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Abstract

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

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Background: Occlusive vascular events such as myocardial infarction (MI), ischaemic stroke and transient ischaemic attack (TIA) are the result of a reduction in blood flow associated with an artery becoming narrow or blocked through atherosclerosis and atherothrombosis. Peripheral arterial disease is the result of narrowing of the arteries that supply blood to the muscles and other tissues, usually in the lower extremities. The primary objective in the treatment of all patients with a history of occlusive vascular events and peripheral arterial disease is to prevent the occurrence of new occlusive vascular events.
Objectives: To assess the clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole (MRD) alone or with aspirin (ASA) compared with ASA (and each other where appropriate) in the prevention of occlusive vascular events in patients with a history of MI, ischaemic stroke/TIA or established peripheral arterial disease. To consider the clinical effectiveness and cost-effectiveness of clopidogrel in patients with multivascular disease. This review is an update of the evidence base for the National Institute for Health and Clinical Excellence (NICE) guidance Technology Appraisal No. 90 (TA90) entitled *Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events* (2005).
Data sources: Four electronic databases (EMBASE, MEDLINE, Web of Science and The Cochrane Library) were searched for randomised controlled trials (RCTs) and economic evaluations. Submissions to NICE by the manufacturers of the interventions were also considered.
Review methods: A systematic review of clinical effectiveness and cost-effectiveness was conducted. To manage heterogeneity between trials, indirect analysis (using a mixed-treatment methodology) was performed on selected clinical outcomes. A new economic model was developed to assess incremental costs per life-year gained [quality-adjusted life-years (QALYs)].
Results: For evidence of clinical effectiveness, four RCTs were identified: CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events), ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial), PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes) and ESPS-2 (Second European Stroke Prevention Study). In CAPRIE (patients with MI, ischaemic stroke or peripheral arterial disease), statistically significant outcomes in favour of clopidogrel were noted for the

primary outcome (first occurrence of ischaemic stroke, MI or vascular death) compared with ASA [relative risk reduction 8.7%; 95% confidence interval (CI) 0.3% to 16.5%; $p = 0.043$]. In ESPRIT (patients with ischaemic stroke/TIA) for the primary outcome (first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication), the risk of event occurrence was statistically significantly lower in the MRD + ASA arm than in the ASA arm [hazard ratio (HR) 0.80; 95% CI 0.66 to 0.98], with no statistically significant difference in bleeding events between the two arms. In PRoFESS (patients with ischaemic stroke) the rate of recurrent stroke of any type (primary outcome) was similar in the MRD + ASA and clopidogrel groups, and the null hypothesis (that MRD + ASA was inferior to clopidogrel) could not be rejected. In ESPS-2 (patients with ischaemic stroke/TIA), on the primary outcome of stroke, statistically significant differences in favour of MRD + ASA were observed compared with ASA and MRD alone (relative risk 0.76; 95% CI 0.63 to 0.93). The outcomes addressed in the mixed-treatment comparisons (limited by the available data) for the ischaemic stroke/TIA population confirmed the results of the direct comparisons. The 11 economic evaluations included in the review of cost-effectiveness indicated that for patients with previous peripheral arterial disease, ischaemic stroke or MI, clopidogrel is cost-effective compared with ASA, and for patients with previous ischaemic stroke/TIA, treatment with MRD + ASA is cost-effective compared with any other treatment in patients in the secondary prevention of occlusive vascular events. The relevance of the review was limited as the economic evaluations were not based on the most current clinical data. Cost-effectiveness results generated from the Assessment Group's de novo economic model suggested that the most cost-effective approach for patients with ischaemic stroke/TIA is clopidogrel followed by MRD + ASA then ASA. For patients with MI, the most cost-effective approach is ASA followed by clopidogrel. For patients with established peripheral arterial disease, the most cost-effective approach is clopidogrel followed by ASA. For patients with multivascular disease, clopidogrel followed by ASA is the most cost-effective approach. Incremental cost-effectiveness ratios (ICERs) were also calculated for patients who are intolerant to ASA. Assuming that the branded price for clopidogrel is used and TA90 guidance is not applied, all of the ICERs range between £2189 and £13,558 per QALY gained. Probabilistic sensitivity analyses were fully consistent with these findings.

Conclusions: The evidence suggests that the most cost-effective treatment for patients with ischaemic stroke/TIA is clopidogrel followed by MRD + ASA followed by ASA; for patients with MI, ASA followed by clopidogrel; and for patients with established peripheral arterial disease or multivascular disease, clopidogrel followed by ASA.

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Contents

Glossary

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

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

Cerebrovascular Pertaining to the blood vessels of the brain.

Clopidogrel (CLOP) A thienopyridine – an inhibitor of platelet aggregation.

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

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

Coronary heart disease Narrowing or blockage of the coronary arteries of the heart by atheroma; often leads to angina, coronary thrombosis or heart attack, heart failure and/or sudden death.

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.

Dipyridamole Inhibitor of platelet aggregation, also available in combination with aspirin.

Dominated A technology is dominated if the comparator is less expensive and more effective; a technology dominates if it is cheaper and more effective than the comparator.

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

Haemorrhagic stroke Death of brain cells because of bleeding in the brain.

Heterogeneity Between-study variation. If heterogeneity exists, the pooled effect size in a meta-analysis has no meaning.

Incremental cost The difference in costs between one intervention and an alternative.

Incremental cost-effectiveness ratio (ICER) The difference in costs between one intervention and an alternative, divided by the difference in outcomes.

Incremental quality-adjusted life-year (QALY) The difference in QALYs between one intervention and an alternative.

Infarction Death of tissue following interruption of the blood supply.

Intention-to-treat (ITT) 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.

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

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 stroke Death of brain cells 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.

Myocardial infarction (MI) Damage to the heart muscle caused by obstruction of circulation to a region of the heart. Also called a heart attack.

Non-ST-segment elevation myocardial infarction (NSTEMI) A myocardial infarction not associated with elevation of the ST-segment on an electrocardiogram.

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

Peripheral arterial disease 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.

Plaque Atheromatous plaque is a swelling on the inner surface of an artery produced by lipid deposition.

Quality-adjusted life-year (QALY) 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.

Qualifying event The event (myocardial infarction, ischaemic stroke, transient ischaemic attack or peripheral arterial disease) for which patients are randomised into a trial.

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.

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

ST-segment elevation MI (STEMI) A myocardial infarction associated with elevation of the ST-segment on the electrocardiogram (ECG).

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

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.

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 (< 24 hours, usually < 1 hour) decrease in brain function.

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

Vascular disease Any disease of the circulatory system.

List of abbreviations

ACS	acute coronary syndrome
ASA	acetylsalicylic acid (i.e. aspirin)
ATTC	Antithrombotic Trialist's Collaboration
BHF	British Heart Foundation
BNF	*British National Formulary*
CAD	coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CLOP	clopidogrel
CVD	cardiovascular disease
DHDS	Diabetes, Heart Disease and Stroke prevention project
ECG	electrocardiogram
ESPRIT	European/Australasian Stroke Prevention in Reversible Ischaemia Trial
ESPS-2	Second European Stroke Prevention Study
GP	general practitioner
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IS	ischaemic stroke
ITT	intention to treat
LYG	life-year gained
LYS	life-year saved
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MIMS	*Monthly Index of Medical Specialities*
MPES	Multi-parameter Evidence Synthesis Research Group
MRD	modified-release dipyridamole
MS	manufacturer's submission
MTA	multiple technology assessment
MTC	mixed-treatment comparison
MVD	multivascular disease
NICE	National Institute for Health and Clinical Excellence
NSF	National Service Framework
NSTEMI	non-ST-segment elevation myocardial infarction
OR	odds ratio
OVE	occlusive vascular event
PAD	peripheral arterial disease
PPI	proton pump inhibitor
PRoFESS	Prevention Regimen For Effectively avoiding Second Strokes
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RRR	relative risk reduction

RR	relative risk
SR	systematic review
STEMI	ST-segment elevation myocardial infarction
TA	technology appraisal
TIA	transient ischaemic attack
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 in the notes at the end of the table.

Executive summary

Background

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

Objectives

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

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

Methods

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

Results of the literature review

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

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

Summary of benefits and risks

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

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

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

The results of the literature review of cost-effectiveness evidence indicated that the use of clopidogrel in patients with previous peripheral arterial disease, ischaemic stroke or MI is a cost-effective option compared with ASA in the secondary prevention of occlusive vascular events. The combination of MRD + ASA appeared cost-effective compared with any other treatment in patients with previous ischaemic stroke/TIA in the secondary prevention of occlusive vascular events. The data are limited as the clinical data have now been superseded by new trial data. The methods used to demonstrate clinical effectiveness in some of the evaluations lacked detail and clarity.

Summary of the Assessment Group's cost-effectiveness results

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

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

Patients with ischaemic stroke/TIA:

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

Patients with MI:

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

Patients with established peripheral arterial disease:

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

Patients with multivascular disease:

- In all scenarios, the incremental cost-effectiveness of clopidogrel followed by ASA is the most cost-effective approach, independent of both the TA90 guidance and the price of clopidogrel.

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

Sensitivity analyses

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

Discussion

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

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

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

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

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

Strengths and limitations

We were able to consider the clinical effectiveness and cost-effectiveness of clopidogrel in people with multivascular disease using information provided by the manufacturer. We re-analysed

data from the CAPRIE trial and estimated the clinical effectiveness and cost-effectiveness of clopidogrel in this clinically important subgroup of patients. We confirmed the findings of other published clinical papers that patients with multivascular disease are often at high risk of future composite and single clinical events.

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

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

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

Uncertainties

The findings of this report for the MI, peripheral arterial disease and multivascular disease patient populations rely on several post hoc subgroup analyses from a single trial; this means that there is inevitable uncertainty associated with these findings. The Appraisal Committee that developed the guidance for TA90 considered it inappropriate to rely on post hoc analyses. However, in this case, reliance on the results of post hoc subgroup analyses from a single trial was unavoidable if the questions set out in the final scope issued by NICE were to be adequately addressed in this report. There were clinical data available from PRoFESS, ESPS-2 and ESPRIT for the ischaemic stroke/TIA population, but the only clinical data available for patients with prior MI, peripheral arterial disease and multivascular disease were from the CAPRIE trial. Patients with MI, peripheral arterial disease and multivascular disease are not considered to constitute a single homogeneous clinical population; this means that use of subgroup analysis to estimate the clinical effectiveness and cost-effectiveness of clopidogrel for these individual subpopulations, although not ideal, is necessary. It is important to note that the size of each of the subgroup populations is considerable (MI 5741, peripheral arterial disease 3713, multivascular disease 4991), and proved sufficient to demonstrate important differences in risk profiles between these groups.

In the absence of any universally agreed definition, the multivascular disease subgroup analyses were based on a population defined using the broadest definition described in the published

literature. However, any differences in definitions of multivascular disease subgroups could lead to differences in patient numbers and relative risks.

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

Conclusions

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

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

Suggested research

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

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

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Chapter 1

Background

Description of the health problem

'Cardiovascular disease' is an umbrella term that includes coronary heart disease, peripheral arterial disease and cerebrovascular disease. Cardiovascular disease is commonly caused by arteries becoming narrowed through atherosclerosis; it is the main cause of death in the UK, accounting for 35% of deaths each year (almost 198,000).[1] Almost half (48%) of all cardiovascular disease deaths are from coronary heart disease, with stroke making up a further quarter (28%).[1] In addition to being the main cause of death, cardiovascular disease is also the major cause of premature death (< 75 years) in the UK; cardiovascular disease caused 30% of premature death in men and 22% in women in 2006.[1]

Occlusive vascular events such as myocardial infarction (MI), ischaemic stroke and transient ischaemic attack (TIA) are classified as subsets of cardiovascular disease. These events are the result of a reduction in blood flow associated with an artery becoming narrow or blocked through atherosclerosis and atherothrombosis. Patients with a history of such events have an increased risk of recurrence when compared with the general population. Peripheral arterial disease is also a subset of cardiovascular disease and is the result of narrowing of the arteries that supply blood to the muscles and other tissues, usually in the lower extremities. Patients with symptomatic peripheral arterial disease (typically intermittent claudication) are at increased risk of experiencing an initial occlusive vascular event. Given the nature of the health problem, some people have what is classified as multivascular disease, i.e. disease in more than one vascular bed, and appear to be at an even greater risk of death, MI or stroke than those with disease in a single bed.[2] Therefore, the primary objective in the treatment of all patients with a history of cardiovascular disease is to prevent the occurrence of new occlusive vascular events.

Aetiology, pathology and prognosis

As noted earlier, the cause of occlusive vascular events is a reduction in blood flow associated with an artery becoming narrow or blocked through atherosclerosis and atherothrombosis. Atherothrombosis involves the formation of a platelet-rich thrombus, frequently 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 the following: elevated and modified low-density lipoproteins; free radicals caused by cigarette smoking, hypertension and diabetes mellitus; genetic alterations; and, combinations of these and other factors.[3]

Epidemiology

The five manifestations of cardiovascular disease considered in this report are MI, ischaemic stroke, TIA, peripheral arterial disease and multivascular disease.

Myocardial infarction

Myocardial infarction (also known as a heart attack) is the interruption of the blood supply to the heart muscle. This is most commonly caused by occlusion of a coronary artery following the rupture of an atherosclerotic plaque. The resulting restriction in blood supply and oxygen

starvation can cause damage to, or the death of, the heart muscle. Typical symptoms of MI include sudden chest pain with sweating or nausea, but MIs can also be symptomless. Women may experience different symptoms to men. Based on the results of changes in electrocardiogram (ECG) readings, MIs are classified into two subtypes: non-ST-segment elevated MI (NSTEMI) or ST-segment elevated MI (STEMI). The distinction has implications for future antiplatelet treatment. After a MI, a patient remains at high risk of a further MI or other occlusive vascular event.

Data from 2006 for the UK demonstrate that, across all ages, there were 146,000 cases of MI: 87,000 in men and 59,000 in women.[1] The incidence of MI varies across regions, between men and women, and increases with age.[1] Higher incidence rates are apparent in northern areas of the UK than in southern areas. In the UK, among men and women aged > 35 years, the prevalence is thought to be over 1.4 million.[1] Approximately 30% of people who experience an acute MI die before they reach hospital.[4] Patients who experience a MI and survive are likely to have a further cardiac event.[5]

Ischaemic stroke

There are a number of different types of stroke; however, the majority of cases (approximately 70%) are ischaemic, caused through the blockage of an artery in the brain.[6] This leads to damage to, or death of, the brain cells due to lack of oxygen. The symptoms of stroke can include: numbness, weakness or lack of movement on one side of the body, slurred speech, difficulty finding words or understanding speech, problems with vision, confusion and/or severe headache.[7] A stroke happens suddenly and the effects are experienced straight away.[7] Anyone who suddenly has symptoms that might be caused by a stroke should be assessed as soon as possible using a test such as FAST (Face, Arm, Speech Test) and, on arrival at hospital, the ROSIER (Recognition of Stroke in the Emergency Room) test may be used.[7] A stroke may be classified as disabling or non-disabling.

The British Heart Foundation (BHF) reports that approximately 98,000 people experience a first ischaemic stroke every year in the UK, with little difference in rates between men and women but an increased risk with age.[8] Additionally, they estimate from 2006 data that, in the UK, as many as 1.1 million people have experienced a stroke; this is equivalent to a prevalence rate of 1.6% in the population in England and 2% in Wales.[8] The risk of recurrent stroke is greatest in the first 6 months following the initial event, but a patient may remain at greater risk of stroke than the general population for a number of years.[3] As many as 30% of strokes are thought to be recurrent.[9] Patients who have experienced a stroke are also at risk of further occlusive vascular events, including MI.[10,11]

Transient ischaemic attack

A TIA is a disorder caused by temporary disturbance of blood supply to an area of the brain that results in a sudden but brief decrease (< 24 hours, usually < 1 hour) in brain functions and causes stroke-like symptoms. If the neurological deficit lasts more than 24 hours it is described as a stroke. Estimates for the UK indicate that between 46,000 and 65,000 people suffer a TIA each year and prevalence of TIA is projected to be 510,000.[8] In contrast with the trend noted in stroke data, there appear to be higher rates of TIA in women, and, as noted for stroke, incidence and prevalence rates increase rapidly with age.[8] Patients experiencing a TIA are at high risk of suffering a subsequent stroke, with 90-day risks of stroke reported to be as high as 10.5%.[12] In patients enrolled in clinical trials after a TIA or non-disabling ischaemic stroke, the annual risk of important vascular events (death from all vascular causes, non-fatal stroke or non-fatal MI) is reported as being between 4% and 11%; the corresponding estimate for population-based studies is 9% per year.[13]

Peripheral arterial disease

Peripheral arterial disease is a condition in which the arteries that carry blood to the arms or legs become narrowed or congested, slowing or stopping the flow of blood. Data related to the prevalence of peripheral arterial disease vary. Detailed data from the USA indicate peripheral arterial disease rates of 4.3% in those < 40 years of age and 14.5% in those > 75 years.[14] Other reports estimate rates at 12–14% in the general population and 20% in those > 75 years of age.[15] The scoping document for this review indicated that, for the UK, approximately 20% of people aged from 55 to 75 years of age have evidence of lower extremity peripheral arterial disease and 5% of these appear to have symptoms, the most common of which is intermittent claudication (pain on walking). As the size of the UK population aged ≥ 55 years is approximately 17 million, this equates to a prevalence of around 170,000 with intermittent claudication.[16] It is thought that worldwide, and in the UK, peripheral arterial disease is underdiagnosed and undertreated.[17,18] Patients with peripheral arterial disease may experience significant pain and poor quality of life (QoL).[19] Over 5 years, about 20% of people with intermittent claudication have a non-fatal cardiovascular event (MI or stroke).[15] People with peripheral arterial disease, including those who are asymptomatic, have a high risk of death from MI and ischaemic stroke, their relative risks (RRs) being two to three times that of age- and gender-matched groups.[19] coronary heart disease is the major cause of death in people with peripheral arterial disease of the legs.[20]

Although the diagnosis of peripheral arterial disease can generally be made from clinical history and examination, objective evidence of significant peripheral arterial disease can be made by obtaining an ankle–brachial pressure index. This index is the ratio of the ankle to brachial systolic pressure and may be measured using a sphygmomanometer and handheld Doppler device.[19] Obtaining an ankle–brachial pressure index is non-invasive and relatively easy, but is rarely used in clinical practice.[21]

Multivascular disease

As noted earlier, there are a number of patients with cardiovascular disease who have disease in more than one vascular bed (otherwise known as multivascular disease patients). The REACH registry (supported by Sanofi–aventis, Bristol–Myers Squibb and the Waksman Foundation) collected data from approximately 67,888 patients who were recruited from 5473 physician practices in 44 countries worldwide.[17,22] Patients in the registry are described as being > 45 years old with least three atherothrombotic risk factors (e.g. treated diabetes mellitus, diabetic nephropathy, ankle–brachial index < 0.9, asymptomatic carotid stenosis of ≥ 70%) or documented cerebrovascular disease, coronary artery disease or peripheral arterial disease. A survey[22] of data from the REduction of Atherothrombosis for Continual Health (REACH) registry identified that 15.9% of patients had symptomatic polyvascular disease, defined as coexistent symptomatic (clinically recognised) arterial disease in two or three territories (coronary, cerebral and/or peripheral). A further analysis indicated that rates of cardiovascular death, MI or stroke at 1 year increase substantially with the number of affected vascular beds.[2] This recognition of the importance of multivascular disease, problems with its definition, and its inherent increased risk of further events is explored in *Chapter 3* (see *Patients with multivascular disease*).

Trends in coronary heart disease and stroke

Coronary heart disease causes over 90,000 deaths a year in the UK: approximately one in five deaths in men and one in six deaths in women. There is geographical variation in prevalence, with greater rates in the northern areas of England than in southern areas and intermediate rates in Wales. There are also social inequalities in mortality from coronary heart disease: higher mortality is noted in people from more deprived areas and those working in manual jobs.[1]

Death rates from coronary heart disease have been declining since the late 1970s and death rates from stroke have declined in the last 10 years, although these trends appear to be plateauing, particularly in younger people. It is thought that the decline in rates of coronary heart disease is owing to reductions in risk factors (mainly smoking) and better treatment (including secondary prevention). Although mortality appears to be falling, coronary heart disease-related morbidity is rising.[1]

Stroke accounts for around 53,000 deaths each year in the UK (approximately 9% of all deaths). According to the BHF[8] it is not possible to know how many deaths each year are attributable to each stroke subtype. However, it reports that age-standardised mortality rates from stroke have decreased markedly in the last four decades, with a 90% reduction in ischaemic stroke mortality.[8] There is geographical variation in death rates from stroke in the UK; the highest rates are in Scotland, followed by northern England, Wales and Northern Ireland. The south of England (particularly London) exhibits the lowest stroke mortality rates. Socioeconomic inequalities in stroke mortality are evident; historically, rates have decreased more quickly in adults from higher social classes and mortality increases with deprivation.[8]

The majority of people survive an initial stroke, but often have significant morbidity.[7] Stroke causes a greater range of disabilities than any other condition and has a greater disability impact than other chronic diseases.[23] It is thought that more than 900,000 people in England are living with the effects of stroke, with half of these being dependent on other people for help with everyday activities.[7]

Impact of health problem

In 2006–7 there were 428,000 inpatient episodes for coronary heart disease in England and over 175,000 for stroke.[1,8] Data from 2006 underline the high cost of coronary heart disease and stroke to the UK health-care system: each cost around £3.2B. A cost per capita of just over £50 for each condition was observed.[1] Hospital care costs for coronary heart disease accounted for 73% of the total cost, whereas for stroke hospital costs accounted for 94%.[1]

Production losses from death and illness and from informal care of people with coronary heart disease and cardiovascular disease are a substantial financial burden.[1] Data from 2006 for the UK demonstrate that production losses owing to mortality and morbidity associated with coronary heart disease cost over £3.9B: 65% owing to death and 35% owing to illness in those of working age. Informal care costs were approximately £1.8B.[1] For stroke, 65% of production losses were owing to illness and costs of informal care were £2.9M, reflecting the debilitating impact of stroke on individuals.[1]

Current service provision

Management of disease

Secondary prevention of occlusive vascular events is antiplatelet therapy. Current recommendations from the National Institute for Health and Clinical Excellence (NICE) in Technology Appraisal No. 90 (TA90)[24] for the secondary prevention of occlusive vascular events in patients with a history of ischaemic stroke or TIA state that modified-release dipyridamole (MRD) in combination with acetylsalicylic acid [ASA (aspirin)] should be used for a period of 2 years from the most recent event. Thereafter, or if MRD is not tolerated, standard care (including long-term, low-dose ASA) should be used. People with a history of occlusive vascular events (except TIA) or peripheral arterial disease who are intolerant to low-dose ASA are advised to use clopidogrel (clopidogrel) alone.

Owing to the evolving nature of treatments, and the different patient groups included in this review, a number of clinical recommendations are relevant. These are described in *Table 1*.

In addition to TA90,[24] there are separate (and different) clinical recommendations for the two subtypes of MI: NSTEMI and STEMI. Clopidogrel plus ASA is the recommended treatment for both types, but for a period of 12 months following a NSTEMI[25] and 4 weeks in the event of a

TABLE 1 Patient populations and clinical recommendations

Patient population	Guidance	Clinical recommendation	Trial evidence	Trial population	Licensed indication for drug
MI	TA90 2005[24] (MTA) Clopidogrel and modified-release dipyridamole in the prevention of OVEs	CLOP if ASA intolerant	CAPRIE[26] CLOP vs ASA	33% MI 34% PAD 33% IS No differentiation between patients with NSTEMI and STEMI	ASA: for the secondary prevention of thrombotic cerebrovascular or CVD CLOP: prevention of atherosclerotic events in people with a history of MI (from a few days until < 35 days), IS (from 7 days until < 6 months) or established PAD CLOP + ASA: For acute coronary syndromes
MI (NSTEMI)	CG94 2010[25] (SR) Clopidogrel in the treatment of non-ST-segment elevation acute coronary syndrome	CLOP + ASA for 12 months after the most recent event. Then standard care (including ASA) or clopidogrel if ASA intolerant	CURE[27] CLOP + ASA vs ASA	100%	
MI (STEMI)	CG48 2007[28] (SR) Secondary prevention in primary and secondary care for patients following a myocardial infarction	CLOP + ASA for 4 weeks after the most recent event. Then standard care (including ASA) or CLOP if ASA intolerant	COMMIT[29] CLOP + ASA vs ASA	93% STEMI 7% NSTEMI	CLOP + ASA: for acute coronary syndromes
IS	TA90 2005[24] (MTA) Clopidogrel and modified-release dipyridamole in the prevention of OVEs	MRD + ASA for 2 years after the most recent event. Thereafter, or if MRD is not tolerated, standard care (including long-term treatment with low-dose ASA)	ESPS-2[30] ASA vs MRD vs MRD + ASA vs placebo	76% IS 24% TIA	MRD (with or without ASA): secondary prevention of IS and TIA
TIA	TA90 2005[24] (MTA) Clopidogrel and modified-release dipyridamole in the prevention of OVEs	MRD + ASA for 2 years after the most recent event. Thereafter, or if MRD is not tolerated, standard care (including long-term treatment with low-dose ASA)			
PAD	TA90 2005[24] (MTA) Clopidogrel and modified-release dipyridamole in the prevention of OVEs	CLOP if ASA intolerant[a]	CAPRIE[26] CLOP vs ASA	33% MI 34% PAD 33% IS	ASA: for the secondary prevention of thrombotic cerebrovascular or CVD CLOP: prevention of atherosclerotic events in people with a history of MI (from a few days until < 35 days), IS (from 7 days until < 6 months) or established PAD
MVD	Not currently included	N/A	N/A	N/A	N/A

CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CLOP, clopidogrel; COMMIT, ClOpidogrel and Metaprolol in Myocardial InfarcTion; CURE, Clopidogrel in Unstable angina to prevent Recurrent Events; CVD, cardiovascular disease; ESPS-2, Second European Stroke Prevention Study; IS, ischaemic stroke; MTA, multiple technology assessment; OVE, occlusive vascular event; PAD, peripheral arterial disease; SR, systematic review; N/A, not available.

a ASA not licensed for peripheral arterial disease.

STEMI. There is currently no guidance for the prevention of occlusive vascular events in patients with multivascular disease.

The purpose of the current review is to update the evidence base that was available to inform NICE's TA90 guidance.[3,24] Patient groups who are beyond its remit include those who have had, or are at risk of, a stroke associated with atrial fibrillation or who require treatment to prevent occlusive vascular events after coronary revascularisation or carotid artery procedures.

Although explicit data on provision of antiplatelet treatment for patients in the various disease categories are not available, general practitioner (GP) prescribing data for England from 2004 to 2009[31] indicate a slow and steady increase in prescribing rates over that time period (*Figure 1*).

Current service cost

The current prices for ASA, MRD and clopidogrel are shown in *Table 2*. All prices are net and are taken from the *British National Formulary* (BNF) No. 58.[32] Generic versions of clopidogrel are now licensed; from 1 April 2010, clopidogrel is listed as category M of Part VIII of the Drug Tariff, meaning that pharmacists will be reimbursed at the generic price of £10.90 for 30 tablets of 75 mg clopidogrel.[33,34]

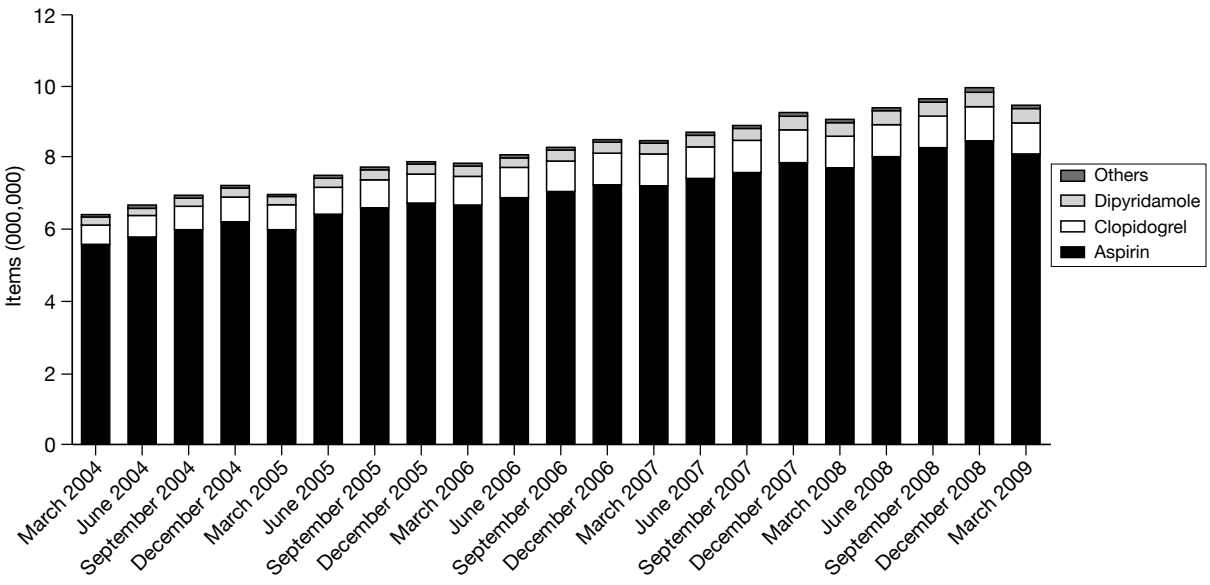

FIGURE 1 Trends in prescribing of antiplatelet drugs in general practice in England. Reproduced with permission from the NHS Business Services Authority (NHSBSA).

TABLE 2 Prices of ASA, MRD and clopidogrel

Drug	Price per pack	Price per day (£)
ASA (75-mg) tablets	£0.94 per 28, £1.07 per 56	0.033, 0.019
MRD + ASA dipyridamole (200 mg), ASA (25 mg)	£7.79 per 60	0.26 (b.i.d.)
MRD (200 mg)	£7.50 per 60	0.25 (b.i.d.)
CLOP (Plavix) (75 mg)	£36.35 per 30	1.21
CLOP (generic)	£10.90 per 30	0.36

b.i.d., twice daily; CLOP, clopidogrel.

In *Figure 2*, trends in spending on the various agents prescribed by GPs in England over the period of 2004–9 are shown.[31]

Variation in services and/or uncertainty about cost

The recent end of patent term for clopidogrel has meant that a number of generic formulations of the drug have been approved by the European Medicines Agency[35] and the Medicines and Healthcare products Regulatory Agency (MHRA).[36] At the time of writing, there are at least eight generic products available in the UK, as listed in *Table 3*. All of those listed are licensed for the 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 peripheral arterial disease. It is currently unclear (because of issues relating to patent) whether or not any of these products may also be used in combination with ASA for the treatment of patients with acute coronary syndromes.

Relevant national guidelines including National Service Frameworks

The design of guidelines and National Service Frameworks (NSFs) is based on overall national goals and targets. The government target for England (set in 1999 and 2004) for cardiovascular disease was to reduce the death rate from coronary heart disease, stroke and related diseases in

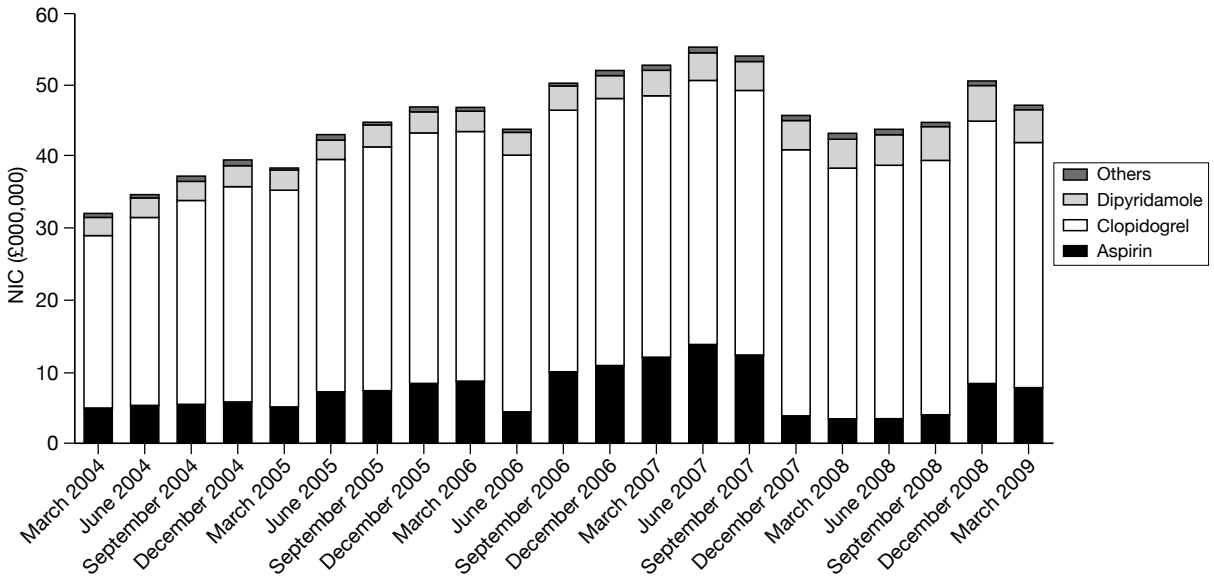

FIGURE 2 Trends in spending on antiplatelet drugs in general practice in England. Reproduced with permission from the NHSBSA. NIC, net ingredient cost.

TABLE 3 Generic versions of clopidogrel available in the UK

Name of manufacturer	Licensed name	Active ingredient
Mylan Pharmaceuticals/Generics UK	Clopidogrel Mylan	Clopidogrel hydrochloride
Consilient Health Ltd	Clopidogrel Consilient	
Sandoz Ltd	Clopidogrel Sandoz	Clopidogrel besilate
Actavis Group PTC EHF	Actavis clopidogrel	
Arrow Generics	Arrow clopidogrel	
Dr Reddy's Laboratories (UK) Ltd	Dr Reddy's clopidogrel	
Dexcel Pharma Ltd	Dexcel clopidogrel	
Beacon Pharmaceuticals	Beacon clopidogrel (Grepid®)	

people aged ≤ 75 years by at least two-fifths by 2010, saving up to 200,000 lives in total, with a milestone of a reduction of one-quarter by 2005.[37,38] A further target was to reduce the inequalities gap in death rates from these diseases between the fifth of areas with the worst health and deprivation indicators and the population as a whole in people aged ≤ 75 years by 40% by 2010.

The Welsh Assembly Government[39,40] set its target for coronary heart disease as a reduction in mortality rates in 65- to 74-year-olds from 600 per 100,000 in 2002 to 400 per 100,00 in 2012. Its health inequality target is to improve coronary heart disease mortality in all groups and at the same time aim for a more rapid improvement in the most deprived groups. The target for stroke is to reduce mortality in people aged 65–74 years by 20% by 2012.

New GP contracts include points for the number of coronary heart disease and stroke patients who are taking antiplatelet therapy for secondary prevention of occlusive vascular events.[41] The contract does not appear to include patients with peripheral arterial disease.[42]

Therefore, the use of antiplatelet agents is the focus of a number of national documents including the National Service Framework[43,44] and NICE guidance documents.[25,45] The nature of multivascular disease means that at times these documents apply to overlapping patient populations.

The *National Service Framework (NSF) for Coronary Heart Disease: Standards and Quality Requirements (England)* states that GPs and primary care teams should identify all patients with established cardiovascular disease and offer them comprehensive advice and appropriate treatment to reduce their risks of coronary heart disease.[43,44]

The *National Stroke Strategy: Ten Point Plan for Action* for England states that in preventing stroke, support for healthier lifestyles should be offered and action to tackle vascular risk taken.[46]

As part of the Diabetes, Heart Disease and Stroke (DHDS) prevention project, the UK National Screening Committee commissioned the *Handbook of vascular risk assessment, risk reduction and risk management*.[47] The handbook is designed to support local health services in meeting the standards for the prevention and early detection of coronary heart disease, set out in the NSF for England. The target population for screening is people aged between 40 and 75 years. The handbook describes the context and outlines evidence for a coordinated vascular disease control programme to identify and reduce risks of cardiovascular disease in the general population; suggest aims, objectives and a delivery strategy framework appropriate for a cardiovascular disease risk management programme; report key messages from the DHDS pilot project; and provide examples of tools, resources and standard operating procedures that can be used by health professionals.[47]

Description of technology under assessment

Two antiplatelet agents, used within their licensed indications, are the focus of this review: clopidogrel® (Plavix®, Bristol–Myers Squibb, Sanofi–aventis) and MRD + ASA in a single capsule (Asasantin Retard®, Boehringer Ingelheim) or MRD alone (Persantin Retard®, Boehringer Ingelheim). Clopidogrel produces an immediate and sustained inhibition of ADP-induced platelet aggregation that helps prevent blood clots.[48] Dipyridamole is thought to inhibit adenosine (a potent inhibitor of platelet activation and aggregation) uptake into blood and vascular cells.[3] Summaries of product characteristics for clopidogrel, MRD + ASA and MRD alone are available from the Electronic Medicines Compendium.[49]

Clopidogrel

Clopidogrel is licensed in adults for the prevention of atherothrombotic events in patients suffering from MI (from a few days to 35 days), ischaemic stroke (from 7 days to 6 months) or established peripheral arterial disease. Clopidogrel is available as 75 or 300 mg film-coated tablets. The recommended dose is 75 mg as a single daily dose, taken with or without food. As previously noted, generic versions of clopidogrel are now available (see *Table 3*), although it is currently unclear whether or not any of these generic versions are licensed for prescribing with ASA for the treatment of acute coronary syndromes.

Contraindications for clopidogrel include hypersensitivity to the active substance or to any of the excipients, severe liver impairment and active pathological bleeding (such as a peptic ulcer or intracranial haemorrhage). Special warnings for clopidogrel use include (but are not limited to) the following:

- use with caution in combination with any other anticoagulant or antiplatelet drug or in patients with bleeding diathesis
- thrombotic thrombocytopenic purpura has been reported very rarely following the use of clopidogrel, sometimes after a short exposure.

Based on literature data, patients with genetically reduced *CYP2C19* function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates after MI than do patients with normal *CYP2C19* function. As clopidogrel is metabolised to its active metabolite partly by *CYP2C19*, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit *CYP2C19* should be discouraged. Although the evidence of *CYP2C19* inhibition varies within the class of proton pump inhibitors (PPIs), clinical studies suggest an interaction between clopidogrel and possibly all members of this class. Therefore, concomitant use of PPIs should be avoided unless absolutely necessary. The Assessment Group is aware that new evidence has led to a new recommendation from the European Medicines Agency[50] that only two specific PPIs (omeprazole and esomeprazole) are a problem (see below).

Important subgroups of patients

Clopidogrel is not licensed for secondary prevention of occlusive vascular events in patients who have experienced a TIA, although in UK clinical practice it may be prescribed for these patients if they are unable to tolerate MRD or ASA (Dr Anil Sharma, Aintree Hospitals NHS Trust, 17 March 2010, personal communication).

There is evidence that two PPIs (omeprazole and esomeprazole) reduce the effectiveness of clopidogrel in preventing the recurrence of adverse cardiac events; current advice is that concomitant use of these with clopidogrel should be discouraged. In addition, the concomitant use of other known *CYP2C19*-inhibiting medicines with clopidogrel is discouraged because these are expected to have a similar effect to omeprazole and esomeprazole.[50]

Modified-release dipyridamole

A non-modified-release (often referred to as immediate release) version of dipyridamole is available; however, only the evidence for MRD is considered in this review. MRD is often also referred to as an 'extended-release dipyridamole'. For clarity, this review will use the term MRD throughout.

Modified-release dipyridamole (alone or with ASA) is licensed for use in adults for the secondary prevention of ischaemic stroke and TIA. It is available in two preparations:

- Asasantin Retard® (Boehringer Ingelheim) capsules containing both dipyridamole (200 mg) and ASA (25 mg).
- Persantin Retard® (Boehringer Ingelheim) capsules containing dipyridamole (200 mg).

The recommended dose of MRD is 200 mg twice daily. Capsules should be taken in the morning and again in the evening, preferably with meals.

Contraindications for Asasantin Retard® include hypersensitivity to any component of the product or salicylates, patients with active gastric or duodenal ulcers, and patients in the last trimester of pregnancy. Special warnings and precautions for use include (but are not limited to):

- Asasantin® should be used with caution in patients with an increased risk of bleeding and such patients should be followed carefully for any signs of bleeding.
- Caution should be advised in patients receiving concomitant medication that may increase the risk of bleeding.
- Headache that may occur at the beginning of treatment should not be treated with analgesic doses of ASA.
- Among other properties, dipyridamole acts as a vasodilator. It should be used with caution in patients with severe coronary artery disease, including unstable angina or recent MI, left ventricular flow obstruction or haemodynamic instability.
- Owing to the ASA component, all appropriate cautions applicable to ASA should also be observed.

Contraindications for Persantin Retard® are limited to hypersensitivity to any component of the product. The same cautions should be observed as for Asasantin Retard® (with the exception of those related to the ASA content).

Chapter 2

Definition of the decision problem

Decision problem

The remit of this appraisal is to review and update (if necessary) the clinical effectiveness and cost-effectiveness evidence base described in TA90.[24] *Table 4* shows the key elements of the decision problem of the appraisal.

The key elements of this appraisal are similar to those that underpin the previous review,[3] with the following exceptions: patients with a history of TIA will not be considered in the assessment of the effectiveness of clopidogrel, as clopidogrel is not licensed for this patient group; MI will be divided into STEMI and NSTEMI; and unstable angina has replaced 'other vascular events'.

Overall aims and objectives of assessment

The purpose of the review is to assess the clinical effectiveness and cost-effectiveness evidence describing the use of clopidogrel and MRD (plus ASA or alone) in the prevention of occlusive vascular events in patients with history of MI, ischaemic stroke or TIA, or established peripheral arterial disease. Evidence relevant to the effectiveness of clopidogrel in patients with multivascular disease will also be considered. This review is an update and focuses on relevant clinical effectiveness and cost-effectiveness evidence that has become available since publication of TA90.[24]

TABLE 4 Key elements of the decision problem

Interventions	Clopidogrel
	MRD used alone or in combination with ASA
Patient population	For clopidogrel, adults with established PAD or those with a history of MI or IS
	For MRD, adults with a history of IS or TIA
Comparators	The interventions will be compared with ASA and, where appropriate, with each other
Outcomes	Any of the following: ■ MI (STEMI and NSTEMI) ■ Unstable angina ■ Stroke ■ Vascular death ■ Death ■ Adverse effects of treatment, including bleeding complications ■ HRQoL ■ Incremental cost per LYG ■ Incremental cost per quality-adjusted LYG
Other considerations	If the evidence allows, the effectiveness of clopidogrel in people with MVD who are considered to be at high risk of recurrent occlusive vascular events will be considered
	If the evidence allows, the duration of treatment with the specified interventions will be considered

HRQol, health-related quality of life; IS, ischaemic stroke; LYG, life-years gained; MVD , multivascular disease; PAD, peripheral arterial disease.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Methods for reviewing clinical effectiveness and cost-effectiveness evidence are described in this chapter.

Search strategies

This review is an update of an existing review.[3] Consequently, the start date for searches of electronic databases is 2003. In addition to searching the two manufacturer's submissions[51,52] for relevant references, the following databases were searched for trials of clopidogrel and MRD:

- EMBASE (2003–9 week 36)
- MEDLINE (2003–9 August week 4)
- Web of Science (2003–9)
- The Cochrane Library (2003–9, Issue 3).

The results were entered into an Endnote X2 (Thomas Reuters, CA, USA) library and the references were de-duplicated. Full details of the search strategies are presented in *Appendix 1*.

Inclusion and exclusion criteria

Two reviewers (JG/RD) independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed (JG/JO) according to the criteria set out below. Studies that did not meet the criteria were excluded and their bibliographic details were listed alongside reasons for their exclusion. These are listed in *Appendix 5*. Any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted.

Study design

Only randomised controlled trials (RCTs) were included in the assessment of clinical effectiveness. Full economic evaluations were included in the assessment of cost-effectiveness.

The Assessment Group also identified and assessed the quality of existing systematic reviews (SRs) in order to cross-check for the identification of additional studies, as well as to gain an understanding of the issues related to the combining of data in this complex area. A summary and critique of relevant SRs is presented in *Appendix 3*.

Interventions and comparators

The effectiveness of two antiplatelet agents, used within their licensed indications, was assessed (1) clopidogrel alone and (2) MRD alone or in combination with ASA. Studies that compared clopidogrel alone or MRD (alone or in combination with ASA) with ASA or, where appropriate, with each other were included in the review. Trials in which clopidogrel was used as an adjunct to percutaneous coronary intervention were excluded from the review. Trials in which clopidogrel was combined with ASA were also excluded, as they were not within the remit of the scope.[16]

Patient populations

For clopidogrel, patients with a history of MI, ischaemic stroke or established peripheral arterial disease were included. Patients with acute coronary syndromes were not included, and neither were those with atrial fibrillation. For MRD, patients with a history of ischaemic stroke or TIA were included.

Outcomes

Data on any of the following outcomes were included in the assessment of clinical effectiveness: MI, stroke, TIA, death and adverse events including bleeding complications. No data relating to health-related quality of life (HRQoL) or unstable angina were identified. For the assessment of cost-effectiveness, outcomes included incremental cost per life-years gained and incremental cost per quality-adjusted life-year (QALY) gained.

Data extraction strategy

Data relating to both study design and quality were extracted by two reviewers (JO/MB) into an Excel 2007 (Excel Software, Henderson, NV, USA) spreadsheet. The two reviewers cross-checked each other's extraction and a third independent reviewer (YD) checked for accuracy and was consulted in cases of disagreement. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Quality assessment strategy

The quality of clinical effectiveness studies was assessed by two reviewers (MB/JO) and checked by a third reviewer (YD) according to criteria based on the NHS Centre for Reviews and Dissemination (CRD) Report 4.[53] The quality of the cost-effectiveness studies was assessed by two reviewers (CMS/AB) according to a checklist updated from that developed by Drummond and Jefferson.[54] All relevant information is tabulated and summarised within the text of the report. Full details and results of the quality assessment strategy for clinical effectiveness and cost-effectiveness studies are reported in *Appendix 2*.

Methods of data synthesis

Direct evidence

The results of (1) clinical and (2) economic data extraction and quality assessment are summarised in structured tables and as a narrative description. The decision problem of interest to this review was made up of the following comparisons: (1) clopidogrel versus ASA; (2) clopidogrel versus MRD alone; (3) clopidogrel versus MRD + ASA; (4) MRD + ASA versus ASA; and (5) MRD alone versus ASA.

Indirect evidence

Owing to the differences between trials in terms of interventions and comparators, indirect analysis (using a mixed-treatment comparison methodology) was performed on a variety of outcomes. The methods and results of the mixed-treatment comparisons are reported below (see *Methods for indirect synthesis*).

Additional analysis by the Assessment Group

Using data provided by the manufacturers of clopidogrel, the Assessment Group undertook subgroup analysis and explored the clinical effectiveness of clopidogrel in patients with multivascular disease. The Assessment Group was also able to explore whether or not key outcome events are distributed evenly across the whole period of trial follow-up or if there are particular time points when patients appear to be at a greater risk.

Results

Quantity and quality of research available

A total of 4576 titles and abstracts were screened for inclusion in the review of clinical effectiveness and cost-effectiveness evidence. The process of study selection is shown in *Figure 3*.[55] The flow chart shows that the two studies identified in our updated searches were added to the two already identified in TA90.[24]

Clinical effectiveness (randomised controlled trials)

Four RCTs – CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events),[26] ESPS-2 (Second European Stroke Prevention Study),[30] ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial)[56] and PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes)[57] – were reported in 28 publications and met the inclusion criteria for this review. These included the two trials[26,30] (reported in 20 publications) that were used to inform the previous guidance.[24] The reference provided in the text refers to the primary report and any subsequent publications describing outcomes of the trials are listed by trial in *Appendix 4*.

The identified trials are summarised in *Table 5*. We did not include trials in which clopidogrel was combined with ASA, as only clopidogrel alone was specified as an intervention or comparator in the scope issued by NICE.[16] This means that both MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients)[58] and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation Management and Avoidance)[59] trials are excluded from the review. A full list of publications excluded following the application of the inclusion criteria is presented in *Appendix 5*.

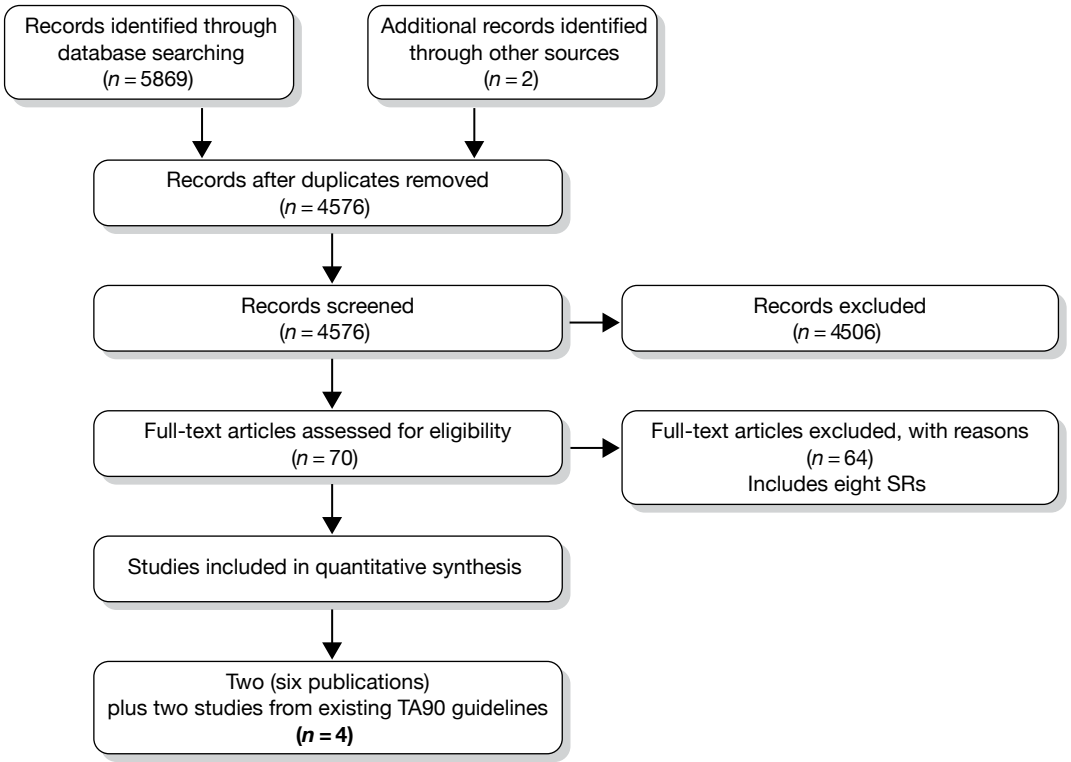

FIGURE 3 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart.

TABLE 5 Identified RCTs

Trial	Study design	Patients	Comparators
CAPRIE[26] 1996	Double-blind, placebo-controlled trial	19,185 patients with atherosclerotic vascular diseases manifested as either IS, MI or symptomatic PAD	CLOP (75 mg/day) vs ASA (325 mg/day)
ESPS-2[30] 1996	Double-blind, placebo-controlled trial (2 × 2 factorial)	6602 patients with prior stroke or TIA	ASA (50 mg/day) vs MRD (400 mg/day) vs ASA (50 mg/day) + MRD (400 mg/day) vs placebo
ESPRIT[56] 2006	Open-label trial	2736 patients with prior TIA or stroke[a]	ASA (30–325 mg/day) vs MRD (400 mg/day) + ASA
PRoFESS[57] (2008)	Double-blind trial	20,332 patients with prior stroke	MRD (400 mg/day) + ASA (50 mg/day) vs CLOP (75 mg/day)

CLOP, clopidogrel; IS, ischaemic stroke; PAD, peripheral arterial disease.
a In total, 2763 were randomised, but 24 patients were excluded because of incomplete data; thus, results are based on 2739 patients.

In addition, six ongoing trials were identified; these are described in *Appendix 6*. Limited detail is available relating to these studies and they are not considered in this review. However, it is worthy of note that the majority of the ongoing trials include clopidogrel + ASA as a comparator.

Quality assessment of included randomised controlled trials

All of the included RCTs were of good quality (see *Appendix 2*). Robust randomisation procedures were used and baseline comparability between treatment groups was achieved. The use of blinding procedures was reported where appropriate and intention-to-treat (ITT) analyses were conducted for each trial. There was no evidence of selective reporting of outcomes in any of the trials.

Trial characteristics

The key characteristics of the included trials are summarised in *Table 6*. Of the four trials, three were double blind and one was an open-label study (ESPRIT[56]). The majority of trials were conducted globally, whereas the participating centres in ESPS-2[30] were located only in Europe. All trials included patients with ischaemic stroke as a qualifying event and two included patients with a qualifying event of TIA.[30,56] Only CAPRIE[26] included patients with MI or peripheral arterial disease. The trial sizes ranged from 2763 to 20,332. Mean length of follow-up ranged between 1.91 and 3.5 years. Three trials were industry funded, while ESPRIT[56] was funded from a variety of non-industry sources. Two trials (CAPRIE[26] and ESPRIT[56]) utilised a composite as a primary end point, the components of which differed between the trials. In ESPS-2,[30] three discrete primary end points were reported, while PRoFESS[57] reported on a single primary end point of recurrent stroke. Across the four trials, ASA dosage ranged from 50 mg per day (ESPS-2[30] and PRoFESS[57]) to 30–325 mg per day in ESPRIT[56] and 325 mg per day in CAPRIE.[26]

Patient characteristics

The key characteristics of patients in the included trials are summarised in *Table 7*. The mean age of the patients was similar across trials. The percentage of males appears to be greatest in CAPRIE.[26] The PRoFESS[57] trial included the greatest proportion of patients with hypertension and diabetes mellitus. None of the trials characterised the patient population in terms of the number of affected vascular beds, so the number of patients per trial with multivascular disease is unknown. However, the history of vascular events for the whole cohort of patients is reported for each trial; these are described in the right-hand column of *Table 7*. Compared with the other trials, in ESPS-2[30] there was a higher percentage of patients with peripheral arterial disease in addition to the qualifying event of ischaemic stroke/TIA. With the exception of CAPRIE,[26] the modified Rankin Scale[60] was used as a measure of patient disability; this scale is widely used as

TABLE 6 Summary of included trial characteristics

Trial name and comparators	Study design	No. of patients (*N*), location	Qualifying events, no. patients (*n*)	Follow-up (mean)	Trial support	Outcomes
CAPRIE[26] 1996 CLOP (75 mg) vs ASA (325mg)	Double-blind, placebo-controlled	*N* = 19,185 Austria, Australia, Canada, Belgium, France, Finland, Germany, Italy, the Netherlands, New Zealand, Portugal, Spain, Sweden, Switzerland, the UK and the USA	IS (*n* = 6431) MI (*n* = 6302) PAD (*n* = 6452)	1.91 years (range 1–3 years)	Sanofi–aventis and Bristol–Myers Squib	*Primary* First occurrence of IS, MI or vascular death *Secondary* First occurrence of IS, MI, amputation or vascular death; vascular death; overall net benefit: any stroke (includes primary intracranial haemorrhage), MI or death from any cause; death from any cause
ESPS-2[30] 1996 ASA (50 mg) vs MRD vs ASA (50 mg) MRD + ASA vs placebo	Double-blind, placebo-controlled (2 × 2 factorial)	*N* = 6602 Austria, Belgium, France, Germany, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the UK	TIA (*n* = 1562) IS (*n* = 5038)	2 years	Boehringer Ingelheim	*Primary* Stroke; all-cause death; stroke and/or all-cause death *Secondary* TIA; MI; IS events (stroke and/or MI, and/or sudden death of thrombotic origin); other vascular events (pulmonary embolism, deep venous thrombosis, peripheral arterial occlusion, venous retinal thrombosis or combination of these events)
ESPRIT[56] 2006 ASA (30–325 mg) vs MRD + ASA[a] (30–325 mg)	Open-label	*N* = 2736 Austria, Belgium, France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, Switzerland, the UK, Australia, China, Singapore and the USA	TIA (*n* = 920) Minor IS (*n* = 1816)	3.5 years (SD 2.0)	Council of Singapore, European Commission; UK Stroke Association; French Ministry of Health *Netherlands*: Janivo Foundation, AEGON N V; Heart Foundation; Thrombosis Foundation; University Medical Center Utrecht	*Primary* First occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication *Secondary* Death from all causes; death from all vascular causes and non-fatal stroke; all major ischaemic events (non-haemorrhagic death from vascular causes, non-fatal IS or non-fatal MI); all vascular events (death from vascular causes, non-fatal stroke or non-fatal MI); major bleeding complications

continued

an outcome measure for stroke in clinical trials. The scale ranges from 0 to 6, where '0' indicates no disability and '6' is death. All patients in ESPRIT[56] were rated as between 0 and 3, with 43% having no disability.

CAPRIE[26]

The key outcomes of the CAPRIE[26] trial are described in *Table 8*. For the whole trial population, statistically significant outcomes in favour of clopidogrel were noted for the primary outcome (first occurrence of ischaemic stroke, MI or vascular death). The relative risk reduction (RRR) was 8.7% in favour of clopidogrel [95% confidence interval (CI) 0.3% to 16.5%; $p = 0.043$]. It has been noted,[3] elsewhere, that the point estimate favoured clopidogrel, but this benefit appeared to be very small; the boundaries of the CIs raise the possibility that clopidogrel is not more beneficial than ASA. A statistically significant risk reduction (23.8%) in favour of clopidogrel

TABLE 6 Summary of included trial characteristics *(continued)*

Trial name and comparators	Study design	No. of patients (*N*), location	Qualifying events, no. patients (*n*)	Follow-up (mean)	Trial support	Outcomes
[b]PRoFESS[57] 2008 MRD + ASA (50 mg) vs CLOP (75 mg)	Double-blind, non-inferiority	*N* = 20,332 Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Denmark, Finland, France, Germany, Greece, Hong Kong, India, Ireland, Israel, Italy, Japan, Malaysia, Mexico, the Netherlands, Norway, Portugal, Russian Federation, Singapore, South Africa, Republic of Korea, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, the UK and the USA	Recent IS (*n* = 20,332)	2.5 years (range 1.5–4.4 years)	Boehringer Ingelheim. In selected countries also supported by Bayer Schering Pharma and GlaxoSmithKline	*Primary* Recurrent stroke of any type *Secondary* Vascular events; first occurrence of stroke (non-fatal or fatal) or MI (non-fatal or fatal) or vascular death; first occurrence of stroke or major haemorrhagic event; death: IS, haemorrhagic stroke, stroke of uncertain cause, MI, haemorrhage excluding intracranial bleeding, other vascular causes, non-vascular causes; life-threatening or non-life-threatening major haemorrhagic events; other designated vascular events; pulmonary embolism or retinal vascular accidents or deep-vein thrombosis or peripheral arterial occlusion or TIA

CLOP, clopidogrel; IS, ischaemic stroke; PAD, peripheral arterial disease; SD, standard deviation.
a Overall, 13% of patients received immediate-release dipyridamole.
b PRoFESS also included two other arms, placebo and telmisartan.

TABLE 7 Patient characteristics

Trial name/ comparators	Mean age (SD)	Gender (male) (%)	Modified Rankin Scale status (%)	Other factors (%)	Percentage of patients with history of vascular events
CAPRIE[26] (CLOP vs ASA)	62.5 years (11.1)	72	NS	Current smoker: 29.5 Ex-smoker: 49 Hypertension: 51.5 DM: 20	MI: 16.5 IS: 9 Intermittent claudication: 4.5 TIA/RIND: 10
ESPS-2[30] (ASA vs MRD vs MRD + ASA vs placebo)	66.7 years	58	0 + 1 + 2 = 69.1 3 = 14.2 4 + 5 = 16.6	Current smoker: 24 Hypertension: 60.5 DM: 15.3	PAD: 22
ESPRIT[56] (ASA vs MRD + ASA)	63 years (11)	66	0 = 43 1 = 33 2 = 18 3 = 6	Current smoker: 36.5 Hypertension: 59.5 DM: 18.5	MI: 7 Intermittent claudication: 5 Stroke: 11.5
PRoFESS[57] (MRD + ASA vs CLOP)	66.1 years (8.6)	64	0 = 14 1 = 37 2 = 25 3 = 14 4 + 5 = 9	Current smoker: 21 Ex-smoker: 36 Never smoker: 42.6 Hypertension: 74 DM: 28	MI: 7 TIA: 8.7 PAD: 3 Stroke: 18.25

CLOP, clopidogrel; DM, diabetes mellitus; IS, ischaemic stroke; NS, not stated; PAD, peripheral arterial disease; RIND, reversible ischaemic neurological disease.

TABLE 8 Key outcomes of CAPRIE[26] trial

Outcomes	Event rate per year		
	CLOP (%)	ASA (%)	RRR, % (95% CI)
Primary			
First occurrence of IS, MI or vascular death	All patients: 5.32	All patients: 5.83	All patients: 8.7 (0.3 to 16.5); $p=0.043$
	Stroke subgroup: 7.15	Stroke subgroup: 7.71	Stroke subgroup: 7.3 (–5.7 to 18.7); $p=0.26$
	MI subgroup: 5.03	MI subgroup: 4.84	MI subgroup: –3.7 (–22.1 to 12); $p=0.66$
	PAD subgroup: 3.71	PAD subgroup: 4.86	PAD subgroup: 23.8 (8.9 to 36.2); $p=0.0028$
Secondary			
First occurrence of IS, MI, amputation or vascular death	All patients: 5.56	All patients: 6.01	All patients: 7.6 (–0.8 to 15.3); $p=0.076$
Vascular death	All patients: 1.90	All patients: 2.06	All patients: 7.6 (–6.9 to 20.1); $p=0.29$
Overall net benefit[a]	All patients: 6.43	All patients: 6.90	All patients: 7.0 (–0.9 to 14.2); $p=0.081$
Death from any cause	All patients: 3.05	All patients: 3.11	All patients: 2.2 (–9.9 to 12.9); $p=0.71$

CLOP, clopidogrel; IS, ischaemic stroke; PAD, peripheral arterial disease.
a Any stroke (includes primary intracranial haemorrhage); MI or death from any cause, fatal bleeding.

was reported for the subgroup of patients with peripheral arterial disease (95% CI 8.9% to 36.2%; $p=0.0028$); however, the trial was not powered to detect differences between patient subgroups and so the finding should be interpreted with caution. No statistically significant differences between clopidogrel and ASA were noted for the subgroup of patients with ischaemic stroke or MI.

ESPS-2[30]

Table 9 shows the key outcomes of ESPS-2.[3,30] For the first primary outcome of stroke, statistically significant differences in favour of MRD + ASA were observed for two comparisons: MRD + ASA vs ASA [relative risk (RR) 0.76; 95% CI 0.63 to 0.93] and MRD + ASA vs MRD alone (RR 0.75; 95% CI 0.61 to 0.91). No difference was observed for the MRD-versus-ASA comparison. No other primary outcome (all-cause death, stroke and/or all-cause death) showed statistically significant differences between any two treatment arms.

Of the secondary outcomes, stroke/TIA, other vascular event, ischaemic events and vascular events, statistically significant differences were recorded in favour of MRD + ASA when compared with ASA (RR 0.80, 95% CI 0.70 to 0.92; RR 0.55, 95% CI 0.33 to 0.94; RR 0.77, 95% CI 0.65 to 0.92; RR 0.78, 95% CI 0.67 to 0.91, respectively).

Of the secondary outcomes of TIA, stroke/TIA, ischaemic events and vascular events, statistically significant differences in favour of MRD + ASA compared with MRD alone were noted (RR 0.80, 95% CI 0.66 to 0.97; RR 0.78, 95% CI 0.69 to 0.90; RR 0.76, 95% CI 0.64 to 0.90; RR 0.76, 95% CI 0.65 to 0.89, respectively).

ESPRIT[56]

The key outcomes of the ESPRIT[56] trial are described in *Table 10*. For the primary outcome of first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication, the risk of event occurrence was statistically significantly lower in the MRD + ASA arm than in the ASA arm [hazard ratio (HR) 0.80; 95% CI 0.66 to 0.98].

TABLE 9 Key outcomes of ESPS-2[30]

Outcomes	Total events			RR (95% CI)
	MRD, *n* (%)	MRD + ASA, *n* (%)	ASA, *n* (%)	
Primary				
MRD + ASA vs ASA				
Stroke		157 (9.5)	206 (12.5)	0.76 (0.63 to 0.93)
Stroke and/or death		286 (17.3)	330 (20.0)	0.87 (0.75 to 1.00)
All-cause death		185 (11.2)	182 (11.0)	1.02 (0.84 to 1.23)
MRD + ASA v MRD				
Stroke	211 (12.8)	157 (9.5)		0.75 (0.61 to 0.91)
Stroke and/or death	321 (19.4)	286 (17.3)		0.89 (0.77 to 1.03)
All-cause death	188 (11.4)	185 (11.2)		0.99 (0.81 to 1.19)
MRD vs ASA				
Stroke	211 (12.8)		206 (12.5)	1.02 (0.85 to 1.22)
Stroke and/or death	321 (19.4)		330 (20)	0.97 (0.85 to 1.11)
All-cause death	188 (11.4)		182 (11.37)	1.03 (0.85 to 1.25)
Secondary				
MRD + ASA v ASA				
TIA		172 (10.4)	206 (12.5)	0.83 (0.69 to 1.01)
Stroke/TIA		18.1	22.6	0.80 (0.70 to 0.92)
MI		35 (2.1)	39 (2.4)	0.90 (0.57 to 1.41)
Other vascular event		21 (1.3)	38 (2.3)	0.55 (0.33 to 0.94)
Ischaemic events[a]		206 (12.5)	307 (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)
MRD + ASA v MRD				
TIA	215 (13.0)	172 (10.4)		0.80 (0.66 to 0.97)
Stroke/TIA	(23.1)	(18.1)		0.78 (0.69 to 0.90)
MI	48 (2.9)	35 (2.1)		0.73 (0.48 to 1.12)
Other vascular event	35 (2.1)	21 (1.3)		0.60 (0.35 to 1.03)
Ischaemic events[a]	271 (16.4)	206 (12.5)		0.76 (0.64 to 0.90)
Vascular death	(7.6)	(7.1)		0.94 (0.74 to 1.20)
MRD vs ASA				
TIA	215 (3.0)		206 (12.5)	1.04 (0.87 to 1.24)
Stroke/TIA	(23.1)		(22.6)	1.02 (0.90 to 1.16)
MI	48 (2.9)		39 (2.4)	1.23 (0.81 to 1.86)
Other vascular event	35 (2.1)		38 (2.3)	0.92 (0.58 to 1.45)
Ischaemic events[a]	271 (16.4)		266 (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)

a Stroke and/or MI, and/or sudden death of thrombotic origin.
All survival data are at 2 years.

TABLE 10 Key outcomes of ESPRIT[56]

Outcomes	Total events		HR (95% CI)
	MRD + ASA, *n* (%)	ASA, *n* (%)	
Primary			
First occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication	173 (12.69)	216 (15.20)	0.80 (0.66 to 0.98)
Secondary			
Death from all causes	93 (6.83)	107 (7.78)	0.88 (0.67 to 1.17)
Death from all vascular causes	44 (3.23)	60 (4.36)	0.75 (0.51 to 1.10)
Death from all vascular causes and non-fatal stroke	132 (9.69)	171 (12.42)	0.78 (0.62 to 0.97)
Major bleeding complications	35 (2.57)	53 (0.39)	0.67 (0.44 to 1.03)
Non-fatal extracranial	21 (1.54)	32 (2.32)	NR
Fatal extracranial	2 (0.15)	0	NR
Non-fatal intracranial	9 (0.66)	17 (12.21)	NR
Fatal intracranial	3 (0.22)	4 (0.29)	NR
Minor bleeding complications	171 (12.55)	168 (12.21)	NR
All major ischaemic events (non-haemorrhagic death from vascular causes, non-fatal IS or non-fatal MI)	140 (10.27)	174 (12.65)	0.81 (0.65 to 1.01)
All vascular events (death from vascular causes, non-fatal stroke or non-fatal MI)	149 (10.93)	192 (13.95)	0.78 (0.63 to 0.97)
First IS	96 (7.0)	116 (8.43)	0.84 (0.54 to 1.10)
First cardiac event	43 (3.15)	60 (4.36)	0.73 (0.49 to 1.08)

IS, ischaemic stroke; NR, not reported.

For the secondary outcome of death from all vascular causes and non-fatal stroke, the rate of event occurrence was also statistically significantly lower in the MRD + ASA arm than in the ASA arm (HR 0.78; 95% CI 0.62 to 0.97). This was also true for the outcome of all vascular events (HR 0.78; 95% CI 0.63 to 0.97).

There were no statistically significant differences reported for any other outcome.

PRoFESS[57]

The key outcomes from the PRoFESS[57] trial are described in *Table 11*. Although the rate of recurrent stroke of any type was very similar in the MRD + ASA and clopidogrel groups [9% vs 8.8%, HR 1.01 (95% CI 0.92 to 1.11)], the null hypothesis (that MRD + ASA is inferior to clopidogrel) could not be rejected as the predefined non-inferiority margin was –1.075.

For the secondary outcomes, the only statistically significant difference was in favour of MRD + ASA for the outcome of new or worsening congestive heart failure [HR 0.78 (95% CI 0.62 to 0.96)].

Adverse events

Adverse events reported for each trial are described in *Table 12*. In ESPS-2[30] and CAPRIE,[26] bleeding events in the trials were reported as secondary outcomes rather than as adverse events. The reporting of adverse events differed between trials. In CAPRIE,[26] adverse events were

TABLE 11 Key outcomes of PRoFESS[57]

Outcomes	Total events		HR for ASA + MRD (95% CI)
	MRD + ASA (%)	CLOP (%)	
Primary			
Recurrent stroke of any type	916 (9)	898 (8.8)	1.01 (0.92 to 1.11)
Secondary/tertiary			
Composite of vascular events (stroke, MI or death from vascular causes)	1333 (13.1)	1333 (13.1)	0.99 (0.92 to 1.07)
MI	178 (1.7)	197 (1.9)	0.90 (0.73 to 1.10)
Death from vascular causes	435 (4.3)	459 (4.5)	0.94 (0.82 to 1.07)
Death from any cause	739 (7.3)	756 (7.4)	0.97 (0.87 to 1.07)
New or worsening CHF	144 (1.4)	182 (1.8)	0.78 (0.62 to 0.96)
Other vascular event	533 (5.1)	517 (5.1)	1.03 (0.91 to 1.16)
First IS	789 (7.7)	807 (7.9)	0.97 (0.88 to 1.07)
First recurrence of stroke or major haemorrhagic event	1194 (11.7)	1156 (11.4)	1.03 (0.95 to 1.11)
Major haemorrhagic event	419 (4.1)	365 (3.6)	1.15 (1.00 to 1.32)
Major haemorrhagic event: life-threatening	128 (1.3)	116 (1.1)	
Major haemorrhagic event: non-life-threatening	291 (2.9)	249 (2.5)	
Haemorrhagic event (minor or major)	535 (5.3)	494 (4.9)	1.08 (0.96 to 1.22)
Intracranial haemorrhage	147 (1.4)	103 (1)	1.42 (1.11 to 1.83)
Intracerebral haemorrhage (haemorrhagic stroke)	90 (0.9)	55 (0.5)	
Haemorrhagic stroke – fatal	28 (0.3)	29 (0.3)	
Haemorrhagic stroke – non-fatal	62 (0.6)	26 (0.3)	
Intraocular haemorrhage	22 (0.2)	22 (0.2)	
Non-stroke intracranial haemorrhage	35 (0.3)	26 (0.3)	
Thrombotic thrombocytopenic or neutropenia	7 (0.1)	8 (0.1)	0.89 (0.32 to 2.44)

CHF, congestive heart failure; CLOP, clopidogrel; IS, ischaemic stroke.

recorded as 'patients ever reporting,' in ESPS-2[30] as 'number of patients reporting at least one adverse event during the study'. In PRoFESS,[57] only selected adverse events leading to treatment discontinuation are presented in the published paper. Adverse events other than those related to bleeding were not reported for ESPRIT[56] (see *Table 10*).

In CAPRIE,[26] patients in the clopidogrel arm were reported as experiencing significantly higher rates of rash and diarrhoea than in the ASA arm. In the ASA arm, patients reported significantly more incidences of indigestion/nausea/vomiting and abnormal liver function. The number of patients experiencing gastrointestinal haemorrhage was greater in the ASA arm than in the clopidogrel arm, a result reported to be statistically significant. The rates of trial discontinuation because of adverse events were similar in both arms of the trial.

In ESPS-2,[30] there was a significant difference between each arm in the occurrence of headaches. These appear to be greater in the arms where MRD was a feature of the treatment regimen. It is recorded in the published paper[30] that bleeding episodes were significantly more frequent and more often moderate or severe/fatal in treatment arms that included ASA. Any site bleeding was reported by 8.2% of patients in the ASA arm and by 8.7% in the MRD + ASA arm, but by 4.7% and 4.5% in the MRD alone and placebo groups, respectively. The rates of trial discontinuation because of adverse events differed significantly, with higher rates reported in the two MRD arms than in the ASA or placebo arms.

TABLE 12 Adverse events reported for each trial

Trial name	Adverse event	CLOP, *n* (%)	MRD + ASA, *n* (%)	ASA, *n* (%)	MRD, *n* (%)	Placebo, *n* (%)
[a]CAPRIE[26]	Rash[b]	578 (6.02)		442 (4.61)		
	Diarrhoea[b]	4 28 (4.46)		322 (3.36)		
	Indigestion/nausea/ vomiting[b]	1441 (15.01)		1686 (17.59)		
	Abnormal liver function[b]	285 (2.97)		302 (3.15)		
	Any bleeding disorder	890 (9.27)		890 (9.28)		
	Intracranial haemorrhage	34 (0.35)		47 (0.49)		
	Gastrointestinal haemorrhage[b]	191(1.99)		255 (2.66)		
	Discontinuation due to AEs	(11.94)		(11.92)		
[c]ESPS-2[30]	Any AEs[b]		1056 (64)	990 (60)	1034 (62.57)	933 (56.58)
	GI event[b]		541 (32.80)	502 (30.44)	505 (30.53)	465 (28.20)
	Vomiting[b]		133 (8.06)	93 (5.64)	119 (7.19)	109 (6.61)
	Diarrhoea[b]		199 (12.06)	109 (6.6)	254 (15.36)	154 (9.33)
	Headache[b]		630 (38.18)	546 (33.11)	615 (37.18)	534 (32.38)
	Bleeding any site[b]		144 (8.73)	135 (8.19)	77 (4.66)	74 (4.49)
	Nausea		254 (15.39)	204 (12.37)	245 (14.81)	226 (13.71)
	Dyspepsia		290 (17.58)	283 (17.69)	274 (16.57)	266 (16.13)
	Gastric pain		274 (16.60)	242 (14.67)	240 (14.51)	219 (13.28)
	Mild bleeding		84 (5.09)	82 (5.01)	53 (3.20)	52 (3.15)
	Moderate bleeding		33 (2.0)	33 (2.0)	18 (1.09)	15 (0.91)
	Severe or fatal bleeding		27 (1.64)	20 (1.21)	6 (0.36)	7 (0.42)
	Dizziness		486 (29.47)	481 (29.16)	498 (30.10)	509 (30.88)
	Discontinuation due to AEs[b]		479 (29)	366 (22)	485 (29)	360 (21)
[d]PRoFESS[57]	Headache	87 (0.9)	593 (5.9)			
	Vomiting	37 (0.4)	158 (1.6)			
	Nausea	58 (0.6)	155 (1.5)			
	Dizziness	52 (0.5)	134 (1.3)			
	Atrial fibrillation	143 (1.2)	122 (1.4)			
	Diarrhoea	42 (0.4)	102 (1.0)			
	Hypotension	35 (0.3)	54 (0.5)			
	Thrombotic thrombocytopenia or neutropenia	8 (0.1)	7 (0.1)			
	Patients with AEs leading to discontinuation[b]	1069 (10.6)	1650 (16.64)			

AEs, adverse events; CLOP, clopidogrel; GI, gastrointestinal.
a AEs categorised as patients ever reporting.
b Reported as significant.
c AEs were number of patients reporting at least one AE during study.
d Only selected AEs leading to treatment discontinuation are presented.

Of the other reported adverse events in ESPS-2,[30] gastrointestinal events, vomiting, diarrhoea and headache were reported as being significantly different between treatment groups, but where the differences lie are unclear.[30]

In PRoFESS,[57] the rates of trial discontinuation were statistically significantly different between trial arms in favour of clopidogrel. Notably, there was an increased risk of a major haemorrhagic event for MRD + ASA compared with clopidogrel (HR 1.15; 95% CI 1.00 to 1.32) as well as intracranial haemorrhage (HR 1.42; 95% CI 1.11 to 1.83). Headache appears to be reported by many more patients in the MRD + ASA arm – an unsurprising outcome, as MRD acts as a vasodilator.

Assessment Group analysis of time to first event rates

An important consideration in the analysis of trials in this area is the length of patient follow-up. It was noted earlier that the mean length of follow-up for the included trials ranged between 1.91 and 3.5 years (see *Table 6*). The Assessment Group, using data from CAPRIE,[26] assessed the event rates over time for the outcome of ischaemic stroke in the ischaemic stroke-only population of the trial and the outcome of MI in the MI-only population. The assessment indicates that patients appear to be at greatest risk of a recurrent event in the first 6–12 months; thereafter, the risk decreases markedly. Therefore, it is important to explore how event rates change over time.

Methods for indirect synthesis

Justification for indirect analysis

The reported outcomes and their definitions varied significantly across the four trials (*Table 13*). For instance, in the CAPRIE[26] trial, data on first ischaemic stroke are available for the ischaemic stroke population, but other outcomes are available for only the total population (i.e. ischaemic stroke, MI and peripheral arterial disease populations as a single group). The single common qualifying event in the four included trials[26,30,56,57] was ischaemic stroke/TIA. Where appropriate, evidence synthesis, using a mixed-treatment comparisons approach, was undertaken using data from the ischaemic stroke/TIA overall populations[26,30,56,57] or subpopulation.[26] The Assessment Group notes that the patient populations in the mixed-treatment comparisons are based on those described in the original trial publications and may therefore include patients with multivascular disease.

Indirect comparison of common clinical outcomes (where available in at least two trials) was undertaken to estimate the relative efficacy between interventions in the ischaemic stroke/TIA populations.

Mixed-treatment comparison

The relative treatment effects of clopidogrel, MRD + ASA, MRD alone and ASA ideally would have been derived from a single, direct, head-to-head RCT. However, such a trial does not exist. Instead, we have four trials[26,30,56,57] assessing the treatment effects of a subset of the interventions of interest. A mixed-treatment comparison is an alternative approach that is used to estimate relative treatment effects when the objective of the analysis is to compare more than two interventions. A mixed-treatment comparison is an explicit analytical framework and has been presented as an extension of standard meta-analysis by including multiple pairwise comparisons across a range of different interventions.[61] The framework can then be used to derive a relative treatment effect of competing interventions in the absence of direct evidence.

The Assessment Group used a Bayesian approach to mixed-treatment comparison to estimate the relative effectiveness measures for the interventions under comparison, ranking and making probability statements about the most effective intervention in a decision context. A fixed-effects model was chosen for all analyses because random-effect models failed to reach convergence. One possible reason for this failure could be the small number of trials (two to three trials in each analysis) and, hence, overparameterisation.

TABLE 13 Outcomes reported by included RCTs for the ischaemic stroke/TIA population group

All outcomes reported (primary, secondary or tertiary)	CAPRIE[26]	ESPS-2[30]	ESPRIT[56]	PRoFESS[57]	No. of studies
First IS event (non-fatal or fatal)	X		X	X	3
Stroke (recurrent any type)		X		X	2
MI	X	X		X	3
Death from vascular cause	X		X	X	3
Death from all causes		X	X	X	3
Bleeding complications (major)			X	X	2
Bleeding complications (any)		X	X	X	3
First cardiac event (fatal and non-fatal MI, sudden death, cardiac death)			X		1
First event (IS, MI, or death from vascular cause)	X				1
First event [any stroke (includes primary intracranial haemorrhage), MI, fatal bleeding or death from all causes]	X				1
First event (IS, MI, amputation, death from all vascular causes)	X				1
First event (non-fatal stroke, death from all vascular causes)			X		1
First event (non-fatal stroke, non-fatal MI or major bleeding complication, death from all vascular causes)			X		1
First event (non-fatal stroke, non-fatal MI or death from all vascular causes)			X		1
First event (stroke (non-fatal or fatal), MI (non-fatal or fatal) or death from all vascular causes)				X	1
First ischaemic event (stroke and/or MI, and/or sudden death of thrombotic origin)		X			1
First major ischaemic events (non-fatal IS, non-fatal MI or non-haemorrhagic death from vascular causes)			X		1
Other vascular events (pulmonary embolism, retinal vascular accidents, deep-vein thrombosis, peripheral arterial occlusion or TIA)				X	1
Other vascular events (pulmonary embolism, deep-venous thrombosis, peripheral arterial occlusion, venous retinal thrombosis or combination of these events)		X			1
Stroke and/or death from all causes		X			1
TIA		X			1

IS, ischaemic stroke.

A non-informative (flat prior) normal distribution was used for the log odds ratio (OR) of each relative comparison; thus, the observed results are completely influenced by the data and not the choice of the priors. We estimated the relative effectiveness for each comparison using Markov chain Monte Carlo for each analysis in WinBUGS version 1.4 statistical software (Medical Research Council Biostatistics Unit, Cambridge, UK).[62] Two chains were used to ensure that model convergence was met after 100,000 iterations with a burn-in of 10,000 or more. Formal convergence of the models was assessed using trace plots and the Gelman–Rubin approach.[63] Results are presented with summary statistics for RR and OR along with 95% CIs. Pairwise ORs were estimated and converted to RR using a standard approach. This

was implemented in the WinBUGS software by applying event rates across included trials from the reference comparator as the baseline probability (prob_baseline). Therefore, the RR = OR/[(1 – prob_baseline) + (prob_baseline × OR)]. The WinBUGS codes used in the analysis were adapted from the Multi-parameter Evidence Synthesis Research Group (MPES) and are presented in *Appendix 7*.

Results of mixed-treatment comparisons for ischaemic stroke/transient ischaemic attack population

All of the results presented in this section are related to ischaemic stroke/TIA populations only.

In this section, for clarity, the data analyses are presented in tables. For ease of reference, significant findings are in bold font within the tables. The networks relevant to each comparison are presented in *Appendix 7*.

It should be noted that the selection of the outcomes included in the mixed-treatment comparison are driven by the available clinical data. In most analyses, the number of studies is small (two to three trials) and, although a large number of patients were included, the data used from the CAPRIE[26] trial were based on a subgroup of patients with ischaemic stroke. The findings of this mixed-treatment comparison analysis should therefore be interpreted with caution.

Stroke

Data on recurrent stroke were available from four trials.[26,30,56,57] However, owing to differences in definition of 'recurrent stroke', analysis was performed separately for the 'first ischaemic stroke' and 'any recurrent stroke'. The CAPRIE[26] trial did not report data on 'any recurrent stroke' and the ESPS-2[30] trial did not present data on the 'first ischaemic stroke'.

First ischaemic stroke

Three trials (CAPRIE,[26] ESPRIT[56] and PRoFESS[57]) provided direct head-to-head data on the 'first ischaemic stroke'. Therefore, it was possible to combine these trials through the mixed-treatment comparison approach to calculate the relative efficacy of clopidogrel versus ASA, MRD + ASA versus ASA and MRD + ASA versus clopidogrel.

Table 14 shows head-to-head trial data and the relative estimates calculated using the mixed-treatment comparison analysis. The results show no major differences between the mixed-treatment comparison results and head-to-head estimates from the included trials. Results from the mixed-treatment comparison showed that no single estimated RRs were found to demonstrate a statistically significant difference between any pair of interventions. The observed RR for clopidogrel and MRD + ASA appeared to reflect a lower risk of the 'first ischaemic stroke' compared with ASA. A RR of 0.968 was observed for MRD + ASA compared with clopidogrel. However, differences were not significant. There is no evidence to suggest that any intervention is superior to another in terms of prevention of 'first ischaemic stroke'.

Any recurrent stroke

Two trials (ESPS-2[30] and PRoFESS[57]) provided direct head-to-head data on recurrent stroke outcome. Therefore, it was possible to combine these trials through the mixed-treatment comparison approach to calculate the relative efficacy of MRD + ASA versus ASA, MRD alone versus ASA, MRD + ASA versus clopidogrel, and MRD alone versus MRD + ASA. We were also able to estimate the indirect estimates from the mixed-treatment comparison for clopidogrel versus ASA and MRD versus clopidogrel. *Table 15* presents head-to-head trial data and results from the mixed-treatment comparison analysis. No major differences in the mixed-treatment

TABLE 14 Relative risk for first ischaemic stroke in ischaemic stroke/TIA populations (MTC)

Trial	ASA		CLOP	MRD + ASA
CAPRIE[26]	226/2370		214/2370	
ESPRIT[56]	116/1376		–	96/1363
PRoFESS[57]			807/10,151	789/10,181
	Direct evidence from head-to-head trials		Results from the mixed-treatment comparison analysis	
Comparison	Trial	RR[a] (95% CI)	RR[a] (95% CI)	OR (95% CI)
CLOP vs ASA	CAPRIE[26]	0.947 (0.79 to 1.13)	0.922 (0.79 to 1.06)	0.915 (0.77 to 1.07)
MRD + ASA vs ASA	ESPRIT[56]	0.835 (0.64 to 1.08)	0.891 (0.75 to 1.04)	0.883 (0.74 to 1.04)
MRD + ASA vs CLOP	PRoFESS[57]	0.975 (0.88 to 1.07)	0.968 (0.88 to 1.05)	0.966 (0.87 to 1.06)

CLOP, clopidogrel.
a RR < 1 is better than comparator; RR > 1 is worse than comparator.

TABLE 15 Relative risk for any recurrent stroke in ischaemic stroke/TIA populations (MTC)

Trial	ASA	CLOP	MRD + ASA	MRD
ESPS-2[30]	206/1649		157/1650	211/1654
PRoFESS[57]		898/10,151	916/10,181	
	Direct evidence from head-to-head trials		Results from the mixed-treatment comparison analysis	
Comparison	Trial	RR[a] (95% CI)	RR[a] (95% CI)	OR (95% CI)
CLOP vs ASA	None	N/A	**0.752 (0.60 to 0.92)**	**0.727 (0.56 to 0.91)**
MRD + ASA vs ASA	ESPS-2[30]	**0.762 (0.62 to 0.92)**	**0.764 (0.62 to 0.92)**	**0.74 (0.59 to 0.91)**
MRD vs ASA	ESPS-2[30]	1.021 (0.85 to 1.22)	1.025 (0.85 to 1.21)	1.03 (0.83 to 1.25)
MRD + ASA vs CLOP	PRoFESS[57]	1.017 (0.93 to 1.1)	1.018 (0.93 to 1.11)	1.02 (0.92 to 1.12)
MRD vs CLOP	None	N/A	**1.376 (1.10 to 1.68)**	**1.431 (1.11 to 1.80)**
MRD vs MRD + ASA	ESPS-2[30]	**1.341 (1.10 to 1.62)**	**1.349 (1.10 to 1.61)**	**1.403 (1.12 to 1.73)**

CLOP, clopidogrel; N/A, not available.
a RR < 1 is better than comparator; RR > 1 is worse than comparator.

comparison results and head-to-head estimates from the included trials were observed. Results from the mixed-treatment comparison showed that clopidogrel and MRD + ASA were associated with fewer recurrent strokes relative to ASA. An increased risk of recurrent stroke was observed for MRD alone compared with clopidogrel or MRD + ASA. There was no difference between MRD alone compared with ASA or between MRD + ASA and clopidogrel, in terms of reducing recurrent stroke.

Myocardial infarction

Three RCTs (CAPRIE,[26] ESPS-2[30] and PRoFESS[57]) provided direct head-to-head data on MI outcome. It was possible to combine these trials through the mixed-treatment comparison approach to calculate the relative efficacy of clopidogrel versus ASA, MRD + ASA versus ASA,

MRD alone versus ASA, MRD + ASA versus clopidogrel, and MRD alone versus MRD + ASA. We were also able to estimate the indirect estimates for MRD alone versus clopidogrel. *Table 16* shows head-to-head trial data and the estimates calculated using the mixed-treatment comparison analysis. No major differences between the mixed-treatment comparison results and head-to-head estimates from the included trials were observed. Results from the mixed-treatment comparison, which are described in *Table 16,* showed that no single estimated RR was found to demonstrate a statistically significant difference between any pair of interventions in terms of prevention of MI events.

Death from vascular causes

Three trials (CAPRIE,[26] ESPRIT[56] and PRoFESS[57]) provided direct head-to-head data on vascular death. Therefore, it was possible to combine these trials through the mixed-treatment comparison approach to calculate the relative efficacy of clopidogrel versus ASA, MRD + ASA versus ASA, and MRD + ASA versus clopidogrel. *Table 17* shows head-to-head trial data and the estimates calculated using the mixed-treatment comparison analysis. No major differences in the mixed-treatment comparison results and head-to-head estimates from the included trials

TABLE 16 Relative risk for MI in ischaemic stroke/TIA populations (MTC)

Trial	ASA	CLOP	MRD + ASA	MRD
CAPRIE[26]	20/2370	24/2370		
ESPS-2[30]	39/1649		35/1650	48/1654
PRoFESS[57]		197/10,151	178/10,181	
	Direct evidence from head-to-head trials		Results from the mixed-treatment comparison analysis	
Comparison	Trial	RR[a] (95% CI)	RR[a] (95% CI)	OR (95% CI)
CLOP vs ASA	CAPRIE[26]	1.200 (0.66 to 2.16)	1.094 (0.73 to 1.56)	1.098 (0.72 to 1.59)
MRD + ASA vs ASA	ESPS-2[30]	0.897 (0.57 to 1.40)	0.972 (0.65 to 1.38)	0.972 (0.65 to 1.39)
MRD vs ASA	ESPS-2[30]	1.227 (0.80 to 1.86)	1.291 (0.84 to 1.88)	1.302 (0.84 to 1.92)
MRD + ASA vs CLOP	PRoFESS[57]	0.901 (0.73 to 1.10)	0.893 (0.73 to 1.07)	0.892 (0.72 to 1.08)
MRD vs CLOP	None	N/A	1.208 (0.75 to 1.81)	1.215 (0.75 to 1.85)
MRD vs MRD + ASA	ESPS-2[30]	1.368 (0.89 to 2.10)	1.352 (0.88 to 1.98)	1.365 (0.88 to 2.02)

CLOP, clopidogrel; N/A, not available.
a RR < 1 is better than comparator; RR > 1 is worse than comparator.

TABLE 17 Relative risk for vascular death in ischaemic stroke/TIA populations (MTC)

Trial	ASA	CLOP	MRD + ASA
CAPRIE[26]	40/2370	35/2370	
ESPRIT[56]	60/1376		44/1363
PRoFESS[57]		459/10,151	435/10,181
	Direct evidence from head-to-head trials		Results from the mixed-treatment comparison analysis
Comparison	Trial	RR[a] (95% CI)	RR[a] (95% CI)	OR (95% CI)
CLOP vs ASA	CAPRIE[26]	0.875 (0.55 to 1.37)	0.829 (0.60 to 1.11)	0.827 (0.59 to 1.12)
MRD + ASA vs ASA	ESPRIT[56]	0.750 (0.51 to 1.01)	0.782 (0.57 to 1.04)	0.775 (0.56 to 1.04)
MRD + ASA vs CLOP	PRoFESS[57]	0.945 (0.83 to 1.07)	0.942 (0.82 to 1.06)	0.939 (0.82 to 1.06)

CLOP, clopidogrel.
a RR < 1 is better than comparator; RR > 1 is worse than comparator.

were noted. Results from the mixed-treatment comparison showed no significant evidence to demonstrate differences in clopidogrel, MRD + ASA and ASA for vascular death outcome. There is no evidence to suggest that any intervention is superior to another in terms of prevention of vascular death.

Death from all causes

Three RCTs (ESPS-2,[30] ESPRIT[56] and PRoFESS[57]) provided direct head-to-head data on all-cause death. It was possible to combine these trials through the mixed-treatment comparison approach to calculate the relative efficacy of MRD + ASA versus ASA, MRD alone versus ASA, MRD + ASA versus clopidogrel, and MRD alone versus MRD + ASA. We also estimated the indirect estimates for clopidogrel vs ASA and MRD alone versus clopidogrel, as no head-to-head data were available. *Table 18* shows head-to-head trial data and the estimates calculated using the mixed-treatment comparison analysis. No major variation in the mixed-treatment comparison results and head-to-head estimates from the included trials were observed. Results from the mixed-treatment comparison showed that there was no evidence to demonstrate significant differences between clopidogrel, MRD + ASA, MRD and ASA for all-cause death.

Bleeding

Data on bleeding were available from three RCTs (ESPS-2,[30] ESPRIT[56] and PRoFESS[57]). The CAPRIE[26] trial did not present bleeding data for patients in this subpopulation. As there was variation in bleeding reporting across trials, analysis was only possible for 'any bleeding' and 'major bleeding', as these were the common bleeding definitions used across the trials.

Any bleeding

Three RCTs (ESPS-2,[30] ESPRIT[56] and PRoFESS[57]) provided direct head-to-head data on any bleeding. It was possible to combine these trials through the mixed-treatment comparison approach to calculate the relative efficacy of MRD + ASA versus ASA, MRD alone versus ASA, MRD + ASA versus clopidogrel, and MRD alone versus MRD + ASA. We also calculated the indirect estimates for clopidogrel versus ASA and MRD alone versus clopidogrel, as no head-to-head data were available. The category of 'any bleeding' includes both minor and major

TABLE 18 Relative risk of death from all causes in ischaemic stroke/TIA populations (MTC)

Trial	ASA	CLOP	MRD + ASA	MRD
ESPS-2[30]	182/1649		185/1650	188/1654
ESPRIT[56]	107/1376		93/1363	
PRoFESS[57]		756/10151	739/10181	
	Direct evidence from head-to-head trials		Results from the mixed-treatment comparison analysis	
Comparison	Trial	RR[a] (95% CI)	RR[a] (95% CI)	OR (95% CI)
CLOP vs ASA	None	N/A	0.992 (0.82 to 1.18)	0.992 (0.80 to 1.20)
MRD + ASA vs ASA	ESPS-2,[30] ESPRIT[56]	ESPS-2:[30] 1.016 (0.83 to 1.23)	0.967 (0.82 to 1.12)	0.964 (0.80 to 1.14)
		ESPRIT:[56] 0.877 (0.67 to 1.14)		
MRD vs ASA	ESPS-2[30]	1.030 (0.85 to 1.24)	1.007 (0.83 to 1.20)	1.010 (0.81 to 1.23)
MRD + ASA vs CLOP	PRoFESS[57]	0.975 (0.88 to 1.07)	0.976 (0.88 to 1.07)	0.974 (0.87 to 1.08)
MRD vs CLOP	None	N/A	1.021 (0.81 to 1.25)	1.024 (0.80 to 1.28)
MRD vs MRD + ASA	ESPS-2[30]	1.014 (0.83 to 1.22)	1.044 (0.86 to 1.24)	1.052 (0.85 to 1.28)

CLOP, clopidogrel; N/A, not available.
a RR < 1 is better than comparator; RR > 1 is worse than comparator.

bleeding. Minor events included haematuria, haematemesis, epistaxis, intraocular bleeding, purpura, and gynaecological, internal and intracranial bleeding. Major bleeding included severe or fatal bleeding, life-threatening bleeding, intracranial bleeding, major haemorrhage and major gastrointestinal tract haemorrhage. *Table 19* shows head-to-head trial data and the estimates calculated using the mixed-treatment comparison analysis. There were no major differences in the mixed-treatment comparison results and head-to-head estimates from the included trials. Results from the mixed-treatment comparison showed that MRD alone was associated with significantly fewer bleeding events than all comparators; the MRD vs clopidogrel estimates are based on indirect comparisons and are not supported by head-to-head trial data. There was no evidence to suggest any differences between 'clopidogrel versus ASA' and 'MRD + ASA versus ASA' for any bleeding.

Major bleeding

Two RCTs (ESPRIT[56] and PRoFESS[57]) provided direct head-to-head data on major bleeding. It was possible to combine these trials through the mixed-treatment comparison approach to calculate the relative efficacy of MRD + ASA versus ASA and MRD + ASA versus clopidogrel. We also estimated the indirect estimates for clopidogrel versus ASA as no head-to-head data were available. The category of 'major bleeding' included severe or fatal bleeding, life-threatening bleeding, intracranial bleeding, major haemorrhage and major gastrointestinal tract haemorrhage. *Table 20* shows head-to-head trial data and the estimates calculated using the mixed-treatment comparison analysis. There were no major variations in the mixed-treatment comparison results and head-to-head estimates from the included trials. Results from the mixed-treatment comparison showed that clopidogrel was associated with significantly fewer bleeding events than ASA; these estimates are based on indirect comparisons and are not supported by head-to-head trial data. No statistically significant differences among MRD + ASA, clopidogrel and ASA in major bleeding events were observed.

TABLE 19 Relative risk for any bleeding in ischaemic stroke/TIA populations (MTC)

Trial	ASA	CLOP	MRD + ASA	MRD
ESPS-2[30]	135/1649		144/1650	77/1654
ESPRIT[56]	221/1376		206/1363	
PRoFESS[57]		494/10,151	535/10,181	
	Direct evidence from head-to-head trials		**Results from the mixed-treatment comparison analysis**	
Comparison	**Trial**	**RR[a] (95% CI)**	**RR[a] (95% CI)**	**OR (95% CI)**
CLOP vs ASA	None	N/A	0.921 (0.75 to 1.10)	0.916 (0.74 to 1.11)
MRD + ASA vs ASA	ESPS-2[30]	1.066 (0.85 to 1.33)		
	ESPRIT[56]	0.941 (0.79 to 1.12)	0.991 (0.85 to 1.14)	0.991 (0.84 to 1.15)
MRD vs ASA	ESPS-2[30]	**0.569 (0.43 to 0.74)**	**0.549 (0.42 to 0.70)**	**0.529 (0.39 to 0.68)**
MRD + ASA vs CLOP	PRoFESS[57]	1.08 (0.95 to 1.21)	1.082 (0.96 to 1.21)	1.087 (0.95 to 1.23)
MRD vs CLOP	None	N/A	**0.593 (0.44 to 0.78)**	**0.582 (0.42 to 0.77)**
MRD vs MRD + ASA	ESPS-2[30]	**0.533 (0.40 to 0.69)**	**0.557 (0.43 to 0.71)**	**0.535 (0.40 to 0.69)**

CLOP, clopidogrel; N/A, not available.
a RR < 1 is better than comparator; RR > 1 is worse than comparator.

TABLE 20 Relative risk for major bleeding in ischaemic stroke/TIA populations (MTC)

Trial	ASA	CLOP	MRD + ASA	
ESPRIT[56]	53/1376		35/1363	
PRoFESS[57]		365/10,151	419/10,181	
	Direct evidence from head-to-head trials		Results from the mixed-treatment comparison analysis	
Comparison	Trial	RR[a] (95% CI)	RR[a] (95% CI)	OR (95% CI)
CLOP vs ASA	None	N/A	**0.596 (0.36 to 0.89)**	**0.587 (0.35 to 0.89)**
MRD + ASA vs ASA	ESPRIT[56]	0.667 (0.43 to 1.01)	0.682 (0.43 to 1.01)	0.674 (0.42 to 1.00)
MRD + ASA vs CLOP	PRoFESS[57]	1.145 (0.99 to 1.31)	1.147 (0.99 to 1.31)	1.154 (0.99 to 1.32)

CLOP, clopidogrel; N/A, not available.
a RR < 1 is better than comparator; RR > 1 is worse than comparator.

Results of the mixed-treatment comparison evidence for myocardial infarction and peripheral arterial disease populations

Owing to the lack of available data, we were unable to carry out indirect analyses for the MI and peripheral arterial disease patient populations. Only CAPRIE[26] included patients with MI and peripheral arterial disease; data on these individual patients groups were not available from the other included studies.[30,56,57]

Summary of the evidence from the mixed-treatment comparison

The mixed-treatment comparison analysis was performed in patients categorised as having an ischaemic stroke/TIA as a qualifying event. The relative effectiveness of clopidogrel, MRD + ASA, MRD alone and ASA was evaluated, based on evidence from four main RCTs[26,30,56,57] that reported seven key clinical outcomes. The four trials included in the mixed-treatment comparison analysis were CAPRIE[26] (clopidogrel vs ASA), ESPS-2[30] (ASA vs MRD + ASA vs MRD alone vs placebo), ESPRIT[56] (MRD + ASA vs ASA) and PRoFESS[57] (MRD + ASA vs clopidogrel). The clinically important outcomes that were included in the mixed-treatment comparison exercise were stroke ('first ischaemic stroke' and 'any recurrent stroke'), MI, vascular death, death from all causes and bleeding ('any bleeding' and 'major bleeding'). The selection of these outcomes was based on the availability of data from two or more of the four RCTs. One study (ESPS-2[30]) contained a placebo arm and was included in the analysis, but placebo results are not presented here. The reference comparator for all the analyses was ASA. The results from the mixed-treatment comparison showed that no single estimated RR was found to demonstrate a statistically important difference between any pair of interventions except for the outcomes of any recurrent stroke, 'any ' and 'major' bleeding. The results further showed that MRD alone was statistically significantly associated with increased risk of any recurrent stroke compared with clopidogrel and MRD + ASA. However, it is worth noting that the findings from clopidogrel versus ASA and MRD alone versus clopidogrel were based on the indirect evidence and were not supported by any head-to-head data.

As detailed at the beginning of the section, caveats apply to the findings of our analysis owing to the limited outcomes that were available for selection, the small number of trials and the use of data from subgroups from one trial.[26]

The MATCH[58] and CHARISMA[59] trials were not included in the Assessment Group's literature review, as these trials included comparators that were not specified in the scope for the appraisal; the combination of clopidogrel + ASA is not licensed in the patient population under evaluation. After much discussion, the Assessment Group decided to also exclude these trials from the indirect comparison exercise undertaken. However, the Assessment Group notes that excluding these trials does not change the ranking of the interventions; their inclusion only strengthens confidence in the results generated. The Assessment Group has checked the methods used by the manufacturer and commends the values from the manufacturer's indirect comparison.

Patients with multivascular disease

The decision problem matrix (see *Table 4*) described in the final scope[16] issued by NICE specified that, if the evidence allows, the effectiveness of clopidogrel in people with multivascular disease who are considered at high risk of recurrent occlusive vascular events should be considered. The Assessment Group notes that in the literature there is a variety of definitions that characterise this population; this is an issue, as the number of patients included in any multivascular disease analysis will be affected by how the group is defined. The simplest and broadest definition of multivascular disease described in the published literature is 'patients with disease in more than one vascular bed'. For completeness, the definitions identified by the Assessment Group from the literature are described in *Table 21*. Owing to the apparent lack of consensus, the Assessment Group has derived a definition of multivascular disease for the purposes of this document that appears to be consistent with the simplest and broadest definition described in the published literature.

Although the original CAPRIE[26] publication did not include a formal definition of multivascular disease, the authors did present the results of a subgroup analysis of patients with peripheral arterial disease/stroke and previous MI. The findings support the view that patients with multivascular disease are at a greater risk of recurrent occlusive vascular events than patients with disease in a single vascular bed (*Table 22*).

Post hoc analysis from the CAPRIE trial

One new publication[64] using data from the CAPRIE[26] trial was identified from the literature review. In this publication, patients with pre-existing symptomatic atherosclerotic disease from

TABLE 21 Definitions of multivascular disease

MVD definition source	Definition of MVD
Bhatt 2006[22] (REACH registry)	Polyvascular disease was defined as coexistent symptomatic (clinically recognised) arterial disease in two or three territories (coronary, cerebral and/or peripheral) within each patient
CAPRIE[26]	No formal definition of MVD was reported (not unusual at time of publication); however, subgroup analysis of 2144 patients with PAD/stroke and previous MI was presented
Ringleb 2004[64]	Patients with MVD are those with pre-existing symptomatic atherosclerotic disease from the overall CAPRIE[26] population defined as having a self-reported history of IS and/or MI before the qualifying event for enrolment into the CAPRIE[26] trial (Note: definition does not include PAD or TIA)
Sanofi–aventis/Bristol–Myers Squibb submission[52]	Patients with pre-existing symptomatic atherosclerotic disease (IS or MI) in addition to qualifying event (see MS, p. 66) Patients with disease in more than one vascular bed (see MS, p. 2)
Assessment Group's reclassification of populations in CAPRIE[26]	Patients with MVD defined as those who had experienced at least two of the following: CAD/MI, IS/TIA or PAD

CAD, coronary artery disease; IS, ischaemic stroke; MS, manufacturer's submission; MVD, multivascular disease; PAD, peripheral arterial disease.

the overall CAPRIE[26] population were described in a subgroup analysis. As noted in *Table 21*, this was defined as a self-reported history of ischaemic stroke and/or MI before the qualifying event for enrolment in CAPRIE.[26] The data describing such events had been routinely collected in the case record forms. However, no standard procedures to validate such a pre-existing event were used.[64] The Assessment Group notes that this subgroup of patients does not appear to include patients with peripheral arterial disease or TIA. The key outcomes of the analysis are described in *Table 23*. Compared with the overall population ($n = 19,185$), the subgroup of patients with pre-existing symptomatic atherosclerotic disease, which included ischaemic stroke or MI ($n = 4496$) was found to have elevated event rates for the primary composite end point of ischaemic stroke, MI or vascular death. The results favour clopidogrel over ASA at 1 year and 3 years on both the composite end points.

The authors[64] do not discuss the clinical effectiveness of clopidogrel on individual subpopulations (e.g. ischaemic stroke, MI or peripheral arterial disease) after removal of patients with multivascular disease from the analysis. However, they do comment that the 3-year composite event rate for the subpopulation without any pre-existing atherosclerotic disease is lower than that of the multivascular disease group.

Assessment Group reclassification of patients from CAPRIE

Using the Assessment Group's definition of multivascular disease (two of the following: coronary artery disease/MI, ischaemic stroke/TIA or peripheral arterial disease) and additional data provided by the manufacturer, the Assessment Group reclassified patients from CAPRIE[26] into those with atherosclerotic disease in a single vascular bed (described as 'MI only', 'ischaemic stroke only' or 'peripheral arterial disease only') and those who had disease in more than one vascular bed (e.g. patients who had experienced coronary artery disease/MI and an ischaemic stroke/TIA or who had peripheral arterial disease and experienced a MI). The Assessment

TABLE 22 Risk of primary outcome event in patients with peripheral arterial disease/stroke and previous MI (CAPRIE[26])

	IS, MI or vascular death		
Patient and treatment subgroup	Events	Rate/year (%)	RRR (95% CI)
PAD/stroke with previous MI (n = 2144)			
CLOP (nyrs 1963)	164	8.35	22.7% (4.9 to 37.2)
ASA (nyrs 1825)	196	10.74	

CLOP, clopidogrel; IS, ischaemic stroke; nyrs, number of patient-years at risk; PAD, peripheral arterial disease.

TABLE 23 Outcomes from CAPRIE[26] multivascular disease subgroup

		Event rate		
Outcomes	Follow-up	CLOP (%) ($n = 2249$)	ASA (%) ($n = 2247$)	RRR[a] (95% CI)
First occurrence of IS, MI or vascular death	1 year	8.8	10.2	14.9 (0.3 to 27.3); $p = 0.045$
	3 years	20.4	23.8	
First occurrence of IS, rehospitalisation for ischaemia	1 year	16.1	18.5	12.0 (0.6 to 22.1); $p = 0.039$
	3 years	32.7	36.6	

CLOP, clopidogrel; IS, ischaemic stroke.

a RRR is not specifically related to a particular time point. It is an overall measure of how much the risk is reduced in the experimental group (CLOP) compared with the control group (ASA). This estimate was obtained from the Cox proportional hazards model, which assumes that the HR is constant over time.

Group then compared the risk of two key outcomes (ischaemic stroke and MI) using the original CAPRIE[26] patient populations and the Assessment Group's reclassifications. The results are described below [see *Table 24* (ischaemic stroke) and *Table 25* (MI)].

From *Table 24* it can be seen that when the patients are reclassified, the risk of a future ischaemic stroke for individual patient groups is different in both treatment arms. The risk for ischaemic stroke-only patients remains stable. The risk for the multivascular disease subgroup is much greater than that of the MI and peripheral arterial disease patients.

From *Table 25* it can be seen that when the patients are reclassified, the risk of a future MI for individual patient groups in both treatment arms is different. The risk for MI-only patients remains stable. The risk for the multivascular disease subgroup is greater than that of the ischaemic stroke and peripheral arterial disease patients.

These findings indicate that patients with multivascular disease (as defined by the Assessment Group) constitute an important clinical subgroup. It should be noted that the Assessment Group

TABLE 24 Changing risk of ischaemic stroke using the Assessment Group's reclassification of populations in CAPRIE[26]

	Original published, IS rate % (*n*/*N*)			New[a] IS rate using additional data from manufacturer, % (*n*/*N*)			
Patient group: qualifying event	CLOP	ASA	RR (95% CI)	Assessment group reclassification	CLOP	ASA	RR (95% CI)
IS	9.74 (315/3233)	10.57 (338/3198)	0.93 (0.80 to 1.07)	IS only	9.03 (214/2370	9.54 (226/2370)	0.9 (0.79 to 1.13)
MI	1.34 (42/3143)	1.33 (42/3159)	1.01 (0.66 to 1.54)	MI only	0.98 (28/2845)	1.00 (29/2896)	0.98 (0.59 to 1.65)
PAD	2.51 (81/3223)	2.54 (82/3229)	0.99 (0.73 to 1.34)	PAD only	2.20 (41/1861)	1.62 (30/1852)	1.36 (0.85 to 2.17)
				MVD	6.14 (155/2523)	7.13 (176/2468)	0.861 (0.70 to 1.06)

CLOP, clopidogrel; IS, ischaemic stroke; MVD, multivascular disease; PAD, peripheral arterial disease.
a After creating MVD population.

TABLE 25 Changing risk of MI using the Assessment Group's reclassification of populations in CAPRIE[26]

	Original published MI rate, % (*n*/*N*)			New[a] MI rate using additional data from manufacturer, % (*n*/*N*)			
Patient group: qualifying event	CLOP	ASA	RR (95% CI)	Assessment group reclassification	CLOP	ASA	RR (95% CI)
IS	1.36 (44/3233)	1.59 (51/3198)	0.85 (0.57 to 1.27)	IS only	1.01 (24/2370)	0.84 (20/2370)	1.20 (0.66 to 2.17)
MI	5.19 (163/3143)	5.51 (174/3159)	0.93 (0.76 to 1.15)	MI only	4.53 (129/2845)	5.18 915/2896)	0.87 (0.69 to 1.10)
PAD	2.11 (68/3223)	3.34 (108/3229)	0.61 (0.42 to 0.83)	PAD only	1.18 (22/1861)	1.78 (33/1852)	0.66 (0.39 to 1.13)
				MVD	3.96 (100/2523)	5.27 (130/2468)	0.75 (0.58 to 0.97)

CLOP, clopidogrel; IS, ischaemic stroke; MVD, multivascular disease; PAD, peripheral arterial disease.
a After creating MVD population.

had access to relevant data from the CAPRIE[26] trial only and, therefore, were unable to conduct similar analyses for the other identified trials.

Summary of clinical evidence

For clarity, *Table 26* describes the main clinical efficacy findings. The direct evidence from the four included RCTs[26,30,56,57] is outlined along with the Assessment Group's assessment of time to event rates, the indirect evidence from the mixed-treatment comparison and the Assessment Group's assessment of the evidence for the multivascular disease population. The dearth of new evidence for the MI and peripheral arterial disease populations is notable.

Discussion of clinical evidence

Direct clinical evidence available

The clinical evidence base supporting the previously published NICE guidance (TA90)[24] for the prevention of occlusive vascular events in patients with a prior history of such events and established peripheral arterial disease was constructed from two trials (CAPRIE[26] and ESPS-2[30]) relevant to the use of clopidogrel, MRD and ASA. Since publication of this guidance, two more

TABLE 26 Summary of clinical evidence

Trial and population	Outcome	Finding
Direct evidence		
CAPRIE:[26] MI, IS, PAD	First occurrence of IS, MI or vascular death	CLOP superior to ASA for overall population
ESPS-2:[30] IS/TIA	Stroke	MRD + ASA superior to MRD alone and superior to ASA
ESPRIT:[56] IS/TIA	First occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication	MRD + ASA superior to ASA
PRoFESS[57]	Recurrent stroke	CLOP and MRD + ASA similar
Time to event rates		
CAPRIE:[26] MI and IS	MI and IS	Recurrent events for patients with disease in a single vascular bed tend to occur within the first 6–12 months
Indirect evidence		
ESPS-2[30] and PRoFESS:[57] IS/TIA	Recurrent stroke	CLOP and MRD + ASA superior to ASA
	Recurrent stroke	MRD alone = increased risk compared with CLOP, MRD + ASA, ASA
	Any bleeding	MRD alone = least risk compared with ASA, CLOP, MRD + ASA
	Major bleeding	CLOP superior to ASA
MVD subgroup		
CAPRIE:[26] MI, IS, PAD	IS and MI	Patients with disease in more than one vascular bed are an important clinical subgroup at a greater risk of recurrent OVEs than patients with disease in a single vascular bed

CLOP, clopidogrel; IS, ischaemic stroke; OVEs, occlusive vascular events; PAD, peripheral arterial disease.

relevant trials have been published (ESPRIT[56] and PRoFESS[57]). The evidence base underpinning this update of TA90[24] is therefore focused on four RCTs.

Only CAPRIE[26] included patients with MI and peripheral arterial disease; the remaining three trials included just patients with ischaemic stroke/TIA. This means that the clinical evidence base for patients with MI and peripheral arterial disease (except for those with multivascular disease) has not changed since the publication of the TA90[24] guidance. Results from CAPRIE[26] indicated that clopidogrel was more effective than ASA in preventing a composite of events comprising ischaemic stroke, MI or vascular death; however, the size of the benefit appeared to be small. A subgroup analysis indicated that for the subgroup of patients with peripheral arterial disease, there was a statistically significant benefit of clopidogrel compared with ASA; however, the trial was not powered to detect differences within subgroups and so the chances of a false-negative finding are high. The Assessment Group notes that the CAPRIE[26] trial does not distinguish between patients with NSTEMI and STEMI, as the trial was carried out and reported before this distinction was used to differentiate between patient pathways. However, this clearly inhibits the interpretation of the results for these clinically important subgroups of patients.

The manufacturer's positive response to the Assessment Group's request for more detailed analyses of the CAPRIE[26] trial allowed the Assessment Group to conduct a new post hoc subgroup analysis of patients with multivascular disease (see *Summary of the evidence from the mixed-treatment comparison*) and explore changes in key event rates for four patient populations (MI, ischaemic stroke, peripheral arterial disease and multivascular disease) instead of the original three (MI, ischaemic stroke and peripheral arterial disease).

For patients with ischaemic stroke/TIA, clinical data from two relevant trials (ESPRIT[56] and PRoFESS[57]) have become available recently in addition to data from ESPS-2[30] and CAPRIE.[26] Unfortunately, PRoFESS[57] yielded inconclusive results, as the trial did not meet the predefined criteria for non-inferiority, but showed similar rates for the primary outcome of recurrent stroke (MRD + ASA vs clopidogrel). Consequently, there is no direct evidence to support the use of clopidogrel instead of MRD + ASA, or vice versa, for the ischaemic stroke/TIA population. ESPS-2[30] showed that MRD + ASA leads to statistically significant RRRs for the primary outcome of stroke and a range of secondary outcomes compared with ASA and MRD alone. The ESPRIT[56] trial also demonstrated statistically significant risk reductions for MRD + ASA versus ASA (first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication; death from all vascular causes and non-fatal stroke; all vascular events). This means that the additional clinical evidence available from the publication of ESPRIT[56] supports the original findings of ESPS-2[30] that MRD + ASA is preferred to ASA across a range of key outcomes.

Key differences between the trials providing direct clinical evidence

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

- *Design* The mean length of follow-up between trials ranged between 1.91 years[26] and 3.5 years.[56] The ESPRIT[56] trial was the only non-industry-funded trial.
- *Population* Patients in ESPRIT[56] were randomised within 6 months of a minor ischaemic stroke/TIA, whereas patients in ESPS-2[30] and PRoFESS[57] were randomised within 3 months of ischaemic stroke/TIA and minor ischaemic stroke, respectively. A marked divergence was observed in the disability ratings (as measured by the Rankin Scale[65]) between the stroke patients in the three trials[30,56,57] that exclusively included only ischaemic stroke/TIA

patients. To illustrate, in the ESPRIT[56] trial the entry criteria limited the study patients to those who had suffered a minor TIA or a minor ischaemic stroke (43% of patients had no stroke symptoms, 53% had minor symptoms), whereas ESPS-2[30] (17%) and PRoFESS[57] (24%) included patients with severe stroke symptoms. The Assessment Group notes that none of the trials identified patients with multivascular disease as being a clinically important subgroup.

- *Interventions* There was also disparity in the daily doses of ASA given in the trial: 'up to 350 mg',[26] 30–325 mg[56] and 50 mg.[30] In the UK, the current standard dose of ASA is 75 mg per day. However, as there appears to be little variation in the efficacy of doses higher than 75mg, there may be no impact on the main outcomes of the trials, although the bleeding risk may be increased with higher doses. The efficacy of lower doses of ASA (< 75 mg per day) is less well established than the efficacy of higher doses.[9,66]
- *Outcomes* First, none of the trials had the same primary outcome. Second, two trials utilised a composite event as a primary oucome.[26,57] The use of composite events in clinical trials has been criticised in a number of papers[67,68] and guidelines[67] for their use have been published. The guidelines[67] state that to be meaningful to clinicians, composite events should include components that are similar in importance to patients, occur with similar frequency and are affected to a similar degree by the intervention. When looking at the primary composite event used in CAPRIE,[26] ischaemic stroke or MI may not be considered as important to patients as death. In addition, there were many more patients with ischaemic stroke in CAPRIE[26] than there were MIs or vascular deaths. The primary composite event described in ESPRIT[56] included death from vascular causes, non-fatal stroke, non-fatal MI and non-fatal major bleeding, but these outcomes may not be considered to be similar by patients. Third, it is difficult to summarise the findings related to adverse events, as the classification of these outcomes differed across the trials; this was especially apparent for 'bleeding events'. However, upon investigation the Assessment Group did not identify any unexpected adverse events associated with any of the drugs – bleeding was associated with ASA and headache was associated with MRD.

Indirect clinical evidence available

As previously discussed, the availability of four good-quality RCTs did not allow the comprehensive comparison of clinical and safety outcomes associated with the relevant interventions across the key populations of interest. In an effort to make best use of all available clinical information, the Assessment Group undertook a mixed-treatment comparison and investigated outcomes, where possible, for the ischaemic stroke/TIA population. The Assessment Group concluded that there were no major differences in the results of the mixed-treatment comparison and the direct estimates from head-to-head trials. However, two of the five newly generated comparisons do yield statistically significant results (1) MRD alone was associated with an increased risk of recurrent stroke when compared with clopidogrel, and (2) clopidogrel was associated with fewer major bleeding events compared with ASA. Owing to the small numbers of trials involved in the mixed-treatment comparison and the forced selection of limited outcomes, caveats apply to the results. In addition, the findings were based on patient populations in which there is no differentiation between patients with vascular disease in a single bed and those with multivascular disease. The results of the indirect analyses, although confirmatory of the direct results, must therefore be interpreted with caution.

Patients with multivascular disease

Recently published data from the REACH[52] registry attest to the view that patients with multivascular disease are at an increased risk of future occlusive vascular events when compared with patients with disease in one vascular bed. Based on the post hoc analyses described by the manufacturer in the manufacturer's submission and the post hoc analyses conducted by the Assessment Group; there is also evidence from CAPRIE[26] to support the view that patients with multivascular disease are an important clinical subgroup whose event risk profiles are different

from other subgroups of patients. In summary, it appears that patients with multivascular disease have elevated risks for more than one event (ischaemic stroke and MI); this is in contrast with the ischaemic stroke-only and MI-only subgroups, which have been shown to have elevated risks for single events (e.g. ischaemic stroke-only patients have high risks of ischaemic stroke, and MI-only patients have high risks of MI).

Currently, there is no NICE guidance available that identifies a specific treatment for a patient who has multivascular disease, and NICE[24] has called for further research in this complex area: 'Further research is recommended on the effectiveness of clopidogrel in people who are at high risk of recurrent occlusive vascular events … and in people who have recurrent events while taking recommended antiplatelet therapy'.

Evidence from the CAPRIE[26] trial allows post hoc exploration of the clinical effectiveness of clopidogrel for patients with multivascular disease and offers a starting point for future discussions regarding appropriate clinical pathways for this subgroup of patients. Existing analyses are based on different definitions of multivascular disease and consensus is required in order to ensure informed and consistent decision-making for patients with multivascular disease.

Commentary on European Medicines Agency approval and guidelines/ guidance issued by NICE

The Assessment Group notes that ASA is not licensed for use in patients with peripheral arterial disease, nor is clopidogrel licensed for use in patients with TIA. However, the Assessment Group's clinical experts are of the opinion that in clinical practice in England and Wales, ASA is routinely prescribed for patients with peripheral arterial disease and sometimes clopidogrel is prescribed for patients with TIA who cannot tolerate MRD or ASA.

The distinction between patients with NSTEMI and STEMI is now important, as recently updated NICE guidelines[25] still state that patients diagnosed as NSTEMI who are at moderate to high risk of MI or death should be treated with clopidogrel + ASA for a period of 12 months after the most recent acute event and after 12 months' treatment should revert to low-dose ASA. At present, there is no NICE guidance for patients diagnosed with STEMI, although NICE clinical guideline 48[28] indicates that these patients should receive clopidogrel + ASA for 4 weeks after the most recent event and thereafter revert to standard treatment, usually low-dose ASA. It is not clear how the recommendations in TA90[24] fit with the published guidelines, as TA90[24] does not differentiate between patients with NSTEMI and STEMI.

Chapter 4

Assessment of cost-effectiveness

Introduction

There are three distinct elements to this section on cost-effectiveness. First, a critical appraisal of the existing economic evidence describing clopidogrel and MRD since the publication of the previous NICE guidance[24] (TA90) is presented. Second, a critique of the two economic models submitted by the manufacturers is described. Third, the results of the Assessment Group's de novo economic evaluation are presented and summarised. It should be noted that a substantive amount of the analysis of cost-effectiveness was based on confidential data provided by the manufacturers. This document has been edited as appropriate so as to maintain confidentiality.

Review of existing cost-effectiveness studies

Full details of the search strategy and the methods for selecting evidence are presented in *Chapter 3*. Of the 34 potentially relevant studies, 11[69–79] met the criteria for inclusion in the cost-effectiveness review; one study[69] was also included in the SR that informed the previous guidance.[24] Of the 11[69–79] included studies, seven[69–75] were published in full, whereas four[76–79] were available only in an abstract format. Most of the studies were of reasonable quality; however, more detail and focused critique of the clinical effectiveness evidence used to inform the economic evaluations would have improved the quality of the studies (see *Appendix 2*).

Characteristics of economic evaluations

Five[69,71,72,74,76] of the 11[69–79] studies included were described as cost-effectiveness analyses and six[70,73,75,77–79] as cost–utility analyses. The cost-effectiveness analyses have used a range of health outcomes including life saved, events avoided, life-years lived, time spent free of stroke recurrence or disability and life expectancy. All of the cost–utility analyses have used QALYs as the main measure of health outcome. As presented in *Table 27*, seven studies[69,71,75–79] compared clopidogrel versus ASA; Karnon *et al.*[73] compared clopidogrel for the first 2 years followed by ASA indefinitely versus ASA; Chen *et al.*[72] compared clopidogrel + low-dose ASA versus ASA; Beard *et al.*[70] compared MRD + ASA versus MRD single agent, low-dose ASA, clopidogrel or no treatment; and Matchar *et al.*[74] compared placebo versus ASA, ASA + MRD or clopidogrel.

The study populations in the included studies were made up of patients with a history of cardiovascular disease (MI, ischaemic stroke, TIA or peripheral arterial disease); this matches the populations described in the key clinical trials used to derive efficacy data. Only one study[78] explicitly considered patients with multivascular disease. The mean age varied according to the trial source used, ranging from 60 to 70 years. Only four studies[70,73,77,78] described a UK population. Most of the studies adopted a lifetime perspective; however, four[69,71,72,77] adopted a short-term perspective (e.g. duration of the clinical study follow-up).

TABLE 27 Characteristics of economic studies

Study	Source	Type of study	Interventions	Study population	Country	Time period	Industry/author affiliation
Annemans 2003[69]	Full text	CEA	CLOP vs ASA	Patients with MI, IS or PAD; mean age of 62.5 years	Belgium	2 years	The paper was supported by a grant from Sanofi–Synthelabo and Bristol–Myers Squibb
Beard 2004[70]	Full text	CUA	MRD + ASA vs: ■ MRD single agent ■ Low-dose ASA ■ CLOP ■ No treatment	Patients who survived an initial acute stroke; mean age of 70 years	UK	25 years	This project was supported with funding from Boehringer Ingelheim
Berger 2008[71]	Full text	CEA	CLOP vs ASA	Patients with MI, IS or PAD	Germany	2 years	Supported by Aventis Pharma Deutschland
Chen 2009[72]	Full text	CEA	CLOP + low-dose ASA vs ASA	Patients with established CVD	USA	Follow up of CHARISMA study[59] (28 months)	This project has been funded by grants from Sanofi (Paris, France) and Bristol–Myers Squibb (New York, NY, USA)
Delea 2003[76]	Abstract	CEA	CLOP vs ASA	Population with recent IS, MI or diagnosed with PAD; subgroups of 55-, 65- and 75-year-olds	USA	Lifetime of patient	NR
Karnon 2005[73]	Full text	CUA	CLOP for 2 years followed by ASA indefinitely vs ASA	Population with recent IS, MI or PAD aged 60 years	UK	40 years	This study was supported by Sanofi–Synthelabo and Bristol–Myers Squibb
Matchar 2005[74]	Full text	CEA	Placebo vs: ■ ASA ■ ASA + MRD ■ CLOP	Population with previous IS or TIA aged 70 and with the characteristics of those patients in the Framingham population with first IS	USA	Lifetime of patient	Source of financial support: The Stroke Policy Model[80] was developed with support from the Agency for Health Care Research, Quality (1 R03 HS11746–01). The current application was developed while Drs Matchar and Samsa served as consultants to Boehringer Ingelheim
Schleinitz 2004[75]	Full text	CUA	CLOP vs ASA	Population with previous MI or stroke or diagnosed with PAD; mean age 63 years	USA	Lifetime of patient	Dr Schleinitz was supported by an ambulatory care training grant from the Department of Veterans Affairs, a training grant from the Agency for Healthcare Research and Quality (AHRQ), and an NIH BIRCWH grant (HD43447)
Palmer 2005[77]	Abstract	CUA	CLOP vs ASA	Population with previous IS or TIA occurred in the last 90 days (median 15 days)	Belgium, France, Switzerland and the UK	18 months	NR

TABLE 27 Characteristics of economic studies *(continued)*

Study	Source	Type of study	Interventions	Study population	Country	Time period	Industry/author affiliation
Stevenson 2008[78]	Abstract	CUA	CLOP vs ASA	Population with previous MI, who sustain an IS or PAD (high-risk patients)	UK	Lifetime of patient	NR
Van Hout 2003[79]	Abstract	CUA	CLOP vs ASA	Population with previous MI or stroke or diagnosed with PAD	Netherlands	Lifetime of patient	NR

CEA, cost-effectiveness analysis; CLOP, clopidogrel; CUA, cost–utility analysis; CVD, cardiovascular disease; IS, ischaemic stroke; NIH BIRCWH, National Institutes of Health Building Interdisciplinary Research in Women's Health; NR, not reported; PAD, peripheral arterial disease.

Economic models

Only one of the included studies was not based on an economic model; Chen *et al.*[72] performed an economic evaluation using data from the CHARISMA[59] trial without any survival projection beyond 28 months. Matchar *et al.*[74] used an individual sampling model based on a model previously developed for the secondary prevention of stroke. Berger *et al.*[71] adapted the model developed by Annemans *et al.*[69] and Beard *et al.*[70] based their model on the model developed by Cambers *et al.*[81] All relevant assumptions and extra information describing the models are summarised in *Table 28*.

Cost data and cost sources

All of the studies stated the currency used; five of them also included the currency year, which ranged from 2002 to 2007. Four studies used euros, three used pounds sterling and four used US dollars. The majority of the studies discussed cost items and provided useful definitions of costs. Drugs costs have been taken from a variety of different sources including local cost lists;[69] published literature;[71] the BNF;[70,73] and the WEB of pharmacy wholesale suppliers.[74,75] Costs of acute events, including hospitalisations and acute care, have been taken from the trial-based papers,[71,73] Medicare diagnosis-related groups data,[74,75] NHS Trust Financial Return data[70] and the published literature.[71,78] Only three papers[76,77,79] do not state the sources of the cost data used. All papers but one[74] have mentioned a discount rate for costs, as *Table 29* shows.

Efficacy data and data sources

Only Palmer *et al.*[77] and Stevenson *et al.*[78] present data related to efficacy; the rest of the studies only point out that efficacy data are taken from a specific trial. *Table 30* describes the information from the main trials used in each of the economic evaluations.

Health outcome data and data sources

Six of the economic evaluations used QALYs as the main measure of health outcome; other outcomes include life-years saved and life expectancy.

Only Matchar *et al.*[74] have not discounted health outcomes. In the study by Delea *et al.*[76] it is not clear if discounting has been applied to both costs and benefits. In the study by Palmer *et al.*,[77] discounting was used, but the discount rate is not explicitly stated. Health outcome information from the included studies is summarised in *Table 30*.

TABLE 28 Description of economic models

Study	Type of model	Perspective	Model assumptions	
			Outcomes	Costs and resource use
Annemans 2003[69]	Markov model Cycle length: 6 months	Belgian public health payer	Risk of death from other causes was equal for CLOP and ASA Risk of vascular death was included in the model separately, because it was assumed that over the 2-year study period both drugs affected only vascular death Life expectancy does not decrease further when a patient has more than one additional event Adverse events were only included where a difference between CLOP and ASA was expected, based on pharmacological profiles, and where hospitalisation and intensive resource use would have been required Concomitant medication continued unchanged for the duration of the analysis or until death and, in view of the small difference in concomitant medication profiles for patients receiving ASA or CLOP, an average of the two groups was used for all patients	DRG derived costs for Belgium were from the year 1997 and were updated to 2002 using an inflation rate of 3% The total cost of patient management was calculated by estimating the total of acute costs and follow-up costs per patient Acute costs covered hospital admission, initial investigations, interventions, re-admission for further interventions and inpatient rehabilitation Follow-up costs comprised outpatient rehabilitation, GP/specialist visits, follow-up examinations, complications, nursing homes and home care
Beard 2004[70]	Model based on Chambers 1999[81] model Markov model Cycle length: 90 days	UK health-care service	Patients entering the model were assumed to have survived an initial acute stroke event Patients who survived an initial acute episode would be considered suitable for treatment with an antiplatelet therapy Patients had already received rehabilitation treatment for the initial stroke event prior to entering the model, and were being placed on standard long-term care, according to their level of permanent disability/functional status Only adverse events associated with withdrawal from therapy are important to outcomes in the model	No assumptions made
Berger 2008[71]	Markov model adapted from Annemans[69] Cycle length: 6 months	German third-party payer	Two scenarios are compared: survival data based on Framingham database and on Saskatchewan databases	German cost data for acute and follow-up treatment of patients with MI, IS or PAD as published by Diener *et al.*[82] were decreased by the included costs for CLOP treatment because of their separate consideration within this Markov model[7]
Chen 2009[72]	No model has been developed	US health-care system (payer)	NR	NR
Delea 2003[76]	Markov model Cycle length: NR	NR	NR	NR

TABLE 28 Description of economic models *(continued)*

Study	Type of model	Perspective	Model assumptions	
			Outcomes	Costs and resource use
Karnon 2005[73]	Markov model Cycle length: 1 year	UK NHS perspective	The model assumes patients receive lifelong therapy with CLOP or ASA	NR
Matchar 2005[74]	Individual sampling model based on the Duke Stroke Policy Model (DSPM)[80] for secondary stroke prevention The model has been run 100 times	Health-care provider	All patients are assigned an initial Rankin Score of 1 The placebo group was assumed to follow the natural history of 70-year-olds with the characteristics of those patients in the Framingham population with first IS For each antiplatelet group, the cost per month was increased by an estimated cost of antiplatelet medications For each antiplatelet group, the risk of subsequent IS was reduced, using a risk ratio that was estimated from the randomised trials	NR
Schleinitz 2004[75]	Markov model Cycle length: 1 month	Societal perspective	When more than two events occurred, the Markov state that combined the two events with the lowest utility was used Inclusion of the variable severity of stroke not included in the main trial on which the model is based It is assumed that CLOP did not alter the distribution of severity, based on studies of other antiplatelet therapies As CAPRIE[26] results were heterogeneous for the three subgroups, the estimates and 95% CIs for the efficacy of CLOP for each subgroup, rather than the primary study estimate, has been used The efficacy of CLOP in reducing haemorrhagic side effects was varied by a factor of 0.5–2	The calculation of chronic care costs after survival of severe stroke or intracranial haemorrhage and other chronic conditions includes 20% of the chronic cost of the other condition to account for overlapping therapy
Palmer 2005[77]	Markov model Cycle length: NR	NR	NR	NR
Stevenson 2008[78]	Markov model Cycle length: NR	NR	NR	NR
Van Hout 2003[79]	Markov model Cycle length: NR	NR	NR	NR

CLOP, clopidogrel; DRG, diagnosis-related group; INAMI, Institut National d'Assurance Maladie Invalidité; IS, ischaemic stroke; NR, not reported; PAD, peripheral arterial disease.

TABLE 29 Cost data and cost data sources

Study	Cost items and cost data sources		Currency and currency year	Discount rate (%)
Annemans 2003[69]	Ambulatory costs from INAMI tariff list for Belgium; AEs, unit costs from Belgian DRG; cost of CLOP and ASA from 'Répertoire Commenté des Médicaments' Public Belgian costing		Euros/2002	3
Beard 2004[70]	The model considered three specific areas of resource use. Hospitalisation costs from the NHS Trust Financial Returns data; community-based resource costs were based on the Personal Social Services Research Unit Health and Social Care Costs; drugs costs from BNF 2002 prices		£/2002	6
Berger 2008[71]	(a) Acute events (b) Follow-up costs (c) Cost of drug	Costs from the literature excluding cost of CLOP	Euros/NR	3
Chen 2009[72]	Hospitalisations, physician costs, procedures, post acute care and medications. Prices were obtained from price weights derived from comparable populations of US patients		US$/2007	3
Delea 2003[76]	Antiplatelet therapy; inpatient and outpatient treatment of IS; long-term care for patients with disability; sources NR		US$/NR	3[a]
Karnon 2005[73]	(a) Hospitalisations, physician costs and procedures (b) Post acute care (c) Cost of drug with 100% compliance (d) Cost of qualifying events and costs of new MI (e) Cost of new stroke and stroke as qualifying event	(a) Chambers *et al.*[81] and Tengs and Lin[83] (b) CAPRIE Steering committee[26] (c) BNF for costs of drugs, 44th edition (d) Robinson *et al.*[84] (e) Chambers *et al.*[81]	£/2002	6
Matchar 2005[74]	Cost of events from Medicare claims data; cost of drugs from the WEB of Pharmacy wholesale and Federal Supply Schedule		US$/NR	NR
Schleinitz 2004[75]	(a) Cost of MI and IS (b) Cost of AEs (c) Annual care costs of stroke (d) Annual care costs of AEs (e) Cost of drugs	(a) to (d) Medicare diagnostic-related group data and literature and published literature (e) Average US wholesale price for medications and based on prices negotiated by a large volume purchaser	US$/2002	3
Palmer 2005[77]	NR	NR	Euros/NR	Local guidelines
Stevenson 2008[78]	NR	Literature review	£/NR	3.5
Van Hout 2003[79]	NR	NR	Euros/NR	4

AEs, adverse events; CLOP, clopidogrel; DRG, diagnosis-related groups; IS, ischaemic stroke; NR, not reported.
a Not clearly stated if for both costs and benefits.

TABLE 30 Health outcome data and data sources

Study	Efficacy data	Efficacy data sources	Health outcomes	Health outcome data sources	Discount rate (%)
Annemans 2003[69]	NR	CAPRIE[26] and Saskatchewan database. Inpatient and outpatient management derived from analysis of Belgian and international publications and official Belgian health statistics, and were validated by a group of eight Belgian clinical experts	Cost per LYS; quantity of events; events avoided	CAPRIE trial[26] and Saskatchewan database	3
Beard 2004[70]	NR	ESPS-2 study[30] for all treatments except CLOP where data came from CAPRIE.[26] Risks for acute stroke recurrence from years 3 to 5 from the Oxford Community Stroke Project and > 5 years risks assumed to rise with age	Life-years lived; QALYs; time spent free of stroke recurrence or disability; avoided strokes; number of events	Original trials (CAPRIE[26]and ESPS-2[30]) and published literature	1.5
Berger 2008[71]	NR	CAPRIE trial[26] and a Delphi panel to adapt efficacy data to Germany setting	Fatal and non-fatal strokes; LYS	CAPRIE study[26] and Delphi panel	3
Chen 2009[72]	NR	CHARISMA[59] and Saskatchewan database	Lost life expectancy	CHARISMA trial[59] and Saskatchewan database	3
Delea 2003[76]	NR	CAPRIE study[26]	Life expectancy	NR	3
Karnon 2005[73]	NR	UK observational studies CAPRIE trial[26] Government Actuary Department (1999–2000)	QALYs; number of events; LYG	CAPRIE study;[26] Harvard utility database; Tengs and Lin;[83] Derdeyn and Powers[85] Zeckhauser and Shepard;[86] Haigh *et al.*;[87] Lee *et al.*;[88] Danese *et al.*[89]	1.5
Matchar 2005[74]	NR	Transition functions from Framingham study; CAPRIE study;[26] ESPS-2 study[30]	QALYs	Duke Stroke Policy Model;[80] 'utilities were estimated from a large survey of patients at risk for major stroke' (no ref.)	NR
Schleinitz 2004[75]	NR	Based on data from CAPRIE[26] and mortality data from life tables. Rate of TTP with CLOP from an observational study	QALYs	Published papers; CAPRIE study[26]	3
Palmer 2005[77]	(a) RR increase of CLOP vs ASA: serious vascular events 1.11 (b) RR increase of ASA vs CLOP: major bleedings 1.12	(c) 'Cochrane review' (d) CAPRIE trial[26]	QALYs	NR	'Discount rates were applied according to the local guidelines'

continued

TABLE 30 Health outcome data and data sources *(continued)*

Study	Efficacy data	Efficacy data sources	Health outcomes	Health outcome data sources	Discount rate (%)
Stevenson 2008[78]	(a) RR high-risk patients vs single-event patients: 1.81 (b) RR CLOP vs ASA in high risk patients: ■ Vascular death: 0.87 (95% CI 0.63 to 1.19) ■ NF IS: 0.83 (95% CI 0.60 to 1.15) ■ NF MI: 0.53 (95% CI 0.32 to 0.86)	(a) and (b) CAPRIE study[26]	QALYs	NR	3.5
Van Hout 2003[79]	NR	CAPRIE study[26]	QALYs	CAPRIE study[26]	4

CLOP, clopidogrel; LYG, life-years gained; LYS, life-years saved; NF, non-fatal; NR, not reported; TTP, thrombocytopenic purpura.
a Not clearly stated if for both costs and benefits.

Cost-effectiveness ratios

The results of the cost-effectiveness analyses are described in *Table 31*. In summary, Annemans *et al.*[69] and Berger *et al.*[71] conclude that, for the overall population (MI, ischaemic stroke and peripheral arterial disease), clopidogrel is cost-effective compared with ASA, with an incremental cost-effectiveness ratio (ICER) of €13,390 per QALY and €14,380 per life-years saved (scenario 1) or €18,790 per life-years saved (scenario 2). Chen *et al.*[72] and Delea *et al.*[76] show an ICER of US$36,343 per life-years saved and a range of US$40,204 to US$49,107 per life-years saved, respectively, concluding that clopidogrel is cost-effective compared with ASA.

Schleinitz *et al.*,[75] Palmer *et al.*[77] and van Hout *et al.*[79] conclude that clopidogrel is cost-effective when compared with ASA (see *Table 31*), although Schleinitz *et al.*[75] also conclude that the current evidence does not support increased efficacy of clopidogrel in MI patients. Stevenson *et al.*[78] estimated that the mean cost per QALY for clopidogrel compared with ASA was £5443 in patients with a previous history of MI who then sustained an ischaemic stroke or a peripheral arterial disease event.

The evaluation by Beard *et al.*[70] concludes that MRD + ASA is a cost-effective option with an ICER below €5000 per QALY when compared with ASA or MRD alone, and it dominates when compared with clopidogrel or no treatment.

The study by Karnon *et al.*[73] concludes that the comparison of clopidogrel followed by ASA versus ASA yields an ICER of £21,489 per QALY.

Matchar *et al.*[74] show that placebo versus ASA and placebo versus MRD + ASA have similarly low ICERs; however, placebo versus clopidogrel yields a high ICER with a low probability of being cost-effective.

The majority of the trials have performed univariate and probabilistic sensitivity analysis. In general, the univariate sensitivity analyses show consistency around the ICER. All univariate

TABLE 31 Cost-effectiveness results

Study	Total costs	Total outcomes	ICERs	Conclusion
Annemans 2003[69]	(a) Cost of CLOP patients: €12,612 per patient (b) Cost of ASA patients: €11,753 per patient	Events in ASA group: 120.22 Events in CLOP group: 107.2	ICER CLOP vs ASA; €13,390/LYG	The findings of this CEA suggest that secondary treatment of MI, IS and PAD patients with CLOP adds approximately 43–114 life-years per 1000 patients compared with ASA (depending on discounting)
Beard 2004[70]	*Primary analysis (per 1000 patients)*: (a) No treatment: €23,489,812 ■ ASA: €23,242,692 ■ MRD: €23,434,359 ■ ASA-MRD: €23,308,578 ■ CLOP: €24,247,730 *Secondary analysis (lifetime)*: (b) No treatment: €37,757,950 ■ ASA: €37,513,168 ■ MRD: €37,662,152 ■ ASA-MRD: €37,726,731 ■ CLOP: €38,870,032	*Primary analysis (per 1000 patients)*: (a) No treatment: 2357 QALYs ■ ASA: 2370 QALYs ■ MRD: 2360 QALYs ■ ASA-MRD: 2385 QALYs ■ CLOP: 2374 QALYs *(b) Secondary analysis (lifetime)*: (c) No treatment: 4199 QALYs ■ ASA: 4248 QALYs ■ MRD: 4219 QALYs ■ ASA-MRD: 4306 QALYs ■ CLOP: 4265 QALYs	5- and 25-year analysis: ■ ASA + MRD vs ASA: ICER, £4207–3666/QALY ■ ASA + MRD vs MRD: ICER, dominated –£742.29/QALY ■ ASA + MRD vs CLOP: ICER, CLOP dominated ■ ASA + MRD vs no treatment: ICER, no treatment dominated	The current model suggests that, based on a consideration of first recurrence of stroke and the acute treatment impacts of TIAs and non-fatal OVEs, antiplatelet therapy based on MRD + ASA is a cost-effective treatment option over standard ASA. The model is sensitive to the long-term costs of very disabled patients
Berger 2008[71]	Overall, the 2-year costs per 1000 patients under immediately initiated CLOP prophylaxis were calculated to be €1,241,440	ASA (events per 1000 patients): ■ Vascular death: 33.12 ■ Non-fatal events: 87.09 ■ All vascular events: 120.22 CLOP: ■ Vascular death: 30.91 ■ Non-fatal events: 76.11 ■ All vascular events: 107.02	ICER: ■ Scenario 1: €14,380/LYS ■ Scenario 2: €18,790/LYS	The presented model shows cost-effectiveness of secondary prevention with CLOP vs ASA in patients with MI, IS or PAD
Chen 2009[72]	Mean cost per patient: ■ ASA group; US$11,136 ■ CLOP + ASA group: US$13,743	Life expectancy without in-trial events (years): Male, age 65 years: 11.63; female, age 65 years: 13.17 Unadjusted lost life expectancy associated with specific in-trial events (years): Male, age 65 years = mild stroke: 6.23; moderate-severe stroke: 8.71; MI: 4.69 Female, age 65 years = mild stroke: 7.53; moderate-severe stroke: 10.34; MI: 5.93	■ Overall population: ICER US$36,343/LYG ■ Population aged < 65 years: ICER US$28,144/LYG ■ Population aged ≥ 65 years: ICER US$61,213/LYG ■ Male population: ICER US$31,024/LYG ■ Female population: ICER US$54,817/LYG	For the prespecified subgroup of CHARISMA[59] patients with established CVD, adding CLOP to ASA for secondary prevention over 28 months of therapy appears to increase life expectancy modestly at a cost commonly considered acceptable within the US health-care system

continued

TABLE 31 Cost-effectiveness results *(continued)*

Study	Total costs	Total outcomes	ICERs	Conclusion
Delea 2003[76]	NR	NR	ICER ranges from US$40,204 to US$49,107 per LYS	CLOP is cost-effective vs ASA in patients with recent IS, recent MI or PAD
Karnon 2005[73]	Lifetime costs: ■ ASA: £18,380,509 ■ CLOP: £19,199,554	Total number of events: ■ ASA 195; CLOP 172 LYG: ■ ASA 14,199; CLOP 14,242 QALYs gained: ■ ASA 11,964; CLOP 12,002	ICER: ■ £21,489/QALY ■ £18,888/LYG	CLOP has been demonstrated to be a cost-effective treatment in patients at risk of secondary OVEs, is clinically superior to ASA and has great potential for reducing the morbidity and mortality caused by these diseases
Matchar 2005[74]	Total cost per patient: ■ Placebo group: US$48,405 ■ ASA group: US$48,681 ■ CLOP group: US$52,721 ■ MRD + ASA: US$53,004	Total QALYs per patient: ■ Placebo group: 3.54 ■ ASA group: 3.70 ■ CLOP group: 3.77 ■ MRD + ASA: 3.93	Based on the means for 100 runs of 10,000 patients each. ■ Placebo vs ASA: US$1725/QALY ■ Placebo vs CLOP: US$57,714/QALY ■ Placebo vs MRD + ASA: US$1769/QALY	ASA is superior to placebo. Choice between ASA and MRD + ASA is less obvious; but the more the decision-maker is WTP for improved outcomes the more likely it is that MRD + ASA will be preferred. CLOP was seldom judged to be the optimal strategy. But, results were not sufficiently robust to select between MRD + ASA and ASA based on statistical considerations alone
Schleinitz 2004[75]	CLOP: ■ PAD US$123,300; stroke US$201,400; MI US$98,500 ASA: ■ PAD US$109,500; stroke US$196,000; MI US$91,700	QALYs (CLOP): ■ PAD 9.58; stroke 8.66; MI 10.83 QALYs (ASA): ■ PAD 9.03; stroke 8.49; MI 11.09	PAD: US$25,100/QALY CLOP more effective Stroke: US$31,200/QALY CLOP more effective MI: –US$26,200/QALY ASA more effective	CLOP provides a large increase in QALYs at a cost that is within traditional societal limits for patients with either PAD or a recent stroke. Current evidence does not support increased efficacy with CLOP vs ASA in patients after MI
Palmer 2005[77]	NR	NR	20,111€/QALY in Belgium 18,882€/QALY in France 15,620€/QALY in Switzerland 15,713€/QALY in UK	In the four countries the ICER falls below the acceptable thresholds, showing that CLOP compared with ASA is cost-effective in the studied population
Stevenson 2008[78]	NR	NR	The mean cost per QALY for CLOP compared with ASA was £5443 (95% CI £2332 to dominated)	The model suggests that, in patients with a previous MI event and a subsequent IS or PAD event, CLOP can be considered cost-effective compared with ASA in terms of current UK thresholds
Van Hout 2003[79]	NR	NR	ICER: €17,279/QALY with event-specific risk reductions and €15,776/QALY using constant RRR of 8.7%	CLOP shows as a dominant strategy in patients not eligible for treatment with ASA. The cost-effectiveness is within an acceptable range when compared with ASA, especially in high-risk patients

CEA, cost-effectiveness analysis; CLOP, clopidogrel; CV, cardiovascular; IS, ischaemic stroke; LYG, life-years gained; LYS, life-years saved; OVEs, occlusive vascular events; PAD, peripheral arterial disease; NR, not reported; WTP, willingness to pay.

sensitivity analyses are summarised in *Appendix 8*. Beard *et al.*[70] state that their model is sensitive to the long-term costs of very disabled patients. Matchar *et al.*[74] conclude that, although the simulations in their model can support the results shown, these are not sufficiently robust.

Summary of evidence and discussion

In general, the results of the literature review of cost-effectiveness evidence show that from a health service perspective, the use of clopidogrel in patients with previous peripheral arterial disease, ischaemic stroke or MI is a cost-effective option compared with ASA in the secondary prevention of occlusive vascular events. However, it is noted that Schleinitz *et al.*[75] conclude that current evidence does not support increased efficacy of clopidogrel in the MI patient group; this is the only evaluation that includes subgroup analysis to estimate ICERs by patients' previous event. This is also the only study not funded by a pharmaceutical manufacturer (four papers[76–79] did not provide details of industry affiliation).

The combination of MRD + ASA seems to be cost-effective compared with any other treatment (vs ASA, vs clopidogrel, vs no treatment) in patients with previous ischaemic stroke or TIA in the secondary prevention of occlusive vascular events. There is only one evaluation[70] that includes this combination (MRD + ASA) and therefore the evidence base is limited.

Although model structures are similar, the length of the cycles differs from one study to another and the assumptions regarding the transition probabilities (e.g. Annemans *et al.*[69] – life expectancy assumptions) are not always reliable. Data in the models are from a broad variety of sources, which makes it difficult to pool the results and make definitive conclusions.

All evaluations except three[71,72,78] were published prior to 2006; this means that more recent trials and papers have not been used to inform the economic evaluations (e.g. clinical data from PRoFESS,[57] REACH[17] or MATCH[58] are not described in the papers). The relevance of this cost-effectiveness review to decision-making is therefore limited as the economic evaluations are not based on the most up-to-date clinical data.

Review of Boehringer Ingelheim submission

See *Table 32*.

Overview of submitted manufacturer's submission

A Markov model was designed to assess the cost-effectiveness of MRD + ASA versus ASA alone, clopidogrel and no treatment for the secondary prevention of occlusive vascular events in patients who have experienced:

- an ischaemic stroke and are tolerant of ASA
- a TIA and are tolerant of ASA.

The model is based on the model developed by the Technology Appraisal Group to inform the previous guidance.[3]

The structure of the manufacturer's model is shown in *Figure 4*.

The model estimates costs from the perspective of the UK NHS, and health outcomes in terms of life-years and QALYs in a simulated cohort of 1000 patients initially aged 45–80 years using a time horizon of 2.5–50 years and a cycle length of 6 months.

Costs and benefits have been discounted at a rate of 3.5% per annum.

TABLE 32 The National Institute for Health and Clinical Excellence reference case checklist

NICE reference case requirements	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	As per the final scope issued by NICE
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	ASA, CLOP, MRD + ASA and no treatment
Perspective on costs	NHS and PSS	As per the final scope issued by NICE
Perspective on outcomes	All health effects on individuals	As per the final scope issued by NICE
Type of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Synthesis of evidence on outcomes	Based on a SR	All data are derived from head-to-head trials (mainly PRoFESS[57])
Measure of health benefits	QALYs	QALYs
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	EQ-5D used to collect data from patients in the PRoFESS[57] trial; published literature
Source of preference data for valuation of changes in HRQoL	Representative sample of general public	EQ-5D used to collect data from patients in the PRoFESS[57] trial; published literature
Discount rate	An annual rate of 3.5% on both costs and QALYs	3.5% per annum for costs and health effects
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the model have the same weight

CLOP, clopidogrel; EQ-5D, European Quality of Life-5 Dimensions; PSS, personal social services.

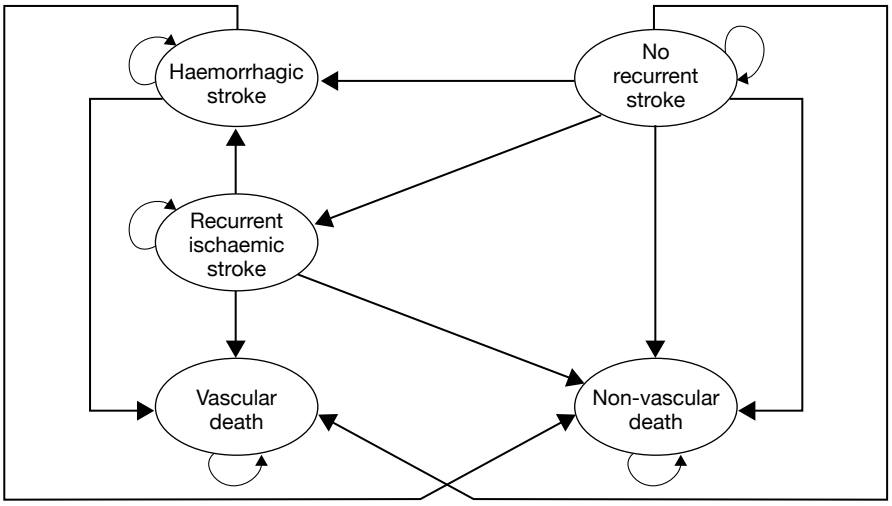

FIGURE 4 Schematic structure of the Boehringer Ingelheim's model.

The model presents five health states:

1. no recurrent stroke
2. recurrent ischaemic stroke
3. haemorrhagic stroke
4. vascular death
5. non-vascular death.

Patients enter into the model in the 'no recurrent stroke' health state, from where they may move to any other state or remain in the same state. From the 'recurrent ischaemic stroke' state patients may move to 'haemorrhagic stroke', 'vascular death' or 'non-vascular death' or remain in the 'recurrent ischaemic stroke' state. In the 'haemorrhagic stroke' state, patients will either remain in this state or die. Once patients enter the 'haemorrhagic stroke' health state, any additional recurrent haemorrhagic stroke events are not recognised in the model. The manufacturer states that this restriction is introduced to avoid the situation where an additional event (e.g. new ischaemic stroke) leads to a patient's utility state improving. If multiple events occur in a single cycle, one event is given priority in allocating patients to a health state in the following order of descending priority: death, haemorrhagic stroke, ischaemic stroke. The model also includes two tunnel health states: 'other haemorrhagic events' and 'new or worsening congestive heart failure'.

Summary of clinical effectiveness data

Transition probabilities during the first 4 years are derived from different trials for each of the arms:

- *MRD + ASA and clopidogrel* – PRoFESS[57] trial
- *ASA alone* – combination of ESPRIT[56] trial and ESPS-2[30] trial
- *no treatment* – ESPS-2[30] trial.

Beyond the first 4 years, the transition probabilities are assumed to remain constant at the values of the last monthly cycle of the fourth-year period for the following transitions:

- new recurrent ischaemic stroke from the 'no recurrent stroke' state
- haemorrhagic stroke from the 'no recurrent stroke' state
- haemorrhagic stroke from the 'new recurrent ischaemic stroke' state.

The manufacturer used published data from the Oxfordshire Community Stroke Project[90] and the Lothian Stroke Registry[91] to estimate the overall death rate among stroke patients compared with the general population. A multiplier of 1.5 was used to generate an overall expected age-related death rate beyond the trial period from the Office for National Statistics death rate data for the general population. The vascular and non-vascular death rates beyond the 4 years of the trial were assumed to sum to this rate.

The manufacturer has assumed that those patients who have experienced a TIA had a rate of previous ischaemic stroke events equal to 80% of those who had experienced a previous ischaemic stroke. This assumption is made on the basis of the previous multiple technology assessment (MTA)[3] in which the Assessment Group made the same assumption.

Summary of costs and resource use

Event costs

Separate costs were assigned to the health states of 'no recurrent stroke', 'recurrent ischaemic stroke' and 'haemorrhagic stroke', based on the estimated percentage of patients who were disabled in each health state. Data from the PRoFESS[57] trial were used to estimate the percentage of patients in each of these three health states who were disabled and non-disabled, based on the modified Rankin Scale; those who score 0–2 are defined as 'non-disabled' and those who score 3–5 are 'disabled'. The cost data used in the model for disabled and non-disabled stroke patients were taken from the same source used in the original MTA[3] updated using an inflation index using data from Personal Social Services Research Unit (PSSRU).[92]

Costs are shown in *Table 33*.

TABLE 33 Stroke event costs

Health-state event			Cost[a] (£)	Reference
IS	Institutional cost	Non-disabled (first cycle)	5930	[b]Jones *et al.*[3]
		Non-disabled (subsequent cycle)	0	
		Disabled (first cycle)	12,689	
		Disabled (subsequent cycle)	0	
		Death	8152	
	Non-institutional cost	Non-disabled (first cycle)	413	
		Non-disabled (subsequent cycle)	825	
		Disabled (first cycle)	1203	
		Disabled (subsequent cycle)	2406	
Haemorrhagic stroke	Institutional cost	Non-disabled (first cycle)	5930	
		Non-disabled (subsequent cycle)	0	
		Disabled (first cycle)	12,689	
		Disabled (subsequent cycle)	0	
		Death	8152	
	Non-institutional cost	Non-disabled (first cycle)	413	
		Non-disabled (subsequent cycle)	825	
		Disabled (first cycle)	1203	
		Disabled (subsequent cycle)	2406	

IS, ischaemic stroke.
a Uplifted for inflation by a factor of 1.2022 (2003–8).
b Technology Assessment report.[3]

Follow-up costs

National reference costs (2006–7) as used in the 2004 Technology Assessment Report[3] were used to calculate the hospitalisation costs following congestive heart failure and other haemorrhagic events. The costs used in the model are summarised in *Table 34*.

Drug costs

Costs of drugs include branded cost for MRD + ASA and clopidogrel and generic costs of ASA. The branded drug costs were taken from MIMS (*Monthly Index of Medical Specialities*)[93] (June 2009) and generic ASA cost from BNF 57[94] (March 2009). These costs are shown in *Table 35*.

Utilities

The utility data for the health states of 'no recurrent ischaemic stroke', 'recurrent ischaemic stroke' and 'haemorrhagic stroke' are taken directly from the PRoFESS[57,95] clinical trial, which used the EQ-5D as a measure at 1 year and 4 years. The 1-year data set was used as it contained the largest number of patients.

The manufacturer has used a paper by Miller *et al.*[96] (based on Galbreath *et al.*[97] and Smith *et al.*[98]) as the source for the disutility value associated with congestive heart failure using the mean that is calculated when moving from New York Heart Association (NYHA) classification II to NYHA III/IV and NYHA I/II. The disutility value associated with other haemorrhagic events was calculated using utility data presented in Robinson *et al.*[99] and in Brown *et al.*[100]

TABLE 34 Follow-up costs

	Adverse event	Cost (£)	Source
Institutional cost	CHF	878	[a]Jones *et al.*[3]
	GI event	1211	
	Haematemesis event	1211	
	Haematuria event	807	
	Intraocular event	1203	
	Epistaxis event	0	
	Other event	1211	

CHF, congestive heart failure; GI, gastrointestinal.
a Technology Assessment report.[3]

TABLE 35 Costs of drugs

Drug	Cost (£)	Source
Asasantin® (MRD + ASA)	Cost per day = 0.13	MIMS June 2009[93]
Plavix (CLOP)	Cost per day = 1.21	MIMS June 2009[93]
Aspirin (ASA)	Cost per day = 0.02	BNF 57 March 2009[94]

CLOP, clopidogrel.

Summary of submitted results

The base-case analysis includes second-line treatment with ASA for those patients discontinuing first-line treatment in clopidogrel and MRD + ASA groups. A summary of the results is shown in *Table 36* for ischaemic stroke patients and in *Table 37* for TIA patients.

Summary of sensitivity analysis

Deterministic sensitivity analysis

In the scenario sensitivity analysis, statistically significantly different variables were set as central estimates from the PROFESS[57] trial for MRD + ASA and clopidogrel arms, i.e. haemorrhagic stroke rates, dropout rates, other haemorrhagic events and congestive heart failure rates; all other transition probabilities were unchanged. Results are shown in *Table 38* for ischaemic stroke patients and in *Table 39* for TIA patients. For the reference case (ischaemic stroke patients), one-way univariate sensitivity analysis results are also shown in *Table 40*.

For the scenario sensitivity analysis (ischaemic stroke patients) outlined above, one- and two-way univariate sensitivity analyses were also performed (*Table 41*).

A univariate sensitivity analysis was performed to demonstrate the impact on the size of the ICER (MRD + ASA vs ASA) of changing the source (ESPRIT[56] or ESPS-2[30]) of the ASA RR data. Using ESPS-2[30] data, the ICER changes from £5377 per QALY in the base case to £9535 per QALY for ischaemic stroke patients, and using ESPRIT[56] data changes the ICER from £6053 per QALY in the base case to £3948 per QALY for TIA patients.

Probabilistic sensitivity analysis

After generating 500 iterations, the results for the probabilistic sensitivity analyses were as follows:

TABLE 36 Results base-case analysis for 1000 ischaemic stroke patients

	MRD + ASA – long term (first-line); ASA (second-line)	CLOP – long term (first-line); ASA (second-line)	ASA	No treatment
Total costs (£)	37,430,180	39,238,555	36,725,769	36,678,013
Total QALYs	8724	8739	8593	8596
ICER (MRD + ASA vs …) (£)	–	114,628	5377	5910

CLOP, clopidogrel.

TABLE 37 Results base-case analysis for 1000 TIA patients

	MRD + ASA and ASA – long term (first-line); ASA (second-line)	CLOP – long term (first-line); ASA (second-line)	ASA	No treatment
Total costs (£)	37,010,692	38,871,872	36,278,556	36,197,693
Total QALYs	8781	8790	8660	8675
ICER (MRD + ASA vs …) (£)	–	199,149	6053	7684

CLOP, clopidogrel.

TABLE 38 Scenario analysis in 1000 ischaemic stroke patients

	MRD + ASA – long term (first-line); ASA (second-line)	CLOP – long term (first-line); ASA (second-line)
Total costs (£)	37,430,180	39,897,888
Total QALYs	8724	8760
ICER (£)	–	68,848

CLOP, clopidogrel.

TABLE 39 Scenario analysis in 1000 TIA patients

	MRD + ASA – long term (first-line); ASA (second-line)	CLOP – long term (first-line); ASA (second-line)
Total costs (£)	37,195,638	39,634,600
Total QALYs	8760	8799
ICER (£)	–	62,702

CLOP, clopidogrel.

- *ischaemic stroke patients* MRD + ASA versus clopidogrel: MRD + ASA has more than 90% probability of being cost-effective at a threshold of £30,000 per QALY.
- *TIA patients* MRD + ASA versus clopidogrel: MRD + ASA has more than 90% probability of being cost-effective at a threshold of £30,000 per QALY.

Critique of Boehringer Ingelheim's economic model by the Assessment Group

The submitted model considers a wide range of treatment alternatives and describes a wide range of resources to populate the model. The model is mainly based on the PRoFESS[57] trial, although some data have been taken from ESPS-2[30] and ESPRIT[56] to obtain probability transitions in the ischaemic stroke group. The transition probabilities during the first 4 years for the MRD + ASA

TABLE 40 Results of one-way univariate sensitivity analyses of reference case: PRoFESS[57] trial central estimates used for clopidogrel and MRD + ASA (ischaemic stroke patients)

Profile letter	Sensitivity analysis	Source of sensitivity analysis assumption	ICER (£)
Base case			114,628
A	Recurrent IS rate of MRD + ASA used for CLOP		MRD + ASA dominates
B	Haemorrhagic stroke rate of MRD + ASA used for CLOP		MRD + ASA dominates
C	Haemorrhagic stroke rate of MRD + ASA multiplied by factor of 1.12	Estimated 80th percentile using SD data from PRoFESS[57] for IH	83,105
D	Non-vascular death rate of MRD + ASA used for CLOP		34,988
E	Vascular death rate of MRD + ASA used for CLOP		54,949
F	Dropout rate of MRD + ASA used for CLOP		234,647
G	Dropout rate of MRD + ASA multiplied by a factor of 1.1	Assumption in the absence of variance data for a categorical variable from PRoFESS[57]	88,872
H	Other haemorrhagic events rate of MRD + ASA used for CLOP		122,270
I	CHF rate of MRD + ASA used for CLOP		113,810
J	Non-drug costs increased by 50%	Assumption	88,278
K	Utility of haemorrhagic strokes multiplied by a factor of 0.9	Estimated 80th percentile using SD data from PROFESS[57] for IH	81,498
L	ESPRIT[56] data alone used to estimate ASA vs MRD + ASA (RR)		95,470
M	ESPS-2[30] data alone used to estimate ASA vs MRD + ASA (RR)		183,875

CHF, congestive heart failure; CLOP, clopidogrel; IH, intracranial haemorrhage; IS, ischaemic stroke; SD, standard deviation.

TABLE 41 One- and two-way sensitivity analysis of scenario sensitivity analysis case (ischaemic stroke patients)

Profile letter (see table 8 in MS)	Sensitivity analysis	ICER (£)
Base case		68,848
C	Haemorrhagic stroke rate of MRD + ASA multiplied by factor of 1.12	58,696
G	Dropout rate of MRD + ASA multiplied by a factor of 1.1	61,142
J	Non-drug costs increased by 50%	65,838
K	Utility of haemorrhagic strokes multiplied by a factor of 0.9	60,397
M	ESPS-2[30] data alone used to estimate ASA vs MRD + ASA RR	82,148
CG		53,242
CJ		55,561
CK		50,922
CM		68,147
GJ		58,255
GK		54,636
GM		70,110
JK		57,756
JM		78,198
KM		70,690

MS, manufacturer's submission.

and clopidogrel arms are derived from the above-mentioned trials, and beyond that point they have used the same transition probability as used for the last 6-monthly cycle. This is an unreliable basis for long-term projection, as close to the end of the trial patient numbers and the

number of events are much reduced. As a consequence, estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations.

Death rates amongst patients who have had strokes have been derived from two main papers;[90,91] when these papers were checked, the figures quoted in appendix 9 of the manufacturer's submission do not clearly match with those in the published papers. In relation to the TIA incidence rates, the manufacturer has assumed that patients who experienced TIAs had a rate of ischaemic stroke events equal to 80% of those who had experienced a previous ischaemic stroke; there is no evidence to support this assumption and it has not been tested in the one-way univariate sensitivity analysis.

The design of the model also includes tunnel health states to model adverse events. The tunnel health states are not depicted in the manufacturer's submission and are poorly addressed in the EXCEL model. The manufacturer's submission is sometimes hard to follow because of several mistakes in the appendices notation (e.g. manufacturer's submission, p. 27, section 3.2.1) and within the EXCEL model (e.g. Overview spreadsheet E35 cell in the EXCEL model says 10 years' time horizon instead of 50 years). The figure describing the model (manufacturer's submission, p. 25) has two arrows from 'no recurrent stroke' health state to 'non-vascular death', which is not consistent with the structure described.

The parameter distributions of costs used in the probabilistic sensitivity analysis are not commonly used distributions and their use is not justified by the manufacturer.

The manufacturer states that 'MRD + ASA long term first line is cost-effective against clopidogrel … Based on these ICERs at a threshold of £20,000 per QALY, it remains cost-effective until clopidogrel drops by 45% of brand price for ischaemic stroke patients or 51% for TIA patients' (manufacturer's submission, pp. 41–2). The Assessment Group notes that the generic price of clopidogrel as listed in the *Electronic drug tariff*[33] March 2010 is £10.90 (30 × 75-mg tablets); this constitutes a 69% reduction in price [branded Plavix (£36.35) was used in the model] and means that compared with MRD + ASA, clopidogrel is cheaper and more effective for both ischaemic stroke and TIA populations.

Review of the Sanofi–aventis/Bristol–Myers Squibb submission

See *Table 42*.

Overview of submitted manufacturer's submission

A Markov model is designed to assess the cost-effectiveness of clopidogrel, MRD + ASA, ASA and MRD alone for the secondary prevention of occlusive vascular events: MI, ischaemic stroke and vascular death. Cost-effectiveness estimates are calculated for four different patient populations:

- patients who have previously suffered a MI
- patients who have previously suffered an ischaemic stroke
- patients who were diagnosed with peripheral arterial disease
- patients with multivascular disease which is described as ischaemic disease in more than one vascular bed.

The same model structure is used throughout, but the baseline risks of vascular events differ for each population. The four treatments under consideration are compared against each other only in the ischaemic stroke population; whereas, in the MI, peripheral arterial disease and multivascular disease populations only clopidogrel is compared with ASA.

TABLE 42 The National Institute for Health and Clinical Excellence reference case checklist

NICE reference case requirements	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	As per the final scope issued by NICE
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	ASA, CLOP, MRD + ASA, MRD
Perspective on costs	NHS and PSS	As per the final scope issued by NICE
Perspective on outcomes	All health effects on individuals	As per the final scope issued by NICE
Type of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Synthesis of evidence on outcomes	Based on a systematic review	All data are derived from head to head trials (mainly CAPRIE[26])
Measure of health benefits	QALYs	QALYs
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Utilities (MI, PAD, stroke) derived from published, population-based studies (TTO or SG); utilities (MVD) based on assumption
Source of preference data for valuation of changes in HRQoL	Representative sample of general public	Population-based studies
Discount rate	An annual rate of 3.5% on both costs and QALYs	3.5% per annum for costs and health effects
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the model have the same weight

CLOP, clopidogrel; MVD, multivascular disease; PAD, peripheral arterial disease; PSS, personal social services; SG, standard gamble; TTO, time trade off.

The model estimates costs from the perspective of the UK NHS and health outcomes in terms of life-years and QALYs. A cohort of 1000 patients with the qualifying diagnosis (MI, stroke peripheral arterial disease or multivascular disease) and aged 65 years progresses through the model over a time horizon of 35 years. The starting age of 65 years was chosen as the average age in the PRoFESS[57] trial was 66.1 years, in CAPRIE[26] 62.5 years and in REACH[17] 68.6 years. The cycle length is 3 months and only one event can occur in each cycle. The model structure is depicted in *Figure 5*. Costs and benefits have been discounted at a rate of 3.5% per annum.

The model utilises six health states (see *Figure 5*):

1. *Initial state* This is the starting condition for all patients, and is considered to be a 'stable' state.
2. *Death* Separately recorded for deaths of non-vascular and vascular origin.
3. *History of MI* The condition of patients following a non-fatal MI.
4. *History of stroke* The condition of patients following a non-fatal ischaemic stroke.
5. *History of MI and stroke* The condition of patients who have suffered both a non-fatal MI and a non-fatal stroke.
6. *TA80 state* This intermediate state relates to the TA80 guidance,[45] which recommends that treatment with clopidogrel+ASA should be continued for up to 12 months (four cycles in the model) after the most recent acute episode of NSTEMI. In the model, after four cycles, patients go back to antiplatelet monotherapy.

All adverse events are included in the cost and QALY calculations, but are not recorded separately as distinct health states or events in the model.

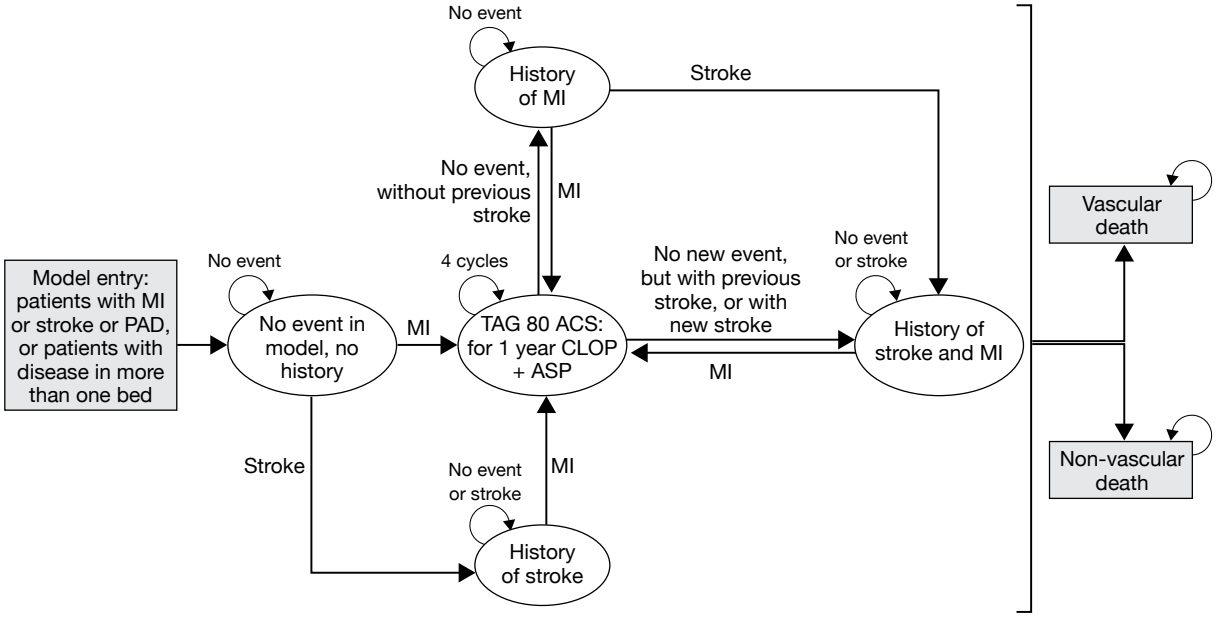

FIGURE 5 Diagram of the Markov model. ACS, acute coronary syndrome; ASP, aspirin; CLOP, clopidogrel; PAD, peripheral arterial disease; TAG, technology assessment guidance.

Each patient population (MI, stroke, peripheral arterial disease and multivascular disease) progresses through the model subject to its specific risk profile and parameters depending on previous history. The presence of previous vascular events thus influences the risk of future health states. Patients in the model can either remain stable or experience a MI or a stroke or death (from vascular or non-vascular causes). Deaths within 30 days of a new MI or stroke are defined as vascular deaths and such patients will progress directly to death.

Summary of effectiveness data

The baseline risk of events related to ASA has been taken from the REACH[17] registry and from a network meta-analysis of six studies: ESPS-2,[30] ESPRIT,[56] CAPRIE,[26] MATCH,[58] CHARISMA[59] and PRoFESS.[57] The REACH[17] registry recruited a large international cohort of patients ($n = 68{,}236$) with either established atherosclerotic arterial disease or at least three risk factors for atherothrombosis, and considered the outcomes of cardiovascular death, non-fatal MI and non-fatal stroke. The event rates were different for year 1 (REACH registry[17]), year 2 (unpublished – academic in confidence) and year 3 (published online[101]). The model assumes the 3-year data to be applicable for all subsequent years (years 3–35).

The manufacturer has constructed a matrix to allocate the correct risk of events to patients as they change health states through the model, such that state- and population-specific event rates and probabilities are assigned. This trace matrix is reproduced in *Table 43*.

The REACH[17] event risks are assumed to be applicable to a population treated with ASA, as 67% of registry patients received ASA monotherapy. Aspirin was chosen to be the treatment of reference to which the three other comparators are modelled. The relative treatment effects of the other three treatments (MRD, MRD + ASA and clopidogrel) versus ASA have been estimated based on direct estimates from clinical trials or indirect estimates from the network meta-analysis of the six studies mentioned above. The network meta-analysis was conducted for the end points – stroke, MI, vascular death, non-vascular death, and major and minor bleeding events.

TABLE 43 Trace matrix

Population no. after new event			Health state			
			No history	History of NF stroke	History of NF MI	History of stroke and MI
Population no. at start of model	1	Patients with previous stroke	1	1	4	4
	2	Patients with previous MI	2	4	2	4
	3	Patients with previous PAD	3	4	4	4
	4	MVD patients	4	4	4	4

MVD, multivascular disease; NF, non-fatal; PAD, peripheral arterial disease.
Source: manufacturer's submission.[52]

The base case in the model considers all ASA arms in the network meta-analysis studies to have equal efficacy. Non-vascular death rates have been derived from life tables. The non-vascular mortality rate is estimated by removing deaths owing to the diseases of circulatory system from age-specific deaths from all causes.

The following assumptions were used by the manufacturer in the model:

- Non-vascular death was assumed to be the difference between 'all-cause mortality' and 'death from vascular causes'.
- When fatal and non-fatal vascular events were not reported separately then the total of fatal and non-fatal events was used as an approximation for non-fatal events in the dataset.
- In the absence of any evidence on non-vascular death having a dose–response relationship with ASA (in contrast with the vascular events and adverse events), it was assumed that the risk of non-vascular death was equal for all ASA doses.
- As the ESPRIT[56] trial did not impose a specific ASA dose, but left the decision on dosing to the local investigators, the ASA arm of this trial was assumed to be a weighted average of the low, medium and high ASA dose arms, with weights equal to the proportion of patients observed on the different doses: 46%, 48% and 5%, respectively.
- The Antithrombotic Trialists' Collaboration (ATTC) data[66] describing the efficacy of ASA versus no treatment reported only on the composite end point of 'serious vascular events' but not on the separate components. Therefore, the assumption was made that the relative efficacy of ASA versus no treatment was equal for all these separate end points: MI, stroke and vascular death.

The model presents six different effectiveness analyses derived from the above sources:

1. network meta-analysis with the six studies above and ASA doses pooled (base case)
2. network meta-analysis splitting up the ASA comparator into three separate comparators: low-, medium- and high-dose ASA
3. head-to-head analysis based solely on the PRoFESS[57] trial
4. head-to-head analysis based solely on the CAPRIE[26] trial
5. head-to-head analysis based on post hoc analysis on multivascular disease patients from CAPRIE[26] trial.

To estimate the efficacy of clopidogrel + ASA in the TA80[45] state versus ASA, data from the CURE[27] trial have been used.

Summary of adverse events data

Baseline risk of adverse events relating to ASA has been derived from three papers: one meta-analysis[66] and two RCTs.[26,30]

The risk of a major bleeding event is taken from a meta-analysis of RCTs of antiplatelet therapy.[66]

The risk of minor bleeding event is derived from the ESPRIT[56] trial. The risk of dyspepsia is taken from the ESPS-2[30] trial comparing ASA with MRD and a combination of MRD + ASA for the secondary prevention of stroke.

Summary of costs and resource use

Event costs

The cost of a non-fatal stroke is a weighted average of the 3-month cost of an acute mild stroke, a moderate stroke and a severe stroke as estimated from a burden-of-illness model using patient-level data.[102]

The cost of a non-fatal MI is taken from a regression analysis[103] calculating the impact of diabetes-related complications on health-care costs. This paper also estimates the cost of a vascular death as the average of the cost of a fatal MI and a fatal stroke.

The cost of a non-vascular death is based on an assumption from another economic model[104] that estimated the cost of dying from unrelated causes to be approximately £250.

The cost of a major bleeding event is an average of all Health Related Groups (HRG) Reference Costs that relate to major bleeding reported in the NICE CG36[105] costing report 2006 for atrial fibrillation, which mentions calculations for major and minor bleeding events applicable to atrial fibrillation patients.

The cost of a minor bleeding event is mentioned in the NICE report[24] as equal to the cost of a visit to an accident and emergency department, and reported upper and lower limits of £61 and £111, respectively.

The adverse event cost of dyspepsia is taken from a detailed cost analysis[106] of the supply and management of upper gastrointestinal and renal toxicity related to low-dose ASA use.

All events costs are summarised in *Table 44*.

TABLE 44 Event costs

Event	Cost (£)	Source
Non-fatal stroke	6307	Assumption: these costs are estimated from a range of UK-specific burden-of-illness papers, where necessary costs have been inflated to represent 2007–8 prices
Non-fatal MI	4893	
Vascular death	2726	
Non-vascular death	250	
Major bleed	2805	
Minor bleed	90	
Dyspepsia	141	
Three months post stroke	516	
Three months post MI	139	

Follow-up costs

The cost of care 3 months post stroke is estimated using the same weighted severity formula[107] used to calculate the costs of non-fatal stroke, and corrects the cost of ongoing care at home and the cost of ongoing care in an institution for the proportion of mild, moderate and severe stroke patients who are discharged to a home or an institution.

The post-MI cost is taken from a regression analysis[103] of costs for a cohort of diabetic patients.

Drug costs

All annual costs of the treatment are derived from MIMS[93] and are listed in *Table 45*.

Utilities

The utility values for patients with a history of stroke, MI or peripheral arterial disease were estimated from a previously published cost-effectiveness analysis,[76] and were derived from published, population-based studies using either the time trade-off or standard gamble techniques. *Table 46* provides the utility values used in the model. For the stroke utilities, severity-specific values were given (mild, moderate and severe), and as for costs, these were weighted to reflect the burden of severity in a patient cohort before being aggregated. The utility value for a patient with multivascular disease is not known, so it is assumed to be the minimum of the three other patient population values, which is the utility value for stroke patients (0.61).

TABLE 45 Drug costs

Treatment	Cost per year (£)
ASA (75 mg/day)	3.50
CLOP (75 mg/day)	442.26
MRD (2 × 200 mg/day)	91.25
MRD + ASA (MRD 2 × 200 mg/day + ASA 2 × 25 mg/day)	94.78

CLOP, clopidogrel.
Source: Manufacturer's submission.[51]

TABLE 46 Utility values

	Patients with previous stroke	Patients with previous MI	Patients with previous PAD	MVD patients
Long-term utility values				
No event	0.61	0.87	0.80	0.61
After stroke	0.61	0.61	0.61	0.61
After MI	0.61	0.87	0.61	0.61
After stroke and MI	0.61	0.61	0.61	0.61
Short-term decrements after event				
Stroke	–0.174	–0.248	–0.228	–0.174
MI	–0.058	–0.082	–0.076	–0.058
Major bleed	–0.300	–0.300	–0.300	–0.300
Minor bleed	–0.001	–0.001	–0.001	–0.001
Dyspepsia	–0.184	–0.184	–0.184	–0.184

MVD, multivascular disease; PAD, peripheral arterial disease.
Source: Manufacturer's submission.[51]

In deriving these utility values, the manufacturer has made several assumptions:

- Utilities need to be differentiated based on the baseline health state of the patient, acknowledging the fact that stroke patients and peripheral arterial disease patients might be more disabled and have lower QoL than MI patients.
- The utility value for multivascular disease patients should not be higher than the utility for those patients with disease in one vascular bed.
- Experiencing a vascular event should decrease QoL temporarily to account for the unpleasantness of the event itself, the time in hospital, recovery time and stress.
- After experiencing an event patients should not be better off in the long term than before the event (i.e. patients experiencing a MI after stroke could not have their utility increased).
- Experiencing adverse events (major and minor bleeds) and side effects (dyspepsia) also decreases a patient's QoL in the short term.

The long-term utility values for each health state reflect the event history of the patient, i.e. a patient with MI who then experiences a stroke is assigned the long-term utility value of a stroke, whereas a patient with MI who experiences another MI is assigned the long-term utility value of a MI (so does not suffer any long-term decrement). A peripheral arterial disease sufferer who then experiences a MI is assigned the long-term utility value of a multivascular disease patient.

Summary of results

Stroke patients

The results of the cost-effectiveness analysis for patients who have a history of stroke show that MRD + ASA (or MRD alone) is the most cost-effective treatment. The manufacturer states that if the NHS is willing to pay £31,200 then clopidogrel could be considered as a second-line treatment followed by ASA. This appears to be consistent with the efficacy results of the main RCTs, where clopidogrel was shown to be superior to ASA in the CAPRIE[26] trial, and similar to MRD + ASA in the PRoFESS[57] trial (*Table 47*).

Myocardial infarction patients

Clopidogrel when compared with ASA in the cost-effectiveness model was found to be more effective and more expensive. With an ICER of approximately £21,000 per QALY gained, clopidogrel appears to be a cost-effective treatment for patients with previous history of MI when compared with ASA (*Table 48*).

Peripheral arterial disease patients

Clopidogrel was found to be more expensive and more effective than ASA, with an estimated corresponding ICER of £18,854 (*Table 49*).

TABLE 47 Results for patients with a history of stroke

	ASA	CLOP	MRD + ASA	MRD
Total costs (£)	10,841	13,165	10,948	10,531
Total QALYs	4.83	4.90	5.28	4.45
Total life-years	7.60	7.75	7.96	6.78
Incremental net benefit vs ASA (£)		–90	13,533	–10,964
Incremental net benefit vs CLOP (£)			–13,623	10,875
ICER vs ASA (£)		31,204	237	825
ICER of CLOP vs comparator (£)			CLOP is dominated	5850

CLOP, clopidogrel.
Source: Manufacturer's submission.[51]

TABLE 48 Results for patients with a history of MI

	ASA	CLOP
Total costs (£)	6349	8992
Total QALYs	6.70	6.83
Total life-years	7.55	7.70
Incremental net benefit (£)		1194
ICER (£)		20,662

CLOP, clopidogrel.
Source: Manufacturer's submission.[51]

TABLE 49 Results for patients with a history of peripheral arterial disease

	ASA	CLOP
Total costs	£6138	£8608
Total QALYs	5.71	5.84
Total life-years	7.06	7.22
Incremental net benefit		£1461
ICER		£18,854

CLOP, clopidogrel.
Source: Manufacturer's submission.[51]

Multivascular disease patients

In this population it was found that clopidogrel was cost-effective compared with ASA with an estimated ICER of £15,524 per QALY gained (*Table 50*).

Summary of sensitivity analysis

The manufacturer has reported a deterministic scenario analysis using the different efficacy analyses included in the model. In the stroke population, clopidogrel is dominated by MRD + ASA in all of the possible efficacy analyses, and with or without treatment effect for non-vascular death. Clopidogrel is shown to be cost-effective when compared with ASA using CAPRIE[26] data only in both treatment-effect scenarios for non-vascular death (*Table 51*).

The ICERs for the other populations (MI, peripheral arterial disease and multivascular disease) also change slightly with the assumption concerning the treatment effect for non-vascular death in each of the efficacy analyses, resulting in clopidogrel appearing cost-effective with an ICER of < £30,000 per QALY. The best results for clopidogrel are in multivascular disease patients using data from the post hoc CAPRIE[26] trial efficacy analysis.

In summary, the cost-effectiveness of treatments for the secondary prevention of occlusive vascular events is sensitive to a range of different scenarios. Removing the treatment effect on non-vascular deaths is found to improve the cost-effectiveness estimates of clopidogrel. Cost-effectiveness is also found to be sensitive to the efficacy estimates: taking account of different ASA doses worsens the cost-effectiveness estimates, whereas using only a head-to-head analysis based on the CAPRIE[26] trial improves them. The estimates in the stroke population are least sensitive to a head-to-head analysis using the PRoFESS[57] trial.

A probabilistic sensitivity analysis was developed by the manufacturer using a Monte Carlo simulation undertaking 3000 iterations. At a threshold of £30,000 per QALY, the treatment

TABLE 50 Results for patients with a history of multivascular disease

	ASA	CLOP
Total costs (£)	8678	10,483
Total QALYs	4.68	4.80
Total life-years	6.00	6.13
Incremental net benefit (£)		1683
ICER (£)		15,524

CLOP, clopidogrel.
Source: Manufacturer's submission.[51]

TABLE 51 Summary of ICERs for patients with a history of stroke with and without treatment effect for non-vascular death

Assumption: treatment effect for non-vascular death	With assumption: ICER CLOP vs ASA (£)	Without assumption: ICER CLOP vs ASA (£)
NMA of ASA doses pooled (base case)	31,204	27,749
NMA of low-, medium- and high-dose ASA	58,070	46,500
CAPRIE[26] data only	28,486	24,010

CLOP, clopidogrel; NMA, network meta-analysis.

option with the highest probability of being cost-effective in MI, peripheral arterial disease and multivascular disease populations is clopidogrel and in stroke it is MRD + ASA, as *Table 52* shows.

In stroke patients, the average incremental net benefit of clopidogrel when compared with ASA is –£6 with an associated 95% CI of –£6320 to £7279.

The probabilistic sensitivity analysis in MI patients reports an incremental net benefit of £1187 (CI –£7692 to £10,260). The cost-effectiveness acceptability curve (CEAC) shows that for a threshold of £30,000 per QALY clopidogrel is cost-effective in 60% of the iterations.

For patients with peripheral arterial disease, the probabilistic sensitivity analysis estimates an average incremental net benefit of clopidogrel versus ASA of £1475 (CI –£6106 to £9476). The CEAC suggests that there is a 64% probability that, at a threshold of £30,000 per QALY, clopidogrel would be considered a cost-effective treatment for the prevention of occlusive vascular events.

For patients with multivascular disease, the average incremental net benefit of clopidogrel versus ASA is £1748 (CI –£5475 to £9179) and the CEAC suggests that there is a 68% probability of clopidogrel being cost-effective at a threshold of £30,000 per QALY.

Critique of Sanofi–aventis/Bristol–Myers Squibb's economic model

The manufacturer of clopidogrel has presented 'new' evidence of the clinical effectiveness and cost-effectiveness of clopidogrel on a set of four re-allocated patient populations (stroke, MI, peripheral arterial disease and multivascular disease); this means that none of the effectiveness results used in their modelling of cost-effectiveness are directly derived from publications from the CAPRIE[26] trial. The review group accepts that this new categorisation is more appropriate and

TABLE 52 Probability of being cost-effective for each patient population

Treatment	Threshold/QALY (£)	Population (%)			
		Stroke	MI	PAD	MVD
ASA	20,000	0	51	48	41
CLOP	20,000	0	49	52	59
MRD + ASA	20,000	97			
MRD	20,000	3			
ASA	30,000	0	40	36	32
CLOP	30,000	0	60	64	68
MRD + ASA	30,000	97			
MRD	30,000	3			

CLOP, clopidogrel; MVD, multivascular disease; PAD, peripheral arterial disease.
Source: Manufacturer's submission.[51]

results in better-defined and less-heterogeneous patient groups. However, the details that would be required to construct and populate a long-term disease model based on CAPRIE[26] are not available beyond the summary statistics presented in the manufacturer's submission.

The Assessment Group notes that the generic price of clopidogrel as listed in the *Electronic drug tariff*[33] March 2010 is £10.90 (30 × 75-mg tablets); this constitutes a 69% reduction in price [branded Plavix (£36.35) was used in the model]. Using this new price in the model improves the cost-effectiveness of clopidogrel.

The manufacturer's model is depicted in *Figure 5* and includes one health state called 'TA80 acute coronary syndrome', which represents treatment after a MI following the TA80[45] guidelines in the treatment of patients with NSTEMI. This document refers only to NSTEMI patients, yet the manufacturer's submission does not differentiate between STEMI and NSTEMI patients so the model does not reflect clearly the recommended treatment of patients following a MI.

The baseline event rates in the ASA arm are taken from the REACH[17] registry, whose population is a mixed population of patients with history of MI, stroke or peripheral arterial disease and patients with risk factors of cardiovascular disease. The original scope issued by NICE does not mention risk factors, only history of previous events. Also, these baseline event rates have been applied to patients in the ASA group; however, only 67% of the population of the REACH[17] registry have received ASA monotherapy.

The model assumes different transition probabilities every year until year 3. Beyond this point the last-cycle transition probabilities are used for the remainder of the time horizon from years 3 to 35. This is an unreliable basis for long-term projection, as close to the end of the trial patient numbers and the number of events are much reduced. As a consequence, estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations.

Calculations used to derive utilities are adequately described in the manufacturer's submission, but sometimes differences between adverse events utilities are not clearly explained (e.g. decrement utility after major bleed and minor bleed: there is a substantial difference between them which is not discussed). Also, utility values are calculated using an assumption of perfect health for patients before the event 1 ('utility' spreadsheet in the model) and this is inappropriate.

In the model, half-cycle correction and discount rate methodologies have been applied incorrectly; this affects the final results of the model and overestimates the number of QALYs generated.

Summary critique of models submitted by the manufacturers

The economic models submitted by the manufacturers are structured in terms of a limited number of disease states that are presumed to be largely homogeneous with respect to health costs and QoL. Moreover, the models do not allow previous health history to be preserved except in the simplest form. There are real dangers that significant interactions between competing risks (e.g. MI vs stroke, vascular death vs non-vascular death) may not be accurately represented in these Markov formulations and that initially minor anomalies can be amplified to large errors when extrapolated over a lifetime. The details that would be required to construct and populate a long-term disease model based on CAPRIE[26] and PRoFESS[57] are not available beyond the summary statistics presented in the manufacturer's submissions. Moreover, the revised definitions for assigning patients to the new groups are not completely clear, leading to some concern about how such data should be modelled. To reduce this problem, the Assessment Group requested that a set of analyses should be carried out by the manufacturer to allow a new model to be developed and calibrated for these four patient groups. For this we provided appropriate definitions of each population, and detailed specifications of the three types of analyses required: survival analyses (Kaplan–Meier and Cox regressions), numbers of outcome events and patient exposure to risk, and event fatality (see *Appendix 9* for details).

Independent economic assessment

Methods

Approach to modelling occlusive vascular events

Modelling disease-related health and the economic effects of chronic lifetime conditions presents additional and different challenges to those encountered when dealing with conditions of an acute or time-limited nature. In particular, over a lifetime, patients are subject to multiple interacting competing risks of fatal and non-fatal events, and the accumulation of complex and dynamic health histories with a resulting dynamic pattern of prognostic risks. To overcome these challenges the Assessment Group has chosen to develop a new model of occlusive vascular events involving individual patient sampling. Instead of considering patients in aggregated groups with average characteristics, we generate a series of individual patients whose combined characteristics are representative of the specified population. The advantage of this approach is that individual patient histories can be generated according to a number of known competing risks, so that interactions are automatically accounted for.

Obtaining these advantages often involves significant technical costs in terms of complex programming and long processing times, which involve the use of very large numbers of random numbers in order to achieve stable results. To reduce these difficulties the Assessment Group has designed the model structure to operate within a Microsoft Excel workbook with limited additional coding and incorporating several 'variance reduction' techniques.

Patient populations

Four mutually exclusive patient populations are modelled using the following definitions:

- *MI only* This population is defined as patients suffering a recent acute MI, who may have a prior history of ischaemic heart disease, but have no prior history of ischaemic stroke, TIA or peripheral arterial disease.
- *ischaemic stroke/TIA only* This population is defined as patients suffering a recent ischaemic stroke or TIA, who may have a prior history of ischaemic cerebrovascular events, but have no prior history of ischaemic heart disease (including MI) or peripheral arterial disease.
- *Peripheral arterial disease only* This population is defined as patients suffering a recent episode of peripheral arterial disease, but who have no prior history of ischaemic stroke or TIA, or ischaemic heart disease (including MI).
- *Multivascular disease* This population is defined as patients suffering a recent episode of acute MI, ischaemic stroke or TIA, or peripheral arterial disease, and who have a prior history involving at least one other type of vascular disease.

In order to characterise each of these populations in terms of age and gender, an analysis of data from the *Health Survey for England 1996*[108] has been carried out, using data on self-reported chronic health conditions to identify samples corresponding to the four modelled populations (*Table 53*). (Note: the *Health Survey for England 1996* was commissioned by the Department of Health and carried out by the Joint Surveys Unit of Social and Community Planning Research and the Department of Epidemiology and Public Health at University College London, who bear no responsibility for the analysis or interpretation of its data presented in this report.)

Treatment strategies

It is clear from the available evidence[56,57] that a significant proportion of patients do not persist with the medication initially prescribed, either because of unacceptable adverse events associated with the drug or for other personal or lifestyle reasons. When discontinuation occurs, it is necessary to prescribe an appropriate alternative treatment if one is available; as a consequence, the effect of treatment on future risks will be modified. It is therefore necessary to assess the effectiveness and cost-effectiveness of preventive medicines within the framework of lifetime treatment strategies. *Tables 54* and *55* set out the treatment strategies that may be compared using the economic model for each patient population.

Model design

The logic flow for generating a full patient history for each sampled patient is shown in *Figure 6* for the first two key events. As event times are estimated as continuous variables, it is not possible for a conflict to arise with two events occurring simultaneously. Subsequent events repeat the same pattern. Each patient continues to accumulate additional events until a fatal event is encountered.

TABLE 53 Modelled populations: age and gender

	IS only			MI only			PAD only			MVD		
	Age (years)		Proportion	Age (years)		Proportion	Age (years)		Proportion	Age (years)		Proportion
Gender	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%
Male	67.75	12.95	54.9	65.01	11.96	49.9	61.75	13.96	48.6	63.92	11.33	53.1
Female	67.62	12.97	45.1	70.50	9.67	50.1	65.17	15.98	51.4	70.39	11.63	46.9

IS, ischaemic stroke; MVD, multivascular disease; PAD, peripheral arterial disease; SD, standard deviation.

TABLE 54 Treatment strategy: ischaemic stroke/TIA population

Intolerance				Strategy stages		
None	ASA	MRD	ASA + MRD	Treatment 1	Treatment 2	Treatment 3
✓	✓	✓	✓	Nothing	Nothing	Nothing
✓	×	✓	×	ASA		
✓	✓	✓	✓	CLOP		
✓	×[a]	×	×	MRD + ASA		
✓	×	✓	×	ASA	CLOP	
✓	×	×	×		MRD + ASA	
✓	×	✓	×	CLOP	ASA	
✓	×[a]	×	×		MRD + ASA	
✓	×	×	×	MRD + ASA	ASA	
✓	×[a]	×	×		CLOP	
✓	×	×	×	ASA		MRD + ASA
✓	×	×	×		MRD + ASA	CLOP
✓	×	×	×	CLOP	ASA	MRD + ASA
✓	×	×	×		MRD + ASA	ASA
✓	×	×	×	MRD + ASA	CLOP	
✓	×	×	×		ASA	CLOP

CLOP, clopidogrel.
a Viable if MRD + ASA replaced by MRD.

TABLE 55 Treatment strategy: MI only, peripheral arterial disease and multivascular disease populations

	Strategy stages		
Intolerant to ASA	Treatment 1	Treatment 2	Treatment 3
✓	Nothing	Nothing	Nothing
×	ASA	Nothing	Nothing
✓	CLOP	Nothing	Nothing
×	ASA	CLOP	Nothing
×	CLOP	ASA	Nothing

CLOP, clopidogrel.

Key events

The following are identified as events that determine the event history of each modelled patient:

- a new fatal or non-fatal ischaemic stroke event
- a new fatal or non-fatal non-ischaemic stroke event (haemorrhagic stroke or intracranial haemorrhage)
- a new fatal or non-fatal MI
- death from other vascular causes
- death from non-vascular causes
- patient discontinues current preventive medication for any reason.

When any of these events occurs, the age, disability status and event history of the patient is updated to the time of the latest event, and the current preventive medication is updated if

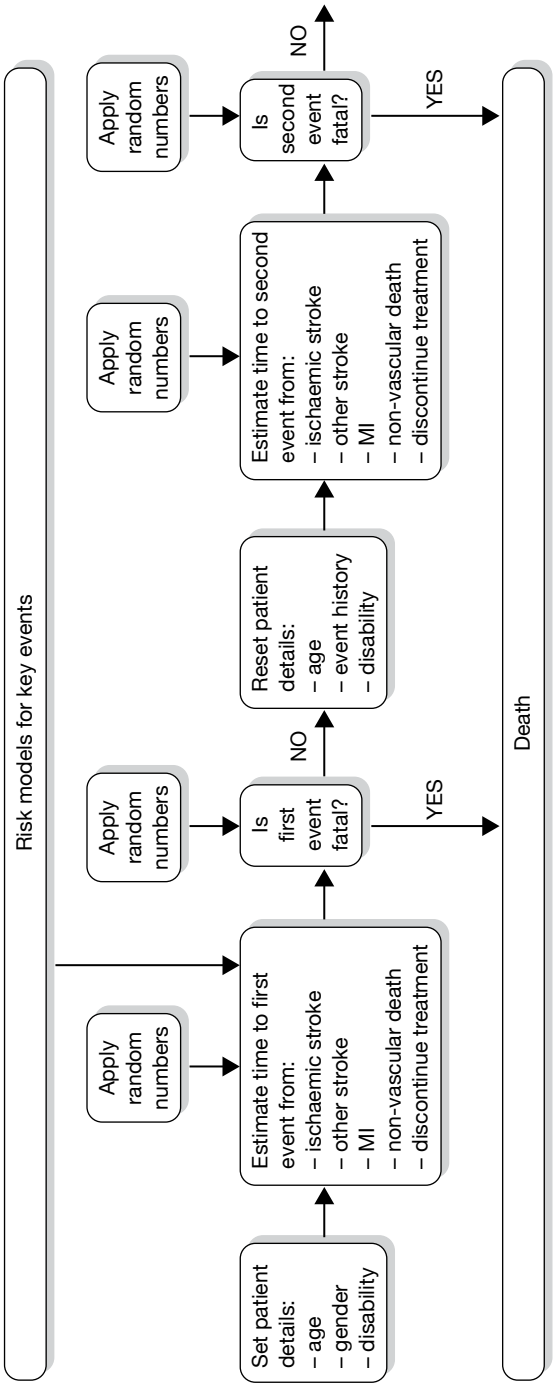

FIGURE 6 Patient sampling model flow chart for a sequence of key events within a single patient history.

necessary to the next stage of the defined treatment strategy. The revised patient details are then used to estimate likely event times for the next key patient event until death occurs.

Other events

Additional non-fatal events may also occur to patients and are estimated independently of the main event pathway to ensure their effects on patient experience and health-care resource use are captured by the model. The current model includes several recognised adverse events associated with antiplatelet therapy (major and minor bleeding, gastric problems, etc.) and additionally new/worsened congestive heart failure as a possible event.

Disability

Continuing functional disability resulting from stroke events is known to be a prognostic indicator for high-risk events and greater mortality among affected patients.[91]

The model includes a binary measure of functional disability equivalent to scores of ≥ 3 on the modified Rankin Scale.[60]

The risk of progression to disabled status following a stroke event was derived from an analysis of PRoFESS results [Boehringer Ingleheim. *Clinical Trial Report for PRoFESS* (unpublished); 2008] and is used as a risk modifier for subsequent events.

Risk models

Confidential information from the two key clinical trials (CAPRIE[26]and PRoFESS[57]) has been provided to the Assessment Group in order to allow calibration of the model, and, in particular, to facilitate development of risk models incorporating all relevant modifying variables, and avoiding errors arising from incorrect application of competing risks. Full details of the derived parameter values for all model events are provided in *Appendix 10*.

Event fatality

Data from the CAPRIE[26] trial provided by the manufacturer of clopidogrel has allowed separate fatality risk models to be developed for the three primary vascular events. Details of the analysis and parameter values are shown in *Appendix 11*.

Duration of treatment

Some patients taking continuous preventive medication will eventually discontinue treatment for a variety of reasons. Analysis of clinical trial data from PRoFESS[57]and ESPRIT[56] (see appendices 5–7 of Boehringer Ingelheim's manufacturer's submission) indicates that continuance falls steadily over time, but that a substantial proportion of patients will continue taking the prescribed treatment indefinitely. The most appropriate representation is found to be an exponential survival function, with a minimum 'floor' probability of continuing treatment. Survival functions have been estimated for clopidogrel from PRoFESS[57] data, for MRD + ASA from PRoFESS[57]and ESPRIT,[56]and for ASA alone from ESPRIT.[56]

A random number is used to place each patient/treatment combination on the appropriate survival curve and to calculate the corresponding time of discontinuation. A facility is included to limit the duration of any treatment to a prespecified maximum duration, after which the patient automatically progresses to the next step in the treatment strategy.

Resource use

Health-care resource use is measured in terms of clinical events and time spent in chronic states, as well as duration of continuing medication as follows:

- Events:
  - ischaemic stroke (fatal/non-fatal)
  - non-ischaemic stroke (fatal/non-fatal)
  - myocardial infarction (fatal/non-fatal)
  - other vascular event (fatal)
  - non-vascular death
  - adverse events related to medication.

- Chronic states:
  - prior disabling stroke
  - no prior disabling stroke
  - prior MI
  - history of peripheral arterial disease
  - history of multivascular disease (disabled/non-disabled).

Cost estimates

Unit costs are drawn from a variety of sources, including those used in the two manufacturer's submissions.[51,52] In all cases the latest costs/prices have been used[33,109,110] and, where appropriate, costs have been inflated to 2009 prices using the Hospital and Community Health Services price inflation index reported by the PSSRU.[92]

Key events Unit costs for the primary events projected in the model are shown in *Table 56*, distinguishing between disabling and non-disabling strokes. The model logic uses two parameters for non-fatal stroke and MI events in which an event cost is assigned to a patient at the time of the event (assumed to encompass excess early recovery/rehabilitation costs not covered by long-term service use) and a continuing care cost related to the time following the time of the event until the patient's status changes.

Costs for stroke events are taken from Youman *et al.*,[102] uplifted for inflation from 2001. MI costs are more problematic, as the only source cited by either manufacturer [the UK Prospective Diabetes Study (UKPDS) No. 65][103] relates only to patients with type 2 diabetes who are known to incur substantially greater unit costs for all types of health care (in terms of both frequency and intensity of resource use). The main trials (PRoFESS[57]and CAPRIE[26]) only include a minority of patients with diabetes, reflective of the prevalence within the general population of vascular patients, and therefore there is a likelihood that without adjustment these costs will be overestimated. In the UKPDS paper[103] two MI costs are estimated: an average for all patients

TABLE 56 Unit costs for key model events by disability status

	Patient status	
Key model event	Not disabled (Rankin Scale 0–2)	Disabled (Rankin Scale 3–5)
Non-fatal IS	£6409.94	£13,647.38
Fatal IS	£8767.69	£8767.69
Non-fatal haemorrhagic stroke/ICH	£6409.94	£13,647.38
Fatal haemorrhagic stroke/ICH	£8767.69	£8767.69
Non-fatal MI	£5761.88	£5761.88
Fatal MI	£2218.39	£2218.39
Other vascular death	£2225.00	£2225.00
Other non-vascular death	£2225.00	£2225.00

ICH, intracranial haemorrhage; IS, ischaemic stroke.

(including 20–26% who received no inpatient care) and a greater average only for those patients admitted to hospital. In recognition of the risk of overestimating MI costs from this source, we selected the lower figure for both fatal and non-fatal MIs and uplifted these unit costs for inflation from 1999.

Continuing care Estimated unit costs are shown in *Table 57*. For stroke survivors, the annual costs of ongoing health and social care services are based on the estimates produced by Youman *et al.*,[102] uplifted for inflation from 2001. For non-disabled stroke survivors the non-institutionalised unit cost was used, and for disabled survivors a weighted average of patients living at home and in institutions was calculated. For non-fatal MI patients, continuing care costs were obtained by combining the inpatient and outpatient costs reported in UKPDS No. 65,[103] uplifted for inflation from 1999. Continuing care costs are assumed to be hierarchical on the basis of accumulating patient history; so, a patient suffering a stroke will continue to incur the higher care costs even after surviving a subsequent MI.

Adverse events To estimate the costs of adverse events related to the various treatments we chose to adopt the categories used in the Sanofi–aventis/Bristol–Myers Squibb submission (major/minor bleeding and dyspepsia), but have also incorporated hospital events involving the initiation or worsening of congestive heart failure as used in the Boehringer Ingelheim submission.[51]

Table 58 shows the frequency parameters used, as well as the unit costs. Costs have broadly followed the methods used by the manufacturers, but using the latest cost sources and inflating costs to 2009. The overall average annual costs are applied to all patients for the periods when each of the treatments is in use.

Antiplatelet therapy The estimated NHS cost of each component of antiplatelet therapy is shown in *Table 59* for the relevant periods of treatment. Clopidogrel has recently become available to the NHS at a slightly reduced price, although it should be noted that the generic form is not licensed for all indications covered by the branded product.

Health valuation

Health-utility values are drawn from a variety of sources, including those used in the two manufacturer's submissions.[51,52]

Mean utility values are assigned to each chronic health state and a specific utility decrement effect is applied for each modelled event.

The European Quality of Life-5 Dimensions (EQ-5D) data collected in the PRoFESS[57] trial have been used to estimate the utility for ischaemic stroke patients prior to any subsequent key events and to determine the long-term utility decrement applicable to suffering stroke-related disability. In addition, the PRoFESS[57] results allowed utility decrements to be applied following the first subsequent non-fatal key event, as well as a single decrement for more than one subsequent key event.

TABLE 57 Annual care costs for key model events by disability status

Patient status	Annual continuing care cost (£)
No key events	0.00
Non-fatal MI	577.60
Non-fatal non-disabling stroke	1686.04
Non-fatal disabling stroke	5175.44

TABLE 58 Costs for adverse events by type of treatment

		Annual event frequency by treatment[a] (%)				
Adverse event	**Unit cost (£)**	**ASA**	**CLOP**	**MRD**	**MRD/ASA**	**None**
Major bleeding event	2010.35	0.54	0.41	0.13	0.46	0.00
Minor bleeding event	111.57	0.93	0.93	0.38	0.87	0.00
Dyspepsia	146.61	2.33	1.99	5.85	6.19	0.00
CHF event/worsening	1074.92	0.63	0.75	0.63	0.63	0.63
Combined average cost (£)		**22.08**	**20.10**	**18.42**	**26.18**	**6.80**

CHF, congestive heart failure; CLOP, clopidogrel.
a Frequency values for bleeding events and dyspepsia taken from Bristol–Myers Squibb model. CHF frequency is the overall average value in the PRoFESS[57] trial, as there is no evidence of increasing/decreasing time trends.

TABLE 59 Unit costs for adverse events by type of treatment

Treatment	Dose	Annual cost (£)	4 weeks' cost (£)	Single-dose cost (£)	Source
ASA	75 mg daily	6.9888	0.5350	–	BNF 58[32]
MRD	200 mg twice daily	91.3125	–	–	BNF 58/NHSDT (April 2010)[33]
MRD + ASA	200 mg/25 mg twice daily	94.8433	–	–	BNF 58[32]
CLOP (branded)	300 mg	–	–	4.8473	BNF 58[32]
CLOP (branded)	75 mg daily	442.5613	33.9267	–	BNF 58[32]
CLOP (generic)	75 mg daily	132.7075	10.1733	–	NHSDT (April 2010)[33]

CLOP, clopidogrel; NHSDT, NHS Electronic Drug Tariff.

The utility values used in the Sanofi–aventis/Bristol–Myers Squibb model for MI and peripheral arterial disease without a subsequent key event (0.87 and 0.80, respectively, drawn from a study by Schleinitz *et al.*[75]) are adopted here. Although no data can be traced relating to multivascular disease patients, we have assumed that they are likely to begin treatment with a rather worse HRQoL than patients with only a single type of vascular disease and we have adopted a value of 0.75.

The estimate of utility decrement applicable to a congestive heart failure event used in the Boehringer Ingelheim model appears to be well sourced and has been adopted for this model, indicating an event decrement of –0.0163 QALYs. The utility impact of the other events (major/minor bleeding events and dyspepsia) proved more difficult to identify.

The reference given for a minor bleed[111] draws upon an earlier paper by O'Brien and Gage,[112] which lists the source as 'assumption'. The suggested decrement (–0.2) is relative to a theoretical 'perfect health' state rather that of a patient with established chronic disease and so may be overstated. As this condition is considered to last for only 2 days, the magnitude of this factor in determining cost-effectiveness must be very small and we have adopted a notional decrement of –0.0033 QALYs in the absence of any more reliable source.

The estimate for dyspepsia is drawn directly from Jansen *et al.*[113] but fails to recognise that each event is estimated to last just 3 weeks rather than the 13 weeks used in the Bristol–Myers Squibb/Sanofi–aventis model. Adjusting for this problem yields an estimated utility decrement per event of –0.0106 QALYs.

The Sanofi–aventis/Bristol–Myers Squibb utility calculations for major bleeding events draw on three patient categories in the paper of Jansen *et al.*,[113] for gastrointestinal events (outpatient treatment, inpatient treatment and treatment involving surgery) and one for intracranial haemorrhage events.[114] Only one of the figures used from Jansen's paper[113] can be traced and validated from the original sources and the events are taken by Jansen *et al.*[113] to last for 5 weeks, rather than the 13 weeks implicit in the Sanofi–aventis/Bristol–Myers Squibb model. The paper by Quinn *et al.*[114] uses a crude approach to estimating the utility decrement of an intracranial haemorrhage event, involving an assumption that utility falls from 1.0 ('perfect health') to 0.0 ('death') for the whole duration of the event, estimated at 11 weeks. This must be taken as a substantial overestimate. Reworking these calculations suggests a decrement in utility from a major bleeding event of –0.1426 QALYs (compared with the Sanofi–aventis/Bristol–Myers Squibb estimate of –0.3003 QALYs).

In principle, utility decrements should be considered for both long-term state of a patient following a significant event and also associated with the short-term impact of the event in the immediate acute and post-acute periods. Only one study[115] has been identified which has attempted in any way to discriminate between these two effects; in table 2 of the paper[115] the authors report results of two regression analyses involving parameters that distinguish the effect of events in the last 12 months from those in previous years. Subtracting the estimated long-term value from the short-term value should indicate[113] the magnitude of the short-term excess disutility associated with experience of the event itself. However, the results are inconclusive, as this approach appears to indicate a net utility gain from a stroke that is not clinically meaningful. Moreover, the numbers of recorded events are insufficient to generate statistically significant differences between coefficients. As a result it has been concluded that it is not currently possible to assign meaningful disutility estimates to model events in addition to the long-term state-related impact described above, and this element of utility estimation has been omitted.

Discounting

Discount rates of 3.5% for both costs and health outcomes (life-years and QALYs) are used. Discounting is applied annually after the first year.

Time horizon

A lifetime perspective is taken for the model.

Variance reduction

Two specific measures are implemented in the model to limit background random variation and improve efficiency of model performance.

Random assignment of age/gender is not used for individual patients. Instead, 100 points across the standard normal probability distribution are used to define a distinct set of baseline ages for each gender drawn from the specified population providing a fully representative spread of patients by age and gender. This basic set is then reproduced 10 times to yield a total of 2000 individual patients. Finally, results are generated separately for males and females and overall mixed population results are obtained by applying the appropriate gender proportions to yield weighted averages.

The random numbers that govern the occurrence of events are not generated every time that the model is run. Instead, a full set of random numbers is stored and accessed identically for each patient when generating patient histories for different treatment strategies. This ensures that differences apparent in the results obtained are solely because of the difference in treatments and are not arising from the uncontrollable impact of large numbers of 'in-process' random

fluctuations. The stability of the incremental results obtained can be assessed by comparing results from a number of stored random number sets.

Assessment of uncertainty

Univariate sensitivity analysis is carried out for a full range of model parameters.

Other modelling issues

Three modelling difficulties are apparent from consideration of previous TAs and the related NICE guidance.

Modelling transient ischaemic attack

The Technology Assessment Report[3] that led to the development of the current guidance[24] on secondary prevention of occlusive vascular events included some consideration of patients suffering from TIA despite the absence of separate trial information for the effectiveness of either treatment for this patient group. A simple assumption was made that TIA patients were at risk of future events at a reduced (80%) rate compared with ischaemic stroke patients. This failed to take into account two published papers presenting results from the Oxfordshire Community Stroke Project, showing the risk of stroke following a first-ever stroke[90] or following a TIA.[116]

More recently a Canadian population study[117] provided similar findings for TIA patients. *Table 60* does not suggest that there is strong evidence to make a distinction between TIA patients and those surviving an ischaemic stroke. On this basis it has been assumed that TIA patients may be subsumed within the stroke model population, as long-term risks appear to be similar.

Technology Appraisal No. 80[45] guidance and the myocardial infarction population

On the basis of evidence from the CURE[27] trial, NICE guidance document TA80[45] recommends that patients surviving a NSTEMI event should receive clopidogrel and low-dose ASA as medication for the prevention of further MI events for a period of 12 months, followed by low-dose ASA alone thereafter. There is no current guidance for surviving STEMI patients beyond the immediate post-MI period.

The only clinical trial evidence submitted for the current appraisal relating to the MI-only patient population is from a subgroup of the CAPRIE[26] trial population, which involves a mix of STEMI and NSTEMI patients. No analyses are provided in the CAPRIE[26] clinical study report distinguishing between STEMI and NSTEMI patients.

Similar concerns apply to the multivascular disease population, as a proportion of these patients may have MI as the qualifying event. No information is available on the composition of the multivascular disease group in CAPRIE[26] by qualifying event so it is difficult to determine how any meaningful subdivisions could be applied.

TABLE 60 Future risk of stroke following TIA or stroke in community

	Stroke risk	
Population	**At 12 months, % (95% CI)**	**At 5 years, % (95% CI)**
Oxford stroke patients	13.2 (10.0 to 16.4)	29.5 (19.8 to 39.0)
Oxford TIA patients	11.6 (6.9 to 15.8)	29.3 (21.3 to 37.3)
Alberta TIA patients	14.5 (12.8 to 16.2)	–

As reviewing the existing TA80 guidance[45] and CG48 guidelines[7] is not within the scope of this appraisal, it is necessary to assume that recommendations for post-MI preventive treatment of both NSTEMI and STEMI patients remain valid. However, it would be inappropriate to begin modelling MI-only patients while still subject to these short-term provisions (12 months for NSTEMI and 4 weeks for STEMI patients). We therefore assume that all MI-only patients have survived to the end of the specified period without suffering a further MI, or any other occlusive vascular event (which would require them to be reclassified as multivascular disease patients), prior to embarking on the chosen long-term preventive treatment strategy. This avoids the necessity of identifying MI patients as either STEMI or NSTEMI from the outset.

Technology Appraisal No. 80[45] and subsequent myocardial infarction events in all populations

In all four populations defined above there is a risk of future MI events, some of which will be non-fatal. Therefore, the TA80 guidance[45] requires that the affected patients (i.e. those suffering an NSTEMI event) should be switched to clopidogrel + ASA for 12 months. For modelling it becomes necessary to estimate the probability of NSTEMI versus STEMI to assign the correct post-event short-term treatment, although none of the available trials provides information on the type of MI suffered. The GRACE (Global Registry of Acute Coronary Events)[118] study of acute coronary syndrome patients is used to estimate the proportions of STEMI/NSTEMI in the population as 53.8%/46.2% (MIs excluding unstable angina). To accommodate the effects of TA80 guidance[45] in the model, a simplification has been applied, which involves a reduction to the short-term post-MI risk that was estimated from the CAPRIE[26] data to reflect the benefits observed in CURE,[27] and a corresponding short-term increase in treatment costs for the 12 months post MI, both averaged by the STEMI/NSTEMI proportions in the GRACE[118]study.

In addition, the follow-on treatment after 12 months (ASA alone or 'standard care') needs to be interpreted in the context of the model treatment strategies. Where an 'MI-only' patient suffers subsequent MI events, but no other type of occlusive event, treatment may resume at the stage of the treatment strategy prior to the latest MI(s) requiring short-term follow-up. If an 'MI-only' patient suffers a different kind of occlusive event, they attract the higher risks associated with multivascular disease patients for the remainder of their life. In the same way a 'stroke-only' or 'peripheral arterial disease-only' patient suffering a MI will also be subject to the higher multivascular disease risks once the short-term follow-up care is complete. Equally, an 'MI-only' or 'peripheral arterial disease-only' patient suffering an ischaemic stroke may receive up to 2 years' MRD + ASA treatment as required by TA90,[24] and, subsequently, resume the long-term care strategy subject to the increased multivascular disease event risks.

Technology Appraisal No. 90[24] and subsequent ischaemic stroke events in all populations

The National Institute for Health and Clinical Excellence TA90 guidance[24] recommends the use of MRD + ASA for up to 2 years following a non-fatal ischaemic stroke event. The Assessment Group model has been adapted to reflect this feature, which may be rendered active or inactive at the user's discretion. The adaptation involves introducing a pseudoevent at the end of the TA90[24] recommended treatment period, before the patient resumes at his or her prior stage in the assigned treatment strategy. This is an effective mechanism for coping with the added complexity of TA90 guidance.[24]

However, it does result in some potential loss of integrity in the matching of random number sequences between comparator model runs (a mechanism used for 'variance reduction' in the model); in principle this might introduce some element of bias into the results, but it would occur in only the later stages of a patient's career when many patients have already died and appears

more likely to underestimate incremental differences than to overestimate them. A simple test of this effect is to compare model results with and without this feature activated, as the model results obtained when the TA90[24] feature is inactive are not subject to any potential bias. To date the Assessment Group has not detected any evidence of any bias affecting the decision analysis results.

A note of caution is necessary here against attempting to use a comparison of model results with and without the TA90[24] feature turned on as a means of reconsidering the validity of TA90 guidance.[24]

As currently constructed, the model would not be valid for this purpose and would require important modifications to achieve such an objective. As this is not within the scope of the current appraisal, no effort has been made to pursue this possibility.

Independent economic model results

Results have been generated from the Assessment Group's model to address two related questions:

1. Which treatment strategy is most cost-effective in avoiding future occlusive vascular events in each of the four specified populations?
2. How does the availability of generic clopidogrel at a lower price than the branded product affect the assessment of cost-effectiveness of clopidogrel containing treatment strategies?

Detailed results are given in this section separately for each of the four populations previously defined and using deterministic analyses. Of particular interest is the stability of cost-effectiveness findings when the size of the sampled patient population is varied. Our initial analyses were based on a sample size of 2000 patients. Further exploratory analyses were then conducted with alternative first-order random number sets and it became evident that there was scope for differing results to be obtained when other random number sets of this size are used to define the sample. Larger sample sizes were found to provide stable results across all populations and scenarios. It was therefore decided to expand the sample size from 2000 to 10,000 simulated patients and re-assess the most cost-effective treatment scenario for each of the four patient groups against the deterministic results reported. For three of the four patient populations ('MI only', 'peripheral arterial disease only' and multivascular disease) the results of the updated analysis based on a sample size of 10,000 were very similar to those based on the 2000 sample size and did not show any alterations in the optimal treatment strategy. However, for the 'ischaemic stroke' population, results for two analyses using generic clopidogrel led to a change in the optimal strategy as reported in the initial Assessment Group submission to NICE. The changes are incorporated into this document.

Ischaemic stroke-only patients

Deterministic analysis

Tables 61 and *62* summarise the main economic results obtained with the Assessment Group model for the ischaemic stroke patient population. *Figures 7–10* illustrate these findings in the form of a cost-effectiveness plane plot with cost-effectiveness frontier. The primary analysis (first block in *Tables 61* and *62* and *Figure 7*) reveals that only two strategies lie on the boundary, but neither of these involves initial use of clopidogrel. In all scenarios, the most cost-effective strategy begins with MRD + ASA, followed by ASA and finally clopidogrel.

TABLE 61 Deterministic results from the Assessment Group's model for treatment of the 'ischaemic stroke-only' population

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	Incremental analysis vs no treatment			Incremental analysis vs ASA			Incremental analysis vs ASA → MRD + ASA		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)
Full	MRD + ASA	None	None	None	35,202	7.056									
		ASA			32,955	7.157	0.102	−2247	**−22,106**[a]						
		CLOP			37,910	7.620	0.564	2709	4802	0.462	4956	10,716	−0.060	3201	Dom
		MRD + ASA			35,266	7.591	0.535	64	120	0.434	2311	5329	−0.089	556	Dom
		ASA	CLOP		35,137	7.687	0.632	−64	−102	0.530	2183	4118	0.007	427	59,033
		ASA	**MRD + ASA**		34,710	7.680	0.624	−492	−787	0.523	1755	**3357**[a]			
		CLOP	ASA		37,809	7.743	0.687	2607	3796	0.585	4854	8295	0.062	3099	49,665
		CLOP	MRD + ASA		38,098	7.744	0.688	2897	4211	0.586	5144	8773	0.063	3388	53,370
		MRD + ASA	ASA		35,187	7.730	0.674	−15	−22	0.573	2232	3898	0.050	477	9581
		MRD + ASA	CLOP		36,321	7.734	0.678	1120	1651	0.577	3367	5840	0.054	1612	29,982
		ASA	CLOP	MRD + ASA	35,161	7.708	0.653	−41	−62	0.551	2206	4003	0.028	451	15,909
		ASA	MRD + ASA	CLOP	34,867	7.696	0.640	−335	−523	0.538	1912	3552	0.016	157	10,098
		CLOP	ASA	MRD + ASA	37,811	7.769	0.713	2609	3657	0.612	4856	7938	0.089	3101	34,857
		CLOP	MRD + ASA	ASA	38,096	7.781	0.725	2895	3992	0.624	5142	8246	0.101	3387	33,621
		MRD + ASA	CLOP	ASA	36,336	7.774	0.719	1134	1579	0.617	3382	5481	0.094	1626	17,267
		MRD + ASA	**ASA**	**CLOP**	35,356	7.759	0.703	155	220	0.601	2402	3994	0.079	647	**8222**[a]

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	Incremental analysis vs no treatment			Incremental analysis vs ASA			Incremental analysis vs ASA → MRD + ASA		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)
	Not used	None	None	None	35,267	7.126									
		ASA			34,594	7.644	0.518	–673	**–1299**[a]						
		CLOP			38,018	7.680	0.554	2751	4966	0.036	3423	95,065	–0.041	3230	Dom
		MRD + ASA	None		35,434	7.651	0.525	167	318	0.007	840	116,441	–0.069	646	Dom
		ASA	CLOP		35,203	7.727	0.601	–64	–106	0.083	609	7336	0.006	415	64,448
		ASA	**MRD + ASA**		34,788	7.721	0.594	–479	–806	0.077	194	**2532**[a]			
		CLOP	ASA		37,981	7.804	0.678	2714	4004	0.160	3386	21,189	0.083	3193	38,344
		CLOP	MRD + ASA		38,267	7.809	0.683	3000	4394	0.165	3673	22,278	0.088	3479	39,394
		MRD + ASA	ASA		35,355	7.783	0.656	88	134	0.138	761	5494	0.062	567	9159
		MRD + ASA	CLOP		36,450	7.789	0.663	1183	1785	0.145	1856	12,813	0.068	1662	24,338
		ASA	CLOP	MRD + ASA	35,234	7.753	0.627	–33	–52	0.109	640	5869	0.033	446	13,721
		ASA	MRD + ASA	CLOP	34,967	7.740	0.614	–300	–489	0.096	373	3878	0.020	179	9150
		CLOP	ASA	MRD + ASA	38,015	7.832	0.705	2748	3896	0.187	3421	18,249	0.111	3227	29,100
		CLOP	MRD + ASA	ASA	38,349	7.856	0.730	3082	4222	0.212	3755	17,704	0.136	3561	26,276
		MRD + ASA	CLOP	ASA	36,539	7.840	0.714	1272	1783	0.196	1945	9933	0.119	1751	14,685
		MRD + ASA	**ASA**	**CLOP**	35,579	7.812	0.685	312	456	0.168	985	5880	0.091	791	**8698**[a]

CLOP, clopidogrel; Dom, dominated; IC, IQ, incremental cost and QALYs.
a Strategy on cost-effectiveness frontier.

TABLE 62 Deterministic results from the Assessment Group's model for treatment of the 'ischaemic stroke-only' population (updated from addendum)

		Strategy					ICER (£)				
CLOP price	TA90[24] status	Treatment 1	Treatment 2	Treatment 3	Total costs (£)	Utility QALYs	Step 1	Step 2	Step 3	Step 4	Step 5
Generic	MRD + ASA	None	None	None	35,202	7.056					
		ASA			32,955	7.157	**–22,106**[a]				
		CLOP			35,534	7.620	590	5578	Dom		
		MRD + ASA			35,266	7.591	120	5329	Dom		
		ASA	CLOP		34,704	7.687	–788	3300	1116		
		ASA	MRD + ASA		34,710	7.680	–787	3357	623		
		CLOP	ASA		35,433	7.743	337	4235	20,716	Dom	
		CLOP	MRD + ASA		35,722	7.744	757	4720	28,305	Dom	
		MRD + ASA	ASA		35,187	7.730	–22	3898	21,432	1204	
		MRD + ASA	CLOP		35,521	7.734	471	4451	31,217	Dom	
		ASA	**CLOP**	**MRD + ASA**	34,727	7.708	–726	**3217**[a]			
		ASA	MRD + ASA	CLOP	34,737	7.696	–725	3312	Dom		
		CLOP	ASA	MRD + ASA	35,435	7.769	327	4054	11,666	20,675	19,262
		CLOP	**MRD + ASA**	**ASA**	35,720	7.781	715	4436	13,717	22,598	**28,288**[a]
		MRD + ASA	**CLOP**	**ASA**	35,535	7.774	464	4183	12,269	**20,200**[a]	
		MRD + ASA	**ASA**	**CLOP**	35,221	7.759	28	3769	**9820**[a]		

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	ICER (£)				
		Treatment 1	Treatment 2	Treatment 3			Step 1	Step 2	Step 3	Step 4	Step 5
	Not used	None	None	None	35,267	7.120					
		ASA			34,594	7.644	**–1283**[a]				
		CLOP			35,545	7.680	496	26,406	Dom		
		MRD + ASA			35,434	7.651	314	116,441	Dom		
		ASA	CLOP		34,791	7.727	–783	2377	1201		
		ASA	MRD + ASA		34,788	7.721	–797	2532	1069		
		CLOP	ASA		35,508	7.804	352	5718	13,508	1249	
		CLOP	MRD + ASA		35,795	7.809	766	7282	17,424	Dom	
		MRD + ASA	ASA		35,355	7.783	132	5494	18,127	3831	
		MRD + ASA	CLOP		35,682	7.789	620	7509	24,023	Dom	
		ASA	**CLOP**	**MRD + ASA**	34,823	7.753	–701	**2096**[a]			
		ASA	**MRD + ASA**	**CLOP**	34,823	7.740	–716	2377			
		CLOP	**ASA**	**MRD + ASA**	35,542	7.832	387	5059	**9185**[a]		
		CLOP	**MRD + ASA**	**ASA**	35,876	7.856	827	6046	10,230	**13,558**[a]	
		MRD + ASA	CLOP	ASA	35,771	7.840	700	6010	10,934	27,336	
		MRD + ASA	ASA	CLOP	35,426	7.812	230	4967	10,328	5835	

CLOP, clopidogrel; Dom, dominated.
a Strategy on cost-effectiveness frontier.

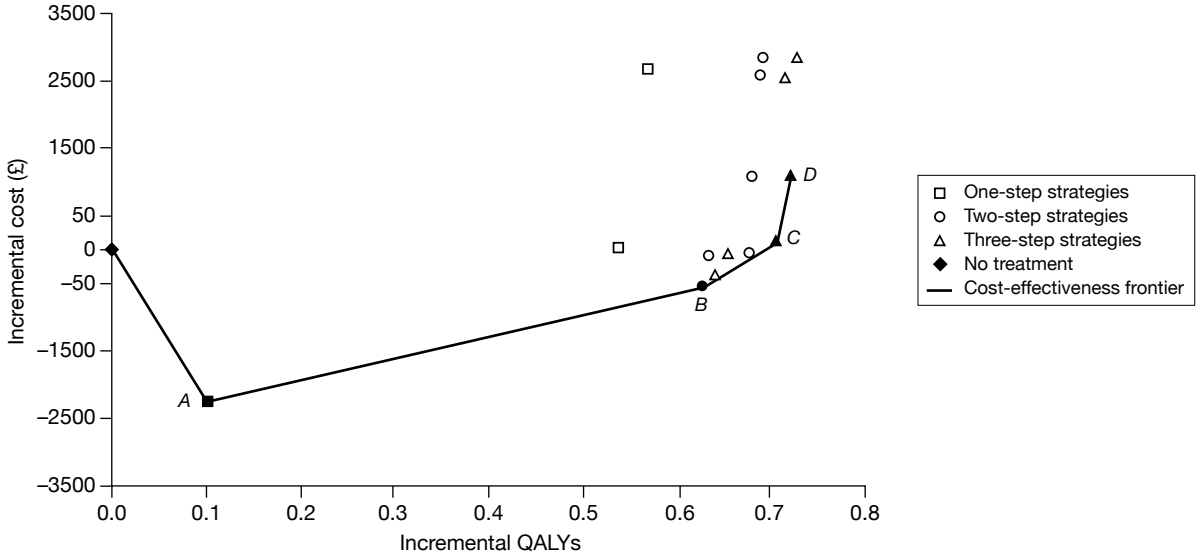

FIGURE 7 The cost-effectiveness plane and frontier showing available treatment strategies for 'ischaemic stroke-only' patients (using MRD + ASA as per the TA90[24] guidance). A = ASA; B = ASA to MRD + ASA; C = MRD + ASA to ASA to clopidogrel; and D = MRD + ASA to clopidogrel to ASA.

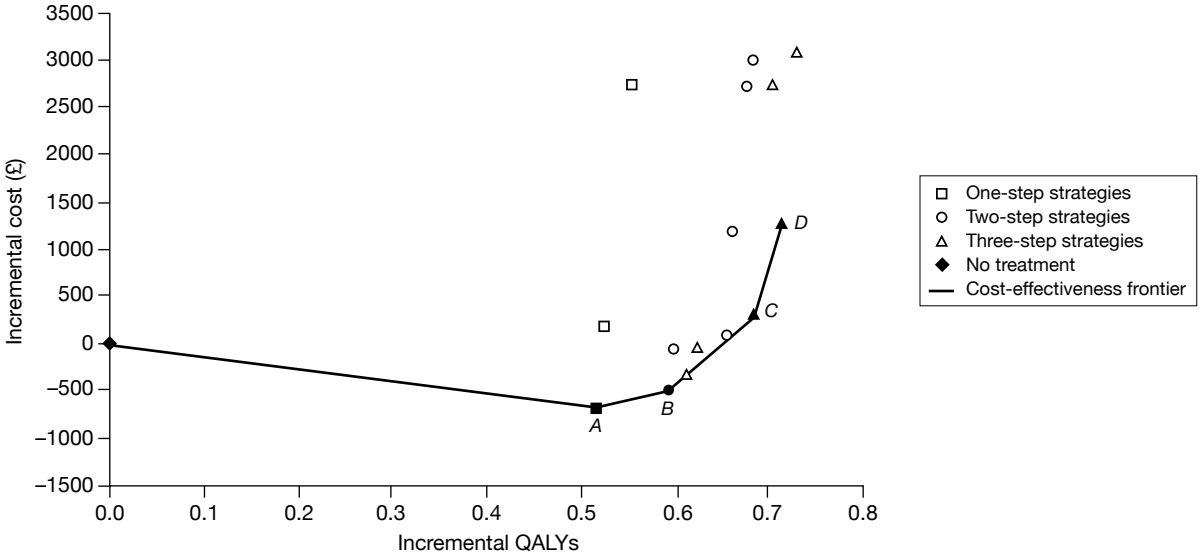

FIGURE 8 The cost-effectiveness plane and frontier showing available treatment strategies for 'ischaemic stroke-only' patients (without applying the TA90[24] guidance). A = ASA; B = ASA to MRD + ASA; C = MRD + ASA to ASA to clopidogrel; and D = MRD + ASA to clopidogrel to ASA.

Intolerance to acetylesalicyclic acid and/or modified-release dipyridamole

In patients who are intolerant of ASA, clopidogrel and MRD are the only available long-term therapy options available, and only MRD may be used post ischaemic stroke events as per the TA90 guidance.[24] These are compared with the 'no-treatment' scenario in *Table 63* and indicate that clopidogrel followed by MRD is the most cost-effective approach to occlusive vascular event prevention, independent of both TA90 guidance[24] and the price of clopidogrel.

For patients who are intolerant of MRD, only clopidogrel and ASA are available for long-term therapy, and TA90 guidance[24] is not relevant (*Table 64*). In this instance the price of clopidogrel

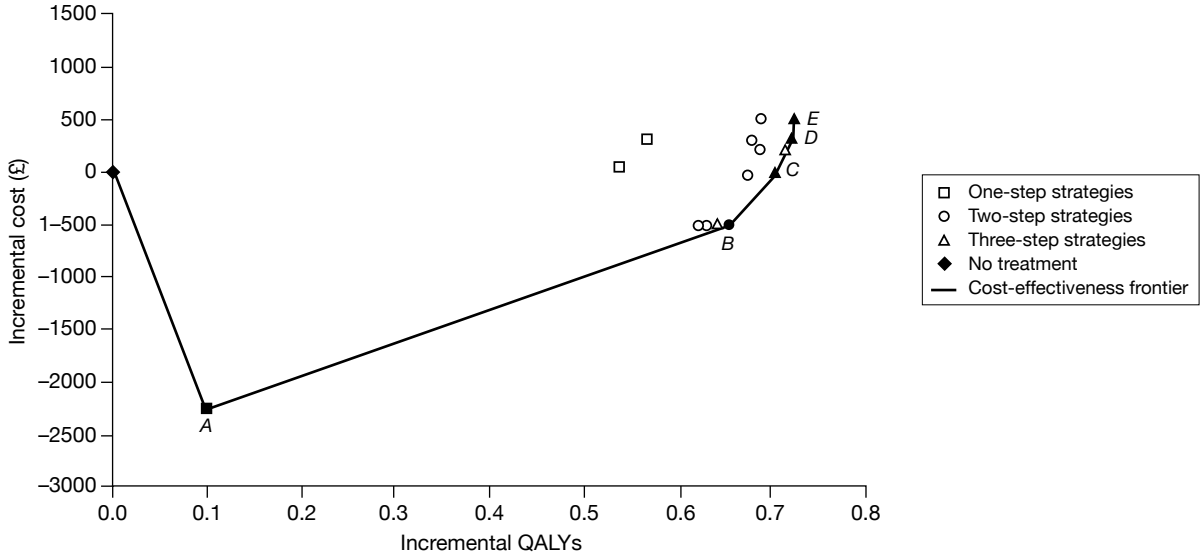

FIGURE 9 The cost-effectiveness plane and frontier showing available treatment strategies for 'ischaemic stroke-only' patients (using MRD + ASA as per the TA90[24] guidance and the generic clopidogrel price). A = ASA; B = ASA to clopidogrel to MRD + ASA; C = MRD + ASA to ASA to clopidogrel; D = MRD +ASA to clopidogrel to ASA; and E = clopidogrel to MRD + ASA to ASA.

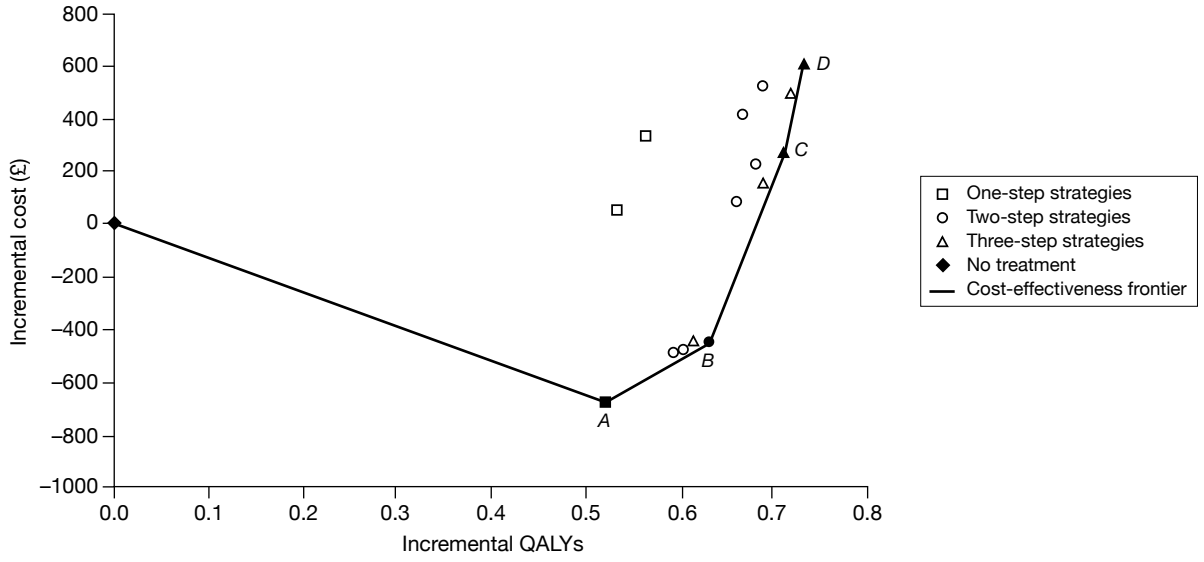

FIGURE 10 The cost-effectiveness plane and frontier showing available treatment strategies for 'ischaemic stroke-only' patients (without applying the TA90[24] guidance and using the generic clopidogrel price). A = ASA; B + ASA to clopidogrel to MRD + ASA; C + clopidogrel to ASA to MRD +ASA; and D = clopidogrel to MRD + ASA to ASA.

is important in determining cost-effectiveness; at the branded price, the preferred strategy is ASA followed by clopidogrel, but for the generic price clopidogrel followed by ASA is more cost-effective. For patients intolerant to both ASA and MRD, only clopidogrel is available for long-term prevention and is seen to be more cost-effective than no preventive therapy.

Myocardial infarction-only patients

Deterministic analysis

Table 65 summarises the main economic results obtained with the Assessment Group model for the MI patient population. *Figures 11–14* illustrate these findings in the form of a

TABLE 63 Deterministic results from the Assessment Group's model for treatment of the 'ischaemic stroke-only' population with intolerance to ASA

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	Incremental analysis vs no treatment			Incremental analysis vs MRD			Incremental analysis vs CLOP		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)
ASA intolerant															
Full	MRD	None	None	None	35,279	7.021									
		CLOP			37,994	7.598	0.576	2715	4713	0.304	1690	**5556**[a]	0.000	0	
		MRD			36,304	7.293	0.272	1025	**3770**[a]						
		CLOP	**MRD**		38,413	7.653	0.632	3135	4964	0.360	2110	5866	0.055	419	**7564**[a]
		MRD	CLOP		37,318	7.440	0.419	2039	4872	0.147	1014	6915	–0.158	–676	4292
	Not used	None	None	None	35,267	7.120									
		CLOP			38,018	7.680	0.560	2751	4908	0.310	1580	**5093**[a]			
		MRD			36,437	7.370	0.250	1170	**4678**[a]						
		CLOP	**MRD**		38,486	7.732	0.612	3219	5257	0.362	2048	5656	0.052	468	**9021**[a]
		MRD	CLOP		37,457	7.512	0.392	2190	5580	0.142	1020	7164	–0.168	–561	3339
Generic	MRD	None	None	None	35,279	7.021									
		CLOP			35,619	7.598	0.576	341	**591**[a]						
		MRD			36,304	7.293	0.272	1025	3770	–0.304	684	Dom			
		CLOP	**MRD**		36,039	7.653	0.632	760	1204	0.055	419	**7564**[a]			
		MRD	CLOP		36,525	7.440	0.419	1246	2977	–0.158	905	Dom			
	Not used	None	None	None	35,267	7.120									
		CLOP			35,545	7.680	0.560	278	**496**[a]						
		MRD			36,437	7.370	0.250	1170	4678	–0.310	892	Dom			
		CLOP	**MRD**		36,013	7.732	0.612	746	1219	0.052	468	**9021**[a]			
		MRD	CLOP		36,688	7.512	0.392	1421	3621	–0.168	1143	Dom			

CLOP, clopidogrel; Dom, dominated; IC, IQ, incremental cost and QALYs.
a Strategy on cost-effectiveness frontier.

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TABLE 64 Deterministic results from the Assessment Group's model for treatment of the 'ischaemic stroke-only' population with intolerance to MRD

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	Incremental analysis vs no treatment			Incremental analysis #2			Incremental analysis #3		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)
MRD intolerant															
Full	Not used	None	None	None	35,267	7.120									
		ASA			34,594	7.644	0.524	–673	**–1283**[a]						
		CLOP			38,018	7.680	0.560	2,751	4908	0.036	3423	95065	–0.047	2815	Dom
		ASA	**CLOP**		35,203	7.727	0.607	–64	–105	0.083	609	**7336**[a]			
		CLOP	**ASA**		37,981	7.804	0.684	2714	3966	0.160	3386	21,189	0.077	2778	**36,155**[a]
Generic	Not used	None	None	None	35,267	7.120									
		ASA			34,594	7.644	0.524	–673	**–1283**[a]						
		CLOP			35,545	7.680	0.560	278	496	0.036	951	26,406	–0.047	754	Dom
		ASA	**CLOP**		34,791	7.727	0.607	–476	–783	0.083	197	**2377**[a]			
		CLOP	**ASA**		35,508	7.804	0.684	241	352	0.160	914	5718	0.077	717	**9328**[a]
ASA and MRD intolerant															
Full	Not used	None	None	None	35,267	7.120									
		CLOP			38,018	7.680	0.560	2751	**4908**[a]						
Generic	Not used	None	None	None	35,267	7.120									
		CLOP			35,545	7.680	0.560	278	**496**[a]						

CLOP, clopidogrel; Dom, dominated; IC, IQ, incremental cost and QALYs.

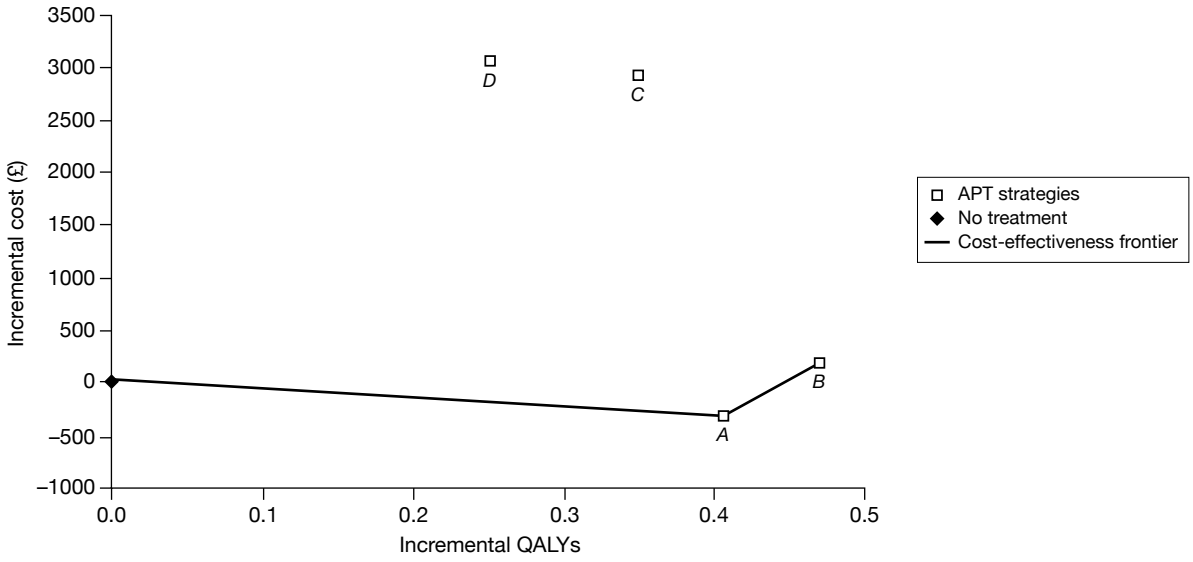

FIGURE 11 The cost-effectiveness plane and frontier showing available treatment strategies for 'MI-only' patients (using MRD + ASA as per the TA90[24] guidance). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

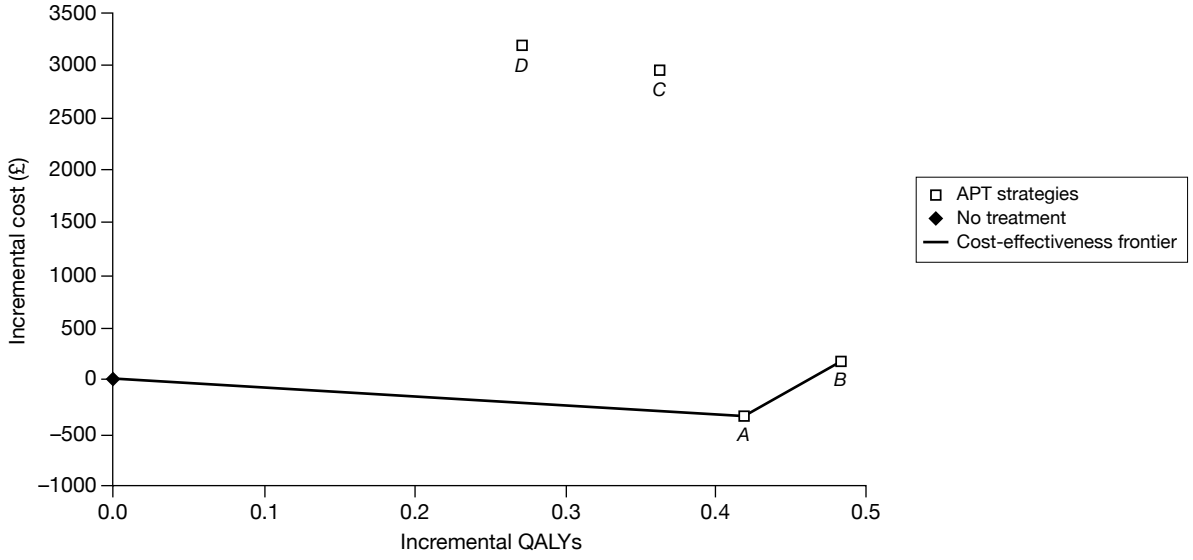

FIGURE 12 The cost-effectiveness plane and frontier showing available treatment strategies for 'MI-only' patients (without applying the TA90[24] guidance). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

cost-effectiveness plane plot with cost-effectiveness frontier. The primary analysis (first block in *Table 65* and *Figure 11*) reveals that only two strategies lie on the boundary, but both strategies involving initial use of clopidogrel are dominated by those where ASA is the first treatment offered to 'MI-only' patients (being both less effective and more expensive), regardless of whether or not TA90 guidance[24] is applied, or whether or not the generic price of clopidogrel is used. In all scenarios, the incremental cost-effectiveness of allowing clopidogrel as a subsequent therapy after failure of ASA therapy compared with ASA treatment alone is < £9000 per QALY gained, suggesting that ASA followed by clopidogrel may be the optimal strategy for this patient group.

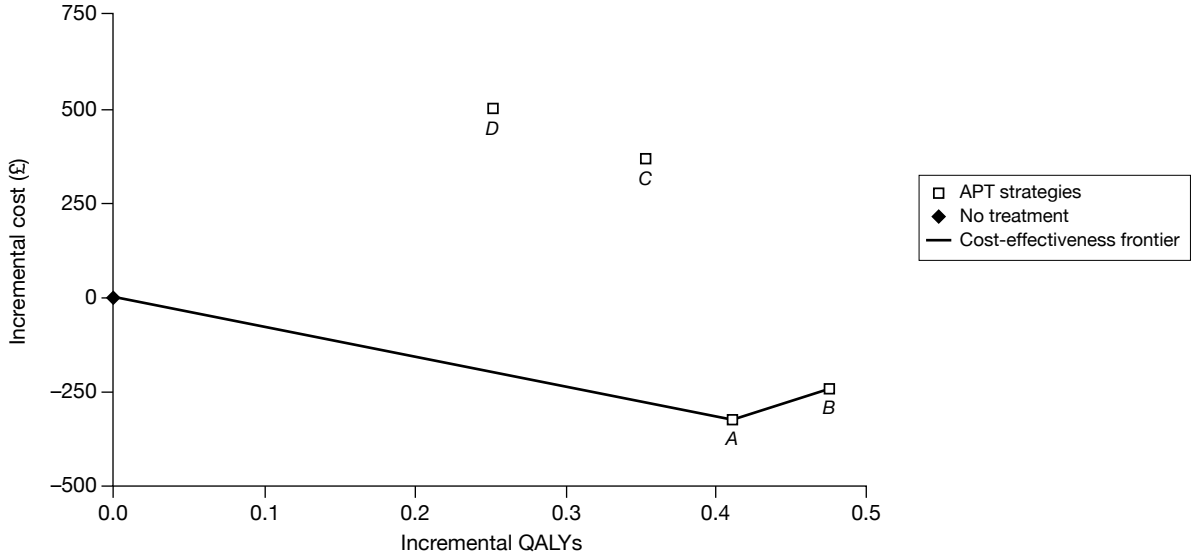

FIGURE 13 The cost-effectiveness plane and frontier showing available treatment strategies for 'MI-only' patients (using MRD + ASA as per the TA90[24] guidance and the generic clopidogrel price). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

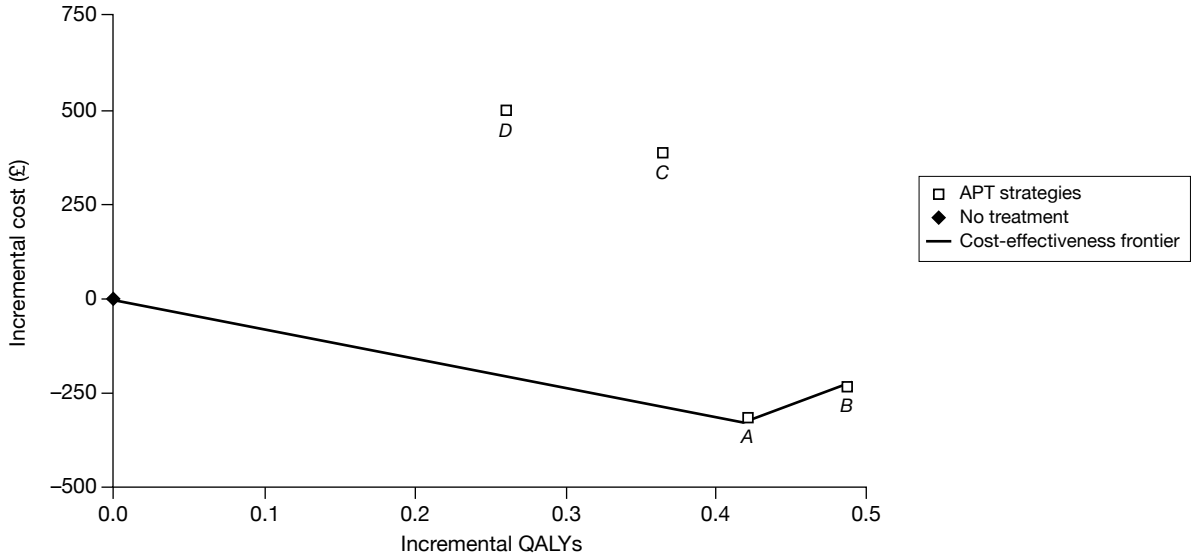

FIGURE 14 The cost-effectiveness plane and frontier showing available treatment strategies for 'MI-only' patients (without applying the TA90[24] guidance and using the generic clopidogrel price). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

Intolerance to acetylsalicyclic acid

In patients who are intolerant of ASA, clopidogrel is the only available long-term therapy available and, therefore, comparisons have been carried out against the 'no-treatment' scenario. The results are given in *Table 66* and indicate that clopidogrel is a cost-effective approach to occlusive vascular event prevention independent of both TA90 guidance[24] and the price of clopidogrel (ICERs ranging between £1961 and £12,391 per QALY gained).

TABLE 65 Deterministic results from the Assessment Group's model for treatment of the 'MI-only' population

		Strategy					Incremental analysis vs no APT treatment			Incremental analysis vs ASA only strategy		
CLOP price	TA90[24] status	Treatment 1	Treatment 2	Treatment 3	Total costs (£)	Utility QALYs	IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)
Full	MRD + ASA	None	None	None	11,781	9.305			–	–	–	–
		ASA			11,465	9.711	0.406	–316	**–778**	–	–	–
		CLOP			14,851	9.553	0.247	3070	12,406	–0.158	3836	Dom
		ASA	**CLOP**		11,980	9.774	0.469	199	425	0.063	515	**8118**
		CLOP	ASA		14,723	9.652	0.347	2942	8480	–0.059	3258	Dom
	Not used	None	None	None	11,806	9.300	–	–	–	–	–	–
		ASA			11,493	9.716	0.416	–313	**–752**	–	–	–
		CLOP			14,891	9.554	0.255	3085	12,112	–0.162	3398	Dom
		ASA	**CLOP**		12,009	9.780	0.481	203	422	0.064	516	**8044**
		CLOP	ASA		14,785	9.659	0.359	2978	8301	–0.058	3291	Dom
Generic	MRD + ASA	None	None	None	11,781	9.305						
		ASA			11,465	9.711	0.406	–316	**–778**	0.000	0	
		CLOP			12,284	9.553	0.247	503	2034	–0.158	819	Dom
		ASA	**CLOP**		11,552	9.774	0.469	–229	–488	0.063	86	**1363**
		CLOP	ASA		12,156	9.652	0.347	375	1,082	–0.059	691	Dom
	Not used	None	None	None	11,806	9.300	–	–	–	–	–	–
		ASA			11,493	9.716	0.416	–313	**–752**	–	–	–
		CLOP			12,306	9.554	0.255	499	1961	–0.162	812	Dom
		ASA	**CLOP**		11,580	9.780	0.481	–226	–471	0.064	87	**1352**
		CLOP	ASA		12,199	9.659	0.359	393	1096	–0.058	706	Dom

APT, antiplatelet therapy; CLOP, clopidogrel; Dom, dominated by another strategy; IC, IQ, incremental cost and QALYs.

TABLE 66 Deterministic results from the Assessment Group's model for treatment of ASA-intolerant patients in the 'MI-only' population

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	Incremental analysis		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)
Full	MRD	None	None	None	11,796	9.297			
		CLOP			14,880	9.546	0.249	3085	**12,523**
	Not used	None			11,806	9.300			
		CLOP			14,891	9.554	0.255	3085	**12,112**
Generic	MRD	None	None	None	11,796	9.297			
		CLOP			12,312	9.546	0.249	516	**2,073**
	Not used	None			11,806	9.300			
		CLOP			12,306	9.554	0.255	499	**1961**

CLOP, clopidogrel; IC, IQ, incremental cost and QALYs.

Peripheral arterial disease-only patients

Deterministic analysis

Table 67 summarises the main economic results obtained with the Assessment Group model for the 'peripheral arterial disease-only' patient population. *Figures 15–18* illustrate these findings in the form of a cost-effectiveness plane plot with cost-effectiveness frontier. The primary analysis (first block in *Table 67* and *Figure 15*) reveals that three strategies lie on the boundary, but the clopidogrel-only strategy is clearly less cost-effective than all other options. This is true in all peripheral arterial disease scenarios. When the requirement is removed to adhere to the TA90 guidance[24] following an ischaemic stroke event, the absolute values of costs and outcomes are modified, but the relativities between strategies remain qualitatively unchanged (see *Figures 16* and *18*). If the full branded price of clopidogrel is replaced by the NHS generic price, the cost differences between the strategies are markedly reduced, but the broad pattern is unchanged. In all scenarios the ICER for a strategy of clopidogrel followed by ASA when compared with ASA followed by clopidogrel appears to be well within the range considered

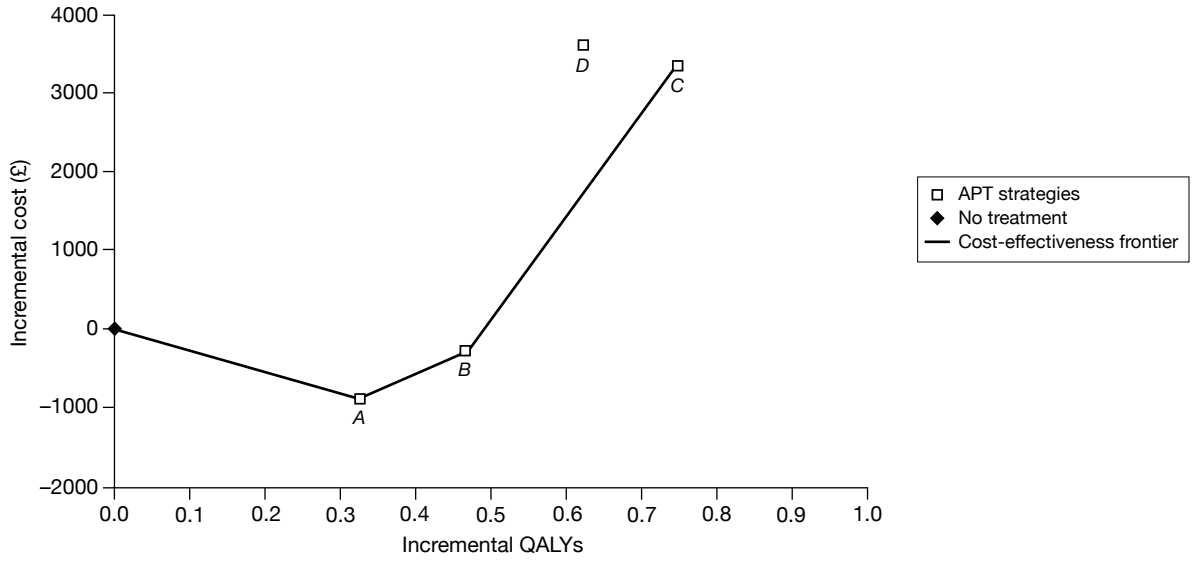

FIGURE 15 The cost-effectiveness plane and frontier showing available treatment strategies for 'peripheral arterial disease-only' patients (using MRD + ASA as per the TA90[24] guidance). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

TABLE 67 Deterministic results from the Assessment Group's model for treatment of the 'peripheral arterial disease-only' population

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	Incremental analysis vs no APT treatment			Incremental analysis vs ASA only strategy			Incremental analysis vs ASA→CLOP strategy		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)
Full	MRD + ASA	None	None	None	7283	9.567	–	–	–	–	–	–	–	–	–
		ASA			6421	9.897	0.391	–862	**–2,612**	–	–	–	–	–	–
		CLOP			10,869	10.222	0.785	3586	5475	0.325	4448	13,691	0.185	3864	20,891
		ASA	**CLOP**		7005	10.037	0.539	–278	–591	0.140	584	**4176**	–	–	–
		CLOP	**ASA**		10,636	10.317	0.909	3353	4468	0.420	4215	10,028	0.280	3631	**12,948**
	Not used	None	None	None	7232	9.551	–	–	–	–	–	–	–	–	–
		ASA			6398	9.894	0.382	–834	**–2425**	–	–	–	–	–	–
		CLOP			10,872	10.219	0.773	3640	5443	0.325	4474	13,768	0.180	3822	21,222
		ASA	**CLOP**		7051	10.039	0.556	–181	–371	0.145	653	**4504**	–	–	–
		CLOP	**ASA**		10,695	10.321	0.905	3464	4498	0.426	4297	10,083	0.281	3645	**12,956**
Generic	MRD + ASA	None	None	None	7283	9.567	–	–	–	–	–	–	–	–	–
		ASA			6421	9.897	0.391	–862	**–2612**	–	–	–	–	–	–
		CLOP			7840	10.222	0.785	557	850	0.325	1419	4368	0.185	1381	7466
		ASA	**CLOP**		6459	10.037	0.539	–824	–1753	0.140	38	**273**	–	–	–
		CLOP	**ASA**		7607	10.317	0.909	324	432	0.420	1186	2822	0.280	1148	**4094**
	Not used	None	None	None	7232	9.551	–	–	–	–	–	–	–	–	–
		ASA			6398	9.894	0.382	–834	**–2425**	–	–	–	–	–	–
		CLOP			7819	10.219	0.773	587	878	0.325	1421	4373	0.180	1307	7257
		ASA	**CLOP**		6512	10.039	0.556	–720	–1473	0.145	114	**787**	–	–	–
		CLOP	**ASA**		7642	10.321	0.905	410	533	0.426	1244	2919	0.281	1130	**4017**

APT, antplatelet therapy; CLOP, clopidogrel; IC, IQ, incremental cost and QALYs.

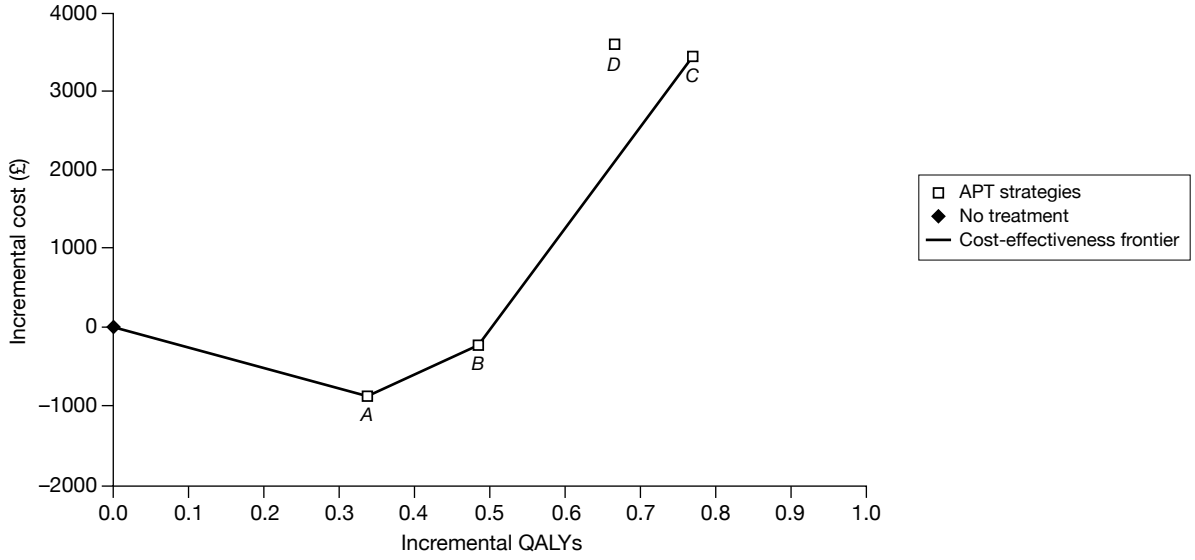

FIGURE 16 The cost-effectiveness plane and frontier showing available treatment strategies for 'peripheral arterial disease-only' patients (without applying the TA90[24] guidance). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

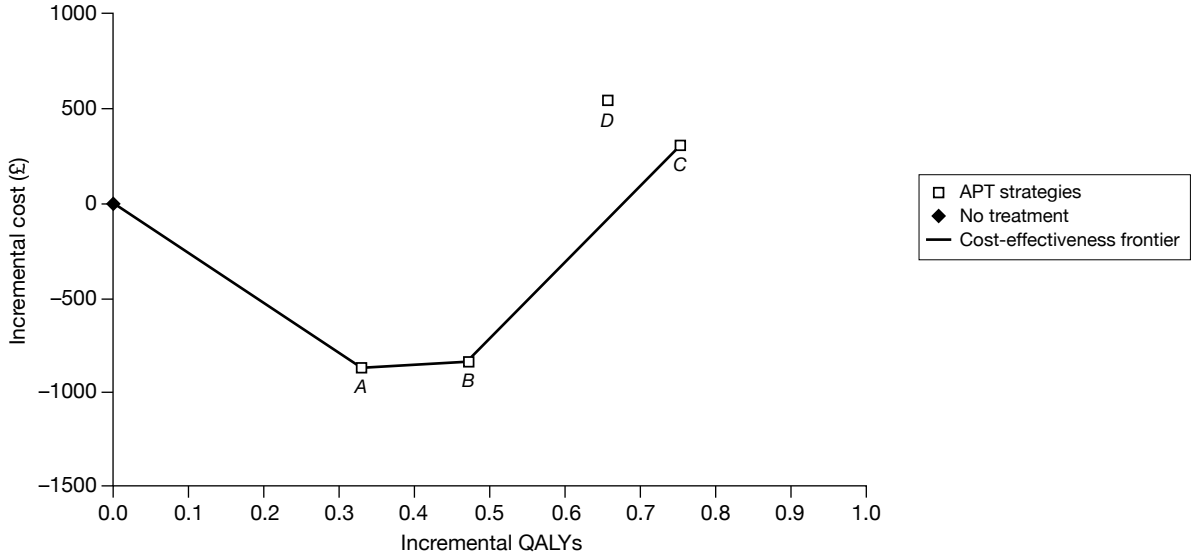

FIGURE 17 The cost-effectiveness plane and frontier showing available treatment strategies for 'peripheral arterial disease-only' patients (using MRD + ASA as per the TA90[24] guidance and the generic clopidogrel price). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

cost-effective (under £13,000 per QALY gained for branded clopidogrel and under £5000 per QALY for generic clopidogrel), suggesting this as the optimal strategy for this patient group.

Intolerance to acetylsalicyclic acid

In patients who are intolerant of ASA, clopidogrel is the only available long-term therapy available, and, therefore, comparisons have been carried out against the 'no-treatment' scenario. The results are given in *Table 68* and indicate that clopidogrel is a cost-effective approach to occlusive vascular event prevention independent of both the TA90 guidance[24] and the price of clopidogrel.

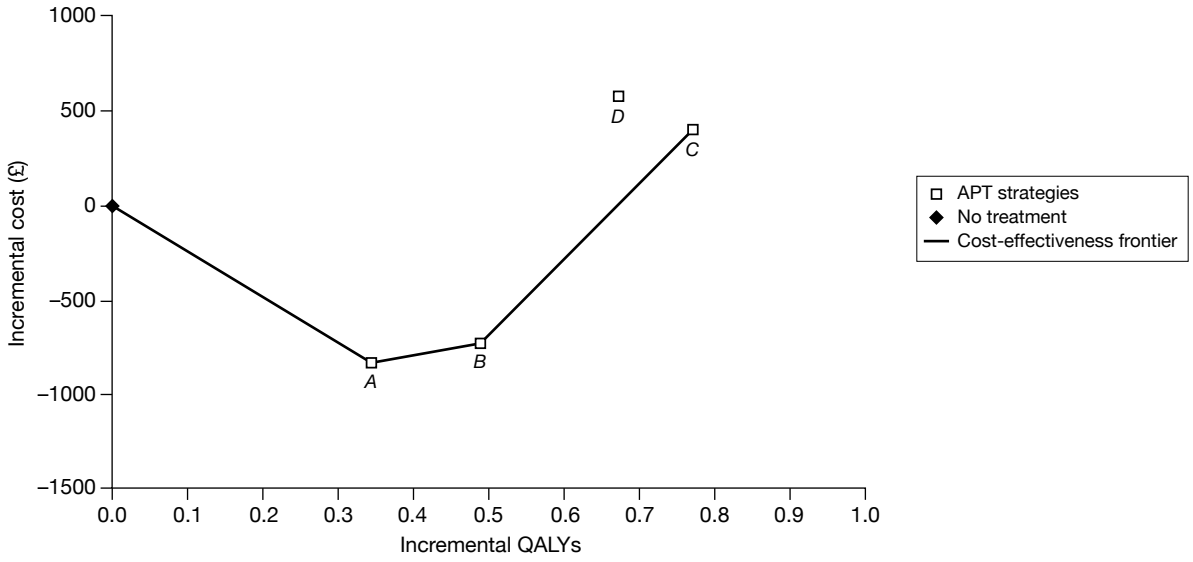

FIGURE 18 The cost-effectiveness plane and frontier showing available treatment strategies for 'peripheral arterial disease-only' patients (without applying the TA90[24] guidance and using the generic clopidogrel price). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

TABLE 68 Deterministic results from the Assessment Group's model for treatment of ASA-intolerant patients in the 'peripheral arterial disease-only' population

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	Incremental analysis		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)
Full	MRD	None	None	None	7293	9.552	–	–	–
		CLOP			10,901	10.210	0.659	3608	**5478**
	Not used	None	None	None	7232	9.551	–	–	–
		CLOP			10,872	10.219	0.669	3640	**5443**
Generic	MRD	None	None	None	7293	9.552	–	–	–
		CLOP			7671	10.210	0.659	578	**878**
	Not used	None	None	None	7232	9.551	–	–	–
		CLOP			7819	10.219	0.669	587	**878**

CLOP, clopidogrel; IC, IQ, incremental cost and QALYs.

Patients with multivascular disease

Deterministic analysis

Table 69 summarises the main economic results obtained with the Assessment Group model for the multivascular disease patient population. *Figures 19–22* illustrate these findings in the form of a cost-effectiveness plane plot with cost-effectiveness frontier. The primary analysis (first block in *Table 69* and *Figure 19*) reveals that three strategies lie on the boundary, but the clopidogrel-only strategy is clearly less cost-effective than all other options. This is true in all multivascular disease scenarios. When the requirement is removed to adhere to TA90 guidance[24] following an ischaemic stroke event, the absolute values of costs and outcomes are modified, but the relativities between strategies remain qualitatively unchanged. If the full branded price of clopidogrel is replaced by the NHS generic price, the cost differences between the strategies are markedly reduced, but the broad pattern is unchanged. In all scenarios, clopidogrel followed by ASA is the most cost-effective strategy.

TABLE 69 Deterministic results from the Assessment Group's model for treatment of the multivascular disease population

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	Incremental analysis vs no APT treatment			Incremental analysis vs ASA-only strategy			Incremental analysis vs ASA → CLOP strategy		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)	IQ	IC (£)	ICER (£)
Full	MRD + ASA	None	None	None	20,819	5.620	–	–	–	–	–	–	–	–	–
		ASA			19,826	6.170	0.550	–993	**–1805**	**–**	–	**–**	**–**	–	**–**
		CLOP			22,809	6.333	0.713	1990	2793	0.163	2983	18,331	0.047	2526	53,582
		ASA	**CLOP**		20,283	6.286	0.665	–536	–805	0.116	457	**3952**	–	–	
		CLOP	**ASA**		22,671	6.481	0.860	1852	2153	0.310	2844	9164	0.195	2388	**12,257**
	Not used	None	None	None	20,733	5.625	–	–	–	–	–	–	–	–	–
		ASA			19,803	6.183	0.558	–930	**–1665**	–	–	–	–	–	–
		CLOP			22,827	6.347	0.722	2095	2,902	0.163	3,024	18,505	0.050	2579	51,729
		ASA	**CLOP**		20,248	6.297	0.672	–484	–721	0.114	445	**3922**	–	–	–
		CLOP	**ASA**		22,730	6.498	0.873	1997	2287	0.315	2927	9,293	0.201	2481	**12,324**
Generic	MRD + ASA	None	None	None	20,819	5.620	–	–	–	–	–	–	–	–	–
		ASA			19,826	6.170	0.550	–993	**–1805**	–	–	–		–	–
		CLOP			20,673	6.333	0.713	–146	–205	0.163	847	5203	0.047	746	15,813
		ASA	**CLOP**		19,927	6.286	0.665	–891	–1339	0.116	101	**875**	–	–	–
		CLOP	**ASA**		20,534	6.481	0.860	–284	–331	0.310	708	2281	0.195	607	**3116**
	Not used	None	None	None	20,733	5.625	–	–	–	–	–	–	–	–	–
		ASA			19,803	6.183	0.558	–930	**–1665**	–	–	–	–	–	–
		CLOP			20,625	6.347	0.722	–108	–149	0.163	822	5031	0.050	727	14,574
		ASA	**CLOP**		19,899	6.297	0.672	–834	–1241	0.114	96	**842**	–	–	–
		CLOP	**ASA**		20,527	6.498	0.873	–205	–235	0.315	725	2301	0.201	629	**3124**

APT, antiplatelet therapy; CLOP, clopidogrel; IC, IQ, incremental cost and QALYs.

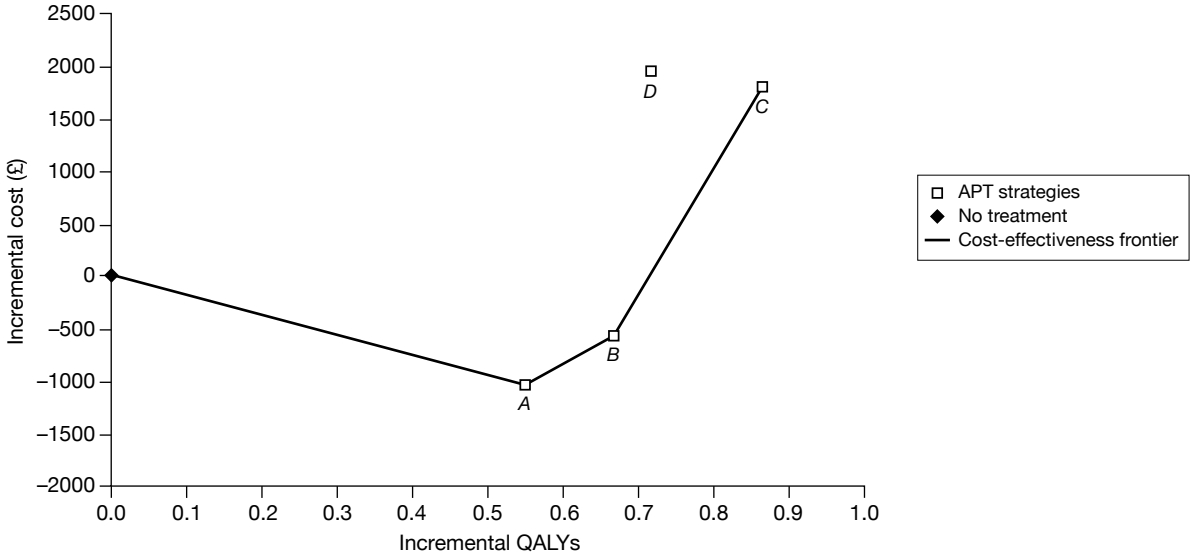

FIGURE 19 The cost-effectiveness plane and frontier showing available treatment strategies for multivascular disease patients (using MRD + ASA as per the TA90[24] guidance). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

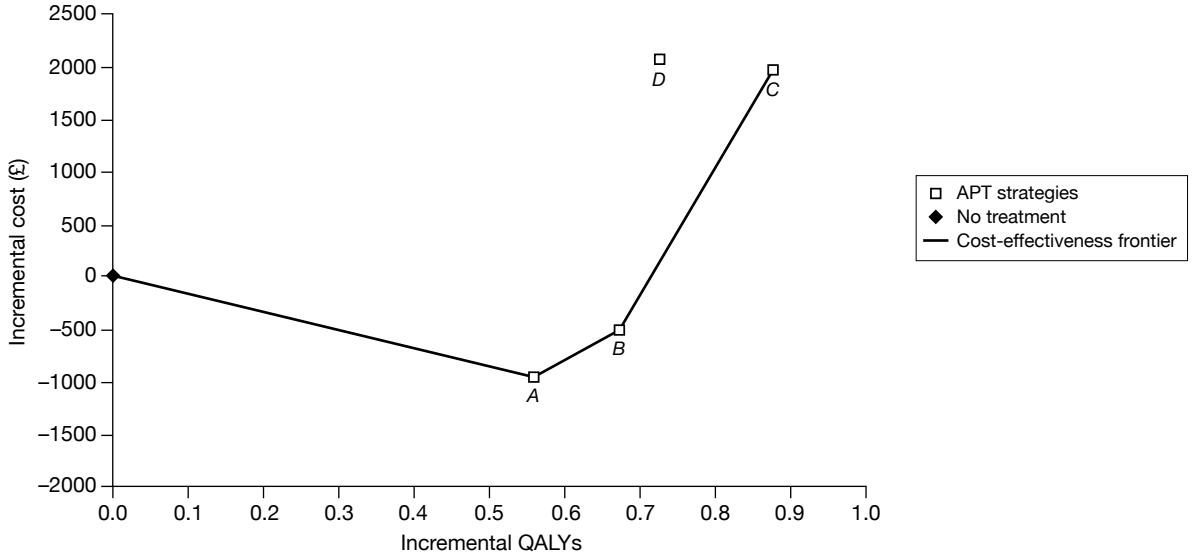

FIGURE 20 The cost-effectiveness plane and frontier showing available treatment strategies for multivascular disease patients (without applying the TA90[24] guidance). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

Intolerance to acetylsalicyclic acid

In patients who are intolerant of ASA, clopidogrel is the only long-term therapy available and, therefore, comparisons have been carried out against the 'no-treatment' scenario. The results are given in *Table 70* and indicate that clopidogrel is a cost-effective approach to occlusive vascular event prevention independent of both the TA90 guidance[24] and the price of clopidogrel.

Univariate sensitivity analysis

The Assessment Group model incorporates 197 parameters involving estimation uncertainty for which their potential influence on the economic results should be examined. Carrying out a comprehensive assessment of each parameter individually was judged to be impractical (because

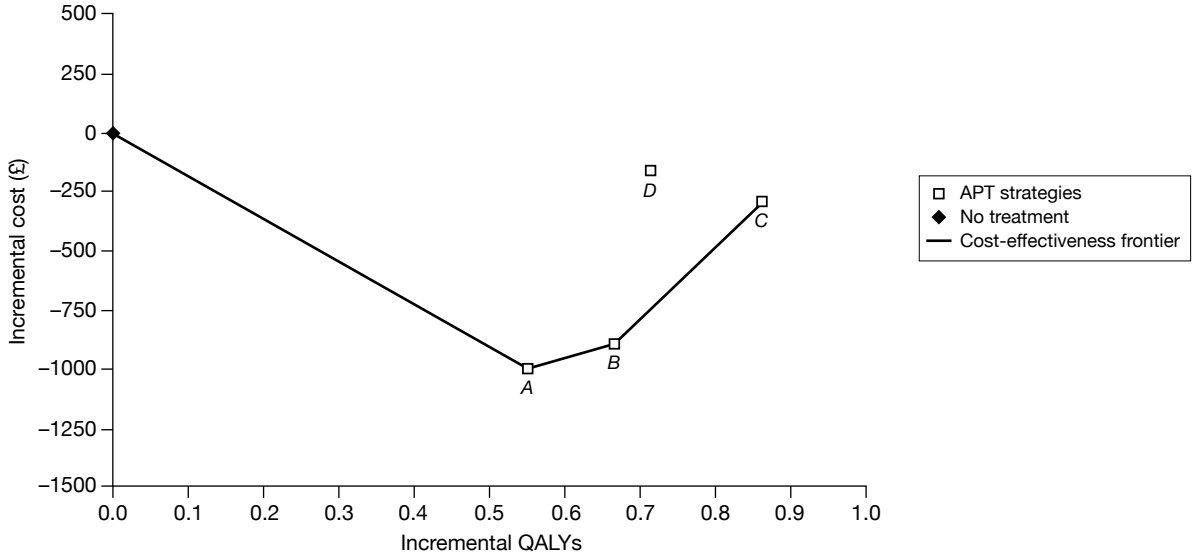

FIGURE 21 The cost-effectiveness plane and frontier showing available treatment strategies for multivascular disease patients (using MRD + ASA as per the TA90[24] guidance and the generic clopidogrel price). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antiplatelet therapy.

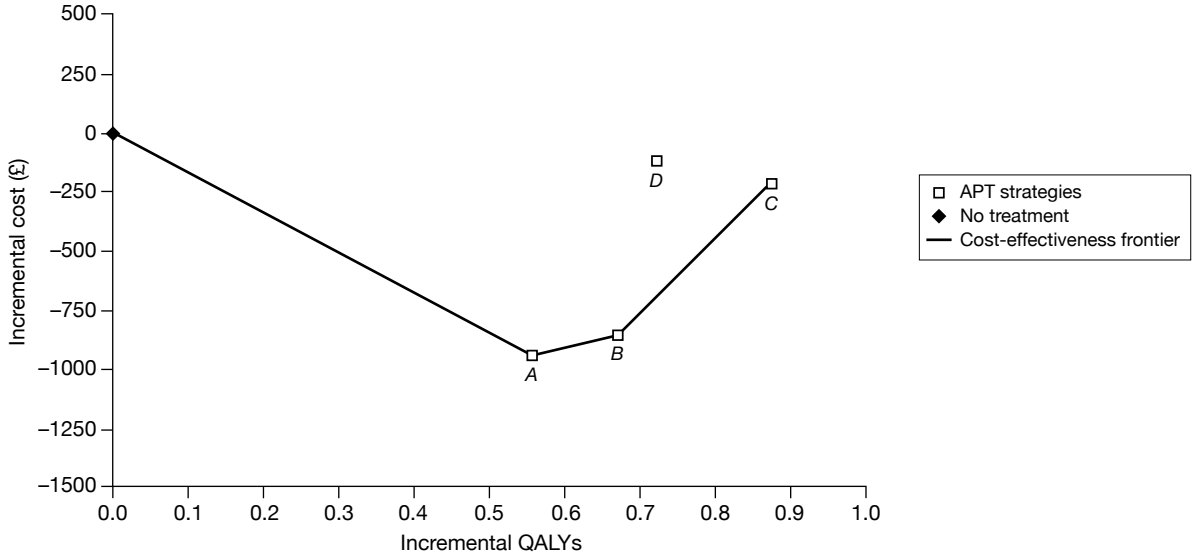

FIGURE 22 The cost-effectiveness plane and frontier showing available treatment strategies for multivascular disease patients (without applying the TA90[24] guidance and using the generic clopidogrel price). A = ASA; B = ASA to clopidogrel; C = clopidogrel to ASA; and D = clopidogrel. APT, antplatelet therapy.

of the model running time involved) and largely uninformative. Instead, the parameters were grouped into 11 sets, which were assessed collectively, taking the maxima of the reasonable value range of all members of a group as a basis for estimating one extreme scenario, and the minima for the other. This is likely to overstate the net effect of the individual factors, as it is very unlikely that all uncertainties within a group will be biased in the same direction. Nonetheless, it was considered to be a helpful approach in identifying which broad categories of parameters that have a greater likelihood of influencing an assessment of cost-effectiveness through parameter uncertainty. In effect, this approach defines an upper limit on the net influence of uncertainty in all the variables within the group.

TABLE 70 Deterministic results from the Assessment Group's model for treatment of ASA-intolerant patients in the multivascular disease population

CLOP price	TA90[24] status	Strategy			Costs IQ	Utility IQ	Incremental analysis		
		Treatment 1	Treatment 2	Treatment 3			IQ	IC (£)	ICER (£)
Full	MRD	None	None	None	20,747	5.588			
		CLOP			22,792	6.311	0.723	2046	**2829**
	Not used	None			20,733	5.625			
		CLOP			22,827	6.347	0.722	2095	**2902**
Generic	MRD	None	None	None	20,747	5.588			
		CLOP			21,079	6.319	0.731	332	**454**
	Not used	None			20,733	5.625			
		CLOP			20,625	6.347	0.722	–108	**–149**

CLOP, clopidogrel; IC, IQ, incremental cost and QALYs.

Wherever possible, the testing intervals have been set to the conventional 95% CI for estimating the parameter value. In the few instances where this information was not available, a general range of ± 10% of the central estimate was adopted. This was used for the duration of effect of the transient component of some event risks (known to have a minimal influence on model results), several events and continuing care costs, and to allow a notional uncertainty to be applied to the assumption, discussed above, that no additional weighting was necessary to the risk of non-vascular mortality in this population.

Ischaemic stroke population

Sensitivity analysis was carried out on the comparison between the strategy recommended above [MRD + ASA followed by ASA followed by clopidogrel (see *Ischaemic stroke-only patients*)] and the de facto current 'standard care' of ASA using the branded price of clopidogrel and without the TA90 guidance[24] applied. This scenario exhibits a deterministic ICER of £5880 per QALY gained.

Figure 23 shows the results for each group of parameters. In most cases there is very little variation from the central ICER estimate. There are two exceptions: 'key event risks' shows a comparatively larger uncertainty (although still well within the range normally considered acceptable) and the asymmetrical range for 'antiplatelet cessation risks' indicates the inherent non-linearity of the model in this feature.

Myocardial infarction-only population

Sensitivity analysis was carried out on the comparison between the strategy recommended above (ASA followed by clopidogrel) and the de facto current 'standard care' of ASA using the branded price of clopidogrel and without the TA90 guidance[24] applied. This scenario exhibits a deterministic ICER of £8044 per QALY gained.

Figure 24 shows the results for each group of parameters. In most cases there is very little variation from the central ICER estimate. In this case the largest uncertainty is associated with antiplatelet treatment cessation risks, and to a lesser extent to event fatality rates. However, in all cases the ICER remains well below £10,000 per QALY gained.

Peripheral arterial disease-only population

Sensitivity analysis was carried out on the comparison between the strategy recommended above (clopidogrel followed by ASA) and the de facto current 'standard care' of ASA, using the

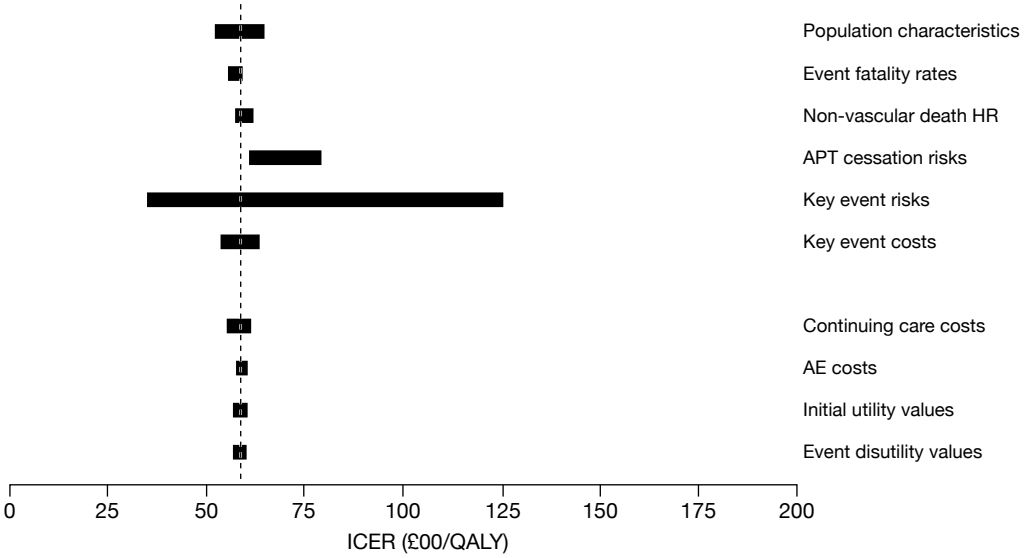

FIGURE 23 Sensitivity analysis for groups of model parameters for a comparison of the recommended strategy for 'ischaemic stroke-only' patients (MRD + ASA → ASA → clopidogrel) vs ASA alone (branded price of clopidogrel/TA90[24] guidance not applied). APT, antiplatelet therapy.

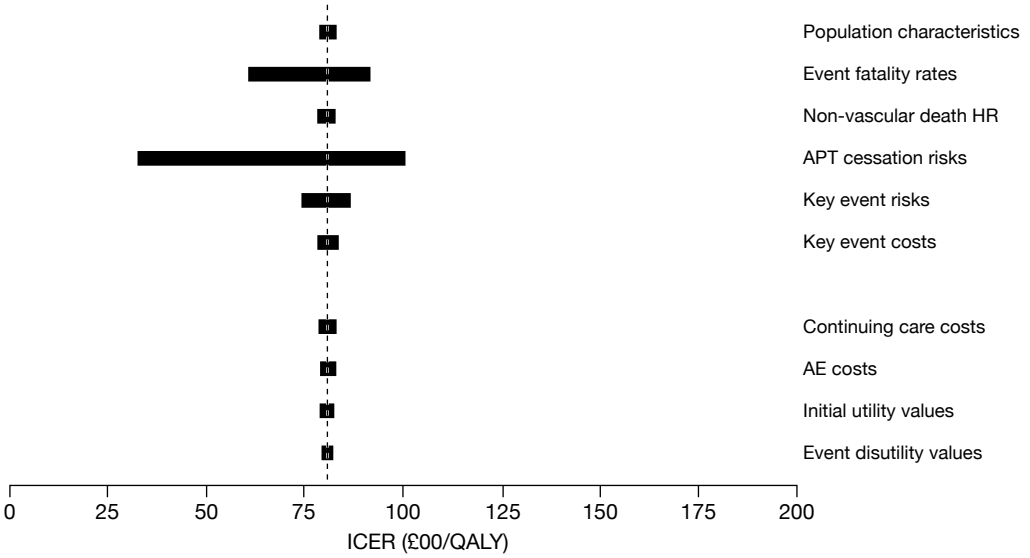

FIGURE 24 Sensitivity analysis for groups of model parameters for a comparison of the recommended strategy for 'MI-only' patients (ASA → clopidogrel) vs ASA alone (branded price of clopidogrel/TA90[24] guidance not applied). APT, antiplatelet therapy.

branded price of clopidogrel and without the TA90 guidance[24] applied. This scenario exhibits a deterministic ICER of £10,083 per QALY gained.

Figure 25 shows the results for each group of parameters. In most cases there is very little variation from the central ICER estimate. However, a very large uncertainty range is associated with key event risks. Examination of the underlying parameter values points to a very few instances where there is evidence of a clear advantage for clopidogrel over ASA in this patient group, and where a benefit is indicated the lower confidence limits are closely aligned. As explained above, this effect may in fact be an artefact of the grouping of parameters in this analysis and can be resolved only through full probabilistic sensitivity analysis.

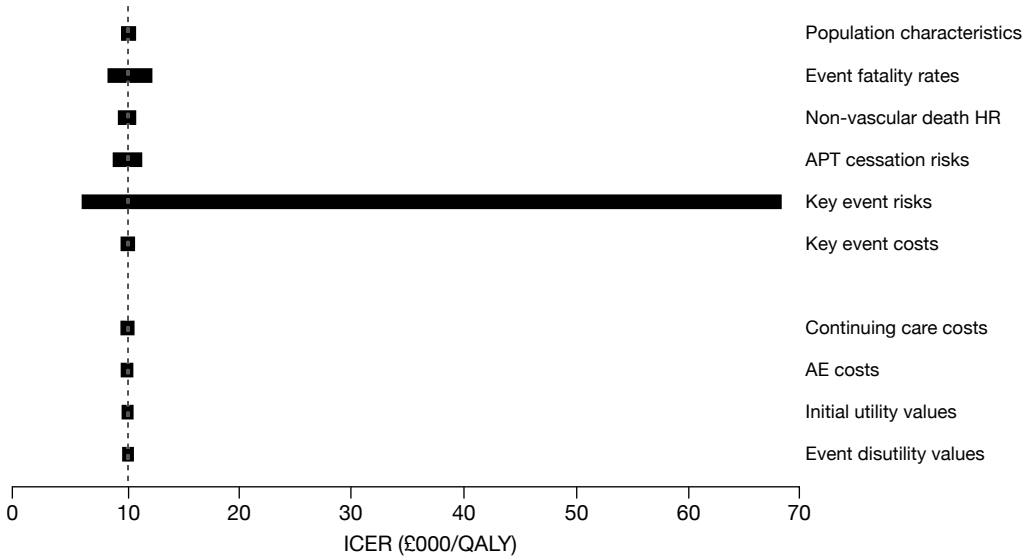

FIGURE 25 Sensitivity analysis for groups of model parameters for a comparison of the recommended strategy for 'peripheral arterial disease-only' patients (ASA → clopidogrel) vs ASA alone (branded price of clopidogrel/TA90[24] guidance not applied). APT, antiplatelet therapy.

Multivascular disease population

Sensitivity analysis was carried out on the comparison between the strategy recommended above (ASA followed by clopidogrel) and the de facto current 'standard care' of ASA using the branded price of clopidogrel and without the TA90 guidance[24] applied. This scenario exhibits a deterministic ICER of £9293 per QALY gained.

Figure 26 shows the results for each group of parameters. In most cases there is very little variation from the central ICER estimate. Exceptions are the event fatality rates group and antiplatelet treatment cessation risks. However, in all cases the ICER remains below £11,000 per QALY gained.

Summary of univariate results

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

Summary of cost-effective strategies from the Assessment Group's economic model

The economic results described above are summarised in terms of preferred long-term preventive treatment strategies in *Table 71*. In only one circumstance (MRD intolerance in the 'ischaemic stroke-only' patient) is the pricing of clopidogrel a determining factor in the choice of strategy.

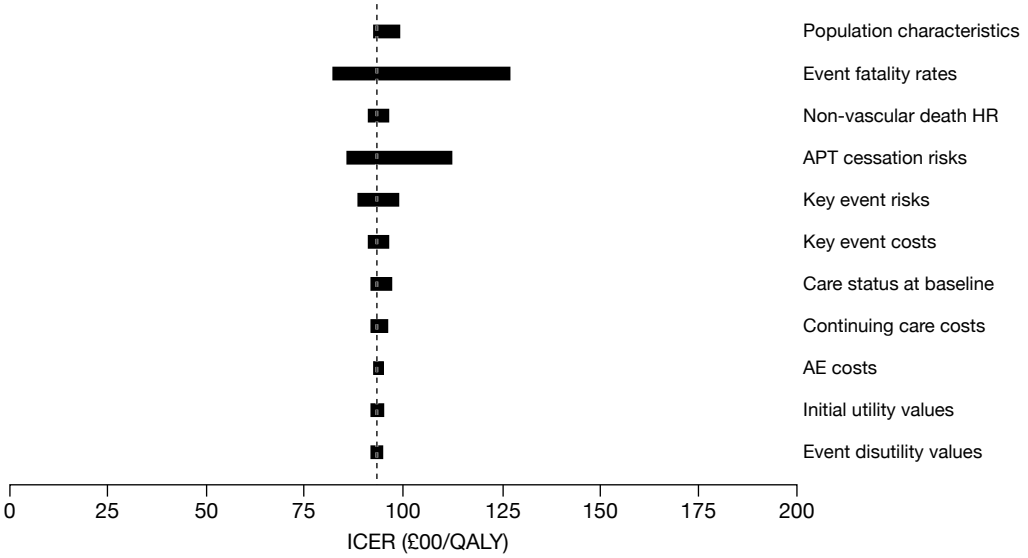

FIGURE 26 Sensitivity analysis for groups of model parameters for a comparison of the recommended strategy for multivascular disease patients (ASA → clopidogrel) vs ASA alone (branded price of clopidogrel/TA90[24] guidance not applied). APT, antiplatelet therapy.

TABLE 71 Summary table of optimal treatment strategy for each patient population obtained from deterministic analysis using the Assessment Group's model

		Patient population			
CLOP price	**TA90[24] guidance**	**IS only**	**MI only**	**PAD only**	**MVD**
No intolerances					
Branded	Applied	MRD + ASA → ASA → CLOP	ASA → CLOP	CLOP → ASA	CLOP → ASA
	Not applied				
Generic	Applied	CLOP → MRD + ASA → ASA			
	Not applied				
ASA intolerant					
Branded	Applied	CLOP → MRD	CLOP	CLOP	CLOP
	Not applied				
Generic	Applied				
	Not applied				
MRD intolerant					
Branded	N/A	ASA → CLOP	N/A	N/A	N/A
Generic		CLOP → ASA			
ASA and MRD intolerant					
	N/A	CLOP	N/A	N/A	N/A

CLOP, clopidogrel; IS, ischaemic stroke; MVD, multvascular disease; N/A, not applicable; PAD, peripheral arterial disease.

Probabilistic sensitivity analyses

Methods

The Assessment Group model was developed as a Microsoft 2007 Excel application, as this facilitated rapid model development and modification within a limited timescale following the availability of the detailed results of trial data (especially from the CAPRIE[26] trial) produced by the manufacturer of clopidogrel. Although modest in its design (a maximum of 10 key events for each of 10,000 simulated patients), it became apparent that the limitations of Excel 2007 in the Windows Vista Business Service Pack 2 Build 6002 (Microsoft Corporation, Redmond, WA, USA) operating environment caused serious restrictions in two respects: the speed at which the model could be recalculated and the size of workbook that could be accommodated.

These problems became critical in the context of carrying out probabilistic sensitivity analyses on the Assessment Group's model results, where it proved necessary to read random number sets from an external data file rather than from within Excel and to severely restrict the number of replications carried out. Commonly, probabilistic sensitivity analysis simulations involve many thousands of replications aimed at achieving stability of results. Instead we used a preprocessing technique previously developed in the context of an earlier MTA project, which uses a much smaller replication random number set designed to ensure full coverage of the distributional space for each parameter together with guaranteed means, variances and correlations with related parameters. By trial and error we determined that a standard set of 100 such replications produced stable and reliable probabilistic sensitivity analysis results, and limited processing times to manageable proportions (typically 45 minutes for each candidate strategy within each population).

In order to limit the amount of probabilistic sensitivity analysis processing required to support decision-making, the Assessment Group restricted attention within each population by not considering any strategy that was subject to dominance or extended dominance within the deterministic analysis, i.e. limiting attention to strategies on the cost-effectiveness frontier.

In all cases but one, consideration was given only to analyses using the full branded price of clopidogrel, on the grounds that previous results had indicated that (with the exception of one subpopulation of 'ischaemic stroke-only' patients), a reduced price of clopidogrel does not alter the choice of optimal strategy.

Probabilistic sensitivity analysis findings for optimal strategies

The results of probabilistic sensitivity analysis are compared with the earlier deterministic findings in *Table 72*. The two sets of ICERs governing the selection of the optimal strategy rather than the 'next best' option are very similar in all cases and show no evidence of consistent bias in either direction. Moreover, in all cases the estimated ICERs fall markedly below the 'standard range' of cost-effectiveness (£20,000–30,000 per QALY gained).

For three of the four patient populations (MI only, peripheral arterial disease only and multivascular disease) the probability of optimal cost-effectiveness is close to 100% when the willingness to pay exceeds £20,000 per QALY. In the case of the ischaemic stroke-only population, probabilities are somewhat lower, but still well above 50%. It is noticeable that in those smaller patient groups where intolerance to either ASA or MRD leaves only a single antiplatelet treatment option, the incremental net benefit is much greater than when comparing between competing antiplatelet treatment strategies, confirming that using any of the available treatments is preferable to not treating at all.

The CEACs indicating the relative cost-effectiveness performance of each of the eligible treatment strategies for each patient population group across a range of WTP values are illustrated in *Figures 27–36*.

TABLE 72 Comparison of deterministic and probabilistic model results (assuming the branded price clopidogrel and the TA90[24] guidance were not applied)

	Treatment strategy		ICER (£/QALY)		WTP threshold			
					£20,000/QALY		£30,000/QALY	
Patient population	Optimal	Next best	Deterministic (£)	PSA (£)	Probability of cost-effectiveness (%)	Incremental net benefit (£)	Probability of cost-effectiveness (%)	Incremental net benefit (£)
MI only	ASA → CLOP	ASA	8118	6250	100	1134	100	1958
MI only (ASA intolerant)	CLOP	No APT	12,112	12,037	98	1911	100	4311
PAD only	CLOP → ASA	ASA → CLOP	12,956	9975	98	3559	100	7110
PAD only (ASA intolerant)	CLOP	No APT	5443	4367	100	12,145	100	19,914
MVD	CLOP → ASA	ASA → CLOP	12,324	11,121	100	1790	100	3806
MVD (ASA intolerant)	CLOP	No APT	2902	2064	100	12,747	100	19,853
IS only	MRD + ASA → ASA → CLOP	MRD + ASA → ASA	N/A	16,833	79	46	89	190
IS only (ASA intolerant)	CLOP → MRD	CLOP	9021	6443	96	2576	96	4277
IS only (MRD intolerant)	ASA → CLOP	ASA	7336	6185	85	1347	65	2322
IS only (MRD intolerant – generic CLOP)	CLOP → ASA	ASA → CLOP	9328	4676	85	989	87	1635

APT, antiplatelet therapy; CLOP, clopidogrel; IS, ischaemic stroke; MVD, multivascular disease; N/A, not available; PAD, peripheral arterial disease; PSA, probabilistic sensitivity analysis.
Note: for the 'ischaemic stroke-only' population the 'next-best' strategy differs in the deterministic analysis from the probabilistic sensitivity analysis.

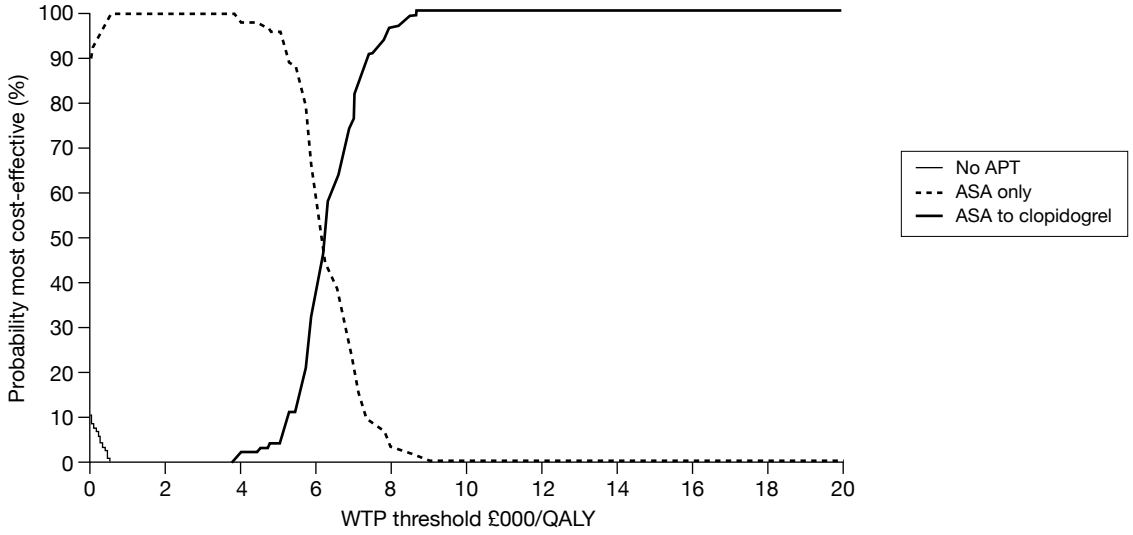

FIGURE 27 The cost-effectiveness acceptability curve for the MI-only population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

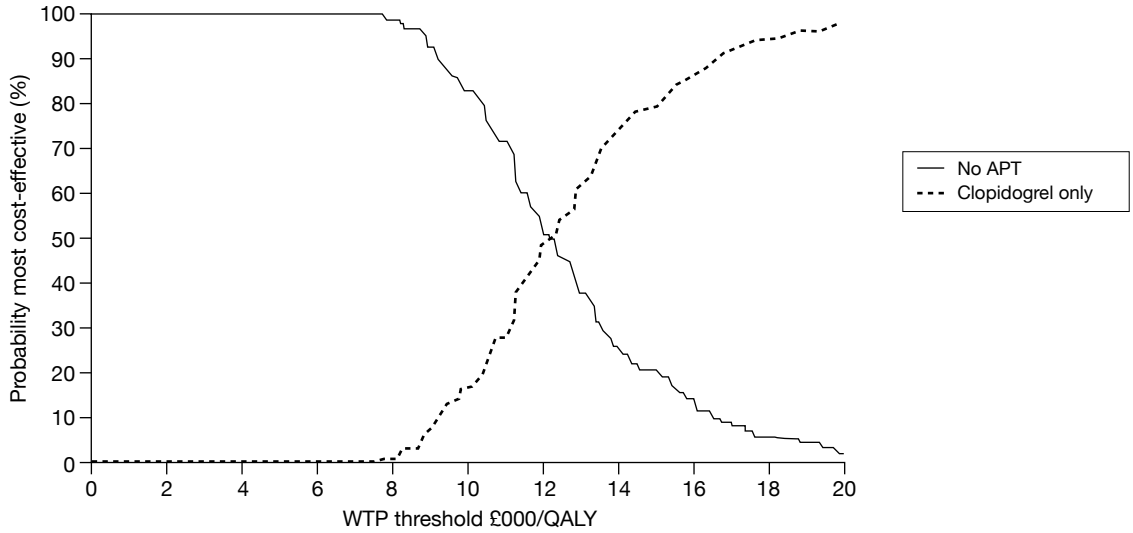

FIGURE 28 The cost-effectiveness acceptability curve for the MI-only ASA-intolerant population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

The probabilistic sensitivity analyses undertaken by the Assessment Group are consistent with the results obtained by deterministic use of the Assessment Group's model. In addition, they have confirmed that the optimal strategies previously described may be considered robust with respect to known parameter uncertainty. In particular, the apparent sensitivity of results in the peripheral arterial disease-only population to uncertainty in event-risk variables is not reflected in greater decision uncertainty when considered in the context of all other model parameters.

Additional probabilistic sensitivity analysis results for the 'ischaemic stroke-only' population

Additional results describing the outcome of the probabilistic sensitivity analysis were carried out on the 'ischaemic stroke-only' population using the extended sample of 10,000 patients and

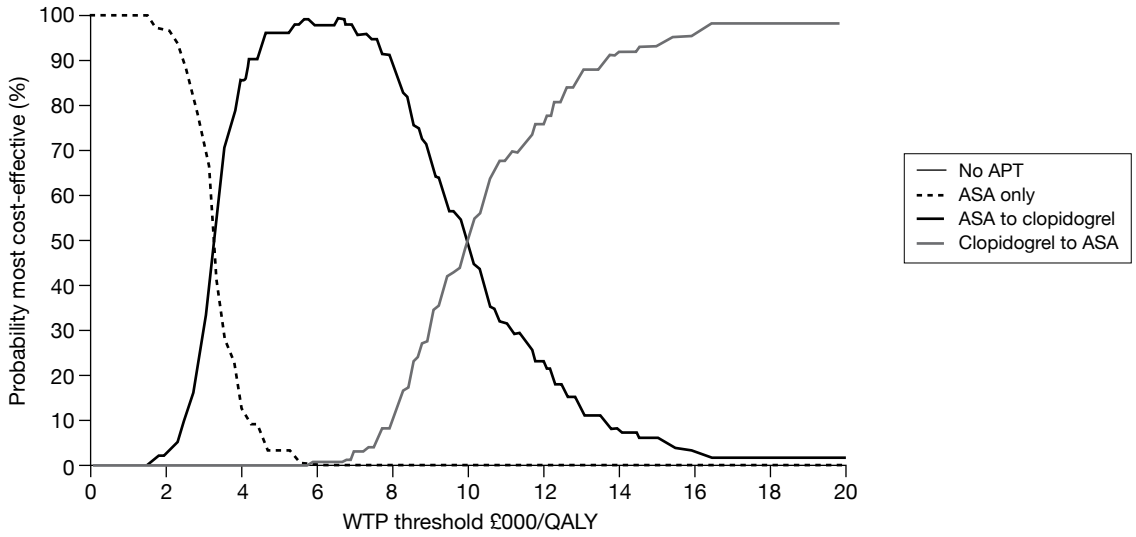

FIGURE 29 The cost-effectiveness acceptability curve for the peripheral arterial disease-only population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

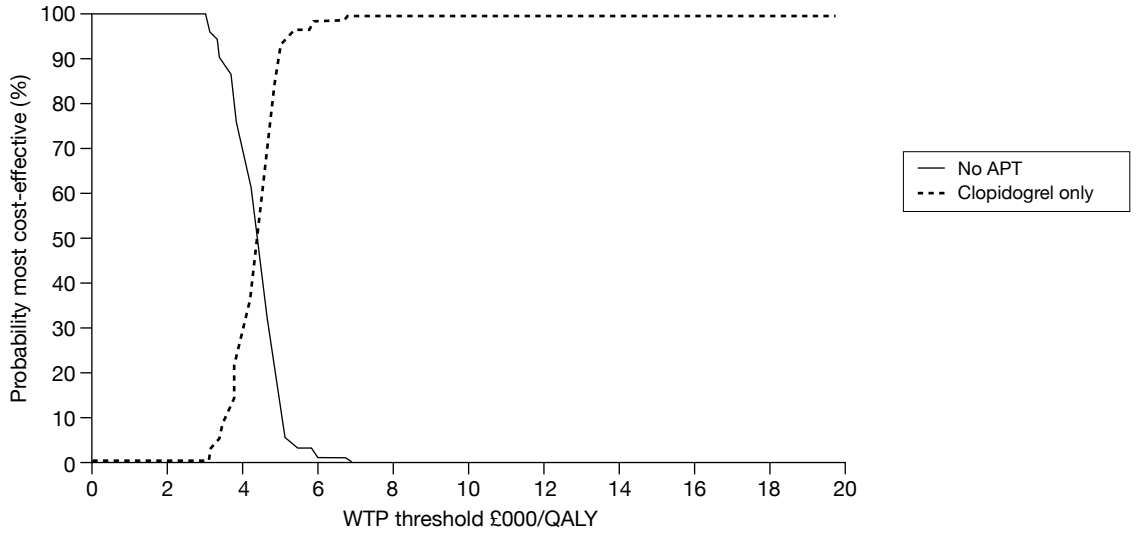

FIGURE 30 The cost-effectiveness acceptability curve for the peripheral arterial disease-only ASA-intolerant population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

generic clopidogrel pricing. Owing to the excessive computational time involved, these results relate only to the scenario in which TA90 guidance is not applied in the model.

Probabilistic results showing effect of parameter uncertainty

In *Table 73* the calculations identifying scenarios lying on the cost-effectiveness frontier are shown, leading to the final preferred scenario in which clopidogrel is used as the first-line treatment, followed respectively by MRD + ASA and ASA, with a stepwise ICER of just over £10,000 per QALY gained.

Figure 37 indicates that the MRD + ASA first-line scenarios lie very close to the frontier, but are consistently slightly less effective than the corresponding clopidogrel first-line scenarios.

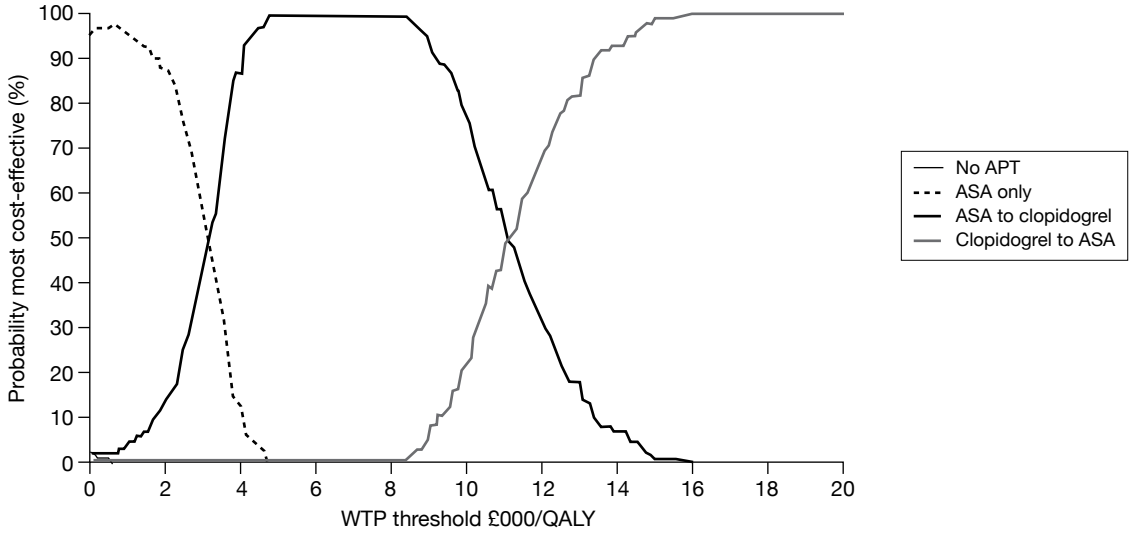

FIGURE 31 The cost-effectiveness acceptability curve for the multivascular disease population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

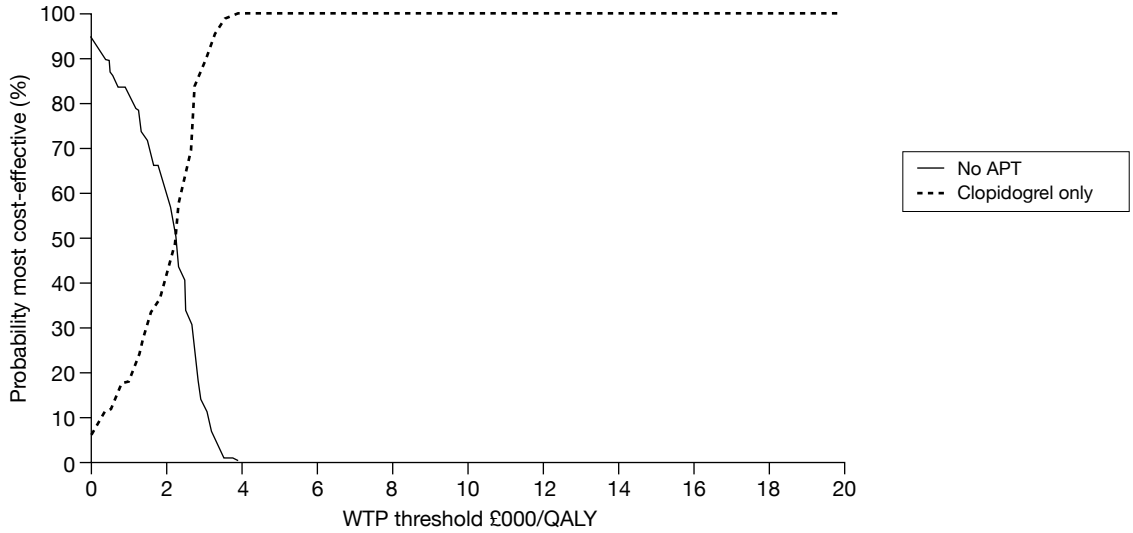

FIGURE 32 The cost-effectiveness acceptability curve for the multivascular disease ASA-intolerant population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

The CEACs (*Figure 38*) indicate that only three scenarios appear to warrant consideration as 'most cost-effective': 'ASA only' for WTP threshold of < £2300/QALY, ASA → clopidogrel → MRD + ASA if WTP is < £8300/QALY and clopidogrel → MRD + ASA → ASA for WTP > £8300/QALY. This last scenario demonstrates a probability of being most cost-effective of 68% (WTP = £20,000/QALY) or 73% (WTP = £30,000/QALY). The degree of difference between the probabilistic sensitivity analysis results for the clopidogrel and MRD + ASA scenarios can be gauged from the scatter plot shown in *Figure 39*.

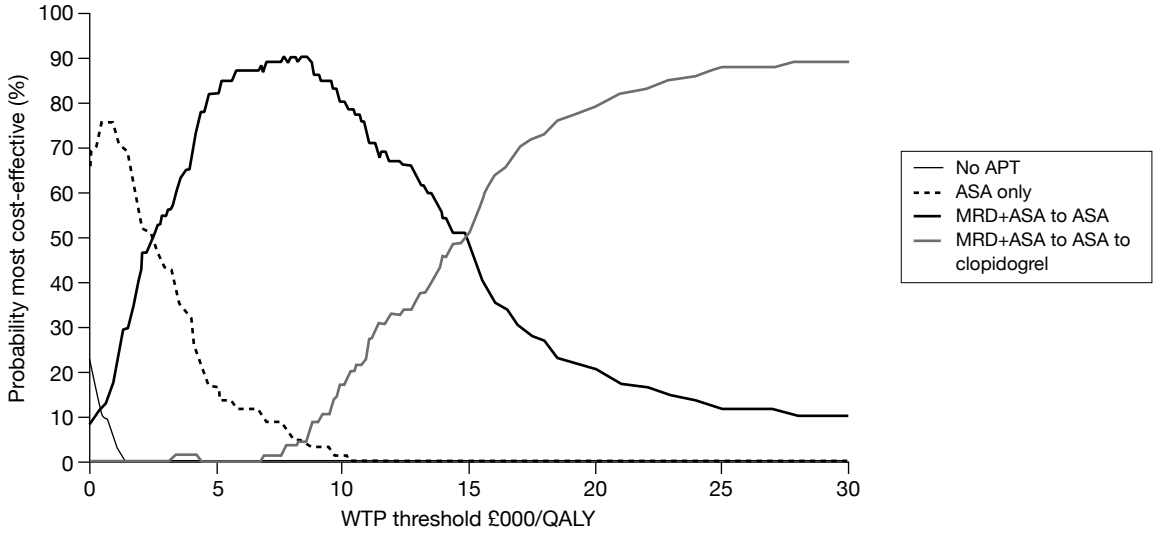

FIGURE 33 The cost-effectiveness acceptability curve for the ischaemic stroke-only population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

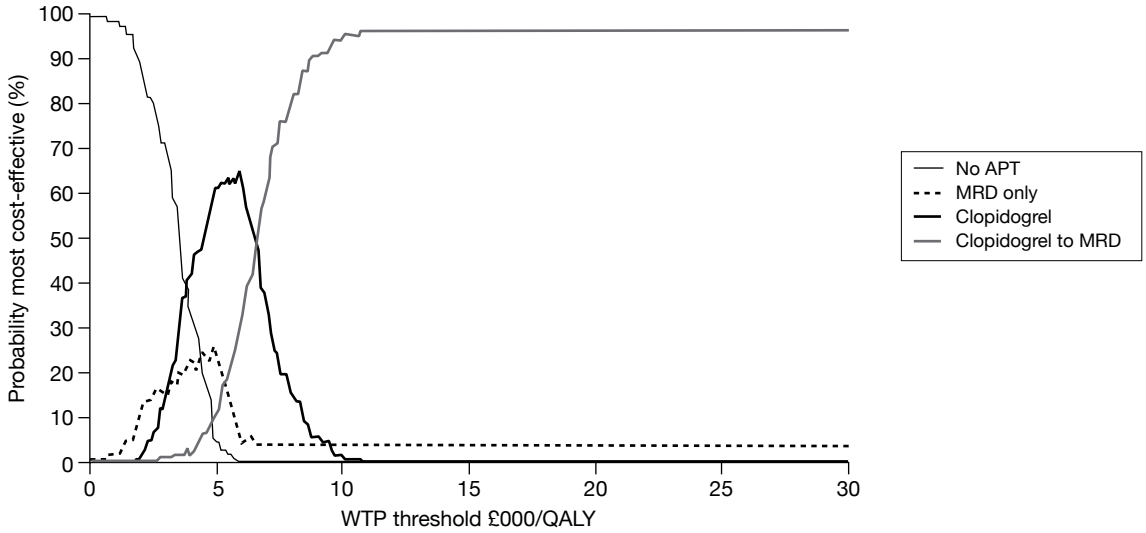

FIGURE 34 The cost-effectiveness acceptability curve for the ischaemic stroke-only ASA-intolerant population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

Although there is a consistent indication of greater effectiveness for use of generic clopidogrel as a first-line therapy, the differences in both costs and effectiveness are small.

Summary of probabilistic analysis

The probabilistic sensitivity analysis findings confirm deterministic results reported indicating that the use of generic clopidogrel leads to first-line clopidogrel being more cost-effective than first-line MRD + ASA for the 'ischaemic stroke-only' population.

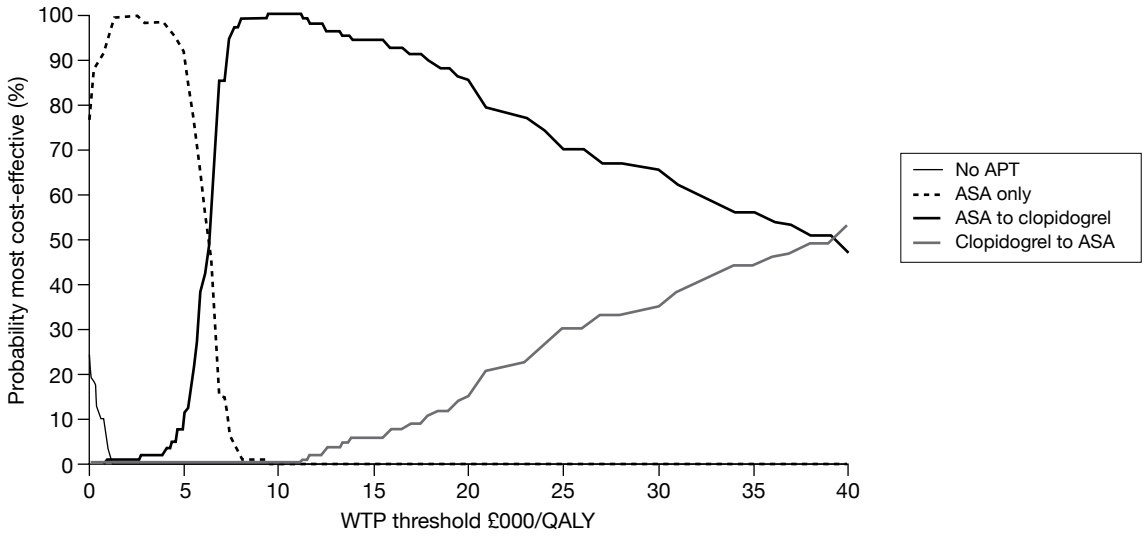

FIGURE 35 The cost-effectiveness acceptability curve for the ischaemic stroke-only MRD-intolerant population (the branded clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

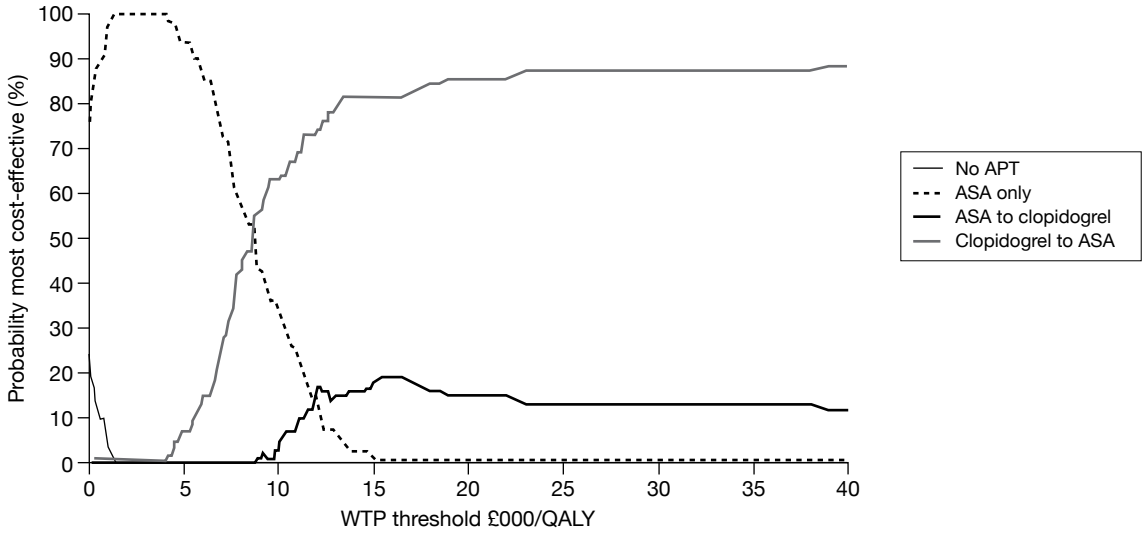

FIGURE 36 The cost-effectiveness acceptability curve for the ischaemic stroke-only MRD-intolerant population (the generic clopidogrel price and the TA90[24] guidance were not applied). APT, antiplatelet therapy.

TABLE 73 Probabilistic results from the Assessment Group's model for treatment of the 'ischaemic stroke-only' population

CLOP price	TA90[24] status	Strategy			Total costs (£)	Utility QALYs	ICER (£)				
		Treatment 1	Treatment 2	Treatment 3			Step 1	Step 2	Step 3	Step 4	Step 5
Generic	Not used	None	None	None	34,825	7.068					
		ASA	None	None	34,289	7.588	**–1033**[a]				
		ASA	**CLOP**	**MRD + ASA**	34,484	7.682	–557	**2077**[a]			
		ASA	MRD + ASA	CLOP	34,497	7.684	–532	2162	**5227**[a]		
		CLOP	**ASA**	**MRD + ASA**	35,187	7.773	513	4858	7729	**7803**[a]	
		CLOP	**MRD + ASA**	**ASA**	35,438	7.798	840	5481	8240	8309	**10,107**
		MRD + ASA	CLOP	ASA	35,318	7.771	701	5610	9314	9436	Dom
		MRD + ASA	ASA	CLOP	35,064	7.751	3500	4578	8402	8526	Dom

Dom, dominated; IC, IQ, incremental cost and QALYs.
a Strategy on cost-effectiveness frontier.
Dominated one- and two-step strategies have been omitted.

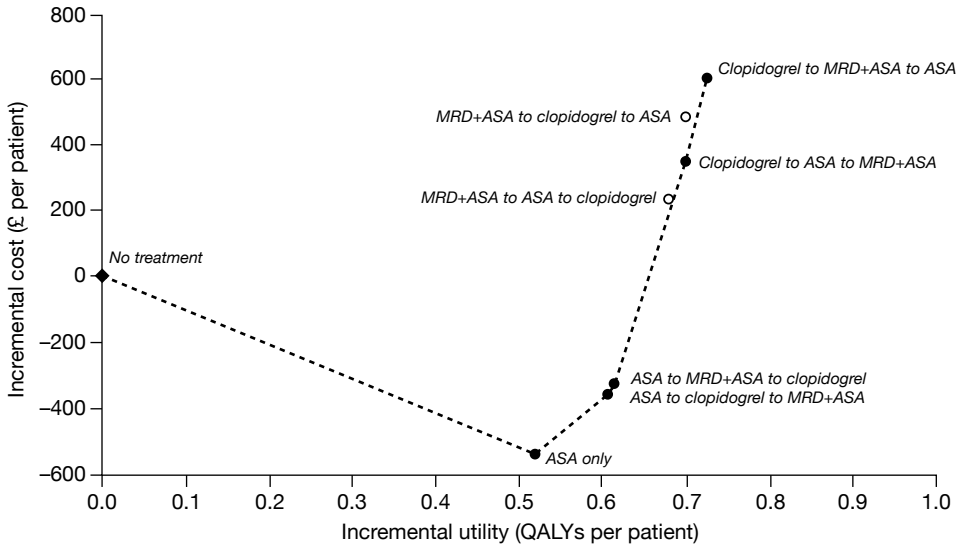

FIGURE 37 The cost-effectiveness plane for the ischaemic stroke-only population (the generic clopidogrel price and the TA90[24] guidance were not applied).

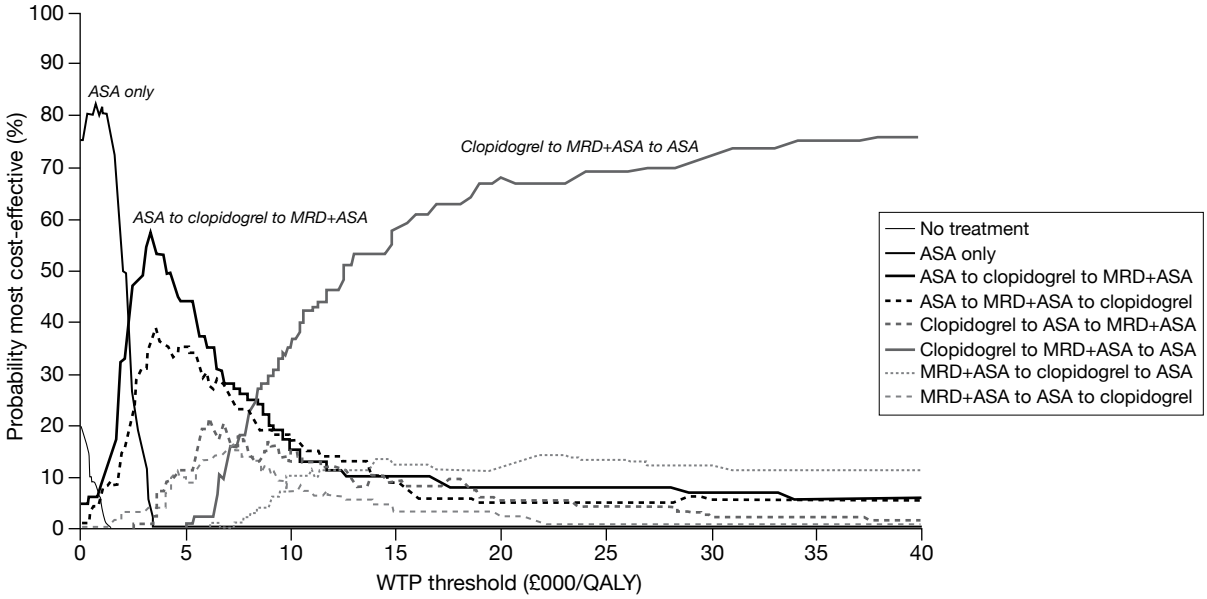

FIGURE 38 The cost-effectiveness acceptability curves for the ischaemic stroke-only population (the generic clopidogrel price and the TA90[24] guidance were not applied).

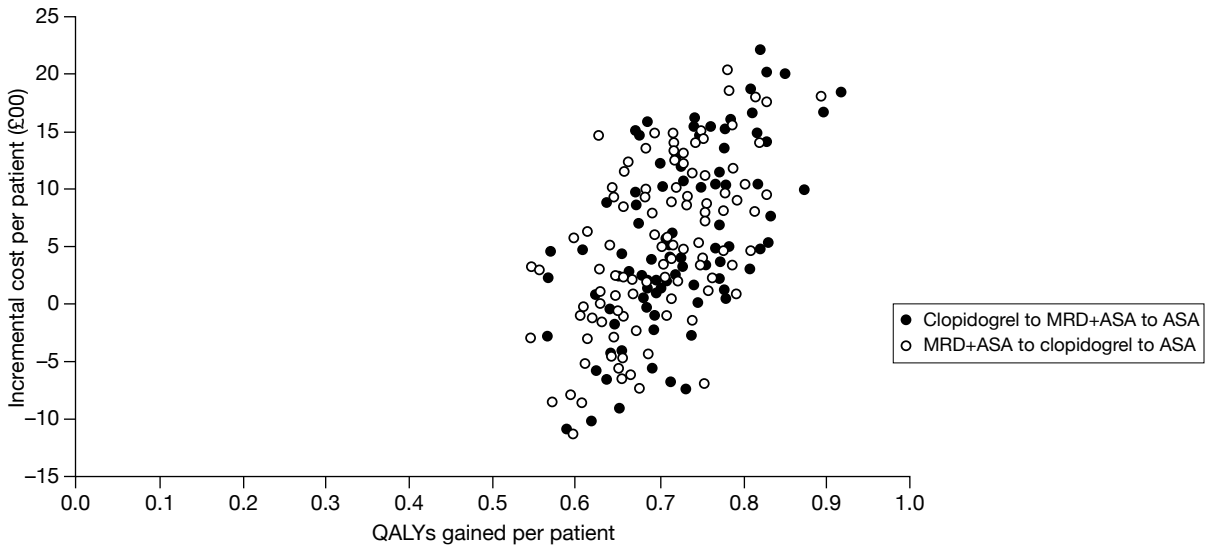

FIGURE 39 Probabilistic sensitivity analysis scatter plot for the ischaemic stroke-only population (the generic clopidogrel price and the TA90[24] guidance were not applied) – comparing two first-line therapies.

Chapter 5

Discussion

Statement of principal findings

The purpose of this report is to assess the clinical effectiveness and cost-effectiveness of (1) clopidogrel and (2) MRD alone or MRD + ASA compared with ASA and, where appropriate, with each other in the prevention of occlusive vascular events in patients with a history of MI or ischaemic stroke/TIA or established peripheral arterial disease. The final scope issued by NICE also called for consideration of the effectiveness of clopidogrel in patients with multivascular disease.

Current NICE guidance in TA90[24] recommends that patients with a history of MI or peripheral arterial disease should be treated with ASA (clopidogrel if ASA intolerant); patients with a history of ischaemic stroke/TIA should be treated with MRD + ASA for 2 years (if MRD is not tolerated, standard care, including long-term treatment with low-dose ASA). Patients with multivascular disease are not considered in TA90.[24]

Clinical effectiveness: direct evidence

Patients with myocardial infarction and established peripheral arterial disease

Only the CAPRIE[26] trial offers evidence of the effectiveness of clopidogrel (vs ASA) in patients with a prior history of MI or established peripheral arterial disease. For the whole population (patients with a prior history of MI or ischaemic stroke or established peripheral arterial disease), the CAPRIE[26] trial favoured clopidogrel; statistically significant outcomes were noted for the primary outcome (first occurrence of ischaemic stroke, MI or vascular death). However, the benefit appeared to be small and the boundaries of the CIs raise the possibility that clopidogrel is not more beneficial than ASA across the patient population as a whole. When the results for each of the subgroups were analysed, there was a statistically significant effect only in patients with peripheral arterial disease (favouring clopidogrel).

Patients with multivascular disease

The clinical effectiveness of clopidogrel in patients with multivascular disease is assessed using data from three distinct sources: the original CAPRIE[26] publication, a post hoc analysis based on the CAPRIE[26] population and the Assessment Group's reclassification of the original patient groups using additional CAPRIE[26] data provided by the manufacturer. The results of all subgroup analyses undertaken suggest that patients with multivascular disease are likely to experience elevated risks of future single and composite events and that treatment with clopidogrel is preferred over ASA.

Patients with ischaemic stroke/transient ischaemic attack

For the ischaemic stroke/TIA population, clinical data are available from four studies: CAPRIE,[26] ESPS-2,[30] ESPRIT[56] and PRoFESS.[57] In the CAPRIE[26] trial there were no statistically significant differences in the primary outcome between the treatment groups (MI, ischaemic stroke, peripheral arterial disease) in patients with prior history of ischaemic stroke. In ESPS-2[30] there was no difference in outcomes when MRD was compared with ASA; there was a statistically significant reduction in incidence of stroke in favour of MRD + ASA compared with ASA and

MRD alone. No other primary outcome (all-cause death; stroke and/or all-cause death) showed statistically significant differences between any two treatment arms. In ESPRIT,[56] for the primary outcome (first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication), the risk of event occurrence was statistically significantly lower in the MRD + ASA arm than in the ASA arm. In the PRoFESS trial,[57] the rate of recurrent stroke of any type (primary outcome) was similar in the MRD + ASA and clopidogrel groups and the null hypothesis (that MRD + ASA is inferior to clopidogrel) could not be rejected. An increased risk of major haemorrhagic event and intracranial haemorrhage was reported for MRD-ASA compared with clopidogrel.

In summary, the clinical evidence appears to suggest that MRD + ASA is preferred to MRD alone and ASA in patients with a prior history of ischaemic stroke/TIA. There is not enough clinical evidence to make an informed decision regarding the use of MRD + ASA vs clopidogrel in patients with a prior history of ischaemic stroke/TIA.

Adverse events

It is difficult to summarise the findings related to adverse events, as the classification of these outcomes differed greatly across the trials; this was especially apparent for 'bleeding' events. However, upon investigation, the Assessment Group did not identify any unexpected adverse events associated with any of the drugs, bleeding was associated with ASA and headache was associated with MRD.

Clinical effectiveness: indirect evidence

Ischaemic stroke/transient ischaemic attack-only populations

There were no major differences in the results of the mixed-treatment comparison and the direct estimates from head-to-head trials. However, two of the five newly generated comparisons did yield statistically significant results: MRD alone had an increased risk of recurrent stroke when compared with clopidogrel; clopidogrel had fewer major bleeding events compared with ASA. Owing to the small numbers of trials involved in the mixed-treatment comparison and the forced selection of limited outcomes, caveats apply to the results. Findings were also based on patient populations in which there is no differentiation between patients with vascular disease in a single bed and those with multivascular disease. The results of the indirect analyses, although confirmatory of the direct results, must therefore be interpreted with caution.

Cost-effectiveness evidence

Summary of previously published cost-effectiveness analyses

All of the economic evaluations, except three,[71,72,78] were published prior to 2006; this means more recent trials and clinical papers have not been used to inform the economic evaluations. The relevance of this review to decision-making is therefore limited as the economic evaluations are not based on the most up-to-date clinical data. Nonetheless, the results of the literature review of cost-effectiveness evidence show that, from a health service perspective, the use of clopidogrel in patients with previous peripheral arterial disease, ischaemic stroke or MI is a cost-effective option compared with ASA in the secondary prevention of occlusive vascular events. However, it is noted that Schleinitz *et al.*[75] conclude that the evidence available to them at the time did not support increased efficacy of clopidogrel in the MI patient group; this is the only evaluation that includes subgroup analysis to estimate ICERs by patients' previous event. The combination of MRD + ASA seems to be cost-effective compared with any other treatment in patients with previous ischaemic stroke/TIA in the secondary prevention of occlusive vascular events. There is only one evaluation that includes this combination (MRD + ASA) and therefore the evidence base is limited.

Summary of industry-submitted economic evaluations

Both manufacturers submitted de novo economic analyses that met the NICE reference case criteria.

Boehringer Ingelheim is the manufacturer of MRD + ASA and the manufacturer's submission appears to demonstrate that:

1. MRD + ASA (first-line) and ASA (second-line) is cost-effective compared with ASA alone (£5377 per QALY gained) and to no treatment (£5910 per QALY gained) in patients with a history of ischaemic stroke/TIA.
2. MRD + ASA (first-line) and ASA (second-line) compared with clopidogrel yields an ICER of £114,628 per QALY gained (patients with a history of ischaemic stroke) and an ICER of £199,149 (patients with a history of TIA).

The main critique of the Boehringer Ingelheim manufacturer's submission is focused on the fact that the transition probabilities during the first 4 years for the MRD + ASA and clopidogrel arms are derived from PRoFESS,[57] ESPS-2[30] and ESPRIT[56] trials, beyond this point the manufacturers have used the same transition probability as used for the last 6-monthly cycle. This is an unreliable basis for long-term projection, as close to the end of the trial patient numbers and the number of events are much reduced. As a consequence, estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations. It is important to note that the manufacturers used Plavix (branded clopidogrel) at a price of £36.35 for 30 tablets (75 mg) in the manufacturer's submission; the price of clopidogrel is now set at £10.90 for 30 tablets (75 mg). This means that for the ischaemic stroke/TIA populations, clopidogrel is now cheaper and more effective than MRD + ASA.

Sanofi–aventis/Bristol–Myers Squibb are the manufacturers of clopidogrel and the manufacturer's submission appears to demonstrate that:

1. For patients with a prior history of ischaemic stroke, clopidogrel is dominated by MRD + ASA and that clopidogrel versus MRD yields an ICER of £5850 per QALY gained.
2. For patients with a prior history of MI, clopidogrel versus ASA yields an ICER of £20,662 per QALY gained.
3. For patients with established peripheral arterial disease, clopidogrel versus ASA yields an ICER of £18,845 per QALY gained.
4. For patients with multivascular disease, clopidogrel versus ASA yields an ICER of £15,524 per QALY gained.

The main critique of the Sanofi–aventis/Bristol–Myers Squibb economic model is focused on the approach used to project health outcomes. The model assumes different transition probabilities every year until year 3. Beyond this point, the last cycle transition probabilities are used for the remainder of the time horizon from years 3 to 35. This is an unreliable basis for long-term projection, as patient numbers and the number of events are much reduced close to the end of the trial. As a consequence, estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations. It is important to note that using the new generic price of clopidogrel in the economic model improves the cost-effectiveness of clopidogrel.

Summary of the Assessment Group's cost-effectiveness analysis

Cost-effectiveness results have been generated from the Assessment Group's economic model to address two related questions:

- Which treatment strategy is most cost-effective in avoiding future occlusive vascular events in each of the four specified populations?
- How does the availability of generic clopidogrel at a lower price than the branded product affect the assessment of cost-effectiveness of clopidogrel containing treatment strategies?

- Patients with ischaemic stroke/TIA:

  - In all scenarios, the most cost-effective strategy begins with generic clopidogrel followed by MRD + ASA, followed by ASA.
  - In patients who are intolerant of ASA, compared with no treatment, clopidogrel followed by MRD is the most cost-effective approach, independent of both the TA90 guidance[24] and the price of clopidogrel.
  - In patients who are intolerant of MRD, at the branded price, the preferred strategy is ASA followed by clopidogrel, but for the generic price clopidogrel followed by ASA is more cost-effective.
  - For patients intolerant to both ASA and MRD, only clopidogrel is available for long-term prevention and it is seen to be more cost-effective than no preventive therapy.

- Patients with MI:

  - In all scenarios, the incremental cost-effectiveness of allowing clopidogrel as a subsequent therapy after failure of ASA therapy compared with ASA treatment alone is < £9000 per QALY gained suggesting that ASA followed by clopidogrel may be the optimal strategy for this patient group.
  - In patients who are intolerant of ASA, clopidogrel is a cost-effective approach independent of both the TA90 guidance[24] and the price of clopidogrel (ICERs ranging between £1961 and £12,391 per QALY gained).

- Patients with established peripheral arterial disease:

  - In all scenarios, the ICER for a strategy of clopidogrel followed by ASA when compared with ASA followed by clopidogrel appears to be well within the range considered cost-effective (under £13,000 per QALY gained for branded clopidogrel and under £5000 per QALY for generic clopidogrel), suggesting this as the optimal strategy for this patient group.
  - In patients who are intolerant to ASA, clopidogrel is a cost-effective approach independent of both the TA90 guidance[24] and the price of clopidogrel.

- Patients with multivascular disease:

  - In all scenarios, the incremental cost-effectiveness of clopidogrel followed by ASA is the most cost-effective approach, independent of both the TA90 guidance[24] and the price of clopidogrel.
  - In patients who are intolerant to ASA, clopidogrel is a cost-effective approach to occlusive vascular event prevention independent of both the TA90 guidance[24] and the price of clopidogrel.

Sensitivity analysis

The sensitivity analyses undertaken using the Assessment Group's de novo model allowed the most likely sources of influential uncertainty to be identified. First, there is no indication that cost and utility parameters, population characteristics or non-vascular mortality give rise to significant uncertainty in economic results. Second, three types of parameter are implicated in

at least one of the sensitivity analyses as likely to be influential on model results – the risk of events occurring, the fatality of such events and the likelihood that patients will cease taking the prescribed preventive medications. Third, model results for the 'peripheral arterial disease-only' population appear to be particularly vulnerable to uncertainty in event risks, which is addressed probabilistically.

Probabilistic sensitivity analysis

The probabilistic sensitivity analyses undertaken support the findings of the deterministic analyses. In addition, they have confirmed that the optimal strategies previously described may be considered robust with respect to known parameter uncertainty. In particular, the apparent sensitivity of the results in the peripheral arterial disease-only population to uncertainty in event-risk variables is not reflected in greater decision uncertainty when considered in the context of all other model parameters.

Strengths and limitations

The key strengths of the report are threefold. First, the Assessment Group was able to consider the clinical effectiveness and cost-effectiveness of clopidogrel in people with multivascular disease as specified in the final scope issued by NICE. Using information provided by the manufacturer, the Assessment Group reanalysed previously published data from the CAPRIE[26] trial and estimated the clinical effectiveness and cost-effectiveness of clopidogrel in this clinically important subgroup of patients. The Assessment Group confirmed the findings of other published clinical papers that patients with multivascular disease are often at high risk of single and composite future clinical events.

Second, the Assessment Group did not simply address the short-term costs and benefits associated with clopidogrel and MRD; the clinical effectiveness and cost-effectiveness of clopidogrel and MRD is considered over time using treatment scenarios. The strength of this approach is that it reflects the real world in which many patients will need to switch between different treatments during their lifetime. Restricting the analysis of costs and benefits of long-term prophylaxis to a few years frequently results in erroneous conclusions.

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

The clinical effectiveness and cost-effectiveness findings of the report are limited by the nature of the clinical evidence available. For the MI, peripheral arterial disease and multivascular disease patient populations, data were available only from the CAPRIE[26] trial (clopidogrel vs ASA) and the clinical results favoured clopidogrel. However, use of a single trial to generate clinical evidence for three individual patient populations inevitably attracts criticism. It is also important to note that the CAPRIE[26] trial did not distinguish between patients with NSTEMI and STEMI, and this clearly inhibits the interpretation of the trial results for these clinically important subgroups of patients. For the ischaemic stroke/TIA population, relevant evidence was available from four published RCTs to inform the Assessment Group's assessment of clopidogrel and MRD. However, the studies were all very different in terms of design, patient populations and clinical outcomes, so that even indirect comparisons proved to be fraught with difficulty. The key

comparison of interest for patients with ischaemic stroke/TIA was clopidogrel vs MRD + ASA and the results of this trial were inconclusive. This is unfortunate as it is unlikely that a trial of this design will ever be repeated. In summary, the clinical evidence available, particularly for MI, peripheral arterial disease and multivascular disease populations, to answer the key questions set out in the final scope is limited.

Uncertainties

The findings of this report for the MI, peripheral arterial disease and multivascular disease patient populations are reliant on several post hoc subgroup analyses from a single trial; this means that there is inevitable uncertainty associated with the findings of this report. During the Appraisal Committee meeting which led to the publication of TA90,[24] the Appraisal Committee '… was persuaded that undue reliance on subgroup analysis was inadvisable principally because of insufficient study power. Consequently, it was considered inappropriate to rely on post hoc analyses …'. However, the Assessment Group is of the opinion that reliance on the results of post hoc subgroup analyses from a single trial was unavoidable if the questions set out in the final scope issued by NICE were to be adequately addressed in this report. To illustrate, there are clinical data available from PRoFESS,[57] CAPRIE,[26] ESPS-2[30] and ESPRIT[56] for the ischaemic stroke/TIA population, but the only clinical data available for patients with prior MI, peripheral arterial disease and multivascular disease are from the CAPRIE[26] trial. Patients with MI, peripheral arterial disease and multivascular disease are not considered to constitute a single homogeneous clinical population; this means that use of subgroup analysis to estimate the clinical effectiveness and cost-effectiveness of clopidogrel for these individual subpopulations, although not ideal, is necessary. It is important to note that the size of each of the subgroup populations is considerable (ischaemic stroke 4740, MI 5741, peripheral arterial disease 3713 and multivascular disease 4991) and proved sufficient to demonstrate important differences in risk profiles between these groups.

In the absence of any universally agreed definition, the multivascular disease subgroup analyses were based on a population defined by the Assessment Group. The Assessment Group's definition appears to be consistent with the simplest and broadest definition described in the published literature; however, it is likely that any differences in definitions of multivascular disease subgroups will lead to differences in patient numbers and RRs.

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

Chapter 6

Conclusions

For patients with ischaemic stroke/TIA, MRD + ASA followed by ASA, followed by clopidogrel, appears to be a cost-effective approach to the prevention of future occlusive vascular events.

For patients with MI, ASA followed by clopidogrel appears to be a cost-effective approach to the prevention of future occlusive vascular events.

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

Suggested research

It is suggested that any future trials in this area should distinguish between patients with single vascular bed and multivascular disease, that definitions of multivascular disease should be prespecified (ideally using a common standard), and that triallists should ensure that trials are sufficiently powered over an extended follow-up period to allow detection of treatment differences between subgroups of patients. To facilitate comparison of primary and secondary outcomes across relevant trials, all outcomes need to be reported consistently and at key time points.

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

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Janette Greenhalgh Project lead, review of clinical evidence.

Adrian Bagust Critical appraisal of manufacturers' economic models, development of de novo model.

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Appendix 1

Literature search strategies

EMBASE 2003–9 week 36

1. Clinical trial/
2. Randomized controlled trial/
3. Randomization/
4. Single blind procedure/
5. Double blind procedure/
6. Crossover procedure/
7. Placebo/
8. Randomi?ed controlled trialUS$.tw.
9. Rct.tw.
10. Random allocation.tw.
11. Randomly allocated.tw.
12. Allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blindUS$.tw.
15. Double blindUS$.tw.
16. ((treble or triple) adj blindUS$).tw.
17. PlaceboUS$.tw.
18. Prospective study/
19. or/1–18
20. Case study/
21. Case report.tw.
22. Abstract report/or letter/
23. or/20–22
24. 19 not 23
25. Ticlopidine/
26. Clopidogrel/
27. clopidogrel.ti,ab.
28. plavix.ti,ab.
29. 90055–48–4.rn.
30. (asasantin retard or persantin retard).ti,ab.
31. DIPYRIDAMOLE/
32. dipyridamole.ti,ab.
33. 58–32–2.rn.
34. or/25–33
35. (myocardUS$infarcUS$or MI).ti.
36. NSTEMI.ti,ab.
37. non ST segment elevation myocardial infarction.ti,ab.
38. stroke.ti.
39. Cerebrovascular Accident/
40. (cerebrovascular accidentUS$or CVA).ti.
41. Transient Ischemic Attack/
42. (isch?emic stroke or transient isch?emic attackUS$).ti,ab.

43. Unstable Angina Pectoris/
44. unstable angina.ti,ab.
45. peripheral arterial disease.ti,ab.
46. (TIA or TIAS).ti.
47. Heart Infarction/
48. or/35–47
49. 24 and 34 and 48
50. limit 49 to (human and english language and yr="2003 – 2009")

MEDLINE August week 4 2009

1. randomized controlled trial.pt.
2. randomized controlled trials/
3. randomi?ed controlled trialUS$.ti,ab.
4. random allocation/
5. double–blind method/
6. single–blind method/
7. (clinUS$ad2 rialUS$).ti,ab.
8. ((singlUS$r doublUS$or treblUS$or triplUS$) adj2 (blindUS$or maskUS$)).ti,ab.
9. placebos/
10. placeboUS$.ti,ab.
11. random.ti,ab.
12. comparative study/
13. exp evaluation studies/
14. follow–up studies/
15. prospective studies/
16. (control or controls or controlled).ti,ab.
17. clinical trials, phase iv/
18. phase iv.ti,ab.
19. phase four.ti,ab.
20. phase 4.ti,ab.
21. post marketUS$surveillance.ti,ab.
22. or/1–21
23. Case report.tw.
24. Letter/
25. Historical article/
26. or/23–25
27. 22 not 26
28. Ticlopidine/
29. clopidogrel.ti,ab.
30. plavix.ti,ab.
31. 90055–48–4.rn.
32. asasantin retard.ti,ab.
33. persantin retard.ti,ab.
34. dipyridamole.ti,ab.
35. dipyridamole/
36. 58–32–2.rn.
37. or/28–36
38. exp MYOCARDIAL INFARCTION/
39. (myocardUS$infarcUS$or MI).ti.
40. NSTEMI.ti,ab.

41. non ST segment elevation myocardial infarction.ti,ab.
42. stroke.ti.
43. CEREBROVASCULAR ACCIDENT/
44. (cerebrovascular accidentUS$or CVA).ti.
45. ISCHEMIC ATTACK, TRANSIENT/
46. sch?emic stroke or transient isch?emic attackUS$).ti,ab.
47. ANGINA, UNSTABLE/
48. unstable angina.ti,ab.
49. peripheral arterial disease.ti,ab.
50. TIA or TIAS).ti.
51. or/38–50
52. 52
53. 27 and 37 and 51
54. 53
55. limit 52 to (english language and humans and yr="2003 – 2009")

Web of Science – now with Conference Proceedings

- 2003–2009.
- Databases searched=SCI-EXPANDED (Science Citation Index Expanded), CPCI-S (Conference Proceedings Citation Index-Science).
- ((Clopidogrel or dipyridamole or plavix or ticlopidine or asasantin or persantin) and (Occlusive vascular event* or ischaemic attack or TIA or ischaemic stroke or myocardial infarction or MI or heart infarction or Peripheral artery disease or cerebrovascular accident* or unstable angina or ST segment elevation)).
- Results: Document Type=(ARTICLE (1257) OR REVIEW (265) OR PROCEEDINGS PAPER (110) OR MEETING ABSTRACT (93)) AND Languages=(ENGLISH).
- Total: 1725.

The Cochrane Library

- 2003 – Issue 3, 2009.
- Databases searched=SCI-EXPANDED (Science Citation Index Expanded), CPCI-S (Conference Proceedings Citation Index- Science).
- ((Clopidogrel or dipyridamole or plavix or ticlopidine or asasantin or persantin) and (Occlusive vascular event* or ischaemic attack or TIA or ischaemic stroke or myocardial infarction or MI or heart infarction or Peripheral artery disease or cerebrovascular accident* or unstable angina or ST segment elevation)) in title, abstract or key words.
- Cochrane Database of Systematic Reviews (Cochrane Reviews): six Database of Abstracts of Reviews of Effects (Other Reviews): six Cochrane Central Register of Controlled Trials (Clinical Trials): 279 Health Technology Assessment Database (Technology Assessments): sixNHS Economic Evaluation Database (Economic Evaluations): 20.
- Total number of references identified: 5869 including duplicate references).
- Total number of references identified: 5109 (excluding duplicate references, removed electronically).

Appendix 2

Quality assessment

Quality assessment of included randomised controlled trials

Checklist item	CAPRIE[26]	ESPS-2[30]	ESPRIT[56]	PRoFESS[57]
Randomisation				
Was the randomisation method adequate?	Yes	Yes	Yes	Yes
Was the allocation of treatment adequately concealed?				
Was the number of participants randomised stated?				
Baseline comparability				
Were details of baseline comparability presented?	Yes	Yes	Yes	Yes
Were the groups similar for prognostic factors?				
Eligibility criteria and co-interventions				
Were the eligibility criteria for study entry specified?	Yes	Yes	Yes	Yes
Were any co-interventions identified?				
Blinding				
Were outcome assessors blinded to treatment allocation?	Yes	Yes	No[a]	Yes
Were administrators blinded to the treatment allocation?				
Were patients blinded to the treatment allocation?				
Was the blinding procedure assessed?	NS	NS	NS	NS
Withdrawals				
Any unexpected imbalances in dropouts between groups? Were they explained or adjusted for?	No/N/A	No/N/A	No/N/A	No/N/A
Were ≥ 80% patients included in the final analysis?	Yes	Yes	Yes	Yes
Were reasons for withdrawals stated?				
Was an ITT analysis included? Was this appropriate? Were appropriate methods used to account for missing data?				
Outcomes				
Evidence of more outcomes measured than reported?	No	No	No	No[a]

N/A, not applicable; NS, not stated.
a Results for extra outcomes reported in supplement.

Quality assessment of identified systematic reviews

Review	Inclusion/ exclusion criteria addressed review questions?	Evidence of a substantial effort to search for all relevant research literature?	Validity of included studies adequately assessed?	Sufficient detail of individual studies?	Primary studies summarised appropriately?
Jones 2004[3]	Good	Good	Good	Good	Good
Leonardi-Bee 2005[5]	Fair		Fair		
Verro 2008[9]				Poor	
De Schryver 2007[13]	Good		Good	Good	
ATTC 2009[119]					
Berger 2009[120]			Fair		
Halkes 2008[121]	Fair	N/A	N/A		
Sudlow 2009[122]	Good	Good	Good		

N/A, not applicable.

Quality assessment of included cost-effectiveness studies

Drummond 10-point checklist[54]	Annemans 2003[69]	Beard 2004[70]	Berger 2008[71]	Chen 2009[72]	Karnon 2005[73]	Matchar 2005[74]	Schleinitz 2004[75]	Delea 2003[76]	Palmer 2005[77]	Stevenson 2008[78]	Van Hout 2003[79]
Well-defined question			✓/×	✓	✓	✓	✓	×	✓/×	✓/×	✓/×
Comprehensive description of competing alternatives	✓	✓	✓	✓	✓	✓/×	✓	✓	✓	✓	✓
Effectiveness established	✓/×	✓/×	✓/×	✓/×	✓/×	✓/×	✓/×	✓/×	✓/×	✓/×	✓/×
All important and relevant costs and consequences for each alternative identified	✓	✓	✓	✓	✓	✓/×	✓	✓	×	×	×
Costs and consequences measured accurately	✓/×	✓	✓	✓/×	✓	✓	✓	✓	✓/×	✓/×	✓/×
Costs and consequences valued credibly	✓	✓	✓/×	✓	✓/×	✓/×	✓	✓	✓/×	✓/×	✓/×
Costs and consequences adjusted for differential timing	✓	✓	✓	✓	✓	✓	✓	✓	✓/×	✓/×	✓/×
Incremental analysis costs and consequences	✓	✓/×	✓/×	✓/×	✓	✓	✓	✓	✓/×	×	✓
Sensitivity analyses to allow for uncertainty in estimates of costs or consequences	✓	✓/×	✓/×	✓	✓	✓/×	✓	✓/×	✓/×	✓/×	✓/×
Study results/discussion include all issues of concern to users	✓	✓	✓	✓	✓	✓/×	✓	✓	✓	✓	✓

✓, fully addressed; ✓/× partially addressed; ×, not addressed.

Appendix 3

Description of systematic reviews

Eight relevant SRs were identified via the electronic searches: Jones *et al.*,[3] Leonardi-Bee *et al.*,[5] Verro *et al.*,[9] De Schryver *et al.*,[13] ATTC,[119] Berger *et al.*,[120] Halkes *et al.*[121] and Sudlow *et al.*[122] The majority of these were of good quality; all but two[9,121] of the reviews were of generally good quality (i.e. were rated as good on three or more criteria out of five). These generally supported current guidance, but highlighted the variety of patients, the different combinations of drugs and outcomes that have been assessed. No additional trials were identified from the reference lists of the identified SRs for inclusion in the review.

Identifying and assessing the quality of existing reviews allowed the Assessment Group to cross-check for the identification of additional studies, as well as to gain an understanding of the issues related to the combining of data in this complex area. The identified reviews served to demonstrate the heterogeneity of patient populations and interventions as well as the different approaches to data analysis.

The SRs are listed in the table below; most of the included studies assessed immediate-release dipyridamole rather than MRD. One of the identified SRs was the review of Jones *et al.*,[3] which underpins the current NICE TA90 guidance.[24] Three further SRs were updates of those reported by Jones *et al.*;[3] their conclusions remained unchanged.[13,119,122] These SRs, although meeting the inclusion criteria, included a variety of patient populations. Although included in the Jones *et al.* review,[3] the patient population in De Schryver *et al.*[13] appears to be different to that described in the scope (those patients with an arterial vascular disease) and is therefore not comparable.

Of the four newly identified SRs (i.e. those that are not updates from Jones *et al.*[3]), three examined dipyridamole (both MRD and the immediate-release version). These reviews had similar patient populations (previous ischaemic stroke or TIA), but Leonardi-Bee *et al.*[5] compared dipyridamole, with or without ASA, with ASA alone. The other two SRs[9,121] only compared dipyridamole + ASA with ASA alone; thus, this was the only comparison that can be considered. The conclusions of all three SRs are generally consistent and favoured the use of dipyridamole + ASA over ASA alone. All three concluded that recurrent stroke was reduced by dipyridamole + ASA, as was the composite of non-fatal stroke, non-fatal MI and vascular death.

Overall, the SRs examine both MRD and the immediate-release version of dipyridamole. De Schryver *et al.*[13] included three trials that used MRD, Leonardi-Bee *et al.*[5] included one trial using MRD and six using the immediate-release version. Halkes *et al.*[121] (an update of Leonardi-Bee *et al.*[5]) included two trials that used MRD; the remainder used the immediate-release version. Verro *et al.*[9] included two trials that used MRD the other four used the immediate-release formula. In the Jones *et al.* review,[3] all trials and economic reviews that investigated dipyridamole used the modified version.

The SR by Berger *et al.*[120] investigated the effect of ASA (alone or with dipyridamole) on cardiovascular event rates in patients with peripheral arterial disease. Dipyridamole is not currently licensed in this population. The included patient population was wide and included groups who were post operative. Treatment with ASA alone or with dipyridamole resulted in

a non-significant decrease in the primary end point of cardiovascular events, but a statistically significant reduction in non-fatal stroke. This suggests that ASA is of benefit to patients with peripheral arterial disease (in this wider population) for the prevention of stroke, which is consistent with the current guidance.[24]

Review	Title	Patient population	Trials using MRD/ immediate-release dipyridamole
Jones 2004[3]	A rapid and systematic review of the clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of OVEs	MI, IS, PAD, TIA	1/1
[a]De Schryver 2007[13]	Dipyridamole for preventing stroke and other vascular events in patients with vascular disease	CAD, MI, angina pectoris, retinopathy, nephropathy, PAD, IS, TIA, amaurosis fugax	3/29
[a]ATTC 2009[119]	Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials	MI, IS,TIA	N/A
[a]Sudlow 2009[122]	Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients	High vascular risk	N/A
Leonardi-Bee 2005[5]	Dipyridamole for preventing recurrent ischaemic stroke and other vascular events	IS, TIA	1/7
Verro 2008[9]	Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis	IS,TIA	2/6
Halkes 2008[121]	Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: a meta analysis by risk	IS,TIA	2/5
Berger 2009[120]	Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials	PAD (many following surgical procedures)	Unclear

CAD, coronary heart disease; IS, ischaemic stroke; N/A, not applicable; OVEs, occlusive vascular events; PAD, peripheral arterial disease.
a Denotes update of previously identified SR.

Appendix 4

Additional publications associated with each of the main trials

***CAPRIE*[26]**

Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W. Clopidogrel versus aspirin in patients at risk of ischemic events I. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. *Stroke* 2004;**35**:528–32.

Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 2002;**90**:625–8.

Cannon CP, Investigators C. Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction with patients with symptomatic atherothrombosis (CAPRIE trial). *Am J Cardiol* 2002;**90**:760–2.

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

Bhatt DL, Foody J, Hirsch AT, Ringleb P, Hacke W, Topol EJ. Complementary, additive benefit of clopidogrel and lipid-lowering therapy in patients with atherosclerosis. *J Am Coll Cardiol* 2000;**35**(Suppl. A):326.

Bhatt DL, Hirsch AT, Ringleb P, Hacke W, Topol EJ. Reduction in the need for hospitalisation for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. CAPRIE investigators. *Am Heart J* 2000;**140**:67–73.

Hacke W, Hirsch AT, Topol EJ. The benefit of clopidogrel over aspirin is amplified in high–risk subgroups with a prior history of ischaemic events. *Eur Heart J* 1999;**20**(Suppl.).

Harker LA, Boissel JP, Pilgrim AJ, Gent M. Comparative safety and tolerability of clopidogrel and aspirin. Results from CAPRIE. *Drug Saf* 1999;**21**:325–35.

Hacke W. On Behalf of The CAPRIE I. Consistency of the benefit of clopidogrel over aspirin in patients with lacunar and non-lacunar stroke. *Cerebrovasc Dis* 1998;**8**:51.

Easton JD. Benefit of clopidogrel in patients with evidence of cerebrovascular disease. *Neurology* 1998;**51**:S1–2.

Morais J. Use of concomitant medications in the CAPRIE trial: clopidogrel is unlikely to be associated with clinically significant drug interactions. *Eur Heart J* 1998;**19**:182.

Coccheri S. Distribution of symptomatic atherothrombosis and influence of atherosclerotic disease on risk of secondary ischaemic events: Results from CAPRIE. *Eur Heart J* 1998;**19**:227.

Blecic S. Atherothrombotic events often indicate disseminated atherosclerosis: data from CAPRIE. *Cerebrovasc Dis* 1998;**8**:34.

Hankey G. The risk of vascular ischaemic events in patients with various clinical manifestations of atherothrombosis: data from CAPRIE. *Cerebrovasc Dis* 1998;**8**:30.

Rupprecht HJ. Consistency of the benefit of clopidogrel across a range of vascular-related endpoints: results from CAPRIE. *Eur Heart J* 1998;**19**(Suppl.):484.

Gent M. Benefit of clopidogrel in patients with coronary disease. *Circ Res* 1997;**96**:2608.

***ESPS–2*[30]**

Ariesen MJ, Algra A, Kappelle LJ. Antiplatelet drugs in the secondary prevention after stroke: Differential efficacy in large versus small vessel disease? A subgroup analysis from ESPS–2. *Stroke* 2006;**37**:134–8.

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

Sivenius J, Cunha L, Diener HC, Forbes C, Laakso M, Lowenthal A. Second European Stroke Prevention Study: antiplatelet therapy is effective regardless of age. ESPS2 Working Group. *Acta Neurol Scand* 1999;**99**:54–60.

Sivenius J, Cunha L, Diener HC, Forbes C, Laakso M, Lowenthal A. Antiplatelet treatment does not reduce the severity of subsequent stroke. European Stroke Prevention Study 2 Working Group. *Neurology* 1999;**53**:825–9.

***ESPRIT*[56]**

Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurology* 2007;**6**:115–24.

Halkes PHA. [Acetylsalicylic acid and dipyridamole offer better secondary protection than acetylsalicylic acid only following transient ischaemic attack or cerebral infarction of arterial origin; the 'European/Australasian stroke prevention in reversible ischaemia trial' (ESPRIT)]. *Ned Tijdschr Geneeskd* 2006;**150**:1832–8.

PRoFESS

Diener HC. The PRoFESS trial: Future impact on secondary stroke prevention. *Expert Rev Neurother* 2007;**7**:1085–91.

Diener HC, Sacco R, Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: The Prevention Regimen for Effectively Avoiding Second Strokes trial (PRoFESS). *Cerebrovasc Dis* 2007;**23**:368–80.

Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, *et al*. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurring stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol* 2008;**7**:875–84.

Appendix 5

Excluded publications with rationale

	Published paper	Reason for exclusion
1	Bezerra DC, Bogousslavsky J. Antiplatelets in stroke prevention: the MATCH trial. Some answers, many questions and countless perspectives. *Cerebrovasc Dis* 2005;**20**(Suppl. 2):109–18.	Review
2	Anand S, Yusuf S, Montague P, Chin SL. The effects of oral anticoagulants in patients with peripheral arterial disease: Rationale, design, and baseline characteristics of the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, including a meta-analysis of trials. *Am Heart J* 2006;**151**:1–9.	Not relevant intervention
3	Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A, *et al.* Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007;**357**:217–27.	Not relevant intervention
4	Bakhru MR, Bhatt DL. Interpreting the CHARISMA study. What is the role of dual antiplatelet therapy with clopidogrel and aspirin? *Cleveland Clinic J Med* 2008;**75**:289–95.	Review
5	Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, *et al.* Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA Trial. *J Am Coll Cardiol* 2007;**49**:1982–8.	Not relevant intervention
6	Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, *et al.* A global view of atherothrombosis: Baseline characteristics in the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (CHARISMA) trial. *Am Heart J* 2005;**150**(3).	Not relevant intervention
7	Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, *et al.* Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;**354**:1744–6.	Not relevant intervention
8	Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Am Heart J* 2004;**148**:263–8.	Not relevant intervention
9	Biller J. Antiplatelet therapy in ischemic stroke: variability in clinical trials and its impact on choosing the appropriate therapy. *J Neurol Sci* 2009;**15**;284:1–9.	Not RCT or SR
10	Bjorklund L, Wallander MA, Johansson S, Lesen E. Aspirin in cardiology: benefits and risks. *Int J Clin Pract* 2009;**6**:468–77.	Not RCT or SR
11	Bowry ADK, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. *Am J Cardiol* 2008;**101**:960–6.	Not relevant patient group
12	Brown J, Lethaby A, Maxwell H, Wawrzyniak AJ, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 2008;**4**:CD000535.	Not patient population
13	Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA. Patients with peripheral arterial disease in the CHARISMA trial. *European Heart J* 2009;**30**:192–201.	Not relevant intervention
14	Calvet D, Touze E, Mas JL. Adding aspirin to clopidogrel in secondary prevention of ischemic stroke: no significant benefits: results of the MATCH study. *Presse Med* 2006;**35**:679–82.	Not relevant intervention
15	Cassar K, Ford I, Greaves M, Bachoo P, Brittenden J. Randomized clinical trial of the antiplatelet effects of aspirin–clopidogrel combination versus aspirin alone after lower limb angioplasty. *Br J Surg* 2005;**92**:159–65.	Not relevant intervention
16	Chairangsarit P, Sithinamsuwan P, Niyasom S, Udommongkol C, Nidhinandana S, Suwantamee J. Comparison between aspirin combined with dipyridamole versus aspirin alone within 48 hours after ischemic stroke event for prevention of recurrent stroke and improvement of neurological function: a preliminary study. *J Med Assoc Thai* 2005;**88**(Suppl. 3):148–54.	Not relevant patient group
17	Chaturvedi S. Acetylsalicylic acid + extended-release dipyridamole combination therapy for secondary stroke prevention. *Clin Ther* 2008;**30**:1196–205.	Review
18	Culebras A, Borja J, Garcia-Rafanell J. Triflusal versus aspirin for the prevention of stroke. *Prog Neurother Neuropsychopharmacol* 2008;**3**:13–33.	Not relevant intervention
19	de Borst GJ, Hilgevoord AA, de Vries JP, van der Mee M, Moll FL, van de Pavoordt HD, *et al.* Influence of antiplatelet therapy on cerebral micro-emboli after carotid endarterectomy using postoperative transcranial Doppler monitoring. *Eur J Vasc Endovasc Surg* 2007;**34**:135–42.	Not relevant patient group
20	Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, *et al.* Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;**364**:331–7.	Not relevant intervention

	Published paper	Reason for exclusion
21	Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, *et al.* Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke (MATCH): study design and baseline data. *Cerebrovasc Dis* 2004;**17**:253–61.	Not relevant intervention
22	Diener HC, editor. Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke (MATCH): rationale and study design. Fifth World Stroke Congress, Vancouver, BC, 23–6 June 2004.	Not relevant intervention
23	Diener HC. Management of atherosclerosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischemic stroke (MATCH): study results. *Stroke* 2004.	Not relevant intervention
24	Donnelly R. Antiplatelet therapy and prevention of ischaemic events: CAPRIE. Br J Diabetes and Vascular Disease. 2005 *Br J Diab Vasc Dis* **5:**203–6.	Not RCT or SR
25	Eikelboom JW, Hankey GJ, Thom J, Claxton A, Yi Q, Gilmore G, *et al.* Enhanced antiplatelet effect of clopidogrel in patients whose platelets are least inhibited by aspirin: a randomized crossover trial. *J Thrombo Haemost* 2005;**3**:2649–55.	Not relevant intervention
26	Einhaupl K. ESPRIT study design and outcomes: a critical appraisal. *Curr Med Res Opin* 2007;**23**:271–3.	Review
27	England T, Bath P. Safety and tolerability of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomised controlled trial. Third UK Stroke Forum Conference, Harrogate, 2–4 December 2008.	Not relevant intervention
28	England TJ, Bath PM. Triple antiplatelets for reducing dependency after ischaemic stroke (TARDIS). Safety and tolerability of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomized controlled trial. International Stroke Conference, San Diego, CA, 17–20 February 2009.	Not relevant intervention
29	Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, *et al.* Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004	Not relevant patient group
30	Gorelick PB, Richardson D, Kelly M, Ruland S, Hung E, Harris Y, *et al.* Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. *JAMA* 2003;**289**:2947–57.	Not relevant intervention
31	Greisenegger S, Tentschert S, Weber M, Ferrari J, Lang W, Lalouschek W. Prior therapy with antiplatelet agents is not associated with outcome in patients with acute ischemic stroke/TIA. *J Neurol* 2006;**253**:648–52.	Review
32	Halkes PHA, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Risk indicators for development of headache during dipyridamole treatment after cerebral ischaemia of arterial origin. *J Neurol Neurosurg Psychiatry* 2009;**80**:437–9.	Review
33	Hart RG, Bhatt DL, Hacke W, Fox KA, Hankey GJ, Berger PB, *et al.* Clopidogrel and aspirin versus aspirin alone for the prevention of stroke in patients with a history of atrial fibrillation: subgroup analysis of the CHARISMA randomized trial. *Cerebrovasc Dis* 2008;**25**:344–7.	Not relevant intervention
34	Hills NK, Johnston SC. Trends in usage of alternative antiplatelet therapy after stroke and transient ischemic attack. *Stroke* 2008;**39**:1228–32.	Registry
35	Hradec J, Spinar J. [CHARISMA. The clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance trial]. *Cor et Vasa* 2006;**5**:202–6.	Not relevant intervention
36	Huang YI, Cheng Y, Wu J, Li YS, Xu E, Hong Z, *et al.* Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. *Lancet Neurol* 2008;**7**:494–9.	Not relevant intervention
37	Ito E, Takahashi A, Kuzuhara S, Uchiyama S, Nakajima M, Riku S, *et al.* Ticlopidine alone versus ticlopidine plus aspirin for preventing recurrent stroke. *Intern Med* 2003;**42**:793–9.	Not relevant intervention
38	Karha J, Bhatt DL, Wolski K, Fox KA, Montalescot G, Topol EJ, editors. The use of COX–2 inhibitors and the risk of myocardial infarction in the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (CHARISMA) trial. 79th Annual Scientific Session of the American Heart Association, Chicago, IL, 12–15 November 2006.	Not RCT
39	Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol* 2007;**6**:961–9.	Not relevant intervention
40	Mahmood A, Sintler M, Edwards AT, Smith SRG, Simms MH, Vohra RK. The efficacy of aspirin in patients undergoing infra-inguinal bypass and indentification of high-risk patients. *Int Angiol* 2003;**22**:302–7.	Not RCT
41	Mak KH, Bhatt DL, Shao M, Haffner SM, Hamm CW, Hankey GJ, *et al.* The influence of body mass index on mortality and bleeding among patients with or at high-risk of atherothrombotic disease. *Eur Heart J* 2009;**30**:857–65.	Not relevant intervention

	Published paper	Reason for exclusion
42	Mak KH, Bhatt DL, Shao M, Hankey GJ, Easton JD, Fox KAA, *et al.* Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. *Am Heart J* 2009;**157:**658–65.	Not relevant intervention
43	Markus H. Antiplatelet therapy vs anticoagulation in cervical artery dissection; Rationale and design of the Cervical Artery Dissection in Stroke Study (CADISS). *Int J Stroke* 2007;**2**:292–6.	Not a relevant population
44	Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, *et al.* Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation* 2005;**111**:2233–40.	Not relevant intervention
45	Matias-Guiu J, Ferro JM, Alvarez-Sabin J, Torres F, Jimenez MD, Lago A, *et al.* Comparison of triflusal and aspirin for prevention of vascular events in patients after cerebral infarction the TACIP study: a randomized, double-blind, multicenter trial. *Stroke* 2003;**34**:840–7.	Not relevant intervention
46	McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. *Eur J Vasc Endovasc Surg* 2005;**29**:522–7.	Not relevant intervention
47	Secondary stroke prevention set to benefit from PRoFESS trial: extended-release dipyridamole plus aspirin (Asasantin Retard) and clopidogrel share very similar benefit–risk ratio in vascular prevention. *Cardiovasc J Africa* 2008;**19**:165.	Comment on PRoFESS
48	Serebruany VL, Malinin AI, Pokov AN, Hanley DF. Randomized single-blind 30-days trial of the antiplatelet profiles after extended-released dipyridamole and low dose aspirin versus clopidogrel with or without aspirin in diabetic patients after TIA. *Cerebrovasc Dis* 2008; **25** (Suppl. 2):159.	Not relevant intervention
49	Serebruany VL, Malinin AI, Ziai W, Pokov AN, Bhatt DL, Alberts MJ, *et al.* Effects of clopidogrel and aspirin in combination versus aspirin alone on platelet activation and major receptor expression in patients after recent ischemic stroke: for the Plavix Use for Treatment of Stroke (PLUTO–Stroke) trial. *Stroke* 2005;**36**:2289–92.	Not relevant intervention
50	Sprigg N, Gray LJ, England T, Willmot MR, Zhao L, Sare GM, *et al.* A randomised controlled trial of triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) in the secondary prevention of stroke: safety, tolerability and feasibility. *PLoS ONE* 2008;**3**:e2852.	Not relevant intervention
51	Squizzato A, Keller T, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2007;**1**:CD005158.	Not relevant intervention
52	Thijs V, Lemmens R, Fieuws S. Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke. *Eur Heart J* 2008;**29**:1086–92.	Not relevant intervention
53	Uchiyama S, Fukuuchi Y, Yamaguchi T. The safety and efficacy of clopidogrel versus ticlopidine in Japanese stroke patients: Combined results of two Phase III, multicenter, randomized clinical trials. *J Neurol* 2009;**256**:888–97.	Not relevant intervention
54	Wang TH, Bhatt DL, Fox KAA, Steinhubl SR, Brennan DM, Hacke W, *et al.* An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. *Eur Heart J* 2007;**28**:2200–7.	Not relevant intervention
55	Dieker HJ, French JK, Joziasse IC, Brouwer MA, Elliott J, West TM, *et al.* Antiplatelet therapy and progression of coronary artery disease: a placebo-controlled trial with angiographic and clinical follow-up after myocardial infarction. *Am Heart J* 2007;**153**:1–8.	Not relevant intervention
56	Serebruany VL, Malinin AI, Pokov AN, Hanley DF. Antiplatelet profiles of the fixed-dose combination of extended-release dipyridamole and low-dose aspirin compared with clopidogrel with or without aspirin in patients with type 2 diabetes and a history of transient ischemic attack: A randomized, single-blind, 30-day trial. *Clin Ther* 2008;**30**:249–59.	Not relevant outcomes

Appendix 6

Identified ongoing trials

Trial name and identification no.	Sponsor	Comparators	Aims of study	Study start date	Estimated primary completion date[a]	Estimated study completion date
Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) NCT00979589	Ministry of Science and Technology of the People's Republic of China	CLOP + ASA (ASA will be replaced by placebo from day 21) Placebo + ASA	To assess the effects of a 3-month regimen of CLOP vs a 3–month regimen of aspirin alone on reducing the risk of any stroke when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke	July 2008	July 2011	December 2011
COMbination of clopidogrel and aspirin for Prevention of early REcurrence in acute atherothrombotic Stroke (COMPRESS) NCT00814268	Sanofi–aventis	CLOP + ASA Placebo + ASA	To compare the efficacy of CLOP + ASA and ASA alone in preventing any recurrent ischaemic lesion	October 2008	December 2010	
Platelet-Orientated Inhibition in New Transient ischemic attack (TIA) (POINT) trial NCT00991029	University of California, San Francisco, CA	CLOP + ASA Placebo + ASA	To evaluate CLOP as a treatment to reduce risk of stroke and MI after TIA in patients also prescribed ASA	October 2009	June 2016	
Secondary Prevention of Small Subcortical Strokes trial (SPS3) NCT00059306	The University of Texas Health Science Center at San Antonio, TX	CLOP + ASA Placebo + ASA	To learn if CLOP + ASA is more effective than ASA alone for prevention of recurrent stroke and cognitive decline	February 2003	June 2011	June 2011
ASpirin non-responsiveness and Clopidogrel Endpoint Trial (ASCET) NCT00222261	Ullevaal University Hospital	CLOP ASA	To investigate whether or not aspirin non-responders have a higher composite event rate than responders or whether or not CLOP treatment in patients non-responsive to aspirin will reduce their risk of future clinical events	April 2003	July 2010	July 2010
JASAP: Japanese Aggrenox Stroke prevention vs Aspirin Programme NCT00311402	Boehringer Ingelheim Pharmaceuticals	Aggrenox (MRD + ASA) ASA	To compare the preventive effect of recurrent stroke and safety of Aggrenox vs ASA	April 2006	March 2009	

CLOP, clopidogrel.
a Estimated date of final data collection for primary outcome measure.

Appendix 7

Example of the mixed-treatment comparison codes for the 'first ischaemic stroke' and networks

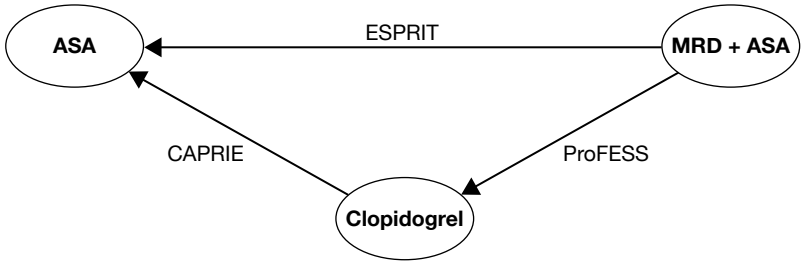
```
model{
for(i in 1:N){
#binomial likelihood
r[i] ~ dbin(p[i],n[i])
#Model for first Ischemic Stroke based on three trials
logit(p[i])<-mu[s[i]]+ d[t[i]] – d[b[i]]
}
# Fixed effect vague priors for the 3 trial baselines
for(j in 1:NS){
mu[j]~dnorm(0,.0001)
}
d[1]<–0
#Give priors for log–odds ratios
for (k in 2:NT){d[k] ~ dnorm(0,.001)}[24]
#Absolute log odds on Treatment ASA based on 2 trials in which it was used
for (i in 1: N){
mu1[i] <- mu[s[i]]*equals(t[i],1)
}
#Calculate the mean treatment effects, T[k] on natural scale
for (k in 1:NT){
logit(T[k]) <- sum(mu1[])/2 + d[k]
}
#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:NT){
rk[k]<- (NT+1) – rank(T[],k)
best[k]<-equals(rk[k],1)
best1[k]<–1-equals(rk[k],1)
}

# Calculate RR from OR by first generating probability of baseline comparator
#prior for the baseline comparator for each pair-wise comparison
p21.base~dbeta(0.5,0.5)
p31.base~dbeta(0.5,0.5)
p32.base~dbeta(0.5,0.5)
# likelihood
r21.base~dbin(p21.base, n21.base)
r31.base~dbin(p31.base, n31.base)
r32.base~dbin(p32.base, n32.base)
prob_baseline[1,2]<-p21.base
prob_baseline [1,3]<-p31.base
prob_baseline [2,3]<-p32.base
```

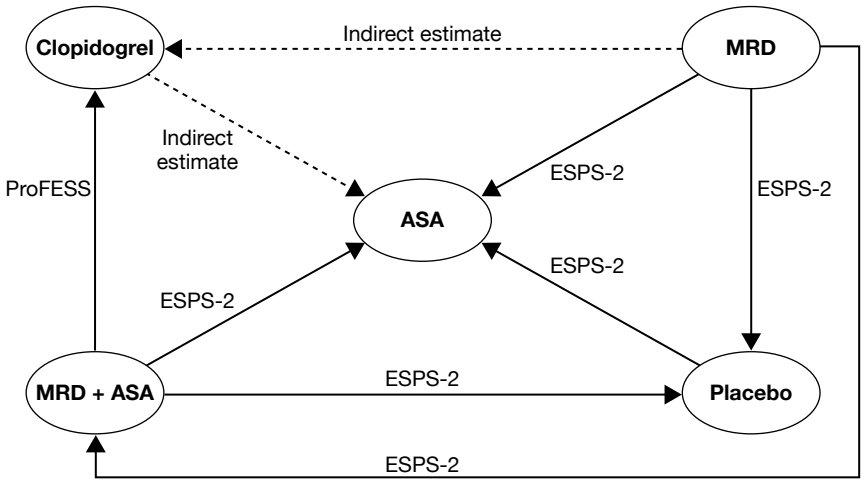
```
#All pair-wise log odds ratios and odds ratios
for (c in 1:(NT-1)){
for (k in (c+1):NT){

lor[c,k] <- d[k] – d[c]
log(or[c,k]) <- lor[c,k]
#All pair-wise relative risk
rr[c,k] <- or[c,k]/((1- prob_baseline [c,k])+(or[c,k]* prob_baseline [c,k]))
RRR[c,k] <-(rr[c, k]–1)
```

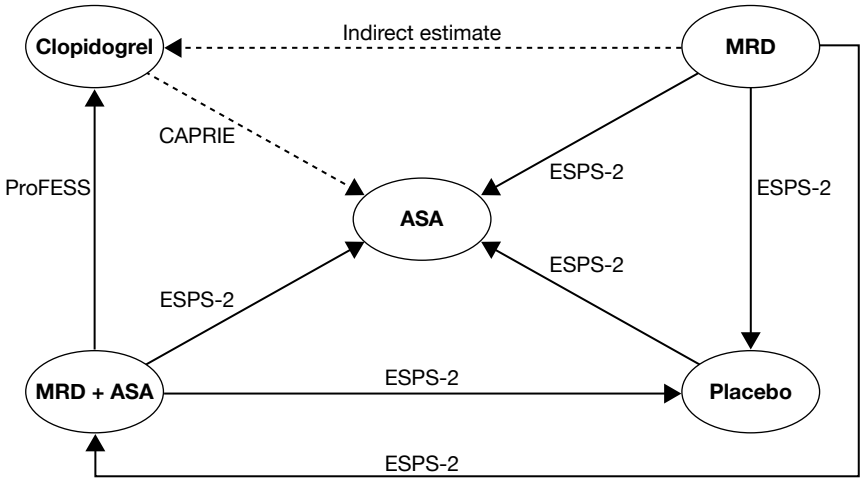
Mixed-treatment comparison network of RCTs 'first ischaemic stroke': ASA/clopidogrel/MRD + ASA. (Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.)



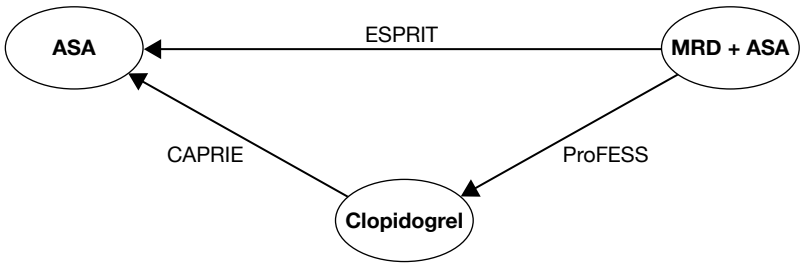
Mixed-treatment comparison network of RCTs 'recurrent stroke': ASA/clopidogrel/MRD + ASA. (Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.)



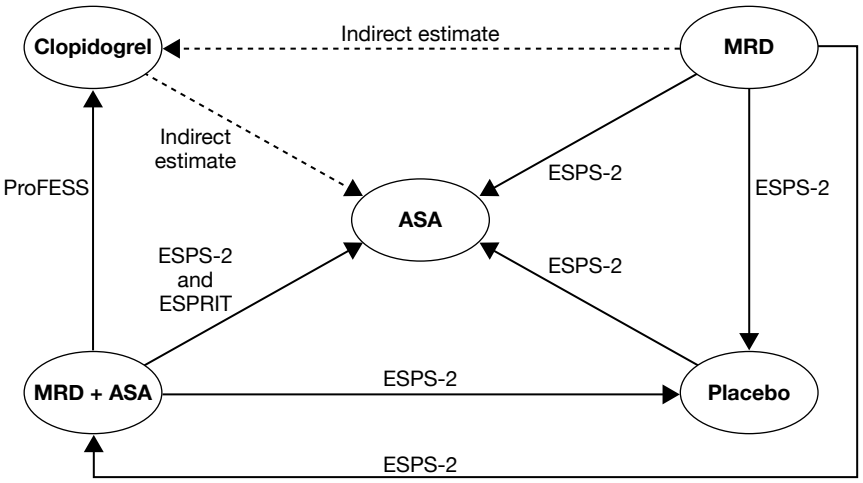
Mixed-treatment comparison network of RCTs 'MI': ASA/clopidogrel/MRD + ASA. (Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.)



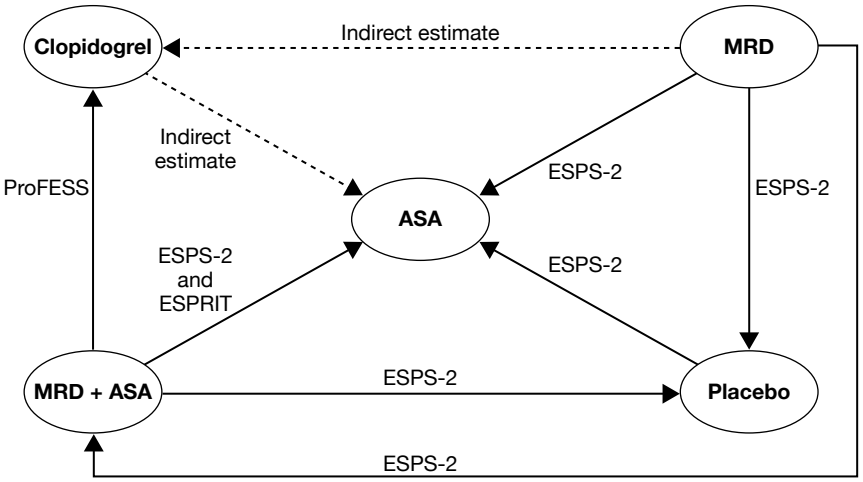
Mixed-treatment comparison network of RCTs 'death from vascular causes': ASA/clopidogrel/MRD + ASA. (Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.)



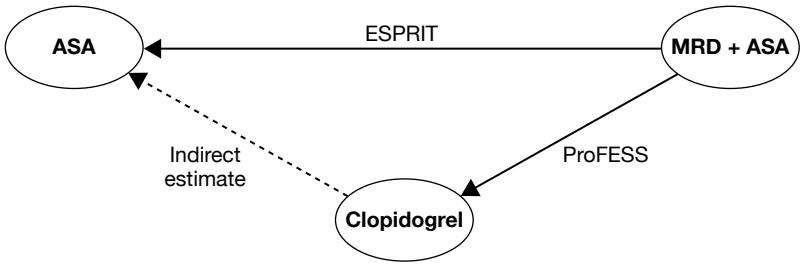
Mixed-treatment comparison network of RCTs 'all-cause death': ASA/clopidogrel/MRD + ASA. (Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.)



Mixed-treatment comparison network of RCTs 'any bleeding': ASA/clopidogrel/MRD + ASA. (Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.)



Mixed-treatment comparison network of RCTs 'death from major bleeding': ASA/clopidogrel/MRD + ASA. (Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.)



The codes used in the mixed-treatment comparison analysis were adapted from the MPES and are freely available for download from their website (www.bris.ac.uk/cobm/research/mpes).

Appendix 8

Sensitivity analysis table from review of cost-effectiveness literature

Study	Sensitivity analysis
Annemans 2003[69]	**One-way SA** (ICER ranges) Discounting rate 0–6% (€7720–19,640), increase and decrease a 50% costs of AE (ICER: €13,170–13,620), IS (ICER: €12,560–14,220) and life expectancy (ICER: €11,140–20,080) **PSA** ICER: €14,320 (95% CI €6990 to €26,470). 86% probability of be cost-effective at a threshold of €20,000
Beard 2004[70]	**Univariate SA** (ICER ranges) Cost of acute stroke (ICER: £3155–6959/QALY); costs of OVE (£3475–4908/QALY); cost of TIA (£4012–4374/QALY); cost of long-term care HD stroke (cost saving £–8757/QALY); cost of long-term care N/LD stroke (£639–7446/QALY); cost of rehabilitation (£2952–5647/QALY); cost of ASA (cost saving –£4801/QALY); RRR of ASA + MRD vs placebo (cost saving £–70,407/QALY); background events risks (£1880–5988/QALY); initial disability level (£3347–4869/QALY); disability risk after stroke (£3053–5888/QALY); and utility weights stroke (£4765–5810/QALY) **PSA** Only with five parameters: 75% chance of being cost-effective at a £35,377 £/QALY threshold
Berger 2008[71]	**Univariate SA** (ICER ranges) Treatment cost patients: scenario 1: €14,240–14,340/QALY, scenario 2: €18,840–18,740/QALY; AE costs, scenario 1 €14,320–14,430/QALY, scenario 2 €18,710–18,870/QALY; concomitant medication costs, scenario 1 €14,370–14,380/QALY, scenario 2 €18,780–18,800/QALY; CLOP costs, scenario 1 €15,750/QALY, scenario 2 €20,580/QALY; discounting costs and effects, scenario 1 €8350–18,610/QALY, scenario 2 €10,700–24,700/QALY; discounting-only costs 3%, scenario 1 €8150/QALY, scenario 2 €10,440/QALY; discounting-only effects at 3%, scenario 1 €14,740/QALY, scenario 2 €19,260/QALY
Chen 2009[72]	**Univariate SA** (ICER ranges) Annual discount rate: US$25,139–44,891/LYG; lost life-years for cardiovascular deaths only US$51,033/LYG; lost life-years for non-fatal events US$31,771–42,453/LYG; CLOP costs average wholesale price US$16,176–56,520/LYG; post acute care costs: US$36,899–35,788/LYG: including indirect costs from lost work productivity US$36,148/LYG; and variation of indirect cost from lost work productivity US$36,051–36,246/LYG **PSA** The probability of being cost-effective at a threshold of < US$50,000/LYG is 70.6%, and 87.4% at < US$100,000/LYG
Delea 2003[76]	ICER is sensitive to the assumed risk reduction for CLOP
Karnon 2005[73]	**Univariate SA** Health-state costs (£21,333–21,819/QALY); initial stroke costs (£24,683/QALY); trial-based compliance (£16,528–24,683/QALY); utilities (£19,232–23,159/QALY); composite outcome RR (£12,835/QALY); RR for MI outcome (£20,026–23,383/QALY), RR for stroke outcome (£15,327–32,894/QALY), RR vascular death (dominated –£7101/QALY); RR for MI, stroke and vascular death (dominated –£5,602/QALY); inclusion of non-vascular death RR (£34,349/QALY); age at start 70 years (£16,222/QALY); age at start 80 years (£16,491/QALY); discount rate 6% for both costs and effects (£32,215/QALY); event rate × 2 (£12,245/QALY); and event rate × 0.5 (£41,486/QALY) **Bivariate SA** (ICER ranges) Health-state costs and utilities (£23,514/QALY). **PSA** CLOP is cost-effective at a threshold of £30,000/QALY in approximately 60% of randomly sampled analysis
Matchar 2005[74]	**Univariate SA** (ICER) RR for ASA: PBO–ASA US$1681–1700/QALY; PBO–CLOP US$50,762–198,150/QALY; PBO-MRD + ASA US$1769–1769/QALY. Costs based on Pharmacy Benefits Management Strategic Health Care Group. Drug & Pharmaceutical Prices: PBO-ASA US$1562/QALY; PBO–CLOP: dominated; PBO–MRD + ASA US$8321/QALY. Efficacy limited to 24 months: PBO–ASA US$3750/QALY; PBO–CLOP: dominated; PBO–MRD + ASA US$195,950/QALY. Accounting for impact of treatment on MI: PBO–ASA US$1,511/QALY; PBO–CLOP US$46,367/QALY; PBO–MRD + ASA US$1667/QALY. **PSA** ASA–MRD 65% probability of cost-effectiveness at a threshold of US$30,000/QALY

Study	Sensitivity analysis
Schleinitz 2004[75]	**SA** Efficacy of CLOP: PAD patients: US$86,400–13,500/QALY per QALY Post stroke patients: US$6300/QALY – CLOP MI patients: more effective and cheaper in the base case to US$42,000/QALY Daily cost of CLOP (US$1.80–7.10): PAD patients: US$14,900/QALY US$–41,800/QALY Stroke patients: dominance of CLOP – US$85,500/QALY **PSA** CLOP has a 50% probability of being cost-effective at a threshold of US$25,600/QALY for patients with peripheral vascular disease and US$30,300/QALY for those with a recent stroke
Palmer 2005[77]	Paper states: 'Sensitivity analyses showed that all results were robust under various assumptions'
Stevenson 2008[78]	**PSA** The probability of the cost per QALY being below £20,000, a significant threshold for cost-effectiveness in the UK, was 79%
Van Hout 2003[79]	Sensitivity analyses revealed that uncertainties surrounding the outcomes are mainly driven by the expected effectiveness, most notably when defining subgroups. The higher the risk for events, the better the cost-effectiveness ratio. In comparison with no treatment (ASA intolerance or previous failure), CLOP is expected to combine gain in effectiveness (0.158 life-years, 0.210 QALYs) with savings (€332 per patient)

AE, adverse event; CLOP, clopidogrel; HD, high disability; IS, ischaemic stroke; LYG, life-years gained; N/LD, n/low disability; OVE, occlusive vascular event; PAD, peripheral arterial disease; PBO, placebo; PSA, probabilistic sensitivity analysis; SA, sensitivity analysis.

Appendix 9

Additional data requested from manufacturers to populate the de novo model

Analyses requested by Liverpool Reviews and Implementation Group from the PRoFESS[57] trial data

Survival analyses

Kaplan–Meier analysis for each treatment arm, stratified by gender (male/female).

Cox proportional hazards analysis for treatment, using gender, age and Rankin Score at time of prior event as covariates.

Outcome estimated	Prior event(s)	Censored for
Time to IS	Randomisation	MI, non-IS, non-vascular death, death from any vascular cause other than IS
Time to non-IS		MI, IS, non-vascular death, death from any vascular cause other than non-IS
Time to MI		Any stroke, non-vascular death, death from any non-MI vascular cause
Time to other vascular death		MI, stroke, non-vascular death, death from MI or stroke
Time to non-vascular death		MI, stroke, vascular death
Time to vascular death		Non-vascular death
Time to death		Lost to follow-up or end of trial only
Time to other haemorrhagic event (excluding stroke)		MI, stroke, non-vascular death, death from MI or stroke
Repeat runs 1–8	Following non-fatal IS as first event	As for runs 1–8
Repeat runs 1–8	Following non-fatal non-IS as first event	
Repeat runs 1–8	Following non-fatal MI as first event	

IS, ischaemic stroke.

For each Kaplan–Meier analysis please provide full survival estimates table [e.g. 'Product-Limit Survival Estimates' table from SAS version (SAS Institute Inc., Cary, NC, USA) or the 'Survival' table from SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and the estimated means table (e.g. 'Mean Estimate' table from SAS or the 'Means and Medians for Survival Time' table from SPSS)]. Cox analyses should show covariate coefficient estimates with CIs.

Patient outcome events and exposure

For each of the following events for each treatment arm please provide a table showing trial numbers in the format shown:

- ischaemic strokes
- non-ischaemic strokes
- MIs
- other haemorrhagic events (excluding strokes)
- congestive heart failure events
- non-vascular deaths
- other vascular deaths (excluding strokes and MIs)
- vascular deaths.

	Exposure		All events			Fatal events		
Time period (months)	Patients at risk in period	Patient-days in period	First trial event for patient	Other events	Total events	First trial event for patient	Other events	Total events
0–6								
7–12								
13–18								
19–24								
25–36								
37–42								
43–48								

Event fatality

Please complete the following table for each subgroup by treatment arm, showing the proportion of each type of vascular event (occurring at any time) that was fatal, analysed by gender and age at the time of the event.

Gender	Age range (years)	ISs			Intracerebral haemorrhages			MIs			Other vascular events		
		Events	Deaths	Percentage fatal	Events	Deaths	Percentage fatal	Events	Deaths	Percentage fatal	Events	Deaths	Percentage fatal
Female	< 60												
	60–65												
	66–71												
	72+												
Male	< 60												
	60–65												
	66–71												
	72+												

Appendix 10

Model risk parameter values and sources

For patients surviving an ischaemic stroke, four long-term treatment options are available to prevent future occlusive vascular events: low-dose ASA, clopidogrel, MRD and ASA + MRD. For the other three patient groups (MI only, peripheral arterial disease only and multivascular disease) only ASA and clopidogrel are licensed for secondary prevention. In all cases it is also necessary to consider periods when no active long-term drug treatment is being taken to reduce the risk of occlusive vascular event.

NICE Clinical Guidance CG48:[28] post myocardial infarction clopidogrel

For patients suffering a new MI, recommendations were made in CG48[28] for the short-term use of clopidogrel + ASA to prevent early vascular events (primarily repeat MIs):

- For patients experiencing a NSTEMI, clopidogrel + ASA is recommended for 12 months.
- For patients experiencing a STEMI, clopidogrel + ASA is recommended for 4 weeks (30 days).

The CURE[27] trial provides the evidence source for the first recommendation. This showed a significant protective effect in relation to repeat MIs, but not for strokes. The absolute risk reduction over 12 months was 1.47% (standard error 0.42%).

The recommendation for STEMI patients derives primarily from the COMMIT[29] trial where a modest reduction was seen in the rate of re-infarctions, but not in strokes. During the 30-day follow-up, an absolute risk reduction of 0.33% was reported (standard error 0.14%).

To accommodate the likely impact of these guidelines a weighted-average effect has been estimated of 0.853% (standard error 0.207%), based on the balance of STEMI and NSTEMI patients in the GRACE[118] study (54.2% and 45.8%, respectively). This reduction is applied to the transient effect risk parameter values shown below for a second MI event after surviving a non-fatal MI, but not to any other MI risks that are much smaller and where no transient effect was identified.

Risks of first occlusive vascular event

Haemorrhagic stroke as first event

The annual risks of suffering an haemorrhagic stroke are generally very low, but vary significantly between patient types and between different treatment options. Reviewing all of the data available, it appears that this risk is effectively constant over quite long periods of time. Evidence in some cases of a small additional early risk is not confirmed from other sources, and may in part be a consequence of differing qualifying criteria among trials, so that some early acute events (in hospital or in the immediate post-discharge period) are counted within some trials, but excluded in others. In estimating model parameters, such transient effects are ignored and only the longer-term annual event rate is used.

For ASA and clopidogrel treatments, risks are estimated from the CAPRIE[26] trial; in the ischaemic stroke-only population, sufficient haemorrhagic stroke events were recorded to allow separate parameter values to be obtained, but for the other groups it was possible to derive only a single risk estimate for the population regardless of the treatment in use.

Haemorrhagic stroke risk for MRD + ASA treatment was estimated from the PRoFESS[57] trial (noting that the clopidogrel arm in PRoFESS[57] yielded a similar event rate to that in CAPRIE[26]). The risk appropriate for untreated patients was based on the ASA estimated RR for 'no treatment' vs ASA in an ATTC[66] analysis of secondary prevention published in 2002: RR 1.22 (95% CI 1.03 to 1.44). Finally, the annual risk of haemorrhagic stroke when using MRD was set at the same level as 'no treatment', based on the finding of very similar risks reported from the ESPS-2[30] trial.

TABLE 74 Model parameter estimates for the risk of haemorrhagic stroke as first event

Population	Detail	ASA	CLOP	ASA + MRD	MRD	No treatment
IS only	Annual risk (%)	0.4900	0.2610	0.4320	0.4020	0.4020
	Standard error (%)	0.0220	0.0170	0.0120	0.0380	0.0380
	Source	CAPRIE[26]	CAPRIE[26]	PRoFESS[57]	CAPRIE[26]/ATTC[66]	
MI only	Annual risk (%)	0.0956	0.0956	N/A	N/A	0.0784
	Standard error (%)	0.0003	0.0003	N/A	N/A	0.0069
	Source	CAPRIE[26]		N/A	N/A	CAPRIE[26]/ATTC[66]
PAD only	Annual risk (%)	0.0910	0.0910	N/A	N/A	0.0746
	Standard error (%)	0.0117	0.0117	N/A	N/A	0.0114
	Source	CAPRIE[26]	CAPRIE[26]	N/A	N/A	CAPRIE[26]/ATTC[66]
MVD	Annual risk (%)	0.1960	0.1960	N/A	N/A	0.1602
	Standard error (%)	0.0120	0.0120	N/A	N/A	0.0170
	Source	CAPRIE[26]	CAPRIE[26]	N/A	N/A	CAPRIE[26]/ATTC[66]

CLOP, clopidogrel; IS, ischaemic stroke; MVD, multivascular disease; N/A, not available; PAD, peripheral arterial disease.

Ischaemic stroke as first event

The risk of suffering a recurrent ischaemic stroke is relatively high for patients in the 'ischaemic stroke-only' and multivascular disease populations. In addition to a long-term steady risk level, an important transient increased risk is also present within the trial data, which applies for slightly different periods for each population.

For the 'ischaemic stroke-only' population model, parameter values have been estimated from CAPRIE[26] for ASA and clopidogrel, and from a comparison of PRoFESS[57] and CAPRIE[26] for ASA + MRD. The 'no-treatment' risk was based on the ATTC[66] RR for ASA versus 'no treatment' applicable to ischaemic stroke. Finally, the annual risk of ischaemic stroke when using MRD was based on the MRD + ASA estimate adjusted by the RRR (24.7%) compared with MRD reported in the ESPS-2[30] trial. No consistent differences were observed in any of the trials relating to gender.

In the 'MI-only' population, no consistent differences were found in the CAPRIE[26] data for the choice of treatment (ASA vs clopidogrel), but long-term risks were much higher for females than for males. Therefore, parameters were estimated for two models (males and females separately), combining patients in the two trial arms.

TABLE 75 Model parameter estimates for risk of ischaemic stroke as first event in the 'ischaemic stroke-only' population

Population	Detail	ASA	CLOP	ASA + MRD	MRD	No treatment
IS only	Long-term annual risk (%)	4.201	3.971	3.971	5.273	6.001
	Standard error (%)	0.027	0.027	0.027	0.484	0.247
	Transient risk (%) (%)	1.962	1.723	1.723	2.288	2.802
	Standard error (%)	0.044	0.047	0.047	0.229	0.127
	Duration of transient risk (months)	2.8	3.1	3.1	3.1	2.8
	Source	CAPRIE[26]	CAPRIE[26]	PRoFESS[57]/ CAPRIE[26]	ProFESS[57]/ CAPRIE[26]/ ESPS–2[30]	CAPRIE[26]/ ATTC[66]

CLOP, clopidogrel; IS, ischaemic stroke.

TABLE 76 Model parameter estimates for risk of ischaemic stroke as first event in the 'MI-only', 'peripheral arterial disease-only' and multivascular disease populations

Population	Detail	ASA	CLOP	No treatment
MI only (females)	Long-term annual risk (%)	0.774	0.774	1.106
	Standard error (%)	0.041	0.041	0.074
	Transient risk (%)	0.314	0.314	0.449
	Standard error (%)	0.055	0.055	0.077
	Duration of transient risk (months)	0.3	0.3	0.3
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]
MI only (males)	Long-term annual risk (%)	0.300	0.300	0.429
	Standard error (%)	0.025	0.025	0.038
	Transient risk (%)	0.323	0.323	0.462
	Standard error (%)	0.044	0.044	0.065
	Duration of transient risk (months)	3.7	3.7	3.7
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]
PAD only	Long-term annual risk (%)	1.145	1.145	1.636
	Standard error (%)	0.012	0.012	0.067
	Transient risk (%)	–0.099	–0.099	–0.141
	Standard error (%)	0.016	0.016	0.023
	Duration of transient risk (months)	0.6	0.6	0.6
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]
MVD (females)	Long-term annual risk (%)	4.316	3.879	6.166
	Standard error (%)	0.070	0.086	0.272
	Transient risk (%)	0.413	0.265	0.591
	Standard error (%)	0.097	0.115	0.144
	Duration of transient risk (months)	0.03	0.5	0.03
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]
MVD (males)	Long-term annual risk (%)	3.376	2.903	4.823
	Standard error (%)	0.030	0.029	0.192
	Transient risk (%)	0.808	0.627	1.154
	Standard error (%)	0.044	0.044	0.079
	Duration of transient risk (months)	1.3	1.6	1.3
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]

CLOP, clopidogrel; MVD, multivascular disease; PAD, peripheral arterial disease.

In the 'peripheral arterial disease-only' population, there was no evidence of differences by either gender or treatment, so a single model was calibrated covering all CAPRIE[26] trial patients.

In the multivascular disease population, there was equivocal evidence in CAPRIE[26] suggesting that females are at greater risk than males, and that ASA may be less effective than clopidogrel at preventing recurrent ischaemic stroke; however, the differences appeared to be quite small. In this case, four separate models were calibrated to ensure that even small differences would be reflected in the economic results.

In all cases, risks for patients not receiving any prophylaxis were estimated by adjusting the ASA rates using the RR from the ATTC[66] meta-analysis.

Myocardial infarction as first event

The risk of suffering a MI is relatively high for patients in the 'MI-only' and multivascular disease populations. In addition to a long-term steady risk level, an important transient increased risk is also present in some cases within the trial data, which applies for different periods for each population.

For the 'ischaemic stroke-only' population model, parameter values have been estimated from CAPRIE[26] for ASA and clopidogrel where no difference was observed within the trial. A comparison of PRoFESS[57] and CAPRIE[26] allowed estimation of the long-term risk when receiving treatment with MRD + ASA. The 'no-treatment' risk was based on the ATTC[66] RR for ASA vs 'no treatment' applicable to MI. Finally, the annual risk of MI when using MRD is assumed to be equal to that of 'no treatment' based on comparable event rates reported in the ESPS-2[30] trial. No consistent differences were observed in any of the trials relating to gender.

TABLE 77 Model parameter estimates for risk of MI as first event in the 'ischaemic stroke-only' population

Population	Detail	ASA	CLOP	ASA + MRD	MRD	No treatment
IS only	Long-term annual risk (%)	0.492	0.492	0.363	0.656	0.656
	Standard error (%)	0.006	0.006	0.006	0.019	0.019
	Transient risk (%)	N/A	N/A	N/A	N/A	N/A
	Standard error					
	Duration of transient risk (months)					
	Source	CAPRIE[26]	CAPRIE[26]	PRoFESS[57]/ CAPRIE[26]	CAPRIE[26]/ ESPS–2[30]	CAPRIE[26]/ ATTC[66]

CLOP, clopidogrel; IS, ischaemic stroke; N/A, not available.

In the 'MI-only' and 'peripheral arterial disease-only' populations, separate estimates of risk were obtained from the CAPRIE data for treatment with ASA and clopidogrel. No differences were apparent between male and female patients.

For the multivascular disease population, there was some evidence in the CAPRIE[26] data supporting risk differences by both gender and treatment. Four separate models were calibrated to ensure that even small differences would be reflected in the economic results. Transient risks were only evident for ASA treatment.

In all cases, risks for patients not receiving any prophylaxis were estimated by adjusting the ASA rates using the RR from the ATTC[66] meta-analysis.

TABLE 78 Model parameter estimates for risk of MI as first event in the 'MI-only', 'peripheral arterial disease-only' and multivascular disease populations

Population	Detail	ASA	CLOP	No treatment
MI only	Long-term annual risk (%)	2.039	1.629	2.719
	Standard error (%)	0.019	0.019	0.076
	Transient risk (%)	1.477	1.589	1.969
	Standard error (%)	0.029	0.029	0.065
	Duration of transient risk (months)	2.2	2.5	2.2
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]
PAD only	Long-term annual risk (%)	0.964	0.953	1.285
	Standard error (%)	0.031	0.030	0.055
	Transient risk (%)	0.181	–0.398	0.241
	Standard error (%)	0.043	0.045	0.058
	Duration of transient risk (months)	6.6	2.6	6.6
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]
MVD (females)	Long-term annual risk (%)	2.386	1.497	3.182
	Standard error (%)	0.071	0.072	0.127
	Transient risk (%)	0.464	N/A	0.619
	Standard error (%)	0.102	N/A	0.141
	Duration of transient risk (months)	0.7	N/A	0.7
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]
MVD (males)	Long-term annual risk (%)	2.794	2.486	3.726
	Standard error (%)	0.025	0.018	0.105
	Transient risk (%)	0.713	N/A	0.951
	Standard error (%)	0.037	N/A	0.054
	Duration of transient risk (months)	1.9	N/A	1.9
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ATTC[66]

CLOP, clopidogrel; MVD, multivascular disease; PAD, peripheral arterial disease.

Other vascular death as first event

The incidence of other vascular death as a first event in the 'ischaemic stroke-only' population was estimated directly jointly from the CAPRIE[26] trial data for ASA and clopidogrel treatments, where no meaningful differences were observed related to either choice of treatment or to gender. Analysis of the PRoFESS[57] trial results similarly show no differences between clopidogrel and MRD + ASA. Occlusive vascular disease was not reported in other trials, but the ESPS-2[30] report allowed calculation of total deaths excluding fatal strokes and this was considered a reasonable proxy for other vascular death, allowing RR multipliers to be calculated for MRD and 'no treatment' compared with ASA + MRD.

TABLE 79 Model parameter estimates for risk of other vascular death as first event in the 'ischaemic stroke-only' population

Population	Detail	ASA	CLOP	ASA + MRD	MRD	No treatment
IS only	Long-term annual risk (%)	1.050	1.050	1.050	1.025	1.156
	Standard error	0.026	0.026	0.026	0.100	0.094
	Transient risk (%)	–0.457	–0.457	–0.457	–0.446	–0.503
	Standard error	0.049	0.049	0.049	0.064	0.067
	Duration of transient risk (months)	6.9	6.9	6.9	6.9	6.9
	Source	CAPRIE[26]	CAPRIE[26]	PRoFESS[57]/ CAPRIE[26]	CAPRIE[26]/ ESPS–2[30]	CAPRIE[26]/ ESPS–2[30]

CLOP, clopidogrel; IS, ischaemic stroke.

In the 'MI-only' population, separate estimates of risk were obtained from the CAPRIE[26] data for treatment with ASA and clopidogrel, and for both genders.

In the 'peripheral arterial disease-only' population, no differences were observed by gender, so combined estimates were obtained for ASA and clopidogrel after combining results for male and female patients.

For the multivascular disease population, there was clear evidence in the CAPRIE[26] data supporting risk differences by gender, but not by treatment. Therefore, two models were calibrated for male and female patients.

In all cases, risks for patients not receiving any prophylaxis were estimated by adjusting the ASA rates using the RR from ESPS-2[30] trial as described above.

TABLE 80 Model parameter estimates for risk of other vascular death as a first event in the 'MI-only', 'peripheral arterial disease-only' and multivascular disease populations

Population	Detail	ASA	CLOP	No treatment
MI only (females)	Long-term annual risk (%)	0.863	1.444	0.951
	Standard error	0.137	0.234	0.167
	Transient risk (%)	0.709	0.658	0.780
	Standard error	0.119	0.118	0.139
	Duration of transient risk (months)	0.8	1.4	0.8
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ESPS–2[30]
MI only (males)	Long-term annual risk (%)	0.646	1.080	0.711
	Standard error	0.019	0.039	0.060
	Transient risk (%)	0.530	0.492	0.583
	Standard error (%)	0.025	0.048	0.054
	Duration of transient risk (months)	0.8	1.4	0.8
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ESPS–2[26]
PAD only	Long-term annual risk (%)	1.499	0.583	1.650
	Standard error (%)	0.392	0.059	0.447
	Transient risk (%)	–1.226	–0.161	–1.351
	Standard error (%)	1.561	0.111	1.751
	Duration of transient risk (months)	16.6	3.4	16.6
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ESPS–2[26]
MVD (females)	Long-term annual risk (%)	1.427	1.427	1.571
	Standard error (%)	0.064	0.064	0.144
	Transient risk (%)	0.701	0.701	0.772
	Standard error (%)	0.109	0.109	0.137
	Duration of transient risk (months)	2.3	2.3	2.3
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ESPS–2[26]
MVD (males)	Long-term annual risk (%)	2.653	2.653	2.922
	Standard error (%)	0.016	0.016	0.232
	Transient risk (%)	–0.230	–0.230	–0.254
	Standard error (%)	0.027	0.027	0.035
	Duration of transient risk (months)	2.4	2.4	2.4
	Source	CAPRIE[26]	CAPRIE[26]	CAPRIE[26]/ESPS–2[26]

CLOP, clopidogrel; MVD, multivascular disease; PAD, peripheral arterial disease.

Risks of subsequent occlusive vascular events

For patients surviving a first occlusive vascular event within the key trials (CAPRIE[26] and PRoFESS[57]), the number of patients suffering a second or third event are very small. In a few cases it is feasible to estimate parameter values relating to specific second events, but in many cases the data are insufficient so it has been necessary to make assumptions based on the available evidence.

Following non-fatal ischaemic stroke as first event: risk of second ischaemic stroke event

A number of patients who survived an ischaemic stroke in the CAPRIE[26] trial went on to experience a second ischaemic stroke event. No significant differences in incidence rates were apparent relating to the choice of treatment. However, those belonging to the 'ischaemic stroke-only' population experienced a lower level of risk than other patients. The same approach to extending these parameters to cover other treatments used as for ischaemic stroke first events.

TABLE 81 Model parameter estimates for risk of ischaemic stroke as a second event following non-fatal ischaemic stroke as a first event

Population	Detail	ASA, CLOP ASA + MRD[a]	MRD	No treatment
IS only	Long-term annual risk (%)	7.323	9.725	10.462
	Standard error (%)	0.694	1.277	1.069
	Transient risk (%)	7.039	9.349	10.056
	Standard error (%)	1.401	2.069	1.997
	Duration of transient risk (months)	6.2	6.2	6.2
	Source	PRoFESS[57]/CAPRIE[26]	ProFESS[26]/CAPRIE[26]/ ESPS–2[26]	CAPRIE[26]/ATTC[26]
MI only, PAD only and MVD	Long-term annual risk (%)	11.627	N/A	16.610
	Standard error (%)	0.201		0.714
	Transient risk (%)	3.335		4.764
	Standard error (%)	0.224		0.365
	Duration of transient risk (months)	1.4		1.4
	Source	CAPRIE[26]	–	CAPRIE[26]/ATTC[66]

CLOP, clopidogrel; IS, ischaemic stroke; MVD, multivascular disease; N/A, not applicable; PAD, peripheral arterial disease.
a Not applicable to populations other than 'ischaemic stroke-only'.

Following non-fatal ischaemic stroke as first event: risk of myocardial infarction event

Very few ischaemic stroke survivors suffered a subsequent MI in the CAPRIE[26] trial. A single overall linear regression hazard model was calibrated for all patient groups, extended additional treatments as before for first MI events.

TABLE 82 Model parameter estimates for risk of MI as a second event following non-fatal ischaemic stroke as a first event

Population	Detail	ASA, CLOP	ASA + MRD	MRD, no treatment
All patients	Long-term annual risk (%)	1.212	0.892	1.616
	Standard error (%)	0.181	0.220	0.243
	Transient risk (%)	N/A	N/A	N/A
	Standard error (%)	N/A	N/A	N/A
	Duration of transient risk (months)	N/A	N/A	N/A
	Source	CAPRIE[26]	PRoFESS/CAPRIE[26]	CAPRIE[26]/ESPS–2[30]/ ATTC[66]

CLOP, clopidogrel; N/A, not available.

Following non-fatal ischaemic stroke as first event: risk of other vascular death event

Very few patients who survived an ischaemic stroke in the CAPRIE[26] trial suffered a subsequent other vascular death event. A single projection model was calibrated for all patient groups, extended additional treatments as before for primary other vascular death events.

TABLE 83 Model parameter estimates for risk of other vascular death as a second event following non-fatal ischaemic stroke as a first event

Population	Detail	ASA, CLOP, ASA + MRD	MRD	No treatment
All patients	Long-term annual risk (%)	1.853	1.809	2.041
	Standard error (%)	0.142	0.218	0.232
	Transient risk (%)	2.354	2.297	2.592
	Standard error (%)	0.211	0.300	0.310
	Duration of transient risk (months)	2.0	2.0	2.0
	Source	CAPRIE[26]	PRoFESS[57]/CAPRIE[26]	CAPRIE[26]/ESPS–2[30]/ATTC[66]

CLOP, clopidogrel.

Following non-fatal ischaemic stroke as first event: risk of haemorrhagic stroke event

Insufficient haemorrhagic stroke events occurred among ischaemic stroke survivors to allow any subdivision by patient subgroups or treatments.

TABLE 84 Model parameter estimates for risk of haemorrhagic stroke as a second event following non-fatal ischaemic stroke as a first event

Population	Detail	All treatments	No treatment
All patients	Long-term annual risk (%)	1.054	0.864
	Standard error (%)	0.090	0.108
	Transient risk (%)	0.250	0.205
	Standard error (%)	0.059	0.049
	Duration of transient risk (months)	0.1	0.1
	Source	CAPRIE[26]	CAPRIE[26]/ATTC[66]

Following non-fatal myocardial infarction as first event: risk of myocardial infarction event

No differences in MI risk were detectable by treatment in the CAPRIE[26] trial data, but the risk among the multivascular disease population was more than double the risk in the other groups.

TABLE 85 Model parameter estimates for risk of MI as a second event following non-fatal MI as a first event

Population	Detail	ASA, CLOP	ASA + MRD	MRD	No treatment
IS only, MI only and PAD only	Long-term annual risk (%)	5.787	4.261	7.716	7.716
	Standard error (%)	0.190	0.817	0.327	0.327
	Transient risk (%)[a]	3.287	3.098	4.383	4.383
	Standard error (%)	0.239	0.605	0.340	0.340
	Duration of transient risk (months)	1.6	1.6	1.6	1.6
	Source	CAPRIE[26]	PRoFESS[57]/ CAPRIE[26]	CAPRIE[26]/ ESPS–2[30]	CAPRIE[26]/ATTC[66]
MVD	Long-term annual risk (%)	12.228	N/A	N/A	16.303
	Standard error (%)	0.513	N/A	N/A	0.819
	Transient risk (%)[a]	8.713	N/A	N/A	11.617
	Standard error (%)	0.462	N/A	N/A	0.734
	Duration of transient risk (months)	0.8	N/A	N/A	0.8
	Source	CAPRIE[26]	–	–	CAPRIE[26]/ATTC[66]

CLOP, clopidogrel; IS, ischaemic stroke; MVD, multivascular disease; N/A, not available; PAD, peripheral arterial disease.
a These transient risks are further reduced by 0.853% for the short-term impact of the CG48 guidance,[28] as described above.

Following non-fatal myocardial infarction: risk of ischaemic stroke event

The risk of suffering an ischaemic stroke event following a non-fatal MI was found to be very low and a single projective model was calibrated using all available CAPRIE[26] data.

TABLE 86 Model parameter estimates for risk of ischaemic stroke as a second event following non-fatal MI as a first event

Population	Detail	ASA, CLOP	ASA + MRD	MRD	No treatment
All patients	Long-term annual risk (%)	1.837	1.837	2.440	2.624
	Standard error (%)	0.267	0.267	0.417	0.394
	Transient risk (%)	1.608	1.608	2.135	2.297
	Standard error (%)	0.307	0.307	0.452	0.431
	Duration of transient risk (months)	2.2	2.2	2.2	2.2
	Source	CAPRIE[26]	PRoFESS[57]/ CAPRIE[26]	CAPRIE[26]/ ESPS–2[30]	CAPRIE[26]/ATTC[66]

CLOP, clopidogrel.

Following non-fatal myocardial infarction: risk of other vascular death event

Although it was not possible to detect any difference in risk by treatment type in the CAPRIE[26] data, it was clear that patients with multivascular disease suffered a threefold risk of other vascular death cause following a non-fatal MI compared with other groups.

TABLE 87 Model parameter estimates for risk of other vascular death as a second event following non-fatal MI as a first event

Population	Detail	ASA, CLOP	ASA + MRD	MRD	No treatment
MI only, IS only and PAD only	Long-term annual risk (%)	3.110	3.110	3.035	3.425
	Standard error (%)	0.152	0.152	0.318	0.317
	Transient risk (%)	N/A	N/A	N/A	N/A
	Standard error (%)				
	Duration of transient risk (months)				
	Source	CAPRIE[26]	PRoFESS[57]/ CAPRIE[26]	CAPRIE[26]/ ESPS–2[30]	CAPRIE[26]/ATTC[66]
MVD	Long-term annual risk (%)	10.850	N/A	N/A	11.949
	Standard error (%)	0.304			1.000
	Transient risk (%)	N/A			N/A
	Standard error (%)				
	Duration of transient risk (months)				
	Source	CAPRIE[26]	–	–	CAPRIE[26]/ATTC[66]

CLOP, clopidogrel; IS, ischaemic stroke; MVD, multivascular disease; N/A, not available; PAD, peripheral arterial disease.

Following non-fatal myocardial infarction: risk of a haemorrhagic stroke event

The risk of haemorrhagic stroke following an initial MI event was found to be extremely low.

TABLE 88 Model parameter estimates for risk of haemorrhagic stroke as a second event following non-fatal MI as a first event

Population	Detail	All treatments	No treatment
All patients	Long-term annual risk (%)	0.190	0.156
	95% confidence limits (LCL, UCL)	0.005% to 0.699%	0.006% to 0.853%
	Transient risk (%)	N/A	N/A
	Standard error (%)	N/A	N/A
	Duration of transient risk (months)	N/A	N/A
	Source	CAPRIE[26]	CAPRIE[26]/ATTC[66]

LC, lower confidence limit; N/A, not available; UCL, upper confidence limit.

Following non-fatal haemhorrhagic stroke as a first event

There were too few events of any type recorded in the CAPRIE[26] trial to patients surviving an initial haemorrhagic stroke. However, in order to provide parameters for this part of the model, a simple device was employed: the overall event rate was subdivided among the possible four types of event (ischaemic stroke, haemorrhagic stroke, MI and other vascular death) in proportion to their frequency among CAPRIE[26] first events, and the figure converted to a single average event rate for each event.

TABLE 89 Model parameter estimates for risk of second events following haemorrhagic stroke as first event

Population	Event	Detail	All treatments	No treatment
All patients	IS	Long-term annual risk (%)	2.875	4.107
		Standard error (%)	0.489	0.726
	Haemorrhagic stroke	Long-term annual risk (%)	1.944	1.594
		Standard error (%)	0.331	0.298
	MI	Long-term annual risk (%)	0.182	0.243
		Standard error (%)	0.031	0.042
	Other vascular death	Long-term annual risk (%)	1.439	1.585
		Standard error (%)	0.245	0.311
		Source	CAPRIE[26]	CAPRIE[26]/ATTC[66]

IS, ischaemic stroke.

Risk modifiers

Cox's proportional hazard regressions were carried out on the CAPRIE[26] data to identify the influence of age and stroke-related disability (using the modified Rankin Score) on the key first events in the trial. From these results event modifying factors were derived to allow the risk values described above to be adjusted to the characteristics of individual patients.

TABLE 90 Risk modifiers for age and stroke-related disability

Event	Age modifier (per year)	Stroke disability (modified Rankin Score)	
		Not disabled (0–2)	Disabled (3+)
IS	1.020	0.945	1.201
Haemorrhagic stroke	1.010	0.855	1.653
MI	1.041	0.981	1.064
Other vascular death	1.043	0.774	2.283
Non-vascular death	1.073	0.862	1.614

IS, ischaemic stroke.

Appendix 11

Event fatality rates estimated from CAPRIE[26] trial data

Ischaemic stroke

There is only evidence to support differences in ischaemic stroke fatality risk arising from patient subgroup and age; gender and type of preventive treatment do not appear to be important predictors. An exponential odds model for risk increasing with age has been calibrated, with separate ORs applied for each patient group (greatest for MI- and peripheral arterial disease-only patients and lowest for ischaemic stroke-only patients). Fatality data from the PRoFESS[57] trial are not directly comparable, as the PRoFESS[57] population is a combination of ischaemic stroke-only and multivascular disease patients in unknown proportions. In addition, only the clopidogrel arms of the two trials could be included in any data synthesis. Nonetheless, simple rate comparisons did not reveal any marked differences in fatality rates between the two sources.

Fatality odds = 0.00212

- × exp(0.0520 × age)
- × population OR
- × event sequence OR.

Odds ratios for patient subgroups are:

- ischaemic stroke only, × 0.686
- MI only, × 1.673
- peripheral arterial disease only, × 1.691
- multivascular disease, × 1.175.

Odds ratios for event sequence (MIs or strokes):

- first, × 0.791
- second, × 1.931
- third, × 4.398.

Myocardial infarction

Myocardial infarction fatality is age and gender-specific, but is not influenced by the choice of treatment. Exponential odds models have been calibrated for exponential age relationships – separately for males and females. Important differences are apparent for population subgroups and for interactions between subgroups and gender, so separate age/group OR modifiers are used. As noted above, CAPRIE[26] and PRoFESS[57] data cannot be compared directly even with the ischaemic stroke population, but visual examination indicates that the PRoFESS[57] results are broadly consistent with those obtained from CAPRIE.[26]

For females:

- Fatality odds = 0.00801
  - × exp(0.0538 × age)
  - × population OR
  - × event sequence OR.

- Odds ratios for patient subgroups are:
  - ischaemic stroke only, × 1.765
  - MI only, × 0.584
  - peripheral arterial disease only, × 0.195
  - multivascular disease, × 1.765.

- Odds ratios for event sequence are:
  - first, × 0.791
  - second, × 1.931
  - third, × 4.398.

For males:

- Fatality odds = 0.00986
  - × exp(0.0455 × age)
  - × population OR
  - × event sequence OR.

- Odds ratios for patient subgroups are:
  - ischaemic stroke only, × 0.679
  - MI only, × 0.574
  - peripheral arterial disease only, × 0.985
  - multivascular disease, × 1.651.

- Odds ratios for event sequence (MIs or strokes) are:
  - first, × 0.791
  - second, × 1.931
  - third, × 4.398.

Non-ischaemic stroke (haemorrhagic stroke)

A small number of non-ischaemic strokes/intracranial haemorrhages were reported in the two trials. When the fatality data from the CAPRIE[26] and PRoFESS[57] trials were combined, no significant differences attributable to age or patient population were detected, so simple average rates have been estimated for age–treatment combinations:

TABLE 91 Average non-ischaemic stroke rates from the CAPRIE and PRoFESS trials combined

Treatment	Males (%)	Females (%)
ASA	32.6	60.0
CLOP	37.0	67.9
MRD + ASA	29.0	53.2
No treatment	30.0[a]	55.0[a]

CLOP, clopidogrel.
a Modeller's estimate in the absence of relevant data.

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We look forward to hearing from you.

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