cost–benefit analyses) were included.

Outcomes

Data on the following outcomes were included:

- MI
- stroke (divided into ischaemic and haemorrhagic where possible)
- other vascular events (OVEs) (including unstable angina)
- vascular death
- death
- bleeding complications (major and minor as defined by trial investigators)
- other adverse events (nausea, vomiting, diarrhoea, constipation, gastric and duodenal ulceration, headache, dizziness, vertigo, paraesthesia, rash, pruritis, urticaria, hepatic and biliary disorders, neutropenia, TTP, thrombocytopenia, myalgia, hypotension, hot flushes and tachycardia, severe bronchospasm and angioedema)
- 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 into an Access database and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus and if necessary a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Quality assessment strategy

The quality of the individual studies was assessed by one reviewer, and independently checked for agreement by a second, into an Access database. Disagreements were resolved through consensus and if necessary a third reviewer was consulted.

The quality of the clinical effectiveness studies was assessed according to criteria based on NHS CRD Report No. 4.[19] The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond and colleagues.[20] This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by NICE. The quality of the systematic reviews was assessed according to the guidelines for the Database of Abstracts of Reviews of Effects (DARE) criteria. This information was tabulated and summarised within the text of the report. Full details of the quality assessment strategy are reported in Appendix 5.

Methods of analysis/synthesis

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

For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality were presented in structured tables. This covered studies based on patient-level data and decision models and included any studies provided by manufacturers.

For analyses based on patient-level data, the validity of the studies was assessed for the source of resource use and effectiveness data, the valuation methods used to cost the resource use and value patient benefits, the methods of analysis and generalisability of results. Studies were classified as follows:

1. prospective resource use and patient outcome data
2. mixed prospective and retrospective data
3. retrospective data.

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

1. structure of model
2. time horizon
3. details of key input parameters and their sources
4. methods of analysis (e.g. handling uncertainty).

Handling the company submissions

No data additional to the publications identified from the literature searches were presented in the company submissions in terms of clinical effectiveness.

All economic evaluations (including accompanying models) included in the company submissions 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.

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. The process of study selection is shown in *Figure 2*.

For the assessment of the clinical effectiveness of clopidogrel, MR-dipyridamole and MR-dipyridamole in combination with aspirin [acetylsalicylic acid (ASA)–MR-dipyridamole], for

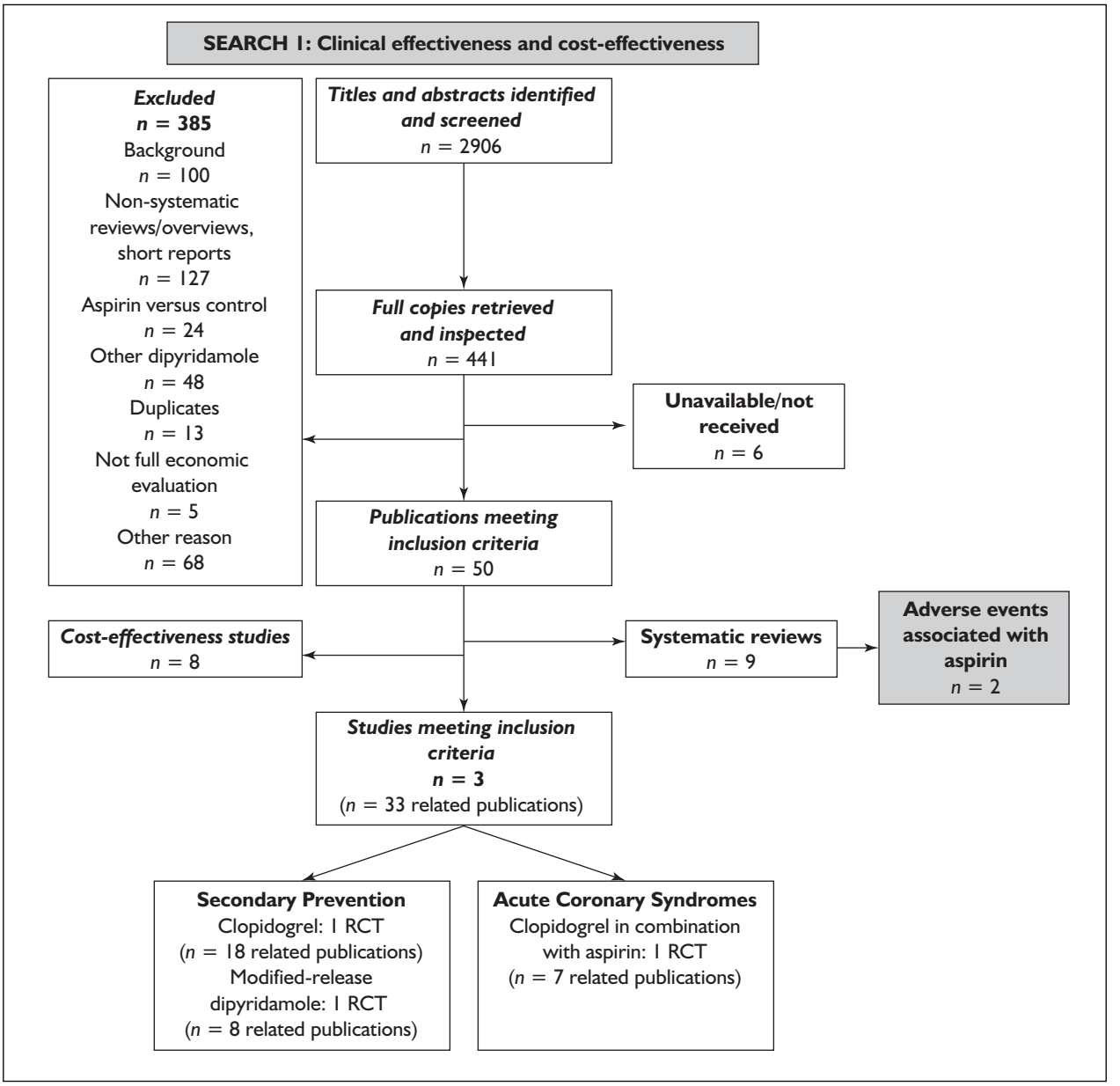

FIGURE 2 *Process of study selection for clinical effectiveness and cost-effectiveness*

the secondary prevention of occlusive vascular events, two RCTs were identified, respectively. The RCT by the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) Steering Committee[21] investigated clopidogrel compared with aspirin for the secondary prevention of ischaemic events in patients with MI, ischaemic stroke or PAD. The Second European Stroke Prevention Study (ESPS-2) by Diener and colleagues[22] investigated MR-dipyridamole and ASA–MR-dipyridamole compared with aspirin alone and placebo for the secondary prevention of stroke in patients with prior stroke or TIA. No postmarketing surveillance studies of clopidogrel or MR-dipyridamole were identified. A summary of the two included RCTs is presented in *Table 1* and full data extraction tables are presented in Appendix 2.

For the assessment of the cost-effectiveness of clopidogrel and MR-dipyridamole, eight cost-effectiveness reviews[24–31] were included. Five of the eight published studies assessed the cost-effectiveness of clopidogrel and MR-dipyridamole in the secondary prevention of occlusive vascular events in patients who have experienced an initial ischaemic stroke. One study referred to the cost-effectiveness of DP in the management of PAD and two studies examined the cost-effectiveness of clopidogrel and MR-dipyridamole in the secondary prevention of occlusive vascular events in patients with coronary or ischaemic heart disease.

Systematic reviews/meta-analyses

In addition to the primary studies, we identified seven systematic reviews and/or meta-analyses that included evaluations of clopidogrel and/or MR-dipyridamole for the secondary prevention of occlusive vascular events. These included the three meta-analyses by the Antithrombotic Trialists' Collaboration (ATT)[15,32,33] and two Cochrane Reviews about clopidogrel[34] and DP,[35] respectively. Of the two remaining reviews, Redman and Ryan[36] investigated DP and Robless and colleagues[37] examined the use of clopidogrel and other antiplatelet treatments in patients with peripheral vascular disease (PVD).

Ongoing studies

Four ongoing studies investigating either clopidogrel or DP for the secondary prevention of occlusive vascular events were identified. ESPRIT[38] is an RCT, the aim of which is to compare the efficacy and safety of mild anticoagulation or the combination of treatment of aspirin and DP with treatment with aspirin alone after cerebral ischaemia of an arterial origin. MATCH[39,40] is an RCT the aim of which is to test the hypothesis that clopidogrel in combination with aspirin is superior to clopidogrel alone in high-risk patients with recent TIA or ischaemic stroke. CHARISMA[41] aims to assess the efficacy of clopidogrel in combination with low-dose aspirin (75–162 mg/day) compared with placebo in patients with previous cardiovascular, neurovascular or peripheral arterial manifestations of atherothrombosis. Details of the PRoFESS study were included in the submission by the manufacturers of DP (Boehringer Ingelheim). PRoFESS will compare the combination of MR-dipyridamole and aspirin with the combination of clopidogrel and aspirin in the prevention of recurrent stroke.

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 full list of the excluded studies with reasons for exclusions is presented in Appendix 4.

TABLE 1 *Summary of included RCTs*

Study	Study design	Participants	Intervention
CAPRIE: CAPRIE Steering Committee[21]	Double-blind, randomised, controlled trial	19,185 patients with atherosclerotic vascular disease manifested as either ischaemic stroke, MI or symptomatic PAD	Clopidogrel (75 mg/day) versus aspirin (325 mg/day)
Second European Stroke Prevention Study (ESPS-2): Diener *et al.*, 1996[22, 23]	Double-blind, randomised, placebo-controlled trial	6602 patients with prior stroke or TIA	Aspirin (50 mg/day) versus MR-dipyridamole (400 mg/day) versus aspirin (50 mg/day) + MR-dipyridamole (400 mg/day) versus placebo

Assessment of adverse events associated with aspirin therapy

A total of 5449 titles and abstracts were screened following the searches for adverse event studies. Of these, 147 studies were ordered as full papers and assessed in detail. Five of these studies were not received and one study was unavailable. The process of study selection is shown in *Figure 3*.

We identified four systematic reviews[42–45] that investigated adverse events associated with long-term aspirin use. Two additional reviews[46,47] were identified from the searches for the assessment of clinical effectiveness and cost-effectiveness.

Excluded studies

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. Six studies were duplicates. A full list of the excluded studies with reasons for exclusions is presented in Appendix 4.

Clopidogrel

One RCT[21] was identified which investigated the use of clopidogrel in the secondary prevention of occlusive vascular events. In addition to the main publication of the trial, we identified 15 papers reporting on additional aspects of the CAPRIE trial.[48–62]

Description of included RCT

The RCT by the CAPRIE Steering Committee[21] evaluated clopidogrel compared with aspirin. Entry into the trial was based on clinical evaluation to establish the diagnosis of one of the following: (1) ischaemic stroke; (2) MI; or (3) symptomatic atherosclerotic PAD. The study included 19,185 patients; 9599 were randomised to receive clopidogrel (75 mg/day) and 9586 patients were randomised to receive aspirin (325 mg/day). The distribution of patients across the three clinical subgroups is summarised in *Table 2*. The mean ages in both groups were the same, 62.5 years. Both groups also appeared to be well matched in terms of prognostic indicators.

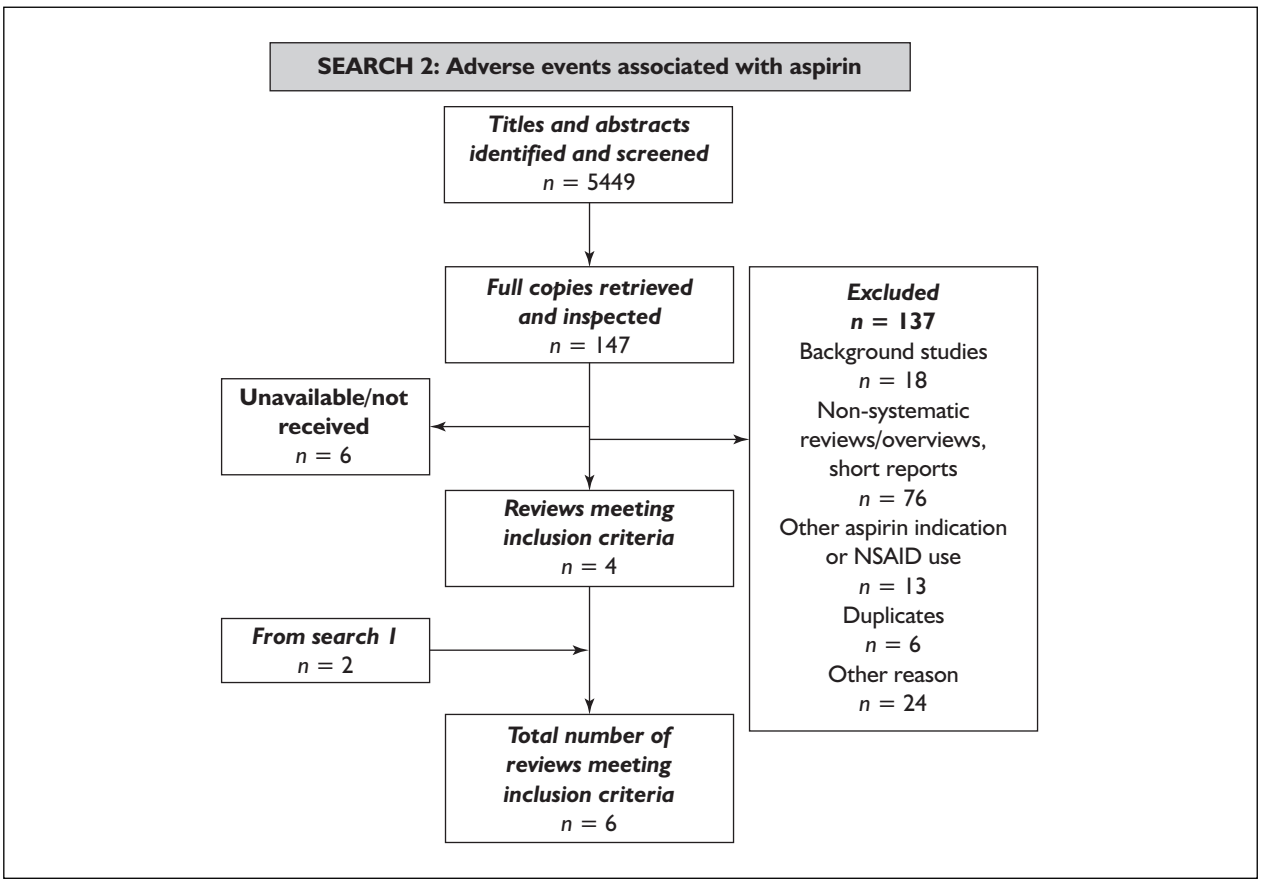

FIGURE 3 *Process of study selection for systematic reviews of adverse events associated with aspirin*

TABLE 2 *Distribution of patients in the CAPRIE trial*

	Clopidogrel	Aspirin
All patients	9599	9586
Stroke subgroup	3233	3198
MI subgroup	3143	3159
PAD subgroup	3223	3229

The primary outcome of interest was a composite of the first occurrence of ischaemic stroke, MI or vascular death. Non-fatal ischaemic stroke was defined as an acute neurological vascular event with focal signs for ≥24 hours and non-fatal MI was defined as for the inclusion criteria [i.e. two of the following: characteristic ischaemic pain for ≥20 minutes; elevation of creatine kinase (CK), creatine kinase myocardial band fraction (CK-MB), lactate dehydrogenase (LDH) or aspartate aminotransferase (AST) to two times the upper limit of laboratory normal with no other explanation; development of ≥40 new Q-waves in at least two adjacent ECG leads or new R-wave in V1 (R ≥1 mm > S in V1)]. The classification of fatal ischaemic stroke or MI was based on either death within 28 days after the onset of signs and symptoms of the acute outcome event or on necropsy findings. Other vascular deaths were any deaths that were clearly not non-vascular and did not meet the criteria for fatal stroke, fatal MI or haemorrhage.

Quality of included RCT

CAPRIE was a high-quality, double-blind, placebo-controlled trial. The evaluation of the CAPRIE trial in relation to study quality is shown in *Table 3*. Full details of the quality checklist are available in Appendix 5.

Effectiveness of clopidogrel for the secondary prevention of occlusive vascular events

This section of the report summarises the trial by the CAPRIE Steering Committee.[21]

Primary outcome(s)

The primary outcome was a composite of the first occurrence of an event in the outcome cluster of ischaemic stroke, MI or vascular death. This outcome occurred in 939 of the 9599 patients randomised to receive clopidogrel (9.8%) compared with 1021 of 9586 patients randomised to receive aspirin (10.7%). The relative risk reduction (RRR) estimated from a Cox proportional hazards model was 8.7% [95% confidence interval (CI): 0.3 to 16.5) in favour of clopidogrel ($p = 0.043$). The results of the primary outcome are summarised in *Table 4* with the calculated relative risk (RR) and in *Figure 4*.

The incidence of the primary outcome (ischaemic stroke, MI or vascular death) by clinical subgroup is presented in *Table 5*. Recurrent stroke and stroke

TABLE 3 *Quality checklist for CAPRIE*

Check	Answer
Was the method used to assign participants to the treatment groups really random?	Y
Was the allocation of treatment concealed?	Y
Was the number of participants who were randomised stated?	Y
Were details of baseline comparability presented in terms of MI, stroke, heart failure, hypertension, diabetes and current or former smoker?	Y
Was baseline comparability achieved in terms of MI, stroke, heart failure, hypertension, diabetes and current or former smoker?	Y
Were the eligibility criteria for study entry specified?	Y
Were any co-interventions identified that may influence the outcomes for each group?	?
Were the outcome assessors blinded to the treatment allocations?	Y
Were the individuals who administered the intervention blinded to the treatment allocation?	Y
Were the participants who received the intervention blinded to the treatment allocation?	Y
Was the success of the blinding procedure assessed?	?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y
Were the reasons for withdrawal stated?	Y
Was an intention-to-treat analysis included?	Y

Y, item addressed; ?, not enough information or not clear.

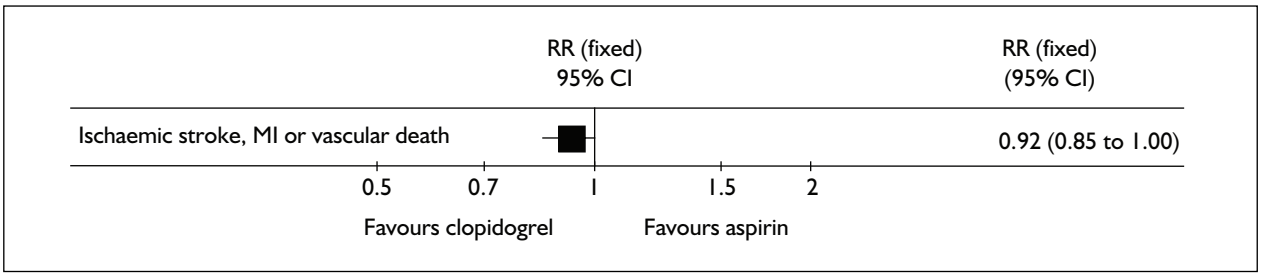

FIGURE 4 *Relative risk for primary outcome for clopidogrel versus aspirin*

TABLE 4 *Incidence of primary outcome in the CAPRIE trial*

Outcome	Clopidogrel (%)	Aspirin (%)	RR (95% CI)
Ischaemic stroke, MI or vascular death	9.8	10.7	0.92 (0.85 to 1.00)

TABLE 5 *Incidence of primary outcome (ischaemic stroke, MI or vascular death) by subgroup in the CAPRIE trial*

Subgroup	Clopidogrel (%)	Aspirin (%)	RR (95% CI)
Stroke (n = 6431)	13.4	14.4	0.93 (0.82 to 1.05)
MI (n = 6302)	9.3	9.0	1.03 (0.88 to 1.21)
PAD (n = 6452)	6.7	8.6	0.78 (0.66 to 0.92)
Test for heterogeneity: χ^2 = 5.86, degrees of freedom = 2 (p = 0.05).			

TABLE 6 *Incidence of secondary outcomes in the CAPRIE trial*

Outcome	Clopidogrel (%)	Aspirin (%)	RR (95% CI)
Ischaemic stroke, MI, amputation or vascular death	10.2	11.0	0.93 (0.86 to 1.01)
Vascular death	3.6	3.9	0.92 (0.80 to 1.07)
Any[a] stroke, MI or death from any cause	11.8	12.6	0.94 (0.87 to 1.01)
Death from any cause	5.8	6.0	0.98 (0.87 to 1.10)
[a] Includes primary intracranial haemorrhage.			

deaths were most common within the stroke subgroup and fatal or non-fatal MI was most common within the MI subgroup. Patients in the PAD subgroup had approximately equal risks of stroke and MI. The authors found that there was statistically significant heterogeneity across the three groups for the treatment effect of clopidogrel versus aspirin. However, given that the trial was not powered to detect differences between the subgroups, these findings should be interpreted with caution.

Further analyses reported by the authors of the CAPRIE trial investigated the incidence of the primary outcome in PAD/stroke patients with a history of MI and all patients with a history of MI. The RRRs for treatment with clopidogrel compared with aspirin were 22.7% (95% CI: 4.9 to 37.2) and 7.4% (95% CI: –5.2 to 18.6), respectively.

Secondary outcome(s)

The secondary outcomes cluster included amputation and a further comparison based on vascular death only. The results of the secondary outcomes are presented in *Table 6* with calculated RRs.

Quality of life

No data were reported on QoL in the CAPRIE trial.

Adverse events

Bleeding complications

There was no significant difference in the number of patients ever reporting any bleeding disorder in the clopidogrel group (9.3%) compared with the aspirin group (9.3%). The number of patients ever reporting a GI haemorrhage was statistically significantly lower in the clopidogrel group (2.0%)

TABLE 7 *Incidence of bleeding complications in the CAPRIE trial*

Bleeding disorder	Clopidogrel (%)	Aspirin (%)	RR (95% CI)
Any bleeding disorder			
Patients ever reporting	9.3	9.3	1.00 (0.91 to 1.09)
Severe	1.4	1.6	0.88 (0.70 to 1.12)
Intracranial haemorrhage			
Patients ever reporting	0.4	0.5	0.72 (0.47 to 1.12)
Severe	0.3	0.4	0.73 (0.46 to 1.17)
GI haemorrhage			
Patients ever reporting	2.0	2.7	0.75 (0.62 to 0.90)
Severe	0.5	0.7	0.69 (0.47 to 1.00)

TABLE 8 *Incidence of other adverse events in the CAPRIE trial*

Adverse event	Clopidogrel (%)	Aspirin (%)	RR (95% CI)
Rash			
Patients ever reporting	6.0	4.6	1.31 (1.16 to 1.47)
Severe	0.3	0.1	2.50 (1.20 to 5.20)
Diarrhoea			
Patients ever reporting	4.5	3.4	1.33 (1.15 to 1.53)
Severe	0.2	0.1	2.00 (0.97 to 4.12)
Indigestion/nausea/vomiting			
Patients ever reporting	15.0	17.6	0.85 (0.80 to 0.91)
Severe	1.0	1.2	0.79 (0.60 to 1.03)
Abnormal liver function			
Patients ever reporting	3.0	3.2	0.93 (0.80 to 1.09)
Severe	0.1	0.1	1.22 (0.51 to 2.94)

TABLE 9 *Incidence of haematological adverse events in the CAPRIE trial*

Adverse event	Clopidogrel (%)	Aspirin (%)	RR (95% CI)
Neutropenia ($<1.2 \times 10^9$/l)	0.10	0.17	0.62 (0.28 to 1.37)
Severe neutropenia ($<0.45 \times 10^9$/l)	0.05	0.04	1.25 (0.34 to 4.65)
Thrombocytopenia ($<100 \times 10^9$/l)	0.26	0.26	1.00 (0.57 to 1.74)
Severe thrombocytopenia ($<80 \times 10^9$/l)	0.19	0.10	1.80 (0.83 to 3.89)

than the aspirin group (2.7%). Bleeding complications are reported in *Table 7* with calculated RRs.

Other adverse events

The incidence of rash was significantly higher in the clopidogrel group than the aspirin group (6.0% versus 4.6%, respectively), as was the incidence of diarrhoea (4.5% versus 3.4%, respectively). Patients in the aspirin group had a higher incidence of indigestion/nausea/vomiting compared with patients in the clopidogrel group (17.6% versus 15.0%, respectively). The incidences of adverse events reported in the CAPRIE trial are shown in *Table 8*.

Haematological adverse events

Treatment with ticlopidine, an analogue of clopidogrel, is associated with haematological adverse events including life-threatening TTP.[63] Haematological adverse events, including severe and any occurrence, were rare in both the clopidogrel group and aspirin group in the CAPRIE trial. No cases of TTP were reported in either group. *Table 9* summarises haematological adverse events reported in the CAPRIE trial.

Additional publications

Fifteen articles[48–62] were identified which reported on additional aspects of the CAPRIE trial. Eight

TABLE 10 *Summary of additional articles related to the CAPRIE trial*

Study	Findings
Gent, 1997[48a]	Patients presenting with MI or having a past history of MI: RRR for patients with an MI or a past history of MI in the stroke and PAD cohorts was 7.4% (95% CI: not reported) in favour of clopidogrel compared with aspirin
Easton, 1998[49a]	Patients with previous CVD: RRR for all patients with a history of CVD was 8.3% (95% CI: –3.5 to 18.8) in favour of clopidogrel compared with aspirin
Hacke, 1998[50a]	Patients with lacunar and non-lacunar stroke: RRRs for patients with lacunar and non-lacunar stroke were 9.9% (95% CI: –14.4 to 29.1) and 3.0% (95% CI: –12.8 to 16.5), respectively, in favour of clopidogrel compared with aspirin
Hacke *et al.*, 1999[51a]	Patients with previous vascular disease: RRRs for the primary outcome were 14.9% ($p = 0.045$) in patients with previous acute events and 11.5% ($p = 0.05$) in patients with previous vascular disease, in favour of clopidogrel compared with aspirin
Bhatt *et al.*, 2000[52a]	Patients treated with lipid-lowering therapy: RRRs for the outcome vascular death, MI, stroke or hospitalisation were 18.6% ($p = 0.038$) in patients on any lipid-lowering therapy ($n = 2094$) and 19.3% ($p = 0.070$) for patients receiving statins ($n = 1460$) for clopidogrel versus aspirin
Bhatt *et al.*, 2001[53b]	Patients with previous cardiac surgery: RRR for the primary outcome was 36.3 (95% CI: 13.4 to 53.1) in favour of clopidogrel compared with aspirin for patients with previous cardiac surgery ($n = 1480$)
Bhatt *et al.*, 2002[54b]	Patients with DM: ARR for the combined end-point vascular death, all stroke, MI or rehospitalisation for ischaemia/bleeding was 2.1% ($p = 0.042$) for all diabetic patients ($n = 3866$) and 3.8% ($p = 0.106$) for patients treated with insulin ($n = 1134$) for clopidogrel compared with aspirin
Cannon and Investigators, 2002[55]	Patients at a higher risk of developing AMI: RRR for the outcome of a new AMI was 19.2% ($p = 0.008$) in favour of clopidogrel compared with aspirin (4.2% versus 5.0%)
Morais, 1998[56a]	Use of concomitant medications: significantly more patients in the aspirin group received treatment with ACE inhibitors (30.5% versus 29.2%; $p = 0.042$) compared with those receiving clopidogrel. There was no difference in safety between clopidogrel and aspirin except for patients receiving anti-epileptic medication (data not reported)
Harker *et al.*, 1999[57]	Data on a number of additional safety end-points were reported
Bhatt *et al.*, 2000[58]	Hospitalisation for recurrent ischaemic events: RRRs for the combined end-points, hospitalisation for ischaemia/bleeding and vascular death, all strokes, MI or hospitalisation for bleeding/ischaemia were 9.1% (95% CI: 1.6 to 16.0) and 7.9% (95% CI: 1.9 to 13.7), in favour of clopidogrel compared with aspirin, respectively
Coccheri, 1998[59a]	Distribution of atherothrombotic history and the influence of atherosclerotic disease burden on the risk of secondary ischaemic events: the event rate for ischaemic events increased with the progression of atherosclerotic disease
Blecic, 1998[60a]	Atherothrombotic history: there was considerable overlap in the atherothrombotic history of patients in the trial
Hankey, 1998[61a]	Risk of vascular ischaemic events: patients with one clinical manifestation of atherothrombosis were at high risk of similar events, and also a second event in a different vascular bed
Rupprecht, 1998[62]	The RRRs for a number of additional end-points including combined end-points of vascular events and combined end-point of major vascular events (e.g. any stroke, MI, death from any cause) favoured clopidogrel compared with aspirin

[a] Article published as abstract only.
[b] Analysis based on per protocol population.
ARR, absolute risk reduction; CVD, cerebrovascular disease; RRR, relative risk reduction.

TABLE 11 *Data for the CAPRIE trial from the ATT meta-analysis*

Outcome	Clopidogrel (%)	Aspirin (%)	RR (95% CI)
Serious vascular event	10.1	11.1	0.91 (0.84 to 0.99)
Death from any cause	5.8	6.0	0.98 (0.87 to 1.10)
Non-fatal MI	2.1	2.6	0.82 (0.68 to 0.99)
Non-fatal stroke	4.2	4.4	0.95 (0.83 to 1.08)
Vascular death	3.9	4.2	0.92 (0.80 to 1.06)
Non-vascular death	2.0	1.7	1.12 (0.91 to 1.38)
Non-fatal major bleeds	1.0	1.0	0.94 (0.71 to 1.24)
Fatal major bleeds	0.1	0.1	1.00 (0.42 to 2.40)
All major bleeds	1.1	1.1	0.94 (0.72 to 1.23)

articles[48–55] reported subgroup analyses based on the CAPRIE trial, four articles[56–58,62] undertook additional analyses of the CAPRIE trial and three articles[59–61] investigated the atherothrombotic history of patients in the CAPRIE trial. A summary of the additional articles is presented in *Table 10* and full details of the data extraction are reported in Appendix 2.

Additional evidence from systematic reviews

Antithrombotic Trialists' Collaboration meta-analysis

The ATT meta-analysis[15] included data from the CAPRIE trial. The data were extracted and are presented in *Table 11* with calculated RRs.

The authors concluded that clopidogrel may be slightly more effective than aspirin. However, the authors commented that the a reliable estimate of the true size of any difference between clopidogrel and aspirin could not be determined owing to the limits of the CIs.

Other reviews

A Cochrane review by Hankey and colleagues[34] was identified. The review investigated the effectiveness of the thienopyridine derivatives ticlopidine and clopidogrel versus aspirin for the secondary prevention of serious vascular events in high-risk vascular patients. Published data were supplemented by additional unpublished data provided by the principal investigators of the CAPRIE trial and one internal report. The authors concluded that the thienopyridine derivatives were modestly but significantly more effective than aspirin in preventing serious vascular events in patients at high risk of vascular events. The authors' stated that there is uncertainty about the size of the additional benefit. Further details of the review are presented in Appendix 3.

Robless and colleagues[37] performed a systematic review of 39 RCTs which investigated antiplatelet therapy in patients with PVD. The CAPRIE trial was one of the included studies. The authors concluded that antiplatelet therapy reduces serious vascular events and vascular death in patients with PVD. They stated that there was evidence to support the use of antiplatelet drugs other than aspirin. In terms of clopidogrel, the authors stated that there was a benefit in favour of a thienopyridine (clopidogrel or ticlopidine) versus aspirin alone. Further details of the review are presented in Appendix 3.

Summary of effectiveness data for clopidogrel

One RCT, the CAPRIE trial, was identified which investigated the use of clopidogrel for the secondary prevention of occlusive vascular events. In addition,15 papers reporting on additional aspects of the CAPRIE trial were identified.

Primary outcome

The point estimate favoured clopidogrel over aspirin but the boundaries of the CIs raise the possibility that clopidogrel is not more beneficial than aspirin.

- Ischaemic stroke, MI or death: 9.8% versus 10.7% (RR 0.92; 95% CI: 0.85 to 1.00).

Secondary outcomes

Point estimates favoured clopidogrel over aspirin but as all confidence intervals crossed unity this benefit was not significant.

- Ischaemic stroke, MI, amputation or vascular death: 10.2% versus 11.0% (RR 0.93; 95% CI: 0.86 to 1.01).
- Vascular death: 3.6% versus 3.9% (RR 0.92; 95% CI: 0.80 to 1.07).
- Any stroke, MI or death from any cause: 11.8% versus 12.6% (RR 0.94; 95% CI: 0.87 to 1.01).

- Death from any cause: 5.8% versus 6.0% (RR 0.98; 95% CI: 0.87 to 1.10).

Quality of life
No data were reported on QoL.

Adverse events
There was no difference in the number of patients ever reporting any bleeding disorder in the clopidogrel group compared with the aspirin group. The incidences of rash and diarrhoea were statistically significantly higher in the clopidogrel group than the aspirin group. Patients in the aspirin group had a higher incidence of indigestion/nausea/vomiting than patients in the clopidogrel group. Haematological adverse events were rare in both the clopidogrel and aspirin groups. No cases of TTP were reported in either group.

- Any bleeding disorder; 9.3% versus 9.3% (RR 1.00; 95% CI: 0.91 to 1.09).
- Rash: 6.0% versus 4.6% (RR 1.31; 95% CI: 1.16 to 1.47).
- Diarrhoea: 4.5% versus 3.4% (RR 1.33; 95% CI: 1.15 to 1.53).
- Indigestion/nausea/vomiting: 15.0% versus 17.6% (RR 0.85; 95% CI: 0.80 to 0.91).

Other systematic reviews/meta-analyses
The findings of other systematic reviews and meta-analyses were all based on data from the CAPRIE trial.

- Serious vascular event: 10.1% versus 11.1% (RR 0.91; 95% CI: 0.84 to 0.99).

MR-dipyridamole

Two publications[22,23] of a single RCT were identified which investigated the use of MR-dipyridamole in the secondary prevention of occlusive vascular events.

Four studies[64–67] were identified that specifically investigated standard-release DP in combination with aspirin for the secondary prevention of vascular events in patients with previous stroke and TIA. As this report only considers the clinical effectiveness and cost-effectiveness of the MR formulation of DP, the findings of these studies will not be discussed further in this section. A short discussion of the findings of these studies is presented in Appendix 8.

Any reference to DP or to DP in combination with aspirin in the main section of the report is to the modified-release formulation of the drug, unless clearly specified.

Description of included RCT
The European Stroke Prevention Study 2 (ESPS-2) by Diener and colleagues[22] evaluated MR-dipyridamole, ASA–MR-dipyridamole and aspirin compared with placebo. ESPS-2 was organised according to a 2 × 2 factorial design, allowing for the comparison of DP with placebo and DP with aspirin and the investigation of the possible interaction between DP and aspirin. The authors stated that the lack of a statistically significant interaction between the effects of aspirin and MR-dipyridamole in reducing stroke or stroke or death suggested that the effects of the two agents were additive.[22] ESPS-2 was therefore analysed under the assumption that there is no interaction between the effects of aspirin and MR-dipyridamole.

Patients were eligible for entry into the trial if they had experienced TIA or a completed ischaemic stroke within the preceding 3 months. The study included 6602 patients, randomised to the following treatment groups: (1) 1649 to aspirin 50 mg/day; (2) 1650 to aspirin 50 mg/day plus MR-dipyridamole 400 mg/day; (3) 1654 to MR-dipyridamole 400 mg/day; and (4) 1649 to placebo. The mean ages between the four groups were similar and patients appeared to be well matched in terms of prognostic indicators.

Data originating from one centre were excluded from the final analysis of ESPS-2 when large inconsistencies in the data reported were detected. Reanalysis of the trial data with the inclusion of the data from the incriminated centre was shown to have 'little or no effect' on the results of ESPS-2.[68]

The primary outcomes of interest in the trial were stroke (fatal and non-fatal), death and stroke and/or death.

Quality of included RCT
The design and rationale for ESPS-2 were well reported and the study was a high-quality RCT. The evaluation of ESPS-2 in relation to study quality is shown in *Table 12*. Full details of the quality checklist are available in Appendix 5.

Effectiveness of MR-dipyridamole and ASA–MR-dipyridamole for the secondary prevention of occlusive vascular events
This section of the report summarised the ESPS-2 trial by Diener and colleagues. As aspirin is the

TABLE 12 *Quality checklist for ESPS-2*

Check	Answer
Was the method used to assign participants to the treatment groups really random?	Y
Was the allocation of treatment concealed?	Y
Was the number of participants who were randomised stated?	Y
Were details of baseline comparability presented in terms of MI, stroke, heart failure, hypertension, diabetes and current or former smoker?	Y
Was baseline comparability achieved in terms of MI, stroke, heart failure, hypertension, diabetes and current or former smoker?	Y
Were the eligibility criteria for study entry specified?	Y
Were any co-interventions identified that may influence the outcomes for each group?	?
Were the outcome assessors blinded to the treatment allocations?	Y
Were the individuals who administered the intervention blinded to the treatment allocation?	Y
Were the participants who received the intervention blinded to the treatment allocation?	Y
Was the success of the blinding procedure assessed?	?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y
Were the reasons for withdrawal stated?	Y
Was an intention-to-treat analysis included?	Y

Y, item addressed; ?, not enough information or not clear.

TABLE 13 *Incidence of primary outcomes in ESPS-2*

Outcome	DP (%)	DP/ASA (%)	ASA (%)	RR (95% CI)
MR-dipyridamole versus aspirin				
Stroke	12.8	–	12.5	1.02 (0.85 to 1.22)
Stroke and/or death	19.4	–	20.0	0.97 (0.85 to 1.11)
Death	11.4	–	11.0	1.03 (0.85 to 1.25)
ASA–MR-dipyridamole versus aspirin				
Stroke	–	9.5	12.5	0.76 (0.63 to 0.93)
Stroke and/or death	–	17.3	20.0	0.87 (0.75 to 1.00)
Death	–	11.2	11.0	1.02 (0.84 to 1.23)
ASA–MR-dipyridamole versus MR-dipyridamole				
Stroke	12.8	9.5	–	0.75 (0.61 to 0.91)
Stroke and/or death	19.4	17.3	–	0.89 (0.77 to 1.03)
Death	11.4	11.2	–	0.99 (0.81 to 1.19)

DP/ASA, ASA–MR-dipyridamole; DP, MR-dipyridamole; ASA, aspirin.

comparator for this review, the results of the placebo group included in the trial will not be presented in the main section of the report. These results are presented in the data extraction tables in Appendix 2.

Primary outcome(s)

The primary outcomes of interest were stroke (fatal and non-fatal), death and a composite of stroke and/or death. Stroke occurred in 157 of the 1650 patients randomised to receive ASA–MR-dipyridamole (9.5%) compared with 211 of the 1654 patients in the MR-dipyridamole group (12.8%) and 206 of the 1649 patients in the aspirin-only group (12.5%). The number of strokes and/or deaths were 286 in the ASA–MR-dipyridamole group, 321 in the MR-dipyridamole group and 330 in the aspirin group. The number of deaths was 185, 188 and 182 in the three groups, respectively. The incidences of the primary outcomes are presented in *Table 13* and *Figure 5* with calculated RRs.

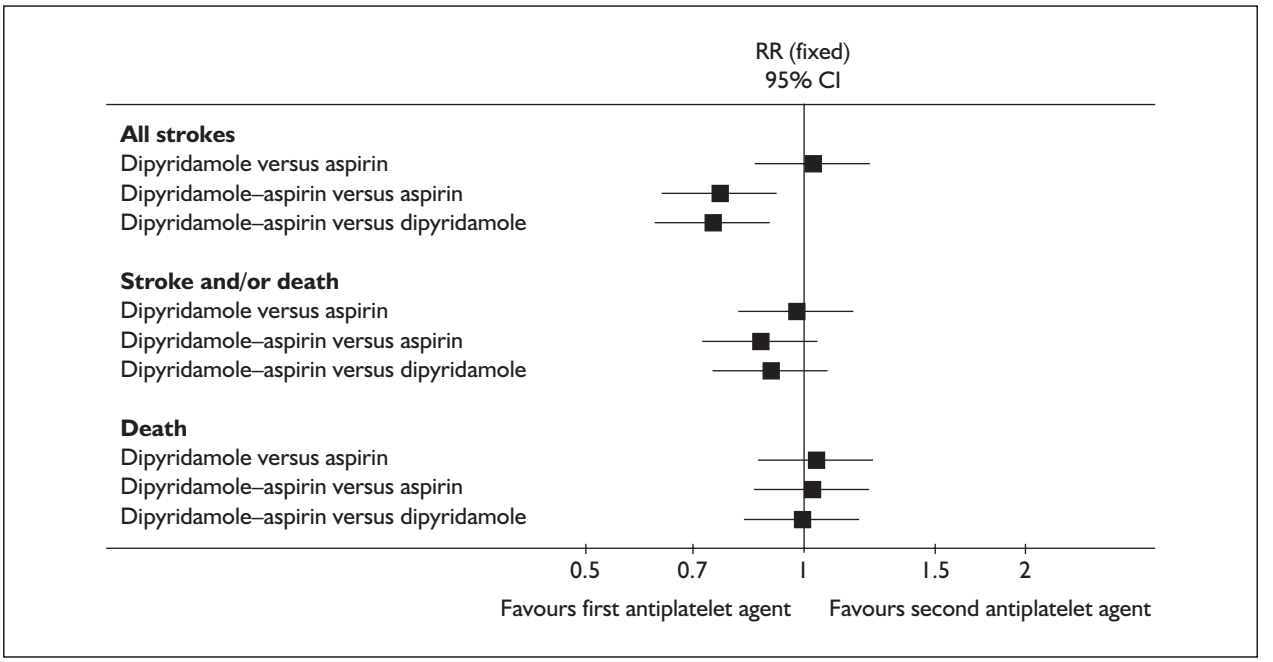

FIGURE 5 *RRs for the primary outcomes*

TABLE 14 *Incidence of secondary outcomes in ESPS-2*

Outcome	DP (%)	DP/ASA (%)	ASA (%)	RR (95% CI)
MR-dipyridamole versus aspirin				
TIA	13.0	–	12.5	1.04 (0.87 to 1.24)
Stroke or TIA	23.1	–	22.6	1.02 (0.90 to 1.16)
MI	2.9	–	2.4	1.23 (0.81 to 1.86)
OVE	2.1	–	2.3	0.92 (0.58 to 1.45)
Ischaemic events[a]	16.4	–	16.1	1.02 (0.87 to 1.19)
Vascular death	7.6	–	7.2	1.06 (0.83 to 1.35)
Vascular events	19.6	–	19.0	1.03 (0.89 to 1.18)
ASA–MR-dipyridamole versus aspirin				
TIA	–	10.4	12.5	0.83 (0.69 to 1.01)
Stroke or TIA	–	18.1	22.6	0.80 (0.70 to 0.92)
MI	–	2.1	2.4	0.90 (0.57 to 1.41)
OVE	–	1.3	2.3	0.55 (0.33 to 0.94)
Ischaemic events[a]	–	12.5	16.1	0.77 (0.65 to 0.92)
Vascular death	–	7.1	7.2	0.99 (0.77 to 1.27)
Vascular events	–	14.9	19.0	0.78 (0.67 to 0.91)
ASA–MR-dipyridamole versus MR-dipyridamole				
TIA	13.0	10.4	–	0.80 (0.66 to 0.97)
Stroke or TIA	23.1	18.1	–	0.78 (0.69 to 0.90)
MI	2.9	2.1	–	0.73 (0.48 to 1.12)
OVE	2.1	1.3	–	0.60 (0.35 to 1.03)
Ischaemic events[a]	16.4	12.5	–	0.76 (0.64 to 0.90)
Vascular death	7.6	7.1	–	0.94 (0.74 to 1.20)
Vascular events	19.6	14.9	–	0.76 (0.65 to 0.89)

[a] Fatal and non-fatal.

Secondary outcome(s)

The secondary outcomes of interest were incidence of TIA, stroke or TIA (first event to occur), MI, ischaemic event and OVE. An 'ischaemic event' was classified as stroke, MI or sudden death. The incidence of the secondary outcomes with calculated relative risks are reported in *Table 14*.

Quality of life

No data on QoL were reported in ESPS-2.

Adverse events

Bleeding complications

The frequency of bleeding complications at any site were similar between the ASA–MR-dipyridamole group (8.7%) and the aspirin group (8.2%). However, the frequency of bleeding complications, including severe and fatal bleeds, was significantly lower in the MR-dipyridamole group (4.7%) than the aspirin group (8.2%). The incidence of bleeding complications are summarised with calculated relative risks in *Table 15*.

Other adverse events

The frequency of headache was significantly higher in both the ASA–MR-dipyridamole group (64.0%) and MR-dipyridamole group (62.5%) than the aspirin-alone group (60.0%). The frequency of diarrhoea was significantly higher in the ASA–MR-dipyridamole group (12.1%) and the MR-dipyridamole group (15.4%) than the aspirin-alone group (6.6%). The frequencies of nausea and vomiting were also significantly higher in the ASA–MR-dipyridamole group than the aspirin-alone group. The incidence of adverse events reported in ESPS-2 are summarised in *Table 16*.

TABLE 15 *Incidence of bleeding complications in ESPS-2*

Bleeding complication	DP (%)	DP/ASA (%)	ASA (%)	RR (95% CI)
MR-dipyridamole versus aspirin				
Any site	4.7	–	8.2	0.57 (0.43 to 0.75)
Mild	3.2	–	5.0	0.64 (0.46 to 0.90)
Moderate	1.1	–	2.0	0.54 (0.31 to 0.96)
Severe or fatal	0.4	–	1.2	0.30 (0.12 to 0.74)
ASA–MR-dipyridamole versus aspirin				
Any site	–	8.7	8.2	1.07 (0.85 to 1.33)
Mild	–	5.1	5.0	1.02 (0.76 to 1.38)
Moderate	–	2.0	2.0	1.00 (0.62 to 1.61)
Severe or fatal	–	1.6	1.2	1.35 (0.76 to 2.40)
ASA–MR-dipyridamole versus MR-dipyridamole				
Any site	4.7	8.7	–	1.87 (1.43 to 2.45)
Mild	3.2	5.1	–	1.59 (1.13 to 2.23)
Moderate	1.1	2.0	–	1.84 (1.04 to 3.25)
Severe or fatal	0.4	1.6	–	4.51 (1.87 to 10.90)

TABLE 16 *Incidence of other adverse events in ESPS-2*

Adverse event	DP (%)	DP/ASA (%)	ASA (%)	RR (95% CI)
MR-dipyridamole versus aspirin				
Any adverse event	62.5	–	60.0	1.04 (0.99 to 1.10)
Gastrointestinal event	30.5	–	30.4	1.00 (0.90 to 1.11)
Headache	37.2	–	33.1	1.12 (1.02 to 1.23)
Dizziness	30.1	–	29.2	1.03 (0.93 to 1.15)
ASA–MR-dipyridamole versus aspirin				
Any adverse event	–	64.0	60.0	1.07 (1.01 to 1.12)
Gastrointestinal event	–	32.8	30.4	1.08 (0.97 to 1.19)
Headache	–	29.5	29.2	1.01 (0.91 to 1.12)
Dizziness	–	38.2	33.1	1.15 (1.05 to 1.26)
ASA–MR-dipyridamole versus MR-dipyridamole				
Any adverse event	62.5	64.0	–	1.02 (0.97 to 1.08)
Gastrointestinal event	30.5	32.8	–	1.07 (0.97 to 1.19)
Headache	37.2	38.2	–	1.03 (0.94 to 1.12)
Dizziness	30.1	29.5	–	0.98 (0.88 to 1.09)

TABLE 17 *Summary of additional articles related to ESPS-2*

Study	Findings
Sivenius *et al.*, 1999[69]	Severity of subsequent stroke: there was no difference in subsequent stroke severity, as measured on the Rankin scale, among the four treatment groups
Sivenius *et al.*, 1999[70]	Effect of age: compared with placebo, combination therapy with DP and aspirin significantly reduced all primary outcomes across three age groups (<65, age 65–74 and ≥75 years)
Diener *et al.*, 2001[71]	*Post hoc* analysis of cardiac safety in patients with CHD or MI at entry: there was a non-significant trend for fewer MIs in patients who were on aspirin (aspirin 2.2% versus no aspirin 2.8%). Mortality was identical across the treatment groups.

TABLE 18 *Data for ESPS-2 from ATT meta-analysis*

	DP (%)	DP/ASA (%)	ASA (%)	RR (95% CI)
MR-dipyridamole versus aspirin				
Serious vascular event	18.0	–	17.8	1.01 (0.87 to 1.17)
Death from any cause	11.4	–	11.0	1.03 (0.85 to 1.25)
Non-fatal MI	1.9	–	1.0	1.82 (1.01 to 3.27)
Non-fatal stroke	8.8	–	9.6	0.91 (0.74 to 1.13)
Vascular death	7.6	–	7.2	1.06 (0.83 to 1.35)
Non-vascular death	3.8	–	3.9	0.98 (0.70 to 1.38)
Non-fatal major bleeds	0.4	–	1.0	0.37 (0.15 to 0.95)
Fatal major bleeds	0.1	–	0.2	0.50 (0.09 to 2.72)
All major bleeds	0.5	–	1.2	0.40 (0.18 to 0.90)
ASA–MR-dipyridamole versus aspirin				
Serious vascular event	–	14.2	17.8	0.80 (0.68 to 0.94)
Death from any cause	–	11.2	11.0	1.02 (0.84 to 1.23)
Non-fatal MI	–	0.7	1.0	0.65 (0.30 to 1.38)
Non-fatal stroke	–	6.6	9.6	0.69 (0.55 to 0.87)
Vascular death	–	7.1	7.2	0.99 (0.77 to 1.27)
Non-vascular death	–	4.1	3.9	1.06 (0.76 to 1.48)
Non-fatal major bleeds	–	1.4	1.0	1.44 (0.76 to 2.71)
Fatal major bleeds	–	0.4	0.2	1.75 (0.51 to 5.96)
All major bleeds	–	1.8	1.2	1.50 (0.85 to 2.63)
ASA–MR-dipyridamole versus MR-dipyridamole				
Serious vascular event	18.0	14.2	–	0.79 (0.68 to 0.93)
Death from any cause	11.4	11.2	–	0.99 (0.81 to 1.19)
Non-fatal MI	1.9	0.7	–	0.36 (0.18 to 0.71)
Non-fatal stroke	8.8	6.6	–	0.75 (0.59 to 0.96)
Vascular death	7.6	7.1	–	0.94 (0.74 to 1.20)
Non-vascular death	3.8	4.1	–	1.08 (0.77 to 1.51)
Non-fatal major bleeds	0.4	1.4	–	3.84 (1.57 to 9.41)
Fatal major bleeds	0.1	0.4	–	3.51 (0.73 to 16.86)
All major bleeds	0.5	1.8	–	3.76 (1.73 to 8.18)

Additional publications

In addition to the main trial publications, three articles[69–71] reporting on *post hoc* analyses of the trial data were identified. *Table 17* summarises the additional articles identified.

Additional evidence from systematic reviews

Antithrombotic Trialists' Collaboration meta-analysis

The ATT meta-analysis[15] included data from ESPS-2. The data were extracted and are presented in *Table 18* with calculated RRs.

The authors concluded that, based on data from standard-release DP trials and ESPS-2, the addition of DP to aspirin has not been shown clearly to produce additional reductions in serious vascular events. The authors stated that data from ESPS-2 alone suggested that there may be a worthwhile further reduction in stroke when DP is added to aspirin.

Other reviews

A Cochrane Review by De Schryver and colleagues[35] was identified. The review investigated standard-release and MR-dipyridamole for preventing stroke and OVEs in patients with vascular disease. The authors found that for patients who presented with arterial vascular disease there was no evidence that DP, alone or in combination with other antiplatelet drugs, reduced the risk of vascular death. There was evidence from a single large trial (ESPS-2) in patients presenting with cerebral ischaemia that ASA–MR-dipyridamole may reduce the risk of further vascular events compared with aspirin alone. The authors state that there was no evidence that DP alone was more efficacious than aspirin. Further details of the review are presented in Appendix 3.

Redman and Ryan[36] conducted a review of clinical trials which investigated the combination of aspirin and DP in the prevention of recurrent stroke in patients who had suffered a first stroke or TIA. The authors found that of the five studies identified, three early studies showed there was no difference in effectiveness when DP was added to aspirin. Two later studies (ESPS and ESPS-2) found that addition of DP to aspirin therapy provided a further reduction in the risk of secondary cerebrovascular events compared with placebo and aspirin alone. The authors conclude that further studies are needed to confirm the long-term benefits of adding dipyridamole to aspirin therapy. Further details of the review are presented in Appendix 3.

Summary of effectiveness data for MR-dipyridamole

One RCT, ESPS-2, was identified which investigated the use of MR-dipyridamole and ASA–MR-dipyridamole for the secondary prevention of occlusive vascular events. In addition, three papers reporting on additional aspects of the trial were identified.

MR-dipyridamole versus aspirin

Primary outcomes

MR-dipyridamole did not show a statistically significant reduction in any of the primary outcomes compared with aspirin.

- Stroke: 12.8% versus 12.5% (RR 1.02; 95% CI: 0.85 to 1.22).
- Stroke and/or death: 19.4% versus 20.0% (RR 0.97; 95% CI: 0.85 to 1.11).
- Death: 11.4% versus 11.0% (RR 1.03; 95% CI: 0.85 to 1.25).

Secondary outcomes

A number of secondary outcomes were reported. MR-dipyridamole was not beneficial compared with aspirin for any of the secondary outcomes.

Quality of life

No data on QoL were reported.

Adverse events

The frequency of bleeding complications was significantly lower in the MR-dipyridamole group than the aspirin group. The frequency of headache was significantly higher in patients treated with MR-dipyridamole. The incidence of GI events was similar in both groups.

- Bleeding complications: 4.7% versus 8.2% (RR 0.57; 95% CI: 0.43 to 0.75).
- Headache: 37.2% versus 33.1% (RR 1.12; 95% CI: 1.02 to 1.23).
- GI event: 30.5% versus 30.4% (RR 1.00; 95% CI: 0.90 to 1.11).

ASA–MR-dipyridamole versus aspirin

Primary outcomes

ASA–MR-dipyridamole was significantly more effective than aspirin in reducing the outcome of stroke. The point estimate for the outcome of stroke and/or death favoured treatment with ASA–MR-dipyridamole over aspirin but the boundaries of the CIs raise the possibility that ASA–MR-dipyridamole may not be more effective at reducing stroke and/or death than aspirin alone. ASA–MR-dipyridamole did not statistically significantly reduce the outcome of death compared with aspirin alone.

- Stroke: 9.5% versus 12.5% (RR 0.76; 95% CI: 0.63 to 0.93).
- Stroke and/or death: 17.3% versus 20.0% (RR 0.87; 95% CI: 0.75 to 1.00).
- Death: 11.2% versus 11.0% (RR 1.02; 95% CI: 0.84 to 1.23).

Secondary outcomes

A number of secondary outcomes were reported. ASA–MR-dipyridamole was statistically significantly more effective than aspirin at reducing stroke or TIA, OVEs, ischaemic events (fatal and non-fatal) and vascular events. The point estimates favoured MR-dipyridamole in combination with aspirin for the other outcomes reported, but the findings were not statistically significant.

Quality of life

No data on QoL were reported.

Adverse events
The frequency of bleeding complications was similar in the ASA–MR-dipyridamole group and to the aspirin group. The frequency of headache was significantly higher in patients treated with MR-dipyridamole. The incidence of GI events was similar in both groups.

- Bleeding complications: 8.7% versus 8.2% (RR 1.07; 95% CI: 0.85 to 1.33).
- Headache: 29.5% versus 29.2% (RR 1.01; 95% CI: 0.91 to 1.12).
- GI event: 32.8% versus 30.4% (RR 1.08; 95% CI: 0.97 to 1.19).

ASA–MR-dipyridamole versus MR-dipyridamole alone

Primary outcomes
MR-dipyridamole in combination with aspirin significantly reduced the risk of stroke compared with MR-dipyridamole alone. Compared with MR-dipyridamole alone, ASA–MR-dipyridamole did not significantly reduce the risk of stroke and/or death, or death.

- Stroke: 9.5% versus 12.8% (RR 0.75; 95% CI: 0.61 to 0.91).
- Stroke and/or death: 17.3% versus 19.4% (RR 0.89; 95% CI: 0.77 to 1.03).
- Death: 11.2% versus 11.4% (RR 0.99; 95% CI: 0.81 to 1.19).

Secondary outcomes
A number of secondary outcomes were reported. MR-dipyridamole in combination with aspirin significantly reduced the risk of TIA, stroke or TIA, ischaemic events (fatal and non-fatal) and vascular events compared with MR-dipyridamole alone.

Quality of life
No data on QoL were reported.

Adverse events
The frequency of bleeding complications was significantly lower in the MR-dipyridamole group than the ASA–MR-dipyridamole group. The frequencies of headache and GI events were similar between the two groups.

- Bleeding complications: 8.7% versus 4.7% (RR 1.87; 95% CI: 1.43 to 2.45).

Other systematic reviews and meta-analyses

The findings of the other systematic reviews of MR-dipyridamole were based on data from ESPS-2.

Serious vascular event (ATT meta-analysis)
- MR-dipyridamole versus aspirin: 18.0% versus 17.8% (RR 1.01; 95% CI: 0.87 to 1.17).
- MR-dipyridamole in combination with aspirin versus aspirin: 14.2% versus 17.8% (RR 0.80; 95% CI: 0.68 to 0.94)

Standard-release dipyridamole

Earlier trials of the standard-release formulation of DP in combination with aspirin did not show a statistically significant reduction in the risk of serious vascular events in patients receiving DP compared with those receiving aspirin alone (RR 0.95; 95% CI: 0.75 to 1.19). Combining the data with that from ESPS-2 suggests that the combination of DP and aspirin is significantly more effective these aspirin alone (RR 0.85; 95% CI: 0.74 to 0.96).

Comparator: aspirin

The effects of aspirin therapy for patients at high risk of occlusive events have been most extensively studied by the ATT.[15,32] The most recent meta-analysis[15] 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'. This was 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[15] 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 statistically significant difference between the different aspirin regimens, but that this could not exclude a clinically important difference. The authors reported that as doses of <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 daily doses of aspirin (≥75 mg/day) versus no aspirin suggested that no particular range of dose was preferable, but that doses <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[42–44,46,47] in addition to the ATT meta-analysis.[15] Further study details and details of the study quality assessment are presented in Appendix 3.

Haemorrhagic stroke

One systematic review[44] of aspirin versus control (placebo or no treatment) for at least 1-month's 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[42] that examined the incidence of haemorrhagic stroke as a secondary outcome also found an excess risk in patients allocated to low-dose aspirin compared with placebo.

Extracranial haemorrhage

The systematic review by the ATT[15] found that aspirin increased the risk of major extracranial haemorrhage by around 50% compared with placebo or no treatment (OR 1.6; 95% CI: 1.4 to 1.8) in high-risk patients, including those with acute stroke. 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[47] 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[46] (including over 10,000 cases of upper GI haemorrhage or perforation which resulted in admission to hospital) found 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 cohort and nested case–control studies (RR 2.2; 95% CI: 2.1 to 2.4). A third review[42] 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 there was almost no association with permanent morbidity (numbers not reported). The last systematic review[43] 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).

Summary of effectiveness data for aspirin

- Compared with control, aspirin at any dose reduced the odds of a serious vascular event by 25% (OR 0.77; 95% CI: 0.73 to 0.81).
- The ATT meta-analysis found that doses of aspirin of 75–150 mg/day are as effective as higher doses in preventing serious vascular events. Insufficient evidence was found to suggest that doses of aspirin of <75 mg/day are as effective as higher doses.
- Aspirin was associated with an increased risk of haemorrhagic stroke and bleeding compared with placebo or no treatment.
- None of the included systematic reviews found any evidence that the risk of haemorrhagic stroke or bleeding differed according to the aspirin dose used.

Comparability between CAPRIE and ESPS-2

Competing interventions have not always been compared in randomised trials. In such cases, an indirect comparison may be carried out. Undertaking simple indirect comparisons means that the power of randomisation is lost and data are subject to the biases associated with observational studies.[72] Bucher and colleagues[72] have proposed an adjusted method for indirect comparisons which aims to overcome these potential problems. However, the method is only valid when the magnitude of the treatment effect is consistent between the different studies being compared. Clopidogrel, MR-dipyridamole and ASA–MR-dipyridamole are licensed for the prevention of occlusive vascular events in patients who have had a stroke and, in the case of MR-dipyridamole, also in patients who have had a TIA. Currently there are no randomised trials where these two drugs are directly compared in this patient group. Below, the feasibility of undertaking an indirect comparison is discussed.

Differences between the CAPRIE trial and ESPS-2

The internal validity and similarity of the trials evaluated in the indirect comparison should be carefully examined.[73] In the case of the CAPRIE

trial and ESPS-2, there are a number of differences between the two studies that may limit the interpretation of the adjusted indirect comparison.

The aspirin doses were different in the two trials

Patients in the aspirin group in the CAPRIE trial received 325 mg/day compared with patients in ESPS-2 who received 50 mg/day. Although there is no evidence from meta-analyses of aspirin trials to suggest that effectiveness decreases with dose, there remains uncertainty about whether doses <75 mg are as effective as daily doses ≥75 mg.[15] In particular, experts disagree about the optimal aspirin dose in preventing stroke.[74] Johnson and colleagues[74] conducted a metaregression analysis of RCTs in patients with previous TIA or stroke. They concluded that the effect of aspirin on stroke is uniform across aspirin doses from 50 to 1500 mg/day. However, based on the existing data, the evidence is insufficient to conclude that doses of aspirin <75 mg/day are as effective as higher doses.

A broader group of patients were included in the CAPRIE trial than in ESPS-2

The CAPRIE trial included patients with atherosclerotic vascular disease manifested as ischaemic stroke, MI and PAD. ESPS-2 included patients with TIA and completed ischaemic stroke only. However, as the pathophysiology of atherothrombosis is thought to be common across the different clinical manifestations of the disease,[13] separate analyses of such patients may be unnecessary.

Definition of outcomes vary across the studies

The primary outcome in the CAPRIE trial was a composite of ischaemic stroke, MI or vascular death. The three primary outcomes in ESPS-2 were stroke, stroke and/or death and death from any cause. The definitions of other outcomes reported in the two trials such as 'vascular events' varied or were not fully reported. However, the outcomes reported for each trial in the ATT meta-analysis[15] (available from www.bmj.com) are matched and may be used to compare the two interventions.

Results of the adjusted indirect comparison

Using the methods proposed by Bucher and colleagues,[72] we undertook an indirect comparison of clopidogrel versus ASA–MR-dipyridamole and clopidogrel versus MR-dipyridamole.

The results of the adjusted indirect comparison suggested that ASA–MR-dipyridamole therapy may be superior to clopidogrel therapy for the outcome 'serious vascular event'. However, as the 95% CIs crossed unity, this finding was not significant. For the outcome 'death from any cause', clopidogrel appeared to be superior to ASA–MR-dipyridamole, but this finding was also not significant. Compared with treatment with MR-dipyridamole alone, the point estimates were in favour of treatment with clopidogrel for both outcomes, but the findings were not significant. The RRs for a 'serious vascular event' and 'death from any cause', estimated using the adjusted method, are presented in *Table 19*. See also *Figure 6*. Full details of the calculations are presented in Appendix 9.

For the adjusted indirect comparison to give an accurate estimate of the difference in treatment effect between competing interventions, the magnitude of the treatment effect must be uniform across both studies. A number of assumptions have to be made about the similarities of the patients in the CAPRIE trial and ESPS-2 with regards to the dose of the comparator and in particular the population under study. Because of these assumptions, the findings of the indirect comparison should be interpreted with caution.

TABLE 19 *Estimated relative risks for the adjusted indirect comparison*

Therapy	Estimated RR[a] (95% CI)	
	Serious vascular event	Death from any cause
Clopidogrel versus ASA–MR-dipyridamole	1.14 (0.95, 1.36)	0.96 (0.77 to 1.21)
Clopidogrel versus MR-dipyridamole	0.90 (0.76, 1.07)	0.95 (0.76 to 1.19)

[a] RR <1 favours clopidogrel.

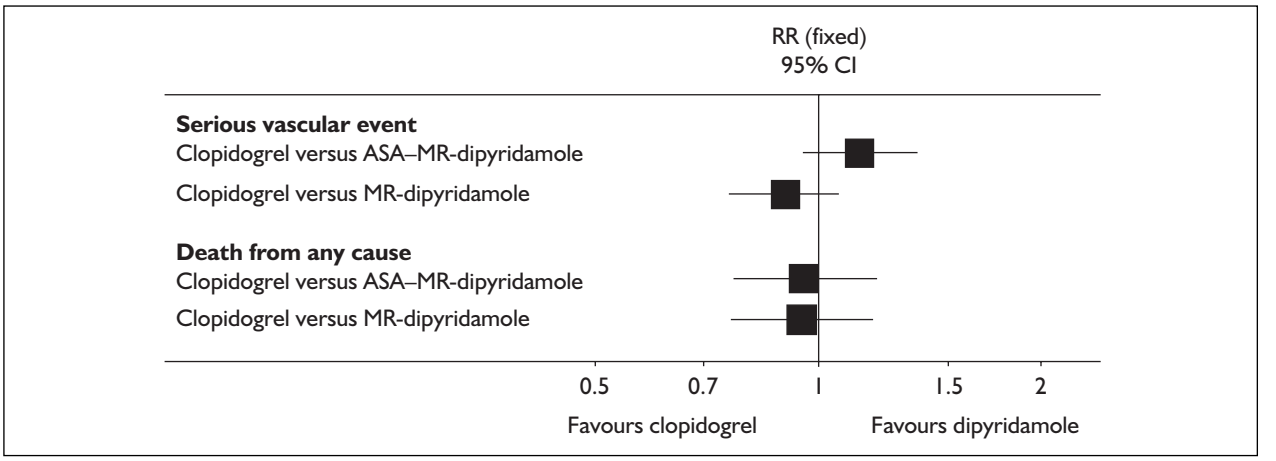

FIGURE 6 *Forest plot for the adjusted indirect comparison*

Chapter 5

Economic analysis

Introduction

The systematic literature search detailed in the first section of Chapter 3 identified eight studies that met the criteria for inclusion in the cost-effectiveness review. In addition, separate economic models with accompanying reports were also submitted by the manufacturers, Boehringer Ingelheim Ltd, Sanofi-Synthelabo Ltd and Bristol-Myers Squib.

This chapter provides 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. This review focuses on secondary prevention and, as such, only considers the evidence related to the cost-effectiveness of antiplatelet agents in those patients who have survived an initial period of acute ischaemic disease. The published cost-effectiveness studies are reviewed separately from the manufacturers' submissions, according to the qualifying event of the patient cohort assessed (stroke, transient ischaemic attack, MI and PVD). The review is followed by an overall summary of the cost-effectiveness evidence. The quality checklists for each of the published studies are reported in Appendix 6.

Review of cost-effectiveness evidence for stroke

Five of the eight published studies assessed the cost-effectiveness of clopidogrel and MR-dipyridamole in the secondary prevention of occlusive vascular events in patients who have experienced an initial ischaemic stroke. In this subgroup, the risk of recurrent stroke is highest compared with the risk of other ischaemic events, and the models therefore focus primarily on the prevention of further recurrent stroke events.

Review of Scott and Scott (1997). Application of the findings of the European Stroke Prevention Study 2 (ESPS-2) to a New Zealand ischaemic stroke cost analysis[28]

Overview

This study evaluated the cost of low-dose aspirin and the combination of low-dose aspirin and MR-dipyridamole (ASA–MR-dipyridamole) in comparison with placebo for the secondary prevention of ischaemic stroke in New Zealand. The study is based on a simple comparison of the costs of the alternative treatments calculated using the appropriate stroke event-rate from ESPS-2.[22] The model considers a 2-year period following ischaemic stroke. The perspective is that of a healthcare provider or funder, although a sensitivity analysis was conducted to include a wider societal perspective.

A cost of stroke care was estimated, and this was multiplied by the number of strokes associated with each treatment in ESPS-2. This was then combined with the cost of the treatment itself to provide an overall cost for comparison.

Summary of effectiveness data

The study simply used the number of strokes recorded in ESPS-2. It also reports these as the number of strokes prevented per 1000 patients in comparison with placebo. ASA–MR-dipyridamole was found to prevent 58 strokes and aspirin monotherapy was estimated to prevent 29 strokes per 1000 patients in comparison with placebo.

Summary of resource utilisation and cost data

Resource use and cost data were obtained from a previously published study that estimated the direct cost of ischaemic stroke in New Zealand. This study also provided an estimate of the number of weeks of productivity lost to stroke. Unit costs are reported separately to resource use and are detailed in *Table 20*.

TABLE 20 *Costs of direct stroke based on a sample of 6724 stroke patients in 1992 and drug cost data (NZ$ 1996) in Scott and Scott (1997)*[28]

Cost parameter	Quantity (1992)	Unit cost (NZ$)	Item cost (NZ$)	Cost per stroke (NZ$)
Direct costs				
GP consultations	18,000	28.89	520,000	77.33
GP prescriptions			460,000	68.41
Hospitalised patients	4707	5943.06	27,974,000	4160.32
Rehabilitation sessions	3694	318.00	1,174,692	174.70
Patients continuing to institutional care	2958	26,216.83	77,549,393	11,533.22
Patients requiring transport to hospital	4707	159.74	751,896	111.82
Subtotal			108,429,981	16,125.82
Indirect costs				
Lost productivity	10,944 weeks	626.97	6,861,560	1020.46
Total			115,291,541	17,146.27
Drugs				
Aspirin	50 mg/day	0.0163	11.91	
MR-dipyridamole	400 mg/day	1.3053	953.52	
ASA–MR-dipyridamole	50 mg aspirin and 400 mg MR-dipyridamole per day	1.3216	965.43	

The price of aspirin was calculated for the lowest dose practical given the doses of aspirin currently prescribed in New Zealand and was therefore the cost of half of one 300-mg tablet per day. The cost of MR-dipyridamole was calculated from published pricing lists and that of ASA–MR-dipyridamole was calculated as the sum of the separate drug costs. ASA–MR-dipyridamole prevented more strokes than aspirin and was estimated to be cost saving over 2 years despite the higher cost of treatment. Both treatments were estimated to be cost saving in comparison with placebo over 2 years. The cost saved per 1000 patients (including indirect costs) is reported as NZ$1,023,536 for ASA–MR-dipyridamole and NZ$982,573 for aspirin alone.

Summary of cost-effectiveness data

The study did not report any cost-effectiveness ratios as both treatments were cost-saving in comparison with placebo. The study could have reported the cost-effectiveness of ASA–MR-dipyridamole in comparison with aspirin alone. It is possible to calculate this incremental cost-effectiveness ratio (ICER) from the data provided. The incremental cost per stroke avoided with ASA–MR-dipyridamole compared to aspirin alone is NZ$1413 if the cost of lost productivity is included or NZ$628 if it is excluded. Univariate sensitivity analyses were conducted, varying certain cost parameters, drug costs and the number of stroke events. The impact of these on the potential implementation decision was not discussed and no data are reported which would allow calculations.

Comments

This study adds only limited information to the ESPS-2 trial data. It is confined to a single outcome, recurrent stroke, and the study does not attempt to expand on, or extrapolate from, the information reported in the trial. The study considers only two of the treatments from the trial and no other potential comparators are considered. The focus is on the pattern and cost of stroke care in New Zealand, taken from a previous study, and as such it is unlikely to be generalisable to a UK setting.

Review of Chambers and colleagues (1999). Cost-effectiveness analysis of antiplatelet therapy in the prevention of recurrent stroke in the UK: aspirin, dipyridamole and aspirin-dipyridamole[29]

Overview

This study evaluated the cost-effectiveness of aspirin, MR-dipyridamole and ASA–MR-dipyridamole for the secondary prevention of stroke in patients who have survived an initial ischaemic stroke in the UK. The study is based on a deterministic, decision-analytic model. The model was run for 5 years in the base-case analysis, although results were also presented for 2 and 25 years. The model was used to estimate the number of future events, costs, disabled life-years, disability-free life-years,

stroke-free life-years and quality-adjusted life-years (QALYs) associated with each treatment strategy. The number of future events includes the number of strokes, TIAs and non-fatal OVEs as defined in ESPS-2. The perspective is that of the UK NHS and Personal Social Services.

The model considers a cohort of 30-day survivors of initial ischaemic stroke with a mean age of 70 years. Patients in the cohort can begin the model in a disabled state and are then assigned either to one of the antiplatelet treatments or to no therapy, or they may immediately have a recurrent stroke. The cycle length is 3 months, and during each cycle patients can withdraw from therapy, experience an adverse event on therapy, die, experience a subsequent stroke, experience TIA or experience OVE. Disablement is measured by the modified Rankin score, with category 3–5 being classified as 'disabled' and category 0–2 as 'non-disabled'. The model considers only the first recurrent stroke, which may be disabling or fatal. Further disablement is only considered following recurrent stroke and is assumed not to vary by therapy. Patients surviving a recurrent stroke event enter one of two groups of absorbing states of long-term care and rehabilitation for stroke differentiated by whether they are disabled or non-disabled. Adverse events were broken down into bleeding events, GI events or headaches and other events, and occur as a proportion of those who withdraw from therapy. The RR of stroke, TIA, OVE, mortality and withdrawal from therapy varies with time from entry to the model. Data used in the model were sourced from published studies, expert panels, published pricing lists and Boehringer Ingelheim Ltd.

Summary of effectiveness data

Probabilities of recurrent stroke, OVE and TIA for the first 2 years were obtained from the ESPS-2 placebo group. Probabilities of OVE and TIA for years 2 onwards were extrapolated from these. Rates of stroke recurrence for years 2–5 were obtained from the Oxfordshire Community Stroke Project (OCSP)[14] and were also used in the extrapolation period beyond 5 years. All-cause mortality rates were derived from the OCSP by multiplying the appropriate cohort age-specific rates by national average age-specific rates to population rates for Oxfordshire. Case fatality rates were derived from ESPS-2, as were the rates of adverse events and withdrawal from therapy. The rate of disablement from recurrent stroke was also obtained from ESPS-2, even though this does not appear to have been reported.

The RRR for recurrent stroke, TIA and OVE, as compared with placebo, taken from ESPS-2 was highest for ASA–MR-dipyridamole, followed by aspirin and then MR-dipyridamole alone (39.96, 18.08, 16.29%). The effectiveness of therapies and the rate of withdrawal from therapy after 1 year were assumed to be constant over the lifetime of the cohort. A summary of the base-case parameters is presented in *Tables 21* and *22*.

The estimates of QALYs were obtained by applying Gage and colleagues'[75] valuation of mild, moderate and severe strokes to the two disability categories derived from the modified Rankin score. Gage and colleagues' paper describes mild stroke as Rankin class 1 or 2, moderate stroke as Rankin class 3 or 4 and major stroke as Rankin class 4 or 5. The mean utilities derived by time trade-off (TTO) method for mild, moderate and major stroke on a scale of 0 (death) to 1 (current health) were 0.76, 0.39 and 0.11, respectively. Current health was also valued by TTO on a scale of 0 (death) to 1 (full health), and the calculated mean utility was 0.82. The utilities used in the study are 0.85 for non-disabled and 0.39 for disabled. The adaptation from Gage and colleagues' valuation is unclear. Health outcomes were not discounted to present values.

TABLE 21 *Base-case parameters applied in the decision analytic model (% per 3-month cycle) in Chambers and colleagues (1999)[29]*

Transition probability	Background event risks/placebo	RRR MR-dipyridamole	RRR aspirin	RRR ASA–MR-dipyridamole
Stroke years 1–2 Stroke years 3–24	4.88→1.53 1.25→2.52	16.29	18.08	39.96
TIA years 1–2 TIA years 3–24	2.68→1.42 1.42	20.06	24.42	35.90
OVE years 1–2 OVE years 3–24	1.18→0.47 0.47	12.69	31.78	56.50

TABLE 22 *Base-case parameters applied in the decision analytic model (% per 3-month cycle) in Chambers and colleagues (1999)*[29]

Transition probability	Placebo	MR-dipyridamole	Aspirin	ASA–MR-dipyridamole
Case fatality at 30 days after recurrent stroke	14.8	20.4	17.5	19.8
Withdrawal from therapy				
Months 1–3	9.0	17.0	9.0	17.0
Months 4–12	3.0→1.5	3.0→1.5	3.0→1.5	3.0→1.5
After 1 year	1.5	1.5	1.5	1.5
Adverse events (AEs)				
% of all withdrawals due to AEs	30	30	30	30
Withdrawals with AEs by type:				
Bleeding events	3	3	16	16
GI/headache	50	50	50	50
Other events	47	47	34	34
Disablement from recurrent stroke	35.6	35.6	35.6	35.6

→, Reducing to, over successive cycles.

TABLE 23 *Breakdown of main cost parameters and pattern of resource use determined by expert panel (£ sterling 1996) in Chambers and colleagues (1999)*[29]

Parameter	Length of use	Unit cost (£)	Item cost (£)
Acute care recurrent stroke (total)			2933
Stroke admission (60%)	30 days	138	4140
Outpatient follow-up (10%)	4 attendances	66	260
Readmissions (24%)	20 days	140	2800
No admission (40%): outpatient care	3 attendances	66	200
Acute care OVE			1500
Acute care TIA			73
Rehabilitation disabled (total)			718
Weekly package of therapy	Varies by severity of disability (13–26 weeks)	Varies by intensity (44–106)	Not specified
Proportion receiving rehabilitation:			
Moderate disability (46%)			640
Severe disability (54%)			173
Proportion in residential facilities (10%)	28 days	119	3330
Rehabilitation not disabled			38
Long-term care (3 months) disabled (total)			2658
Nursing home care package (38%)			4868
Care/sheltered home package (57%)			1391
Own home/independent package (5%)			194
Long-term care (3 months) not disabled			206
Withdrawal event			
Aspirin or ASA-MR-dipyridamole			62.40
MR-dipyridamole or placebo			22.00
Drugs (3 months)			
ASA-MR-dipyridamole (Boehringer Ingelheim)	Once daily	0.325	29.58
MR-dipyridamole (Boehringer Ingelheim)	Once daily	0.325	29.58
Aspirin (MIMS)	Once daily	0.0025	0.23

Summary of resource utilisation and cost data

Treatment patterns for stroke care were estimated by an expert panel and these were combined with national average unit costs to determine the costs of stroke care (*Table 23*). Productivity costs and personal or informal care were not included in the analysis. The estimated drug acquisition costs of the two treatments containing MR-dipyridamole were obtained from Boehringer Ingelheim Ltd and the costs of aspirin from the Monthly Index of Medical Specialties (MIMS). The costs of MR-dipyridamole and ASA–MR-dipyridamole are currently available from published formularies, although they may not have been available at the time of the study. The price given by Boehringer Ingelheim for the MR-dipyridamole preparations matches that are available in the BNF,[76] but the cost used for low-dose aspirin of £0.0025 per day seems low compared with the BNF[76] quoted cost of £0.036 per day. Costs were discounted at 6%.

The 5-year average costs per patient were estimated to be £15,093, £14,817, £15,056 and £14,873 for initial stroke survivors on placebo, aspirin, MR-dipyridamole or ASA–MR-dipyridamole, respectively. All three treatments were therefore reported as cost saving in comparison with no treatment and this was attributable to the reduction in the number of recurrent strokes. Although this result is maintained in the 25-year analysis, in the 2-year analysis MR-dipyridamole alone is no longer cost saving since the reductions in the costs of recurrent stroke were not sufficient to offset the additional drug costs during the first 2 years. A series of univariate sensitivity analyses were performed to examine the impact of key model parameters on the outcome of the model (*Table 24*). The results were sensitive to the costs of stroke care, the scope of costs considered in the study and the choice of effectiveness measure for reduction of stroke recurrence. The results were also sensitive to the background risk of recurrent stroke. If the effectiveness of antiplatelet therapies was assumed to cease at 2 years (the length of the ESPS-2 study), the cost per stroke averted rose.

Summary of cost-effectiveness data

The study focuses on the cost-effectiveness of ASA–MR-dipyridamole in comparison with aspirin alone for the prevention of recurrent

TABLE 24 *Sensitivity analyses around key parameters: base-case 5-year analysis (£ sterling 1996) in Chambers and colleagues (1999)*[29]

Parameter	Base-case value	Alternative value	Cost per QALY: ASA–MR-dipyridamole vs aspirin
Base case			£2900
Cost of aspirin	£0.23	£3.06	£900
Cost of acute care recurrent stroke	£2933	£2000 £4000	£2800 £900
Cost of long-term care (disabled)	£2658	£1500 £3500	£3900 £400
Scope of included costs	Health and social services	NHS only	£5700
Baseline risk of stroke	ESPS-2/OCSP	20% higher 20% lower	£500 £4000
RRs of ASA–MR-dipyridamole vs placebo (all events)	ESPS-2	Upper 95% CIs Lower 95% CIs 0% after 2 years	£–1300 £17800 £5500
RRs of aspirin vs placebo (all events)	ESPS-2	19% 23%	£1900 £4700
Discount rate for health benefits	0% per annum	6% per annum	£2000
Case fatality rate of recurrent stroke	ESPS-2	17.8% for all treatments	£3400
Mortality by disability status	Equal	Disabled mortality 2× non-disabled	£1800
Proportion of cohort assumed to be disabled initially	30.9%	25% 35%	£1200 £2400
Proportion of cohort assumed to be disabled following recurrent stroke	35.6%	30% 40%	£3100 £900

strokes. In the base case, the incremental cost per QALY gained was estimated to be £2900 for ASA–MR-dipyridamole compared with aspirin over 5 years (the equivalent ICERs over 2 and 25 years were £6800 and £1000 per QALY, respectively). MR-dipyridamole alone was estimated to be more costly and less effective than aspirin (i.e. MR-dipyridamole was dominated by aspirin).

Comments

The model is applied solely to the effectiveness results from the ESPS-2 study. Alternative sources mentioned in the study, such as the CAPRIE[21] trial of clopidogrel compared with aspirin and the meta-analyses from the ATT,[33] are not used to inform the parameters in the model. There is no discussion about the potential limitations of excluding clopidogrel as relevant treatment alternatives. The outcome of the model is sensitive to the estimated cost of stroke care, which was derived from an expert panel. This would not appear to change the decision based on the 5-year analysis, however, the cost per QALY gained over the 25-year (lifetime) analysis is likely to be higher and so the decision may be affected, although the relevant results are not reported.

The background risk of recurrent stroke was derived from the ESPS-2 placebo group for the first 2 years, and thereafter from the Oxfordshire Community Stroke Project (OCSP), a prospective cohort study undertaken in the UK. The rates of stroke recurrence observed in ESPS-2 were lower than those from the OCSP, predicting the proportion of cohort members that would have experienced a recurrent stroke by 5 years to be 20.4% compared with 29.5% in OCSP. Other published cohort studies report proportions near to 30% of stroke recurrence at 5 years,[14] highlighting the fact that participants in RCTs are generally not typical of the general population from which they are drawn. However, as the cost-effectiveness of ASA–MR-dipyridamole improved at higher background risks of recurrent stroke, this choice of background risk appears to be a conservative estimate.

A more direct valuation of the utilities of the health states used in the model would have been desirable for reporting cost per QALY gained. Gage and colleagues' valuation of stroke types was undertaken in a small US sample dominated by elderly white men (mean age 70.1 years, 86% male, 87% white) who were deemed to be at high risk of experiencing a stroke and who were asked to rate potential strokes in comparison with their current health. Consequently, these valuations may not be generalisable to a UK setting. Furthermore, although the model records the number of other vascular events and adverse events, these are not assumed to affect utility.

In the study, health benefits were not discounted. Incorporating discounting on both costs and health outcomes would result in an increase in the incremental cost per QALY gained. The decision not to discount health benefits thus results in an overestimate of their value (in net-present terms). The study only presents the average, overall undiscounted costs so no further comparisons are possible.

Review of Shah and Gondek (2000). Aspirin plus extended-release dipyridamole or clopidogrel compared with aspirin monotherapy for the prevention of recurrent ischemic stroke: a cost-effectiveness analysis[26]

Overview

This study evaluated the cost-effectiveness of ASA–MR-dipyridamole or clopidogrel against aspirin alone in the prevention of recurrent ischaemic stroke. The study is based on a simple deterministic model designed to estimate the cumulative cost of stroke care for a cohort of 1000 initial ischaemic stroke survivors during the 2-year period after stroke. The study is undertaken from a US payer perspective. Cost-effectiveness was reported using the incremental cost per stroke averted.

The model structure was simple and applied the RRR for each of the treatments in combination with a baseline risk of stroke recurrence to predict the number of recurrent strokes expected by the cohort during the 2-year time horizon. All deaths during the period were assigned to the mid-point of the analysis, although no data were reported on mortality risk or number of deaths. No other events were modelled. The model only allowed one recurrent stroke per patient in the 2-year time frame. Data used in the model were sourced from published studies and Boehringer Ingelheim Ltd.

Summary of effectiveness data

The RRR for aspirin compared with placebo in the prevention of recurrent stroke was taken from a meta-regression analysis of the dose–response effect of aspirin on stroke.[74] This meta-regression analysis considered 11 studies with aspirin dose in the range 50–1500 mg/day. The study reported that no evidence was found for a dose–response trend and hence estimated an overall mean risk

reduction of ~15%. The corresponding RRRs for clopidogrel and ASA–MR-dipyridamole, compared with aspirin, were obtained from the CAPRIE trial stroke subgroup and ESPS-2, respectively. A dose of 325 mg/day of aspirin was used in CAPRIE and 50 mg/day in ESPS-2. The RRR was highest for ASA–MR-dipyridamole, followed by clopidogrel (23.1% and 8%, respectively). The baseline risk of stroke was obtained from the OCSP.

Summary of resource utilisation and cost data

The estimates of cost for stroke care were obtained from a published study based on an analysis of the Medicare claims database. The costs of stroke in the model are those directly attributed to recurrent stroke that are reimbursable under Medicare and include drug costs. Drug costs for aspirin and clopidogrel were obtained from published pricing lists and the cost of ASA–MR-dipyridamole was obtained from Boehringer Ingelheim Ltd. The potential for double counting these drug costs is not addressed even though aspirin is routinely prescribed to such patients. However, due to the low acquisition cost of aspirin, this is unlikely to impact significantly on the results.

Summary of cost-effectiveness data

The cost per stroke averted was estimated to be US$28,472 for ASA–MR-dipyridamole compared to aspirin and US$161,316 for clopidogrel compared with aspirin, over 2 years. The cost-effectiveness of ASA–MR-dipyridamole and clopidogrel was reported relative to aspirin on the basis that treatment with aspirin was current practice for stroke survivors. Although no direct comparison was made between ASA–MR-dipyridamole and clopidogrel, the number of strokes averted and the cost per stroke averted are reported for both treatments and hence it is possible to calculate from this that clopidogrel is dominated by ASA–MR-dipyridamole.

One-way sensitivity analyses were performed (*Table 25*), the results of which demonstrated that the incremental cost per stroke averted for ASA–MR-dipyridamole never exceeded US$50,000 and that the ICER for clopidogrel never dropped below US$50,000. The value of US$50,000 is the stated threshold of willingness to pay (WTP) to avert one stroke. The authors report this threshold as a cost per health effect ratio from a published review of cost-effectiveness studies in stroke. The general term 'health effect' indicates that this valuation does not necessarily reflect a WTP value to avert one stroke specifically, since these valuations are not transferable between different health outcomes such as life-years and strokes. The sensitivity analyses involved varying the cost of stroke by 20%, the baseline risk of recurrent stroke by 20% and the RRR of aspirin versus placebo, ASA–MR-dipyridamole versus aspirin and clopidogrel versus aspirin by 10%. The outcome of the evaluation was not sensitive to these changes if assessed against the high threshold of US$50,000 per stroke averted. If a lower threshold was used (e.g. US20,000 or $30,000 per stroke averted) then the decision is affected by the sensitivity analysis, such that neither ASA–MR-dipyridamole or clopidogrel would be considered cost-effective.

TABLE 25 *Sensitivity analyses around key parameters: base-case 2-year analysis (US$ 1999) in Shah and Gondek (2000)*[26]

		Cost per stroke averted (US$)	
Parameter	**Alternate value**	**ASA–MR-dipyridamole**	**Clopidogrel**
Cost of stroke	Increased by 20%	24,110	155,749
	Decreased by 20%	32,835	166,884
Baseline risk of recurrent stroke	Increased by 20%	20,216	129,687
	Decreased by 20%	40,854	208,819
RR of aspirin vs placebo	Increased by 10%	29,335	164,693
	Decreased by 10%	27,640	158,057
RR of ASA–MR-dipyridamole vs placebo	Increased by 10%	23,901	N/A
	Decreased by 10%	34,060	N/A
RR of clopidogrel vs placebo	Increased by 10%	N/A	144,121
	Decreased by 10%	N/A	182,333

N/A, not applicable.

A time-frame of only 2 years was considered and so extrapolation of trial data was not necessary.

Comments

This study perspective is very narrow, both in time horizon and the scope of disease and treatment considered. No justification is given for the choice of comparators, although MR-dipyridamole alone is a potential alternative therapy. There is no attempt to comment on the relative cost-effectiveness of ASA–MR-dipyridamole as compared to clopidogrel. Since the common comparator of aspirin was given in different doses in the two trials (ESPS-2 and CAPRIE), this may make the risk reductions incomparable, and consequently the conclusion about the relative cost-effectiveness of the two regimens is potentially uncertain. However, the study references a previous meta-regression analysis that failed to find a statistically significant dose–response effect in aspirin studies in the secondary prevention of stroke. This provides limited support to conduct a direct comparison in the model of ASA–MR-dipyridamole and clopidogrel.

The use of the Medicare claims database makes the study difficult to generalise to the UK and unrepresentative of the true direct cost of stroke care as any payments falling outside the remit of the scheme are unaccounted for. This evaluation adds little to the clinical trial data but it does serve as a prototype for later models sponsored by Boehringer Ingelheim.

Review of Sarasin and colleagues (2000). Cost-effectiveness of new antiplatelet regimens used as secondary prevention of stroke or transient ischemic attack[25]

Overview

This study evaluated the cost-effectiveness of high-dose aspirin, low-dose aspirin and MR-dipyridamole (ASA–MR-dipyridamole) and clopidogrel for the secondary prevention of occlusive vascular events in patients who have experienced stroke or TIA. The study assesses the effect of the treatments on recurrent stroke, MI and treatment-related adverse events. The study is based on a deterministic, decision-analytic model designed to assess the lifetime costs and effects of antiplatelet treatment. Cost-effectiveness was assessed by comparing the incremental cost per QALY gained. The study was undertaken from a US payer perspective.

The model begins with a hypothetical cohort of patients who have experienced stroke or TIA and who are not candidates for carotid surgery. Patients are initially assigned to one of the three treatment options. The cycle length is 1 month and over successive cycles patients face the risk of death from other causes, MI, adverse effects of treatment or stroke, in that order. MI may be fatal or non-fatal. Stroke may be disabling, fatal or non-fatal. Adverse events may lead to withdrawal from treatment. The model considers only the first recurrent stroke. Once patients experience a recurrent stroke, those who survive remain either as long-term disabled or long-term non-disabled. Data used in the model were obtained from published studies, published pricing lists and estimated from published sources.

Summary of effectiveness data

The RRRs for recurrent stroke and MI for clopidogrel, ASA–MR-dipyridamole and aspirin monotherapy were sourced from the CAPRIE trial stroke subgroup, the ESPS-2 trial and the ATT overview of antiplatelet therapies, respectively. These were combined with age-specific risk of stroke in the general population taken from the Framingham Study and a population study of Rochester, MN, USA. The RRR for stroke was highest for ASA–MR-dipyridamole in comparison with aspirin at 24% and 8% for clopidogrel. This was reversed for MI with an RRR of 14% for clopidogrel as opposed to 10% for ASA–MR-dipyridamole, in comparison with aspirin. The risks of adverse events and MI were sourced from ESPS-2 and CAPRIE. The proportion of strokes assumed to be disabling were not considered to vary by treatment.

Base-case parameters are given in *Table 26*.

QALYs were calculated by multiplying the number of life-years spent in a particular health state by a quality-adjustment factor derived from published studies. It is not made clear how these quality-adjustment factors were calculated and they may contain information from non-preference-based functionality measures. There is no statement about discounting, so we must assume that this was not done.

Summary of resource utilisation and cost data

The costs of aspirin and ASA–MR-dipyridamole were based on market prices. The cost of clopidogrel was estimated from the market price of ticlopidine using the average relative difference in price of ticlopidine and clopidogrel from different markets. The cost of clopidogrel is available from published pricing lists and this was

TABLE 26 *Base-case parameters used in the economic model (%) in Sarasin and colleagues (2000)[25]*

Parameter	Baseline	Aspirin	Clopidogrel	ASA–MR-dipyridamole
Stroke risk, year 1	12	Relative risk reduction compared to aspirin		
Stroke risk, years 2–11	5	0	8	24
Stroke risk, years 12–21	8	(23% RRR		
Stroke risk, year 21 onwards	11	vs placebo)		
Risk of fatal MI	0.21	0	14	10
Risk of non-fatal MI	0.65	(25% RRR vs placebo)		
Adverse effects of treatment (monthly transition probability)				
GI haemorrhage leading to withdrawal	N/A	0.03	0.02	0.07
Any haemorrhage leading to withdrawal	N/A	0.05	0.02	0.05
Non-haemorrhagic	N/A	1.2	1.1	3.0
Proportion non-haemorrhagic leading to withdrawal	N/A	25	25	30
Stroke				
Case fatality rate	20	Constant across all treatments		
Proportion leading to severe disability	8	Constant across all treatments		

N/A, not applicable.

TABLE 27 *Breakdown of main cost parameters (US$ 1998) in Sarasin and colleagues (2000)[25]*

Parameter	Cost ($)
Therapy (per day)	
Aspirin	0.02
Clopidogrel	2.40
ASA–MR-dipyridamole	0.60
Adverse events	
Major GI haemorrhage	10,724
Minor haemorrhage	1,145
Non-haemorrhagic events	34.7
Stroke	
Acute stroke, hospital costs	9,256
Rehabilitation for disabled, hospital costs	53,745
Ongoing treatment following acute stroke (monthly)	1,021
MI	
Fatal MI, hospital costs	10,478
Non-fatal MI, hospital costs	14,763
Ongoing treatment following MI (yearly)	1,175

also true at the time of the study. The reason for the estimation and the calculation used is unclear. Hospital-based costs were obtained from published estimates from US hospitals and average Medicare reimbursements by diagnosis-related group (DRG). Rehabilitation costs were based on data from rehabilitation services and the cost of long-term care was based on Medicare data. The costs of CHD, other than stroke, were extracted from the Coronary Heart Disease Policy Model.[77] Indirect costs and personal or informal care were not included in the analysis. A breakdown of main cost parameter is given in *Table 27*.

The lifetime costs of treatment with aspirin, clopidogrel and ASA–MR-dipyridamole were estimated to be US$44,396, $50,388 and $41,425, respectively. The cost savings generated by ASA–MR-dipyridamole in comparison with aspirin stems from the increased number of strokes prevented. Clopidogrel prevents more strokes than aspirin alone but the drug acquisition costs are considerably higher and these offset the reduction in cost of stroke treatment. A series of univariate sensitivity analyses for most of the variables in the model showed that the results were sensitive to the efficacy of clopidogrel and the cost of clopidogrel.

Summary of cost-effectiveness data

ASA–MR-dipyridamole was estimated to be more effective and less costly than aspirin and so was cost-saving over the lifetime of the cohort considered. Clopidogrel had an estimated incremental cost-effectiveness ratio of $26,580 per QALY compared with aspirin. The study presents no conclusions regarding the relative cost-effectiveness of ASA–MR-dipyridamole in comparison with clopidogrel owing to the lack of trial information for a direct comparison. From the indirect data reported we can calculate that clopidogrel is dominated by ASA–MR-dipyridamole with a lifetime cost of $50,388 and a gain in QALYs of 11.0 per patient, compared with a lower lifetime cost of $41,425 and higher QALY gain of 11.1 per patient with ASA–MR-dipyridamole.

Comments

This study appears to be comprehensive and well presented. The study models MI events as potentially fatal and incurring a utility decrement. This is in contrast to the other studies reviewed for this patient population. There are a few limitations with respect to the cost data and the results are unlikely to be generalisable to the UK. The bulk of the cost data rely on Medicare reimbursements, which reflect only the cost of those components of stroke treatment covered by the scheme. The cost of nursing home care is not included, although this accounts for a large proportion of the cost of stroke care. Although the price of clopidogrel was directly available, an estimated price was calculated, anchored to the price of ticlopidine as it exhibited less variation than the price of clopidogrel. As this model is deterministic, the amount of variation is not relevant, and an accurate estimate of the average price of clopidogrel would be more useful in describing the cost of treatment in the USA, compared with an estimated price which may not adequately reflect the true cost.

Ticlopidine is excluded on the basis that it is likely to be replaced by clopidogrel because of its better haemotologic tolerance There is no justification for the absence of MR-dipyridamole alone. The calculation of QALYs is unclear and the quality adjustment factors used may contain information from non-preference-based measures. However, because lifetime treatment with ASA–MR-dipyridamole is less costly than aspirin alone and is demonstrated to prevent more strokes (so that more people are alive without recurrent stroke), so long as the utility associated with recurrent stroke is lower than or equal to the utility without a recurrence, ASA–MR-dipyridamole will dominate both aspirin and clopidogrel.

Review of Chambers and colleagues (2002). Development of a decision-analytic model of stroke care in the United States and Europe[30]

Overview

This study was designed to assess the cost-effectiveness of ASA–MR-dipyridamole, aspirin monotherapy, MR-dipyridamole monotherapy, ticlopidine and clopidogrel, compared with placebo, in the secondary prevention of stroke. The study also includes an initial acute-phase module to assess primary stroke treatment, the survivors of which form the initial cohort for the long-term secondary prevention module. The two modules are assessed independently, and for the purpose of this review, we shall concentrate on the long-term module for secondary prevention as the acute module is outside the scope of this review. The long-term care module is a deterministic, decision-analytic model. The model is undertaken from a national perspective for the USA, France, Germany and the UK. The study is an updated version of the model of Chambers and colleagues which was reviewed earlier in this section.[29]

The long-term care module begins with a cohort of 30-day survivors of initial ischaemic stroke. Patients may begin the model in a disabled or non-disabled state. Patients are assigned to one of the treatment strategies under consideration. The cycle length is 3 months and, over successive cycles, patients face a risk of death, stroke, OVEs or TIA, or they may withdraw from therapy. Withdrawal from therapy can be associated with treatment-related adverse events but it is not made clear how this is incorporated into the model. It is stated that patients who withdraw from therapy may go on to a second-line therapy, but this is not modelled. Stroke may be fatal or disabling. Patients experiencing a recurrent stroke enter a long-term care state defined by their level of disability. The cost-effectiveness of the alternative strategies is assessed by comparing the incremental cost per QALY gained. The model also records the number of events, average time on therapy, the number of disability-free life-years and the number of stroke-free life-years. The model is run for 5 years in the base case. Data used in the model were sourced from published studies, expert panels, published pricing lists and Boehringer Ingelheim Ltd.

Summary of effectiveness data

The RRRs for recurrent stroke, TIA and OVE, in comparison with placebo, for ASA–MR-dipyridamole, aspirin and MR-dipyridamole were obtained from ESPS-2. The RRRs of clopidogrel in comparison with aspirin were obtained from the CAPRIE trial and the RRRs of ticlopidine in comparison with aspirin were obtained from the Ticlopidine Aspirin Stroke Study (TASS).[78] The RRRs for clopidogrel and ticlopidine were then combined with the RRR for aspirin compared with placebo from ESPS-2, in order to estimate an indirect RRR for clopidogrel and ticlopidine in comparison with placebo. This indirect comparison must be interpreted with potential caution as the dosage of aspirin, the common comparator, varies between the trials. Although there is no conclusive evidence about any dose–response effect in aspirin, the very high dose of 1300 mg/day used in TASS is at the top end of the range of dosages so far considered, with the

low dose of 50 mg/day in ESPS-2 being at the very bottom end of the range. The proportion of disabling strokes is derived from ESPS-2, although this does not appear to be reported. This proportion is assumed not to vary by treatment.

The rate of recurrent stroke was modelled from the ESPS-2 placebo group for the first 2 years in the model. The rates of recurrent stroke for years 3–5 were obtained from the OCSP and these were also used to extrapolate beyond the 5-year period. The case fatality of recurrent stroke was taken from ESPS-2. The case fatality rates for clopidogrel and ticlopidine were calculated by assuming that overall mortality was the same as that for aspirin. This was because ESPS-2 and CAPRIE failed to find any significant reduction in risk of death alone from any of the treatments. In order to satisfy this assumption, the case fatality rates applied in the model for clopidogrel and ticlopidine were 18.98 and 22.13%, respectively (compared with the aspirin case fatality rate of 17.48%). These case fatality rates remain constant throughout the model. Although overall mortality is assumed to be the same for clopidogrel and ticlopidine compared with aspirin, the case-fatality rates applied in the model are actually higher compared with the rate for aspirin. This apparent anomaly is due to the use of separate health states to model fatal and non-fatal strokes. Since clopidogrel and ticlopidine are associated with a reduction in the total number of strokes (primarily non-fatal strokes) compared with aspirin, in order to maintain the same overall mortality rates as aspirin, the probability of a fatal stroke for each these treatment has to be adjusted accordingly. The same was true for ASA–MR-dipyridamole, and MR-dipyridamole, which were assigned case fatality rates of 19.75 and 20.38%, respectively.

Rates of withdrawal from therapy (ASA–MR-dipyridamole, MR-dipyridamole and aspirin) were obtained from ESPS-2. The rate of withdrawal from ticlopidine was assumed to be 50% higher than the rate for aspirin and the withdrawal rate for clopidogrel was assumed to be 11% lower. The reason for these assumptions rather than using direct withdrawal rates from TASS and CAPRIE is not stated. Given that the study utilises the RRRs from the intention-to-treat analyses, the inclusion of withdrawals from treatment is unnecessary.

QALYs were calculated by applying Gage and colleagues' utility values for mild, moderate and severe stroke to the two disability categories in the model which were defined as modified Rankin score 0–2 (non-disabled) and modified Rankin score 3–5 (disabled).[75] The utility values are the same as those used in a preceding paper by Chambers and colleagues.[29]

Summary of resource utilisation and cost data

The costs of stroke care were estimated for four countries. For the purpose of this review, we shall focus on the costs estimated for the UK. The pattern of resource use is derived predominantly from expert panels and costed with published price lists. The costs of the treatments were obtained from published pricing lists with the exception of the MR-dipyridamole preparations, for which the cost was obtained from Boehringer Ingelheim. Productivity costs and personal or informal care were not included in the analysis.

The cost of stroke care for a cohort of 1000 patients over 5 years in the UK was estimated to be £14.87 million and £14.82 million for ASA–MR-dipyridamole and aspirin, respectively. The costs for the other treatment options are not reported. Both costs and health outcomes were discounted at 6%.

Summary of cost-effectiveness data

The cost per QALY gained, compared with aspirin, was estimated as £5800 for ASA–MR-dipyridamole and the cost per stroke averted was £2100. ASA–MR-dipyridamole is the only treatment for which cost-effectiveness is reported. Both aspirin and ASA–MR-dipyridamole are stated to be cost saving over 5 years, compared with no treatment (i.e. placebo). The study claims that more favourable cost-effectiveness results were achieved when the model was run over the lifetime of the cohort, but these are not presented. The results were stated to be sensitive to the background rate of stroke recurrence, the effectiveness of therapies and the cost of long-term care of stroke survivors, although again these results are not presented. The type of sensitivity analysis is not specified but is likely to be univariate.

Comments

This study appears comprehensive, but the lack of transparency in the reported results reduces its value. Although the model was run for a range treatment options, and with baseline stroke recurrence and cost data from four countries, the results for ASA-MR-dipyridamole compared to aspirin in the UK were the only results reported. Although the study populates the model based on an indirect comparison of ASA-MR-dipyridamole, clopidogrel and ticlopidine, no statements are made about their relative cost-effectiveness.

The costs are based mainly on expert opinion which is a potential limitation that increases the uncertainty in the results. Although the costs are country-specific, only one common source of quality of life measurement is used which was derived from an elderly US population. The estimated cost per QALY gained with ASA-MR-dipyridamole compared to aspirin is higher than in the previous model in 1999,[29] and this is because of adaptations to the model such as the updated cost data and alternative source of utility data.

Review of cost-effectiveness evidence for PAD

Only one study found in the review referred to the cost-effectiveness of dipyridamole in the management of PAD. Although MR-dipyridamole is not currently licensed for use if the treatment of PAD in the UK, the study is included due to the inclusion of aspirin as a comparator and to illustrate previous attempts to assess the cost-effectiveness of antiplatelet treatment in PAD. Patients diagnosed with PAD face an elevated risk of occlusive vascular events such as stroke and MI relative to the general population. The antiplatelet therapies considered in this review will benefit these patients by reducing the incidence of stroke and MI but they will not affect the diagnosis of PAD.

Review of Zachry and colleagues (1999). Procedure costs and outcomes associated with pharmacologic management of peripheral arterial disease in the Department of Defense[27]

Overview

This study evaluates the cost-effectiveness of aspirin, pentoxifylline and DP in relation to four PAD-related outcomes in the US Department of Defense (DOD) healthcare system. The hypothesis is that pentoxifylline treats the symptoms of PAD and may reduce the risk of vascular surgery and that aspirin and dipyridamole slow the progression of the disease. The four outcomes are (1) PAD-related invasive procedures, (2) PAD-related examination procedures, (3) PAD-related hospitalisation days and (4) the cost of PAD-related procedures. This is an observational study that makes use of retrospective data and considers a period of 5 years. As can be seen in the title, the perspective is that of the US DOD.

The study included patients over 40 years of age who were discharged from US Army hospital with a record of at least one inpatient admission for PVD or atherosclerosis of the native arteries or extremities with or without intermittent claudication between October 1992 and July 1997. Inpatient admissions were classified according to the primary diagnosis, or the secondary diagnosis in combination with disease-related activities, recorded in PASBA (the Patient Administration Systems and Biostatistics Activity database maintained by the DOD), both of which defined admission for PAD. Patients were only included if they had a prescription fill rate >80% and had received medication for a period >90 days. The prescription fill rate was calculated by dividing the number of days of medication supplied by the number of days between prescription fills.

The study initially included papaverine as a fourth comparator, but this was dropped as the sample consisted of <10 patients. The number of previous PAD-related hospitalisations was used as a covariate for disease severity. An initial generalised linear model (GLM) model was constructed and tested using multivariate analysis of covariance (MANCOVA) for any interactions between treatment group and number of previous disease-related hospitalisations. Separate models were then fitted by outcome and assessed in the same way by analysis of covariance (ANCOVA). The subsequent GLM models included interaction terms for those treatment groups that showed a significant interaction in the initial model. One-way analysis of variance (ANOVA) was then used to explore differences between treatment group by age, prescription fill rate, total number of days' supply of medication (TNDS), total number of days under study (TNDUS) and number of past hospitalisations. One patient was dropped from the DP group as they were deemed to be an outlier with respect to prescription fill rate. Following this there were no statistically significant differences between treatment groups in age, ethnic origin, sex, co-morbid diseases or the length of treatment. The co-morbid diseases considered are diabetes, MI, angina and hypertension.

The study group consisted of 222 patients on aspirin, 60 on pentoxifylline, 24 of whom were cross-exposed to aspirin, and 57 on DP, 31 of whom were cross-exposed to aspirin.

Summary of effectiveness data

Data on the four PAD-related outcomes were obtained from the PASBA database. Outcome (4), the cost of PAD-related procedures, was calculated by adding the cost of invasive procedures to the cost of examination procedures. It included balloon angioplasty, femoropopliteal bypass, bypass graft vein, bypass graft other than vein,

lower extremity amputation, revision of vascular procedures of the lower extremities, thromboendarterectomy and skin grafts in the lower extremities. Each outcome measure was calculated from 90 days after the first recorded exposure to medication in order to allow the medications to have had a pharmacological effect. Patients were excluded if they had any record of seeking care outside the DOD so that the PASBA database could be assumed to include all healthcare usage by the patients under study. Data are given in *Table 28*.

Summary of resource utilisation and cost data

Cost data were calculated by multiplying the resource use recorded in the PASBA database by the hospitals' charge for the activity. The median charge was used rather than the mean and as such each charge could relate to a different geographical area. Costs were reported in 1996 US dollars.

Summary of cost-effectiveness data

The only outcome measure for which there was a significant treatment effect was (1), PAD-related invasive procedures. The least-squares mean (LSM) for the pentoxifylline group was significantly higher than that for the aspirin group. Patients in the DP and pentoxifylline groups had not been excluded if they were also receiving aspirin, so a sensitivity analysis was conducted in which these groups were separated according to cross-exposure. In this, a significant treatment group effect was found again for outcome (1) but this time also for outcome (4), cost of PAD-related procedures. With respect to outcome (4), the LSM for the pentoxifylline-alone group was significantly higher than that for the aspirin-alone group, the DP and aspirin group and the pentoxifylline and aspirin group. With respect to outcome (1), the LSM for the pentoxifylline-alone group was significantly higher than that for the aspirin-alone group and the DP and aspirin group. However, the sample size for the pentoxifylline and aspirin group and the DP alone group was <30.

Comments

MR-dipyridamole is not currently licensed for use in PAD in the UK, and therefore this study is not directly relevant to the current review, which considers only clopidogrel and aspirin for the treatment of PAD. This study did not make use of a disease or preference related outcome measure and instead used resource use items as a proxy. The implicit assumption is that a lower volume of hospital use indicates a less severe, or less progressed, disease state. Being an observational study, the results are subject to bias or confounding by unknown covariates. The study could also be confounded by the treatment groups themselves if doctors' choices of treatment are related to disease characteristics. The study relates to a very specific patient population of US DOD personnel, and to a specific DOD healthcare setting in the USA. As such, the results are unlikely to be generalisable to the UK.

Review of cost-effectiveness evidence for ischaemic heart disease

Two studies were identified which examined the cost-effectiveness of clopidogrel and MR-dipyridamole in the secondary prevention of occlusive vascular events in patients with coronary or ischaemic heart disease. Included within this definition are patients who have experienced MI as their initial event. We found no studies that evaluated the cost-effectiveness of clopidogrel or MR-dipyridamole in only patients who have experienced MI. The patients considered in the following studies face an elevated risk of ischaemic events such as stroke, TIA and MI in relation to the general population. The existence of heterogeneity (e.g. differences between the baseline event rates, costs and QoL) between the qualifying event groups may result in different conclusions concerning the relative cost-effectiveness of the treatments in each of these separate groups.

TABLE 28 *Unadjusted means and standard deviations of each outcome variable by treatment group in Zachry and colleagues (1999)*[27]

PAD-related dependent variable	Aspirin, *n* = 222: mean (SD)	Pentoxifylline, *n* = 60: mean (SD)	Dipyridamole, *n* = 57: mean (SD)
1. No. of invasive procedures per patient	0.018 (0.164)	0.167 (0.490)	0.070 (0.320)
2. No. of examination procedures per patient	0.090 (0.416)	0.100 (0.354)	0.035 (0.186)
3. No. of past hospitalisation days per patient	0.829 (4.150)	1.367 (5.725)	1.930 (7.275)
4. Procedure costs per patient (US$)	100.665 (516.807)	393.521 (1338.179)	198.059 (878.361)

SD, standard deviation.

Review of Gaspoz and colleagues (2002). Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease[79]

Overview

The following review refers to the corrected version of this paper, published in the following year.[80]

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. Option (4) employs the most optimistic estimate of the RRR associated with the combination of clopidogrel and aspirin whereas option (5) uses the trial data from CURE[81] and assumes that patients only receive clopidogrel for 1 year. The model also estimates the costs and effects of current aspirin use. The main outcome measure was cost per QALY gained. The model also recorded the 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 tracks patients who survive the first 30 days following a coronary event, which may be cardiac arrest, AMI or angina. Those patients face a yearly risk of cardiac arrest, AMI, 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 intention-to-treat 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.

Summary of effectiveness data

The percentage reductions in odds of CHD events and non-coronary mortality for aspirin were taken from the ATT overview.[33] The percentage reduction in CHD events for clopidogrel and the combination of clopidogrel and aspirin were obtained from the CAPRIE and CURE trials, respectively. The percentage reduction in 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 stroke is taken from an overview of secondary statin trials, and the RRR 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.

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.

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 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 for the whole US population. The corresponding cost associated with strategies 1–5 was estimated to be $1,874,000 million, $1,888,000 million, $2,054,000 million, $2,090,000 million and $1,898,000 million, respectively. The estimated cost of current usage of aspirin was $1,867,000 million.

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

Summary of cost-effectiveness data

The current use of aspirin is estimated to be cost-effective, with a ratio of $11,000 per QALY gained compared with no treatment. Extending the use of aspirin 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 by the high price 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 (i.e. contraindicated) 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

The study focuses on the general disease area of CHD rather than focusing on any particular aspect. As such, it may represent patients outside the scope of this review, and the relevance of the result to stroke or MI patients in particular is unclear. However, the risks of stroke and adverse events from treatment are modelled is comparable to the other models reviewed for the cost-effectiveness of secondary prevention of stroke. 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 model.[77]

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 for patients with stroke and MI 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 Annemans and colleagues (2003). Cost-effectiveness analysis of clopidogrel versus aspirin in patients with atherothrombosis based on the CAPRIE trial[31]

Overview

This study was designed to assess the cost-effectiveness of clopidogrel compared with aspirin in the secondary prevention of ischaemic events in vascular disease. The model is deterministic and is undertaken from the perspective of the public healthcare payer in Belgium.

The model begins with a cohort of hypothetical patients whose qualifying event is stroke, MI or PAD. The proportion of patients with each event corresponds to the proportions observed in

patients included in the CAPRIE trial. From this initial health state of stroke, MI or PAD patients face the risk of recurrent non-fatal stroke or MI and death from vascular or non-vascular causes, or they could remain event-free. The model considers all events rather than first events, and the cycle length is 6 months. A lifetime horizon is used in the model, which calculates event rates over a period of 2 years, after which the number of life-years lost to fatal and non-fatal events is estimated from a Canadian data source. The main outcome is cost per life-year gained (LYG). Data used in the model were sourced from published studies, expert panels and published pricing lists.

Summary of effectiveness data

The RRRs for stroke and MI for clopidogrel compared with aspirin were taken from the CAPRIE trial, but the values used are not reported. The rates of adverse events were taken from the CAPRIE trial also, and were included as a cost parameter. Only those adverse events that differed between aspirin and clopidogrel were included, although how this was defined is not reported. The adverse events included were intracranial haemorrhage, GI bleed, severe neutropenia, GI pain, peptic ulcer and all rashes. The actual rates used in the model are not reported. Clopidogrel and aspirin were assumed to affect only the risk of vascular death and so the risk of non-vascular death was assumed to be equal for the two treatments.

The effect of the qualifying events and first recurrent events on life expectancy were estimated from the Saskatchewan Health databases, a set of databases recording healthcare usage in a population of about 1 million in west Canada. Subjects in the database were defined by the first diagnosis of either PAD, stroke or MI, and further divided according to whether their first subsequent event was MI or stroke. The final population for assessing life expectancy was more than 50,000. The life expectancies used in the model are shown in *Table 29*.

All of the life expectancies were varied together by 50% in univariate sensitivity analyses.

Summary of resource utilisation and cost data

The costs employed were the cost of clopidogrel, aspirin and any concomitant medications, the cost of stroke, MI and PAD and the cost of adverse events. The cost of the drugs was based on the actual usage in CAPRIE. Although this reflects the cost of the drugs that the patients actually took, the cost to the health service could be higher if the patients were prescribed a full course of drugs but failed to take the full amount. The cost of drugs in the model were also determined by the rate at which they were reimbursed in the Belgian public health system. Clopidogrel is 75% reimbursed so the price used was €1.59 per day. Aspirin is not reimbursed and so incurred zero cost in the model. It was assumed that concomitant medicines recorded at entry to CAPRIE would continue for the subsequent 2 years. The cost of concomitant medicines was calculated by averaging use over broad drug classes and applying the cost of the most commonly used product. Further details are not given but the 6-month cost of concomitant medication was reported as €166.

Resource use patterns for the clinical management of MI, stroke and PAD were obtained by examining published studies and published Belgian healthcare statistics and were verified by clinicians. These were multiplied by unit cost data obtained from published pricing lists. DRG-based costs were taken for 1997 and inflated to 2002 values at a rate of 3% per year. Productivity costs and personal or informal care were not included in the analysis. The cost data used in the analysis are shown in *Table 30*.

The costs of events of GI pain and all rashes were calculated by assuming that they would incur at least one GP visit. The costs of the other adverse events were derived from the Belgian diagnosis-related group system, which approximates the hospital cost of each event. The way in which amputation is included in the model is not reported.

The total cost of all adverse events and the total cost of all ischaemic events were varied by 50% in univariate sensitivity analyses. Both costs and

TABLE 29 *Life expectancy by disease profile in Annemans and colleagues (2003)*[31]

Event profile	Life expectancy (years)
Initial MI	12.9
Initial MI followed by new MI	6.4
Initial MI followed by stroke	7.4
Initial stroke	11.1
Initial stroke followed by MI	4.1
Initial stroke followed by new stroke	8.9
Initial diagnosis of PAD	13.6
PAD followed by MI	4.4
PAD followed by stroke	4.7

TABLE 30 *Cost parameters used in the economic model in Annemans and colleagues (2003)*[31]

Cost parameter	Cost (€ 2002)
Acute MI	6,178
First 6 months post-MI	2,660
Second 6 months post-MI	1,197
Further 6 months post-MI	991
Acute stroke	7,366
First 6 months post-stroke	3,712
Second 6 months post-stroke	2,591
Further 6 months post-stroke	1,774
Initial diagnosis of PAD	197
Long-term follow up of PAD (6 months)	375
Amputation (total cost including nursing home)	17,683
Intracranial haemorrhage	4,522
GI bleed	1,805
Severe neutropenia	4,665
GI pain	16
Peptic ulcer	2,991
All rashes	13
Concomitant medications (6 months)	166

benefits were discounted at 3% per annum. This rate was varied from 0 to 6% in univariate sensitivity analyses.

Summary of cost-effectiveness data

The ICER of clopidogrel compared with aspirin is estimated to be €13,390 per LYG in the base case. The authors state several thresholds against which to assess cost-effectiveness from The Netherlands, the UK, the USA and Canada. The lowest of these is €20,000 and so the authors imply that clopidogrel is cost-effective.

In all but one of the univariate sensitivity analyses, the ICER of clopidogrel was <€20,000. Only when the life expectancies were decreased by 50% does the ICER for clopidogrel exceed €20,000.

A probabilistic sensitivity analysis was also performed. The RRs from CAPRIE were assigned beta distributions based on their mean and variance as reported in the trial. Cost data were assigned triangular distributions based on minimum and maximum values derived from expert opinion. The average ICER from 1000 simulations was €14,320 with a 95% CI of €6990 to €26,470. Under these assumptions, the use of clopidogrel for 2 years is cost-effective with a probability of 86% for a WTP threshold of €20,000 per life-year.

Comments

This study appears comprehensive, although there is a lack of transparency in both the the sources of data and the methods applied. The details of how some components were included in the model are unclear, especially some of the cost parameters such as adverse events and amputations for PAD patients. The study makes use of a large Canadian database to extrapolate the results from the 2-year model. This database may not be generalisable to a non-Canadian setting, since the patterns of care and the characteristics of patients with the disease can differ greatly between countries.

The study includes a detailed range of costs associated with stroke, MI and PAD. The use of triangular distributions and expert-derived maxima and minima for the cost data is not ideal as cost data are more typically characterised by a log-normal or gamma distribution, and the opinion of clinical experts is a weak data source which generates additional uncertainty in the results.

The study does not include a measure of QoL. Stroke in particular can lead to high levels of disability, and the inclusion of QoL data could affect the implementation decision based on assessment of the cost per QALY gained, as opposed to the cost per LYG.

Review of the manufacturers' submissions

Both Boehringer Ingelheim Ltd and Sanofi-Synthelabo Ltd and Bristol-Myers Squib supplied economic models and reports assessing the cost-effectiveness of clopidogrel or MR-dipyridamole in the secondary prevention of occlusive vascular events. The model and report submitted by Boehringer Ingelheim Ltd included clopidogrel, ASA–MR-dipyridamole, MR-dipyridamole and aspirin, allowing a direct comparison to be made between the alternative drugs. Due to the licensing of dipyridamole, the submission was specific to patients with an initial event of stroke or TIA. The model submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squib assessed only clopidogrel in comparison with aspirin, and assessed a cohort of patients with initial qualifying events of either stroke, MI or PAD.

Review of the Boehringer Ingelheim submission

Overview

This model is designed to assess the cost-effectiveness of MR-dipyridamole, ASA–MR-dipyridamole, clopidogrel and aspirin alone against placebo in the secondary prevention

of stroke. It is an updated version of the model presented by Chambers and colleagues,[30] which has been reviewed in a previous section. There are few differences, although ticlopidine has now been excluded as a treatment option.

In brief, the model separates the patient cohort into disabled and non-disabled, and this determines the cost and utility associated with the health states considered in the model. The definition of disabled corresponds to a modified Rankin score of 3–5 and non-disabled to a score of 0–2. The modified Rankin score is a frequently used scale for assessing functionality in stroke patients.

The level of disability is assumed to have no effect on the incidence of the main clinical outcome (recurrent stroke), although separate estimates of utility and costs are applied to each disability level. The average age of the cohort is assumed to be 70 years. In the base case, the model considers only patients who have experienced stroke. In this instance, 30.9% of patients begin the model as disabled based on the proportion observed in ESPS-2. The model can be run separately for patients who have experienced TIA as their initial event, in which case all patients begin the model as non-disabled. This seems like a reasonable assumption given that, by definition, the symptoms of a TIA cannot persist beyond 24 hours.

From the initial health state, patients face the risk (per 3-month cycle) of death, TIA and OVEs, withdrawal from treatment or recurrent stroke. Withdrawal from treatment is associated with a cost and patients who withdraw face the same risks and costs associated with no treatment. Recurrent stroke may be fatal, and following such an event a proportion of patients will become disabled. The model considers only the first recurrent stroke, at which point the patients enter a series of tunnel states to calculate their remaining lifetime costs. The model runs with a cycle length of 3 months for alternative durations of 2, 5, 25 or 30 years. Data used in the model are sourced from published studies, expert panels, published pricing lists and Boehringer Ingelheim Ltd. The perspective is that of the UK NHS and personal social services.

Source of effectiveness data

The model uses the RR of first events for stroke, TIA and OVE. The definition of OVE applied in the model differs slightly from that in the ESPS-2 trial as this event also includes MI. The RRs used for stroke and OVE include both fatal and non-fatal events. The RRs for aspirin, MR-dipyridamole and ASA–MR-dipyridamole in comparison with placebo are taken from the ESPS-2 trial. In order to obtain the RR for OVE, the RR for OVE as defined in the ESPS-2 trial is combined with that for MI according to the proportion of each event type. The RRs for clopidogrel compared with aspirin are taken from the CAPRIE trial. These are then combined with the RR for aspirin versus placebo from ESPS-2 to obtain an indirect measure of the RRR of clopidogrel compared with placebo according to the equation:

RRR clopidogrel to placebo = 1 – (1 – RRR aspirin to placebo) × (1 – RRR clopidogrel to aspirin) (1)

The RRR of clopidogrel compared with placebo for OVE is calculated using the RRR associated with clopidogrel for MI from CAPRIE.

The baseline risk of events (recurrent stroke, OVE and TIA) is taken from the ESPS-2 placebo arm for the first 2 years in the model. The baseline risk of TIA and OVE is then assumed to be continuous from the second year. The baseline risk of stroke for years 3–5 in the model is obtained from the average rate of recurrence in the OCSP,[14] which monitored a cohort of patients with a mean age of 72 years. As there was no direct evidence on the risk of recurrent stroke for year 6 onward in the model, it is estimated from the OCSP. The rates used are from Chambers and colleagues.[30] and are based on five times the incidence of stroke in the general population.

A background age-related risk of all-cause mortality is applied. This is derived from the OCSP for years 0–5. After this, the mortality rates are based on published statistics on mortality by age, adjusted by the corresponding age group in the OCSP. To model fatal stroke events, the baseline risk of death is adjusted to remove deaths due to stroke. The baseline risk of all-cause mortality was altered to 83% of the observed risk in order to adjust out stroke-related mortality. This adjustment was calculated from the rate of death from stroke and the rate of death from all causes observed in the OCSP. The case-fatality rate of stroke differs by treatment and this is calculated from ESPS-2 postpublication results where a number of non-fatal strokes were reclassified as fatal (15 of those on no treatment, 16 on aspirin, 15 on MR-dipyridamole and 11 on ASA–MR-dipyridamole). The case-fatality rate for clopidogrel is calculated by assuming that the overall mortality for clopidogrel is the same as for the aspirin group in ESPS-2. The case-fatality rates were placebo 14.8%, MR-dipyridamole

20.38%, ASA–MR-dipyridamole 19.75%, clopidogrel 18.98% and aspirin 17.48%. These case-fatality rates remain constant throughout the model. The case-fatality rates applied in the model are therefore higher with all treatments compared with the placebo rate and as such no longer appear to reflect the data reported in ESPS-2. This apparent anomaly is due to the use of separate health states to model fatal and non-fatal strokes. Since the treatments are associated with a reduction in the total number of strokes (primarily non-fatal strokes) compared with placebo, in order to maintain the same case-fatality rates as observed in ESPS-2, the probability of a fatal stroke for each treatment has to be adjusted accordingly. MI is modelled as a non-fatal event even though the relative risk used is for both fatal and non-fatal MI.

For TIA patients, the baseline risk of all events (stroke, OVE, TIA) is altered to 80% of the risk applied for patients with an initial qualifying event of stroke. This adjustment was based on the observed ratio of events in TIA patients compared with stroke patients as reported in ESPS-2. This assumption was necessary as the results of ESPS-2 were not reported separately by qualifying event.

The source of utility estimates has been updated from that in the earlier paper by Chambers and colleagues,[30] and is now based on a review of QoL studies in poststroke patients.[82] The review reports the results of 67 studies which provide 161 utility estimates for stroke. The model uses the median value from the range of utilities presented for minor, moderate and major stroke. The values extracted were 0.76 for minor stroke, which corresponds to the category of non-disabled, and 0.36 for major stroke, which corresponds to the category of disabled. Stroke was the only event assumed to affect utility, as all other events (except death) were considered transient. No separate utility estimates were applied for TIA patients. When the model is run for TIA patients, their initial utility is assumed to be that of an independent stroke survivor.

Withdrawal from clopidogrel is now assumed to be the same as withdrawal from aspirin in ESPS-2. The risk of withdrawal is highest in the first cycle, at 9% for aspirin and clopidogrel and 17% for both of the MR-dipyridamole preparations. The probability then declines until the fourth cycle, from when it remains constant at 1.5% for all drugs.

Summary of resource utilisation and cost data

The costs are still based on expert opinion as in Chambers and colleagues' model but appear to have been revised slightly and updated to the current price year. The health states assigned a cost include acute stroke, acute OVE, acute TIA, cost of ambulatory rehabilitation after stroke for disabled and non-disabled and the cost of long-term care after stroke for disabled and non-disabled, the cost of withdrawal from therapy and the cost of the drugs. The acquisition cost of the drugs is obtained from the BNF.[76] The cost of acute stroke includes the cost of the initial admission for stroke, the outpatient follow-up and the readmission rate for those patients who are admitted to hospital, and the cost of outpatient follow-up for those patients that are not admitted for stroke. *Table 31* shows the costs used in the model.

TABLE 31 *Cost parameters used in the model submitted by Boehringer Ingelheim Ltd*

Cost parameter	Cost per 3-month cycle (£)
Cost of long-term care, high disability	2670.58
Cost of ambulatory rehabilitation, high disability	3309.87
Cost of long-term care, low disability	1076.62
Cost of ambulatory rehabilitation, low disability	143.71
Cost of acute OVE	1271.07
Cost of acute TIA	230.36
Cost of acute stroke	3991.30
Aspirin	1.17
MR-dipyridamole	29.25
Combination of aspirin and MR-dipyridamole	29.25
Clopidogrel	113.50
Cost of withdrawal from aspirin or ASA–MR-dipyridamole	62.40
Cost of withdrawal from all other drugs	22.00

Summary of cost-effectiveness data

Costs are discounted at 6% and health benefits at 1.5%. In the base-case analysis (based on the deterministic results for a 30-year analysis calculated from the model by the University of York), clopidogrel is dominated by ASA–MR-dipyridamole and MR-dipyridamole is dominated by aspirin (*Table 32*). All of the treatments are cost saving compared with no treatment, with the exception of clopidogrel. The incremental cost per QALY gained with ASA–MR-dipyridamole is £3655 compared with aspirin. The ICERs for clopidogrel and MR-dipyridamole are not estimated since these are dominated in the base-case analysis.

TABLE 32 *Cost-effectiveness results for ASA–MR-dipyridamole compared with aspirin from the model submitted by Boehringer Ingelheim Ltd: 30-year analysis undertaken by the University of York for a cohort of 1000 patients*

Drug	Cost (£)	Life years	QALYs	Cost per QALY (vs aspirin) (£)
Placebo	37,804,957	6877	4212	Dominated
Aspirin	37,561,704	6921	4260	–
MR-dipyridamole	37,709,840	6875	4231	Dominated
Clopidogrel	38,919,361	6935	4277	Dominated
ASA–MR-dipyridamole	37,777,355	6986	4319	3655

TABLE 33 *Univariate sensitivity analysis on cost parameters in the model submitted by Boehringer Ingelheim Ltd: base-case 5-year analysis*[a]

Parameter	Base-case value (£)	Alternative value (£)	Cost per stroke avoided (£)	Cost per QALY[b] (£)
Base case			**2255**	**4207**
Cost of acute stroke	3991.30	2400	3729	6959
		4600	1691	3155
Cost of OVE	1271.07	0	2630	4908
		2600	1862	3475
Cost of TIA	230.36	0	2344	4374
		500	2150	4012
Cost of long-term care, high disability	2670.58	1300	4693	8757
		4000	Cost saving	Cost saving
Cost of long-term care, no/low disability	1076.62	500	342	639
		1600	3990	7446
Cost of rehabilitation, high disability	3309.87	1600	3027	4801
		4800	1582	Cost saving
Cost of aspirin (higher cost of drug)	1.17	0.23	2573	4801
		10.00	Cost saving	Cost saving

[a] Some figures differ from those in the report submitted by Boehringer Ingelheim Ltd. In replicating their analysis, a number of minor errors in the submission were found. The correct figures are reported here.
[b] Cost per QALY gained with treatment with ASA–MR-dipyridamole compared with aspirin.

Deterministic sensitivity analysis

Several univariate (one-way) sensitivity analyses were conducted for a period of 5 years. The results are presented in *Tables 33* and *34* for ASA–MR-dipyridamole compared with aspirin. Clopidogrel and MR-dipyridamole monotherapy were excluded since they were both dominated in the base-case analysis. It is unclear whether these strategies would have continued to be dominated in each scenario considered.

Since the initial treatment decision may have consequences which will affect patients for the rest of their lifetime, it is more appropriate to consider the sensitivity analyses over the 30-year (lifetime) run of the model. This approach also mirrors the main assumption made by Boehringer Ingelheim that patients will continue on treatment for the remainder of their lives. As such, the same sensitivity analyses presented in *Tables 33* and *34* for a 5-year analysis are presented in *Tables 35* and *36* over a 30-year period. These results are based on additional analyses carried out by the University of York team using the model submitted by Boehringer Ingelheim Ltd. The only parameter altered for these analyses by the University of York is the number of years for which the model runs.

After extending the analysis to 30 years, the cost per QALY was lower and the cost per stroke avoided higher in comparison with the 5-year base-case analysis. This is because, by 5 years, about 20% of the cohort have experienced a recurrent stroke. Once a patient has a recurrent stroke, they then enter a series of tunnel states in which they incur no further strokes but can accrue QALYs. At 30 years, the number of patients

TABLE 34 *Univariate sensitivity analysis on non-cost parameters in model submitted by Boehringer Ingelheim Ltd: base-case 5-year analysis*[a]

Parameter	Base-case value (£)	Alternative value (£)	Cost per stroke avoided (£)	Cost per QALY[b] (£)
Base case			**2,255**	**4,207**
RRR of ASA–MR-dipyridamole vs placebo	ESPS-2: 0.370 stroke; 0.359 TIA; 0.405 OVE	Upper 95% CI: 0.487 stroke; 0.474 TIA; 0.744 OVE	Cost saving	Cost saving
RRR of ASA–MR-dipyridamole vs placebo	ESPS-2	Lower 95% CI: 0.252 stroke; 0.386 TIA; 0.244 OVE	16,113	70,407
RRR of ASA–MR-dipyridamole vs placebo	ESPS-2	Limited to 2 years	25,125	20,262
No treatment risks (= background risks of events)	ESPS-2/OCSP	+20%	836	1,544
No treatment risks	ESPS-2/OCSP	–20%	3,192	5,988
Mortality of disabled compared to non-disabled	Equal	2× non-disabled level	1,857	3,760
Initial disability	30.9%	25% 35%	1,901 2,500	3,347 4,869
Disability after stroke	35.6%	30% 40%	2,920 1,732	5,888 3,053
Utility weights	0.76 and 0.36	0.72 and 0.41 0.55 and 0.26 0.89 and .072	2,255 2,255 2,255	4,765 5,810 4,714

[a] See footnote *a* in *Table 33*.
[b] Cost per QALY gained with treatment with ASA-MR-dipyridamole compared with aspirin.

experiencing recurrent stroke has increased to just over 30%. Consequently, whereas the majority of recurrent strokes avoided are incurred during the first 5 years, the QALYs gained continue to accrue throughout the entire follow-up period.

The sensitivity analysis demonstrated that the results appeared robust to a range of alternative scenarios. With the exception of one scenario, the cost per QALY gained with ASA–MR-dipyridamole, compared with aspirin, reaches a maximum of £20,009 across the univariate sensitivity analyses considered. However, when the effectiveness of ASA–MR-dipyridamole is restricted to the first 2 years of the model only, while also assuming that the drug acquisition costs are continued for the rest of the patient's life, the treatment is no longer cost-effective compared with aspirin. Although this represents a 'worse-case' scenario, it does indicate that the cost-effectiveness of lifetime treatment with ASA–MR-dipyridamole is, in part, dependent on the assumption of a continued relative treatment effect compared with aspirin over this longer period.

TIA

For patients with TIA, the baseline risk of events was adjusted to 80% of those in the stroke model, as outlined previously. Aside from this adjustment, all the other model parameters remain the same as those used in the stroke model (including the RRs).

The base-case 30-year analysis of the cost-effectiveness of ASA–MR-dipyridamole was calculated from the model by the University of York team and is estimated as £2038 per QALY gained. The lower cost-effectiveness ratio in TIA patients compared with that in stroke patients is due to the assumption that all patients in the TIA group initially start the model in the non-disabled state. Consequently, a higher proportion of patients will become disabled (and incur a higher cost) following the first stroke in TIA patients,

TABLE 35 *Univariate sensitivity analysis on cost parameters in model submitted by Boehringer Ingelheim Ltd: 30-year analysis conducted by University of York*

Parameter	Base-case value (£)	Alternative value (£)	Cost per stroke avoided (£)	Cost per QALY[a] (£)
Base case			**6330**	**3655**
Cost of acute stroke	3991.30	2400	7768	4486
		4600	5780	3338
Cost of OVE	1271.07	0	6696	3867
		2600	5948	3435
Cost of TIA	230.36	0	6405	3699
		500	6242	3605
Cost of long-term care, high disability	2670.58	1300	9634	5564
		4000	3125	1805
Cost of long-term care, no/low disability	1076.62	500	2109	1218
		1600	10162	5868
Cost of rehabilitation, high disability	3309.87	1600	7103	4102
		4800	5657	3266
Cost of aspirin (higher cost of drug)	1.17	0.23	6690	3864
		10.00	2946	1701

[a] Cost per QALY gained with treatment with ASA–MR-dipyridamole compared with aspirin.

TABLE 36 *Univariate sensitivity analysis on non-cost parameters in model submitted by Boehringer Ingelheim Ltd: 30-year analysis conducted by University of York*

Parameter	Base-case value (£)	Alternative value (£)	Cost per stroke avoided (£)	Cost per QALY[a] (£)
Base case			**6330**	**3655**
RRR of ASA–MR-dipyridamole vs placebo	ESPS-2: 0.370 stroke; 0.359 TIA; 0.405 OVE	Upper 95% CI: 0.487 stroke; 0.474 TIA; 0.744 OVE	3466	1853
RRR of ASA–MR-dipyridamole vs placebo	ESPS-2	Lower 95% CI: 0.252 stroke; 0.386 TIA; 0.244 OVE	19083	20009
RRR of ASA–MR-dipyridamole vs placebo	ESPS-2	Limited to 2 years	Additional cost, no benefit	Additional cost, no benefit
No treatment risks (= background risks of events)	ESPS-2/OCSP	+20%	4924	2812
No treatment risks	ESPS-2/OCSP	–20%	7225	4198
Mortality of disabled compared with non-disabled	Equal	2× non-disabled level	Cost saving	Cost saving
Initial disability	30.9%	25%	5432	2982
		35%	6954	4166
Disability after stroke	35.6%	30%	7415	4496
		40%	5478	3049
Utility weights	0.76 and 0.36	0.72 and 0.41	6330	3980
		0.55 and 0.26	6330	5050
		0.89 and .072	6330	3495

[a] Cost per QALY gained with treatment with ASA–MR-dipyridamole compared with aspirin.

compared with patients in the stroke model, since a proportion of patients in the stroke model are already assumed to be disabled from the start.

In this additional analysis in TIA patients undertaken by the University of York team, MR-dipyridamole monotherapy is still more costly and less effective than aspirin in the secondary prevention of stroke among patients experiencing TIA as their initial event. Clopidogrel is not licensed for patients who have experienced only TIA, and as such is not currently a potential comparator. However, it is dominated by ASA–MR-dipyridamole when included in the analysis.

Probabilistic sensitivity analysis

Although the base-case model is deterministic, a partial probabilistic sensitivity analysis was also conducted as part of Boehringer Ingelheim Ltd's submission. Five variables considered important in the univariate sensitivity analysis were assigned a distribution. These variables were as follows:

1. the RRR associated with ASA–MR-dipyridamole
2. the background risk of recurrent stroke
3. the cost of acute stroke
4. the cost of long-term care for stroke survivors with a high level of disability
5. the cost of long-term care for stroke survivors with a low level of disability.

The RRR was modelled as a normal distribution using the 95% CIs reported in ESPS-2. The other variables were all modelled as triangular distributions, using the range of values applied in the univariate sensitivity analysis.

The probabilistic analysis reported the ICER using alternative outcomes (LYG, QALYs gained and strokes avoided). However, the analysis reported by the manufacturers was based on the sampled values of the ratio itself (as opposed to monitoring the costs and outcomes separately). This causes a potential problem since a negative ratio could either reflect a dominant (e.g. cost savings, improved outcomes) or a dominated scenario (higher costs, lower outcomes). In the manufacturer's submission, all negative ratios were considered to represent dominated scenarios in which ASA–MR-dipyridamole would not be considered cost-effective. However, since a proportion of these instances may actually represent a scenario in which ASA–MR-dipyridamole actually dominates aspirin, the interpretation of the probabilistic sensitivity analyses presented in the submission is uncertain. This assumption, however, appears conservative in this instance.

One way to overcome the problems associated with probabilistic analysis of the ratio statistic (ICER) is to monitor costs and effects separately. These can then be used to generate a net benefit associated with treatment. In contrast to the ICER, there are no problems of interpretation using the net-benefit statistic.[83] In order to address this potential limitation, supplementary analyses were conducted by the University of York team using the model submitted by Boehringer Ingelheim Ltd. In addition, the probabilistic analysis was also extended by incorporating additional distributions to reflect the relative risks for clopidogrel and MR-dipyridamole monotherapy compared with aspirin. Although these options were dominated in the base-case analysis, it is unclear whether they would still be dominated in the sensitivity analysis. Consequently, it is more appropriate to include all the comparators in the probabilistic sensitivity analysis. All the RRRs were modelled as log-normal distributions, either directly or indirectly. Where a mean and CI were reported, the standard error was calculated and used with the reported mean to inform a log-normal distribution in Crystal Ball 2000. Where CIs were not reported, the variance in the (log) RR was calculated directly from the event data reported according to the standard formula.[84] This was used with the (log) RRR to inform a normal distribution, and the exponentiated value from this distribution was used as the estimated RRR in the model. By incorporating these additional parameters, the cost-effectiveness of all relevant strategies can be considered fully. The cost-effectiveness acceptability curves for all four treatments based on these additional analyses are shown in *Figure 7*.

The revised analysis shows that if the NHS is prepared to pay above £4000 per QALY then ASA–MR-dipyridamole appears cost-effective. For values less than this amount, treatment with aspirin alone is the most cost-effective option. The probability that ASA–MR-dipyridamole is cost-effective increases as the threshold WTP increases. At a value of £30,000 per QALY, ASA–MR-dipyridamole has a 78% probability of being cost-effective.

Due to the lack of available data to assign distributions to the remaining parameters in the model, a full probabilistic analysis was not undertaken.

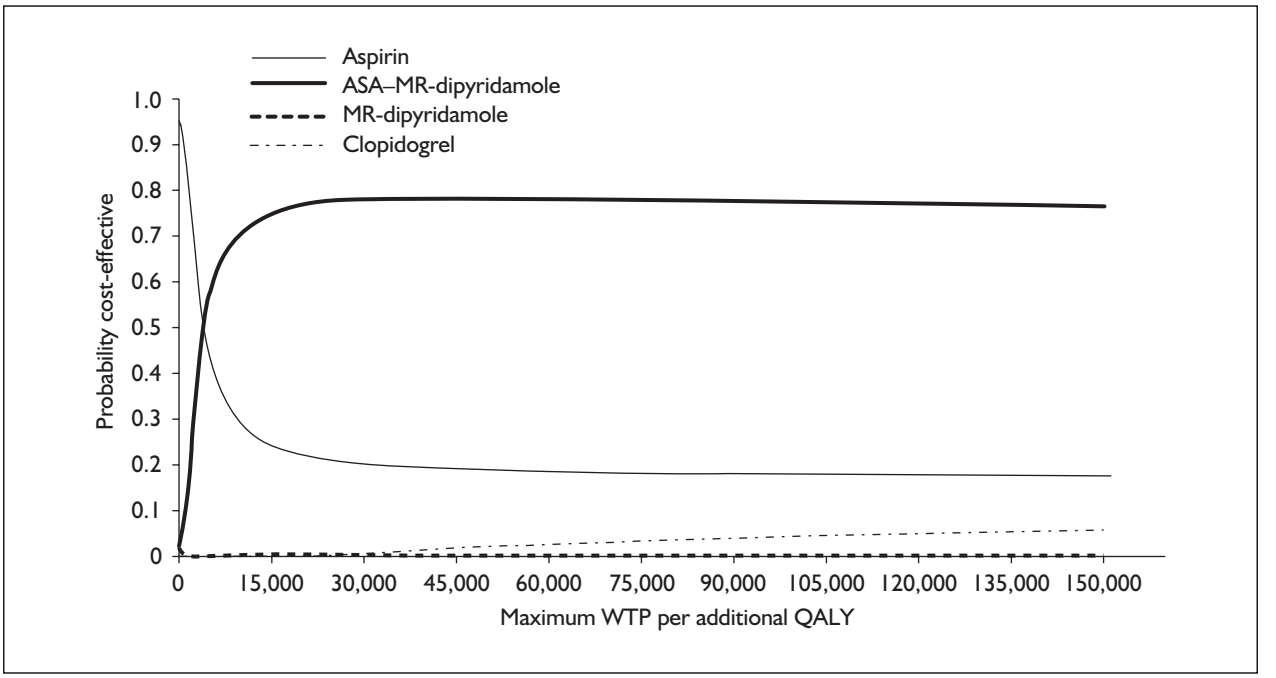

FIGURE 7 *Cost-effectiveness acceptability curves calculated from additional analyses undertaken by the University of York team using the model submitted by Boehringer Ingelheim Ltd*

Comments

Validity of assumptions

The submitted model considers a comprehensive range of treatment alternatives, ensuring that the subsequent results address the relevant decision facing the NHS. However, there are a number of potential issues which need to considered when assessing the validity of these findings. First, in the absence of direct head-to-head evidence for all the strategies, indirect methods were used to facilitate the comparison between the alternative strategies. Estimates of the relative risks for ASA–MR-dipyridamole and MR-dipyridamole, in comparison with aspirin, were taken directly from the ESPS-2 trial. In the absence of direct evidence on the relative effectiveness of clopidogrel, ASA–MR-dipyridamole and MR-dipyridamole, an indirect comparison was made by using the RRs reported for a common comparator (aspirin) in ESPS-2 and CAPRIE. However, the CAPRIE and ESPS-2 trials used very different doses of aspirin monotherapy as comparators. A dose of 325 mg/day was employed in the CAPRIE trial whereas a much lower dose of 50 mg/day was given in ESPS-2. If these doses of aspirin are not expected to have the same effects, then the indirect comparison of clopidogrel with MR-dipyridamole in this manner may be invalid. A recent study conducted a meta-regression of aspirin trials to assess any possible dose–response effect of aspirin in stroke patients.[74] That study failed to find a statistically significant relationship, and the estimated coefficient (0.000068/mg) suggested that if a relationship did exist then lower doses would in fact be very marginally more effective than higher doses. Several other studies have confirmed this finding that lower doses of aspirin perform equally as well as higher doses.[85,86] This evidence provides provisional support to facilitate a comparison in the model of ASA–MR-dipyridamole and clopidogrel using the methods proposed.

The model is focused primarily on stroke as this is the indication for which MR-dipyridamole is licensed, and is the principal risk faced by the cohort under consideration. The model considers only the first recurrent stroke, which appears reasonable given the limited data available for multiple recurrent strokes. The OCSP is considered suitable for modelling the baseline risk for patients taking placebo as only 6% of the patients who survived to 6 months received antiplatelet treatment and only 1% received anticoagulants.[14] Aspirin is now more commonly prescribed to patients who have experienced stroke, and so modern cohort studies would not represent the risk of recurrent stroke for patients receiving no treatment. However, more prevalent use of aspirin is not the only difference between stroke care now and in 1981–86 when the OCSP recruited patients, and so there may be a question of the relevance of these baseline risks to stroke patients today. However, in the absence of

alternative sources of evidence from the UK, the OCSP probably represents the most reliable source of baseline risk of events for the purpose of this model.

As there was no direct evidence on the risk of recurrent stroke for year 6 onward in the model, this risk is estimated from the OCSP. The rates used from Chambers and colleagues are based on five times the incidence of stroke in the general population. This relationship was estimated from that between the observed number of strokes in the OCSP population compared with the number expected in the general population from the second up to the fifth year following initial stroke.[14] This is a rough approximation of the average relationship over these 4 years. However, the relationship showed a trend with the ratio of observed to expected strokes falling from year 2 to 5. This relationship is assumed to remain constant for the lifetime of the cohort and may therefore result in an overestimate of the number of recurrent strokes.

MI and death

Both ESPS-2 and CAPRIE indicate that the treatments may also have an effect on the risk of MI and death. The exclusion of these events from the model submitted by Boehringer Ingelheim may have an important impact on the overall results presented here. MIs are modelled in Boehringer Ingelheim's model as transient, non-fatal events that do not incur a utility decrement. As this is a cohort of patients who have had stroke, and the predominant risk is of recurrent stroke, only a relatively small proportion will experience an MI, this assumption may be reasonable. With respect to the inclusion of death, the use of case-fatality rates rather than the direct modelling of vascular death may be expected to impact on the results. Although the RRR for fatal and non-fatal strokes was used, the majority of the reduction observed in the ESPS-2 trial stemmed from the reduction in non-fatal strokes, and therefore the case-fatality rates assigned in the model are aimed at adjusting the proportion of fatal strokes accordingly. This is a rather complex method of modelling the effect of treatment on vascular death, which could have been included more readily by modelling vascular death as a separate state in the model. A further criticism is that the model does not consider a treatment effect on non-vascular death. One of the primary end-points in ESPS-2 was death from any cause. Pairwise comparisons following factorial analysis show a non-significant RR increase of 2.7% in all-cause death for ASA–MR-dipyridamole compared with aspirin alone. The CAPRIE trial also indicates that clopidogrel is associated with a non-significant RR increase for non-vascular death when compared with aspirin alone. The lack of statistical significance in this instance is not sufficient evidence of equivalence in this outcome. This could have been addressed either by modelling all-cause mortality or by quantifying the uncertainty in both vascular and non-vascular mortality parameters in the probabilistic analysis. Excluding the potential impact of treatment of non-vascular death may lead to an overestimate of the benefits associated with treatment with ASA–MR-dipyridamole or clopidogrel.

TIA

The model can be run for patients with TIA as qualifying events by an adjustment to the proportion of baseline events. The distinction between TIA and minor ischaemic stroke is more relevant for epidemiological purposes than for clinical decision-making. The 24-hour cut-off allows for consistent measurement of the number of TIAs across many countries, but the risks associated with a patient whose symptoms persisted for 36 hours may in practice be almost identical with those for a patient whose symptoms persist for 20 hours. Several observational studies, including the OCSP,[14] have found that the long-term risk of recurrent stroke following TIA is indistinguishable from that following a minor ischaemic stroke. Therefore, the 80% event rate observed in the trial may underestimate the baseline number of events. As the same RRR is used for TIA-qualifying as for stroke-qualifying patients, the effect of applying this to a lower baseline risk would be to make the treatment look less cost-effective – in other words, the assumptions in the model would appear to be conservative with respect to the cost-effectiveness of ASA–MR-dipyridamole. In the model this is partially offset by the improvement in cost-effectiveness seen through assuming that no TIA patients begin the model as disabled.

Utility

The utility values used in the model were selected from the median estimates from a range of published utility values by stroke severity. This is rather arbitrary as the studies in the review use five different measures for assessing utility which consist of time trade-off (TTO), standard gamble (SG), rating scale (RS), expert or author opinion or some other health status instrument. The studies are also of varying size and assess the utilities of different groups, including patients, experts, community members or the authors

themselves. The upper and lower bounds of the health states described when eliciting the utilities also varied between studies. By selecting the median utility for each type of stroke from the separate distributions of utilities for each, it is possible that each utility is sourced from a separate study. A more rigorous extraction of utility values could have considered only those studies using the same method of elicitation in members of the community with a similarly framed question.

The studies used in Tengs and colleagues' review[82] were available on request from the author. By reviewing these, it is revealed that the utility of major stroke of 0.36 applied in the model was that reported in a study using an RS in members of the community. The value of 0.76 for minor stroke is the average of two studies reporting the authors' judgements. Stroke was the only event determined to affect utility as all other events (except death) were considered transient. TIA patients were assigned the same utility as independent stroke survivors.

Costs

The model considers withdrawal from treatment and assigns a small cost to patients who withdraw on the assumption that this could have been the result of a patient experiencing an adverse event. The RRRs used are from the intention-to-treat analysis and therefore the additional modelling of withdrawals is unnecessary. The cost associated with withdrawals which pertains to associated adverse events could have been modelled directly as an additional health state representing adverse events, or the cost could have been apportioned in another way. The cost of withdrawal of £62.40 or £22.00 assigned in the model must implicitly represent the costs of minor adverse events only, as the cost of a major adverse event such as a GI bleed would be considerably higher.

The costs for the health states used in the model are based on expert opinion, and as such their validity and accuracy could be questioned. The long-term care costs, in particular, could affect the outcome of the model as they represent a large proportion of the costs over the lifetime of the cohort.

Review of the Sanofi-Synthelabo Ltd and Bristol-Myers Squib submission

Overview

This model is designed to assess the cost-effectiveness of clopidogrel or aspirin in the secondary prevention of occlusive vascular events. The model is probabilistic and decision-analytic. The model begins with a cohort of patients who have experienced occlusive vascular events, which comprise patients with a qualifying event of MI, stroke or PAD. The patients then face the risk of stroke, MI, vascular death or death from other causes, or may remain event-free over successive cycles. Patients experiencing stroke or MI enter a health state specific to the first year after the event where the risk of further events is higher than in subsequent years. If they survive this first year event-free they enter post-stroke and post-MI states, where the risks of experiencing further events are lower. Event-free PAD patients remain in the initial health state for PAD as they are assumed to have a chronic condition without an acute phase. No other events, such as adverse events associated with treatment, are modelled. The cycle length in the model is 1 year and the model is run for 40 cycles. The cohort is assumed to have a mean starting age of 60 years in the base case and each qualifying event is represented according to the estimated proportion of people in the UK with stroke, MI and PAD.

Patients are assumed to take clopidogrel for only 2 years and then move on to lifetime treatment with aspirin. The justification given for this assumption is based on the duration of follow-up reported in CAPRIE. Data used in the model are sourced from published studies, national statistics and published price lists. The model also employs patient-level data obtained in personal correspondence with the authors of published studies. The model runs for the lifetime of the cohort and is undertaken from the perspective of the UK NHS.

Summary of effectiveness data

The RRR for all events rather than first event was used. These data from CAPRIE were taken from an abstract by Easton.[49] The RRRs for clopidogrel in comparison with aspirin for all MI, stroke and vascular death are 19.2, 5.2 and 7.6%, respectively. The risk of MI following stroke is also taken from CAPRIE and is 0.72% per annum. The baseline risks of events according to qualifying event of stroke, MI or PAD are taken from three cohort studies: the Nottingham Heart Attack Registry (NHAR), the South London Stroke Register (SLSR)[87] and the Edinburgh Claudication Study (ECS).[88] The baseline risk of non-vascular death is calculated from published national statistics on cause of death by International Classification of Diseases (ICD) code, and by excluding the proportion of deaths with ICD codes corresponding to diseases of the circulatory system. These baseline risks of events from the

observational cohorts are implicitly assumed to be the risks associated with treatment with aspirin. The baseline risk of events is calculated by the initial age of the cohort (modelled between 60 and 90 years old). The proportions of patients with MI, stroke and PAD in the UK were estimated and used to determine the initial baseline event rates in the model. As a result, the model produces a weighted average set of results obtained from the three distinct subgroups.

The baseline probability of any event was calculated using a logistic regression to model the risk of any event at each age from 60 to 90 years old from each of the cohort studies. 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. The risk of MI for stroke patients in the SLSR was assumed to be the risk of MI following stroke in CAPRIE, and this is constant throughout the model. These equations were calculated separately for the first year after a qualifying event and all subsequent years by splitting the observational cohort groups accordingly. The probability of events in all subsequent years more than 1 year post-qualifying event were estimated using an exponential parametric survival analysis.

The probabilities of MI, stroke and vascular death can be calculated from the ratios estimated in the multinomial regression. The probabilities of these events were modelled as log-normal distributions. As this distribution is not bounded at one, a potential error is incurred since the probability of stroke, vascular death and stroke or vascular death could exceed one in some simulations. Where this was the case, the probability of the remaining event in the regression (MI) was predicted to be <0 in order to ensure that the total sum of probabilities for all health states equals one. This problem can be overcome by modelling the ratios directly in a distribution, such that when they are converted into probabilities these automatically sum to one. The impact of this error is addressed in later sections of this report.

QALYs were calculated by applying utility values taken from published studies to four health states: MI year 1, MI post-year 1, stroke (combined disabled and non-disabled) and PAD. The utilities for MI were taken from the three separate studies. The utility for stroke was taken from a meta-analysis of utilities for stroke. This provided an estimate of 0.778 for the utility of a patient who remains independent following stroke and an estimate of 0.519 for the utility of a patient who is left dependent following stroke. These were then combined on the assumption that 35% of stroke survivors will be dependent.[29] The utility for PAD was taken from a study which estimated the utility in relation to TTO and functional status utilities for other vascular diseases. The utilities for each health state are shown in *Table 37*.

TABLE 37 *Utility values used in the model submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squib*

Heath state	Utility (range)
Non-disabling stroke	0.78 (0.66–0.90)
Disabling stroke	0.52 (0.42–0.62)
New MI, year 1	0.80 (0.70–0.90)
New MI, post-year 1	0.93 (0.88–0.98)
PAD	0.90 (0.85–1.00)

The utility values were assigned triangular distributions. Three utility values were obtained for the MI 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. The bounds of the utility of PAD were based on the opinion of the authors.

Summary of resource utilisation and cost data

The costs associated with stroke are taken from the study by Chambers and colleagues[29] and inflated to the current price year. These include long-term care but not informal, personal or productivity costs. The costs associated with MI are taken from the decision model recently undertaken to evaluate the cost-effectiveness of glycoprotein IIb/IIIa inhibitors in patients with non-ST-elevation acute coronary syndrome (ACS).[89] The costs associated with MI were calculated from data collected alongside the 1998 cohort of the NHAR. The cost of revascularisation procedures are taken from NHS reference costs and the costs of bleeding events are taken from a published study.[90,91] The cost of long-term care for PAD patients is estimated at £1000 per year, which is an assumption made by the model authors. The costs associated with the MI states were modelled as normal distributions truncated at a minimum of £500. The stroke costs are modelled as triangular distributions, the bounds of which are based on the opinions of the authors. The cost of PAD was modelled as a triangular distribution with the bounds based on an assumption by the authors. The mean costs used in the model are displayed in *Table 38*.

TABLE 38 *Cost parameters used in the model submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squib (sterling 2002)*

Cost parameter	Cost per year (range) (£)
Stroke qualifying event (0% disabled)	862.00 (690–1,724)
New stroke year 1	7,465.80 (5,599–11,199)
New stroke post-year 1	4,532.80 (3,400–6,799)
MI year 1	3,966.00 (3,209–4,723)
MI post-year 1	1,587.00 (840–2,334)
PAD	1,000.00 (500–1500)
Aspirin	3.47
Clopidogrel	460.29

TABLE 39 *Summary of the cost-effectiveness results from the model submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squib: base-case 40-year (lifetime) analysis*

Result	Aspirin	Clopidogrel
Number of MIs	564	544
Number of strokes	233	233
Number of vascular deaths	469	466
LYG	14,121	14,190
QALYs gained	11,928	11,987
Intervention costs (£)	6,739	894,528
Total cost (£)	18,246,868	19,098,867
Cost per QALY gained vs aspirin (£)	–	14,525

Summary of cost-effectiveness data

Costs are discounted at 6% and heath benefits are discounted at 1.5%. The model calculates the total cost and total number of events, and presents cost per QALY or cost per LYG. A summary of these results is reported in *Table 39*.

In the deterministic base case, the incremental cost per QALY gained with clopidogrel compared with aspirin over the 40-year modelling period was estimated as £14,525. The probabilistic analysis suggests that the incremental cost per QALY has an ~74% probability of being less than £30,000.

In order to inform about the cost-effectiveness of clopidogrel in each of the patient subgroups separately, additional analyses were undertaken by the University of York team. The secondary prevention model was conducted for the average proportion of MI, stroke and PAD patients in the UK. These proportions were assigned distributions and allowed to vary in the probabilistic model. Due to the potential heterogeneity in the different patient groups considered in the model, it may 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 in each patient group. Due to the potential heterogeneity across these groups, it is important to consider them separately in the model.

To explore this issue in more detail, we ran the model for each subgroup separately to obtain an estimate of the cost-effectiveness of clopidogrel in each patient group. We used the same model structure and data sources used by the manufacturers in their submission. However, we also ran the model with the age-related event data modelled by assigning a normal distribution to the (log) ratio of events, rather than modelling the probability of each event as a log-normal, in order that the probabilities always summed to one (to address the potential source of error highlighted earlier). This is the only other alteration to the model made by the University of York team in this section. To explore the impact that this error made to the base-case model, we re-estimated the base-case results for the weighted analysis across the separate groups using the revised formulae. The results indicated that although the error had an impact on the results (e.g. the probability that clopidogrel was cost-effective at a threshold of £30,000 per QALY fell from 74% to 69%), the error did not impact qualitatively on the implementation decision, that is, clopidogrel remained cost-effective for reasonable threshold values for the ICER.

The deterministic cost per QALY for each qualifying event subgroup estimated from these additional analyses is £12,527 in the MI group, £15,896 in the stroke group and £17,218 in the PAD group. These results are consistent with the base-case estimate reported by the manufacturers, which used proportions of approximately 0.25, 0.53 and 0.23 for stroke, MI and PAD, respectively. The RRR from clopidogrel is higher for MI events than for stroke, and since the MI subgroup has the highest probability of recurrent MI, the use of clopidogrel has the lowest ICER in this group.

Deterministic sensitivity analysis

Several univariate and multivariate sensitivity analyses were conducted (*Table 40*).

The ICER is most affected by sensitivity analyses numbers 11, 12 and 15. The upper 95% CI values

TABLE 40 *Univariate and multivariate sensitivity analyses in the model submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squib*

Assumption	Cost per QALY (clopidogrel vs aspirin) (£)
Base case	**14,525**
1. Health state costs set to upper 95% CI	14,721
2. Health state costs set to lower 95% CI	14,618
3. Initial stroke cost including disabled survivors	17,017
4. Trial compliance rates	11,301
5. RRRs set to 80%	18,298
6. Utilities set to upper 95% CI	13,035
7. Utilities set to lower 95% CI	15,775
8. Health state costs set to upper 95% CI and utilities set to lower 95% CI	15,988
9. RR for MI set to upper 95% CI	15,735
10. RR for stroke set to upper 95% CI	19,386
11. RR for vascular death set to upper 95% CI	More costly, less effective
12. RR for MI, stroke and vascular death set to upper 95% CI	More costly, less effective
13. Age at start of model 70 years	11,340
14. Age at start of model 80 years	11,598
15. Equal 6% discount rate for costs and effects	21,852

of the RRs of stroke and vascular death on clopidogrel constitute relative risk increases (analyses 11 and 12), which explains why clopidogrel is dominated in these analyses. The assumptions about the discount rates in sensitivity analysis number 15 cause the cost per QALY gained to rise above £20,000. This assumption reduces the net present value of the future health gains associated with clopidogrel while leaving the net present value of the cost the same, in comparison with the base-case analysis.

Sensitivity analysis number 3 explores the impact of changing the initial stroke cost. This cost refers to the long-term care following the initial stroke rather than the acute event itself. As more patients on clopidogrel remain longer in this initial state without a recurrent event, the cost-effectiveness of clopidogrel becomes less favourable as the cost of this state increases. This is also because the value of preventing recurrent events is reduced. It would seem more realistic to assume that a proportion of the qualifying patients are disabled, as this is borne out in the trial data (ESPS-2), and therefore the cost associated with the initial stroke event state should reflect this.

When the compliance is entered as 80% instead of 100% in the base case, the cost-effectiveness becomes more favourable. More people remain alive and on treatment with clopidogrel so the result will be a proportionally lower cost in this treatment arm. The effectiveness is assumed to remain the same as it was based on intention-to-treat analyses. Sensitivity analysis number 5 is the more realistic assumption that 100% of the cost of the drugs will be incurred as they will be prescribed to all patients, but when there is reduced compliance there may be a reduction in effect and this is modelled by adjusting the RRRs to 80% of those observed in the trial. Clopidogrel remains cost-effective under this assumption.

Clopidogrel appears more cost-effective if given to older patients. This is because the RR is applied to a higher absolute background risk. This effect begins to tail off when the starting age reaches 80 years as non-vascular death becomes a greater competing risk and the benefits of preventing a stroke accrue over a shorter time period.

Comments

The model submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squib has a flexible structure and is probabilistic, facilitating full sensitivity analysis. The model realistically attempts to evaluate all recurrent events rather than simply the first recurrent event, although the data used to inform this are arguably poorer than those available for first events. The source for relative risk data was only an abstract[49] and so the method of calculation is uncertain. Although relative risks were calculated for each qualifying event subgroup as defined in CAPRIE, they were not used and instead the overall RR was applied to each group. The subgroups were defined according to each patient's most recent qualifying event, irrespective of previous events. For example, a patient diagnosed with PAD who then later suffered an MI before being recruited to the trial would be classified only according to their MI. It is not clear that the same distinction would be made in clinical treatment. The CAPRIE trial was not designed to detect a difference between these subgroups;

however, a post-trial test for heterogeneity between the three subgroups was significant at a 5% significance level.[21]

The treatment duration in the model is 2 years. However, this may reflect current practice and it may be helpful to envisage alternate scenarios of length of treatment by extrapolating the trial results. When extending the treatment duration to lifetime, the exclusion of adverse events may become more important.

The baseline event rate data come from cohort studies in three distinct and somewhat dissimilar areas of the UK. An error was made in the modelling of the baseline risks of recurrent events. This resulted in the probability of stroke, vascular death or the sum of both exceeding one in some simulations, with the probability of an MI becoming negative in these instances in order to maintain the correct number of patients in the cohort. The consequence of this was that clopidogrel appeared to have a slightly higher probability of being cost-effective, but it made no difference to the deterministic results. The logistic and multinomial regression analyses used only age as a covariate after rejecting gender as insignificant. There may be further covariates associated with the likelihood of recurrent events, but this does not appear to have been explored. This is especially important given that patients are switched between sources of baseline event risk according to their most recent event and there is no information on the differences in risk factors between the three cohorts.

A further problem arises in the measurement of costs and utilities when patients are allowed to switch between health states without a history of their preceding events. The utility associated with the qualifying event or recurrent event of stroke is much lower than the utility associated with MI. This implies that a stroke-qualifying patient experiences an increase in utility if they suffer an MI. A proportion of this increase is because MI is considered a non-disabling event and patients who were implicitly assumed to be disabled following stroke lose that definition when they incur an MI. Furthermore, the cost associated with stroke-qualifying patients and new stroke events is higher than the cost associated with MI events. This then implies that the long-term care costs of stroke patients fall when they experience an MI. This is clearly counter-intuitive and a consequence of the limitation of the Markov assumptions inherent design of the model. In order to overcome this problem, it may be necessary to fix all patients at the utility and cost levels associated with stroke from the time of their first stroke. In doing so, patients' utilities would not alter following an MI, but neither would they be allowed to increase.

A further criticism of the model is that it did not include a treatment effect on non-vascular death. The CAPRIE trial indicated that, although clopidogrel reduced the risk of vascular death, it increased the risk of non-vascular death. Although these effects did not reach conventional levels of statistical significance, this is not surprising given the trial was not powered to show a difference in this end-point, and the model assumes there is zero effect of clopidogrel on non-vascular events. To model the effect of clopidogrel only on vascular death may overestimate the number of life-years and QALYs associated with this treatment. The results from CAPRIE indicate that clopidogrel is associated with a small relative risk reduction in all-cause death when compared with aspirin. This is smaller than the reduction shown in vascular death that is included in the model.

The model considered a mixed cohort with three different qualifying events. Although this may reflect the cost-effectiveness in practice were clopidogrel prescribed to all these groups, it is sensible to consider the cost-effectiveness in each group separately as this is a source of variability in the overall cost-effectiveness estimates. When the analysis was run for each group separately, the cost per QALY gained with clopidogrel compared with aspirin was <£20,000 in each group.

The utility for MI applied in the model is potentially misleading. The reported estimates are based on estimates from three separate studies. The assumption that each of the values represents an alternate valuation of the same health state is potentially incorrect since there will be variation between the values derived due to differences in the question asked, the way in which the health state is described, the method of valuation and the sample population. There is no justification provided to support the assumption that the lowest of the three values represents the minimum value, the central estimate the most likely and the highest the maximum value of utility for MI. It would potentially be more accurate to obtain a single estimate of the utility associated with MI and the standard error surrounding that estimate. Alternatively, if several estimates were found that were deemed sufficiently homogeneous for statistical pooling, this could also be used. A more direct measurement of the utility for PAD patients

would be preferred to the indirect calculation currently used. It is hoped that this would also allow a more accurate estimate of the utility rather than one based on opinion.

The costs used for the stroke and PAD health states in the model are based solely on expert and author opinion and as such their validity is uncertain. The bounds of the distributions assigned to these costs were also decided by expert and author opinion. As such, this is a rather arbitrary costing exercise with respect to PAD and more evidence would be desirable. The assumption that none of the stroke qualifying patients begins the model having been left dependent by their qualifying event is not representative of the stroke population eligible for treatment. It may be more realistic to assume that a certain proportion are disabled from their initial event.

Summary of the cost-effectiveness evidence

Overview

Of the cost-effectiveness evidence reviewed, only the manufacturers' submissions and two of the published studies were undertaken from a UK perspective. Two published studies reported on secondary prevention in stroke patients and used earlier versions of the model submitted by Boehringer Ingelheim Ltd. The model submitted by Boehringer Ingelheim Ltd directly addressed the cost-effectiveness of the full range of strategies in the secondary prevention of occlusive vascular events in stroke patients, although the review has highlighted potential limitations in the model structure and the data used.

The manufacturers' submission from Sanofi-Synthelabo Ltd and Bristol-Myers Squib reported on the cost-effectiveness of clopidogrel compared with aspirin in a cohort of patients who have experienced either stroke, MI or with PAD. Since ASA–MR-dipyridamole and MR-dipyridamole are only licensed for one of these indications, these were not considered as relevant treatment alternatives in the manufacturers' submission. However, for patients with an initial qualifying event of stroke, both ASA–MR-dipyridamole and MR-dipyridamole are clearly relevant treatment alternatives. Consequently, for this subgroup of patients, the conclusions arising from manufacturers' submission are based on a restricted range of treatments. The impact that the inclusion of ASA–MR-dipyridamole and MR-dipyridamole would have on these results is unclear. The review also highlighted a minor error and potential limitations in Sanofi-Synthelabo Ltd and Bristol-Myers Squib's submission for addressing the decision problem faced in the review.

Summary of cost-effectiveness evidence for patients with stroke

Of the five cost-effectiveness studies reviewed for patients with stroke,[25,26,28–30] only two sought to assess the cost-effectiveness of the antiplatelet regimens from the perspective of the UK NHS. They are essentially the same model, initially presented by Chambers and colleagues in 1999[29] and then updated in 2002.[30] These appear to have been superseded by the submission by Boehringer-Ingelheim Ltd. Due to the similarities between these sources, only the results of the manufacturers' submission are reported here. In the base-case lifetime analysis, clopidogrel and MR-dipyridamole were dominated by ASA–MR-dipyridamole and aspirin, respectively. The incremental cost per QALY gained with ASA–MR-dipyridamole was reported to be £3655 compared with aspirin. Sensitivity analysis (univariate and probabilistic) indicated that these results were robust to a wide range of uncertainties. With the exception of one scenario, the cost per QALY gained with ASA–MR-dipyridamole, compared with aspirin, reached a maximum of £20,009 across the univariate sensitivity analyses considered. The key uncertainty identified in the results based on lifetime treatment was the assumption of a continued relative treatment effect compared with aspirin over this longer-period. A 'worse-case' scenario analysis, this indicates that the cost-effectiveness of lifetime treatment with ASA–MR-dipyridamole is potentially sensitive to this assumption.

The comparison between clopidogrel, ASA–MR-dipyridamole and MR-dipyridamole reported in the Boehringer Ingelheim Ltd submission was undertaken based on an indirect comparison. Since the CAPRIE and ESPS-2 trials used very different doses of aspirin monotherapy as comparators, the potential bias that may be introduced is unclear. However, the available evidence on the dose–response relationship of aspirin in patients with stroke appears to provide provisional support for an indirect comparison using the methods proposed by Boehringer Ingelheim Ltd.

No direct estimates for the cost-effectiveness in stroke patients were reported by Sanofi-Synthelabo Ltd and Bristol-Myers Squib. A separate analysis in the stroke group was undertaken by the

University of York using the manufacturers' model. This analysis estimated that the ICER for clopidogrel compared with aspirin was ~£15,896. No attempt was made by the manufacturers to assess whether these results would change if either ASA–MR-dipyridamole or MR-dipyridamole were included. Consequently, it would be inappropriate to conclude that clopidogrel would remain cost-effective when all relevant comparators are considered.

Summary of cost-effectiveness evidence for patients with PAD

Only one study found in the review referred to the cost-effectiveness of DP in the management of PAD.[27] This study was not considered to be relevant from an NHS perspective. No direct estimates for the cost-effectiveness in PAD patients were reported by Sanofi-Synthelabo Ltd and Bristol-Myers Squib. A separate analysis in the PAD group was undertaken by the University of York using the manufacturers' model. This analysis estimated that the ICER for clopidogrel compared with aspirin was ~£17,218.

Summary of cost-effectiveness evidence for patients with MI

No published studies were identified that considered the cost-effectiveness of clopidogrel in only patients who have experienced MI. As with the stroke and PAD groups, no direct estimates for the cost-effectiveness in MI patients were reported by Sanofi-Synthelabo Ltd and Bristol-Myers Squib. A separate analysis in this group was undertaken by the University of York using the manufacturers' model. This analysis estimated that the ICER for clopidogrel compared with aspirin was ~£12,517 in MI patients.

Summary of cost-effectiveness evidence for patients with occlusive vascular events (mixed cohort)

Neither of the two studies identified for this general indication were considered directly relevant to a UK NHS perspective.[31,79] In the deterministic base case, the incremental cost per QALY gained with clopidogrel compared with aspirin over the 40-year modelling period was estimated as £14,525. The probabilistic analysis suggested that the incremental cost per QALY has an ~74% probability of being <£30,000. A revised analysis undertaken by the University of York demonstrated that the estimates of uncertainty were conservative estimates for clopidogrel owing to an error in the model. The revised probability estimates did not appear to impact quantitatively on the implementation decision.

Conclusions

This review has highlighted the potential limitations in both the published evidence and the analyses submitted by the manufacturers from the perspective of the NHS. In particular, the differences between the alternative model structures, data sources and range of treatment strategies evaluated by the separate manufacturers makes any direct comparison of the results difficult. To facilitate a more appropriate comparison between the various sets of results, a number of additional analyses have been undertaken, and are reported in full in Chapter 6.

Chapter 6

Extended economic model

Introduction

The review of the economic evidence from the literature and manufacturers' submissions highlighted a number of potential limitations in existing studies assessing the cost-effectiveness of clopidogrel and MR-dipyridamole in the secondary prevention of occlusive vascular events. In order to overcome these limitations, it has been necessary for the University of York TAR group to undertake further modelling. This 'extended' model uses those models submitted by the manufacturers but employs a range of further analyses.

The extended analyses were undertaken to address the main limitations and uncertainties outlined in Chapter 5. In particular, the following areas were explored in more detail:

- an assessment of all licensed agents in each relevant subgroup (stroke, TIA, MI, PAD)
- a comparison of the alternative assumptions used in the manufacturers' submissions related to treatment duration (lifetime treatment or 2-year treatment duration only)
- the impact of including the reported treatment effects on both vascular and non-vascular mortality.

Methods

In order to overcome these limitations and to assist the decision-making process in the context of the NHS, a new model was developed to assess the cost-effectiveness of clopidogrel and MR-dipyridamole across the four separate subgroups using a consistent approach. The following sections outline the structure of the model and provide an overview of the key assumptions and data sources used to populate the model.

Overview

The model was developed to estimate costs from the perspective of the UK NHS and health outcomes in terms of QALYs. The model separately addresses the cost-effectiveness of all relevant treatment options in the secondary prevention of occlusive vascular events for patients with stroke, TIA, MI and PAD. The extended model is adapted from the model submitted by Sanofi-Synthelabo Ltd and Bristol-Myers Squib (SSBMS). The choice of this model, rather than that of Boehringer Ingelheim Ltd, for the extended modelling is based on the fact that that the former provided a flexible structure and was probabilistic. The model submitted by Boehringer Ingelheim Ltd contained only partial probabilistic elements, and the structure of the model was such that the adaptation to a fully probabilistic model could not be undertaken easily. In addition, the model submitted by SSBMS considered a range of health outcomes, including both recurrent stroke events and MIs. This was important in developing a consistent framework with which to evaluate cost-effectiveness in the separate subgroups of stroke, TIA, MI and PAD. The primary focus of the model submitted by Boehringer Ingelheim Ltd was the prevention of recurrent strokes and was restricted to the first-recurrence only. MI's were only included as transient events, and so Boehringer Ingelheim Ltd's model was not directly suitable for assessing the cost-effectiveness of clopidogrel in MI or PAD patients. Concern was also raised in the previous section regarding the method of handling mortality in the submission by Boehringer Ingelheim Ltd. The use of separate health states to model fatal and non-fatal events in the submission by SSBMS provided a more intuitive approach which did not require the underlying event rates to be adjusted.

For the base-case analysis, a lifetime horizon has been used to represent both the treatment duration for each agent and the associated lifetime costs and outcomes, that is, the model considers the costs and outcomes of a hypothetical cohort of patients, with a mean age of 60 years, over a period of 40 years. A series of sensitivity analyses were conducted in order to explore the impact of alternative assumptions related to the duration of treatment. Where there were differences between our modelling approach and that undertaken as part of SSBMS's submission, these are reported in each section. Justification for the use of alternative data or assumptions are also reported. Where uncertainty remained regarding the most appropriate assumption, these were addressed using sensitivity analysis to explore the robustness of the model to alternative assumptions proposed in the manufacturers' submissions.

Rationale for the approach undertaken using the extended model

The review of the manufacturers' submissions highlighted the potential problems in making a direct comparison of the different sets of results. In particular, the use of alternative model structures, data sources and range of treatment strategies evaluated by the separate manufacturers made a direct comparison of the results difficult. The primary rationale for adapting the model submitted by SSBMS was to provide a consistent model structure with which to assess the cost-effectiveness of the full range of licensed agents in the four patient subgroups (stroke, TIA, MI and PAD) for the secondary prevention of occlusive vascular events.

Although the model structure from SSBMS was used in the extended analyses, a number of alterations were made to that model. The review of the manufacturers' submissions identified a number of potential errors made in the modelling process and highlighted a series of inconsistencies and limitations in the methods and sources of data used to populate the submitted models. In particular, the source of utility estimates, and the methods for combining estimates from separate sources using alternative valuation methods, were identified as a potential limitation in both manufacturers' submissions. We undertook a series of separate searches for each subgroup to identify relevant utility estimates (and associated measures of uncertainty) using consistent valuation approaches. Where a range of sources was identified, those valuations reflecting UK public preferences [e.g. EuroQol (EQ)-5D] were given priority. The use of expert opinion as the basis for estimating the costs of particular events (e.g. stroke care) was also considered a potential limitation in both manufacturers' submissions. A series of separate searches was undertaken to identify alternative UK sources of cost data in each subgroup of patients. Where more reliable cost data from patient-level data sources were identified, these were used in preference to those derived from expert opinion. Finally, the exclusion of the cost of adverse events (bleeding) was a potentially important omission from the SSBMS submission. This was addressed by incorporating the costs of these events in the extended model.

In addition to the limitations noted above, the issue of treatment duration was identified as a potentially important assumption in the manufacturers' submissions. The submission by Boehringer Ingelheim Ltd considered a number of alternative scenarios (e.g. lifetime treatment duration, treatment for 2 years only), whereas the submission by SSBMS considered the cost-effectiveness of using clopidogrel for 2 years only (followed by lifetime treatment with aspirin). Although evidence from CAPRIE[21] and ESPS-2[22] is restricted to a 2-year follow-up, patients may continue on these treatments beyond the follow-up period reported in the trial. Consequently, the potential impact of treatment beyond 2 years should be considered in full. The base-case analysis undertaken using the extended model is based on the assumption that the agents will continue to be prescribed for the duration of patients' remaining lifetimes. A series of additional scenarios were also undertaken to explore the impact of alternative assumptions, including restricting the treatment duration to the maximum period of follow-up reported in the relevant trials (2 years).

A further source of uncertainty outlined in Chapter 5 is the method used by the manufacturers to model the impact of these agents on vascular and non-vascular mortality. Neither ESPS-2 nor CAPRIE reported statistically significant differences in the combined estimate of all-cause mortality or in either of the separate vascular and non-vascular mortality end-points. Although the model submitted by SSBMS included the treatment effect on vascular mortality for clopidogrel, no attempt was made to quantify the potential impact on **non-vascular** mortality. The lack of statistical significance is not sufficient evidence of equivalence in this outcome and excluding the potential impact of treatment

TABLE 41 *Relative risk of events compared with aspirin for each treatment for the model submitted by the University of York team*

Event	Clopidogrel	ASA–MR-dipyridamole	MR-dipyridamole
Non-fatal MI[21,23]	0.808	1.058	1.935
Non-fatal stroke[21,23]	0.948	0.736	0.981
Vascular death[21,23]	0.925	0.991	1.056
Non-vascular death[21,23]	1.087	1.062	0.981
Fatal bleed[92]	0.999	1.749	0.499
Non-fatal bleed[92]	0.938	1.437	0.374

of non-vascular death may lead to an overestimate of the cost-effectiveness of treatment with ASA–MR-dipyridamole, MR-dipyridamole or clopidogrel, compared with treatment with aspirin alone. Although many non-vascular deaths will have no association with the use of antiplatelet therapies, it is not possible to rule out a link in a proportion of non-vascular deaths. Given the absence of data to look at the causes of non-vascular deaths in more detail, it is important to present scenarios where the treatment effects on these deaths are reflected in the cost-effectiveness estimates. Hence the impact of including and excluding the reported treatment effect on non-vascular death is reported in separate analyses.

Treatment strategies under comparison

Due to separate indications and licences for clopidogrel and MR-dipyridamole, different combinations of treatment strategies are compared in each patient subgroup. The full range of licensed agents is considered in all analyses. In order to avoid confusion in the reporting of results from each subgroup, each treatment is represented by the same strategy number throughout. These strategies are as follows:

- Strategy 1: treatment with aspirin for the remainder of the patient's lifetime
- Strategy 2: treatment with clopidogrel for the remainder of the patient's lifetime
- Strategy 3: treatment with aspirin and MR-dipyridamole (ASA–MR-dipyridamole) for the remainder of the patient's lifetime
- Strategy 4: treatment with MR-dipyridamole for the remainder of the patient's lifetime.

The combinations of strategies considered for each patient subgroup are as follows:

- stroke: Strategy 1 (aspirin), Strategy 2 (clopidogrel), Strategy 3 (ASA–MR-dipyridamole) and Strategy 4 (MR-dipyridamole)
- MI: Strategy 1 (aspirin) and Strategy 2 (clopidogrel)
- PAD: Strategy 1 (aspirin) and Strategy 2 (clopidogrel)
- TIA: Strategy 1 (aspirin), Strategy 3 (ASA–MR-dipyridamole) and Strategy 4 (MR-dipyridamole).

Strategies for sensitivity analysis for treatment duration

For the sensitivity analysis used to explore a treatment duration of only 2 years, Strategy 1 remains unaltered. However, Strategies 2–4 now represent treatment with the relevant agent for 2 years only, followed by treatment with aspirin for the remainder of the patient's lifetime. The combination of the strategies for each patient subgroup remains the same as for the base-case model.

Treatment effects for clopidogrel, ASA–MR-dipyridamole and MR-dipyridamole compared with aspirin

The treatment effects reflected in the model are derived from the relative risks of non-fatal MI, non-fatal stroke, vascular and non-vascular death, from the ESPS-2 and CAPRIE trials. Due to differences in the definition of bleeding applied in the trials, the relative risks of the adverse events of fatal major bleeds and non-fatal major bleeds are taken from the data reported in the meta-analysis by the ATT.[92] This approach ensures that a consistent definition is used throughout the analyses. This definition of major bleed includes all extracranial bleeds considered by the trialist to be serious, for example requiring admission to hospital or a blood transfusion. The RRRs are shown in *Table 41*. Uncertainty in the RRRs is characterised by a log-normal distribution.

In the base-case analysis, patients are assumed to remain on their given treatment for the remainder of their lifetime. The trial data from both CAPRIE and ESPS-2 demonstrate the effectiveness of each agent over a period of 2 years. It was therefore necessary to extrapolate the treatment effect for the base-case model. In the absence of any trial evidence as to the longevity of the treatment effects, we chose to assume, in the base case, that the treatment effect would remain constant over the period for which the drug is taken. This is an important assumption, and it was the one used by Boehringer Ingelheim Ltd in their submission. SSBMS's approach was to model a treatment duration of only 2 years, and the impact of this has been explored in further analyses.

Model structure

Stroke and TIA

Patients begin the model in the first year after their qualifying event. Patients then face an annual probability (baseline risk) of either a recurrent stroke, vascular death, death from other causes (non-vascular death) or no further event. Separate annual probabilities are applied to patients in their first year after a stroke event (first or recurrent) and in subsequent years conditional on no further event in the preceding year. If patients survive the first year of any stroke event without experiencing a further event, they enter a post-stroke state in which the risks of further events and the costs

incurred are lower than the in the year immediately following an event. The model includes as a cost the risk of fatal and non-fatal major bleeding events. This cost is calculated as a proportion of, respectively, those moving to the dead states and of those alive for each year in the model. The cost of the major fatal bleed is assumed to occur on the patient's entry into one of the dead states. *Figure 8* illustrates the health states and the transitions allowed in the model for stroke. The dashed lines illustrate additional transitions when the model is run with a hypothetical cohort of patients with TIA.

The structure of the model differs slightly from that supplied by SSBMS. In the extended model the transition to MI and post-MI states has been excluded owing to the source of the data used to inform this transition and the potential logical inconsistencies that are introduced into the model. Due to the lack of data from the observational dataset of stroke patients for the risk of MI, this transition probability was taken directly from the CAPRIE trial. It is unclear whether data from the CAPRIE trial are representative of the rate in a UK setting. More importantly, the utility and cost data applied to those patients experiencing an MI, applied in the SSBMS submission, are actually higher in comparison with the utility and cost of patients who remain event free (year 1 post-stroke). By allowing this transition, the model would therefore favour a treatment that increased the risk of MI following stroke. Finally, the impact of this logical inconsistency is continued in the model after patients enter the MI state. Once patients move into the MI state, subsequent transitions are then obtained from a separate observational dataset from the NHAR. Since patients in the NHAR face a higher risk of recurrent MI than stroke, once a patient experiences an increase in utility (and lower costs) by moving from a stroke state to an MI state, they are likely to continue to benefit from this inconsistency in the SSBMS model. The risk of MI following stroke from CAPRIE was estimated as 0.72% per annum. In a typical cohort of 1000

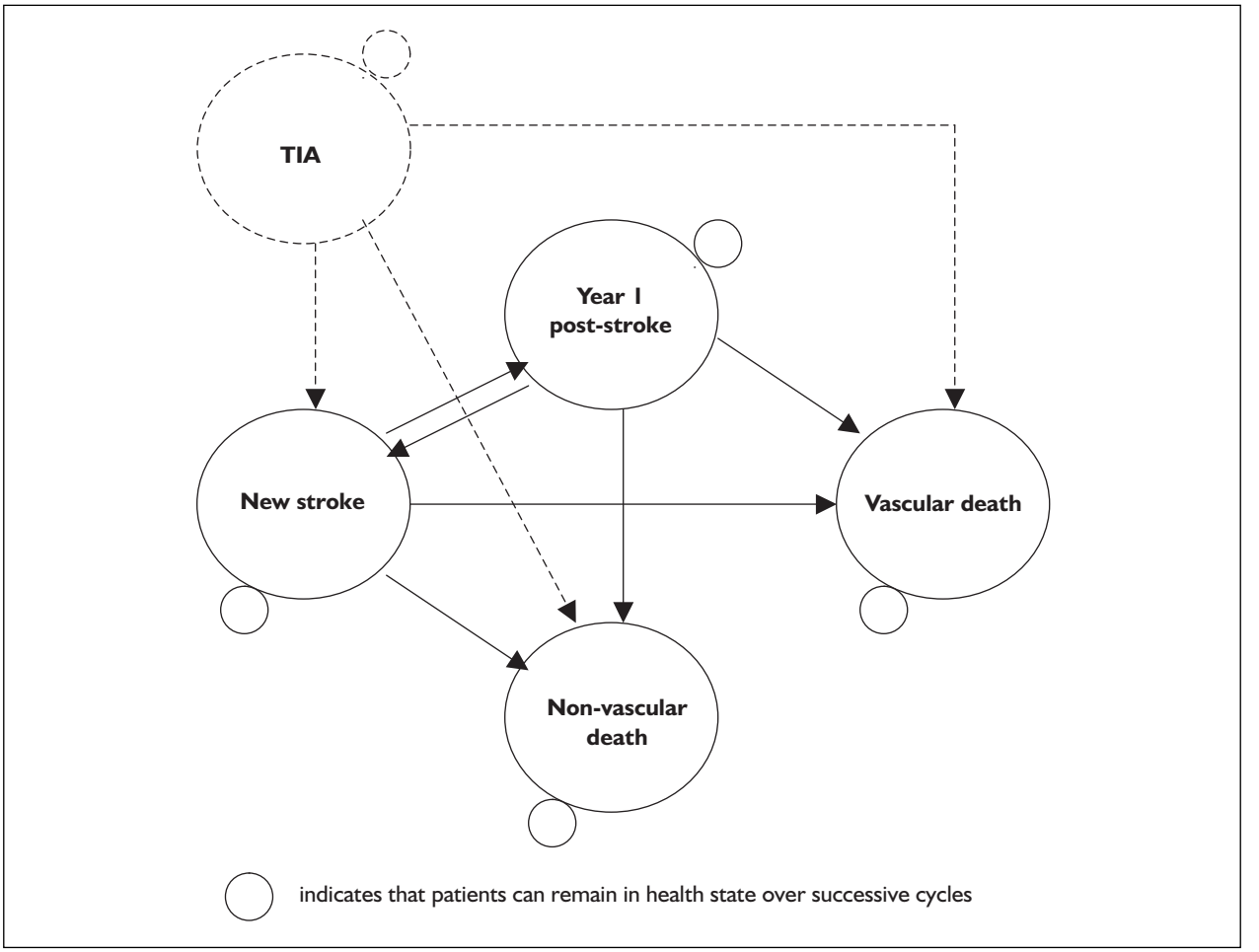

FIGURE 8 *Structure of the extended model by University of York to assess cost-effectiveness of clopidogrel and MR-dipyridamole in the secondary prevention of occlusive vascular events in patients who have experienced stroke or TIA*

stroke patients, only seven would experience an MI in the first year, in comparison with about 48 experiencing recurrent stroke and around 36 experiencing a fatal vascular event. It was therefore decided that the risk of MI for stroke patients was small enough that its exclusion would not compromise the model, and that the benefit from removing the inconsistency and the assumption about a constant risk of recurrent MI was greater.

MI and PAD

The model is similar to that described for stroke and TIA patients. Patients begin the model in the first year after their qualifying event. In contrast to the model structure used for stroke and TIA patients, the model for MI and PAD patients allows patients to experience stroke following MI. There is no inconsistency associated with this transition and the UK observational cohort of MI patients used to inform the model included data on the risk of stroke in MI patients. However, due to the inconsistencies already outlined, no transition is allowed from stroke to MI. *Figure 9* describes the model. The dashed lines illustrate additional transitions when the model is run with a hypothetical cohort of patients with PAD.

Baseline probabilities in the model

In order to generalise the results from the CAPRIE and ESPS-2 trials to a UK NHS setting, baseline probabilities in both company submissions were derived from UK-based observational datasets. In the SSBMS submission, the baseline event rates were derived from three separate sources and were assumed to represent patients treated with aspirin.

Stroke and TIA

The baseline event rates for patients who experience stroke were based on the SLSR.[87] This was a prospective community-based register that recruited 1254 cases of first-ever stroke from 1995 to 1998, using the WHO clinical definition. Patient-level data from the SLSR were used to calculate the age-related risk of recurrent stroke and vascular death applied in the model. We used the analyses reported in the SSBMS submission to populate the baseline probabilities applied in the extended model. The coefficients from the logistic

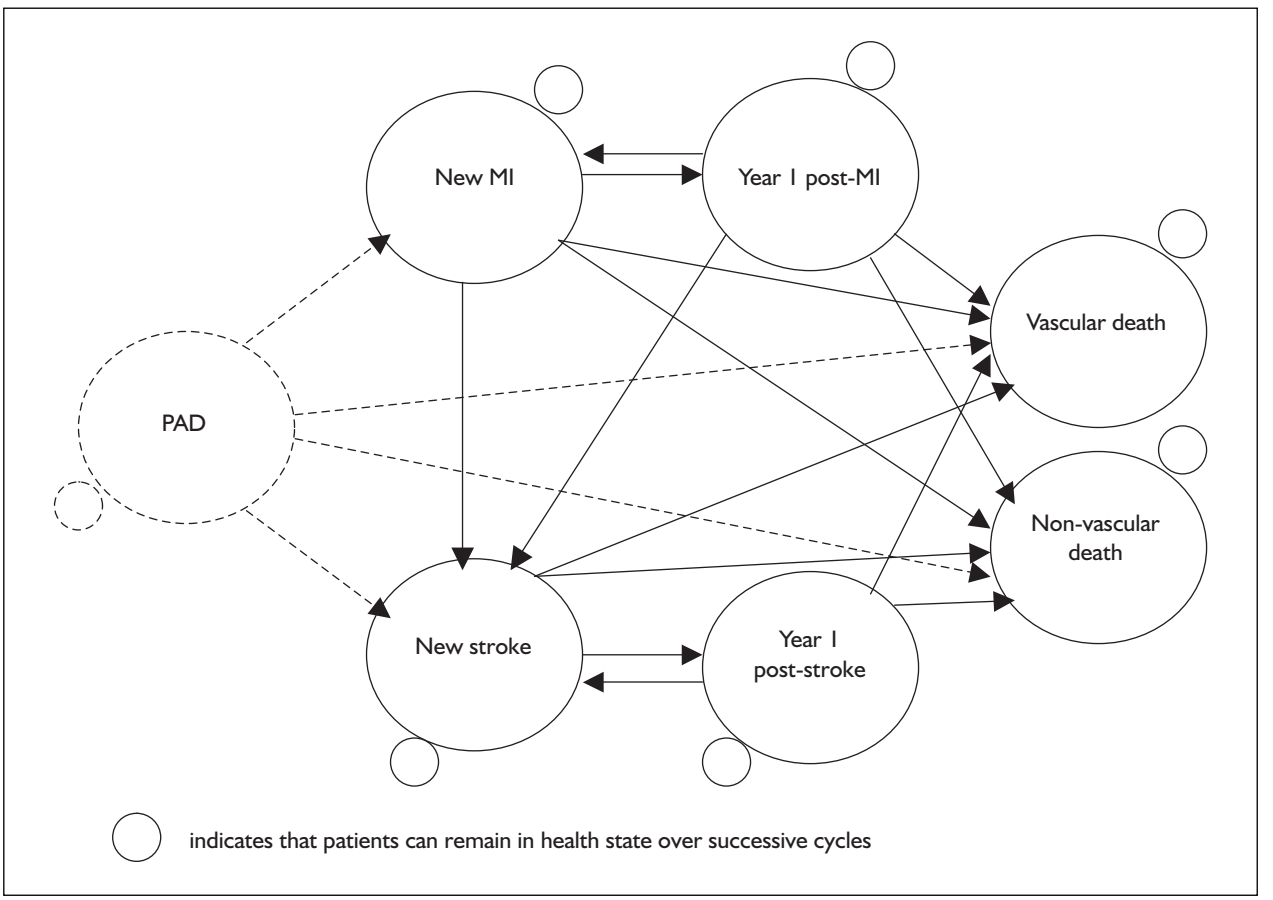

FIGURE 9 *Structure of the extended model by University of York to assess cost-effectiveness of clopidogrel and MR-dipyridamole in the secondary prevention of occlusive vascular events in patients who have experienced MI or have been diagnosed with PAD*

and multinomial regressions were used to calculate the baseline probability of each possible transition. The uncertainty in the coefficients (representing the log-odds) from the regression were characterised using a normal distribution. This approach differs to that applied in SSBMS's submission, which assigned log-normal distributions directly to the probability estimates. This revision was necessary to address the logical problems outlined in Chapter 5: to ensure that the individual probabilities applied in the model were positive, to ensure that the probability of any individual event did not exceed one and to ensure that the probabilities for mutually exclusive events sum to one.

Both the initial stroke and any recurrent strokes are potentially disabling events. Since a disabling stroke is associated with a larger utility decrement and higher resource use for long-term care compared to a non-disabling stroke,[93,94] it is important that this is appropriately quantified in the model inputs. The impact that these differences in utility and cost estimates have on the results is also dependent on the proportions of patients assumed to start the model in the disabled and non-disabled states. As the proportion of patients who start the model in the disabled state increases, the less cost-effective the treatments will become (since a high proportion of patients will already have been assigned a higher cost and lower utility at the outset); in other words, there is a reduced **potential** to benefit from the treatment. In the SSBMS submission, it was assumed that all patients in the stroke model started in the non-disabled state. This represents the most favourable scenario for the treatments considered. A more conservative approach would be to assume that a proportion of patients start the model in the disabled state. Since data on the proportion of events that are disabling were not available from the SLSR, the rates observed in ESPS-2 were used (30.9% of initial strokes and 35.6% of recurrent strokes). This is also the assumption employed in the model submitted by Boehringer Ingelheim Ltd. While this approach provides a useful summary of the overall cost-effectiveness of the alternative treatments in the stroke group, it may be argued that the proportion of patients who start treatment having been disabled by a stroke is a source of heterogeneity, and a more appropriate approach would be to report separate estimates of the cost-effectiveness in the separate subgroups of patients who are either initially disabled or non-disabled. An additional sensitivity analysis was therefore conducted to determine the cost-effectiveness of the alternative treatments in each subgroup.

No suitable UK-based data sources were found to describe the baseline risk of events in patients who have experienced TIA. Since TIA is considered clinically to be almost identical with a minor ischaemic stroke,[95] the baseline event rate data from the SLSR are applied in the extended model. As the SLSR contained patients who had experienced more serious strokes as their qualifying events, sensitivity analysis was used to explore the impact of reducing the baseline risk of events seen in the SLSR to adjust for a higher risk of recurrent events associated with a moderate or major stroke. Since by definition a TIA is non-disabling (symptoms persist for less than 24 hours), the initial event is assumed to incur the same costs and utilities of patients in the non-disabled stroke state. Further stroke events are assumed to be disabling in the same proportion as observed in ESPS-2.

MI

The baseline event rates for patients who experience MI were based on the NHAR, an ongoing prospective registry of heart attacks in the Nottingham area using its own definition of MI. Patient-level data from the NHAR were used by SSBMS to calculate the age-related risk of MI, stroke and vascular death applied in their model. In a similar manner to that reported for the stroke group, the analyses reported in the SSBMS submission were used to populate the baseline probabilities applied in the extended model. The coefficients from the logistic and multinomial regressions were used to calculate the baseline probability of each possible transition. The uncertainty in the coefficients (representing the log-odds) from the regression were characterised using a normal distribution. The same revision as outlined previously was necessary to ensure that the individual probabilities applied in the model were positive and that the sum of probabilities for mutually exclusive events summed to one.

PAD

The baseline event rates for patients who are diagnosed with PAD were based on the ECS,[88] a cross-sectional survey that assessed 1592 men and women aged 55–74 years for the presence of PAD. Patient-level data from the ECS were used by SSBMS to calculate the probability of recurrent events. The probability of events in the extended model was predicted in the same way as those for stroke and MI patients, incorporating the required logical revision.

Adverse events

The extended model includes a risk of major fatal and non-fatal bleeds as an adverse effect of

treatment with antiplatelet agents. The type of bleeding event recorded and the definition used can vary considerably between sources, and often the information provided does not allow an assessment of whether the data from different sources refer to the same event. In order to ensure a consistent definition of bleeding events, both for the baseline risk and for the RRRs associated with treatment, data from the ATT meta-analysis[92] were used. The baseline risk of bleeding events were taken from the aspirin group in the CAPRIE trial, as defined by the ATT.

Non-vascular death

The extended model separates deaths into those that are due to vascular causes and those that are due to non-vascular causes using the same approach as in the model submitted by SSBMS. The baseline event rate of vascular death is thus informed by the relevant observational cohort study. The age-dependent baseline risk of non-vascular death was estimated from published national statistics by excluding those deaths recorded with an ICD code pertaining to diseases of the circulatory system, as reported by SSBMS. Separate analyses are then undertaken to explore the impact of including and excluding the RRRs reported in CAPRIE and ESPS-2 for non-vascular mortality.

Baseline resource use and cost data

Costs have been incorporated into the model by attaching a mean annual cost to the PAD, new MI, post-year 1 MI, new stroke, post-year 1 stroke and TIA states. The costs of fatal and non-fatal adverse events were included as a proportion of those patients in the dead states and those still alive in the model for each year. Costs are discounted at a rate of 6% per annum in the base case. As the duration of treatment is assumed to be for a patient's lifetime (as opposed to 2 years of treatment only), the cost of each drug[96] is much higher in the extended base-case model than in the model submitted by SSBMS. The approach used by SSBMS most closely reflects the secondary analyses undertaken for the extended model, specifically the scenario in which treatment with the agents (except aspirin) are discontinued after 2 years, and all patients are then prescribed aspirin alone for the remainder of their lifetime.

Stroke and TIA

The cost for stroke is taken from a separate source than that used in SSBMS's submission. The cost-effectiveness review highlighted the potential limitations of the use of expert opinion for the cost of acute stroke care. The literature review described in the first section of Chapter 3 identified one study that prospectively recorded patient-level resource use following stroke in the UK.

The annual cost associated with stroke was derived from a large, randomised, prospective trial of stroke care in the UK.[97] This trial recorded resource use in hospital, primary care, healthcare contacts and utilisation of social services over a period of 1 year following stroke. These data were then used in a study describing the economic burden of stroke to the UK.[93] This study applied national unit costs to the resource use data to calculate the 3-month cost of acute events and long-term care according to the severity of the stroke, and which also reported the probabilities of incurring each event. Stroke was divided into mild, moderate and severe events, defined by Barthel Index. For the purpose of the model, we assumed that mild and moderate strokes described the costs of non-disabled stroke survivors and that severe stroke described the cost of dependent and disabled stroke survivors. *Table 42* present the data used to calculate the annual cost of stroke care.

The cost associated with TIA is assumed to be that associated with a non-disabling stroke. A combined cost of stroke events is calculated using the proportion of patients assumed to be disabled and non-disabled. The uncertainty in the cost of each health state is reflected by assigning gamma distributions to the 3-month costs used to calculate the annual cost.

MI

In the absence of any more appropriate data identified in the systematic review, the costs associated with the MI states are taken directly from the submission by SSBMS. These costs, originally reported by Palmer and colleagues,[89] include hospital resource use only, and were calculated by aggregating resource use recorded in the NHAR according to whether patients were in the first year or subsequent years following an MI. The uncertainty in these costs is characterised by a gamma distribution. This distribution was applied, in contrast to the normal distribution applied in the SSBMS submission, due to the more appropriate properties of the gamma distribution (e.g. truncated at zero and positively skewed).[98] The cost of a MI in year 1 is estimated as £3966 (standard error £386) and the yearly cost of patients who survive 1 year event-free is estimated as £1587 (standard error £381).

PAD

No separate estimates for UK-specific cost data in PAD were identified with which to inform the

TABLE 42 *Cost data from Youman and colleagues (2003)[93] used to calculate the cost of stroke in the extended model developed by the University of York team*

Parameter	Value	95% CI
3-month cost of ongoing care at home (including accommodation) (£)	326	195 to 457
3-month cost of ongoing care in an institution (including accommodation) (£)	3,872	3,669 to 4,865
Mild stroke		
3-month cost of acute event (£)	5,099	4,558 to 5,636
Percentage discharged home	100	NA
Percentage discharged to an institution	0	NA
Percentage dead	0	NA
Moderate stroke		
3-month cost of acute event (£)	4,816	4,406 to 5,225
Percentage discharged home	95.9	NA
Percentage discharged to an institution	0.8	NA
Percentage dead	3.3	NA
Severe stroke		
3-month cost of acute event (£)	10,555	9,575 to 11,535
Percentage discharged home	73.2	NA
Percentage discharged to an institution	17.2	NA
Percentage dead	9.6	NA
Proportion of mild to moderate strokes observed	0.413	
Calculated cost of non-disabled stroke year 1	$0.413 \times (£5099 + 3 \times 326) + 0.587 \times (£4816 + 3 \times (0.959/(1 - 0.033) \times £326 + 0.008/(1 - 0.033) \times £3872)) = £5963$	
Calculated cost of non-disabled stroke post-year 1	$0.413 \times 4 \times £326 + 0.587 \times 4 \times (0.959/(1 - 0.033) \times £326 + 0.008/(1 - 0.033) \times £3872) = £1373$	
Calculated cost of disabled stroke year 1	$£10555 + 3 \times (0.732/(1 - 0.096) \times £326 + 0.172/(1 - 0.096) \times £3872) = £13557$	
Calculated cost of disabled stroke post-year 1	$4 \times (0.732/(1 - 0.096) \times £326 + 0.172/(1 - 0.096) \times £3872) = £4003$	

N/A, not available.

long-term cost of care in the model. In the absence of alternative data, the costs associated with PAD were taken from the estimate provided in the submission by SSBMS (£1000 per annum). Additional sensitivity analysis is used in the extended model to determine the impact of alternative assumptions due to the uncertainty concerning the true value of this input parameter. The uncertainty in the model was again characterised by a gamma distribution and the range used to inform the distribution was an assumed 95% CI of ±50%.

Quality adjustment

In order to estimate QALYs, it is necessary to quality-adjust the period that the average patient is alive within the model using an appropriate utility or preference score. A number of data sources were identified which provided estimates of utilities associated with stroke, MI and PAD. In order to use consistent valuations methods for each health state in the model, we selected three data sources that provided estimates of utility for the stroke, MI and PAD health states using UK societal preferences derived from the EQ-5D questionnaire.[99] We were unable to find utility values for stroke that distinguished between patients in their first or subsequent year following the event, and so the utility associated with stroke is assumed to remain constant with time from the event. Uncertainty in the utility associated with each health state was characterised by distributions informed using the mean and standard errors reported in each source. This differs from the approach used in SSBMS's submission, which employed utilities calculated by different methods,

TABLE 43 *EQ-5D utilities of health states in the model by the University of York team*

Health state	Mean utility (standard error)
Non-disabled stroke (year 1 and post-year 1)[94]	0.74 (0.026)
Disabled stroke (year 1 and post-year 1)[94]	0.38 (0.046)
Combined stroke (assuming 35.6% disabled)[94]	0.612
MI year 1[100]	0.683 (0.015)
MI post-year 1[100]	0.718 (0.016)
PAD[101]	0.75 (0.022)

and which characterised the uncertainty associated with these utilities in a different manner for stroke, MI and PAD. The utilities used in the model are shown in *Table 43*. Again, the utility for TIA is assumed to be that associated with an independent (non-disabled) stroke patient.

Although the absolute estimates differ from those proposed in the manufacturers' submissions, the utility values applied in the extended model maintain the order of the severity of the initial health states assumed in SSBMS's model. The chronic condition of PAD is assumed to have the smallest utility decrement. The combined stroke event is assumed to have a larger utility decrement than an MI, which appears reasonable given that stroke is assumed to be potentially disabling whereas MI is not. The use of these utility estimates also removes an additional inconsistency identified in the submission by SSBMS where the utility for the post-MI state was higher than that associated with PAD. In a similar manner to the logical inconsistency outlined previously for the transition from stroke to MI, the use of a higher utility estimate for MI, relative to PAD, would allow PAD patients to experience an increase in utility after experiencing MI, compared with PAD patients without such an event. In order to maintain the consistency of utility transitions in the probabilistic sensitivity analysis, a single randomly generated number was used to inform all of the utility distributions, ensuring that the simulated estimates came from the same point on each distribution (ensuring the ordering based on the severity of the alternative health states was maintained). QALYs (and other health outcomes) are discounted at a rate of 1.5% per annum in the base case.

Analytical methods

The overall model is run for a period of 40 cycles (equivalent to 40 years), after which the majority of patients will have died in the model. Therefore, the mean (expected) life-years and QALYs per patient can be calculated for each strategy, in addition to the mean lifetime costs.

The results of the model are presented according to the qualifying event of the patient subgroup under consideration. The mean lifetime costs and QALYs of the relevant strategies are presented and their cost-effectiveness is compared. ICERs are estimated as appropriate, using standard decision rules.[102]

When more than two programmes are being compared, the ICERs are calculated using the following process:

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 dominated 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.

Finally, the ICERs are recalculated excluding any strategies that are ruled out using the notions of dominance and extended dominance.

The model is fully probabilistic in that, as described above, parameters are entered random variables rather than fixed-point estimates. Monte Carlo simulation is used to propagate parameter uncertainty through the model.[103] To present the uncertainty in the cost-effectiveness of the alternative strategies, cost-effectiveness acceptability curves (CEACs) are used.[104,105] These show the probability that any particular strategy is more cost-effective than all the other strategies under consideration using alternative values for the maximum value the health service is willing to pay for an additional QALY in these patients.

The model has been developed in Excel 2000. 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 to explore the key uncertainties in the model.

The following analyses were undertaken in each subgroup, representing the main assumptions applied in the extended model:

- Scenario I: an analysis based on lifetime treatment (representing the base-case analysis) excluding the impact on non-vascular mortality
- Scenario II: an analysis based on lifetime treatment including the impact on non-vascular mortality
- Scenario III: an analysis based on 2-year treatment duration (followed by lifetime treatment with aspirin) excluding the impact on non-vascular mortality
- Scenario IV: an analysis based on 2-year treatment duration (followed by lifetime treatment with aspirin) including the impact on non-vascular mortality.

Results

Stroke

Table 44 (see Appendix 7) presents the analysis of the ICER in a hypothetical cohort of patients who have experienced an initial ischaemic stroke for the four scenarios considered in the extended model. Clopidogrel, ASA–MR-dipyridamole and MR-dipyridamole are licensed for use in patients who have experienced stroke and therefore Strategies 1–4 are relevant in this subgroup. The main results are based on the assumption that 30.9% of the group will be disabled at the outset based on data reported in ESPS-2. Additional analyses assuming 0% and 100% of the initial cohort are disabled were also undertaken. The results of these additional analyses are reported in Appendix 7 (*Table 49*).

Scenario I – lifetime treatment (excluding relative risk of non-vascular death)

In the analysis based on lifetime treatment duration (excluding the RR of non-vascular death), MR-dipyridamole is dominated by aspirin (i.e. more expensive and less effective). ASA–MR-dipyridamole and clopidogrel are both more expensive and more effective than aspirin. Neither ASA–MR-dipyridamole nor clopidogrel is ruled out by extended dominance. The ICER for Strategy 3 (treatment with ASA–MR-dipyridamole) compared with Strategy 1 (aspirin) is £26,432. The ICER for Strategy 2 (treatment with clopidogrel) compared with Strategy 3 is £78,640.

At a WTP value of £10,000 per QALY, aspirin has the highest probability of being cost effective (0.59), compared with ASA–MR-dipyridamole (0.32) and clopidogrel (0). At a WTP value of £30,000 per QALY, the probability that ASA–MR-dipyridamole (0.46) is cost-effective is higher than that of either aspirin (0.36) or clopidogrel (0.03). The CEAC for each strategy is outlined in *Figure 10*.

Hence the results of this scenario indicate that ASA–MR-dipyridamole is the optimal decision as long as the NHS is willing to pay between £26,432 and £78,639 for an additional QALY. If the NHS is willing to pay over £78,639 per QALY then treatment with clopidogrel appears cost-effective. If the NHS is willing to pay less than £26,432 for an additional QALY, then Strategy 1 (treatment with aspirin) is the optimal decision.

Scenario II – lifetime treatment (including relative risk of non-vascular death)

In the analysis based on lifetime treatment duration (including the RR of non-vascular death), MR-dipyridamole, ASA–MR-dipyridamole and clopidogrel are all dominated by aspirin (i.e. more expensive and less effective in comparison with aspirin). In this scenario the optimal strategy is the use of aspirin. The CEAC for each strategy is outlined in *Figure 11*. Aspirin has the highest probability of being cost-effective at WTP values of £10,000, £30,000 and £50,000 per QALY as it is the dominant treatment option.

Scenario III – 2-year treatment duration only (excluding relative risk of non-vascular death)

In the analysis based on 2-year treatment duration (excluding the RR of non-vascular death), MR-dipyridamole is dominated by aspirin and clopidogrel is dominated by ASA–MR-dipyridamole. ASA–MR-dipyridamole is both more expensive and more effective than aspirin. The ICER for Strategy 3 (treatment with ASA–MR-dipyridamole) compared with Strategy 1 (aspirin) is £5500.

At a WTP value of £10,000 per QALY, ASA–MR-dipyridamole has the highest probability of being cost effective (0.62), compared with aspirin (0.26) and clopidogrel (0). At a WTP value of £30,000 per QALY, the probability that ASA–MR-dipyridamole (0.62) is cost-effective remains unaltered, whereas the probabilities for clopidogrel (0.12) and aspirin (0.14) are higher and lower than their respective estimates at £10,000 per QALY.

Hence the results of this scenario indicate that ASA–MR-dipyridamole is the optimal decision as

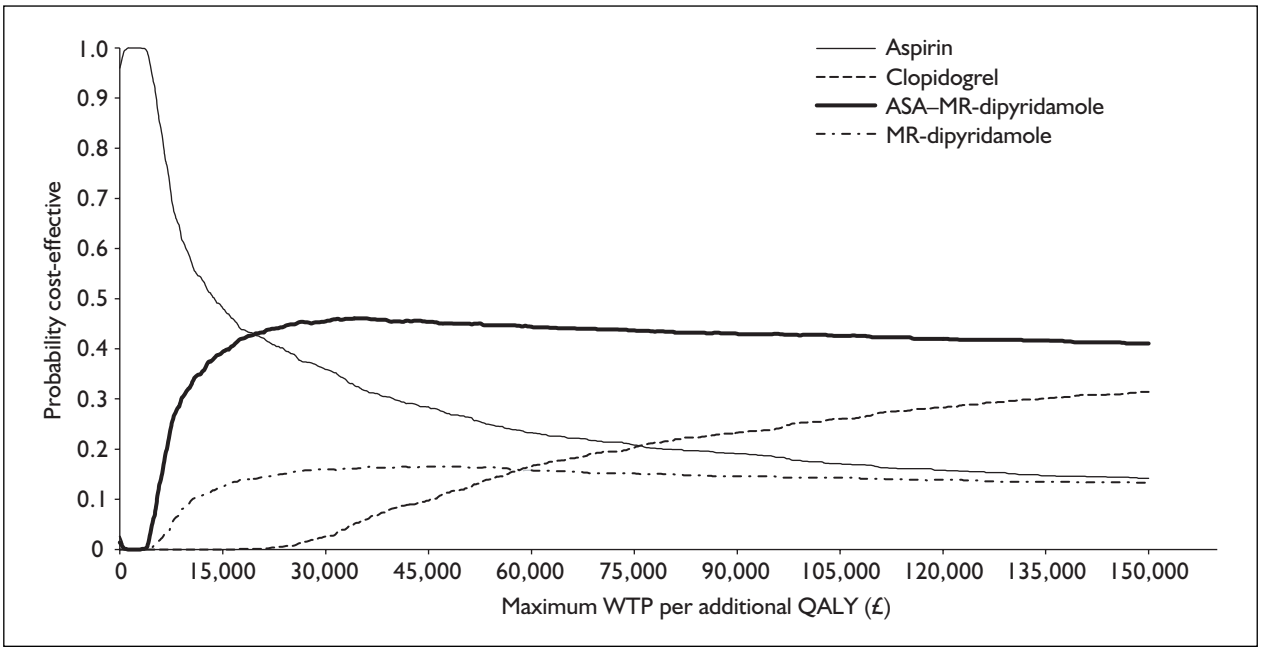

FIGURE 10 *Base-case results in the form of a cost-effectiveness acceptability curve: 40-year analysis in stroke subgroup, excluding treatment effects on non-vascular death*

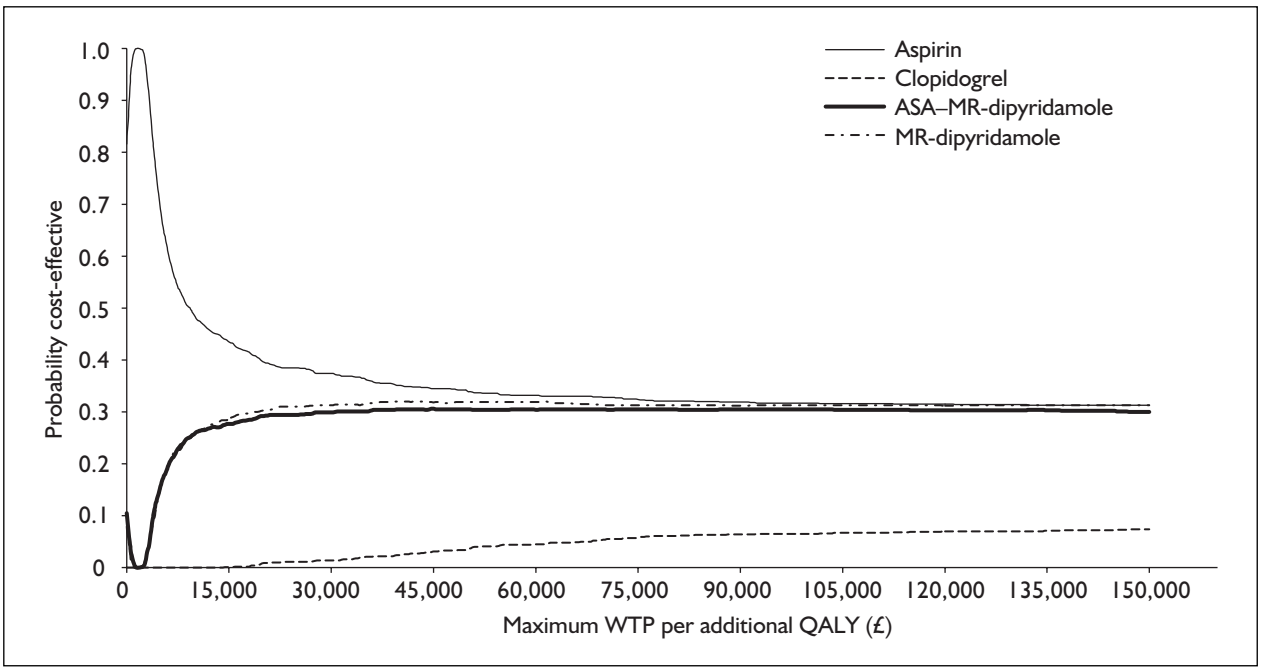

FIGURE 11 *Base-case results in the form of a cost-effectiveness acceptability curve: 40-year analysis in stroke subgroup, including treatment effects on non-vascular death*

long as the NHS is willing to pay at least £5500 for an additional QALY. If the NHS is willing to pay less than £5500 for an additional QALY, then Strategy 1 (treatment with aspirin) is the optimal decision.

Scenario IV – 2-year treatment duration only (including relative risk of non-vascular death)

In the analysis based on 2-year treatment duration (including the RR of non-vascular death), both MR-dipyridamole and clopidogrel remain dominated. The ICER for Strategy 3 (treatment with ASA–MR-dipyridamole) compared with Strategy 1 (aspirin) increases to £7968 per QALY gained (compared with the figure of £5500 excluding the RR of non-vascular death).

At a WTP value of £10,000 per QALY, ASA–MR-dipyridamole has the highest probability

of being cost effective (0.52), compared with aspirin (0.35) and clopidogrel (0). At a WTP value of £30,000 per QALY, the probability that ASA–MR-dipyridamole is cost-effective increases marginally to 0.53. As in Scenario III, the probabilities for clopidogrel (0.10) and aspirin (0.22) are higher and lower than their respective estimates at £10,000 per QALY.

Hence the results of this scenario indicate that ASA–MR-dipyridamole is the optimal decision as long as the NHS is willing to pay at least £7968 for an additional QALY. If the NHS is willing to pay less than £7968 for an additional QALY, then Strategy 1 (treatment with aspirin) is the optimal decision.

Additional analysis

In order to address the heterogeneity in disability level in the stroke subgroup, two additional analyses were undertaken, assuming that 0 and 100% of the initial cohort were disabled. The analysis in which 0% of the initial cohort are assumed to be disabled is identical with the analysis in TIA patients when the baseline risks of recurrence are set equal to those for stroke, the results of which are reported in Appendix 7 (*Table 46*). The results of the analysis when 100% of the initial cohort are disabled are reported in Appendix 7 (*Table 49*).

In the analysis based on 0% of the initial cohort being disabled (Scenario I, lifetime treatment excluding relative risk of non-vascular death), MR-dipyridamole remains dominated. The ICER for Strategy 3 (treatment with ASA–MR-dipyridamole) compared with Strategy 1 (treatment with aspirin) is £8941. The ICER for Strategy 2 (treatment with clopidogrel) compared with Strategy 3 is £171,646.

In the analysis based on 100% of the initial cohort being disabled (Scenario I, lifetime treatment excluding relative risk of non-vascular death), MR-dipyridamole remains dominated. The ICER for Strategy 3 (treatment with ASA–MR-dipyridamole) compared with Strategy 1 (aspirin) increases to £84,364. The ICER for Strategy 2 (treatment with clopidogrel) compared with Strategy 3 falls to £100,238.

Summary and comments

Clopidogrel, ASA–MR-dipyridamole and MR-dipyridamole are licensed for the secondary prevention of occlusive vascular events in patients who have experienced a stroke. As there was no direct trial evidence comparing both drugs, an indirect comparison was made based on the results from two separate RCTs of each drug versus aspirin (CAPRIE and ESPS-2). In considering this indirect comparison, it was necessary to take account of the comparability of the two trials and to assess whether the different doses of aspirin used in the two trials meant that aspirin could still be considered a common comparator. With respect to the second of these two concerns, a meta-regression was found which assessed the dose–response effect of aspirin in patients who have experienced stroke.[74] This meta-regression found a weak and non-statistically significant relationship between the dose of aspirin and its effectiveness in preventing recurrent stroke. This provides limited support for considering aspirin to be a common comparator between clopidogrel and MR-dipyridamole.

The results of the base-case model analysis based on lifetime treatment duration in the stroke subgroup suggest that treatment with aspirin only is the optimal decision at low values of WTP for an additional QALY. The results then depend on the inclusion or exclusion of treatment effects of therapies on non-vascular death. When treatment effects on non-vascular death are excluded, if the NHS is willing to pay £26,432 for an additional QALY, then treatment with ASA–MR-dipyridamole is the optimal decision, and if the NHS is willing to pay £78,640 for an additional QALY, then treatment with clopidogrel is the optimal decision. If treatment effects on non-vascular death are included, then treatment with aspirin dominates the other treatment options over the range of values of WTP for an additional QALY.

The base-case extended model assumed that 30.9% of initial stroke survivors are left disabled by the event and, as such, assessed the cost-effectiveness of clopidogrel and MR-dipyridamole in a mixed cohort of stroke patients. When the stroke subgroup is split further into non-disabled and disabled stroke survivors, the cost-effectiveness of ASA–MR-dipyridamole looks more favourable in non-disabled survivors and less favourable in the disabled survivors, with an ICER compared with aspirin of £8941 and £84,364, respectively, in the case that treatment effects on non-vascular death are excluded. This is because the benefit in preventing recurrent non-fatal strokes in disabled survivors is smaller as they are already in the worst health state possible in the model following a non-fatal event. In contrast, the cost-effectiveness of clopidogrel looks less favourable in both of these subgroups, which is mainly due to its comparison with the changed cost and benefit profile of ASA–MR-dipyridamole in these subgroups.

When the duration of treatment is assumed to be 2 years rather than lifetime, the cost-effectiveness of ASA–MR-dipyridamole looks more favourable, with an ICER compared with aspirin of £5500 in the case that treatment effects on non-vascular death are excluded. The inclusion of treatment effects on non-vascular death has less impact if they are assumed only to affect patients for 2 years, and the corresponding ICER for ASA–MR-dipyridamole compared with aspirin is £7968. The difference in health benefit between treatments is small in this secondary analysis as their differential effects are only applied for 2 years and then all patients are assumed to receive aspirin. Treatment with clopidogrel is dominated by treatment with ASA–MR-dipyridamole in this analysis, but the difference in QALYs per patient is very small. The difference between the cost of treatment with clopidogrel and that with aspirin, MR-dipyridamole or ASA–MR-dipyridamole is still marked in this 2-year analysis, although it is less pronounced than in the lifetime treatment base-case analysis. The results for the 2-year treatment duration probably indicate that the potential for accruing health benefits falls as the cohort ages. This is because the risk of non-vascular death increases, and neither clopidogrel nor ASA–MR-dipyridamole has a protective effect against non-vascular death. With a lifetime duration of treatment, the costs of the drugs remain constant, but the associated health benefits may fall as the cohort ages, meaning that the ratio of costs to health benefits is more favourable in the earlier years of the model.

TIA

Table 45 (see Appendix 7) presents the results based on a hypothetical cohort of patients who have experienced an initial TIA. In this analysis, it is assumed that the baseline risk of events is equal to 80% of the baseline risk in the stroke subgroup and that no patients are disabled on entry to the model (as assumed in the submission by Boehringer Ingelheim Ltd). Although aspirin, ASA–MR-dipyridamole and MR-dipyridamole and clopidogrel are all licensed for use in patients who have experienced a stroke, clopidogrel is not currently licensed for patients who have experienced TIA. In clinical practice, the distinction between TIAs and minor ischaemic strokes appears to be rather arbitrary, and therefore Strategies 1–4 are presented for this subgroup rather than Strategies 1, 3 and 4. An additional series of analyses are undertaken assuming that the baseline risk of events is the same as in the stroke group, although all patients are still assumed to be non-disabled at the start of the model.

Scenario I – lifetime treatment (excluding relative risk of non-vascular death)

In the analysis based on lifetime treatment duration (excluding the RR of non-vascular death), MR-dipyridamole is dominated by aspirin (i.e. more expensive and less effective). ASA–MR-dipyridamole and clopidogrel are both more expensive and more effective than aspirin. Neither ASA–MR-dipyridamole nor clopidogrel is ruled out by extended dominance. The ICER for Strategy 3 (treatment with ASA–MR-dipyridamole) compared with Strategy 1 (aspirin) is £12,458. The ICER for Strategy 2 (treatment with clopidogrel) compared with Strategy 3 is £138,743.

At a WTP value of £10,000 per QALY, aspirin has the same probability of being cost effective (0.45) as ASA–MR-dipyridamole (0.45). At a WTP value of £30,000 per QALY, the probability that ASA–MR-dipyridamole (0.53) is cost-effective is higher than either aspirin (0.30) or clopidogrel (0.02). The CEAC for each strategy is outlined in *Figure 12*.

Hence the results of this scenario indicate that ASA–MR-dipyridamole is the optimal decision as long as the NHS is willing to pay over £12,458. If the NHS is willing to pay over £138,743 per QALY, then treatment with clopidogrel appears cost-effective. If the NHS is willing to pay less than £12,448 for an additional QALY, then Strategy 1 (treatment with aspirin) is the optimal decision.

The additional sensitivity analysis adjusting the ratio of baseline risk of events for TIA patients to the same rate applied for stroke patients is reported in Appendix 7 (*Table 46*). This has the effect of reducing the ICER for Strategy 3 compared with Strategy 1 to £8941, and increasing the ICER for Strategy 2 compared with Strategy 3 to £171,646.

Scenario II – lifetime treatment (including relative risk of non-vascular death)

In the analysis based on lifetime treatment duration (including the RR of non-vascular death), MR-dipyridamole, ASA–MR-dipyridamole and clopidogrel are all dominated by aspirin (i.e. more expensive and less effective in comparison with aspirin). In this scenario the optimal strategy is the use of aspirin. The CEAC for each strategy is outlined in *Figure 13*. Altering the baseline event rates did not alter these results. Aspirin has the highest probability of being cost-effective at WTP values of £10,000, £30,000 and £50,000 per QALY as it is the dominant treatment option.

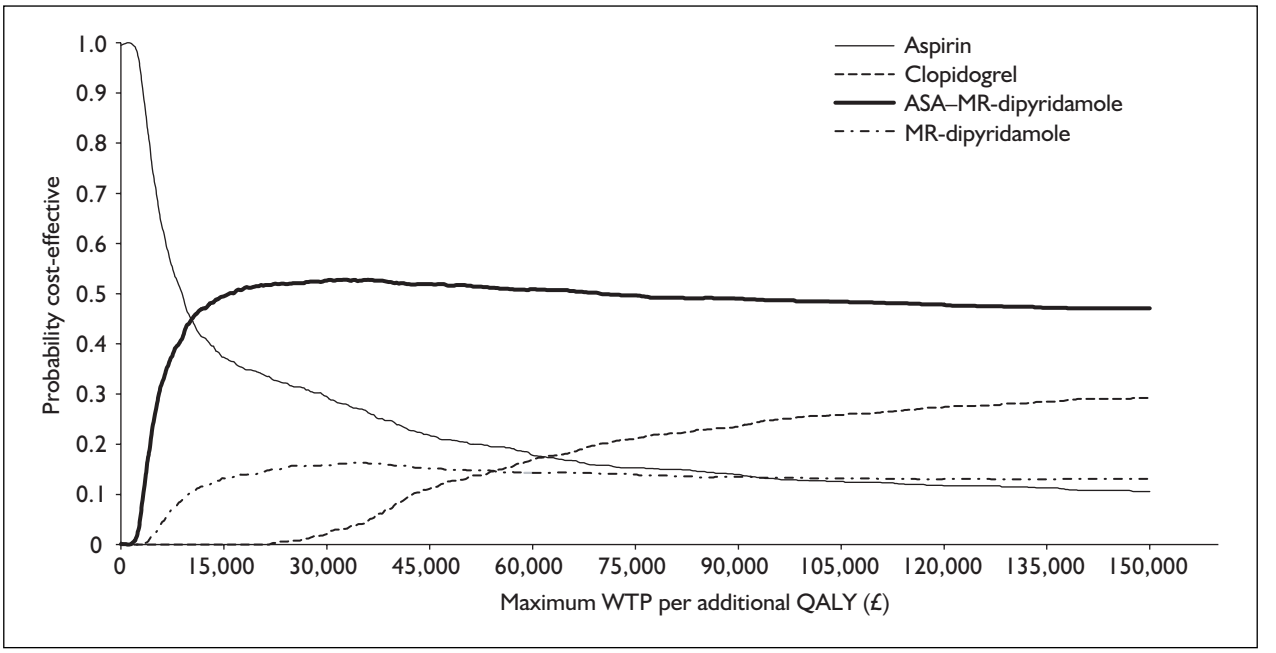

FIGURE 12 *Base-case results in the form of a cost-effectiveness acceptability curve: 40-year analysis in TIA subgroup assuming baseline event rates 80% of those for stroke, excluding treatment effects on non-vascular death*

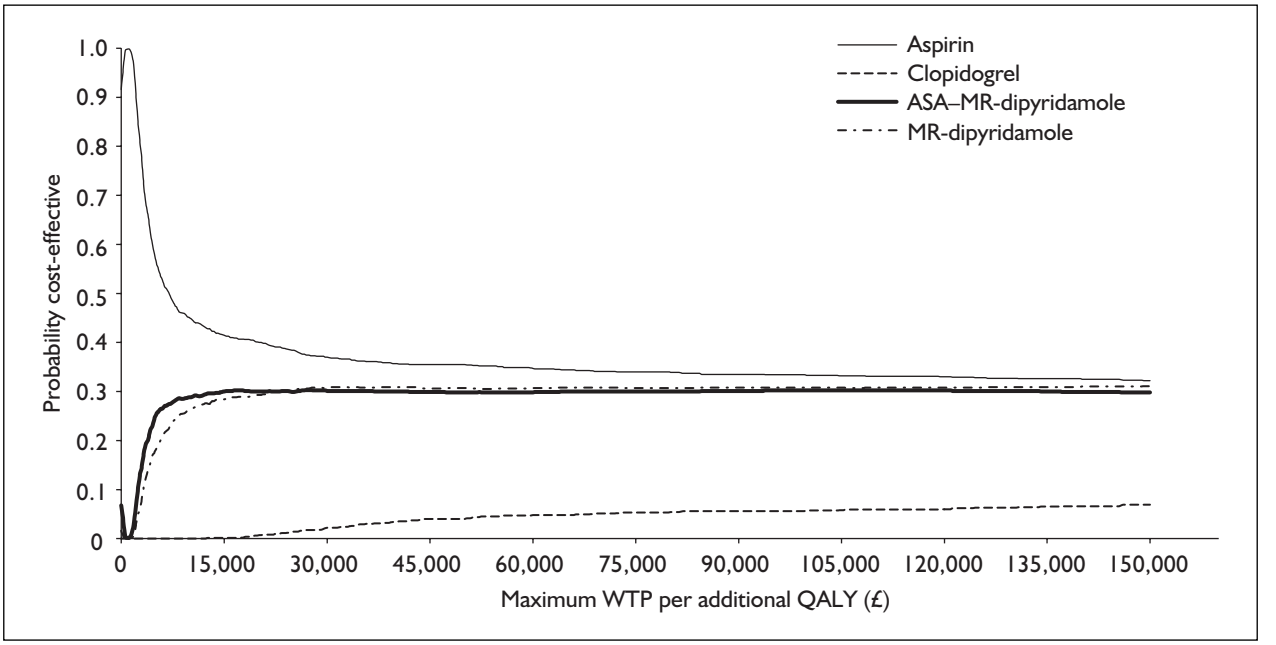

FIGURE 13 *Base-case results in the form of a cost-effectiveness acceptability curve: 40-year analysis in TIA subgroup assuming baseline event rates 80% of those for stroke, including treatment effects on non-vascular death*

Scenario III – 2-year treatment duration only (excluding relative risk of non-vascular death)

In the analysis based on 2-year treatment duration (excluding the RR of non-vascular death), MR-dipyridamole is dominated by aspirin and ASA–MR-dipyridamole. ASA–MR-dipyridamole and clopidogrel are more expensive and more effective than aspirin. The ICER for Strategy 3 (treatment with ASA–MR-dipyridamole) compared with Strategy 1 (aspirin) is £2241. The ICER for Strategy 4 (clopidogrel) compared with Strategy 3 is £46,459.

At a WTP value of £10,000 per QALY, ASA–MR-dipyridamole has the highest probability of being cost-effective (0.58), compared with aspirin (0.29) and clopidogrel (0). At a WTP value of £30,000 per QALY, the probability that

ASA–MR-dipyridamole is cost-effective is reduced to 0.51, whereas the probabilities for clopidogrel (0.19) and aspirin (0.17) are higher and lower than the respective estimates at £10,000 per QALY.

Hence the results of this scenario indicate that ASA–MR-dipyridamole is the optimal decision as long as the NHS is willing to pay between £2241 and £46,459, for an additional QALY. If the NHS is willing to pay £46,459, then treatment with clopidogrel appears cost-effective. If the NHS is willing to pay less than £2,241 for an additional QALY, then Strategy 1 (treatment with aspirin) is the optimal decision. If WTP is as high as £46,949 per QALY gained, then clopidogrel is the optimal intervention.

The additional sensitivity analysis adjusting the ratio of baseline risk of events for TIA patients to the same rate as applied for stroke patients improved the cost-effectiveness of Strategy 3, and the results are reported in Appendix 7 (*Table 46*). The ICER for Strategy 3 compared with Strategy 1 reduced to £835 per QALY and the ICER for Strategy 2 compared with Strategy 3 increased to £48,276.

Scenario IV – 2-year treatment duration only (including relative risk of non-vascular death)

In the analysis based on 2-year treatment duration (including the RR of non-vascular death), MR-dipyridamole remained dominated. The ICER for Strategy 3 (treatment with ASA–MR-dipyridamole) compared with Strategy 1 (aspirin) increased to £4266 per QALY gained (compared with the figure of £2241 excluding the RR of non-vascular death). The ICER for Strategy 2 compared with Strategy 3 is £52,339.

At a WTP value of £10,000 per QALY, ASA–MR-dipyridamole has the highest probability of being cost effective (0.49), compared with aspirin (0.35) and clopidogrel (0). At a WTP value of £30,000 per QALY, the probability that ASA–MR-dipyridamole is cost-effective reduces marginally to 0.45. The probabilities for clopidogrel (0.12) and aspirin (0.25) are higher and lower than their respective estimates at £10,000 per QALY.

Hence the results of this scenario indicate that ASA–MR-dipyridamole is cost-effective provided that the NHS is willing to pay at least £4266 for an additional QALY. If the NHS is willing to pay more than £52,339 for an additional QALY, then treatment with clopidogrel is the optimal decision.

Summary and comments

Only ASA–MR-dipyridamole, MR-dipyridamole and aspirin are currently licensed for use in patients who have experienced a TIA. However, given that the clinical distinction between TIA and minor ischaemic stroke appears arbitrary, the results of the analyses in TIA patients with clopidogrel is included as a potentially relevant treatment option. We found less data on the costs and utility associated with TIA as distinct from minor strokes, and so the assumption was made that TIA was equivalent to a minor, non-disabling stroke. The baseline event rate data in the model were informed from a prospective cohort study in patients suffering a first-ever stroke.[87] To explore the impact of assuming that more severe strokes would lead to a higher rate of recurrence, the analysis for TIA patients was conducted under the assumption that baseline event rates would be 80% of those observed in a stroke cohort. This assumption was made by Boehringer Ingelheim Ltd in their submission. We also conducted the analysis with the baseline event rates left unadjusted.

The results of the analyses in TIA patients indicate that treatment with aspirin is the optimal decision at low values of WTP. The ICER for ASA–MR-dipyridamole compared with aspirin is £12,458 when baseline event rates are set to 80% of those for stroke, and £8941 when they are left unadjusted. The cost-effectiveness of ASA–MR-dipyridamole looks more favourable in TIA patients than in stroke patients as the value of preventing recurrent non-fatal events is higher. The utility decrement associated with first recurrent events is higher, as is the increase in the long-term cost of care. The cost-effectiveness of clopidogrel looks less favourable in TIA patients than in stroke patients and this is mainly because of its comparison with the changed cost and benefit profile of ASA–MR-dipyridamole. Although clopidogrel could be considered not to be an alternative treatment option in TIA patients, we present the results here anyway as they will bear a close relation to the results of an analysis in sufferers of minor strokes. The ICER for clopidogrel compared with ASA–MR-dipyridamole is £138,743 per additional QALY when baseline event rates are set to 80% of those observed in a stroke cohort, and £171,646 when the baseline event rates are left unadjusted.

The results for ASA–MR-dipyridamole look more favourable still in the secondary analysis of a 2-year treatment duration. Under this assumption, the ICER for ASA–MR-dipyridamole stays under

£5000 for baseline event rates assumed to be 80% of those for stroke, for baseline event rates equal to those for stroke and whether or not treatment effects on non-vascular death are included. The ICER for clopidogrel is in the range £46,949–£54,591 for these four analyses.

MI

Table 47 (see Appendix 7) presents the analysis of the ICER in a hypothetical cohort of patients with an initial qualifying event of MI for the four scenarios considered in the extended model. Only clopidogrel and aspirin are licensed for use in patients who have experienced MI and therefore Strategies 1 and 2 are the relevant comparators in this subgroup.

Scenario I – lifetime treatment (excluding relative risk of non-vascular death)

In the analysis based on lifetime treatment duration (excluding the treatment effect on non-vascular death), clopidogrel is both more expensive and more effective than aspirin. The ICER for clopidogrel compared with aspirin is £31,400. At a WTP value of £10,000 per QALY, aspirin has the highest probability of being cost-effective (1), compared with clopidogrel (0). At a WTP value of £30,000 per QALY, the probability that aspirin is cost-effective is 0.52, compared with clopidogrel (0.48). The CEAC for this scenario is reported in *Figure 14*.

Hence the results of this scenario indicate that clopidogrel is cost-effective provided that the NHS is willing to pay £31,400 for an additional QALY. If the NHS is willing to pay less than this amount, then Strategy 1 (treatment with aspirin) is more cost-effective.

Scenario II – lifetime treatment (including relative risk of non-vascular death)

In the analysis based on lifetime treatment duration (including the RR of non-vascular death), the ICER for clopidogrel compared with aspirin rises to £94,446 per QALY, compared with £31,400 when the relative risk of non-vascular death is excluded. At a WTP value of £10,000 per QALY, aspirin has the highest probability of being cost-effective (1), compared with clopidogrel (0). At a WTP value of £30,000 per QALY, the probability that aspirin is cost-effective is 0.75 (0.25 for clopidogrel). The CEAC for this scenario is reported in *Figure 15*.

Hence the results of this scenario indicate that clopidogrel is cost-effective provided that the NHS is willing to pay £94,446 for an additional QALY. If the NHS is willing to pay less than this amount, then Strategy 1 (treatment with aspirin) is more cost-effective.

Scenario III – 2-year treatment duration only (excluding relative risk of non-vascular death)

In the analysis based on 2-year treatment duration (excluding the RR of non-vascular death), the ICER for clopidogrel compared with aspirin is £17,081. At a WTP value of £10,000 per QALY, aspirin has the highest probability of being cost-effective (0.83), compared with clopidogrel (0.17). At a WTP value of £30,000 per QALY, the probability that aspirin is cost-effective is only 0.29, compared with 0.71 for clopidogrel.

The results of applying Scenario III to patients with an initial qualifying event of MI indicate that clopidogrel is cost-effective provided that the NHS is willing to pay £17,081 for an additional QALY. If the NHS is willing to pay less than this amount, then Strategy 1 (treatment with aspirin) is more cost-effective.

Scenario IV – 2-year treatment duration only (including relative risk of non-vascular death)

In the analysis based on 2-year treatment duration (including the RR of non-vascular death), the ICER for clopidogrel compared with aspirin is £21,448 (compared with the figure of £17,081 excluding the relative risk on non-vascular death). At a WTP value of £10,000 per QALY, aspirin has the highest probability of being cost-effective (0.88), compared with clopidogrel (0.12). At a WTP value of £30,000 per QALY, the probability that aspirin is cost-effective is 0.39, compared with the probability of 0.61 for clopidogrel.

In Scenario IV the results indicate that clopidogrel is cost-effective provided that the NHS is willing to pay £17,081 for an additional QALY. If the NHS is willing to pay less than this amount, then Strategy 1 (treatment with aspirin) is more cost-effective.

Summary and comments

ASA–MR-dipyridamole is not licensed for use in patients who have experienced an MI as their initial event, so clopidogrel and aspirin are the relevant treatment comparators in this subgroup. In the extended base-case analysis, the ICER for clopidogrel compared with aspirin is £31,400 when treatment effects on non-vascular death are not included and £94,446 when they are included. The MI subgroup in the CAPRIE trial showed a relative risk increase in the composite outcome of ischaemic stroke, MI or vascular death with the use of clopidogrel, compared with aspirin. If these

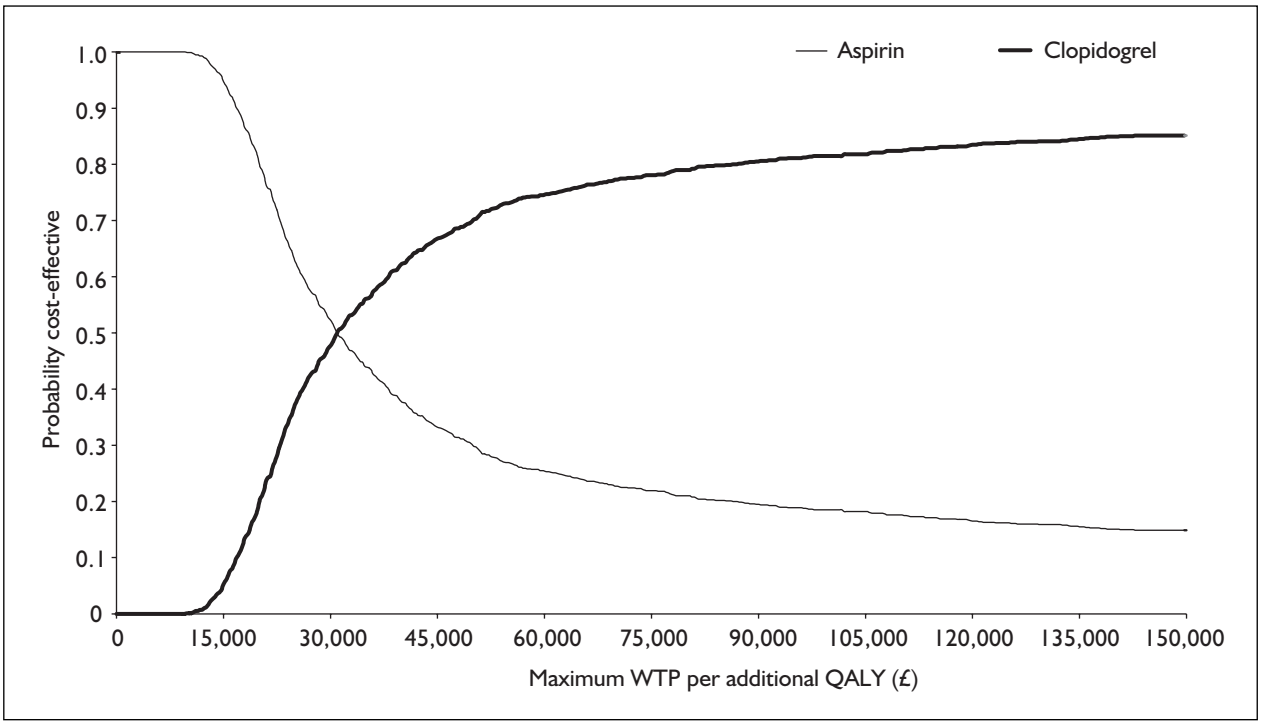

FIGURE 14 *Base-case results in the form of a cost-effectiveness acceptability curve: 40-year analysis in MI subgroup, excluding treatment effects on non-vascular death*

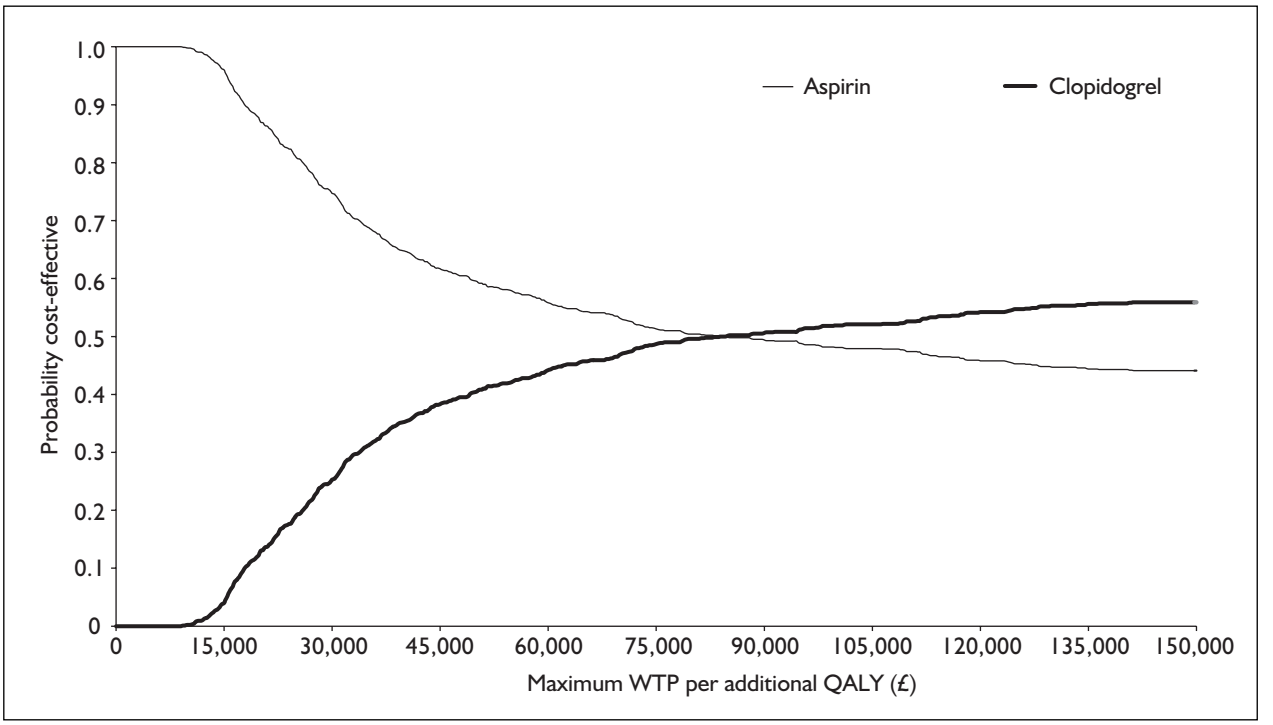

FIGURE 15 *Base-case results in the form of a cost-effectiveness acceptability curve: 40-year analysis in MI subgroup, including treatment effects on non-vascular death*

RRs were to be used in the model, treatment with aspirin would dominate treatment with clopidogrel. However, as mentioned earlier, there was considerable overlap in the atherothrombotic history of the qualifying event subgroups in CAPRIE. An additional analysis of the CAPRIE trial data, which included all patients who had experienced MI, rather than those whose qualifying event was MI, indicated that clopidogrel was associated with an RRR of 7.4% in the

composite end-point. Therefore, there seems reasonable justification for using overall treatment effects rather than subgroup specific estimates.

In the secondary analyses which consider a treatment duration of 2 years, rather than the lifetime treatment duration in the base-case analysis, the ICER for clopidogrel compared with aspirin is £17,081 when treatment effects on non-vascular death are excluded and £21,448 when they are included. The 2-year treatment duration appears more favourable than lifetime treatment, probably because the ratio of health benefits to the cost of the drug is highest in the earlier years of treatment, falling as the risk of non-vascular death increases.

PAD

Table 48 (see Appendix 7) presents the cost-effectiveness results in a hypothetical cohort of patients with an initial qualifying event of PAD for the four scenarios considered in the extended model. Only clopidogrel and aspirin are licensed for use in patients who have experienced PAD and therefore Strategies 1 and 2 are the relevant comparators in this sub-group.

Scenario I – lifetime treatment (excluding relative risk of non-vascular death)

In the analysis based on lifetime treatment duration (excluding the RR of non-vascular death), clopidogrel is both more expensive and more effective than aspirin. The ICER for clopidogrel compared with aspirin is £35,182. At a threshold WTP value of £10,000 per QALY, aspirin has the highest probability of being cost effective (1), compared with clopidogrel (0). At a WTP value of £30,000 per QALY, the probability that aspirin is cost-effective is 0.59, compared with clopidogrel (0.41). The CEAC for this scenario is reported in *Figure 16*.

Hence the results of this scenario indicate that clopidogrel is cost-effective provided that the NHS is willing to pay £35,182 for an additional QALY. If the NHS is willing to pay less than this amount, then Strategy 1 (treatment with aspirin) is more cost-effective.

Scenario II – lifetime treatment (including relative risk of non-vascular death)

In the analysis based on lifetime treatment duration (including the RR of non-vascular death), clopidogrel is dominated by aspirin. In this scenario, the optimal strategy is the use of aspirin. The CEAC for this scenario is reported in *Figure 17*.

Scenario III – 2-year treatment duration only (excluding relative risk of non-vascular death)

In the analysis based on 2-year treatment duration (excluding the RR of non-vascular death), the ICER for clopidogrel compared with aspirin is £20,733. At a WTP threshold value of £10,000 per QALY, aspirin has the highest probability of being cost effective (0.96), compared with clopidogrel (0.04). At a WTP value of £30,000 per QALY, the probability that aspirin is cost-effective reduces to 0.30 and the probability of that clopidogrel is cost-effective increases to 0.70.

The results of applying Scenario III to patients with an initial qualifying event of PAD indicate that clopidogrel is cost-effective provided that the NHS is willing to pay £20,733 for an additional QALY. If the NHS is willing to pay less than this amount, then Strategy 1 (treatment with aspirin) is more cost-effective.

Scenario IV – 2-year treatment duration only (including relative risk of non-vascular death)

In the analysis based on 2-year treatment duration (including the RR of non-vascular death), the ICER for clopidogrel compared with aspirin is £31,300 (compared with the figure of £20,733 in Scenario III). At a WTP value of £10,000 per QALY, aspirin has the highest probability of being cost effective (0.96), compared with clopidogrel (0.04). At a WTP value of £30,000 per QALY, the probability that aspirin is cost-effective is 0.52, compared with the probability of 0.48 for clopidogrel.

In Scenario IV, the results indicate that clopidogrel is cost-effective provided that the NHS is willing to pay £31,300 for an additional QALY. If the NHS is willing to pay less than this amount, then Strategy 1 (treatment with aspirin) is more cost-effective.

Additional analysis

As mentioned earlier in the report, there was concern that the cost of long-term care for PAD patients came from a weak data source. Two additional sensitivity analyses were undertaken in which the cost of PAD was altered to £180 per year and £2000 per year. Under these assumptions, and in the analysis based on lifetime treatment (excluding the RR of non-vascular death), the ICER for Strategy 2 (treatment with clopidogrel) compared with Strategy 1 (aspirin) changed to £32,857 when the cost of PAD was £180 per year and to £35,572 when the cost of PAD was £2000 per year (compared with £35,182 in the base-case). Hence the results of the model were relatively robust to a large variation in the annual cost of long-term care for PAD.

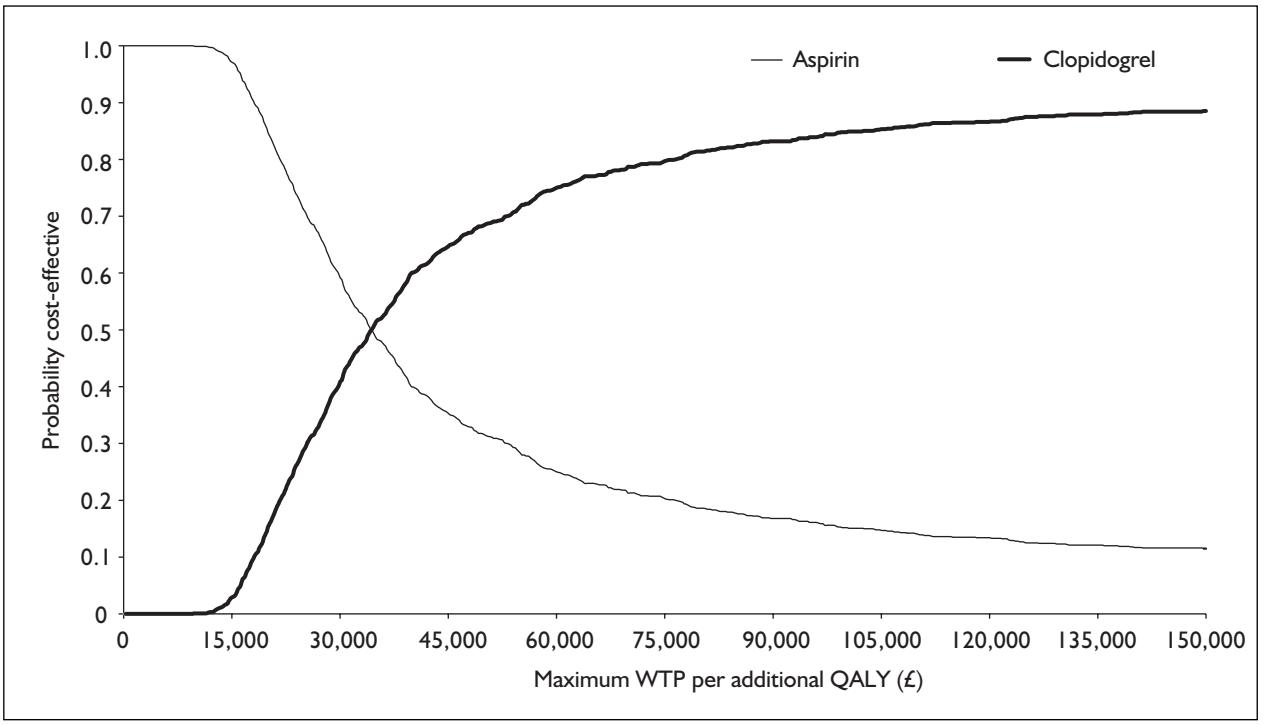

FIGURE 16 *Base-case results in the form of a cost-effectiveness acceptability curve: 40-year analysis in PAD subgroup, excluding treatment effects on non-vascular death*

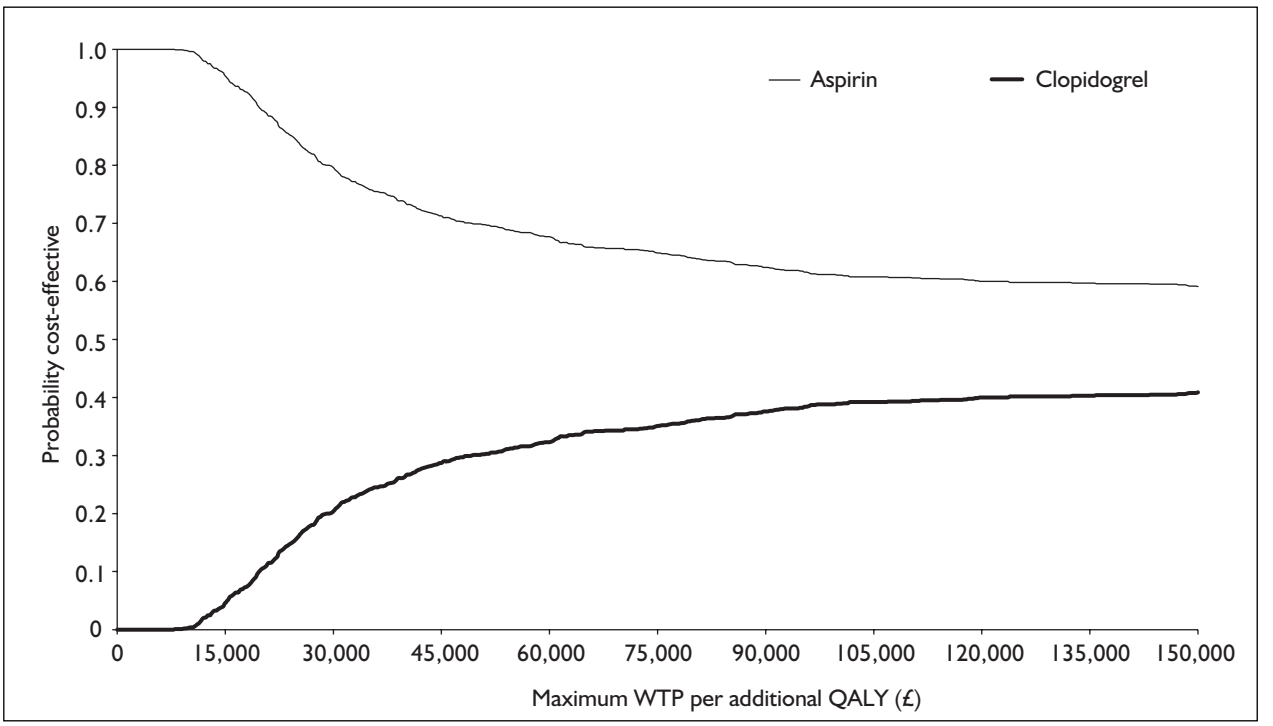

FIGURE 17 *Base-case results in the form of a cost-effectiveness acceptability curve: 40-year analysis in PAD subgroup, including treatment effects on non-vascular death*

Summary and comments

The results in the PAD subgroup are strikingly similar to those in the MI subgroup. The long-term care costs associated with PAD are assumed to be £1000 in the model, in comparison with £1587 for MI patients who remain event-free for 1 year following their MI. The utility associated with PAD is higher than that associated with event-free MI patients, at 0.75 compared with 0.72. This indicates that the value of preventing

recurrent non-fatal events is higher in PAD patients than in MI patients. However, clopidogrel does not look more cost-effective in PAD patients than MI patients, which is because of the different risk profile for recurrent events. The risk of any event is lower for PAD patients and so the relative risk reduction with clopidogrel is applied to a lower absolute baseline risk, making it look relatively less cost-effective. In the first year of the model, 1000 MI patients will typically incur around 123 recurrent MIs, four recurrent strokes and 41 vascular deaths. In contrast, 1000 PAD patients will typically incur around 25 recurrent MIs, 18 recurrent strokes and 16 vascular deaths.

The ICER for clopidogrel compared with aspirin in the extended base-case analysis is £35,182 per QALY when treatment effects on non-vascular death are excluded, but treatment with aspirin dominates when treatment effects on non-vascular death are included. Hence the competing effects of a greater value of preventing recurrent events and the lower baseline risk of events have resolved to make the cost-effectiveness of clopidogrel appear marginally less favourable in PAD patients than MI patients, and not favourable altogether if treatment effects on non-vascular death are included.

If the treatment duration is assumed to be only 2 years, the ICER for clopidogrel compared with aspirin is £20,733 when treatment effects on non-vascular death are excluded and £31,300 when they are included. As observed in the MI subgroup, the cost-effectiveness of clopidogrel appears more favourable over a 2-year treatment duration as compared with a lifetime treatment duration.

Results from the manufacturers' submissions

Boehringer Ingelheim Ltd found that the ICER for ASA–MR-dipyridamole compared with aspirin was £4207 in their base-case 5-year analysis. Boehringer Ingelheim Ltd's model assessed the cost-effectiveness of ongoing treatment with ASA–MR-dipyridamole, MR-dipyridamole and clopidogrel compared with aspirin in a hypothetical cohort of stroke patients, with a mean age of 70 years.

SSBMS found that the ICER for clopidogrel compared with aspirin was £14,525 in their base-case 40-year analysis. SSBMS's model assessed the cost-effectiveness of 2 years of treatment with clopidogrel (followed by aspirin for the remainder of patients' lifetimes), compared with treatment with aspirin in a hypothetical cohort of stroke, MI and PAD patients, with a mean age of 60 years.

The results from the manufacturers' submissions are not directly comparable to the results from the 'extended' base-case model developed by the University of York. This is because of the adaptations and changes detailed throughout this chapter, which were made to address the limitations of the manufacturers' models detailed in Chapter 5. These changes will have had varied, and sometimes competing, effects and so the difference between the outcome of the University of York model and those submitted by the manufacturers cannot be attributed to specific alterations.

Conclusions

The purpose of extending the modelling was to explore a range of uncertainties and sources of variability which were considered to have been inadequately addressed in the models submitted by the manufacturers. Clearly, any conclusions about cost-effectiveness will depend on the NHS' threshold WTP for additional health gain (in terms of QALYs). An important aspect of any decision about appropriate therapy relates to the duration of treatment. In the extended modelling we considered lifetime therapy and short-term (2-year) treatment.

Identifying the most cost-effective therapy for all subgroups is complicated by uncertainty over the impact of therapy on non-vascular deaths. CAPRIE and ESPS-2 show elevated risk of non-vascular death with clopidogrel and ASA–MR-dipyridamole, respectively. The lack of statistical significance is not sufficient evidence of equivalence in this outcome. Although a proportion of non-vascular deaths will not be associated with the use of antiplatelet therapies, it is not possible to rule out a link in some non-vascular deaths. The estimates of cost-effectiveness presented here which include treatment effects on non-vascular deaths essentially represent worst case scenarios for the clopidogrel and ASA–MR-dipyridamole. This is particularly the case for lifetime therapy because, as the patient ages, their baseline risk of non-vascular deaths increases.

Taking these factors into consideration, the following conclusions are possible assuming the NHS is willing to pay up to £20,000–40,000 per additional QALY.

- For the stroke and TIA subgroups, ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration as long as all patients were not left disabled by their initial (qualifying) stroke. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke. In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy. Clopidogrel would not be considered cost-effective under any scenario.
- For the MI and PAD subgroups, clopidogrel would be considered cost-effective for a treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

Chapter 7
Discussion

Clopidogrel and MR-dipyridamole for the secondary prevention of occlusive vascular events

In summary, the assessment of clinical effectiveness included two high-quality, multicentre RCTs, the CAPRIE trial and ESPS-2, respectively. The CAPRIE trial compared clopidogrel (75 mg/day) with aspirin (325 mg/day) and included 19,185 patients with atherothrombotic vascular disease. ESPS-2 compared MR-dipyridamole (400 mg/day) alone, and in combination with aspirin (50 mg/day), with aspirin (50 mg/day) and placebo. ESPS-2 included 6602 patients with previous stroke or TIA.

Both of the studies identified for the assessment of clinical effectiveness were high-quality, double-blind controlled trials.

Summary of clinical effectiveness data

Clopidogrel versus aspirin

Clopidogrel was marginally more effective than aspirin for the composite outcome of ischaemic stroke, MI or vascular death in patients with atherosclerotic vascular disease. That is, the point estimate favoured treatment with clopidogrel but the lower boundary of the 95% CIs suggested that the size of this benefit may be very small. Treatment with clopidogrel did not statistically significantly reduce the risk of vascular death or death from any cause compared with treatment with aspirin.

When the incidence of the primary outcome was analysed by clinical subgroup (according to qualifying event), there was a clear benefit of clopidogrel versus aspirin in patients with PAD. In patients with a qualifying stroke, there was a non-significant benefit in favour of clopidogrel versus aspirin. In patients with a qualifying MI, there was a non-significant benefit in favour of aspirin. However, the findings from these analyses should be interpreted with caution as the trial was not powered to detect differences between the subgroups. There was also a considerable overlap in the atherothrombotic history of the patients included in the trial.[60] Further analysis of a subgroup of patients with any previous MI showed a non-significant benefit for the primary outcome in favour of clopidogrel versus aspirin.

There was no difference in the number of patients ever reporting any bleeding disorder in the clopidogrel and aspirin treatment groups. More patients in the aspirin treatment group than in the clopidogrel treatment group experienced GI haemorrhage. The number of patients ever reporting rash and diarrhoea were statistically significantly higher in the clopidogrel group than the aspirin group. More patients in the aspirin group experienced indigestion, nausea and vomiting. The number of patients reporting haematological adverse events was rare in both the clopidogrel and aspirin groups.

MR-dipyridamole and ASA-MR-dipyridamole versus aspirin

ASA–MR-dipyridamole was significantly more effective than aspirin alone in patients with stroke or TIAs at reducing the outcome of stroke and marginally more effective at reducing stroke and/or death. Treatment with ASA–MR-dipyridamole did not significantly reduce the risk of death compared with treatment with aspirin. Treatment with MR-dipyridamole did not statistically significantly reduce the risk of any of the primary outcomes reported in ESPS-2 compared with treatment with aspirin.

There was no difference in the number of bleeding complications between the ASA–MR-dipyridamole and the aspirin groups. The incidence of bleeding complications (including severe and fatal bleeds) was significantly lower in the MR-dipyridamole treatment group. More patients in the MR-dipyridamole treatment groups experienced headaches compared with treatment with aspirin alone.

MR-dipyridamole in combination with aspirin versus MR-dipyridamole alone

The number of strokes was statistically significantly reduced in the ASA–MR-dipyridamole group compared with the MR-dipyridamole group. In terms of the other primary outcomes, stroke and/or death and death, the results favoured treatment with ASA–MR-dipyridamole combination therapy but the findings were not statistically significant.

Compared with MR-dipyridamole, the incidence of any bleeding complications, including mild, moderate and severe, was statistically significantly higher in the ASA–MR-dipyridamole group. There was no difference in the incidence of other adverse events, such as GI event and headache, between the two groups.

Clopidogrel versus MR-dipyridamole alone and in combination with aspirin

The results of the adjusted indirect comparison were equivocal. The findings suggested that in terms of reducing serious vascular events treatment with ASA–MR-dipyridamole may be superior to treatment with clopidogrel. However, in terms of preventing death from any cause, the point estimates favoured clopidogrel over MR-dipyridamole and ASA–MR-dipyridamole.

Due to the assumptions that have to made about the similarity of the CAPRIE trial and ESPS-2, the results of the adjusted indirect comparison should be interpreted with caution.

Summary of cost-effectiveness data

Eight studies were found which met the criteria for inclusion in the economic review. Boehringer Ingelheim Ltd and SSBMS also submitted economic models accompanied by assessment reports. The published studies and manufacturers' submissions were assessed, and a modified, extended model was developed to address the limitations identified in the assessment. The model assessed the cost-effectiveness of differing combinations of treatment strategies in four patient subgroups, under a number of different scenarios. The results of the model were sensitive to the assumptions made in the alternate scenarios, in particular the impact of therapy on non-vascular deaths. CAPRIE and ESPS-2 showed an elevated risk of non-vascular death with clopidogrel and ASA–MR-dipyridamole, respectively. The lack of statistical significance is not sufficient evidence of equivalence in this outcome. Although a proportion of non-vascular deaths will not be associated with the use of antiplatelet therapies, it is not possible to rule out a link in some non-vascular deaths. The estimates of cost-effectiveness presented here, which include treatment effects on non-vascular deaths, essentially represent worst case scenarios for the clopidogrel and ASA–MR-dipyridamole. This is particularly the case for lifetime therapy because, as the patient ages, their baseline risk of non-vascular deaths increases.

Summary of cost-effectiveness data in stroke patients

Five studies were identified which addressed the cost-effectiveness of clopidogrel or MR-dipyridamole for the secondary prevention of occlusive vascular events in patients who have experienced an initial stroke. The only two published studies relevant to the perspective of the UK NHS were superseded by Boehringer Ingelheim Ltd's submission. Boehringer Ingelheim Ltd found that ASA–MR-dipyridamole was more costly and more effective than treatment with aspirin, with an ICER of £4207 per QALY gained in their base-case 5-year analysis. The results from the extended model developed by the University of York TAR team were sensitive to the scenario under consideration.

- ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration provided that all patients were not left disabled by their initial (qualifying) stroke.
- For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin provided that treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke.
- In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy.
- Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.

Summary of cost-effectiveness data in TIA patients

None of the published studies or company submissions explicitly addressed the cost-effectiveness of ASA–MR-dipyridamole in patients who have experienced an initial TIA. The model submitted by Boehringer Ingelheim Ltd contained reference to TIA patients but they did not present the results of a cost-effectiveness analysis in TIA patients in their report. The results from the extended model developed by the University of York TAR team were sensitive to the scenario under consideration. The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY.

- ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration.
- For a lifetime treatment duration, ASA–MR-dipyridamole would be considered

more cost-effective than aspirin provided that treatment effects on non-vascular deaths are not considered.
- Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.

Summary of cost-effectiveness data in MI patients

No studies were identified that assessed the cost-effectiveness of clopidogrel for the secondary prevention of occlusive vascular events in patients who have experienced an initial MI. The results from the extended model developed by the University of York TAR team were sensitive to the scenario under consideration. The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY.

- Clopidogrel would be considered cost-effective for treatment duration of 2 years.
- For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin provided that treatment effects on non-vascular deaths are not considered.

Summary of cost-effectiveness data in PAD patients

One study was identified that assessed the cost-effectiveness of DP in patients diagnosed with PAD. However, this study is not relevant to a UK analysis. The results from the extended model developed by the University of York TAR team were sensitive to the scenario under consideration. The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY.

- Clopidogrel would be considered cost-effective for treatment duration of 2 years.
- For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

Summary of cost-effectiveness data in ischaemic heart disease

Two studies were identified that assessed the cost-effectiveness of clopidogrel in patients with ischaemic heart disease, but neither was relevant to a UK NHS perspective. The submission by SSBMS assessed the cost-effectiveness of clopidogrel compared with aspirin in a mixed cohort of patients with MI, stroke or PAD. SSBMS found that clopidogrel was more costly and more effective than aspirin, with an ICER of £14,525 per QALY gained in their base-case 40-year analysis. The results from the extended model developed by the University of York TAR team considered stroke, TIA, MI and PAD patients separately. The results were sensitive to the scenario under consideration and to the underlying patient population.

Comparison with other systematic reviews

Clopidogrel

The results presented in the ATT meta-analysis[15] agreed with those presented in the main publication of the CAPRIE trial. Clopidogrel was shown to be marginally more effective than aspirin at reducing serious vascular events and there was no evidence that clopidogrel was more or less effective than aspirin at reducing vascular or non-vascular death. The Cochrane review[34] also found that clopidogrel was modestly but significantly more effective than aspirin in preventing serious vascular events. Robless and colleagues[37] also found that there was a benefit in favour of clopidogrel versus aspirin alone in patients with PVD.

MR-dipyridamole alone

The results of the ATT meta-analysis[15] showed that there was no evidence that DP alone was more effective than aspirin alone in terms of reducing serious vascular events or death from any cause. Compared with aspirin the risk of bleeding complications was significantly lower in patients treated with MR-dipyridamole alone. The Cochrane Review[35] also found that there was no evidence that DP alone was more efficacious than aspirin.

MR-dipyridamole in combination with aspirin

The results of the ATT meta-analysis[15] found that MR-dipyridamole in combination with aspirin was superior to aspirin alone in reducing serious vascular events. There was no evidence that MR-dipyridamole in combination with aspirin was more or less effective than aspirin alone at reducing vascular or non-vascular death. The Cochrane Review[35] also found that MR-dipyridamole in combination with aspirin was significantly more effective than aspirin alone at reducing the risk of further vascular events. There was no evidence that MR-dipyridamole in combination with aspirin reduced the risk of vascular death. Redman and Ryan[36] also found that the addition of MR-dipyridamole to aspirin provided a further reduction in the risk of stroke compared with aspirin alone.

Assumptions, limitations and uncertainties

Assessment of clopidogrel

- The design of the CAPRIE trial is based on the assumption that the effect of antiplatelet drugs is common across the various clinical manifestations of atherothrombosis. In this respect, the trial was not powered to detect differences between the three clinical subgroups included.
- The dose of aspirin used in the CAPRIE trial is somewhat higher than that used in UK clinical practice. Data from the Intercontinental Marketing Services (data derived from British Pharmaceutical Index and Hospital Index and Hospital Pharmacy Audit) demonstrate that the most common UK ASA dosage is 75 mg/day. However, as there is no evidence of a significant difference in effectiveness between different aspirin regimens, and as systematic reviews have found no evidence of a difference in risk, it seems unlikely that this should affect the assessment of clopidogrel.

Assessment of MR-dipyridamole

- The dose of 50 mg/day aspirin used in ESPS-2 is relatively low compared with standard UK practice, where 75 mg/day is most common. However, as there is no evidence of a significant difference in effectiveness between different aspirin regimens, and as systematic reviews have found no evidence of a difference in risk, it seems unlikely that this should affect the assessment of MR-dipyridamole.
- ESPS-2 used a factorial design and is sensitive to the assumption that the effects of aspirin and DP are additive (i.e. there is no statistical interaction). It is important that the assumption of no interactions is fully justified in order for the trial to be sufficiently powered to detect treatment effects.
- Earlier studies of the standard-release formulation of DP in combination with aspirin showed a non-significant reduction in serious vascular events compared with treatment with aspirin alone.

Implications for further research and research recommendations

The effectiveness of the combination of clopidogrel and aspirin has been evaluated in patients with ACS and is the subject of a parallel appraisal. It also seems reasonable that the combination should be evaluated for the secondary prevention of occlusive vascular events. An ongoing study, CHARISMA,[41] should provide evidence in this area, as should another trial, MATCH,[39,40] which has recently finished.

Randomised, direct comparisons of clopidogrel and MR-dipyridamole in combination with aspirin are required to inform the treatment of patients with a history of stroke and TIA. The PRoFESS trial will investigate the combination of clopidogrel and aspirin compared with the combination of MR-dipyridamole with aspirin in patients with a history of TIA and stroke.

The treatment of aspirin-intolerant patients was not covered by any of the included trials identified for this review. That is, all of the trials specifically excluded patients who had a history of aspirin sensitivity. Trials are required which compare treatment with clopidogrel and MR-dipyridamole for the secondary prevention of vascular events in patients who demonstrate a genuine intolerance to aspirin.

Chapter 8
Conclusions

Clinical effectiveness

Clopidogrel

- Clopidogrel was marginally more effective than aspirin at reducing the risk of ischaemic stroke, MI or vascular death in patients with atherosclerotic vascular disease. That is, the point estimate favoured treatment with clopidogrel but the lower boundary of the 95% CIs suggests that the size of this benefit may be very small.
- Treatment with clopidogrel did not statistically significantly reduce the risk of vascular death or death from any cause compared with aspirin.
- There was no statistically significant difference in the number of bleeding complications experienced in the clopidogrel and aspirin groups.

MR-dipyridamole alone and in combination with aspirin

- Compared with aspirin alone, treatment with MR-dipyridamole alone did not significantly reduce the risk of any of the primary outcomes reported in ESPS-2.
- ASA–MR-dipyridamole was superior to aspirin alone at reducing the risk of stroke and marginally more effective at reducing the risk of stroke and/or death. Compared with treatment with MR-dipyridamole alone, ASA–MR-dipyridamole significantly reduced the risk of stroke.
- Treatment with MR-dipyridamole in combination with aspirin did not statistically significantly reduce the risk of death compared with aspirin.
- Compared with treatment with MR-dipyridamole alone, bleeding complications were statistically significantly higher in patients treated with aspirin and MR-dipyridamole in combination with aspirin.
- Due to the assumptions that have to be made, no conclusions could be drawn about the relative effectiveness of MR-dipyridamole, alone or in combination with aspirin, and clopidogrel from the adjusted indirect comparison.

Cost-effectiveness

- The extended model developed by the University of York TAR team sought to assess the cost-effectiveness of clopidogrel, ASA–MR-dipyridamole and MR-dipyridamole in comparison with aspirin in the secondary prevention of occlusive vascular events.
- The model considered four patient subgroups (stroke, TIA, MI and PAD) and several alternate scenarios, with different assumptions about treatment duration and the RR of non-vascular death.
- The results of the model were sensitive to the scenario and the patient subgroup under consideration.
- MR-dipyridamole was consistently dominated by alternative treatment strategies in each analysis and so is not cost-effective for the secondary prevention of occlusive vascular events in patients who have experienced an initial stroke or TIA.

The following conclusions are possible assuming the NHS is willing to pay up to £20,000–40,000 per additional QALY.

- For the stroke and TIA subgroups, ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration, provided that all patients were not left disabled by their initial (qualifying) stroke. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin provided that treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke. In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy. Clopidogrel would not be considered cost-effective under any scenario.
- For the MI and PAD subgroups, clopidogrel would be considered cost-effective for a treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin provided that treatment effects on non-vascular deaths are not considered.

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Lisa Jones (Research Fellow) was lead reviewer responsible for writing the protocol, study selection, data extraction, validity assessment and writing the final report. Susan Griffin (Research Fellow) was involved in the cost-effectiveness section; writing the protocol, study selection, data extraction, development of the economic model and report writing. Steve Palmer (Senior Research Fellow) was involved in the cost-effectiveness section; writing the protocol, study selection, data extraction, development of the economic model and report writing. Caroline Main (Research Fellow) 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; 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; overall responsibility for cost-effectiveness section of the report. Cathie Sudlow (Wellcome Clinician Scientist) provided input all stages of the review, commented on various drafts of the report and contributed to the discussion section of the report. Rob Henderson (Consultant Cardiologist) provided input all stages of the review, commented on various drafts of the report and contributed to the discussion section of the report. Neil Hawkins (Research Fellow) was involved in the cost-effectiveness section; advised on the development of the economic model. Rob Riemsma (Reviews Manager) provided input at all stages, commented on various drafts of the report; overall responsibility for the clinical effectiveness section of the report and supervised the overall process.

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

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Appendix 1

Search strategy

The full search strategies used to identify studies are listed below.

Cochrane Database of Systematic Reviews (CDSR)

#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)

This search identified 8 CDSR records and 200 Central records trials.

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.

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.

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.

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.

JICST (Dialog)

S1 8093 (RANDOMI?ED(W)CONTROLLED(W)-TRIAL?)
S2 15360 RANDOMIZATION
S3 117525 (CLINICAL(2W)TRIAL?)
S4 45104 ((SINGL? OR DOUBL? OR TREBL? OR TRIPL?)(2W)(BLIND? OR MASK?))
S5 42073 PLACEBO?
S6 125100 RANDOM
S7 116854 METHODOLOGY
S8 381345 COMPARATIVE(W)STUDY
S9 733337 EVALUATION
S10 152450 FOLLOW(W)UP
S11 22572 PROSPECTIVE(W)STUDY
S12 1535990 (CONTROL OR CONTROLS OR CONTROLLED)
S13 673 PHASE(W)IV
S14 160 PHASE(W)FOUR
S15 448 PHASE(W)4
S16 292 POST(W)MARKET?(W)SURVEILLANCE

S17 2887580 S1:S16
S18 395 CLOPIDOGREL
S19 10 PLAVIX
S20 1 ASASANTIN(W)RETARD
S21 0 PERSANTIN(W)RETARD
S22 3539 DIPYRIDAMOLE
S23 3887 S18:S22
S24 1309 S17 AND S23
S25 15 HEART(W)INFARCTION
S26 49283 MYOCARD?(W)INFARC?
S27 31 NSTEMI/TI,AB
S28 58 NON(W)ST(W)SEGMENT(W)-ELEVATION(W)MYOCARDIAL(W)-INFARCTION
S29 36956 STROKE
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 4183 UNSTABLE(W)ANGINA
S34 637 PERIPHERAL(W)ARTERIAL(W)-DISEASE1088381 NON
S35 88437 S25:S34
S36 289 S24 AND S35

This search identified 47 records.

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.

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.

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 search identified 916 records.

The strategies used to identify studies of the side-effects of aspirin are presented below.

CDSR

#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 search identified eight records.

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 search identified 6517 records.

HEED

DN=aspirin
AB=aspirin
DN=acetylsalicylic acid
AB=acetylsalicylic acid
CS=1 or 2 or 3 or 4

This search identified 133 records.

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 search 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 search identified 133 records.

NHSEED

1. aspirin or acetylsalicylic acid

This search identified 79 records.

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 search identified 34 records.

Appendix 2

Details of data extraction for clinical effectiveness studies

Data extraction tables for the CAPRIE trial

Study details	Inclusion criteria	Intervention details
Author CAPRIE Steering Committee, 1996[21] **Study design** Double-blind, randomised, placebo-controlled trial	**Definition of high-risk groups** See inclusion criteria **Inclusion/exclusion criteria** Clinical evaluation had to establish the diagnosis of ischaemic stroke, MI or symptomatic atherosclerotic peripheral arterial disease. Ischaemic stroke – focal neurological deficit likely to be of atherothrombotic origin, onset ≥ 1 week and ≤6 months before randomisation, neurological signs persisting ≥ 1 week from stroke onset, CT or MRI ruling out haemorrhage or non-relevant disease. MI – onset <35 days before randomisation, two of: characteristic ischaemic pain for ≥20 minutes; elevation of CK, CK-MB, LDH or AST to 2× upper limit of laboratory normal with no other explanation; development of new ≥40 Q-waves in at least two adjacent ECG leads or new dominant R-wave in V_1 (R-wave ≥ 1 mm greater than the S-wave). Atherosclerotic peripheral arterial disease – intermittent claudication (WHO: leg pain on walking, disappearing in <10 minutes on standing) of presumed atherosclerotic origin; and ankle/arm systolic ratio ≤0.85 in either leg at rest (two assessments of separate days); or history of intermittent claudication with previous leg amputation, reconstructive surgery or angioplasty with no persisting complications from intervention. Exclusion criteria were as follows: age <21 years; severe cerebral deficit likely to lead to patients being bedridden or demented; carotid endarterectomy after qualifying stroke; qualifying stroke induced by carotid endarterectomy or angiography; patient unlikely to be discharged alive after qualifying event; severe co-morbidity likely to limit patient's life expectancy to <3 years; uncontrolled hypertension; scheduled for major surgery; contraindications to study drugs; women of childbearing age not using reliable contraception; currently receiving investigation drug; previously entered in other clopidogrel studies; and geographic or other factors making study participation impractical	**Intervention 1** Clopidogrel 75 mg/day **Intervention 2** Aspirin 325 mg/day **Further information** None reported

AST, aspartate aminotransferase; CK, creatinine kinase; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging.

Intervention	Number of patients	Number of patients lost to follow-up	Mean age (SD) (years)	Qualifying event	Prognostic indicators, *n* (%)							
					MI	Stroke	Heart failure	Hypertension	Current/former smoker	Diabetes	Other	
Clopidogrel	9599	22	62.5 (11.1)	Stroke: 3233 MI: 3143 PAD: 3223	1632 (17)	864 (9)	576 (6)	4992 (52)	2784 (29)/ 4704 (49)	1920 (20)	TIA Reversible Ischaemic Neurologic Deficit (RIND): 960 (10) Hypercholesterolaemia: 3936 (41) Angina (stable/unstable): 2212 (22)/864 (9)	Cardiomegaly: 480 (5) Atrial fibrillation: 384 (4) Intermittent claudication: 480 (5)
Aspirin	9586	20	62.5 (11.1)	Stroke: 3198 MI: 3159 PAD: 3229	1534 (16)	863 (9)	479 (5)	4889 (51)	2876 (30)/4697 (49)	1917 (20)	TIA/RIND: 959 (10) Hypercholesterolaemia: 3930 (41) Angina (stable/unstable): 2109 (22)/863 (9)	Cardiomegaly: 383 (4) Atrial fibrillation: 383 (4) Intermittent claudication: 383 (4)

Definition of primary outcomes	Definition of secondary outcomes	Definition of bleeding complications
Primary analysis of efficacy was based on the first occurrence of an event in the outcome cluster of ischaemic stroke, MI, or vascular death. The classification of fatal ischaemic stroke or MI was based on either death within 28 days after the onset of signs and symptoms of the acute outcome event, in the absence of other clear causes, or on necropsy findings. Other vascular deaths were any deaths that were not clearly non-vascular and did not meet the criteria for fatal stroke, fatal MI or haemorrhage. Deaths considered to be clearly related to the qualifying event were classified as other vascular	A secondary outcome cluster included amputation and a further comparison based on vascular death only. Overall net benefit: any stroke, MI, intracranial haemorrhage, fatal bleed or death from any cause. All-cause mortality	Primary intracranial haemorrhage and fatal bleeds

Outcome 1: ischaemic stroke, MI or vascular death	Non-fatal	Fatal	Total	Event rate per year (%)
Clopidogrel (nyrs = 17,636)	631	308	939	5.32
ASA (nyrs = 17,519)	700	321	1021	5.83
RRR (95% CI) 8.7% (0.3 to 16.5) $p = 0.043$				

Outcome 2: ischaemic stroke, MI, amputation or vascular death	Non-fatal	Fatal	Total	Event rate per year (%)
Clopidogrel (nyrs = 17,594)	677	302	979	5.56
ASA (nyrs = 17,482)	737	314	1051	6.01
RRR (95% CI) 7.6% (–0.8 to 15.3) $p = 0.076$				

Outcome 3: vascular death	Non-fatal	Fatal	Total	Event rate per year (%)
Clopidogrel (nyrs = 17,482)	N/A	350	350	1.90
ASA (nyrs = 18,354)	N/A	378	378	2.06
RRR (95% CI) 7.6% (–6.9 to 20.1) $p = 0.29$				

Outcome 4: any stroke, MI, or death from any cause

	Non-fatal	Fatal	Total	Event rate per year (%)
Clopidogrel (nyrs = 17,622)	643	490	1133	6.43
ASA (nyrs = 17,519)	720	487	1207	6.90

RRR (95% CI) 7.0% (–0.9 to 14.2) $p = 0.081$

Outcome 5: death from any cause

	Non-fatal	Fatal	Total	Event rate per year (%)
Clopidogrel (nyrs = 18,377)	N/A	560	560	3.05
ASA (nyrs = 17,519)	N/A	571	571	3.11

RRR (95% CI) 2.2% (–9.9 to 12.9) $p = 0.71$

Outcome 6: validated events

	Clopidogrel	ASA	Total
Non-fatal			
Ischaemic stroke	472	504	976
MI	255	301	556
Amputation	52	47	99
Fatal			
Ischaemic stroke	37	42	79
MI	53	75	128
Other vascular death	260	261	521
Non-vascular death	187	166	353
Haemorrhagic death	23	27	50
Total	1353	1447	2800

Outcome 7: individual first-outcome events for each qualifying event

	Stroke		MI		Other vascular death	Total	Event rate per year (%)	RRR (%) (95% CI)	*p*
	Non-fatal	Fatal	Non-fatal	Fatal					
Stroke									
Clopidogrel (nyrs = 6054[a])	298	17	33	11	74	433	7.15	7.3 (–5.7 to 18.7)	0.26
Aspirin (nyrs = 5979)	322	16	37	14	72	461	7.71		
MI									
Clopidogrel (nyrs = 5787)	37	5	143	20	86	291	5.03	–3.7 (–22.1 to 12.0)	0.66
Aspirin (nyrs = 5843)	34	8	152	22	67	283	4.84		
PAD									
Clopidogrel (nyrs = 5795)	70	11	50	18	66	215	3.71	23.8 (8.9 to 36.2)	0.0028
Aspirin (nyrs = 5797)	74	8	81	27	87	277	4.86		

N/A, not applicable.
[a] Patient years at risk.

Adverse events					
Bleeding complications	**Clopidogrel**	**ASA**	**Other adverse events**	**Clopidogrel**	**ASA**
Validated events			**Patients ever reporting**		
Non-fatal primary intracranial haemorrhage	14	24	Rash	578 (6.02%)	442 (4.61%)*
Haemorrhagic death	23	27	Diarrhoea	428 (4.46%)	322 (3.36%)*
			Indigestion/nausea/vomiting	1441 (15.01%)	1686 (17.59%)*
Patients ever reporting			Abnormal liver function	285 (2.97%)	305 (3.15%)*
Any bleeding disorder	890 (9.27%)	890 (9.28%)			
Intracranial haemorrhage	34 (0.35%)	47 (0.49%)	**Severe**		
GI haemorrhage	191(1.99%)	255 (2.66%)*	Rash	25 (0.26%)	10 (0.10%)*
			Diarrhoea	22 (0.23%)	11 (0.11%)*
Severe			Indigestion/nausea/vomiting	93 (0.97%)	118 (1.23%)*
Any bleeding disorder	132 (1.38%)	149 (1.55%)	Abnormal liver function	11 (0.11%)	9 (0.09%)*
Intracranial haemorrhage	30 (0.31%)	41 (0.43%)			
GI haemorrhage	47 (0.49%)	68 (0.71%)*	**Study drug permanently discontinued**		
			Rash	86 (0.90%)	9 (0.41%)*
Study drug permanently discontinued			Diarrhoea	40 (0.42%)	26 (0.27%)
Any bleeding disorder	115 (1.20%)	131 (1.37%)	Indigestion, nausea, vomiting	182 (1.90%)	231 (2.41%)*
Intracranial haemorrhage	20 (0.21%)	32 (0.33%)	Abnormal liver function	22 (0.23%)	28 (0.29%)
Gastrointestinal haemorrhage	50 (0.52%)	89 (0.93%)*			

* Statistically significant, $p < 0.05$.

Additional safety data

Extracted from Harker* et al., *1999*[57] *(Comparative safety and tolerability of clopidogrel and aspirin: results from CAPRIE)

The objective of the paper was to provide a comprehensive comparison of the long-term safety and tolerability of clopidogrel and aspirin. The analyses are based on the intention-to-treat population.

Outcome 1: overall safety analysis

	Clopidogrel	ASA
Early permanent discontinuation of study drug due to adverse event (%)	11.94	11.92
GI disorders (%)	3.21	4.02*
Skin and appendage disorders (%)	1.52**	0.76
Fatal adverse event during study drug treatment + 28 days after stopping drug (%)	4.15	4.39
Fatal adverse event judged to be drug related by the investigator (%)	0.11	0.14

Patients may be counted in more than 1 body system, but appear only once in the total.
* $p < 0.01$; ** $p < 0.001$, clopidogrel vs aspirin.

Outcome 2: number of cases (%) of validated neutropenia and thrombocytopenia

	Clopidogrel	ASA
Neutropenia ($<1.2 \times 10^9$/l)	10 (0.10%)	16 (0.17%)
Severe neutropenia ($<0.45 \times 10^9$/l)	5[a] (o.05%)	4[b] (0.04%)
Thromocytopenia ($<100 \times 10^9$/l)	25 (0.26%)	25 (0.26%)
Severe thrombocytopenia ($<80 \times 10^9$/l)	18 (0.19%)	10 (0.10%)

[a] Includes 1 case which was judged to be due to underlying aplastic anaemia.
[b] Includes 2 cases that were judged to be due to underlying disorders (acute leukaemia and myelogenous leukaemia, respectively).
No cases of thrombotic thrombocytopenic purpura were reported with either clopidogrel or aspirin.

Outcome 3: haemorrhagic events

The overall incidence of haemorrhagic events did not differ statistically significantly between treatment groups (9.27% clopidogrel vs 9.28% aspirin, $p = 0.98$). Overall there was a trend towards a lower frequency of primary intracranial haemorrhages in the clopidogrel group compared with the aspirin group; 30 (0.31%) (16 fatal) vs 40 (0.42%) (16 fatal) cases, respectively.

Number of cases (%) of GI haemorrhage	Clopidogrel				Aspirin			
	All	severe	hospitalised	fatal	All	severe	hospitalised	fatal
Any GI bleed	191 (1.99%)	47 (0.49%)	71 (0.74%)	1 (0.01%)	255 (2.66%)*	68 (0.71%)	104 (1.08%)**	2 (0.02%)
Bloody diarrhoea	3	0	0	0	5	2	3	0
Haemorrhagic duodenal ulcer	17	12	17	0	14	10	13	0
Haemorrhagic gastric ulcer	8	5	6	0	12	7	11	0
Haemorrhagic gastritis	4	3	4	0	4	2	3	0
GI haemorrhage	32	17	24	1	51	30	39	1
Haematemesis	22	5	9	0	20	7	12	1
Rectal haemorrhage	52	2	4	0	75	5	13	0
Melena	58	2	4	0	75	5	8	0
Haemorrhagic oesophageal ulceration	3	3	3	0	4	2	4	0
Oral haemorrhage	2	0	0	0	5	0	1	0

Table is based on WHO system of nomenclature for adverse events.
* $p < 0.002$; ** $p = 0.012$, clopidogrel vs aspirin (other observed differences were not statistically significant: $p > 0.05$).

Outcome 4: incidence of GI adverse events

	Clopidogrel		Aspirin	
	All (%)	Severe (%)	All (%)	Severe (%)
Any GI adverse event	27.14	2.98	29.82**	3.60
Abdominal pain	5.64	0.38	7.14**	0.64
Dyspepsia	5.22	0.19	6.10*	0.25
Diarrhoea	4.46**	0.23	3.36	0.11
Constipation	2.38	0.08	3.33**	0.09
Gastritis	0.75	0.08	1.32**	0.07
Ulcer (gastric, duodenal, peptic)	0.68	0.25	1.15**	0.38

* $p < 0.01$; ** $p < 0.001$, clopidogrel vs aspirin (other observed differences were not statistically significant: $p > 0.05$).

Outcome 5: incidence of skin and appendage disorders

	Clopidogrel		Aspirin	
	All (%)	Severe (%)	All (%)	Severe (%)
Any skin and appendage disorders	15.81*	0.71	13.08	0.47
Pruritus	3.26*	0.14	1.63	0.0
Rash (any)	6.02*	0.26	4.61	0.10
Allergic reaction (any)	0.92	0.08	1.01	0.11

* $p < 0.001$, clopidogrel vs aspirin (other observed differences were not statistically significant: $p > 0.05$.

Other published CAPRIE subgroup analyses

Data extracted from Gent, 1997[48] (Benefit of clopidogrel in patients with coronary disease)

The author carried out additional analyses based on the finding that the RRR for patients in CAPRIE presenting with recent MI was less than for those presenting with stroke or PAD.

Outcome 1: ischaemic stroke, MI, or vascular death

	RRR (%)
Patients with a history of MI or having a past history of MI in the stroke or PAD cohorts ($n = 8446$)	7.4
Patients with any history of cardiovascular disease ($n = 10,047$)	7.6

Outcome 3: MI alone

	RRR (%)
All CAPRIE patients ($n = 19,185$)	19.2 ($p = 0.008$)

Data extracted from Blecic, 1998[60] (Atherothrombotic events often indicate disseminated atherosclerosis: data from CAPRIE)

The author analysed the atherothrombotic history of the CAPRIE cohort and examined the incidence of TIAs.

Outcome 1: atherothrombotic history	Outcome 2: incidence of TIA
The author reports that a sizeable proportion of patients in each qualifying subgroup condition were found to have an additional prior history of atherothrombotic disease. For patients with qualifying IS, 21.0% also had a past history of CVD (IS, reversible ischaemic neurological deficit, TIA or amaurosis fugax), 11.5% also had a prior history of CAD (MI or stable/unstable angina), 3.1% also had intermittent claudication, and 11.7% had a past history of 2 or more of the above. The author reports that similar overlaps were seen in patients qualifying with MI and PAD	For the overall population, the incidence of TIA was 2.29% for clopidogrel and 2.65% for aspirin

IS, ischaemic stroke.

Data extracted from Hankey, 1998[61] (The risk of vascular ischaemic events in patients with various clinical manifestations of atherothrombosis: data from CAPRIE)

Using data on validated outcome events for the ITT population, the author analysed the risk of (1) fatal or non-fatal IS; (2) fatal or non-fatal MI; and (3) fatal or non-fatal MI/other vascular death (excluding fatal IS) in the patients whose qualifying condition was IS (n = 6431) and in patients whose qualifying condition was PAD (n = 6452).

Outcome 1: fatal or non-fatal stroke

		Event rate at 3 years (%)
Ischaemic stroke	Clopidogrel	13.6
	Aspirin	14.0
PAD	Clopidogrel	3.5
	Aspirin	5.2

Outcome 2: fatal or non-fatal MI at 3 years

		Event rate at 3 years (%)
Ischaemic stroke	Clopidogrel	2.1
	Aspirin	2.7
PAD	Clopidogrel	NR
	Aspirin	NR

Outcome 3: fatal or non-fatal MI/other vascular death at 3 years

		Event rate at 3 years (%)
Ischaemic stroke	Clopidogrel	6.2
	Aspirin	7.0
PAD	Clopidogrel	8.7
	Aspirin	9.0

ITT, intention-to-treat; NR, not-recorded.

Data extracted from Hacke, 1998[50] (Consistency of the benefit of clopidogrel over aspirin in patients with lacunar and non-lacunar stroke)

The aim of the analysis was to compare the protective effects of clopidogrel and aspirin for the outcomes of lacunar stroke and non-lacunar stroke in the CAPRIE population (n = 19,185)

Outcome 1: primary outcome for patients with lacunar stroke

	Event rate	RRR (95% CI)
Clopidogrel	128	9.9% (–14.4 to 29.1)
Aspirin	141	

Outcome 2: primary outcome for patients with non-lacunar stroke

	Event rate	RRR (95% CI)
Clopidogrel	337	3.0% (–12.8 to 16.5)
Aspirin	346	

Data extracted from Coccheri, 1998[59] (Distribution of symptomatic atherothrombosis and influence of atherosclerotic disease burden on risk of secondary ischaemic events: results from CAPRIE)

The authors assessed the distribution of atherothrombotic history and the influence of atherosclerotic disease burden on the risk of secondary ischaemic event in the CAPRIE cohort. The authors defined several disease subgroups taking into account either the qualifying condition or previous medical history of ischaemia in the three different vascular beds.

Outcome 1: influence of atherosclerotic disease burden on risk of secondary ischaemic events

Disease history	Patients (%)	Event rate (%)
PAD only	19.2	2.6
Coronary disease only	29.9	4.3
CVD only	24.7	6.2
Qualifying PAD – any history	38.1	5.2
Qualifying MI – any history	52.4	6.2
Qualifying IS – any history	39.1	7.5
Disease in ≥2 beds	26.2	8.6

Data extracted from Easton, 1998[49] (Benefit of clopidogrel in patients with evidence of cerebrovascular disease)

The author examined the effect of clopidogrel in patients with previous CVD.

Results 1: patients with qualifying event ischaemic stroke

	Clopidogrel	Aspirin
Mean time to randomisation (days)	533 (±47.6)	527 (± 473)
Type of stroke		
Atherothrombotic (%)	60.3	58.3
Lacunar (%)	38.7	40.7
Retinal (%)	1.1	1.0
Stroke severity		
Moderate (%)	55.8	54.9
Severe (%)	21.9	22.3

Results 2: primary outcome cluster of ischaemic stroke, MI or vascular death

Stroke qualifying subgroup	RRR 7.3% (95% CI: –5.7 to 18.7)[a]
All patients with history of CVD (stroke, transient ischaemic attack, reversible ischaemic neurological deficit or omaurosis fugax)	RRR 8.3% (95% CI: –3.5 to 18.8)[a]

[a] In favour of clopidogrel.

Data extracted from Morais, 1998[56] (Use of concomitant medications in the CAPRIE trial: clopidogrel is unlikely to be associated with clinically significant drug interactions)

The author investigated the safety and tolerability of clopidogrel when given concomitantly with other drugs.

Outcome 1: number of patients receiving concomitant medication

Treatment	% of patients		Total
	Clopidogrel	Aspirin	
ACE inhibitors	29.2	30.5	29.8
Antidiabetic therapy	17.5	17.8	17.6
Anti-epileptic therapy	3.8	4.1	3.9
Beta-blocking agents	39.1	40.1	39.6
Calcium antagonists	38.6	38.9	38.7
Cholesterol reducers	25.5	25.5	25.5
Coronary vasodilators	34.9	35.5	35.2
Diuretics	28.9	29.5	29.2
Peripheral vasodilators	6.9	7.0	7.0

Significantly more patients in the aspirin group received ACE inhibitors than patients in the clopidogrel group ($p = 0.042$). There were no statistically significant differences in the number of patients receiving concomitant medications.

Outcome 2: safety

For all concomitant medications (except anti-epileptic medications), there was no difference in safety between the clopidogrel and aspirin groups, as assessed by the % of patients reporting an adverse event. Patients receiving anti-epileptic medications were at a higher risk of adverse events if they received aspirin than clopidogrel

Data extracted from Rupprecht, 1998[62] (Consistency of the benefit of clopidogrel across a range of vascular-related end-points: results from CAPRIE)

The authors estimated the RRR with clopidogrel for a number of additional outcome clusters including TIA and hospitalisation due to angina.

Outcome 1: single end-points

	RRR (95% CI)
IS	5.2 (–7.9 to 16.7)
MI	19.2 (5.3 to 31.0)
Vascular death	7.6 (–6.9 to 20.1)

Outcome 2: combined end-points of vascular death

	RRR (95% CI)
IS, MI	10.9 (1.5 to 19.5)
TIA, hospitalisation due to angina	7.5 (–1.2 to 15.5)
IS, TIA, hospitalisation due to angina	7.9 (1.5 to 13.8)

Outcome 3: combined end-points of major vascular events

	RRR (95% CI)
Any stroke[a], MI, vascular/haemorrhagic death (net benefit cluster)	9.5 (1.3 to 17.0)
Any stroke[a], MI, death from any cause	7.0 (–0.9 to 14.2)

[a] ischaemic or haemorrhagic.

Data extracted from Hacke* et al., *1999*[51] *(The benefit of clopidogrel over aspirin is amplified in high-risk subgroups with a prior history of ischaemic events)

The authors undertook an analysis of established risk factors and the presence of pre-existing vascular disease (previous MI, stable or unstable angina, TIA, RIND, stroke, claudication or amputation) for all patients in CAPRIE.

Outcome 1: IS, MI, hospitalisation for angina/claudication/peripheral ischaemia/TIA/myocardial ischaemia

	RR (*p*)
Previous ischaemic stroke	1.23 (0.031)
Previous MI	1.25 (<0.001)
Previous claudication	1.44 (<0.001)

Outcome 2: IS, MI, hospitalisation for angina/claudication/peripheral ischaemic/TIA/myocardial ischaemia by patient history of events

	3-year event rate (%)	ARR (%)	RRR (%) (*p*)
Previous acute events (IS or MI)			
Clopidogrel (*n* = 2249)	32.6	3.9	12.4 (0.034)
Aspirin (*n* = 2247)	36.5		
Previous vascular disease			
Clopidogrel *n* = 4421	30.5	2.6	9.3 (0.033)
Aspirin (*n* = 4433)	33.1		

Results were consistent for the combined end-point IS, MI or vascular death for patients with previous acute events (IS or MI) [ARR = 3.4%, RRR = 14.9% ($p = 0.045$)] and for patients with previous vascular disease [ARR = 2.8%, RRR = 11.5% ($p = 0.05$)].

Data extracted from Bhatt* et al., *2000*[52] *(Complementary, additive benefit of clopidogrel and lipid-lowering therapy in patients with atherosclerosis)

The authors sought to determine whether clopidogrel would be more efficacious than aspirin in preventing ischaemic events in patients with atherosclerosis who were already being treated with lipid-lowering therapy.

Outcome 1: relative risk reduction in rates of vascular death, MI, stroke or hospitalisation

	n	Clopidogrel (%) (*n* = 1080)	Aspirin (%) (*n* = 1014)	RRR (%)	*p*
Number with hypercholesterolaemia	11,217	12.8%	13.7%	6.8	0.097
Hypercholesterolaemia (on any drug)	2,094	11.9%	14.6%	18.6	0.038
Hypercholesterolaemia (on statin)	1,460	12.2%	15.1%	19.3	0.070

A reduction in events was also seen for each of the individual end-points examined (data not reported). The RRR for MI was most marked (RRR 56.0%, $p = 0.010$).

Outcome 2: multivariate modelling

In multivariate modelling that controlled for baseline features, clopidogrel therapy in patients being treated for hypercholesterolaemia was associated with a 20.0% reduction in vascular death, MI, stroke and rehospitalisation for ischaemia or bleeding ($p = 0.026$)

Data extracted from Bhatt* et al., *2000*[58] *(Reduction in the need for hospitalisation for recurrent ischaemic events and bleeding with clopidogrel instead of aspirin)

The purpose of the analysis was to determine whether clopidogrel, in addition to decreasing vascular death, MI or stroke, also decreases the need for hospitalisation for recurrent ischaemic events, namely angina, TIA or severe limb ischaemia as well as hospitalisation for bleeding. The analysis is based on the number of patients who received their treatment (clopidogrel or aspirin, respectively) as allocated (i.e. the authors did not carry out an ITT analysis).

Outcome 1: patients hospitalised for angina, TIA or severe limb ischaemia caused by peripheral arterial disease, bleeding all causes combined

	Clopidogrel (*n* = 9553)	Aspirin (*n* = 9546)	RRR (95% CI)	(χ^2)
Any cause	3500 (36.6)	3573 (37.4)	2.1% (–1.6 to 5.7)	0.257
Any ischaemic event or bleeding event	1183 (12.4)	1295 (13.6)	8.7% (1.7 to 15.2)	0.015
Any ischaemic event	1040 (10.9)	1126 (11.8)	7.7% (0.1 to 14.7)	0.048
Angina	654 (6.9)	686 (7.2)	4.7% (–5.6 to 14.1)	0.357
TIA	73 (0.8)	98 (1.0)	25.6% (–0.6 to 45.0)	0.054
PAD	349 (3.7)	384 (4.0)	9.2% (–4.7 to 21.2)	0.184
Any bleeding event	169 (1.8)	205 (2.2)	17.6% (–0.8 to 32.7)	0.059
Intracranial	32 (0.3)	40 (0.4)	20.1% (–27.1 to 49.7)	0.343
GI	71 (0.7)	104 (1.1)	31.8% (7.9 to 49.5)	0.012

Values are *n* (%). Note that a patient may have been hospitalised from more than one event during the treatment period but appears only once in the totals.

Outcome 2: event rates for clopidogrel and aspirin for various composite end-points

Outcome	Average event rate/year (%)		RRR (95% CI)	*p*
	Clopidogrel (*n* = 9553)	Aspirin (*n* = 9546)		
Death (all cause), stroke (all cause), MI	5.69	6.12	7.2 (–1.8 to 15.3)	0.113
Stroke (all cause, fatal or not), MI (fatal or not)	4.10	4.66	12.2 (2.2 to 21.1)	0.017
Hospitalisation for ischaemia and bleeding	8.03	8.85	9.1 (1.6 to 16.0)	0.018
Vascular death, stroke (all cause), MI, hospitalisation for ischaemia or bleeding	12.57	13.67	7.9 (1.9 to 13.7)	0.011
Stroke (all cause), MI, hospitalisation for ischaemia or bleeding	11.60	12.76	9.0 (2.7 to 14.8)	0.006

Outcome 3: RRs for factor in the multivariate model for vascular death, stroke, MI, or rehospitalisation for ischaemic or bleeding events

Variable	RR	p
Clopidogrel vs aspirin	0.918	0.009
Age	1.178/10 years	<0.001
Weight	0.975/10 kg	0.050
Race	1.071	0.364
Female	0.986	0.737
Hypertension	1.059	0.099
Prior MI	1.269	<0.001
Prior cerebrovascular event	1.225	0.002
Congestive heart failure (CHF)	1.225	0.001
Cigarette smoking	1.144	0.009
Diabetes	1.289	<0.001
Claudication	1.435	<0.001
Angina	1.584	<0.001

Data extracted from Bhatt et al., *2001*[53] *(Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery) with additional data from Bhatt* et al., *2001*[106]

The authors sought to determine whether clopidogrel would be more effective than aspirin in reducing recurrent ischaemic events in patients with previous cardiac surgery. The analysis is based on the number of patients who received their treatment (clopidogrel or aspirin, respectively) as allocated (i.e. the authors did not carry out an ITT analysis).

Baseline characteristics 1: patients with history of prior cardiac surgery

	Clopidogrel (*n* = 775)	Aspirin (*n* = 705)	p
Age (years)	63.3	63.9	0.23
Male (%)	83	84	0.69
White (%)	95	97	0.05
Diabetes (%)	30	27	0.27
Hypertension (%)	64	55	0.001
Elevated cholesterol (%)	56	55	0.84
Heart failure (%)	14	14	0.83
Prior MI (%)	59	56	0.23
Stable angina (%)	60	57	0.31
Unstable angina (%)	37	35	0.28
Prior stroke (%)	10	11	0.53
Prior TIA (%)	10	11	0.58
Intermittent claudication (%)	9	6	0.06
Current smoker (%)	20	20	0.23

Baseline characteristics 2: patients with a history of prior cardiac surgery vs those without

	Cardiac surgery (*n* = 1480)	No cardiac surgery (*n* = 17,619)	p
Age (years)	63.6	62.4	0.0001
Male (%)	84	71	0.001
White (%)	96	95	0.036
Diabetes (%)	29	20	0.001
Hypertension (%)	60	51	0.001
Elevated cholesterol (%)	55	40	0.001
Heart failure (%)	14	5	0.001
Prior MI (%)	58	13	0.001
Stable angina (%)	58	19	0.001
Unstable angina (%)	36	6	0.001
Prior stroke (%)	11	9	0.005
Prior TIA (%)	11	8	0.001
Intermittent claudication (%)	7	4	0.001
Current smoker (%)	20	30	0.001

Outcome 1: event rates and risk ratios per year for clopidogrel and aspirin for various individual and composite end-points

	Clopidogrel (%)	Aspirin (%)	*p*	RR (95% CI)	NNT (95% CI)[a]
All-cause death	2.6	3.4	0.195	–	–
Vascular death	2.0	3.3	0.03	43 (5 to 66)[a]	71 (46 to 659)
MI	2.4	3.9	0.037	39 (2 to 62)[a]	66 (41 to 1070)
Stroke	2.6	3.5	0.237	–	–
Hospitalisation: all-cause	35.8	47.5	0.002	22 (9 to 33)[a]	10 (6 to 24)
Hospitalisation: ischaemia/bleeding	10.6	14.6	0.015	–	–
Death, MI, stroke, all-cause hospitalisation	39.7	52.9	0.001	22.4 (10.4 to 32.8)	–
Vascular death, MI, stroke, hospitalisation for ischemia/bleeding	15.9	22.3		28.9 (13.1 to 14.8)	–
Vascular death, MI, stroke	5.8	9.1	0.001	36.3 (13.4 to 53.1)	30 (21 to 82)
All-cause death, MI, Stroke	6.4	9.3	0.004	31.8 (8.2 to 49.4)	–

[a] Additional data extracted from Bhatt *et al.*, 2001.[106]

Outcome 2: patients rehospitalised for ischaemic events (unstable angina, TIA or limb ischaemia), bleeding and all causes combined

	Clopidogrel *n* (%)	Aspirin *n* (%)	RRR (95% CI)	*p*
Any cause	333 (43.0)	353 (50.1)	14.2 (4.2 to 23.1)	0.006
Any ischaemic or bleeding event	123 (15.9)	141 (20.0)	20.6 (1.2 to 36.3)	0.038
Any ischaemic event	115 (14.8)	133 (18.9)	21.3 (1.2 to 37.4)	0.038
Any bleeding event	11 (1.4)	14 (2.0)	28.5 (–56.4 to 67.3)	0.398

Outcome 3: multivariate model showing the benefit of clopidogrel over aspirin in reducing all-cause death, MI, stroke and all-cause rehospitalisation after adjustment for baseline characteristics

Factor	RR (95% CI)	*p*
Clopidogrel	0.772 (0.668 to 0.893)	0.001
Claudication	1.435 (1.101 to 1.871)	0.003
DM	1.311 (1.116 to 1.542)	0.001
CHF	1.286 (1.055 to 1.568)	0.013
Prior cerebrovascular event	1.281 (1.023 to 1.604)	0.031
Angina	1.187 (0.997 to 1.413)	0.054
Age (years)	1.099/10 (1.004 to 1.204)	0.040

Data extracted from Bhatt* et al., *2002*[54] *(Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus)

The authors sought to determine whether clopidogrel compared with aspirin would be particularly efficacious in preventing ischaemic events in patients with atherosclerosis. Analyses were based on the number of patients who received their treatment as allocated, not ITT population.

Baseline characteristics: patients with history of diabetes

	Clopidogrel (%) (*n* = 1914)	Aspirin (%) (*n* = 1952)
Age	63.9 years	64.1 years
Men	69	68
Unstable angina	9	10
Hypertension	68	64
Hyperlipidaemia	45	46
Heart failure	10	10
Prior MI	22	21
Prior stroke	15	14
Claudication	7	7
Current smoker	22	23

Outcome 1: vascular death, all-cause stroke, MI or rehospitalisation for ischaemia or bleeding

	Event rate per year (%)	ARR (%)	*p*
Non-diabetic			
Clopidogrel (*n* = 7639)	11.8	NR	0.096
Aspirin (*n* = 7594)	12.7		
All diabetic patients			
Clopidogrel (*n* = 1914)	15.6	2.1	0.042
Aspirin (*n* = 1952)	17.7		
Treated with insulin (*n* = 1134)			
Clopidogrel	17.7	3.8	0.106
Aspirin	21.5		

Outcome 2: number of patients rehospitalised for ischaemia (transient ischaemic attack, angina or limb ischaemia) or bleeding

	Clopidogrel (*n* = 1914)	Aspirin (*n* = 1952)	RRR (%) (95% CI)	*p*
Any ischaemic or bleeding event	255 (13.3%)	304 (15.6%)	14.5 (0.2 to 26.7)	0.047
Any ischaemic event	222 (11.6%)	260 (13.3%)	12.9 (–3.0 to 26.4)	0.105
Any bleeding event	34 (1.8%)	55 (2.8%)	37.0 (3.8 to 58.7)	0.031

Outcome 3: multivariate model

In a multivariate model incorporating baseline clinical characteristics (including age, gender, race, weight, hypertension, prior MI, prior cerebrovascular event, CHF, smoking, claudication and angina), clopidogrel therapy was independently associated with a decrease in vascular death, MI, stroke and rehospitalisation for ischaemia or bleeding in diabetic patients. In the model, the RRR for clopidogrel compared to aspirin was 13.1% (95% CI: 1.2 to 23.7%; $p = 0.032$). Significant predictors of an event in the model included age, angina, prior MI and claudication

Data extracted from Cannon and Investigators 2002[55] [Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (CAPRIE trial)]

Using data from the CAPRIE trial, the author hypothesised that AMI could be predicted with baseline characteristics and that patients at a higher risk of developing AMI would have a greater relative benefit from clopidogrel than from aspirin. Patients were divided into 2 groups: those who did versus those who did not develop AMI during follow-up. AMI was defined as the presence of ≥ 2 of the following 3 criteria: (1) characteristic ischaemic pain lasting ≥ 20 minutes; (2) elevation of CK or CK-MB, lactate dehydrogenase or aspartate aminotransferase ≥ 2 times the upper limit of normal with no other explanation; (3) development of new Q-waves of at least 0.4 mV in 2 adjacent electrocardiographic leads or a new dominant R-wave in lead V_1 (with R-wave ≥1 mm greater than the S-wave in V_1).

Outcome 1: development of new AMI

Of the total 19,185 patients, a new AMI developed in 617.

	Kaplan–Meier event rate (1–3 years) (%)	RRR (%)	*p*
Aspirin	5.04%	19.2%	0.008
Clopidogrel	4.20%		

Outcome 2: significant multivariate predictors

Multivariate	Odds ratio	95% CI	*p*
Age ≥65 years	1.23	1.04 to 1.45	0.0154
DM	1.27	1.05 to 1.54	0.0134
Previous ischaemic stroke	1.45	1.00 to 2.10	0.0497
Previous MI	1.72	1.32 to 2.24	<0.0001
Previous PAD	1.80	1.34 to 2.42	<0.0001
Previous angina	1.87	1.58 to 2.22	<0.0001
Baseline creatine (>1.3 mg/dl)	1.42	1.19 to 1.68	<0.0001
Study drug (clopidogrel)	0.80	0.68 to 0.94	0.0067

Outcome 3: risk of developing AMI stratified by number of risk factors (up to 3 years)

Number of risk factors	MI to 3 years (%)	RRR (%)	NNT
1			
Clopidogrel	2.9	30	77
Aspirin	4.2		
2			
Clopidogrel	2.9	27	91
Aspirin	4.0		
3			
Clopidogrel	6.0	12	125
Aspirin	6.8		
4			
Clopidogrel	7.8	1	1000
Aspirin	7.9		
5+			
Clopidogrel	12.0	30	19
Aspirin	17.2		

Outcome 4: rate of AMI between clopidogrel and aspirin in various subgroups

The benefit of clopidogrel was consistent across all subgroups (data shown in figure) with only borderline evidence of interaction ($p = 0.048$) by history of hypercholesterolaemia, with a greater benefit of clopidogrel treatment in patients having a history of hypercholesterolaemia, especially when receiving drug therapy for this condition

Data extraction tables for ESPS-2

Study details	Inclusion criteria	Intervention details
Author(s) Diener *et al.*, 1996[22] and 1997[23] Additional data were extracted from Forbes, 1997[107] **Study design** Randomised, placebo-controlled, double-blind trial	**Definition high risk** A TIA was defined as clinical neurological symptoms persisting for <24 hours Completed ischaemic stroke was defined as clinical neurological deficits lasting >24 hours **Inclusion/exclusion criteria** Patients were eligible if they were more than 18 years old and had experienced a TIA or a completed ischaemic stroke within the preceding 3 months. Diagnosis based on clinical neurological examination only was acceptable but CT and MRI were recommended to confirm the diagnosis. Patients with a recent history of peptic ulcer or other GI bleeding, hypersensitivity or intolerance to either study medication, bleeding disturbances, any condition requiring continued use of ASA or anticoagulants or any life-threatening condition were excluded	**Intervention 1** Aspirin (ASA) 25 mg twice daily **Intervention 2** ASA + MR-dipyridamole (DP) 25 mg twice daily (ASA) + 200 mg twice daily (DP) **Intervention 3** MR-dipyridamole (DP) 200 mg twice daily **Intervention 4** Placebo **Further information** None reported

Intervention	Number of patients	Number of patients lost to follow-up	Mean age (SD) (years)	Qualifying event	Prognostic indicators, *n* (%)							
					MI	Stroke	Heart failure	Hypertension	Current/former smoker	Diabetes	Other	
ASA	1649	7	66.8	Stroke: 1257 (76.2) TIA: 392 (23.8)	NR	NR	134 (8.1)	983 (59.6)	388 (23.5)	240 (14.6)	Ischaemic heart disease: 571 (34.6) Atrial fibrillation: 104 (6.3) PVD: 362 (22.0)	Hypercholesterolaemia: 377 (22.9) Alcohol (>5 units/day): 87 (5.3)
ASA + DP	1650	10	66.8	Stroke: 1246 (75.6) TIA: 403 (24.4)	NR	NR	140 (8.5)	980 (59.4)	422 (25.6)	254 (15.4)	Ischaemic heart disease: 573 (34.7) Atrial fibrillation: 104 (6.3) PVD: 358 (21.7)	Hypercholesterolaemia: 410 (24.8) Alcohol (>5 units/day): 84 (5.1)
DP	1654	12	66.7	Stroke: 1265 (76.5) TIA: 388 (23.5)	NR	NR	143 (8.6)	1012 (61.2)	395 (23.9)	278 (16.8)	Ischaemic heart disease: 598 (36.2) Atrial fibrillation: 114 (6.9) PVD: 371 (22.4)	Hypercholesterolaemia: 375 (22.7) Alcohol (>5 units/day):100 (6.0)
Placebo	1649	13	66.6	Stroke: 1270 (77.0) TIA: 379 (23.0)	NR	NR	138 (8.4)	1022 (62.0)	386 (23.5)	239 (14.5)	Ischaemic heart disease: 577 (35.0) Atrial fibrillation: 107 (6.5) PVD: 363 (22.0)	Hypercholesterolaemia: 347 (21.0) Alcohol (>5 units/day): 96 (5.8)

Definition of primary outcomes	Definition of secondary outcomes	Definition of bleeding complications
Stroke (fatal and non-fatal), death from any cause and stroke and/or death	TIA, MI, other vascular events (pulmonary embolism, deep venous thrombosis, peripheral arterial occlusion, venous retinal thrombosis or combination of these events) and ischaemic events (stroke and/or MI, and/or sudden death of thrombotic origin). Any death of uncertain or unknown aetiology, occurring within 24 h after onset of symptoms was regarded as a case of sudden death. Additional outcomes were: stroke or TIAs (first event to occur), vascular deaths (defined by cause of death; fatal stroke, fatal MI, death due to cardiac failure or to any other vascular event, sudden death, non-cerebral haemorrhagic death) and vascular events (vascular death, non-fatal stroke, non-fatal MI and non-fatal other vascular event)	

Outcome 1: stroke

	Placebo	ASA	DP	ASA–DP	*p*
All strokes[a]	250	206	211	157	<0.001
Number of end-points					
'Survival' (%)	84.2	87.1	86.8	90.1	
RR (%)	N/A	18.1	16.3	37.0	
% persons saved from end-point	N/A	28.5	25.7	58.3	
Non-fatal strokes only[a]					
Number of end-points[b]	228 (213)	186 (170)	183 (168)	137 (126)	<0.001
'Survival' (%)	85.5	88.2	88.4	91.3	
RR (%)	N/A	19.2	20.0	39.9	
% persons saved from end-point	N/A	27.9	29.2	58.0	

Outcome 2: stroke – factorial comparisons

	RRR	SE	*p*
Overall test			<0.001
Factorial design analysis			
ASA versus non-ASA	21.2	5.3	<0.001
DP versus non-DP	19.3	5.4	0.001
Interaction	–	–	0.777
Pairwise comparisons			
ASA versus placebo	18.1	7.2	0.013
DP versus placebo	16.3	7.3	0.039
ASA–DP versus placebo	37.0	6.0	<0.001
DP versus ASA	-	-	0.677
ASA–DP versus ASA	23.1	7.1	0.006
ASA–DP versus DP	24.7	7.0	0.002

Outcome 3: death

	Placebo	ASA	DP	ASA–DP
All causes (n)	202	182	188	185
Survival (%)	87.7	89.1	88.6	88.8
RR (%)	N/A	10.9	7.3	8.5
CVA (all fatal stroke) (*n*):	43	39	56	38
MI (*n*):	16	21	15	17
Other vascular event (*n*):	8	3	4	7

Outcome 1: stroke (*cont'd*)

	Placebo	ASA	DP	ASA–DP	*p*
Fatal strokes (first stroke only)[a]					
Number of end-points[b]	22 (37)	20 (36)	28 (43)	20 (31)	0.46
'Survival' (%)	98.5	98.7	98.2	98.7	
RR (%)	N/A	8.4	–24	8.6	
% persons saved from end-point	NA	1.2	–3	1.2	
All fatal strokes[c]					
Number of end-points	43	39	56	38	0.17
'Survival' (%)	97.3	97.6	96.5	97.6	
RR (%)	N/A	9.8	–29.5	10.7	
% persons saved from end-point	N/A	2.7	–8	2.9	

CVA, cardiovascular accident; SE, standard error.
[a] Fatal outcome or not of the first stroke.
[b] Numbers in parentheses show reclassification of first stroke after publication of the trial.
[c] Fatal outcome of any stroke (first or later one).

Outcome 4: death – factorial analysis

	RRR	SE	*p*
Overall test	–	–	0.616
Factorial design analysis			
ASA versus non-ASA	6.3	6.4	0.287
DP versus non-DP	2.5	7.2	0.732
Interaction	–	–	0.461
Pairwise comparisons			
ASA versus placebo	10.9	8.6	0.204
DP versus placebo	7.3	8.8	0.453
ASA–DP versus placebo	8.5	8.8	0.324
DP versus ASA	–	–	0.609
ASA–DP versus ASA	–2.7	9.6	0.777
ASA–DP versus DP	1.3	9.3	0.815

Outcome 5: stroke and/or death

	Placebo	ASA	DP	ASA–DP
Stroke and/or death (*n*)	378	330	321	286
Survival (%)	77.0	80.1	80.6	82.6
RR (%)	N/A	13.2	15.4	24.4
Persons saved from end-point (%)	N/A	30.4	35.3	56.0

Outcome 6: stroke and/or death – factorial analysis

	RRR	SE	*p*
Overall test	–	–	<0.001
Factorial design analysis			
ASA versus non-ASA	12.0	4.4	0.003
DP versus non-DP	14.2	4.3	0.002
Interaction	–	–	0.628
Pairwise comparisons			
ASA versus placebo	13.2	5.8	0.016
DP versus placebo	15.4	5.7	0.015
ASA–DP versus placebo	24.4	5.3	<0.001
DP versus ASA	–	–	0.942
ASA–DP versus ASA	12.9	6.0	0.056
ASA–DP versus DP	10.7	6.1	0.073

Outcome 5: secondary outcomes

	Placebo	ASA	DP	ASA–DP
Stroke or TIA (first event to occur)				
Number of end-points	473	372	382	299
Survival (%)	68.9	75.7	75.1	80.1
RR (%):	N/A	22.1	20.0	36.1
Persons saved from end-point (%)	N/A	68.8	62.1	112.5
MI				
Number of end-points	45	39	48	35
Risk reduction (%)	N/A	13.2	–7.2	22.1
Persons saved from end-point (%)	N/A	3.8	–2.1	6.4
Fatal MI (*n*)	16	22	15	17
Non-fatal MI (*n*)	29	17	33	18
Other vascular events				
Number of end-points (*n*)	54	38	35	21
Survival (%)	96.5	97.6	97.8	98.7
RR (%)	N/A	31.6	36.7	61.7
Persons saved from end-point (%)	N/A	11.0	12.8	21.5
Specific clinical entities (*n*)				
Deep venous thrombosis	21	15	15	6
Pulmonary embolism	14	147	11	10
Peripheral arterial occlusion	21	11	10	6
Retinal vascular events	1	2	2	1

Outcome 6: secondary outcomes

	Placebo	ASA	DP	ASA–DP
Ischaemic events				
All ischaemic events (*n*)	307	266	271	206
Survival (%)	80.9	83.5	83.2	87.1
RR (%)	N/A	13.6	12.1	32.6
Persons saved from end-point (%)	N/A	26.1	23.2	62.3
Non-fatal ischaemic events (*n*)	249	203	212	153
Survival (%)	84.1	87.2	86.5	90.2
RR (%)	N/A	19.1	15.2	38.6
Persons saved from end-point (%)	N/A	30.3	23.9	61.2
Fatal ischaemic events (*n*)	90	88	95	80
Survival (%)	94.4	94.5	94.1	95.0
RR (%)	N/A	2.6	–5.1	10.4
Persons saved from end-point (%)	N/A	1.4	–2.9	5.9
Vascular death				
Number of end-points	124	118	125	117
Survival (%)	92.3	92.8	92.3	92.7
RR (%)	N/A	6.7	–0.5	5.3
Persons saved from end-point (%)	N/A	5.2	–0.4	4.1
Vascular events				
Number of end-points	361	314	324	246
Survival (%)	77.7	80.7	80.1	84.7
RR (%)	N/A	13.3	10.5	31.6
Persons saved from end-point (%)	N/A	29.6	23.5	70.3

Other outcomes

	Placebo	ASA	DP	ASA–DP
Summary of treatment interruptions				
Adverse events	127	141	249	262
Other medical reason	148	149	136	136
Non-medical reason	81	72	95	79
Unknown reason	4	4	5	2
No cessations	931	981	890	923
Lost to follow-up or end-point	358	302	279	248
Reasons for treatment cessation				
Any reason	360 (21.3%)	366 (21.7%)	485 (28.7%)	479 (28.3%)
Any medical reason	275 (20.4%)	290 (21.5%)	D385 (28.6%)	398 (29.5%)
Adverse event	127 (16.3%)	141 (18.1%)	D249 (32.0%)	262 (33.6%)
Other medical reason	148 (26.0%)	149 (26.2%)	136 (23.9%)	136 (23.9%)
Non-medical reason	81 (24.8%)	72 (22.0%)	95 (29.1%)	79 (24.2%)
TIA occurrence according to treatment				
Patients with TIAs during 2 years of follow-up	267/1622 (16.46%)	206/1631 (12.63%)	215/1628 (13.21%)	172/1631 (10.55%)

Adverse events

	Placebo	ASA	DP	ASA–DP
Bleeding complications				
Bleeding 'alone' (primary cause of death)				
Bleeding (*n*)	2	1	2	4
All cases (*n*)	7	10	7	11
Bleeding (no of pts reporting at least once)				
Any site	74 (4.5%)	135 (8.2%)	77 (4.7%)	144 (8.7%)
Mild	52	82	53	84
Moderate	15	33	18	33
Severe or fatal	7 (0.4%)	20 (1.2%)	6 (0.4%)	27 (1.6%)
Other adverse events				
Common adverse events (no of patients reporting at least once)				
n	1649	1649	1654	1650
Any	933 (56.6%)	990 (60.0%)	1034 (62.5%)	1056 (64.0%)
GI event	465 (28.2%)	502 (30.4%)	505 (30.5%)	541 (32.8%)
Nausea	226	204	245	254
Dyspepsia	266	283	274	290
Vomiting	109	93	119	133
Gastric pain	219	242	240	274
Diarrhoea	154 (9.3%)	109 (6.6%)	254 (15.4%)	199 (12.1%)
Headache	534 (32.4%)	546 (33.1%)	615 (37.2%)	630 (38.2%)
Dizziness	509 (30.9%)	481 (29.2%)	498 (30.1%)	486 (29.5%)
Any serious adverse event	254	247	181	240

Laboratory variables

Amongst the haematological analyses. No treatment-related effects were observed for white blood cell or blood platelet counts, sedimentation rate or fibrinogen. Differences were observed, however, for erythrocyte counts, haematocrit and haemoglobin values. In both DP-treated groups mean erythrocyte counts after 12–24 months of treatment blood were 3.2% lower than the corresponding counts in the non-dipyridamole groups ($p < 0.001$)

Additional data and subgroup analyses

Data extracted from Diener et al., *2001*[71] *[Cardiac safety in the European Stroke Prevention Study 2 (ESPS2)]*

The authors undertook a *post hoc* analysis of cardiac events in patients with CHD and MI (i.e. all patients with a history of angina pectoris or MI, or signs of cardiac ischaemia or MI on ECG) at entry to ESPS-2.

Outcome 1: distribution of patients with pre-existing CHD or MI in the 4 groups and in the factorial analysis

	ASA/DP	DP	ASA	Placebo
CHD	573/1650 (34.7%)	598/1654 (36.2%)	571/1649 (34.6%)	577/1649 (35.0%)
Prior MI	237/1650 (14.4%)	214/1654 (12.9%)	221/1649 (13.4%)	219/1649 (13.3%)

Factorial analysis

	DP	No DP	ASA	No ASA	Total
CHD	1121/3304 (35.4%)	1148/3298 (34.8%)	1144/3299 (34.7%)	1175/3303 (35.6%)	2319/6602 (35.1%)
Prior MI	458/3304 (13.9%)	433/3298 (13.1%)	451/3299 (13.7%)	440/3303 (13.3%)	891/6602 (13.5%)

Outcome 2: event rates for MI and mortality in patients who received DP or aspirin and in those who did not

	DP	No DP	ASA	No ASA
MI	83/3304 (2.5%)	84/3298 (2.5%)	74/3299 (2.2%)	93/3303 (2.8%)
Mortality	375/3304 (11.3%)	386/3298 (11.7%)	368/3299 (11.2%)	393/3303 (11.9%)

There was a trend for fewer MIs in patients who were on aspirin than in those who were not on aspirin (numbers too small to achieve significance). Mortality was identical in patients with CHD or prior MI irrespective of whether they took DP or not, or aspirin or not.

553 (8.4%) patients reported new episodes of angina pectoris or deterioration of pre-existing angina; 481 (7.4%) patients were under treatment. A total of 289 patients (8.7%) with angina were treated with DP and 264 (8.0%) were not treated with DP (not significant, $p = 0.276$). 274 (8.3%) patients on aspirin reported angina compared with 279 (8.4%) without aspirin.

Data extracted from Sivenius et al., *1999*[70] *(Second European Stroke Prevention Study: antiplatelet therapy is effective regardless of age)*

The aim of the study was to evaluate the influence of age on the efficacy of aspirin and DP, alone or in combination, in the secondary prevention of ischaemic stroke in the ESPS2 population.

Outcome 1: patients <65 years

	ASA	DP	ASA–DP
Stroke	49/655 (7.5%)	58/648 (9.0%)	41/623 (6.6%)
Stroke and/or death	68/655 (10.4%)	72/648 (11.1%)	53/623 (8.5%)
Vascular event	81/655 (12.4%)	80/648 (12.3%)	49/623 (739%)

Outcome 2: patients 65–74 years

	ASA	DP	ASA–DP
Stroke	73/526 (13.9%)	76/561 (13.5%)	52/570 (9.1%)
Stroke and/or death	109/526 (20.7%)	107/561 (19.1%)	99/570 (17.4%)
Vascular death	101/526 (19.2%)	120/561 (21.4%)	83/570 (14.6%)

Outcome 3: patients >75 years

	ASA	DP	ASA–DP
Stroke	84/468 (17.9%)	77/445 (17.3%)	64/457 (14.0%)
Stroke and/or death	153/468 (32.7%)	142/445 (31.9%)	134/457 (29.3%)
Vascular death	132/468 (28.2%)	124/445 (27.9%)	114/457 (24.9%)

Data extracted from Diener and Lowenthal, 1997[68] (Reply to Rosendaal and Algra regarding recalculation of ESPS-2 results including data of all patients originating from one centre)

Data from 438 patients originating from one centre were excluded from the published ESPS-2 analyses owing to irregularities with the data collection. The authors performed a new analysis of the data including the incriminated centre.

Outcome 1: stroke							**Outcome 2: death**							**Outcome 3: stroke and/or death**						
	n		**No. of events**		**RR (%)**			***n***		**No. of events**		**RR (%)**			***n***		**No. of events**		**RR (%)**	
	P	**R**	**P**	**R**	**P**	**R**		**P**	**R**	**P**	**R**	**P**	**R**		**P**	**R**	**P**	**R**	**P**	**R**
Placebo	1649	1758	250	256	–	–	Placebo	1649	1758	202	212	–	–	Placebo	1649	1758	378	394	–	–
ASA	1649	1758	206	212	18.1	17.7	ASA	1649	1758	182	186	10.9	13.1	ASA	1649	1758	330	339	13.2	14.4
DP	1654	1764	211	217	16.3	16.0	DP	1654	1764	188	196	7.3	8.0	DP	1654	1764	321	332	15.4	16.1
ASA–DP	1650	1760	157	162	37.0	36.5	ASA–DP	1650	1760	185	192	8.5	9.5	ASA–DP	1650	1760	286	295	24.4	25.1
Total	6602	7040	824	847			Total	6602	7040	757	786			Total	6602	7040	1315	1360		
p			<0.001	<0.001			*p*			<0.001	<0.001			*p*			<0.001	<0.001		

P, published results; R, after centre reinclusion.

Appendix 3

Details of data extraction for systematic reviews

Antithrombotic Trialists' Collaboration

Review details

Author, year
Baigent *et al.*, 2002[15] (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). 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: 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, cerebrovascular, 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, 89 with data on vascular events).

Participant baseline characteristics: Previous stroke/transient ischaemic attack ($n = 18{,}270$); acute stroke ($n = 40{,}821$); stable angina ($n = 2920$); atrial fibrillation ($n = 2770$); peripheral arterial disease ($n = 9214$); 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 coronary heart disease ($p < 0.001$).

continued

Review details

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 absolute risks 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 MI: data on 19,288 patients with suspected acute MI 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 transient ischaemic attack: 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 myocardial infarction [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, coronary artery bypass grafting (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 CABG was smaller [4% (14%)].

continued

Review details
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 peripheral arterial disease 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)]. 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 acute MI 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 of 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; NS, not significant; SE, standard error.

Cochrane Reviews

Review details	Study selection criteria	Results
Author, year De Schryver *et al.*, 2003[35] **Objective:** To assess the efficacy and safety of DP versus control in the secondary prevention of vascular events in patients with vascular disease in the presence and absence of other antiplatelet drugs. **Searches**: Cochrane Stroke Group Trials Register, other relevant Cochrane Group registers, Cochrane Controlled Trials Register, MEDLINE, EMBASE and the Dutch manufacturers of DP.	Randomised, secondary prevention trials of DP treatment lasting >1 month in the presence and absence of other antiplatelet drugs compared with no drug or another antiplatelet drug, starting within 6 months after presentation of arterial vascular disease.	26 trials were included (n = 19,842). Compared with control, DP had no clear effect on vascular death [RR 1.20 (95% CI: 0.90 to 1.17)]. DP appeared to reduce the risk of vascular events [RR 0.90 (95% CI: 0.83 to 0.98)] but this effect was only due to a single large trial in patients, presenting with cerebral ischaemia (n = 6602). Comparing DP plus aspirin with aspirin alone, there was no clear difference in vascular death [RR 1.03 (95% CI: 0.87 to 1.22)]; the combination was associated with fewer vascular events [RR 0.90 (95% 0.80 to 1.00)]. Combination treatment of DP and aspirin compared with placebo had an RR of 0.89 (95% CI: 0.79 to 1.01) for vascular death and an RR of 0.74 (95% CI: 0.68 to 0.80) for vascular events. **Authors' conclusions:** For patients who presented with arterial vascular disease, there was no evidence that DP, in the presence or absence of another antiplatelet drug (namely aspirin), reduced the risk of vascular death, although it may reduce the risk of further vascular events. However, this benefit was found only in a single large trial and only in patients presenting after cerebral ischaemia. There was no evidence that DP alone was more efficacious than aspirin. Further trials comparing the effects of the combination of DP with aspirin alone are justified.
Hankey *et al.*, 2000[34] **Objective:** To determine the effectiveness and safety of thienopyridine derivatives (ticlopidine and clopidogrel) versus aspirin for the prevention of serious vascular events in patients at high risk of such events, and specifically in patients with previous TIA or ischaemic stroke. **Searches:** Cochrane Stroke Group trials register, the Antithrombotic Trialists' database and the pharmaceutical manufacturers, Sanofi.	Double-blind, randomised trials comparing ticlopidine or clopidogrel with aspirin in high-risk vascular patients.	4 trials were included (n = 22,656), aspirin was compared with ticlopidine in 3 trials (n = 3471) and with clopidogrel in 1 trial (n = 19,185). Allocation to a thienopyridine was associated with a modest, yet statistically significant, reduction in the odds of a serious vascular event [OR 0.91 (95% CI: 0.84 to 0.98); p = 0.01], corresponding to the avoidance of 11 (95% CI: 2 to 19) serious vascular events per 1000 patients treated for about 2 years. There was also a reduction in stroke [OR 0.88 (95% CI: 0.79 to 0.98)]. Compared with aspirin, thienopyridines produced a significant reduction in the odds of GI haemorrhage and other upper GI tract upset, but a significant increase in the odds of skin rash and diarrhoea. Allocation to ticlopidine was associated with a significant increase in the odds of neutropenia [OR 2.7 (95% CI: 1.5 to 4.8)]. Allocation to a thienopyridine was associated with a larger absolute reduction in stroke in the subset of patients with TIA/ischaemic stroke [OR 0.86 (95% CI: 0.75 to 0.97)]. **Authors' conclusions:** Thienopyridine derivatives are modestly but significantly more effective than aspirin in preventing serious vascular events in patients at high risk (and specifically in patients in TIA/ischaemic stroke patients), but there is uncertainty about the size of the additional benefit. The thienopyridines are also associated with less GI haemorrhage and other GI upset than aspirin, but an excess of skin rash and diarrhoea.

Additional unpublished data from CAPRIE reported by Hankey *et al.*, 2000[34]

Outcome 1: stroke, MI or vascular death during follow-up

	Clopidogrel	Aspirin	Peto OR (95% CI)
All patients	976/9599	1063/9586	0.91 (0.83 to 0.99)
TIA/stroke patients	453/3233	488/3198	0.90 (0.79 to 1.04)

Outcome 2: stroke (all types) during follow-up

	Clopidogrel	Aspirin	Peto OR (95% CI)
All patients	464/9599	505/9586	0.91 (0.80 to 1.04)
TIA/stroke patients	336/3233	364/3198	0.90 (0.77 to 1.06)

Outcome 3: ischaemic/unknown stroke during follow-up

	Clopidogrel	Aspirin	Peto OR (95% CI)
All patients	450/9599	471/9586	0.95 (0.83 to 1.09)
TIA/stroke patients	320/3233	341/3198	0.92 (0.78 to 1.08)

Outcome 4: haemorrhagic stroke during follow-up

	Clopidogrel	Aspirin	Peto OR (95% CI)
All patients	30/9599	38/9586	0.79 (0.49 to 1.27)
TIA/stroke patients	21/3233	25/3198	0.83 (0.46 to 1.48)

Outcome 5: MI during follow-up

	Clopidogrel	Aspirin	Peto OR (95% CI)
All patients	276/9599	341/9586	0.80 (0.68 to 0.94)

Outcome 6: vascular death during follow-up

	Clopidogrel	Aspirin	Peto OR (95% CI)
All patients	373/9599	405/9586	0.92 (0.79 to 1.06)

Outcome 7: Extracranial haemorrhage during follow-up

	Clopidogrel	Aspirin	Peto OR (95% CI)
All patients	98/9599	102/9586	0.96 (0.73 to 1.27)

Outcome 8: serious vascular event

	Clopidogrel	Aspirin	Peto OR (95% CI)
All patients	978/9599	1065/9586	0.91 (0.83 to 0.99)

Other systematic reviews for the assessment of clinical effectiveness

Review details	Study selection criteria	Results
Author, year Redman *et al.*, 2001[36] **Objective:** To investigate whether the addition of DP to ASA further reduces the risk of stroke occurrence. **Searches:** MEDLINE, International Pharmaceutical Abstracts, EMBASE and BIOSIS (1966 to May 2001)	RCTs of the combinations of ASA and DP in the prevention of recurrent stroke in patients who have suffered a first stroke or TIA.	Of 5 published studies, 3 detected no differences in outcome when DP was added to aspirin therapy for stroke prophylaxis. Two more recent studies found that the addition of DP to ASA therapy provided further reduction on the risk of secondary cerebrovascular events compared with placebo and with ASA alone. **Authors' conclusions:** Further studies are needed to confirm long-term benefit.
Robless *et al.*, 2001[37] **Objective:** To provide evidence-based recommendations on the use of antiplatelet treatment for the prevention of cardiovascular events and stroke in patients with PVD. **Searches:** MEDLINE (1966 to January 1999), EMBASE (1996 to January 1999), Cochrane Controlled Trials Register, Proceedings from Vascular Surgical Society meetings, register of trials held by the APTC and pharmaceutical companies.	Double-blind RCTs of antiplatelet treatment versus placebo or versus other antiplatelet agents in patients with stable intermittent claudication or critical ischaemia or undergoing surgical vascular intervention.	For patients with PVD, the number suffering a non-fatal MI, non-fatal stroke or vascular death in the antiplatelet group was 6.5% compared with 8.1% in the placebo group [OR 0.78 (95% CI: 0.63 to 0.96); $p = 0.02$]. In 5 trials of aspirin versus another antiplatelet agent, 8.4% in the aspirin group suffered a vascular event compared with 6.6% in the second antiplatelet group [OR 0.76 (95% CI: 0.64 to 0.91); $p < 0.01$], favouring ticlopidine/clopidogrel/aspirin + DP against aspirin alone. **Authors' conclusions:** Antiplatelet therapy reduces serious vascular events and vascular death in patients with PVD.

Systematic reviews/meta-analyses investigating the safety of aspirin

Review details	Study selection criteria	Results
Author, year Weisman *et al.*, 2002[42] **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 <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 cardiovascular events in otherwise healthy individuals (primary prevention). **Participants:** Participants who had experienced a previous stroke, MI, 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.	**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 ($n = 1266$). **Participant baseline characteristics:** Specific indications for aspirin: Previous MI $n = 2427$; previous stroke or TIA: $n = 1757$ Weighted mean age: 59.5 years Weighted mean % male: 83.8. **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. Absolute risk increases ranged from less than 0% to 2.0% ± 1.4% (52-month follow-up). No significant heterogeneity between studies on this outcome measure was observed ($p = 0.5$).

continued

Review details	Study selection criteria	Results
		Cerebral haemorrhage: only 2/6 of the trials reported cases of haemorrhagic stroke (UK-TIA and SALT) and in both trials cerebrovascular 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.
Stalnikowicz-Darvasi *et al.*, 1995[43] **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 cardiovascular 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 55–75 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.	**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 ($n = 22071$). **Participant baseline characteristics:** Reported use of aspirin: Primary prevention: 2 studies ($n = 2207$) Transient ischaemic attack: 2 studies ($n = 2980$) Secondary preventions : 2 studies ($n = 1654$) CABG: 2 studies ($n = 297$) Prevention of emboli in atrial fibrillation: 1 study ($n = 627$). 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.

continued

Review details	Study selection criteria	Results
	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 haematocrit levels during the study were analysed in three.	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. **Authors' conclusions:** Low-dose aspirin carries a certain risk of GI bleeding, but in general it is not life-threatening.
Garcia Rodriguez *et al.*, 2001[46] **Objective:** To assess the relative risk of serious upper gastrointestinal 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 relative risk 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 tract complications (UGIC) defined as bleeding, perforation, or other serious upper GI tract 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.	**Number of included studies:** 17 studies (overall total $n = 67,722$). Cases $n = 12,140$; controls $n = 55,582$. 3 cohort studies ($n = 1159$). 14 case-control studies ($n = 66,563$), of which three were nested within a well-defined cohort ($n = 46,487$). **Participant baseline characteristics:** No participant baseline characteristics were reported. 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	Study selection criteria	Results
	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.	
He *et al.*, 1998[44] **Objective:** To estimate the risk of haemorrhagic 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 and 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, (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:** Only trials that provided information on the occurrence of stroke subtype during follow-up were included. The primary	**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 transient ischaemic attack 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 transient ischaemic attack or minor ischaemic stroke. **Participant baseline characteristics:** Specific indications for aspirin: TIA: 2135 (ASA 1069; placebo 1066) MI: 19069 (ASA 9419; placebo 9650) Cerebral ischaemia: 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) 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; $p = 0.60$).

continued

Review details	Study selection criteria	Results
	outcome was the incidence of stroke subtype, and the secondary outcome measures the incidence of total stroke, MI, cardiovascular mortality and all-cause mortality.	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 haemorrhagic 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 haemorrhagic 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 haemorrhagic 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 haemorrhagic 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.
Derry and Kong Loke, 2000[47] **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	**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 ($n = 16{,}060$). **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); cardiovascular risk factors, 2540 (ASA 1268; placebo 1272); unstable angina, 796 (ASA 399; placebo 397); primary prevention, 22,471 (ASA 11,237; placebo 11,234); 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). Sex: Male 74 %.

continued

Review details	Study selection criteria	
	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). Cross-over 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:** 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.	Participants were predominantly middle-aged (no age definition or range provided). 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.

AR, absolute; NNT, number-needed-to-treat.

Details of quality assessment according to DARE criteria

Review details	Quality assessment criteria				
	1	2	3	4	5
Author, year					
Weisman and Graham, 2002[42]	Good	Fair/good	N/A	Fair	Fair
Stalnikowicz-Darvasi, 1995[43]	Fair	Poor/fair	Fair	Fair	Fair
He *et al.*, 1998[44]	Good	Fair	N/A	Fair	Fair
Garcia Rodriguez *et al.*, 2001[46]	Good	Fair	Fair	Fair	Fair/good
Derry and Kong Loke, 2000[47]	Good	Fair/good	Good	Fair	Good

Appendix 4

Details of excluded studies

Clinical and cost-effectiveness searches

Study details	Reason for exclusion
Acheson, 1969[108]	Controlled trial of standard-release DP versus placebo
Adams, 1995[109]	Article about the management of TIA
Alberts, 2002[111]	Letter to the editor about clopidogrel in combination with aspirin for stroke prevention
Algra, 1999[112]	Letter to the editor about miscounting in reports of the CURE trial
American Heart Association Task Force, 2002[113]	Guideline update for the management of ACS
ACCSG, 1985[66]	Standard-release DP and aspirin versus aspirin; not licensed indication
ACCSG, 1986[360]	RCT comparing standard-release DP in combination with aspirin to aspirin; not licensed indication
AMIS Research Group, 1980[123]	RCT of aspirin versus placebo (AMIS study)
Anonymous, 1980[114]	Comment on PARIS (standard-release DP versus aspirin)
Anonymous, 1985[138]	Report on PARIS-II trial (standard-release DP) (German)
Anonymous, 1999[115]	Comment on ESPS-2 (Dutch)
Anonymous, 1999[116]	Short news report about the CAPRIE trial (clopidogrel)
Anonymous, 2000[117]	Not a full economic evaluation
Anonymous, 2001[118]	Comment on the CURE trial
Anonymous, 2001[119]	Commentary on clopidogrel trials (German)
Anonymous, 2002[120]	Article on use of clopidogrel in ACS (German)
Anonymous, 2002[121]	News report of use of clopidogrel in patients undergoing PCI
Aronow, 1999[122]	General article about antiplatelet agents in older patients with vascular disease; not a systematic review
Bachmann, 1996[124]	Pilot study of clopidogrel. Studied anti-aggregatory effect in human volunteers
Benavente, 1997[125]	Letter to the editor on ESPS-2
Bennett, 2000[126]	Case reports of TTP associated with clopidogrel – patients not all taking clopidogrel for secondary prevention and not all patients were in RCTs
Bertrand, 2000[127]	CLASSICS study; clopidogrel with and without a loading dose in combination with aspirin versus ticlopidine in combination with aspirin after coronary stenting
Bhatt, 1999[128]	CAPRIE – repeat hospitalisation (abstract). Available as full report[58]
Bhatt, 2000[129]	Subgroup analyses of patients in CAPRIE with history of cardiac surgery (abstract). Full publication available[53]
Bogousslavsky, 2001[130]	Review of ADP receptor antagonists; not a systematic review
Bollinger, 1985[131]	Not secondary prevention. Patients had undergone femoro-popliteal endarterectomy
Born, 1997[132]	Letter to the editor; comment on the CAPRIE trial
Bousser, 1981[133]	Protocol of AICLA (standard-release DP and aspirin versus aspirin)
Bousser, 1982[134]	Report on AICLA (standard-release DP)
Bousser, 1983[135]	Results of AICLA (standard-release DP)
Bousser, 1983[65]	Standard-release DP and aspirin versus aspirin (AICLA); not licensed indication
Boysen, 1988[136]	Low-dose aspirin versus placebo. Patients had undergone carotid endarterectomy
Boysen, 1999[137]	Review of antiplatelet drugs in secondary stroke prevention; not a systematic review
Brechter, 1980[139]	Trial of anticoagulants in TIA (German)

continued

Study details	Reason for exclusion
Breddin, 1980[140]	RCT of aspirin versus placebo for the secondary prevention of MI
Breddin, 1981[141]	General discussion of secondary prevention of MI (German)
Britton, 1987[142]	RCT of aspirin versus placebo for the secondary prevention of stroke (Swedish cooperative study)
Brown, 1993[143]	Study on the incidence of strokes following PCI
Cairns, 2001[144]	General overview of antithrombotic agents; not a systematic review
Calverley, 2001[145]	General article on antiplatelet therapy in the elderly; not a systematic review
Campbell, 1996[146]	Observational study about outpatient cardiac rehabilitation
Canadian Cooperative Study Group, 1978[147]	Aspirin alone and in combination with sulfinpyrazone versus placebo
CAPRIE Steering Committee, 1996[148]	Duplicate copy of CAPRIE Steering Committee[21]
Carolei, 2002[149]	Description of the MATCH trial from the Office of Clinical Trials (Columbia University)
CCS-2 Collaborative Group, 2000[150]	Chinese Cardiac Study (CCS-2): patients with acute MI; not licensed indication
CCS-2 Collaborative Group, 2000[150]	Not secondary prevention. Patients have suspected acute MI
Chapman, 2001[151]	Letter to the editor on use of clopidogrel (case study)
Cheung, 2000[152]	Letter to the editor regarding thrombotic thrombocytopenia purpura
Cohen, 2000[153]	Letter to the editor: comment on the DP trials
Colwell, 1989[154]	Not licensed indication; standard-release DP and aspirin (VA cooperative study)
Coronary Drug Project Research Group, 1980[155]	Early aspirin study
Coukell, 1997[156]	Duplicate copy of Coukell, 19971[57]
Coukell, 1997[157]	Short article about the pharmacology of clopidogrel
Crassard, 2000[158]	Overview of aspirin in CHD (French)
Crawford, 2001[159]	Short article about antiplatelet therapy in secondary stroke prevention; not a systematic review
Creager, 1998[160]	Overview of results from the CAPRIE trial
Cristallini, 1979[161]	General discussion of primary prevention of MI (Italian)
Culliton, 1980[162]	Commentary on PARIS and AMIS trials (standard-release DP)
CURE Study Investigators, 2000[163]	Duplicate copy of CURE 2000[81]
D'Addato, 1992[164]	Comparator is not aspirin (indobufen). Patients had undergone grafting
D'Agostino, 2003[165]	Trial design (methodology article)
Dale, 1989[166]	Background on stroke; incidence and prevalence (data from 1980s)
Dalton, 1996[172]	Comment on ESPS-2
De Boer, 1983[167]	Study of platelet survival time in patients with CAD
De Schryver, 1999[168]	Comment of the design and rational of ESPRIT (French)
De Schryver, 2001[169]	Protocol change to ESPRIT
Degeorges, 1981[170]	Commentary on secondary prevention of MI (French)
Department of Health, 2001[171]	Hospital episode statistics
Diener, 1998[173]	Letter to the editor; aspirin dose in secondary prevention of stroke
Diener, 1998[174]	Comment on secondary prevention DP trials
Diener, 1999[175]	Report of ESPS-2; same as Diener *et al.*, 1996[22] (German)
Diener, 1999[176]	Discussion article about aspirin in the prevention of stroke
Diener, 2000[177]	Discussion article about stroke prevention with antiplatelet therapy
Diener, 2001[178]	Report on post hoc analysis of ESPS-2; same as Diener *et al.*, 2001[71] (German)

continued

Study details	Reason for exclusion
Diener, 2002[179]	Discussion article about aspirin for secondary prevention of stroke
Doggrell, 2002[180]	Comment on the CURE trial
Donaldson, 1985[181]	Versus placebo. Patients had undergone grafting
Donnan, 2002[182]	Discussion article about aspirin for secondary prevention of stroke
Du, 1997[183]	Background on incidence of stroke in a high-risk area
Dutch TIA Trial Study Group, 1991[184]	Low-dose versus high-dose aspirin
Duval, 2000[185]	Background on trial methodology
Dyken, 1998[186]	Article about antiplatelet agents and stroke prevention; not a systematic review
Easton, 1991[187]	Overview of antiplatelet therapy in the prevention of stroke; not a systematic review
Easton, 1998[188]	Discussion article about recent antiplatelet trials
Easton, 1999[189]	Discussion article about antiplatelet therapy
Easton, 2001[190]	General overview of antiplatelet therapy; not a systematic review
Ehresmann, 1977[191]	Aspirin versus placebo
Elmi, 2000[192]	Case report of TTP with clopidogrel use
Elwood, 1974[193]	Aspirin versus placebo
Elwood, 1979[194]	Aspirin versus placebo
Elwood, 2000[195]	Review article on the use of aspirin in cardiovascular prophylaxis; not a systematic review
Escolar, 2000[196]	Overview of clopidogrel: pharmacodynamics, pharmacokinetics and clinical studies
ESPS-2 Working Group, 1996[197]	Early report of ESPS-2 (abstract)
ESPS Group, 1987[67]	Standard-release DP and aspirin versus placebo (ESPS-1); not licensed indication
ESPS Group, 1990[198]	Duplicate of ESPS Group 1990[199]
ESPS Working Group, 1995[200]	Early report on the rationale for ESPS-2; includes baseline data
ESPS-1 Investigators, 1988[201]	Report of ESPS-1 (standard-release DP) (Spanish)
ESPS-2 Working Group, 1992[202]	Interim report of ESPS-2
Evans, 1986[203]	Commentary on secondary preventative measures after acute MI
Ferguson, 1996[204]	Duplicate copy of Ferguson, 1996[205]
Ferguson, 1996[205]	News report of the results of ESPS-2
Fields, 1977[206]	Aspirin versus placebo (cerebral ischaemia)
Fields, 1978[207]	Aspirin versus placebo
Fields, 1979[208]	General background article on the antiplatelet agents
Fields, 1983[359]	Early report of the American–Canadian Persantine–Aspirin trial (standard-release DP)
Forbes, 1998[209]	Letter about ESPS-2 and CAPRIE
Forbes, 1998[210]	Background on stroke, includes brief discussion of ESPS-2 and CAPRIE
Forbes, 1998[211]	Summary of ESPS-2 trial; same as Diener *et al.*, 1996[22]
Forbes, 1999[212]	Review article of antiplatelet therapy for stroke prevention; not a systematic review
Franck, 1995[213]	Report of ESPS-2 (French)
Friedewald, 1984[214]	Overview of aspirin trials; not a systematic review
FRISC Study Group, 1996[215]	FRISC study; low-molecular-weight heparin (dalteparin) versus placebo for patients with CAD
Frison, 1992[216]	Background article on trial design
Furberg, 1980[217]	Commentary on the design of antiplatelet trials
Furberg, 1984[218]	Overview of treatments for acute myocardial infarction
Gallus, 1985[273]	General overview of antiplatelet agents. Not a systematic review
Gent, 1980[219]	Aspirin and sulfinpyrazone versus placebo
Gent, 1997[220]	Letter to the editor on behalf of the CAPRIE Steering Committee

continued

Study details	Reason for exclusion
Gent, 1998[221]	Overview of the CAPRIE trial
Gent, 1999[222]	Article describes the preregistration programme for CAPRIE
Gentile, 1986[223]	Abstract. DP versus isosorbide dinitrate
Gerschutz, 2002[224]	Comment on the CURE trial
Gianetti, 1998[228]	Cost-effectiveness study – not relevant to the scope of the review
Giansante, 1990[225]	Not licensed indications. Study examines ticlopidine, aspirin/DP and xanthinol nicotinate in patients with PAD
Gibbs, 1998[226]	Discussion article about DP
Gibbs, 1998[227]	Letter to the Editor – comment of review of secondary prevention for recurrent ischaemic stroke and TIAs
Goldman, 1984[229]	Aspirin plus DP for patients with vascular grafts
Goodnight, 1993[230]	Article about the antiplatelet agents; not a systematic review
Goodnight, 1993[231]	Article about the antiplatelet agents; not a systematic review
Goodnight, 1995[232]	Article about aspirin for patients with vascular disease and the influence of clinical trials. Not a systematic review
Gorelick, 1998[233]	Letter to the editor on the results of the CAPRIE trial
Gorelick, 1999[234]	Discussion article about aspirin and clopidogrel
Gorter, 1998[235]	Report of the ESPRIT trial (Dutch)
Gorter, 1999[236]	Comment on ESPRIT (German)
Grau, 2003[237]	Case-crossover study investigating platelet function under aspirin, clopidogrel or both
Green, 1982[238]	Study examined aspirin/DP, aspirin and placebo in patients who had undergone PTFE grafting
Guiraud-Chaumeil, 1982[239]	Duplicate copy of Guiraud-Chaumeil[64]
Guiraud-Chaumeil, 198[264]	Standard release DP and aspirin versus aspirin (Toulouse-TIA); not licensed indication
Guiu, 1987[240]	Standard-release DP + ASA versus ASA. Not an RCT
Hacke, 1999[241]	Background article on acute stroke
Haldemann, 2001[242]	Foreign language economics paper
Hankey, 1997[243]	Comment on the CAPRIE trial
Hankey, 1999[244]	Cost study, did not include a full economic evaluation
Hankey, 2000[245]	Duplicate report of Hankey *et al.*[246]
Hankey, 2001[246]	Systematic review of the thienopyridines. Based on Cochrane Review by the same authors
Hanssen, 1998[247]	Case report – DP used as a vasodilator
Harjola, 1981[248]	Not secondary prevention. Patients had undergone arterial reconstructive surgery
Harrington, 1994[249]	Overview of antiplatelet trials (no results reported)
HOPE Investigators, 2000[250]	HOPE study; ramipril versus placebo in high-risk patients
HPSCG, 2002[251]	MRC/BHF Heart Protection Study; simvastatin versus placebo
Heiss, 1990[252]	Not licensed indication. Patients had had percutaneous transluminal angioplasy (PTA)
Hennekens, 1990[253]	Overview of the aspirin trials; not a systematic review
Hennekens, 1991[254]	Overview of aspirin trials; not a systematic review
Hennekens, 1997[255]	Discussion on the aspirin trials; not a systematic review
Hennekens, 2002[256]	Background on ASA; general article, not a systematic review
Heptinstall, 1996[257]	Editorial article about ESPS-2
Hervey, 1999[258]	Overview of extended-release DP/aspirin; not a systematic review
Hess, 1975[259]	Abstract; theoretical background to antiplatelet treatment (German)
Hess, 1985[260]	Not licensed indication (standard-release DP)
Hess, 1994[261]	Not licensed indication (standard-release DP) (German)
Hillis, 1997[262]	Comment on DP as an antiplatelet agent

continued

Study details	Reason for exclusion
Hirsh, 1984[263]	Overview article reporting on standard-release DP; not a systematic review
Hodara, 1984[264]	Article on the secondary prevention of MI (French)
Huber, 2001[265]	News report on the CURE trial (German)
Humphreys, 2002[266]	Adverse events from DP studies. Not a systematic review or post-marketing study
Ishikawa, 1997[267]	Not licensed indication (standard-release DP)
Jackson, 2001[268]	Editorial on use of clopidogrel, based on the results of the CURE trial
Jarvis, 2000[269]	Review of the role of clopidogrel in the prevention of atherothrombosis; not a systematic review
Jonas, 1998[270]	Summary of meta-analysis of antiplatelet agents versus placebo. No search reported
Jonas, 2001[271]	Comment on ESPS-2 and CAPRIE (abstract)
Kerins, 1991[272]	Commentary on the role of antiplatelet drugs in ischaemic heart disease; not a systematic review
Klimt, 1986[274]	Standard-release DP and aspirin for the long-term therapy of CHD after MI (Persantine–Aspirin Reinfarction Study); not licensed indication
Kohler, 1984[275]	Patients had undergone PTFE grafts. Not licensed indication
Kubler, 2002[276]	Overview of antiplatelet therapy (German)
Kurz, 1998[277]	Economics paper – foreign language (French)
Kurz, 1998[278]	Duplicate copy of Kurz, 1998[277]
Lamy, 2002[279]	Not a full economic evaluation (abstract)
Lee, 1990[280]	DP (standard release). Not an RCT
Lenz, 2000[281]	Overview of DP trials; not a systematic review
Libretti, 1986[282]	Not licensed indication. Treatment of claudication with DP and aspirin
Lowe, 2003[283]	Overview of the role of clopidogrel as an antiplatelet agent
Lowenthal, 1994[284]	Meta-analysis on ASA and standard-release DP; search not reported (would not pass DARE criteria)
Lubsen, 1981[285]	Commentary on the PARIS trial (Dutch)
Lucas, 2002[286]	Comment on the PROGRESS trial (French)
MacWalter, 1999[287]	General overview of secondary prevention of stroke; not a systematic review
MacWalter, 2002[288]	Benefit–risk assessment of agents used in secondary stroke prevention; not a systematic review
Malinin, 2003[289]	Background review on clopidogrel for CHF
Malinin, 2002[290]	Background on pharmacological action of aspirin and DP; not a systematic review
Marx, 1980[291]	Commentary on the AMIS trial
Matsagas, 2003[292]	Comment on CAPRIE and CURE trials for patients with PAD
McCollum, 1991[293]	Not licensed indication. (standard-release DP following bypass)
Mehta, 2002[295]	Overview of aspirin for the prophylaxis of CAD; not a systematic review
Millan-Guerrero, 1999[296]	Article about intravenous DP for acute stroke (Spanish)
Minar, 1995[297]	High-dose versus low-dose aspirin after angioplasty
Misson, 1998[298]	Non-systematic review of clopidogrel. No new data reported
Mueller, 2003[299]	Use of new device for monitoring ASA and clopidogrel intake
Muhlestein, 1997[300]	Economic evaluation on abciximab and ticlopidine
Muller, 1994[301]	General overview of the pharmacology of current and future antithrombotic therapies
Muller, 2001[302]	Trial in healthy subjects to investigate the inhibition of thrombus formation by low-dose aspirin and DP
Mustard, 1983[303]	Review of aspirin trials; not a systematic review
Nappi, 2002[304]	Overview of antiplatelet therapy; not a systematic review
Nenci, 1996[305]	General review article on the antiplatelet agents. Not a systematic review
Noble 1996[306]	Overview of ticlopidine; not a systematic review

continued

Study details	Reason for exclusion
Oostenbrink, 2001[307]	Cost-effectiveness study; not relevant to the scope of the review
Overall, 1999[308]	Not a full economic evaluation (abstract)
Paradiso-Hardy, 2002[309]	Bayesian analysis of TTP associated with clopidogrel therapy
PARIS Study Group, 1980[362]	Report on the PARIS trial (standard-release DP)
PARIS Study Group, 1980[363]	Report on the PARIS trial (standard-release DP)
PARIS Study Group, 1980[364]	Standard release DP (German)
Patrono, 1998[310]	Discussion article about aspirin doses and mechanisms of action
Pechlaner, 2002[311]	Letters to the editor regarding RITA 3 trial (early angiography)
Persantine–aspirin Reinfarction Study Group 1980[312]	Duplicate copy of PARIS 1980[313]
Petrucci, 1996[314]	Assessment of DP for stress testing using echocardiographic test results
Picano, 1998[315]	Article about the potential pharmacological actions of DP
Prandoni, 1991[316]	DP + ASA in unstable angina (Italian)
Prandoni, 1991[317]	Pilot study of DP in patients with ACS
Puranen, 1997[318]	Subgroup analysis of ESPS-1
Puranen, 1998[319]	Subgroup analysis of patients with TIA or stroke from ESPS 1
Rajah, 1979[320]	Effect of DP on bleeding time; study conducted on healthy participants
Ranke, 1994[321]	High-dose versus low-dose aspirin. Patients had undergone PTA
Regensteiner, 2002[322]	Meta-analysis of current medical therapies for patients with PVD
Reuther, 1978[323]	Aspirin versus placebo
Reyero, 2002[324]	Letter to the editor on the CURE trial (Spanish)
Richardson, 2001[325]	Discussion on data quality assurance and control in stroke trials
Riekkinen, 1988[326]	Discussion article about aspirin and DP (Swedish)
Ringleb, 2003[327]	Overview of antiplatelet therapy for stroke; not a systematic review
Robinson, 1991[328]	Background on trial methodology
Roderick, 1993[329]	Review using only the trial reported in the first ATT meta-analysis; not systematic review as no search performed
Ruhle, 1985[330]	Background article on antiplatelet agents (German)
Rumboldt, 1995[331]	Letter regarding impact of clinical trial on clinical practice
Sakai, 1992[332]	Retrospective study on warfarin, ticlopidine and aspirin (Japanese)
SALT Collaborative Group, 1991[333]	Low-dose aspirin versus placebo
Saniabadi, 1991[334]	Study of the effect of DP on antiplatelet aggregation in whole blood ($n = 16$)
Schellinger, 1997[335]	General discussion on antithrombotic therapy (German)
Schoop, 1983[336]	Abstract. Not licensed indication (standard-release DP)
Schoop, 1983[337]	Not licensed indication (standard-release DP) (German)
Schror, 1995[338]	Comparative review of antiplatelet agents; not a systematic review
Sculpher, 1998[339]	Systematic review of effectiveness, costs and cost-effectiveness of interventions for stable angina
Sempere, 2000[340]	Not an RCT (community based observational study) (Spanish)
Sherry, 1982[341]	Comment on the persantin–aspirin reinfarction study (standard release DP) (German)
Shukla, 1999[294]	Comment on the CAPRIE trial
Sivenius, 1991[342]	ESPS-1: subgroup analysis of stroke or death in women
Sivenius, 1991[343]	ESPS-1 (placebo control): results stratified by arterial distribution
Sivenius, 1991[344]	ESPS-1 (comparator is placebo): results stratified by sex
Sivenius, 1993[345]	ESPS-1: subgroup analysis of elderly patients
Sivenius, 1992[346]	ESPS 1: placebo controlled
Sivenius, 1995[347]	Subgroup analysis of ESPS-1

continued

Study details	Reason for exclusion
Sivenius, 1996[348]	Article about the role of DP in stroke prevention; not a systematic review
Sivenius, 1996[349]	Overview of DP in stroke prevention; not a systematic review
Sivenius, 1997[350]	Article about ESPS-2
Sorensen, 1983[351]	Aspirin versus placebo; Danish Co-operative Study
Stachenko, 1991[352]	Meta-analysis on ASA but no adverse events data are reported
Steinhubl, 2002[353]	CREDO study – included patients who were to undergo elective PCI
Study group on pharmacological treatment after PTA, 1994[354]	Versus placebo. Patients had undergone percutaneous balloon angioplasty
Swedish Council on Technology Assessment in Health Care, 2000[355]	Not a full economic evaluation
Sze, 1988[356]	Meta-analysis investigating antiplatelet agents. Does not included modified-release DP or clopidogrel
Taddei, 1992[357]	Study of the effect of DP on adenosine renin release
Tejedor, 1980[358]	Anticoagulant (coumarin drugs) in combination with antiplatelet drugs (ASA and DP) (Spanish)
The ESPS Group, 1987[361]	Duplicate copy of first ESPS article[67]
Theis, 1999[366]	Bioequivalence trial on DP and aspirin
Theiss, 1979[367]	Overview of antiplatelet therapy; not a systematic report (German)
Thizon-de-Gaulle, 1998[368]	Background and secondary report of CAPRIE
Thommen, 1990[369]	General comment on secondary prevention of MI (German)
Tijssen, 1997[370]	Comment of DP versus ASA trials
Tijssen, 1998[371]	Review of ESPS-2 and other DP studies; not a systematic review
Troche, 1998[372]	Cost-effectiveness study; not relevant to the scope of the review
Uchiyama, 1998[373]	Comment of the results of the CAPRIE trial (Japanese)
Uchiyama, 2002[374]	Overview on antiplatelet therapy (Japanese)
Ufkes, 1998[375]	Background on DP (Dutch)
UK-TIA study, 1991[376]	Aspirin versus placebo
Valentin, 2001[377]	Clinical implications of the results of the CURE trial (Spanish)
Vázquez, 1978[110]	Study on the effects of DP and DP plus dihydroergotoxine methanesulphonate on cerebral circulation
Verheugt, 1996[378]	Systematic review of studies that combine aspirin or DP with warfarin versus aspirin or placebo
Violi, 1997[379]	Letter to the editor; comment on the CAPRIE trial
Vogel, 1981[380]	Aspirin versus placebo
Wahlgren, 1998[381]	Overview of standard-release and modified-release DP trials for the secondary prevention of stroke
WASH Study Steering Committee, 1999[365]	Pilot study on effectiveness of warfarin, aspirin and placebo
Warlow, 2002[382]	Discussion article about aspirin for secondary prevention of stroke
Weichert, 1994[383]	Low-dose versus high-dose aspirin after angioplasty
White, 1995[384]	Study examined the effect of aspirin/DP on the patency of infarct-related artery versus placebo
Wilterdink, 1999[385]	Meta-analysis of data from Antiplatelet Trialists' Collaboration and ESPS-2. No search reported (would not meet DARE criteria)
Yusuf, 2001[386]	Early conference report of CURE (abstract)
Yusuf, 2001[387]	Conference report on the CURE trial (German)
Zekert, 1975[388]	Aspirin versus placebo (German)
Zielinski, 1999[389]	Letter to editor; summary of ESPS-2 trial results

Aspirin/adverse event searches

Study details	Reason for exclusion
Abrishami, 1977[390]	Overview of literature on aspirin intolerance from 1970s; not a systematic review
Almony, 1996[391]	General article about antiplatelet and anticoagulant use after MI; not a systematic review
Anonymous, 2000[392]	Background on the use of antiplatelet drugs in secondary prevention; not a systematic review
Anonymous, 1999[393]	Short article about the benefits and risks of prophylactic aspirin
Anonymous, 2000[394]	Commentary on the use of clopidogrel and CAPRIE (no new data reported)
Anonymous, 2002[395]	Comment on publication of ATT meta-analysis in *BMJ*
Arnau, 1997[396]	Overview of the use of aspirin in MI (not systematic)
Awtry, 2000[397]	Overview of aspirin in the treatment of CVD; not a systematic review
Baker, 1970[398]	Short report about cutaneous responses to aspirin; not a systematic review
Barnett, 1990[399]	Overview of aspirin in stroke prevention; not a systematic review
Baume, 1992[400]	Short article giving a general overview of aspirin therapy; not a systematic review
Bennett, 2001[401]	Overview of platelet function inhibitors; not a systematic review
Berger, 1999[402]	Overview of clopidogrel and ticlopidine (no new data on CAPRIE represented)
Berkes, 2003[403]	Overview of anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs; not a systematic review
Bertele, 1993[404]	Article about the primary and secondary prevention of atherosclerosis; not a systematic review (Italian)
Bhatt, 2001[405]	Overview of use of antiplatelet agents in secondary prevention (not systematic)
Bjarnason, 1993[406]	SR on adverse effects of NSAIDs on the large and small intestine (not aspirin specific)
Bjorkman, 1998[407]	Overview of adverse events associated with NSAIDs (not systematic review)
Black, 2001[408]	Overview of ticlopidine and clopidogrel; not a systematic review
Borg, 2002[409]	General article about the emergency treatment of transient ischaemic attacks; not a systematic review
Born, 1990[410]	Overview of aspirin trials – both primary and secondary prevention (not systematic review)
Borsch, 1984[411]	Report about drug-induced lesion in the upper GI tract; not a systematic review
Cairns, 1991[412]	Overview of antithrombotic trials (not systematic review)
Carson, 1993[413]	Overview of the toxicity associated with NSAIDs; not a systematic review
Catella-Lawson, 1995[414]	Overview of aspirin trials (not systematic)
Cavusoglu, 2003[415]	General article about clopidogrel; not a systematic review
Claxton, 2001[416]	Systematic review of medication compliance and dose regimens
Cleland, 1992[417]	Discusses the uses of aspirin and warfarin in ischaemic heart disease; not a systematic review
Cooke, 1970[418]	Brief review of effects of aspirin and ethanol on the stomach; not a systematic review
Dammann, 1998[419]	Overview of gastroduodenal tolerability of low dose aspirin (not systematic review)
del Zoppo, 2000[420]	Article about antithrombotic treatments in acute ischaemic stroke
Derry, 2000[421]	Duplicate copy of Derry, 2000[47]
Derry, 2000[422]	Duplicate article[47]

continued

Study details	Reason for exclusion
Di Pasquale, 1998[423]	Editorial about antiplatelet agents and anticoagulants in the secondary prevention of MI; not a systematic review (Italian)
Dickinson, 1998[424]	Overview of benefits and risks of aspirin use; not a systematic review
Dippel, 1998[425]	Short report of the CAPRIE, IST and CAST trials
Dobrilla, 1997[426]	Article reviews gastroduodenal damage induced by aspirin and other NSAIDs; not a systematic review
Duggan, 1980[427]	Overview of GI toxicity associated with minor analgesics; not a systematic review
Eichenberger, 2003[428]	Brief overview of the pharmacological actions of aspirin
Elwood, 1998[429]	Overview of the use of aspirin in CVD; not a systematic review
Feret, 1999[430]	Brief report about clopidogrel
Fiorucci, 2001[431]	Article about the mechanisms of NSAID-associated gastropathy
Fisher, 1999[432]	Article about antithrombotic therapy for ischaemic stroke; not a systematic review
Fitzmaurice, 2002[433]	General review of bleeding risks with antithrombotic therapy
Fitzmaurice, 2002[434]	Duplicate article[433]
Forster, 1993[435]	Pharmacological action of aspirin (German)
Fowler, 1987[436]	Comparative review of aspirin, paracetamol and NSAIDS; not a systematic review
Friend, 1974[437]	General article about aspirin; not a systematic review
Gabriel, 1991[438]	Meta-analysis investigated the risk of serious GI complications associated with non-aspirin NSAIDs
Garcia Rodriguez, 1997[439]	Systematic review of risk of development of ulcers with NSAID use; data from aspirin not reported separately
Gaziano, 2000[440]	Overview of aspirin use in the treatment and prevention of CVD; not a systematic review
Giri, 1993[441]	Article on genetic toxicology of aspirin (animal models)
Girolami, 1999[442]	Meta-analysis investigating antithrombotic drugs in the primary medical management of intermittent claudication
Gonzalez, 2000[443]	General article about antiplatelet therapy; not a systematic review
Gore, 1999[444]	Article about drug-induced disorders of the stomach and duodenum (NSAIDs); not a systematic review
Graham, 1998[445]	Overview of NSAIDs and gastric injury (not systematic and not aspirin specific)
Hankey, 1999[446]	Duplicate of article[244]
Harding, 2002[447]	Commentary on all the clopidogrel trials including CAPRIE and CURE (no new data reported)
Hartmann, 1995[448]	Article investigates the administration of high-dose aspirin for the prevention of acute cerebral ischaemia; not a systematic review
Hassan, 2001[449]	Report of the prevalence of aspirin use for both primary and secondary prevention
Hawkey, 1994[450]	Review article on aspirin and bleeding (not systematic)
Hawkey, 1996[451]	General article about gastropathy associated with NSAIDs; not a systematic review
Hawkey, 2000[452]	Overview of the management of NSAID-induced gastroduodenal ulcers
Hawkins, 2000[453]	Literature review on NSAIDs (does not include aspirin)
He, 1998[454]	Duplicate article[44]
Heller, 1985[455]	Review of antiarthritic efficacy of NSAIDs (not systematic)
Hennekens, 1999[456]	Overview of the use of aspirin in the treatment and prevention of CVD; not a systematic review
Henry, 1987[457]	Case-control study investigating fatal peptic ulcer complications and the use of NSAIDs
Henry, 1988[458]	Overview of side-effects associated with NSAIDs; not a systematic review
Henry, 1996[459]	Meta-analysis investigating the risk of GI complications with NSAIDs; not secondary prevention or ACS

continued

Study details	Reason for exclusion
Heras, 2003[460]	Article about the use of clopidogrel in ACS
Herbert, 1994[461]	Pharmacological action of clopidogrel
Hirschowitz, 2001[462]	Consensus report on adverse events associated with aspirin; not based on a systematic review
Hirsh, 1985[463]	Review of the relationship between aspirin dose and side-effects; not a systematic review
Hirsh, 1989[464]	Article about the association of aspirin dose, effectiveness and side-effects; not a systematic review
Hudson, 1993[465]	Article about GI ulceration and complications associated with NSAIDs
Joseph, 1997[466]	Article about antiplatelet drugs; not a systematic review
Kelton, 1980[467]	Overview of bleeding associated with antithrombotic therapy; not a systematic review
Klijn, 2001[468]	Meta-analysis investigating outcome in patients with symptomatic occlusion of the internal carotid artery or intracranial arterial lesions
Knodel, 1992[469]	Overview of adverse events of NSAIDs (not systematic)
Kolts, 1992[470]	General article about the GI side-effects associated with NSAIDs; not a systematic review
Lanas, 1999[471]	Review of association between NSAID use and GI bleeding (not aspirin specific); not a systematic review
Lavie, 2003[472]	Article discusses a multifactorial approach to the primary and secondary prevention of atherosclerosis; not a systematic review
Leschke, 1998[473]	Article includes a comparative review of antiplatelet drugs but is not a systematic review (German)
Lewis, 1996[474]	Overview of hepatotoxicity associated with NSAIDs; not a systematic review
Lichtenstein, 1995[475]	Overview of NSAID-mediated GI injury; not a systematic review
Lockhart, 2000[476]	Review of literature on secondary prevention after an MI (not systematic)
Lubbe, 2002[477]	General article about the thienopyridines (clopidogrel and ticlopidine); not a systematic review
Majhail, 2003[478]	Case reports of TTP associated with clopidogrel use
Maynard, 2000[479]	Background on the management of ACS (risk stratification)
McCabe, 2000[480]	Article about the prevention of ischaemic stroke using antiplatelet therapy; not a systematic review
Michaels, 1999[481]	Article about the secondary prevention of MI. Discusses pharmacological and non-pharmacological interventions; not a systematic review
Mikhailidis, 1998[482]	Discussion article about PVD subgroup results from the CAPRIE trial
Mohr, 2002[483]	Overview of trials investigating prevention of recurrent ischaemic stroke; not a systematic review
Morassut, 1989[484]	Article about aspirin intolerance; not a systematic review
Namazy, 2002[485]	Overview of sensitivity to NSAIDS; not a systematic review
Orford, 2001[486]	Commentary on CAPRIE, CURE and PCI-CURE (no new data reported)
Patrono, 2001[487]	Overview of aspirin dose and its relation to effectiveness and side-effects; not a systematic review
Pepine, 1998[488]	Editorial on CAPRIE trial
Picano, 2001[489]	RCT of DP in chronic stable angina
Pueyo, 2002[490]	Meta-analysis of the use of aspirin in primary prevention (Spanish)
Quiralte, 1998[491]	Article about aspirin sensitivity; not a systematic review
Rahman, 1996[492]	General article about NSAIDs; not a systematic review
Righini, 2000[493]	Article about alternative antiplatelet agents to aspirin; not a systematic review (French)
Rodgers, 1996[494]	Review of antiplatelet therapy; not a systematic review
Rodriguez, 1998[495]	Systematic review of GI complications of NSAIDs (not aspirin specific)
Rodvien, 1975[496]	Overview of aspirin from the 1970s; not a systematic review

continued

Study details	Reason for exclusion
Sainte-Laudy, 2001[497]	Article on mechanism of action of aspirin (French)
Salter, 1968[498]	General article about aspirin and GI bleeding; not a systematic review
Sandercock, 2000[499]	Overview of aspirin trials in stroke (not systematic); the only adverse events data represented are from CAST and IST (acute stroke)
Sanmuganathan, 2001[500]	Systematic review of aspirin use in primary prevention
Schulz, 2002[501]	Comment on trial methodology in ACS
Sheridan, 2002[502]	Review of unstable angina and STEMI; not a systematic review
Steinhubl, 2003[503]	Review on aspirin as an antiplatelet agent; not a systematic review
Szczeklik, 1987[504]	Overview of adverse reactions to aspirin and NSAIDs; not a systematic review
Tramer, 2000[505]	Commentary on systematic review of aspirin[422]
Tramer, 2000[506]	Quantitative estimation of rare adverse events associated with NSAIDs; not aspirin specific
Van De Graaff, 2001[507]	Overview of complication associated with oral antiplatelet medications; not a systematic review
Weber, 1997[508]	Article discusses the pharmacology of ticlopidine and clopidogrel compared with aspirin.

NSAID, non-steroidal anti-inflammatory drug; STEMI, ST-segment elevation myocardial infarction.

Appendix 5

Details of quality assessment for clinical effectiveness studies and systematic reviews

Clinical effectiveness studies were assessed using the following criteria based on CRD Report 4[19]

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, whereas 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 **Y** yes (item properly addressed), **N** no (item not properly addressed), **Y/N** partially (item partially addressed), **?** unclear or not enough information or **N/A** not applicable.

Systematic reviews and meta-analyses were assessed using the criteria for the Database of Abstracts of Reviews of Effect (DARE)

1. Are inclusion/exclusion criteria reported that address the review question?

N/A	Inclusion/exclusion criteria are not addressed.
POOR	One of the four components is addressed by the inclusion/exclusion criteria.
FAIR	At least two components are addressed by the inclusion/exclusion criteria. One or more reviewer(s) applied the criteria to assess the individual studies (or the number of reviewers is not clear).
GOOD	Three or four components are addressed by the inclusion/exclusion criteria. In addition, the criteria are applied by more than one reviewer (double-checked).

2. Is there evidence of a substantial effort to search for all relevant research literature?

N/A	Sources searched are not mentioned
POOR	Only one named database searched with minimal description of date and search terms.
FAIR	EITHER one named database searched with search dates and search

terms reported, along with following up references from retrieved papers and/or handsearching and/or contacting researchers.
OR more than one named database searched (search dates and search terms may be reported, but may be omitted owing to space).

GOOD More than one database searched with description of dates and more detailed information on search terms. In addition, other retrieval methods are reported: handsearching, locating unpublished literature, experts in the field, Internet searches, citation searching.

3. Is the validity of included studies adequately assessed?

N/A Validity of individual studies was not assessed or not reported.

POOR Validity of individual studies may be assessed but not systematically.

FAIR Validity of individual studies was assessed systematically by one reviewer (or the number of reviewers is not clear).

GOOD Validity of individual studies was assessed systematically by more than one reviewer.

4. Is sufficient detail of the individual studies presented?

N/A Details of individual studies are not available.

POOR Some detail of individual studies may be found in the text of the review. Or studies are inadequately presented in tables.

FAIR Details of individual studies are presented in tables but one or more important study characteristic may not be included, or details of individual studies are well described in the review text. Sometimes it may not be possible to present details of all individual studies because of the large number of trials included but details may be available elsewhere, for example on the website of the journal in which the review was published.

GOOD Details of individual studies are adequately presented in tables and text. The tables include most, or all, relevant information (e.g. design, participants, sample size, intervention and outcome). There is enough information to judge whether the authors' summary and conclusions are appropriate.

5. Are the primary studies summarised appropriately?

N/A No effort is made to combine or summarise evidence from individual studies.

POOR Evidence is summarised but not synthesised. The methods used to pool data are not adequate. Heterogeneity is not assessed.

FAIR Individual studies are synthesised with appropriate techniques (either by narrative or meta-analysis) but heterogeneity is not assessed.

GOOD Individual studies are synthesised appropriately. Heterogeneity between studies is investigated adequately.

Appendix 6

Details of quality assessment for economic studies

Studies of cost-effectiveness were assessed using an updated version of the checklist developed by Drummond and colleagues[20] All items were graded as either **Y** yes (item adequately addressed), **N** no (item not adequately addressed), **?** unclear or not enough information, **N/A** not applicable or **N/S** not stated.

Review of Scott and Scott (1997).[28] Application of the findings of the European Stroke Prevention Study 2 (ESPS-2) to a New Zealand ischaemic stroke cost analysis

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Y	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	N	DP monotherapy, clopidogrel and ticlopidine are not included as alternative treatment strategies
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	Y	The proposed dosage of the drugs considered is not declared
6. The rationale for choosing the alternative programmes or interventions compared is stated	N	Based on direct comparisons made a trial but not all comparators in trial included
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	Y	
11. Potential biases identified (especially if data not from RCTs)	N/A	
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)	N/A	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	Y	

continued

Study question	Answer	Comments
14. All the important and relevant resource use measured accurately (with methodology)	?	From previously published study
15. Appropriate unit costs estimated (with methodology)	Y	
16. Unit costs reported separately from resource use data	Y	
17. Productivity costs treated separately from other costs	Y	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y	
20. Methods to value health states and other benefits are stated (e.g. TTO)	N	No health states were valued
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals etc.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	N/A	Model not used
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	N/A	
24. All model outputs described adequately	N/A	
Discounting		
25. Discount rate used for both costs and benefits	N	No discounting
26. Do discount rates accord with NHS guidance (1.5–2% for benefits, 6% for costs)?	N	
Allowance for uncertainty		
Stochastic analysis of patient-level data	N	
27. Details of statistical tests and CIs are given for stochastic data	N/A	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	N/A	
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)	N/A	
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	N/A	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	

continued

Study question	Answer	Comments
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)	N/A	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	Y	Univariate
35. The choice of variables for sensitivity analysis is justified	N	No justification
36. The ranges over which the variables are varied are stated	Y	
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	N	
39. Applicable to the NHS setting	N	

Review of Zachry and colleagues (1999).[27] Procedure costs and outcomes associated with pharmacologic management of peripheral arterial disease in the Department of Defense

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Y	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	N	Only compared those treatments for which they found sufficient data
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	?	The dosage of the drugs is not declared
6. The rationale for choosing the alternative programmes or interventions compared is stated	N	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	N	
11. Potential biases identified (especially if data not from RCTs)	Y	Potential biases highlighted in discussion

continued

Study question	Answer	Comments
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)	N/A	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)	Y	
15. Appropriate unit costs estimated (with methodology)	N	Used median hospital charge for each item
16. Unit costs reported separately from resource use data	Y	
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y	
20. Methods to value health states and other benefits are stated (e.g. TTO)	N	No health states valued
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	?	Regression-based model
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	N	
24. All model outputs described adequately.	Y	
Discounting		
25. Discount rate used for both costs and benefits	N	No discounting
26. Do discount rates accord with NHS guidance (1.5–2% for benefits, 6% for costs)?	N	
Allowance for uncertainty		
Stochastic analysis of patient-level data	N	
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)	N/A	
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)	N/A	
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	N/A	

continued

Study question	Answer	Comments
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	
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)	N/A	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	?	
35. The choice of variables for sensitivity analysis is justified	N	Explores impact of cross-exposure to treatments
36. The ranges over which the variables are varied are stated	Y	
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	N	Specific to US Department of Defense

Review of Chambers and colleagues (1999).[29] Cost-effectiveness analysis of antiplatelet therapy in the prevention of recurrent stroke in the UK: aspirin, dipyridamole and aspirin-dipyridamole

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Y	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	N	Clopidogrel and ticlopidine are not included as alternative treatment strategies
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	?	The proposed dosage of the drugs considered is not declared
6. The rationale for choosing the alternative programmes or interventions compared is stated	Y	Based on direct comparisons made a trial
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	

continued

Study question	Answer	Comments
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	Y	
11. Potential biases identified (especially if data not from RCTs)	N	ATT?
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)	N/A	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	Y	
14. All the important and relevant resource use measured accurately (with methodology)	N	Long-term resource use based on expert opinion. Method used to elicit expert opinion is unclear
15. Appropriate unit costs estimated (with methodology)	Y	
16. Unit costs reported separately from resource use data	Y	
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y	
20. Methods to value health states and other benefits are stated (e.g. TTO)	?	Utility values for health states are calculated from Gage[75] according to Rankin score but the method used is unclear
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals etc.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Y	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Y	
24. All model outputs described adequately	Y	
Discounting		
25. Discount rate used for both costs and benefits	N	Costs discounted at 6%, health benefits not discounted
26. Do discount rates accord with NHS guidance (1.5–2% for benefits, 6% for costs)?	N	
Allowance for uncertainty		
Stochastic analysis of patient-level data	N	
27. Details of statistical tests and CIs are given for stochastic data	N/A	Deterministic analysis

continued

Study question	Answer	Comments
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	N/A	
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)	N/A	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	N/A	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	
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)	N/A	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	Y	Univariate
35. The choice of variables for sensitivity analysis is justified	N	No justification
36. The ranges over which the variables are varied are stated	Y	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	Y	
38. Major outcomes are presented in a disaggregated as well as aggregated form	Y	
39. Applicable to the NHS setting	?	

Review of Shah and Gondek (2000).[26] Aspirin plus extended-release dipyridamole or clopidogrel compared with aspirin monotherapy for the prevention of recurrent ischemic stroke: a cost-effectiveness analysis

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Y	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	N	DP alone and ticlopidine are not included as alternative treatment strategies
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	?	The proposed dosage of the drugs considered is not declared

continued

Study question	Answer	Comments
6. The rationale for choosing the alternative programmes or interventions compared is stated	Y	Based on direct comparisons made in two trials
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	Y	
11. Potential biases identified (especially if data not from RCTs)	N	Have not 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)	N/A	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	Y	Given US payer perspective
14. All the important and relevant resource use measured accurately (with methodology)	N	Resource use not measured, aggregate costs used
15. Appropriate unit costs estimated (with methodology)	N	Unit costs not used, instead aggregate costs from claims database
16. Unit costs reported separately from resource use data	N/A	
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y	
20. Methods to value health states and other benefits are stated (e.g. TTO)	N/A	Study does not value health states
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals etc.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Y	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Y	
24. All model outputs described adequately	Y	
Discounting		
25. Discount rate used for both costs and benefits	N	

continued

Study question	Answer	Comments
26. Do discount rates accord with NHS guidance (1.5–2% for benefits, 6% for costs)?	N	
Allowance for uncertainty		
Stochastic analysis of patient-level data	N	
27. Details of statistical tests and CIs are given for stochastic data	N/A	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	N/A	
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)	N/A	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	N/A	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	
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)	N/A	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	Y	Univariate
35. The choice of variables for sensitivity analysis is justified	N	No justification
36. The ranges over which the variables are varied are stated	Y	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	Y	
38. Major outcomes are presented in a disaggregated as well as aggregated form	Y	
39. Applicable to the NHS setting	N	US based and not relevant in UK setting

Review of Sarasin and colleagues (2000).[25] Cost-effectiveness of new antiplatelet regimens used as secondary prevention of stroke or transient ischaemic attack

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Y	

continued

Study question	Answer	Comments
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	N	DP alone and Ticlopidine are not included as alternative treatment strategies
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	Y	Based on two published trials
6. The rationale for choosing the alternative programmes or interventions compared is stated	Y	Based on direct comparisons made in two published trials
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	Y	
11. Potential biases identified (especially if data not from RCTs)	N	Have not 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)	N/A	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	Y	
14. All the important and relevant resource use measured accurately (with methodology)	Y	
15. Appropriate unit costs estimated (with methodology)	Y	
16. Unit costs reported separately from resource use data	?	Resource use data not presented
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y	
20. Methods to value health states and other benefits are stated (e.g. TTO)	N	Quality adjustment factors synthesised from literature, methods not stated
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals etc.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Y	

continued

Study question	Answer	Comments
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Y	
24. All model outputs described adequately	Y	
Discounting		
25. Discount rate used for both costs and benefits	?	No explicit statement regarding discounting
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	N	
27. Details of statistical tests and CIs are given for stochastic data	N/A	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	N/A	
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)	N/A	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	N/A	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	
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)	N/A	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	Y	Univariate
35. The choice of variables for sensitivity analysis is justified	N	No justification
36. The ranges over which the variables are varied are stated	Y	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	Y	
38. Major outcomes are presented in a disaggregated as well as aggregated form	Y	
39. Applicable to the NHS setting	N	US based and not relevant in UK setting. Medicare costs included

Review of Gaspoz and colleagues (2002).[24] Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	N	Can be assumed to be US 3rd-party payer
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	N	DP preparations and Ticlopidine are not included as alternative treatment strategies
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	Y	
6. The rationale for choosing the alternative programmes or interventions compared is stated	Y	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	Y	
11. Potential biases identified (especially if data not from RCTs)	N	Have not 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)	N/A	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	Y	
14. All the important and relevant resource use measured accurately (with methodology)	Y	
15. Appropriate unit costs estimated (with methodology)	Y	
16. Unit costs reported separately from resource use data	?	Resource use data not presented
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y	

continued

Study question	Answer	Comments
20. Methods to value health states and other benefits are stated (e.g. TTO)	N	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.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Y	
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	Y	
Discounting		
25. Discount rate used for both costs and benefits	N	Only costs discounted
26. Do discount rates accord with NHS guidance (1.5–2% for benefits, 6% for costs)?	N	3% for costs and 0% for health benefits
Allowance for uncertainty		
Stochastic analysis of patient-level data	N	
27. Details of statistical tests and CIs are given for stochastic data	N/A	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	N/A	
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)	N/A	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	N/A	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	
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)	N/A	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	Y	Univariate
35. The choice of variables for sensitivity analysis is justified	Y	
36. The ranges over which the variables are varied are stated	Y	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	Y	
38. Major outcomes are presented in a disaggregated as well as aggregated form	Y	
39. Applicable to the NHS setting	N	US based and not relevant in UK setting. Medicare costs included

Review of Chambers and colleagues (2002).[30] Development of a decision-analytic model of stroke care in the United States and Europe

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Y	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	Y	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	?	Dosages considered not stated
6. The rationale for choosing the alternative programmes or interventions compared is stated	Y	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	Y	
11. Potential biases identified (especially if data not from RCTs)	N	Have not discussed unconfirmed dose–response effect of aspirin. Model makes indirect comparison. Some data for clopidogrel and ticlopidine estimated from aspirin arm of ESPS-2
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)	Y	RRR for clopidogrel and ticlopidine vs aspirin combined with RRR for aspirin vs placebo to get indirect RRR for clopidogrel and ticlopidine vs placebo
Costs		
13. All the important and relevant resource use included	Y	
14. All the important and relevant resource use measured accurately (with methodology)	N	Expert panel estimates
15. Appropriate unit costs estimated (with methodology)	Y	
16. Unit costs reported separately from resource use data	Y	
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y	

continued

Study question	Answer	Comments
20. Methods to value health states and other benefits are stated (e.g. TTO)	N	Calculated from secondary source of TTO utility, method unclear
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals etc.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Y	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Y	
24. All model outputs described adequately	N	Very little reporting of output of model
Discounting		
25. Discount rate used for both costs and benefits	Y	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits, 6% for costs)?	N	6% for both
Allowance for uncertainty		
Stochastic analysis of patient-level data	N	
27. Details of statistical tests and CIs are given for stochastic data	N/A	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CACs)	N/A	
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)	N/A	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	N/A	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	
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)	N/A	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	Y	Univariate
35. The choice of variables for sensitivity analysis is justified	Y	
36. The ranges over which the variables are varied are stated	Y	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	?	Little analysis reported
38. Major outcomes are presented in a disaggregated as well as aggregated form	N	
39. Applicable to the NHS setting	Y	

Review of submission by Boehringer Ingelheim Ltd

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Y	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	Y	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	Y	
6. The rationale for choosing the alternative programmes or interventions compared is stated	Y	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	Y	
11. Potential biases identified (especially if data not from RCTs)	N	Have not 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)	N/A	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	Y	
14. All the important and relevant resource use measured accurately (with methodology)	Y	
15. Appropriate unit costs estimated (with methodology)	Y	
16. Unit costs reported separately from resource use data	?	
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y	
20. Methods to value health states and other benefits are stated (e.g. TTO)	Y	Published study

continued

Study question	Answer	Comments
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals etc.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Y	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Y	
24. All model outputs described adequately	Y	
Discounting		
25. Discount rate used for both costs and benefits	Y	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits, 6% for costs)?	Y	
Allowance for uncertainty		
Stochastic analysis of patient-level data	?	Partial probabilistic analysis
27. Details of statistical tests and CIs are given for stochastic data	?	Range for costs based on expert opinion
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	Y	
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)	Y	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	N	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	Y	
32. Are the probability distributions adequately detailed and appropriate?	N	Triangular distributions used for cost data
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)	N	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	Y	Univariate
35. The choice of variables for sensitivity analysis is justified	Y	
36. The ranges over which the variables are varied are stated	Y	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	?	Probabilistic sensitivity analysis excluded all cases where effect difference was negative
38. Major outcomes are presented in a disaggregated as well as aggregated form	Y	
39. Applicable to the NHS setting	Y	

Review of submission by Sanofi Synthelabo Ltd and Bristol-Myers Squib

Study question	Answer	Comments
1. Costs and effects examined	Y	
2. Alternatives compared	Y	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Y	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	N	DP preparations not included as alternative treatment strategies
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	Y	
6. The rationale for choosing the alternative programmes or interventions compared is stated	Y	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Y	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Y	
10. Effectiveness data from RCT or review of RCTs	Y	
11. Potential biases identified (especially if data not from RCTs)	N/A	
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)	N/A	No formal synthesis undertaken
Costs		
13. All the important and relevant resource use included	Y	
14. All the important and relevant resource use measured accurately (with methodology)	Y	
15. Appropriate unit costs estimated (with methodology)	Y	
16. Unit costs reported separately from resource use data	?	Resource use data not presented
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Y	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	Y N	Secondary source for utility unclear
20. Methods to value health states and other benefits are stated (e.g. TTO)		

continued

Study question	Answer	Comments
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	N/A	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Y	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Y	
24. All model outputs described adequately	Y	
Discounting		
25. Discount rate used for both costs and benefits	Y	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits, 6% for costs)?	Y	
Allowance for uncertainty		
Stochastic analysis of patient-level data	Y	
27. Details of statistical tests and CIs are given for stochastic data	Y	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	Y	
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).	Y	One-way sensitivity analyses performed on key variables
Stochastic analysis of decision models	N/A	
30. Are all appropriate input parameters included with uncertainty?	Y	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	Y	
32. Are the probability distributions adequately detailed and appropriate?	N	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)	Y	
Deterministic analysis	Y	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	Y	Univariate
35. The choice of variables for sensitivity analysis is justified	Y	
36. The ranges over which the variables are varied are stated	Y	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	Y	
38. Major outcomes are presented in a disaggregated as well as aggregated form	Y	
39. Applicable to the NHS setting	Y	

Appendix 7

Base estimates of the mean expected lifetime costs and QALYs

TABLE 44 *Base-case estimates of the mean expected lifetime costs and QALYs associated with treatment for the secondary prevention of occlusive vascular events in patients who have experienced an initial ischaemic stroke: base-case 40-year analysis*

Strategy	Treatment duration (years)	RR non-vascular death[a]	Cost (£)	QALY	ICER (£)	Probability cost-effective for a maximum WTP[b]		
						£10,000	£30,000	£50,000
Scenario I: lifetime treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	Lifetime	Excluded	30,540	9.77	–	0.59	0.36	0.27
2. Clopidogrel	Lifetime	Excluded	38,098	9.91	78,640	0	0.03	0.12
3. ASA–MR-dipyridamole	Lifetime	Excluded	32,161	9.83	26,432	0.32	0.46	0.45
4. MR-dipyridamole	Lifetime	Excluded	32,014	9.65	D	0.09	0.16	0.17
Scenario II: lifetime treatment duration, including treatment effects on non-vascular death								
1. Aspirin	Lifetime	Included	30,270	9.76	–	0.48	0.37	0.34
2. Clopidogrel	Lifetime	Included	37,487	9.67	D	0	0.01	0.04
3. ASA–MR-dipyridamole	Lifetime	Included	31,582	9.62	D	0.26	0.30	0.31
4. MR-dipyridamole	Lifetime	Included	31,782	9.66	D	0.26	0.31	0.32
Scenario III: 2-year treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	2	Excluded	30,680	9.77	–	0.26	0.14	0.10
2. Clopidogrel	2	Excluded	31,648	9.81	D	0	0.12	0.18
3. ASA–MR-dipyridamole	2	Excluded	30,940	9.82	5,500	0.62	0.62	0.60
4. MR-dipyridamole	2	Excluded	30,758	9.73	D	0.12	0.13	0.12
Scenario IV: 2-year treatment duration, including treatment effects on non-vascular death								
1. Aspirin	2	Included	30,544	9.75	–	0.35	0.22	0.18
2. Clopidogrel	2	Included	31,481	9.78	D	0	0.10	0.16
3. ASA–MR-dipyridamole	2	Included	30,751	9.78	7,968	0.52	0.53	0.52
4. MR-dipyridamole	2	Included	30,621	9.71	D	0.14	0.15	0.15

D, dominated option.

[a] The model is presented using the treatment effect on all transition probabilities except non-vascular death, i.e. the RR of non-vascular death is excluded, and also with the treatment effect on non-vascular death included.

[b] The probability that each strategy is the more cost-effective than the others conditional on different maximum WTP for an additional QALY.

TABLE 45 *Base-case estimates of the mean expected lifetime costs and QALYs associated with treatment for the secondary prevention of occlusive vascular events in patients who have experienced an initial TIA: base-case 40-year analysis with baseline event rates set to 80% of those for stroke*

Strategy	Treatment duration (years)	RR non-vascular death[a]	Cost (£)	QALY	ICER (£)	Probability cost-effective for a maximum WTP[b]		
						£10,000	£30,000	£50,000
Scenario I: lifetime treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	Lifetime	Excluded	22,137	11.68	–	0.45	0.30	0.20
2. Clopidogrel	Lifetime	Excluded	29,541	11.83	138,743	0	0.02	0.13
3. ASA–MR-dipyridamole	Lifetime	Excluded	23,442	11.79	12,458	0.45	0.53	0.52
4. MR-dipyridamole	Lifetime	Excluded	23,708	11.58	D	0.10	0.16	0.15
Scenario II: lifetime treatment duration, including treatment effects on non-vascular death								
1. Aspirin	Lifetime	Included	22,084	11.73	–	0.42	0.34	0.33
2. Clopidogrel	Lifetime	Included	29,209	11.60	D	0	0.02	0.03
3. ASA–MR-dipyridamole	Lifetime	Included	23,190	11.65	D	0.30	0.32	0.32
4. MR-dipyridamole	Lifetime	Included	23,696	11.66	D	0.28	0.32	0.32
Scenario III: 2-year treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	2	Excluded	21,908	11.65	–	0.29	0.17	0.13
2. Clopidogrel	2	Excluded	22,811	11.69	46,949	0	0.19	0.28
3. ASA–MR-dipyridamole	2	Excluded	21,956	11.68	2,241	0.58	0.51	0.47
4. MR-dipyridamole	2	Excluded	22,052	11.62	D	0.13	0.14	0.12
Scenario IV: 2-year treatment duration, including treatment effects on non-vascular death								
1. Aspirin	2	Included	22,085	11.70	–	0.35	0.25	0.21
2. Clopidogrel	2	Included	22,963	11.72	52,339	0	0.12	0.43
3. ASA–MR-dipyridamole	2	Included	22,111	11.71	4,266	0.49	0.45	0.18
4. MR-dipyridamole	2	Included	22,220	11.66	D	0.16	0.19	0.19

D, dominated option.

[a] The model is presented using the treatment effect on all transition probabilities except non-vascular death, i.e. the RR of non-vascular death is excluded, and also with the treatment effect on non-vascular death included.

[b] The probability that each strategy is the more cost-effective than the others conditional on different maximum WTP for an additional QALY.

TABLE 46 *Base-case estimates of the mean expected lifetime costs and QALYs associated with treatment for the secondary prevention of occlusive vascular events in patients who have experienced an initial TIA: base-case 40-year analysis with baseline event rates set equal to those for stroke*

Strategy	Treatment duration (years)	RR non-vascular death[a]	Cost (£)	QALY	ICER (£)	Probability cost-effective for a maximum WTP[b]		
						£10,000	£30,000	£50,000
Scenario I: lifetime treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	Lifetime	Excluded	21,940	11.10	–	0.39	0.25	0.18
2. Clopidogrel	Lifetime	Excluded	29,363	11.27	171,646	0	0.05	0.15
3. ASA–MR-dipyridamole	Lifetime	Excluded	23,184	11.24	8,941	0.53	0.58	0.55
4. MR-dipyridamole	Lifetime	Excluded	23,475	10.97	D	0.09	0.13	0.12
Scenario II: lifetime treatment duration, including treatment effects on non-vascular death								
1. Aspirin	Lifetime	Included	22,053	11.13	–	0.40	0.33	0.29
2. Clopidogrel	Lifetime	Included	29,225	11.05	D	0	0.02	0.04
3. ASA–MR-dipyridamole	Lifetime	Included	23,086	11.08	D	0.33	0.34	0.35
4. MR-dipyridamole	Lifetime	Included	23,688	11.07	D	0.26	0.32	0.32
Scenario III: 2-year treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	2	Excluded	22,206	11.11	–	0.26	0.15	0.12
2. Clopidogrel	2	Excluded	23,123	11.15	48,276	0	0.21	0.29
3. ASA–MR-dipyridamole	2	Excluded	22,231	11.14	835	0.60	0.51	0.47
4. MR-dipyridamole	2	Excluded	22,337	11.07	D	0.13	0.13	0.12
Scenario IV: 2-year treatment duration, including treatment effects on non-vascular death								
1. Aspirin	2	Included	22,149	11.14	D	0.30	0.22	0.17
2. Clopidogrel	2	Included	23,044	11.17	54,491	0	0.14	0.22
3. ASA–MR-dipyridamole	2	Included	22,148	11.15	–	0.53	0.46	0.43
4. MR-dipyridamole	2	Included	22,281	11.10	D	0.17	0.18	0.18

D, dominated option.

[a] The model is presented using the treatment effect on all transition probabilities except non-vascular death, i.e. the RR of non-vascular death is excluded, and also with the treatment effect on non-vascular death included.

[b] The probability that each strategy is the more cost-effective than the others conditional on different maximum WTP for an additional QALY.

TABLE 47 *Base-case estimates of the mean expected lifetime costs and QALYs associated with treatment for the secondary prevention of occlusive vascular events in patients who have experienced an initial MI: base-case 40-year analysis*

Strategy	Treatment duration (years)	RR non-vascular death[a]	Cost (£)	QALY	ICER (£)	Probability cost-effective for a maximum WTP[b]		
						£10,000	£30,000	£50,000
Scenario I: lifetime treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	Lifetime	Excluded	18,286	8.86	–	1	0.52	0.30
2. Clopidogrel	Lifetime	Excluded	25,773	9.10	31,400	0	0.48	0.70
Scenario II: lifetime treatment duration, including treatment effects on non-vascular death								
1. Aspirin	Lifetime	Included	18,285	8.86	–	1	0.75	0.60
2. Clopidogrel	Lifetime	Included	25,585	8.94	94,446	0	0.25	0.40
Scenario III: 2-year treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	2	Excluded	18,284	8.90	–	0.83	0.29	0.22
2. Clopidogrel	2	Excluded	19,202	8.95	17,081	0.17	0.71	0.78
Scenario IV: 2-year treatment duration, including treatment effects on non-vascular death								
1. Aspirin	2	Included	18,182	8.87	–	0.88	0.39	0.31
2. Clopidogrel	2	Included	19,078	8.91	21,448	0.12	0.61	0.70

D, dominated option.

[a] The model is presented using the treatment effect on all transition probabilities except non-vascular death, i.e. the RR of non-vascular death is excluded, and also with the treatment effect on non-vascular death included.

[b] The probability that each strategy is the more cost-effective than the others conditional on different maximum WTP for an additional QALY.

TABLE 48 *Base-case estimates of the mean expected lifetime costs and QALYs associated with treatment for the secondary prevention of occlusive vascular events in patients who have been diagnosed with PAD: base-case 40-year analysis*

Strategy	Treatment duration (years)	RR non-vascular death[a]	Cost (£)	QALY	ICER (£)	Probability cost-effective for a maximum WTP[b]		
						£10,000	£30,000	£50,000
Scenario I: lifetime treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	Lifetime	Excluded	15,182	11.04	–	1	0.59	0.31
2. Clopidogrel	Lifetime	Excluded	22,450	11.25	35,182	0	0.41	0.69
Scenario II: lifetime treatment duration, including treatment effects on non-vascular death								
1. Aspirin	Lifetime	Included	15,233	11.01	–	1	0.80	0.70
2. Clopidogrel	Lifetime	Included	22,282	10.99	D	0	0.20	0.30
Scenario III: 2-year treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	2	Excluded	15,180	11.04	–	0.96	0.30	0.17
2. Clopidogrel	2	Excluded	16,041	11.08	20,733	0.04	0.70	0.83
Scenario IV: 2-year treatment duration, including treatment effects on non-vascular death								
1. Aspirin	2	Included	15,279	11.03	–	0.96	0.52	0.36
2. Clopidogrel	2	Included	16,123	11.05	31,300	0.04	0.48	0.64

D, dominated option.

[a] The model is presented using the treatment effect on all transition probabilities except non-vascular death, i.e. the RR of non-vascular death is excluded, and also with the treatment effect on non-vascular death included.

[b] The probability that each strategy is the more cost-effective than the others conditional on different maximum WTP for an additional QALY.

TABLE 49 *Base-case estimates of the mean expected lifetime costs and QALYs associated with treatment for the secondary prevention of occlusive vascular events in patients who have been left disabled by their initial stroke: base-case 40-year analysis*

Strategy	Treatment duration (years)	RR non-vascular death[a]	Cost (£)	QALY	ICER (£)	Probability cost-effective for a maximum WTP[b]		
						£10,000	£30,000	£50,000
Scenario I: lifetime treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	Lifetime	Excluded	53,312	5.93	–	0.84	0.31	0.25
2. Clopidogrel	Lifetime	Excluded	61,062	6.01	100,238	0	0	0.01
3. ASA–MR-dipyridamole	Lifetime	Excluded	54,824	5.94	84,364	0.16	0.59	0.62
4. MR-dipyridamole	Lifetime	Excluded	54,624	5.86	D	0.01	0.10	0.13
Scenario II: lifetime treatment duration, including treatment effects on non-vascular death								
1. Aspirin	Lifetime	Included	53,443	5.93	–	0.69	0.42	0.38
2. Clopidogrel	Lifetime	Included	60,576	5.87	D	0	0	0.01
3. ASA–MR-dipyridamole	Lifetime	Included	54,414	5.84	D	0.15	0.25	0.27
4. MR-dipyridamole	Lifetime	Included	54,899	5.90	D	0.17	0.33	0.35
Scenario III: 2-year treatment duration, excluding treatment effects on non-vascular death								
1. Aspirin	2	Excluded	53,232	6.67	–	0.86	0.57	0.43
2. Clopidogrel	2	Excluded	54,268	6.68	68,563	0	0.08	0.23
3. ASA–MR-dipyridamole	2	Excluded	53,357	6.62	D	0.01	0.08	0.09
4. MR-dipyridamole	2	Excluded	53,262	6.64	D	0.14	0.26	0.26
Scenario IV: 2-year treatment duration, including treatment effects on non-vascular death								
1. Aspirin	2	Included	53,340	6.67	–	0.85	0.61	0.52
2. Clopidogrel	2	Included	54,313	6.68	163,002	0	0.05	0.14
3. ASA–MR-dipyridamole	2	Included	53,412	6.61	D	0.01	0.07	0.08
4. MR-dipyridamole	2	Included	53,356	6.64	D	0.14	0.26	0.26

D, dominated option.

[a] The model is presented using the treatment effect on all transition probabilities except non-vascular death, i.e. the RR of non-vascular death is excluded, and also with the treatment effect on non-vascular death included.

[b] The probability that each strategy is the more cost-effective than the others conditional on different maximum WTP for an additional QALY.

Appendix 8

Summary of standard-release dipyridamole studies

Four studies were identified from the Antiplatelet Trialists' Collaboration meta-analysis,[15] which investigated the standard-release formulation of DP in patients with CVD. We did not identify any more studies from our own searches. Three studies[64–66] included comparisons of standard-release DP in combination with aspirin with aspirin alone. One study[67] compared standard-release DP in combination with aspirin with placebo only. The details of these four studies are summarised in *Table 50*.

The data reported in the ATT meta-analysis[15] for serious vascular events for each of the DP studies is shown in *Table 51*. Combining data from the three studies[64–66] that investigated standard-release DP in combination with aspirin with aspirin alone showed a non-significant trend in favour of DP in combination with aspirin for the outcome serious vascular events (RR 0.95; 95% CI: 0.75 to 1.19).

With the addition of the results from ESPS-2,[22] treatment with the DP–aspirin combination significantly reduced the risk of a serious vascular event compared with treatment with aspirin alone (RR 0.85; 95% CI: 0.74 to 0.96).

TABLE 50 *Summary of standard-release dipyridamole studies*

Study details	Study design	Participants	Interventions
Standard-release DP–aspirin versus placebo			
ESPS 1[67]	Multicentre, randomised, double-blind, placebo-controlled trial	2500 patients with previous cerebrovascular disorders	Aspirin 975 mg/day + DP 225 mg/day versus placebo
Standard-release DP–aspirin versus aspirin			
Toulouse TIA[64]	Randomised, controlled trial	284 patients with TIAs	Aspirin 900 mg/day versus aspirin 900 mg/day + DP 150 mg/day
AICLA[65]	Double-blind, randomised, controlled trial	604 patients with atherothrombotic cerebral ischaemic events	Aspirin 1 g/day versus aspirin 1 g/day + DP 225 mg/day versus placebo
ACCSG[66]	Double-blind, multicentre randomised, controlled trial	890 patients with carotid territory TIAs with or without persistent minor deficit	Aspirin 1300 mg/day versus aspirin 1300 mg/day + DP 300 mg/day

TABLE 51 *Serious vascular events extracted from ATT meta-analysis*

Study	DP–ASA	Control	RR (95% CI)
ESPS 1[67]	183/1250	263/1250	0.78 (0.65 to 0.93)
Toulouse TIA[64]	12/137	11/147	1.17 (0.53 to 2.56)
AICLA[65]	30/202	31/198	0.95 (0.60 to 1.51)
ACCSG[66]	79/448	85/442	0.92 (0.70 to 1.21)
ESPS-2[22]	235/1650	293/1649	0.80 (0.68 to 0.94)

Appendix 9

Adjusted indirect comparison

Using the method proposed by Bucher and colleagues[72] and adapted from Song and colleagues,[73] we undertook an indirect comparison of clopidogrel and MR-dipyridamole. Using the adjusted method means that the power of randomisation in the original studies is maintained. However, the method is only valid when the magnitude of the treatment effect is consistent between the different studies being compared.

The estimate of the adjust indirect comparison is calculated by

$$T_{BC} = T_{BA} - T_{CA}$$

where T_{BA} is the treatment effect for intervention B versus A and T_{CA} is the treatment effect for intervention C versus A. T_{BC} is the estimate of the treatment effect for intervention B versus C and its standard error is

$$SE(T_{BC}) = \sqrt{SE(T_{BA})^2 + SE(T_{CA})_2}$$

where $SE(T_{BA})$ and $SE(T_{CA})$ are the standard errors of T_{BA} and T_{CA}, respectively.

Clopidogrel versus dipyridamole alone or in combination with aspirin

Comparable data for the CAPRIE trial and ESPS-2 were available from the Antithrombotic Trialists' Collaboration meta-analysis on the *BMJ* website (www.bmj.com). These data are presented in *Table 52*.

The RR and log RR were calculated for clopidogrel versus aspirin and DP alone, and in combination with aspirin versus aspirin. These are presented in *Table 53*.

Worked example

Using the adjusted method, the treatment effect for clopidogrel versus DP in combination with aspirin for the outcome 'serious vascular event' is given by

$$T_{BC} = T_{BA} - T_{CA} = -0.0929 - (-0.2212) = 0.1283$$

The standard error is

$$SE(T_{BC}) = \sqrt{SE(T_{BA})^2 + SE(T_{CA})_2} = \sqrt{0.0420^2 + 0.0803^2} = 0.0907$$

According to this estimate, the 95% CIs are

$$0.1283 \pm 1.96 \times 0.0907 = -0.0494 \text{ to } 0.3060$$

After anti-log transformation, this gives an RR (95% CI) equal to 1.14 (0.95 to 1.36).

TABLE 52 *Summary of data used for the adjusted indirect comparison*

Outcome	CAPRIE		ESPS-2		
	CLOP (n = 9599)	ASA (n = 9586)	DP/ASA (n = 1650)	DP (n = 1654)	ASA (n = 1649)
Serious vascular event	970	1063	235	297	293
Death from any cause	560	571	185	188	182
Non-fatal MI	205	249	11	31	17
Non-fatal stroke	401	422	109	145	158
Vascular death	373	405	117	125	118
Non-vascular death	187	166	68	63	64
Non-fatal major bleeds	92	98	23	6	16
Fatal major bleeds	10	10	7	2	4
All major bleeds	102	108	30	8	20

TABLE 53 *Calculated RR and log RR for the adjusted indirect comparison*

	RR (95% CI)	LogRR (SE)
Serious vascular event		
Clopidogrel versus aspirin	0.91 (0.84 to 0.99)	–0.0929 (0.0420)
DP–aspirin versus aspirin	0.80 (0.68 to 0.94)	–0.2212 (0.0803)
DP versus aspirin	1.01 (0.87 to 1.17)	0.0105 (0.0746)
Death from any cause		
Clopidogrel versus aspirin	0.98 (0.87 to 1.10)	–0.0208 (0.0577)
DP–aspirin versus aspirin	1.02 (0.84 to 1.23)	0.0157 (0.0984)
DP versus aspirin	1.03 (0.85 to 1.25)	0.0294 (0.0980)
Non-fatal MI		
Clopidogrel versus aspirin	0.82 (0.68 to 0.99)	–0.1958 (0.0932)
DP–aspirin versus aspirin	0.65 (0.30 to 1.38)	–0.4359 (0.3854)
DP versus aspirin	1.82 (1.01 to 3.27)	0.5977 (0.2998)
Non-fatal stroke		
Clopidogrel versus aspirin	0.95 (0.83 to 1.08)	–0.0524 (0.0682)
DP–aspirin versus aspirin	0.69 (0.55 to 0.87)	–0.3719 (0.1195)
DP versus aspirin	0.91 (0.74 to 1.13)	–0.0889 (0.1096)
Vascular death		
Clopidogrel versus aspirin	0.92 (0.80 to 1.06)	–0.0837 (0.0703)
DP–aspirin versus aspirin	0.99 (0.77 to 1.27)	–0.0091 (0.1257)
DP versus aspirin	1.06 (0.83 to 1.35)	0.0546 (0.1235)
Non-vascular death		
Clopidogrel versus aspirin	1.12 (0.91 to 1.38)	0.1178 (0.1057)
DP–aspirin versus aspirin	1.06 (0.76 to 1.48)	0.0600 (0.1706)
DP versus aspirin	0.98 (0.70 to 1.38)	–0.0188 (0.1740)
Non-fatal major bleeds		
Clopidogrel versus aspirin	0.94 (0.71 to 1.24)	–0.0645 (0.1444)
DP–aspirin versus aspirin	1.44 (0.76 to 2.71)	0.3623 (0.3237)
DP versus aspirin	0.37 (0.15 to 0.95)	–0.9839 (0.4774)
Fatal major bleeds		
Clopidogrel versus aspirin	1.00 (0.42 to 2.40)	–0.0014 (0.4470)
DP–aspirin versus aspirin	1.75 (0.51 to 5.96)	0.5590 (0.6258)
DP versus aspirin	0.50 (0.09 to 2.72)	–0.6962 (0.8653)
All major bleeds		
Clopidogrel versus aspirin	0.94 (0.72 to 1.23)	–0.0585 (0.1373)
DP–aspirin versus aspirin	1.50 (0.85 to 2.63)	0.4049 (0.2866)
DP versus aspirin	0.40 (0.18 to 0.90)	–0.9193 (0.4169)

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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.

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