NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90)

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

Background

The condition

Occlusive vascular events include ischaemic stroke, transient ischaemic attack, and myocardial infarction. They occur when blood flow is impeded because an artery is blocked or restricted because of atherosclerosis and atherothrombosis. Atherosclerotic plaques form in artery walls because of damage to the vascular endothelium. Damage is caused by factors working together over a long period, such as elevated low-density lipoproteins, cigarette smoking, hypertension and diabetes mellitus. If the atherosclerotic plaque is suddenly disrupted, platelet activation and thrombus (clot) formation follows, leading to atherothrombosis. The thrombus can block an artery, either at the original site of the plaque formation or further down the artery. People who have had an occlusive vascular event are at increased risk of another.

Peripheral arterial disease is 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. It occurs most often due to atherosclerosis. People who have peripheral arterial disease are at high risk of experiencing an occlusive vascular event. People with cardiovascular disease who have disease in more

than one vascular bed are said to have multivascular disease. These people may be at increased risk of death, myocardial infarction or stroke, compared with those with disease in a single bed.

Each year in the UK an estimated 98,000 people have a first ischaemic stroke, between 46,000 and 65,000 people have a transient ischaemic attack, and 146,000 have a myocardial infarction. Approximately 2% of the population of England and Wales have had a stroke and approximately 70% of all strokes are ischaemic. In the UK, in total approximately 510,000 people have had a transient ischaemic attack and 1.4 million have had a myocardial infarction. Approximately 20% of the UK population aged 55 to 75 years have evidence of lower extremity peripheral arterial disease, equating to a prevalence of 850,000 people, of whom 5% have symptoms. An estimate suggests that 16% of people with cardiovascular disease have multivascular disease.

Ischaemic stroke and myocardial infarction are associated with high mortality rates. Approximately 23% of people die within 30 days of having a stroke, and of the people who survive, 60% to 70% die after 3 years. Thirty per cent of people die from their first myocardial infarction. In terms of morbidity, an occlusive vascular event can lead to a stay in hospital, reduced health-related quality of life, and long-term disability, with a knock-on impact on caregivers. Stroke is the leading cause of disability in the UK and it is thought that more than 900,000 people in England are living with the effects of stroke, with about half dependent on others for support with everyday activities.

Current management

The aim of treatment is to prevent (recurrent) occlusive vascular events, and can include drug therapy with one or more antiplatelet agents such as aspirin, clopidogrel and modified-release dipyridamole.

NICE has produced guidance on ‘Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events’ (NICE technology appraisal guidance 90). In addition, two NICE clinical guidelines make

recommendations about treatment with clopidogrel plus aspirin during the acute phase of myocardial infarction (acute coronary syndromes), these are 'Unstable angina and NSTEMI' (NICE clinical guideline 94) and Myocardial infarction: secondary prevention (NICE clinical guideline 48). Table 1 summarises the guidance and appendix C includes the recommendations in NICE technology appraisal guidance 90.

Table 1 Summary of recommendations in NICE guidance

Patient population	Guidance	Recommendation
Myocardial infarction	Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events (NICE TA90)	Clopidogrel alone if aspirin intolerant
NSTEMI	Unstable angina and NSTEMI (NICE CG94)	Clopidogrel plus low-dose aspirin for 12 months after the most recent event. Then standard care (including low-dose aspirin) or clopidogrel alone if aspirin intolerant
STEMI	Myocardial infarction: secondary prevention (NICE CG48)	Clopidogrel plus low-dose aspirin for 4 weeks after the most recent event. Then standard care (including low-dose aspirin) or clopidogrel if aspirin intolerant
Ischaemic stroke	Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events (NICE TA90)	Modified-release dipyridamole plus aspirin for 2 years after the most recent event. Thereafter, or if modified-release dipyridamole is not tolerated, standard care (including long-term treatment with low-dose aspirin)
Transient ischaemic attack	Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events (NICE TA90)	Modified-release dipyridamole plus aspirin for 2 years after the most recent event. Thereafter, or if modified-release dipyridamole is not tolerated, standard care (including long-term treatment with low-dose aspirin)
Peripheral arterial disease	Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events (NICE TA90)	Clopidogrel alone if aspirin intolerant
Multivascular disease	Not currently included	–

NSTEMI, non-ST-segment-elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction

'National service framework for coronary heart disease' states that GPs and primary care trusts should identify all people with established cardiovascular disease and offer them comprehensive advice and appropriate treatment to reduce their risks of recurrent occlusive vascular events. GP contracts include points for the number of people with coronary heart disease or who have had a stroke who are taking antiplatelet therapy for secondary prevention.

The technologies

Table 2 Summary description of technologies

Non-proprietary name	Clopidogrel	Modified-release dipyridamole	Modified-release dipyridamole with aspirin
Proprietary name	Plavix	Persantin Retard	Asasantin Retard
Manufacturer	Bristol-Myers Squibb, Sanofi-Aventis	Boehringer Ingelheim	Boehringer Ingelheim
Dose	75 mg once daily	200 mg twice daily	One tablet containing: 200 mg plus 25 mg aspirin, twice daily
Acquisition cost (British national formulary edition 59)	75 mg, 30-tablet pack = £36.35	200 mg, 60-caplet pack = £7.50	200mg + 25mg, 60-caplet pack = £7.79

Clopidogrel

Clopidogrel is an irreversible adenosine diphosphate-receptor antagonist with antiplatelet properties. Clopidogrel has a marketing authorisation for the prevention of atherothrombotic events in adults who have had a myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7days until less than 6 months) or established peripheral arterial disease. It is also licensed for use in combination with aspirin for acute coronary syndromes; this indication is not included in this appraisal. There are a number of generic versions of clopidogrel now available.

Contraindications to clopidogrel include severe liver impairment and active pathological bleeding such as peptic ulcer and intracranial haemorrhage.

Because of its antiplatelet activities, clopidogrel increases the risk of bleeding. For full details of side effects and contraindications, see the summary of product characteristics.

The cost of treatment with branded clopidogrel (Plavix) for 30 days at a dose of 75 mg daily is £36.35 per person (British national formulary [BNF], edition 59). The cost of generic clopidogrel 75 mg in the NHS drug tariff is £10.90 for 30 days. Costs may vary in different settings because of negotiated procurement discounts.

Modified-release dipyridamole

Dipyridamole (Boehringer Ingelheim) has both antiplatelet and vasodilating properties and is thought to inhibit the uptake of adenosine (a potent inhibitor of platelet activation and aggregation) into blood and vascular cells. Dipyridamole may also inhibit the breakdown of cyclic guanosine monophosphate. This appraisal considers the modified-release formulation of dipyridamole only, which has a marketing authorisation for the secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in conjunction with aspirin.

Because of dipyridamole's activity as a vasodilator, it should be used with caution in people with severe coronary artery disease, including unstable angina and/or recent myocardial infarction, left ventricular outflow obstruction or haemodynamic instability (for example, decompensated heart failure). Contraindications include active gastric or duodenal ulcers or bleeding disorders and patients in the last trimester of pregnancy. For full details of side effects and contraindications, see the summary of product characteristics.

The 30 day cost of treatment with modified-release dipyridamole alone is £7.50 and modified-release dipyridamole plus aspirin is £7.79 per person (BNF, edition 59). There are currently no generic versions of modified-release

dipyridamole or modified-release dipyridamole plus aspirin available. Costs may vary in different settings because of negotiated procurement discounts.

The evidence

Clinical effectiveness

Four randomised controlled trials (RCTs) were identified by the Assessment Group, two (CAPRIE and ESPS-2) were used in the original appraisal of clopidogrel and modified-release dipyridamole in occlusive vascular events (NICE technology appraisal guidance 90) and two (ESPRIT and PRoFESS) were published after the guidance. The RCTs were considered by the Assessment Group to be of good quality.

The key characteristics of the four trials are summarised in table 3.

Table 3 Patient characteristics (adapted from tables 5.1, 5.2 and 5.3 in the assessment report)

Trial	Study design	Number of patients	Patient population	Patient characteristics	Treatment arms	Follow-up	Primary outcome
CAPRIE 1996	Double-blind, placebo-controlled trial	19,185	Ischaemic stroke (n = 6431) Myocardial infarction (n = 6302) Symptomatic peripheral arterial disease (n = 6452)	Mean age 62.5 years, 72% male, global recruitment	Clopidogrel (75 mg/day) Aspirin (325mg/day)	1.91 years; follow-up while on treatment: 1.63 years	First occurrence of ischaemic stroke, myocardial infarction, or vascular death
ESPS-2 1996	Double-blind, placebo-controlled trial	6602	Ischaemic stroke (n = 5038) Transient ischaemic attack (n = 1562)	Mean age 66.7 years, 58% male, European recruitment	Modified-release dipyridamole (400 mg/day) plus aspirin (50 mg/day) Modified-release dipyridamole (400 mg/day) Aspirin (50 mg/day) Placebo	2 years	Stroke; all-cause death; stroke and/or all-cause death
ESPRIT 2006	Open-label trial	2763	Transient ischaemic attack (n = 920) Minor ischaemic stroke (n = 1816)	Mean age 63 years, 66% male, global recruitment	Modified-release dipyridamole (400 mg/day) plus aspirin Aspirin (30–325 mg/day)	3.5 years (standard deviation 2.0)	First occurrence of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication
PRoFESS 2008	Double-blind, non-inferiority trial	20,332	Recent ischaemic stroke (n = 20,332)	Mean age 66.1 years, 64% male, global recruitment	Modified-release dipyridamole (400 mg/day) plus aspirin (25 mg/day) Clopidogrel (75 mg/day)	2.5 years (range: 1.5–4.4)	Recurrent stroke of any type

Modified-release dipyridamole compared with aspirin

The ESPS-2 trial included a comparison of modified-release dipyridamole with aspirin in patients who had has a transient ischaemic attack or ischaemic stroke. For this comparison no statistically significant differences were reported for primary or secondary outcomes (see table 4).

Table 4 Key outcomes of the ESPS-2 trial: modified-release dipyridamole compared with aspirin (from table 5.5 in the assessment report, page 45)

Outcomes	Relative risk (95% CI)
Primary	
Stroke	1.02 (0.85 to 1.22)
Stroke and/or death	0.97 (0.85 to 1.11)
All-cause death	1.03 (0.85 to 1.25)
Secondary	
Transient ischaemic attack	1.04 (0.87 to 1.24)
Stroke or transient ischaemic attack	1.02 (0.90 to 1.16)
Myocardial infarction	1.23 (0.81 to 1.86)
Other vascular event	0.92 (0.58 to 1.45)
Ischaemic events	1.02 (0.87 to 1.19)
Vascular death	1.06 (0.83 to 1.35)
Vascular events	1.03 (0.89 to 1.18)

CI, confidence interval

Modified-release dipyridamole plus aspirin compared with aspirin

Both ESPS-2 and ESPRIT compared modified-release dipyridamole plus aspirin with aspirin. Both trials enrolled people who had had an ischaemic stroke or transient ischaemic attack.

In the ESPS-2 trial, patients treated with modified-release dipyridamole plus aspirin had a statistically significantly reduced risk of stroke, stroke or transient ischaemic attack, other vascular events, ischaemic events and vascular events compared with patients treated with aspirin alone. For other outcomes, no statistically significant difference between the treatments was seen (see table 5).

Table 5 Key outcomes of the ESPS-2 trial: modified-release dipyridamole plus aspirin compared with aspirin (from table 5.5 in the assessment report, page 45)

Outcomes	Relative risk (95% CI)
Primary	
Stroke	**0.76 (0.63 to 0.93)**
Stroke and/or death	0.87 (0.75 to 1.00)
All cause death	1.02 (0.84 to 1.23)
Secondary	
Transient ischaemic attack	0.83 (0.69 to 1.01)
Stroke or transient ischaemic attack	**0.80 (0.70 to 0.92)**
Myocardial infarction	0.90 (0.57 to 1.41)
Other vascular event	**0.55 (0.33 to 0.94)**
Ischaemic events	**0.77 (0.65 to 0.92)**
Vascular death	0.99 (0.77 to 1.27)
Vascular events	**0.78 (0.67 to 0.91)**

CI, confidence interval

Statistically significant results are in bold

In the ESPRIT trial, patients treated with modified-release dipyridamole plus aspirin had a statistically significant reduction in risk of events: for the primary outcome, and for the secondary outcomes; death from all vascular causes and non-fatal stroke and all vascular events compared with patients treated with aspirin alone. For other outcomes, no statistically significant difference between the treatments was seen (see table 6).

Table 6 Key outcomes of the ESPRIT trial: modified-release dipyridamole plus aspirin compared with aspirin (from table 5.6 in the assessment report, page 46)

Outcomes	Hazard ratio (95% CI)
Primary	
First occurrence of one of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication	**0.80 (0.66 to 0.98)**
Secondary	
Death from all causes	0.88 (0.67 to 1.17)
Death from all vascular causes	0.75 (0.51 to 1.10)
Death from all vascular causes and non-fatal stroke	**0.78 (0.62 to 0.97)**
Major bleeding complications	0.67 (0.44 to 1.03)
All major ischemic events (non-haemorrhagic death from vascular causes, non-fatal ischaemic stroke, or non-fatal myocardial infarction)	0.81 (0.65 to 1.01)
All vascular events (death from vascular causes, non-fatal stroke or non-fatal myocardial infarction)	**0.78 (0.63 to 0.97)**
First ischaemic stroke	0.84 (0.64 to 1.10)
First cardiac event	0.73 (0.49 to 1.08)

CI, confidence interval

Statistically significant results are in bold

Modified-release dipyridamole plus aspirin compared with modified-release dipyridamole

The ESPS-2 trial also compared modified-release dipyridamole plus aspirin with modified-release dipyridamole in patients who had had an ischaemic stroke or transient ischaemic attack. Patients treated with modified-release dipyridamole plus aspirin had a statistically significantly reduced risk of stroke; transient ischaemic attack; stroke or transient ischaemic attack; ischaemic events; and vascular events compared with patients treated with modified-release dipyridamole alone. No difference in risk between the treatment groups was seen for other outcomes (see table 7).

Table 7 Key outcomes of the ESPS-2 trial: modified-release dipyridamole plus aspirin compared with modified-release dipyridamole (from table 5.5 in the assessment report, page 45)

Outcomes	Relative risk (95% CI)
Primary	
Stroke	**0.75 (0.61 to 0.91)**
Stroke and/or death	0.89 (0.77 to 1.03)
All-cause death	0.99 (0.81 to 1.19)
Secondary	
Transient ischaemic attack	**0.80 (0.66 to 0.97)**
Stroke or transient ischaemic attack	**0.78 (0.69 to 0.90)**
Myocardial infarction	0.73 (0.48 to 1.12)
Other vascular event	0.60 (0.35 to 1.03)
Ischaemic events	**0.76 (0.64 to 0.90)**
Vascular death	0.94 (0.74 to 1.20)
Vascular events	**0.76 (0.65 to 0.89)**

CI, confidence interval

Statistically significant results are in bold

Clopidogrel compared with aspirin

The CAPRIE trial compared clopidogrel with aspirin. This trial enrolled people who had had an ischaemic stroke, myocardial infarction or who had peripheral arterial disease. Results show that clopidogrel reduced the risk of a first occurrence of: ischaemic stroke, myocardial infarction or vascular death in two groups: in the all patients group and in a subgroup of people with peripheral arterial disease. No statistically significant differences were seen for other outcomes or for the stroke and myocardial infarction subgroups (see table 8).

Table 8 Key outcomes of the CAPRIE trial: clopidogrel compared with aspirin (from table 5.4 in the assessment report, page 44)

Outcomes	Subgroup	Relative risk reduction (%) (95% CI)
Primary		
First occurrence of ischaemic stroke, myocardial infarction, or vascular death	**All patients**	**8.7 (0.3 to 16.5) p = 0.043**
	Stroke	7.3 (−5.7 to 18.7) p = 0.26
	Myocardial infarction	−3.7 (−22.1 to 12) p = 0.66
	Peripheral arterial disease	**23.8 (8.9 to 36.2) p = 0.0028**
Secondary		
First occurrence of ischaemic stroke, myocardial infarction, amputation, or vascular death	All patients	7.6 (−0.8 to 15.3) p = 0.076
Vascular death	All patients	7.6 (−6.9 to 20.1) p = 0.29
Any stroke (includes primary intracranial haemorrhage) myocardial infarction or death from any cause, fatal bleeding	All patients	7.0 (−0.9 to 14.2) p = 0.081
Death from any cause	All patients	2.2 (−9.9 to 12.9), p = 0.71

CI, confidence interval

Statistically significant results are in bold

Multivascular disease

The CAPRIE trial compared clopidogrel with aspirin in a subgroup of people with multivascular disease. The definition of multivascular disease differs between submissions, but results from the manufacturer's submission and from the assessment report suggest that clopidogrel reduces the risk of first occurrence of ischaemic stroke, myocardial infarction or vascular death compared to treatment with aspirin alone (see table 9).

Table 9 Analyses of the CAPRIE trial for patients with multivascular disease: clopidogrel compared with aspirin (from tables 5.20 and 5.21 in the assessment report, page 63)

Submission	Subgroup	Relative risk reduction (%) (95% CI)
Manufacturer	Patients with peripheral arterial disease or stroke and previous myocardial infarction	**22.7** **(4.9 to 37.2)**
Assessment report	Patients with experience of at least two of: ischaemic stroke only, myocardial infarction only or peripheral arterial disease only (defined by AG)	**14.9** **(0.3 to 27.3)** **p = 0.045**

CI, confidence interval

Statistically significant results are in bold

Modified-release dipyridamole plus aspirin compared with clopidogrel

The PRoFESS trial enrolled people with recent ischaemic stroke and compared clopidogrel with modified-release dipyridamole plus aspirin. Patients treated with modified-release dipyridamole had a reduced risk of new or worsening congestive heart failure compared with patients treated with clopidogrel. However, modified-release dipyridamole was associated with a greater risk of intracranial haemorrhage than clopidogrel. In all other outcomes, there was no difference between the treatments (see table 10).

Table 10 Key outcomes of the PRoFESS trial: modified-release dipyridamole plus aspirin compared with clopidogrel (from table 5.7 in the assessment report, page 47)

Outcomes	Hazard ratio (95% CI)
Primary	
Recurrent stroke of any type	1.01 (0.92 to 1.11)
Secondary/tertiary	
Composite of vascular events (stroke, myocardial infarction, or death from vascular causes)	0.99 (0.92 to 1.07)
Myocardial infarction	0.90 (0.73 to 1.10)
Death from vascular causes	0.94 (0.82 to 1.07)
Death from any cause	0.97 (0.87 to 1.07)
New or worsening congestive heart failure	**0.78 (0.62 to 0.96)**
Other vascular event	1.03 (0.91 to 1.16)
First ischaemic stroke	0.97 (0.88 to 1.07)
First recurrence of stroke or major haemorrhagic event	1.03 (0.95 to 1.11)
Major haemorrhagic event	1.15 (1.00 to 1.32)
Haemorrhagic event (minor or major)	1.08 (0.96 to 1.22)
Intracranial haemorrhage	**1.42 (1.11 to 1.83)**
Thrombotic thrombocytopenic or neutropenia	0.89 (0.32 to 2.44)

CI, confidence interval
Statistically significant results are in bold

Indirect comparison for patients with ischaemic stroke or transient ischaemic attack

The Assessment Group carried out an indirect comparison using data from the four RCTs, for patients who had had an ischaemic stroke or transient ischaemic attack. The Assessment Group reports no major differences between the results of the indirect comparison and the direct estimates from the head-to-head trials. The results are described in appendix B (assessment report page 52 onwards).

Adverse events

The adverse events reported in CAPRIE, ESPS-2 and PRoFESS are presented in table 11. Adverse events other than bleeding (see table 6) were not reported for ESPRIT.

Table 11 Adverse events reported for CAPRIE, ESPS-2 and PRoFESS (from table 5.8 in the assessment report, page 49)

		Patients (n [%])				
Trial	Adverse event	Clopidogrel	Modified-release dipyridamole + aspirin	Aspirin	Modified-release dipyridamole	Placebo
CAPRIE	Rash	578 (6.02)		442 (4.61)		
	Diarrhoea	4 28 (4.46)		322 (3.36)		
	Indigestion, nausea and/or vomiting	1441 (15.01)		1686(17.59)		
	Abnormal liver function	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	191(1.99)		255 (2.66)		
	Discontinuation due to adverse events	(11.94)		(11.92)		
ESPS-2	Any adverse event		1056 (64)	990 (60)	1034 (62.57)	933 (56.58)
	Gastrointestinal event		541 (32.80)	502 (30.44)	505 (30.53)	465 (28.20)
	Vomiting		133 (8.06)	93 (5.64)	119 (7.19)	109 (6.61)
	Diarrhoea		199 (12.06)	109 (6.6)	254 (15.36)	154 (9.33)
	Headache		630 (38.18)	546 (33.11)	615 (37.18)	534 (32.38)
	Bleeding at any site		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)

		Patients (n [%])				
Trial	Adverse event	Clopidogrel	Modified-release dipyridamole + aspirin	Aspirin	Modified-release dipyridamole	Placebo
	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 adverse events		479 (29)	366 (22)	485 (29)	360 (21)
PRoFESS	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 thrombocytopenic or neutropenia	8 (0.1)	7 (0.1)			
	Patients with adverse events leading to discontinuation	1069 (10.6)	1650 (16.64)			

Cost effectiveness

Evidence on cost effectiveness was presented by both manufacturers and the Assessment Group. These submissions are described in detail below.

Bristol-Myers Squibb and Sanofi-aventis (clopidogrel)

Model design

The Bristol-Myers Squibb and Sanofi-aventis model estimated the cost effectiveness of four treatments for the secondary prevention of occlusive vascular events. These treatments were: aspirin, clopidogrel, modified-release dipyridamole plus aspirin and modified-release dipyridamole alone. In line with the licensed indications of the products, all four treatments were compared for use in people with a prior ischaemic stroke. In people with a history of myocardial infarction, peripheral arterial disease and multivascular disease, clopidogrel was compared with aspirin.

The manufacturers submitted a Markov model to support their submission. The Markov model comprised six health states: no event in model, history of stroke, history of myocardial infarction, TA80 state (an intermediate state reflecting NICE guidance TA80 (now updated in CG94) recommending clopidogrel plus aspirin for up to 12 months after an NSTEMI event), history of stroke and myocardial infarction, and death (split into vascular and non-vascular death). Patients entering the model can remain stable, have a myocardial infarction or stroke, or die. The modelled patient population comprised 1000 patients entering the model aged 65 years. The model was run with 3-month cycles for 35 years (to reflect a lifetime horizon). The perspective adopted was that of the UK NHS in line with the NICE reference case and costs and utilities were discounted at a rate of 3.5%.

Each patient population was modelled in the same way, with the exception that the baseline risks of vascular events differed by cohort (ischaemic stroke, myocardial infarction, peripheral arterial disease and multivascular disease). Event rates were different for year 1, 2 and 3 of the model. Event rates in

year 3 were used to inform the model from year 3 onwards. Event rates and baseline risk for treatment with aspirin were derived from an international disease registry that included 68,000 people (the REACH registry). Relative treatment effects for clopidogrel, modified-release dipyridamole and modified-release dipyridamole plus aspirin were based on either direct evidence, or on indirect evidence, using a network meta-analysis. Life tables were employed to estimate non-vascular death rates in the model.

The non-treatment costs used in the model were based on information from published burden of illness studies. Event costs in the model included: £6307 for non-fatal stroke, £4893 for non-fatal myocardial infarction, £2726 for vascular death, £250 for non-vascular death, £2805 for major bleed and £90 for a minor bleed. Treatment costs were sourced from MIMS. All costs were inflated to 2007/08 prices, if necessary. Utility values were derived from the published literature and were between 0.61 and 0.87. A disutility associated with events of between −0.3 and −0.001 was also applied in the model.

Results

In people who had had an ischaemic stroke, treatment with modified-release dipyridamole plus aspirin had an incremental cost-effectiveness ratio (ICER) of £237 per quality-adjusted life year (QALY) gained compared with aspirin. Clopidogrel had an ICER of £31,204 per QALY gained in comparison with aspirin. Clopidogrel was associated with greater costs and fewer QALYs than modified-release dipyridamole plus aspirin.

For treatment with clopidogrel compared with aspirin, the ICER for people who had had myocardial infarction was £20,662 per QALY gained, for people with peripheral arterial disease it was £18,854 per QALY gained, and for people with multivascular disease it was £15,524 per QALY gained, (see table 12).

At a threshold of £30,000 per QALY, the probability of modified-release dipyridamole being cost effective in people who have had a stroke was 97%. In people who have had a myocardial infarction, peripheral arterial disease or

multivascular disease, the treatment option with the highest probability of being cost effective was clopidogrel.

Table 12 Results from the manufacturer's submission

		Aspirin	Clopidogrel	Modified-release dipyridamole + aspirin
Ischaemic stroke	Total costs	£10,841	£13,165	£10,948
	Total QALYs	4.83	4.90	5.28
	ICER vs aspirin	–	£31,204	£237
Myocardial infarction	Total costs	£6349	£8992	–
	Total QALYs	6.70	6.83	–
	ICER vs aspirin	–	£20,662	–
Peripheral arterial disease	Total costs	£6138	£8608	–
	Total QALYs	5.71	5.84	–
	ICER vs aspirin	–	£18,854	–
Multivascular disease	Total costs	£8678	£10,483	–
	Total QALYs	4.68	4.80	–
	ICER vs aspirin	–	£15,524	–

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Boehringer-Ingelheim (modified-release dipyridamole)

Model design

The model estimated the cost-effectiveness of modified-release dipyridamole plus aspirin compared with aspirin, clopidogrel and no treatment. The manufacturer did not estimate the cost effectiveness of modified-release dipyridamole alone, because no new information was available for this treatment. Separate analyses were conducted for people who had had an ischaemic stroke, and for people who had had a transient ischaemic attack. Only patients tolerant to aspirin were considered in the analysis.

The manufacturer submitted a Markov model based on the Assessment Group model from the guidance on clopidogrel and modified-release dipyridamole in occlusive vascular events [NICE technology appraisal guidance 90]. The model has five health states: no recurrent stroke;

haemorrhagic stroke; recurrent ischaemic stroke; vascular death or non-vascular death. Patients enter the model at the 'no recurrent stroke' stage and after each cycle of 6 months can move to any of the other four stages, or can remain in the current state. After each cycle, transitions can occur to the other stages.

The baseline age in the model was 66 years, with a time horizon of 50 years. The perspective adopted was that of the NHS and personal social services. Transition probabilities between the states in the model for the first 4 years were taken from the PRoFESS, ESPRIT and ESPS-2 trials. Different transition probabilities were calculated for each 6-month period over the 4 years. Transition probabilities in subsequent years for the stroke states were based on the final 6-month period of the 4 years. Transition probabilities to death were estimated based on a factor of 1.5 applied to Office for National Statistics death rate data on the general population.

Costs of stroke events were calculated from the literature and varied according to disabled or non-disabled status. Costs of hospital stay following congestive heart failure and other haemorrhagic events were sourced from the 2006 to 2007 National Reference Costs. Drug acquisition costs were based on branded drug costs for modified-release dipyridamole and aspirin, and clopidogrel, and on the generic price for aspirin (2009 prices). Utility data from the PRoFESS trial at 1 year were used and were: [redacted] for no recurrent stroke, [redacted] for recurrent ischaemic stroke and [redacted] for haemorrhagic stroke. The literature was searched for disutilities associated with congestive heart failure and 'other haemorrhagic events'. A short term disutility associated with different events was also included in the model. Costs and utilities were discounted at a rate of 3.5% per year.

Results

In patients who had had an ischaemic stroke, compared with aspirin, treatment with modified-release dipyridamole plus aspirin gave an ICER of £5377 per QALY gained as shown in table 13. The ICER for clopidogrel

compared with modified-release dipyridamole plus aspirin was £114,628 per QALY gained. The results were similar in patients who had had a transient ischaemic attack: comparing modified-release dipyridamole with aspirin gave an ICER of £6053 per QALY gained (see table 13).

Table 13 Results from the manufacturer's submission

		Modified-release dipyridamole + aspirin	Clopidogrel	Aspirin	No treatment
Ischaemic stroke	Total costs	£37,430,180	£39,238,555	£36,725,769	£36,678,013
	Total QALYs	8724	8739	8593	8596
	ICER (modified-release dipyridamole + aspirin vs comparator)	–	£114,628	£5377	£5910
Transient ischaemic attack	Total costs	£37,010,692	£38,871,872	£36,278,556	£36,197.693
	Total QALYs	8781	8790	8660	8675
	ICER (modified-release dipyridamole + aspirin vs comparator)	–	£199,149	£6053	£7684

Results are for 1000 patients

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Probabilistic sensitivity analysis showed that in both the ischaemic stroke and transient ischaemic attack cohorts, at a willingness-to-pay of £20,000 per QALY gained, the likelihood of treatment with modified-release dipyridamole plus aspirin being cost effective was greater than 95%.

Assessment Group model

Model design

The Assessment Group developed an individual patient sampling model, in which a series of individual patients were generated whose combined characteristics were representative of the specified population. Analyses were

split by patient population: ischaemic stroke, myocardial infarction, peripheral arterial disease and multivascular disease. The ischaemic stroke and transient ischaemic attack populations were assumed to be equivalent in risk and outcomes and so were modelled together. Within the myocardial infarction group, treatment strategies as described in the clinical guidelines on STEMI and NSTEMI (NICE clinical guideline 48 and 94) were initially modelled. Once initial treatment was completed according to the guidelines, potential treatment strategies for this appraisal were considered as follow-on treatment. The multivascular disease group were defined by the Assessment Group as having had a recent episode of acute myocardial infarction, ischaemic stroke or peripheral arterial disease, and who had a prior history involving at least one other type of vascular disease.

The Assessment Group presented different treatment strategies, depending on the population and intolerances (see page 113 of the assessment report). The Assessment Group considered that this approach reflected the real world, in which patients may switch between different treatments.

For each patient in the model, age, sex and disability status was set. According to these variables, estimates of time to first event were applied. These events determined the event history of the patient and included: a fatal or new non-fatal ischaemic stroke event; a fatal or new non-fatal non-ischaemic stroke event; a fatal or new non-fatal myocardial infarction; death from other vascular causes; death from non-vascular causes; patient discontinues current preventive medication for any reason. Only one event could occur at any one time. If the event was non-fatal then the patient continued in the model, with an updated age, sex and disability and updated risks, with the potential to incur additional events over time, moving through the model over a lifetime. Each patient was modelled in the same way. Data provided by the manufacturers from the CAPRIE and PRoFESS trials were used to develop risk models for the economic model and to work out event fatality. An exponential survival function was used to model medication continuance over time. Adverse events were incorporated into the model.

Resource use was measured in terms of clinical events and time spent in chronic states, and differed by disability status. Drug costs were taken from the BNF58 and for generic clopidogrel from the NHS drug tariff. Unit costs were drawn from various sources, including the manufacturers' submissions and inflated, if necessary to 2009. The cost of non-fatal ischaemic or haemorrhagic stroke was £6410 if the patient was not disabled and £13,647 if they were disabled; £8768 for fatal ischaemic or haemorrhagic stroke; £5762 for non-fatal myocardial infarction, £2218 for fatal myocardial infarction and £2225 for other vascular or non-vascular death.

Utility values were also drawn from a variety of sources, including the manufacturers' submissions and additional analysis requested from the manufacturer. Mean utility values were assigned to each chronic health state and a specific utility decrement effect was applied for each modelled event. Utility values for the myocardial infarction and peripheral arterial disease groups were 0.87 and 0.80 respectively. Utility values for the ischaemic stroke group, and utility decrements were taken from the Boehringer-Ingelheim submission. Discounting at 3.5% was applied to costs and benefits, after the first year. A lifetime horizon was used.

Deterministic and probabilistic sensitivity analyses were conducted to explore the impact of uncertainty on the cost effectiveness estimates.

Results

The results from the assessment report are summarised in table 14.

Table 14 (continued overleaf) Comparison of deterministic and probabilistic model results (from table 1.1 of the addendum 1, pages 138, 143 and 148 of the Assessment Report and addendums 2 and 3)

Patient population	Treatment strategy		ICER (£/QALY)		At £20,000/QALY WTP Prob. cost-effective	At £30,000/QALY WTP Prob. cost-effective	ICER (£/QALY)
	Optimal	Comparator[a]	Deterministic with **full price** clopidogrel	PSA			Deterministic with **generic price** clopidogrel
Myocardial infarction	ASA → Clop	ASA	6381	6250	100%	100%	1964
Myocardial infarction (aspirin intolerant)	Clop	No treatment	12,802	12,037	98%	100%	2020
Peripheral Arterial disease	Clop → ASA	ASA → Clop	9769	9975	98%	100%	2815
Peripheral Arterial disease (aspirin intolerant)	Clop	No treatment	4563	4367	100%	100%	721
Multivascular disease	Clop→ ASA	ASA → Clop	10,432	11,121	100%	100%	2604
Multivascular disease (aspirin intolerant)	Clop	No treatment	2189	2064	100%	100%	-758

ICER, incremental cost effectiveness ratio; QALY quality adjusted life year; ASA, aspirin; Clop clopidogrel; MRD, modified release dipyridamole; NA, not applicable

[a] The comparator is the next best treatment strategy in the sequence

Patient population	Optimal treatment strategy	comparator	ICER (£/QALY)		Prob. cost-effective £20,000	Prob. cost-effective £30,00	ICER (£/QALY)
			Deterministic with **full price** clopidogrel	Probabilistic analysis			Deterministic with **generic** price clopidogrel
Ischaemic stroke	MRD+ASA → ASA → Clop	MRD+ASA → ASA	16,894	16,833	79%	89%	NA[b]
Ischaemic stroke (aspirin intolerant)	Clop → MRD	Clop	7142	6443	96%	96%	7142
Ischaemic stroke (modified-release dipyridamole intolerant)	ASA → Clop	ASA	6797	6185	85%	65%	NA[b]

Optimal treatment strategies using the price of generic clopidogrel

Patient population	Optimal treatment strategy	comparator	ICER (£/QALY)		Prob. cost-effective £20,000	Prob. cost-effective £30,00
			Deterministic with **generic** clopidogrel	Probabilistic analysis		
Ischaemic stroke	Clop → MRD+ASA → ASA	Clop → ASA → MRD+ASA	13,558	10,107	68%	73%
Ischaemic stroke (modified-release dipyridamole intolerant)	Clop → ASA	ASA → Clop	3970	4676	85%	87%

ICER, incremental cost effectiveness ratio; QALY quality adjusted life year; ASA, aspirin; Clop clopidogrel; MRD, modified release dipyridamole; NA, not applicable

[b] when the generic price of clopidogrel is used, the optimum strategy is different to that when the branded price of clopidogrel is used, these analyses are shown in the second half of the table

Comparison of the results from the manufacturers' submissions and the assessment report

Patients with ischaemic stroke or transient ischaemic attack

When the branded price for clopidogrel is used the Assessment Group reported that the optimal strategy began with modified-release dipyridamole plus aspirin, followed by aspirin and finally clopidogrel. When the generic price for clopidogrel is used, the optimum strategy changes so that it begins with clopidogrel, followed by modified-release dipyridamole and finally aspirin. However, the differences in the total costs and QALYs between the strategy that starts with clopidogrel and is followed by modified-release dipyridamole plus aspirin and vice versa are small (table 15; Assessment report addendums 2 and 3).

Table 15: Total costs and QALYs from deterministic analyses for patients with ischaemic stroke and no intolerances

Strategy	Total Costs	Total QALYs
Clop →M+A →ASA	£35,876	7.856
M+A → Clop → ASA	£35,771	7.840

In the Assessment Group's model, for patients who are intolerant of aspirin, compared with no treatment, clopidogrel followed by modified-release dipyridamole was the optimal strategy. In patients who are intolerant of modified-release dipyridamole, the optimal strategy depended on the price of clopidogrel. At the branded price, the preferred strategy was aspirin followed by clopidogrel, but for the generic price it was clopidogrel followed by aspirin. For patients intolerant to both aspirin and modified-release dipyridamole, only clopidogrel is available for long-term prevention and was considered optimal by the Assessment Group compared with no preventive therapy.

The Sanofi-aventis/Bristol-Myers Squibb submission reported that for people who had had an ischaemic stroke, treatment with modified-release dipyridamole plus aspirin had an ICER of £237 per QALY gained compared with aspirin. Clopidogrel was dominated by modified-release dipyridamole

plus aspirin with lower costs and fewer QALYs (analyses assumed the branded price for clopidogrel). The Boehringer Ingelheim submission reported an ICER of £5377 per QALY gained for modified-release dipyridamole plus aspirin compared with aspirin.

Patients with myocardial infarction

The Assessment Group reported that aspirin followed by clopidogrel was the optimal strategy for these people. In patients who are intolerant of aspirin, treatment with clopidogrel was likely to be the optimal treatment.

The Sanofi-aventis/Bristol-Myers Squibb submission reported that in people with myocardial infarction, treatment with clopidogrel had an ICER of £20,662 per QALY gained compared with aspirin. The Boehringer Ingelheim submission did not conduct any analyses in this patient population.

Patients with established peripheral arterial disease

The Assessment Group reported that clopidogrel followed by aspirin was the optimal strategy for this patient group. In patients who are intolerant to aspirin, clopidogrel alone was the optimal treatment strategy.

The Sanofi-aventis/Bristol-Myers Squibb submission reported that in people with peripheral arterial disease, treatment with clopidogrel had an ICER of £18,854 per QALY gained compared with aspirin. The Boehringer Ingelheim submission did not conduct an analysis in this patient population.

Patients with multivascular disease

The Assessment Group reported that clopidogrel followed by aspirin was the optimal strategy for this patient group. In patients who are intolerant to aspirin, clopidogrel alone was the optimal treatment strategy.

The Sanofi-aventis/Bristol-Myers Squibb submission found that in people with multivascular disease, clopidogrel had an ICER of £15,524 per QALY gained compared with aspirin. The Boehringer Ingelheim submission did not conduct an analysis in this patient group.

Issues for consideration

Available evidence

In NICE technology appraisal guidance 90 “the Committee was persuaded that while both of these antiplatelet agents [clopidogrel and modified release dipyridamole] were effective in reducing the risk of further occlusive vascular events, neither drug had a proven effect on mortality over and above that seen with aspirin as sole antiplatelet agent”. Since the publication of this guidance, two further trials ESPRIT and PRoFESS have become available for the ischaemic stroke population. Does the Committee consider that the new data affects the conclusions about the efficacy of clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events?

Branded and generic clopidogrel

Since the publication of NICE technology appraisal guidance 90 clopidogrel has become available in branded and generic formulations. The use of a generic as opposed to a branded formulation affects the optimal strategy in some of the analyses by the Assessment Group. What is the Committee consideration about the use of branded and generic clopidogrel?

Multivascular disease

Data from the CAPRIE trial enables a post-hoc analysis of data for a subgroup of people with multivascular disease. This data is subsequently incorporated into cost effectiveness analysis. This subgroup was not specifically considered in the guidance in technology appraisal 90. Does the Committee consider this subgroup to be clinically meaningful and relevant? Does the data presented in the manufacturer submission and assessment report support the efficacy and cost effectiveness of clopidogrel in this subgroup?

Myocardial infarction

The Assessment Group report that the optimal strategy for patients with myocardial infarction without intolerance to aspirin was aspirin followed by clopidogrel. However, in the manufacturer’s model clopidogrel has an ICER of £20,662 per QALY gained compared with aspirin. Related NICE clinical

guidelines 48 and 94 (see table 1) recommend that after an initial treatment period with clopidogrel plus aspirin for acute coronary syndrome, treatment reverts to standard care including aspirin, except where a patient is intolerant to aspirin in which case clopidogrel may be continued. Does the Committee consider that clopidogrel has been shown to be cost effective for the prevention of occlusive vascular events compared with aspirin for the group of patients who have had a myocardial infarction?

Ischaemic stroke

The analyses by the Assessment Group for people who have had an ischaemic stroke suggest that when the generic price of clopidogrel is used the optimum strategy includes the use of clopidogrel before the use of modified release dipyridamole plus aspirin. However, the differences between the costs and QALYs for the different strategies are small. Does the Committee consider that either clopidogrel or modified release dipyridamole have been shown to be the preferred treatment strategy?

Peripheral arterial disease

For people with peripheral arterial disease, technology appraisal 90 recommended the use of clopidogrel only in those people who are intolerant to aspirin. Does the Committee consider that the new analyses available support a recommendation for clopidogrel in a broader population?

Ongoing research

Six RCTs were identified by the Assessment Group. The first, ASCET, includes people on aspirin treatment and compares event rates for people who switch to clopidogrel with event rates for people continuing aspirin. The second study compares the preventive effect on recurrent stroke and safety of modified-release dipyridamole compared with aspirin. The other four studies compare treatment with clopidogrel plus aspirin with aspirin plus placebo.

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Appendix A: Sources of evidence considered in the preparation of the overview

The assessment report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

- Greenhalgh J, Saborido, CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90), April 2010.
- Greenhalgh J, Saborido, CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90) addendum, April 2010.
- Greenhalgh J, Saborido, CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90) addendum 2, May 2010.
- Greenhalgh J, Saborido, CM, Bagust A et al. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal 90) addendum 3, June 2010.

Submissions or statements were received from the following organisations:

Manufacturers/sponsors:

- Sanofi-aventis and Bristol-Myers Squibb (joint submission)
- Boehringer-Ingelheim

Professional/specialist, patient/carer and other groups:

- Association of British Clinical Diabetologists and Diabetes UK (Joint Submission)
- British Association of Stroke Physicians (personal statement)

Appendix B: Indirect comparison

Table 16 presents the results from an indirect analysis using a mixed treatment comparison conducted in patients who had an ischaemic stroke or transient ischaemic attack.

Table 1 Mixed treatment comparison in patients with ischaemic stroke/transient ischaemic attack (from tables 5.12 to 5.18 in the assessment report, page 55–61)

	Relative risk					
Event	Clopidogrel vs aspirin	MRD + aspirin vs aspirin	MRD + aspirin vs clopidogrel	MRD vs aspirin	MRD vs clopidogrel	MRD vs MRD + aspirin
First ischaemic stroke	0.922 (0.79 to 1.06)	0.891 (0.79 to 1.04)	0.968 (0.88 to 1.05)	Not presented	Not presented	Not presented
Any recurrent stroke	**0.752 (0.62 to 0.92)**	**0.764 (0.62 to 0.92)**	1.018 (0.93 to 1.11)	1.025 (0.85 to 1.21)	**1.376 (1.10 to 1.68)**	**1.349 (1.10 to 1.61)**
Myocardial infarction	1.094 (0.73 to 1.56)	0.972 (0.65 to 1.38)	0.893 (0.731 to 1.07)	1.291 (0.84 to 1.88)	1.208 (0.75 to 1.81)	1.352 (0.883 to 1.98)
Vascular death	0.829 (0.60 to 1.11)	0.782 (0.57 to 1.04)	0.942 (0.82 to 1.06)	Not presented	Not presented	Not presented
Death from all causes	0.992 (0.82 to 1.18)	0.967 (0.82 to 1.12)	0.976 (0.88 to 1.07)	1.007 (0.83 to 1.20)	1.021 (0.81 to 1.25)	1.044 (0.86 to 1.24)
Any bleeding	0.921 (0.75 to 1.10)	0.991 (0.85 to 1.14)	1.082 (0.958 to 1.21)	**0.549 (0.418 to 0.70)**	**0.593 (0.437 to 0.78)**	**0.557 (0.425 to 0.71)**
Major bleeding	**0.596 (0.36 to 0.89)**	0.682 (0.433 to 1.008)	1.147 (0.99 to 1.31)	Not presented	Not presented	Not presented

Statistically significant results are in bold: If the relative risk and the 95% confidence interval are less than one, the risk of events is statistically significantly lower in the first treatment group compared with the second treatment group. If the relative risk and the 95% confidence interval are greater than one, the risk of events is statistically higher in first treatment group compared with the second treatment group.

MRD, modified-release dipyridamole

Appendix C: Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events' (NICE technology appraisal guidance 90)

Guidance

This guidance applies to people who have had an occlusive vascular event, or who have symptomatic peripheral arterial disease. This guidance does not apply to people who have had, or are at risk of, a stroke associated with atrial fibrillation, or who require treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures.

As part of the prevention of occlusive vascular events:

- the combination of modified-release (MR) dipyridamole and aspirin is recommended for people who have had an ischaemic stroke or a transient ischaemic attack for a period of 2 years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy should revert to standard care (including long-term treatment with low-dose aspirin)

- clopidogrel alone (within its licensed indications) is recommended for people who are intolerant of low-dose aspirin and either have experienced an occlusive vascular event or have symptomatic peripheral arterial disease.

For the purposes of this guidance, aspirin intolerance is defined as either of the following:

- proven hypersensitivity to aspirin-containing medicines

- history of severe dyspepsia induced by low-dose aspirin.