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Abstract

The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis

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Objective: To update the previous systematic review of the use of clopidogrel in combination with aspirin for patients with non-ST-elevation acute coronary syndrome (NSTE-ACS), investigating the optimal duration of treatment and effects of withdrawal from treatment.

Data sources: Ten electronic databases and internet resources were searched from 2003 to February 2007, including MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, CENTRAL and CINAHL.

Review methods: Randomised controlled trials (RCTs) of clopidogrel plus aspirin compared with aspirin alone were used to evaluate clinical effectiveness and safety. Inclusion criteria included any comparator trial for duration of treatment studies, and any study design conducted in patients with NSTE-ACS, percutaneous coronary intervention (PCI), stroke, peripheral artery disease (PAD) or ST-elevation myocardial infarction (STEMI) for evidence of rebound on withdrawal of treatment. The existing model was updated to provide a more robust approach to evaluating the cost-effectiveness of alternative durations of clopidogrel and to assess the potential value of further research using value of information approaches.

Results: Two RCTs were included for the review of clinical effectiveness and safety. The only RCTs identified that evaluated different durations of clopidogrel treatments were conducted in patients with stroke, PAD, STEMI or PCI. Two small RCTs and one uncontrolled retrospective cohort study were identified for the review of rebound after thienopyridine withdrawal in patients with medically-treated NSTE-ACS. On broadening the criteria, five RCTs, two observational cohorts, nine case series and 33 case reports were identified in patients post-PCI, and two case series and two case reports were identified in patients with stroke, PAD or STEMI. The CURE trial reported that the proportion of patients experiencing cardiovascular death, myocardial infarction or stroke was lower in the clopidogrel group at 30 days [relative risk (RR) 0.79; 95% confidence interval (CI) 0.67–0.92] and from 30 days to 12 months (RR 0.82; 95% CI 0.70–0.95). Clopidogrel seems to be effective in reducing adverse cardiovascular events in patients with NSTE-ACS at intermediate and high risk of ischaemic events, and appears to increase the risk of bleeding when compared with aspirin in patients with intermediate risk of ischaemic events. In terms of the cost-effectiveness of alternative durations of clopidogrel, the updated model reinforced the conclusions from the earlier analysis, i.e. a policy of 12 months of clopidogrel for patients with NSTE-ACS appears to be cost-effective in both 'average' patients and higher-risk patients. The incremental cost-effectiveness (ICER) of 12 months' duration ranged from £13,380 to £20,661 per additional quality-adjusted life-year (QALY) across the different scenarios. For lower-risk patients, treatment beyond 3 months does not appear to be cost-effective. The ICER of 12 months' treatment with clopidogrel varied between £49,436 and £58,691 per QALY. Estimates of expected value of perfect information (EVPI) were higher for the combined analysis and for analysis of high-risk patients alone (between £48.69 million and £108.4 million at a threshold of £30,000 per QALY). At a threshold of £20,000–£30,000 per QALY, total EVPI ranged between £3.27 million and £20.38 million in the lower-risk group.

Conclusions: The review was limited by the lack of available data. There is considerable variation in the costs of uncertainty surrounding the different scenarios and populations considered. The validity of these may also be less reliable in the higher-risk groups owing to changes in clinical practice. An adequately powered, well-conducted RCT that directly compares different durations of clopidogrel treatment in patients with NSTE-ACS would ideally be required to provide more robust evidence in relation to the impact of clopidogrel withdrawal.

Contents

List of abbreviations

ACS	acute coronary syndrome
ADP	adenosine diphosphate
BCIS	British Cardiac Intervention Society
CABG	coronary artery bypass graft
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CHE	Centre for Health Economics
CI	confidence interval
COX-2	cyclo-oxygenase-2 (enzyme responsible for inflammation)
CRD	Centre for Reviews and Dissemination
CURE	Clopidogrel in Unstable angina to prevent Recurrent Events trial
ECG	electrocardiogram
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
F1+2	prothrombin fragment 1 + 2
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease
IQR	interquartile range
IRR	incidence rate ratio
ITT	intention to treat
MACE	major adverse cardiovascular event
MI	myocardial infarction
NHAR	Nottingham Heart Attack Register
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NSAIDs	non-steroidal anti-inflammatory drugs
NSTE-ACS	non-ST-elevation acute coronary syndrome
NSTEMI	non-ST-elevation myocardial infarction
OR	odds ratio
$P2Y_{12}ADP$	receptor on the surface of platelets inhibited by clopidogrel
PA	platelet aggregation
PAD	peripheral artery disease
PAI	plasminogen activator inhibitor
PCI	percutaneous coronary intervention
PRAIS-UK	Prospective Registry of Acute Ischaemic Syndromes in the UK
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
RRI	relative risk increase
RRR	relative risk reduction
SD	standard deviation
SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
STEMI	ST-elevation myocardial infarction
TAT	thrombin–antithrombin complex
TIA	transient ischaemic attack
TIMI	thrombolysis in myocardial infarction
tPA	tissue-type plasminogen activator antigen
VOI	value of information
VWF	von Willebrand factor

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

Acute coronary syndrome (ACS) is a fissuring or rupturing of atheromatous plaques leading to occlusive thrombi in the arteries. Non-ST-elevation-ACS (NSTE-ACS) can be classified as unstable angina with undetectable markers but with electrocardiogram changes, or non-ST-elevation myocardial infarction (NSTEMI) where there is evidence of myocardial necrosis. Sixteen-year survival rates for men aged 50–59 years are 34% with a history of myocardial infarction (MI) and 53% with a history of angina, compared with 72% of those with no history of coronary disease. For patients with confirmed NSTE-ACS, UK guidelines recommend early treatment with antiplatelets, which are effective in preventing ischaemic vascular events in patients at increased risk. Guidance by the National Institute for Health and Clinical Excellence (NICE) in 2004 was based in part on a Technology Assessment Report undertaken by the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE), and published as a Health Technology Assessment (HTA) report (Main *et al*., 2004). The report presented the results of a systematic review assessing the clinical effectiveness and cost-effectiveness of clopidogrel in combination with aspirin for people with NSTE-ACS. Only one relevant trial was identified for inclusion in the systematic review [the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial]. For patients with NSTE-ACS at moderate to high risk of ischaemic events treated with clopidogrel, the NICE guidance recommended that it be given in combination with aspirin.

Objectives

The objective of this research project was to update the previous model, and formally assess the potential value and feasibility of further research to address the optimal duration of clopidogrel treatment using value of information (VOI) analysis and a Bayesian decision theoretic approach. In line with this we aimed to update the previous systematic review of the use of clopidogrel in combination with aspirin for patients with NSTE-ACS, investigating the optimal duration of treatment and effects of withdrawal from treatment.

Methods

We conducted a systematic review of the clinical effectiveness and cost-effectiveness literature. Ten electronic databases and internet resources were searched from 2003 to February 2007, including MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, CENTRAL and CINAHL. Randomised controlled trials (RCTs) of clopidogrel plus aspirin compared with aspirin alone were used to evaluate clinical effectiveness and safety. Inclusion criteria were broadened to include any comparator trial for duration of treatment studies, and any study design conducted in patients with NSTE-ACS, percutaneous coronary intervention (PCI), stroke, peripheral artery disease (PAD) or ST-elevation myocardial infarction (STEMI) for evidence of rebound (a reactivation of the condition or concentration of adverse events) on withdrawal of treatment. The primary outcomes for the evaluation of efficacy, safety and the duration of treatment were non-fatal MI, ischaemic heart disease (IHD) without MI, death and bleeding complications.

The systematic reviews were used to assist in updating the existing model in order to provide a more robust approach to evaluating the cost-effectiveness of alternative durations of clopidogrel. The previous work was also extended to include a formal assessment of the potential value of further research using VOI approaches. These approaches were applied to estimate the expected costs of decision uncertainty predicted by the model and the maximum value that can be placed on additional research aimed at reducing this uncertainty. The costs of decision uncertainty were quantified using the expected value of perfect information (EVPI). These were used to help identify the potential design and value of further research which could be undertaken in this area. Consideration was also given to the potential impact that the introduction of a generic version of clopidogrel may have on the VOI results.

Results

Two RCTs were included for the review of clinical effectiveness and safety. The only RCTs identified that evaluated different durations of clopidogrel treatments were conducted in patients with stroke, PAD, STEMI or PCI. Two small RCTs and one uncontrolled retrospective cohort study were identified for the review of rebound after thienopyridine withdrawal in patients with medically-treated NSTE-ACS. When the criteria were broadened, five RCTs, two observational cohorts, nine case series and 33 case reports were identified in patients post-PCI, and two case series and two case reports were identified in patients with stroke, PAD or STEMI.

The CURE trial reported that the proportion of patients experiencing cardiovascular death, MI or stroke was lower in the clopidogrel group at 30 days [relative risk (RR) 0.79; 95% confidence interval (CI) 0.67–0.92] and from 30 days to 12 months (RR 0.82; 95% CI 0.70–0.95). Overall, clopidogrel seems to be effective in reducing adverse cardiovascular events in patients with NSTE-ACS at intermediate (RR 0.86; 95% CI 0.75–0.98) and high (RR 0.77; 95% CI 0.64–0.93) risk of ischaemic events, and there is evidence that clopidogrel increases the risk of bleeding when compared with aspirin in patients with intermediate risk of ischaemic events (RR 1.44; 95% CI 1.12–1.86). A post hoc analysis indicated that the treatment effect in the first 3 months may be greater than in later periods; however, this analysis comprised non-randomised comparisons. There were no direct comparisons of the effectiveness of different durations of clopidogrel treatment in patients with NSTE-ACS. The evidence available relating to the potential rebound effect on withdrawal of clopidogrel therapy in patients with NSTE-ACS was limited and provided no conclusive evidence of its presence or absence.

In terms of the cost-effectiveness of alternative durations of clopidogrel, the updated model reinforced the conclusions from the earlier analysis. That is, a policy of 12 months of clopidogrel for patients with NSTE-ACS appears to be cost-effective both in 'average' patients (i.e. based on the average across all patient risks considered) and in the subgroup of higher-risk patients (presence of any of the following: age > 70, presence of ST depression or diabetes), compared with shorter-term durations. The incremental cost-effectiveness ratio (ICER) of 12 months' duration ranged from £13,380 to £20,661 per additional quality-adjusted life-year (QALY) across the different scenarios considered. However, for lower-risk patients (absence of any of the risk factors) treatment with clopidogrel beyond 3 months does not appear to be cost-effective. The ICER of 12 months' treatment with clopidogrel varied between £49,436 and £58,691 per QALY. These conclusions appeared robust to alternative assumptions related to whether the relative effect of clopidogrel was assumed to remain constant over time or where the treatment effect in the first 3 months was assumed to be greater than in later periods.

Estimates of EVPI were markedly higher for the combined analysis of all patients (representing an average of the risks) and for analysis of high-risk patients alone, compared with those for lower-risk patients (ranging between £48.69 million and £108.4 million at a threshold of £30,000 per QALY). It was also acknowledged that more recent changes in routine clinical practice in the UK has shifted to the extent that the CURE trial itself (or the model presented here) may no longer considered to be representative of current practice for groups at high risk, and as such the EVPI results for this group of patients may be overstated.

At a threshold of £20,000–£30,000 per QALY, total EVPI ranged between £3.27 million and £20.38 million in the lower-risk group. Given that a trial is unlikely to be able to report until after the entry of generic clopidogrel, equivalent EVPI estimates for this scenario ranged between £10.8 million and £11.9 million. The expected value of partial perfect information (EVPPI) calculations demonstrated that approximately 40–45% of this value was related to the treatment effectiveness parameters for clopidogrel (i.e. those for which an RCT would be required).

Limitations and uncertainties

Our review was limited by the lack of available data. Although one additional trial was identified that provided information on the clinical effectiveness of clopidogrel in patients with NSTE-ACS, this trial was likely to be underpowered and reported limited results. Thus the CURE trial remains the primary source of data.

No studies directly compared different durations of clopidogrel treatment, and insufficient evidence was identified to adequately assess the clinical significance of any rebound effect after withdrawal of clopidogrel in these patients. Therefore, there is

still a large degree of uncertainty surrounding both the optimal duration of clopidogrel treatment and the impact of withdrawal of clopidogrel treatment, which can only be addressed by further research.

The cost-effectiveness and VOI analyses are subject to a number of potential limitations. These relate not only to the limitations noted above pertaining to the clinical effectiveness data, representing important assumptions and parameters of the model, but also to the uncertainty surrounding a range of other factors. Firstly, the issue of risk stratification is clearly an important consideration. However, it should be noted that the pragmatic approach to risk stratification applied in the decision model (due to limited patient numbers and information available from the epidemiological data used) dichotomised the population into two separate risk categories (higher- and lower-risk patients). This meant that consideration could not be given to a wider categorisation (i.e. including a third group to represent patients at intermediate risk). Similarly, these definitions are not directly comparable with other risk stratification approaches that have been applied elsewhere. Indeed, it should be recognised that the sample of patients included in the epidemiological data set were all hospitalised for NSTE-ACS and hence are likely to be more representative of patients at intermediate to high risk using conventional classifications. Thus, the interpretation of the results in low- and high-risk groups should be seen in this context. Secondly, changes in routine clinical practice (particularly for the high-risk group) may mean that the results presented here are more reliable for the lower-risk group. Finally, the results of the VOI demonstrate considerable variation in the potential value of further research. More importantly, the EVPI results present an upper bound to further research and hence do not provide both a necessary and a sufficient condition, even if the cost of trial fell below this amount. This is because a trial will resolve only a proportion of the uncertainty and, as such, the amount of uncertainty that is likely to be resolved would have to be assessed against the cost of the trial to ensure that any further research was considered an efficient use of resources.

Conclusions

- Clopidogrel combined with aspirin reduces adverse cardiovascular events in comparison with aspirin alone in patients with NSTE-ACS, but may increase the risk of bleeding.
- The optimal duration of clopidogrel treatment in patients with NSTE-ACS is uncertain and requires further research.
- There is some evidence that a rebound effect occurs following the withdrawal of thienopyridine treatment, but its clinical significance is uncertain.
- The results of the updated decision model suggest that durations of clopidogrel treatment beyond 3 months do not appear to be cost-effective in patients at lower risk. However, for an average-risk patient (and in higher-risk patients), 12 months of treatment with clopidogrel appear to be cost-effective.
- These conclusions appeared robust to alternative assumptions related to whether the treatment effect remained constant over a 12-month period or was assumed to decline after 3 months.
- There is considerable variation in the costs of uncertainty surrounding the different scenarios and populations considered. The validity of these may also be less reliable in the higher-risk groups owing to changes in clinical practice. The results in the lower-risk group suggested that the upper bound of the value of a future trial was between £10.8 million and £11.9 million (and of this total, approximately 40–45% related to parameters for which a randomised design would be essential).

Recommendations for research

An adequately powered, well-conducted RCT that directly compares different durations of clopidogrel treatment in patients with NSTE-ACS would ideally be required to provide more robust evidence in relation to the impact of clopidogrel withdrawal. The use of an RCT would minimise possible biases associated with establishing causality with any potential rebound effect and providing robust estimates of the relative effect of alternative durations of treatment, However, the design and cost of this trial need to be evaluated carefully in relation to the VOI estimates reported here and against other uses of NHS resources. In lower-risk groups, for which shorter durations of clopidogrel appear more cost-effective, it would seem unlikely that an adequately powered RCT would be considered to provide value for money owing to the significant cost that would be required to undertake such a study and the cost of the uncertainty that such a trial might resolve.

Chapter 1
Aim of the review

The aim of this review was to update previous guidance and to establish the potential value and feasibility of future research into the optimal duration of clopidogrel treatment, by means of value of information analysis (VOI) and a Bayesian decision theoretic approach. Our intention was to build on the previous systematic review of the use of clopidogrel in combination with aspirin for patients with a non-ST-elevation acute coronary syndrome (NSTE-ACS). Additionally, we proposed to investigate both the optimal duration of treatment and the effects of withdrawal from treatment.

Chapter 2
Background

Description of health problem

Pathology

Ischaemic heart disease (IHD) refers to a wide range of conditions resulting from a reduced blood supply to the heart usually due to atherosclerosis, plaques and thrombosis. Acute coronary syndrome (ACS) is caused by a fissuring or rupturing of these atheromatous plaques leading to occlusive thrombi in the arteries.[1] Symptoms can include chest pain and pressure, tightness, or heaviness radiating to the neck, jaw, shoulders, back or arms.[2] The primary focus in this review is patients who have experienced an NSTE-ACS. NSTE-ACS can be further classified as unstable angina, characterised by undetectable markers but with electrocardiogram (ECG) changes, or non-ST-segment elevation myocardial infarction (NSTEMI); a diagnosis of NSTEMI is given only where there is evidence of myocardial necrosis.

Epidemiology and risk factors

Unstable angina and NSTEMI are major causes of morbidity and mortality worldwide.[1] Data for the UK suggest that an estimated 178,500 men and 159,500 women are newly diagnosed with angina, and that 147,000 men and 121,000 women experience a myocardial infarction (MI) each year.[3] The *Health Survey for England* (2003) reported that approximately 7.5% of men and 5% of women have experienced symptoms of a possible MI at some point in their lives.[4] The prevalence of these symptoms increase with age in men, ranging from 2.3% in the 16–24 years age group to 16.4% in the 75+ years age group. The association with age was less evident in women, with prevalence ranging from 2.7% in the 25–34 years age group to 8.5% in the 75+ years age group.[4] Risk also appears to vary by socioeconomic status, ethnic group and geographical area; factors associated with an increased risk of heart disease include smoking, alcohol consumption, unhealthy diet, lack of exercise and psychosocial factors, such as work-related stress and depression.[3–5]

The risk of death, MI or stroke for patients with ACS is considerable. Long-term prevention is important, given that after a first attack of unstable angina or NSTEMI, patients are at an increased risk of subsequent acute ischaemic events.[6] Up to 20% of people die or suffer a further infarction within the first month.[1] At 6 months, the estimated risk of dying is 5–8% following an episode of unstable angina and 12–15% following an acute MI.[7] Looking at long-term survival, one study calculated 16-year survival rates for males aged 50–59 years to be only 34% for those with a history of MI and 53% for those with a history of angina, compared with 72% of those with no history of coronary disease.[8] Patients with ACS are categorised as having high, intermediate or low risk of a further adverse event, based on their risk factors in terms of background risk (age, history of previous coronary events), current clinical presentation, electrocardiogram results and biochemical markers.[9]

Burden of disease

The economic burden of heart disease is high. The last 5 years have seen a 76% increase in the prescription of drugs to prevent and treat heart disease to nearly 50 million per quarter, with the cost of these drugs increasing fivefold to £529 million per quarter.[10] It is estimated that heart disease cost the UK £7.06 billion in 1999 in direct and indirect costs, including informal care and loss of productivity.[11]

Current service provision

For patients with confirmed NSTE-ACS, UK guidelines recommend early treatment with antiplatelets,[12] which have been shown to be effective in preventing ischaemic vascular events in patients at increased risk.[13] They work by inhibiting platelet thrombus formation and by protecting the distal tissues through inhibiting microembolisation.[12] Aspirin is the 'gold standard' antiplatelet therapy for the long-term treatment and prevention of ischaemic vascular events. It was the only antiplatelet drug recommended by the National Service Framework for Coronary Heart Disease in 2000[5] and accounts for 86% of all prescribed antiplatelet drugs.[10] It prevents

platelet aggregation by deactivating the enzyme cyclo-oxygenase (COX) which, in turn, blocks the production of thromboxane A2. Newer thienopyridine derivative drugs, which include clopidogrel, ticlopidine and prasugrel, inhibit the $P2Y_{12}$ADP receptor, which interferes with the function of the platelet membrane and inhibits both platelet aggregation and the release of platelet granule constituents.[14] Clopidogrel is said to be six times more effective than its predecessor, ticlopidine, with fewer haematological side effects.[15] Clopidogrel is the second-most commonly prescribed antiplatelet drug, accounting for nearly 10% of all antiplatelet drug prescriptions.[10]

Definition of problem

Guidance by the National Institute for Health and Clinical Excellence (NICE) in 2004 recommended that clopidogrel be taken in combination with aspirin in the management of NSTE-ACS for people at moderate to high risk of ischaemic events.[16] This guidance was based in part on a Technology Assessment Report undertaken by the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE) in 2004 and published as a Health Technology Assessment (HTA) report.[12] The report presented the results of a systematic review assessing the clinical effectiveness and cost-effectiveness of clopidogrel in combination with aspirin for people with NSTE-ACS. It also included an economic model of the cost-effectiveness of clopidogrel in combination with aspirin from a National Health Service (NHS) perspective.

Only one relevant trial was identified for inclusion in the systematic review. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, was a large multicentre, randomised, double-blind, placebo-controlled trial of 12,562 patients who presented at one of 482 hospital centres in 28 countries within 24 hours of experiencing an NSTE-ACS event. The trial compared clopidogrel (300 mg initially followed by 75 mg each day) in combination with aspirin (75–325 mg/day) with aspirin alone (75–325 mg/day).[17–22] The trial reported that the proportion of patients experiencing cardiovascular death, MI or stroke was greater in the aspirin-only group at 30 days [relative risk (RR) 0.79; 95% confidence interval (CI) 0.67–0.92) and from 30 days to 12 months (RR 0.82; 95% CI 0.70–0.95).[18] Clopidogrel also reduced the overall incidence of Q-wave MI (RR 0.60; 95% CI 0.48–0.76).[21] In terms of adverse effects, clopidogrel increased the risk of major bleeding (RR 1.38; 95% CI 1.13–1.67), but not of life-threatening bleeds.[18,21] The economic model was developed to assess the short- and long-term cost-effectiveness of 12 months' treatment with clopidogrel in addition to aspirin, compared with aspirin alone in the UK. The model estimated the short-term costs over a period of 12 months following NSTE-ACS and the long-term costs over a patient's lifetime, conditional on surviving the first 12 months. The incremental cost-effectiveness ratio (ICER) of clopidogrel plus aspirin compared with treatment with aspirin alone was estimated to be £6078 per quality-adjusted life-year (QALY) gained. At a threshold willingness to pay of £30,000 per QALY, the probability that clopidogrel in combination with aspirin was cost-effective was 0.79. As the absolute benefit of clopidogrel, relative to standard care, appeared to decline over the course of the initial 12-month period, the incremental cost-effectiveness of providing clopidogrel for a range of durations was evaluated. In addition to the base-case analysis, which evaluated a strategy of 12 months' treatment with clopidogrel, a series of sensitivity analysis were undertaken to explore the potential cost-effectiveness of shorter treatment durations, on the basis that cost-effectiveness may be sensitive to the absolute risk at different follow-up periods. This analysis comprised five strategies: lifetime treatment with aspirin, or clopidogrel as an adjunct to aspirin for 1 month, 3 months, 6 months or 12 months. While treatment with clopidogrel for 12 months appeared to remain cost-effective for the overall cohort, the provisional findings indicated that the shorter treatment durations may be more cost-effective in patients at lower risk at the start of treatment (defined as < 70 years of age, with an absence of ST depression and diabetes). For lower-risk patients, the ICER of providing treatment with clopidogrel for 6 months compared with only 3 months was approximately £30,786 per QALY. The ICER of providing clopidogrel for 12 months compared with only 6 months was £34,629 per QALY. These results indicated that the optimal duration of clopidogrel, based on cost-effectiveness considerations, appeared potentially sensitive to the risk stratification applied. However, the authors also concluded that these results should be seen as provisional for a number of reasons. Firstly, in the absence of appropriate RR data for these separate risk groups, and for the separate time periods, a common RR was applied throughout the model. In other words, the cost-effectiveness of alternative durations was evaluated by varying the baseline risk itself. Secondly, the effect of withdrawing

from clopidogrel treatment was not formally considered (aside from reverting back to the risk associated with standard care) and the possibility of a 'rebound' effect following early discontinuation of treatment with clopidogrel was not systematically evaluated.

There are a number of generic definitions of the rebound effect:

- 'A spontaneous reaction, especially a return to a previous state or condition following removal of a stimulus or cessation of treatment'[23]
- 'The return of original symptoms when treatment stops'[24]
- 'The characteristic of a drug to produce reverse effects when the effect of the drug has passed or the patient no longer responds to it'[25]
- 'A reactivation of a condition or concentration of adverse events after withdrawal of a treatment'.[26]

There is thought to be a rebound response in platelet activity with the withdrawal of aspirin,[27–32] heparin,[26,33–36] and non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors.[37] A recent systematic review reported a statistically significant (almost twofold) increase in the incidence of major adverse cardiovascular events (MACEs) in patients with ACS or those being treated for secondary prevention of coronary artery disease who did not adhere to aspirin therapy [odds ratio (OR) 1.82; 95% CI 1.52–2.18; $p < 0.00001$; 3 studies].[32] Interestingly, the mean time from discontinuation of aspirin and the MACEs was 10.66 days (95% CI 10.25–11.07), a similar time to the half-life of platelets.[32] One study reported significant median increases in the production of 12-L-hydroxy-5,8,10-hepatadecatrienoic acid (which can be indicative of increased thromboxane A2) in angina patients 1 week (from 40 to 240 g/750×10^6 platelets; $p < 0.001$) and 2 weeks (to 390 g/750×10^6 platelets) after withdrawal of aspirin.[29] Withdrawal from aspirin has also reportedly increased the risk of stroke or transient ischaemic attack (TIA) (OR 3.4; 95% CI 1.08–10.63; $p < 0.05$)[30] and lower limb ischaemia in patients with stable peripheral artery disease (PAD).[31]

There is some evidence from biochemical markers for rebound platelet activity after withdrawal from heparin,[33,34,36] and NSAIDs and COX-2 inhibitors.[37] This response tended to occur within hours of discontinuing heparin,[33,34,36] and was still evident at least 14 days after withdrawal of NSAIDs and COX-2 inhibitors.[37]

It is unclear whether a similar rebound response occurs after clopidogrel withdrawal, and if so, what the time lapse would be from withdrawal to maximum platelet activity. The authors of the previous HTA report[12] recommended a prospective trial that would randomise patients to various durations of clopidogrel therapy to estimate its optimum duration of use for patients with NSTE-ACS. Such a trial would also confirm the existence or not of a rebound phenomenon in patients following withdrawal of clopidogrel. However, no formal consideration was made as to the potential value and/or feasibility of conducting such a trial. The present work was undertaken, therefore, to update the previous model and to formally assess the potential value and feasibility of further research to address the optimal duration of clopidogrel treatment.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

Search strategy

The first searches were carried out to retrieve systematic reviews, randomised controlled trials (RCTs) and economic evaluations of clopidogrel and prasugrel. A date limit of entry on to the databases of 2003 onwards was applied to the searches for clopidogrel where possible, as these searches updated a previous published systematic review.[12] No date limits were applied to the searches for prasugrel, as this was developed more recently.

A second set of searches was carried out to retrieve papers relating to the withdrawal of clopidogrel. No language or date restrictions were applied to any of these searches. The following databases were searched; full details of all the searches are contained in Appendix 1.

Databases of systematic review

- Cochrane Database of Systematic Reviews (CDSR).
- Database of Abstracts of Reviews of Effects (DARE).
- HTA Database.

Health-related bibliographic databases

- CENTRAL.
- Cumulative Index to Nursing & Allied Health Literature (CINAHL).
- EMBASE.
- MEDLINE.
- MEDLINE In-Process & Other Non-Indexed Citations.

Databases of economic evaluations

- NHS Economic Evaluation Database (NHS EED).
- Health Economic Evaluations Database (HEED).

Shortly after the submission of this report to the HTA in December 2007, a retrospective cohort study was published; data from this study were added subsequently.[38] The literature searches were not updated.

Inclusion and exclusion criteria

The clinical review had three main aims: to identify and update the data relating to the efficacy and safety of clopidogrel; to investigate the optimal duration of clopidogrel treatment; and to examine the evidence relating to a possible rebound effect associated with the withdrawal of clopidogrel. Inclusion criteria were developed a priori for each part of the review question.

Study designs

Only RCTs were used to evaluate the efficacy and safety of clopidogrel. When investigating the duration of treatment, this was broadened to include any comparator trial that directly compared the outcomes of patients receiving different durations of clopidogrel treatment. This criterion was broadened still further to include any study design when seeking evidence of the rebound effect, as it was assumed that much of the evidence would be presented as case studies.

Interventions and comparators

For the evaluation of efficacy, safety and duration of treatment of clopidogrel, studies had to administer the drug in combination with aspirin, reflecting its use in clinical practice in the NSTE-ACS population, and compare this with placebo combined with aspirin or aspirin alone. When evaluating the evidence for the potential rebound effect after withdrawal, studies evaluating any thienopyridine (clopidogrel, ticlopidine or prasugrel), with or without aspirin, were included.

Population

For the evaluation of efficacy, safety and duration of treatment of clopidogrel, studies had to recruit patients with NSTE-ACS, namely unstable angina or NSTEMI. Where no studies evaluating different durations of clopidogrel in the preferred population were found, the search was broadened to patients having undergone a percutaneous coronary intervention (PCI), stroke, PAD and ST-elevation myocardial infarction (STEMI). For the

assessment of the potential rebound effect, patients with NSTE-ACS, PCI, stroke, PAD and STEMI were eligible.

Outcomes

The primary outcomes for the evaluation of efficacy, safety and duration of treatment were non-fatal MI, IHD without MI, death and bleeding complications. Secondary outcomes included refractory ischaemia, severe ischaemia, heart failure, revascularisation, unstable angina and other vascular or adverse events. When evaluating the potential rebound effect, the main outcomes were changes in biomarkers. A conservative definition of rebound was used, i.e. platelet biomarkers returned to at least their original levels following discontinuation of treatment. The occurrence/rates of adverse events post-withdrawal were also included.

Review process

Titles and abstracts were screened by two independent reviewers for potentially relevant studies (JB and CC). Disagreements regarding which studies should be retrieved as full papers were resolved by consensus. Where resolution could not be achieved, the paper was retrieved for detailed assessment. The inclusion criteria were applied to full papers by two independent reviewers (JB and CC). Data were extracted by one reviewer and checked for accuracy by a second (JB and CC). Disagreements at final stage screening and data extraction were resolved by discussion, or where consensus could not be reached, by consultation with a third reviewer (NW).

Quality assessment strategy

RCTs were assessed in terms of randomisation, allocation concealment, blinding, the reporting of withdrawals, reporting of a sample size calculation and the use of an intention-to-treat (ITT) analysis. RCTs in which patients were randomised to receive different types of stent and went on to receive the same thienopyridine therapy were treated as case series and did not undergo this assessment. The quality of included RCTs was assessed by two independent reviewers (JB and CC); all disagreements were resolved by consensus.

Data analysis

Given the clinical heterogeneity in relation to the study designs, populations recruited, medication regimens prescribed and outcome measures reported, the results of the included studies are summarised in tables and discussed in a narrative.

Results of the clinical evaluation

Quantity of research available

Two RCTs, across seven publications, were included for the review of clinical effectiveness and safety;[17–22,39] six of these publications were related to the CURE trial.[17–22]

No RCTs evaluating different durations of clopidogrel treatments were identified in patients with NSTE-ACS. When the search was broadened to include patients with PCI, stroke, PAD and STEMI, four RCTs were identified, across seven publications.[40–46]

The searches for evidence of rebound after thienopyridine withdrawal identified two small RCTs published in Russian and reported across three publications,[47–49] that assessed the changes in biomarkers following clopidogrel or ticlopidine initiation and withdrawal for patients with NSTE-ACS. An additional study, a retrospective cohort of 3137 patients,[38] was published after completion of this report; the report has been updated to incorporate this new information. No further studies were identified in patients with medically-treated NSTE-ACS. When the criteria were broadened to include patients with PCI, stroke, PAD and STEMI, most of the retrieved data were for patients who had undergone PCI. Of these: five RCTs,[50–54] two observational cohorts,[38,55] nine case series,[56–64] and 33 case reports across 17 publications[65–81] investigated clopidogrel and ticlopidine therapy. Only two case series[82,83] and two case reports in a single publication[84] were identified for patients who had not undergone PCI.

Quality of research available

Table 1 shows the results for each criterion of the assessment of the quality for each included RCT. Two RCTs were included in the efficacy and safety section. The CURE trial was a good-quality RCT, failing only on the criterion relating to the reporting of withdrawals; there was some indication from the publications that withdrawals did occur during the course of the trial.[17–22] The second RCT did not blind patients or carers, but did report an appropriate method of randomisation and blinding of outcome assessors.[39]

TABLE 1 *Results of quality assessment of included RCTs; each criterion was described as 'Yes' (reported and considered adequate), 'No' (reported but considered inadequate) or 'Unclear' (not reported)*

Study	Randomisation	Allocation concealment	Patients blinded	Care givers blinded	Outcome assessors blinded	Sample size calculation	Withdrawals	ITT analysis used
Efficacy and safety								
CURE trial[17–22]	Yes	Yes	Yes	Described as double-blind with matching placebo		Yes	Unclear	Yes
Vavuranakis (2006)[39]	Yes	Unclear	No	No	Yes	Yes	Yes	Unclear
Duration of clopidogrel treatment								
Akbulut (2004)[41]	Unclear	Unclear	Unclear	Unclear	Yes for angiography only	No	Unclear	Yes
Bernardi (2007)[42]	Yes	Unclear	No	No	No	Yes	Yes	No
Pekdemir (2003)[40]	Yes	Unclear	No	No	Yes	No	Yes	Yes
CREDO trial (2002)[43–45]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Rebound								
Berger (1999)[54]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Yes	Yes
Bertrand (2000)[53]	Unclear	Yes	Yes	Described as double-blind with double-dummy placebo		Yes	Yes	Yes
Biondi-Zoccai (2006)[52]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Yes	No
Juergens (2004)[51]	Unclear	Unclear	No	No	No	Yes	Yes	Yes
Mueller (2003)[50]	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Yes
Averkov (2003);[47] Slavina (2003/2005)[48,49]	Published in Russian							

ITT, intention-to-treat.

The quality of the RCTs included in the duration section of the review was variable, with one good-quality RCT being the only study to have reported adequate allocation concealment and blinding of patients.[43–45]

The quality of the RCTs included in the rebound section of the review was mainly low. The one RCT that appeared to be of good quality did not report the method of randomisation used.[53] The largest and most directly relevant study was a retrospective uncontrolled cohort study.[38] It utilised data from all eligible patients over an 18-month period, but the cohort was obtained from Veterans Affairs hospital discharges, consisting predominantly of male veterans (99%; mean age 66 years). Data were abstracted from electronic and paper medical records using standardised forms and then entered into a database. The duration of clopidogrel use was calculated from the day of discharge to the final day supplied at the last refill date. Data on adherence to statins were used as a surrogate for adherence to clopidogrel treatment. The remaining studies included in the rebound section were primarily case series and case reports.

Assessment of the clinical evidence

Effectiveness and safety

Two RCTs evaluated the effectiveness of clopidogrel in patients with NSTE-ACS: the CURE trial,[17–22] and a trial by Vavuranakis *et al*. (2006).[39]

The CURE trial

The CURE trial,[17–22] is discussed extensively in the previous HTA report.[12] Briefly, the CURE trial was a multicentre, double-blinded RCT that recruited 12,562 patients who presented within 24 hours of experiencing an NSTE-ACS event. The trial compared clopidogrel (300 mg initially followed by 75 mg daily) in combination with aspirin (75–325 mg/day), with placebo plus aspirin (75–325 mg/day). The dose of aspirin prescribed was < 100 mg in 42%, 101–199 mg in 25% and > 200 mg in 33% of patients.[17] *Table 2* provides an overview of the published outcomes for the CURE trial. The CURE trial reported that the proportion of patients experiencing cardiovascular death, MI or stroke was greater in the aspirin-only group at 30 days (RR 0.79; 95% CI 0.67–0.92) and from 30 days to 12 months (RR 0.82; 95% CI 0.70–0.95).

In summary, the previous HTA report concluded that the results of the CURE trial indicate that clopidogrel in combination with aspirin was significantly more effective than placebo combined with aspirin, and this benefit was related largely to a reduction in Q-wave MI. The risk of cardiovascular death, non-fatal MI or stroke was reduced with up to 3 months of clopidogrel treatment, with a further small benefit over the remaining 9 months of chronic treatment. There was no statistically significant benefit in relation to mortality.

A further analysis of the originally reported CURE data was presented in the recent Scottish Intercollegiate Guidelines Network (SIGN) guidelines (No. 93).[85] The results are presented in *Table 3*, along with 95% CIs calculated by the review team. These results indicate that the event rate is statistically significantly lower in the clopidogrel group compared with the placebo group for the periods 0–1 month, 1–3 months and 0–12 months, but not for the periods 3–6 months, 6–9 months and 9–12 months. It should be noted that this was a post hoc, exploratory analysis and comprises non-randomised comparisons. Patients were randomised to treatment at time 0, but not at the start of later time periods; differential selection pressures may well have acted upon the treatment groups so that they were not comparable at 1, 3, 6 or 9 months.

Results of the CURE trial, stratified by the thrombolysis in myocardial infarction (TIMI) risk score, have been published.[19,86] Patients were categorised as low risk (score of 0–2), intermediate risk (score of 3–4) or high risk (score of 5–7); results reported are shown in *Table 4* (with RRs and 95% CIs for the composite outcome cardiovascular death, MI or stroke calculated by the reviewers using the reported rates of events and total number of patients).[19] The results show that there was still a significant reduction in the risk of the composite outcome cardiovascular death, MI or stroke in patients with an intermediate risk of ACS, but a significant increase in the risk of major bleeding.[19]

Vavuranakis *et al*. (2006)[39]

The second RCT, conducted by Vavuranakis *et al*.[39] was not available for the previous HTA report.[12] Vavuranakis and colleagues reported changes in biomarkers, the incidence of MACEs (defined as non-fatal MI, recurrent ischaemia and cardiovascular-related death), the number of patients requiring hospitalisation for ACS and the number dying as a result of cardiovascular causes in 86 patients with NSTE-ACS. Of these, 43 patients

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TABLE 2 *Results available from publications relating to CURE trial (clopidogrel, n = 6259; placebo, n = 6303),*[17–22] *n (%)*

	Time point									
	0–24 hours		0–7 days		0–30 days		31 days to 1 year		0 days to 1 year	
Outcome	Clopidogrel	Placebo	Clopidogrel	Placebo	Clopidogrel	Placebo	Clopidogrel	Placebo	Clopidogrel	Placebo
MI, stroke, cardiovascular death	27 (0.4)	34 (0.5)	131 (2.1)[a]	158 (2.5)[a]	270 (4.3)	343 (5.4)	326 (5.2)[a]	397 (6.3)[a]	582 (9.3)	719 (11.4)
MI, stroke, cardiovascular death, refractory ischaemia	53 (0.9)	70 (1.1)	219 (3.5)[a]	265 (4.2)[a]	480 (7.7)	580 (9.2)	601 (9.6)[a]	668 (10.6)[a]	1035 (16.5)	1187 (18.8)
MI, stroke, cardiovascular death, severe ischaemia	89 (1.4)	135 (2.1)	325 (5.2)[a]	422 (6.7)[a]	602 (9.6)	740 (11.7)	–	–	–	–
MI: fatal/non-fatal unspecified	–	–	–	–	–	–	–	–	324 (5.2)	419 (6.6)
Refractory ischaemia	–	–	–	–	232 (3.7)[a]	271 (4.3)[a]	232 (3.7)[a]	340 (5.4)[a]	544 (8.7)	587 (9.3)
Severe ischaemia	–	–	–	–	238 (3.8)[a]	315 (5.0)[a]	–	–	–	–
Unstable angina: rehospitalisation	–	–	–	–	–	–	314 (5.0)	318 (5.0)	–	–
Stroke: fatal/non-fatal unspecified	–	–	–	–	–	–	–	–	75 (1.2)	87 (1.4)
Mortality: cardiovascular	–	–	–	–	–	–	–	–	318 (5.1)	345 (5.5)
Mortality: non-cardiovascular	–	–	–	–	–	–	–	–	41 (0.7)	45 (0.7)
Bleeding: life threatening	–	–	30 (0.5)[a]	28 (0.4)[a]	80 (1.3)[a]	61[a] (1.0)	57 (0.9)[a]	52 (0.8)[a]	135 (2.2)	112 (1.8)
Bleeding: major	–	–	54 (0.9)[a]	46 (0.7)[a]	126 (2.0)[a]	97 (1.5)[a]	110 (1.8)[a]	74 (1.2)[a]	231 (3.7)	169 (2.7)
Bleeding: life threatening/major	5 (0.1)	6 (0.1)	–	–	–	–	–	–	–	–
Bleeding: fatal	–	–	–	–	–	–	–	–	11 (0.2)	15 (0.2)
Bleeding: requiring surgery	–	–	–	–	–	–	–	–	45 (0.7)	43 (0.7)
Bleeding: causing haemorrhagic stroke	–	–	–	–	–	–	–	–	7 (0.1)	5 (0.1)
Bleeding: requiring inotropics	–	–	–	–	–	–	–	–	34 (0.5)	34 (0.5)

continued

TABLE 2 *Results available from publications relating to CURE trial (clopidogrel, n = 6259; placebo, n = 6303),*[17–22] *n (%) (continued)*

	Time point									
	0–24 hours		0–7 days		0–30 days		31 days to 1 year		0 days to 1 year	
Outcome	**Clopidogrel**	**Placebo**	**Clopidogrel**	**Placebo**	**Clopidogrel**	**Placebo**	**Clopidogrel**	**Placebo**	**Clopidogrel**	**Placebo**
Bleeding: requiring transfusion ≥ 2 units	–	–	–	–	–	–	–	–	177 (2.8)	137 (2.2)
Bleeding: requiring transfusion ≥ 4 units	–	–	–	–	–	–	–	–	74 (1.2)	60 (1.0)
Bleeding: major non-life threatening	–	–	–	–	–	–	–	–	96 (1.5)	57 (0.9)
Bleeding: gastrointestinal	–	–	–	–	–	–	–	–	83 (1.3)	47 (0.8)
Bleeding: retroperitoneal	–	–	–	–	–	–	–	–	8 (0.1)	5 (0.1)
Bleeding: urinary	–	–	–	–	–	–	–	–	4 (0.1)	5 (0.1)
Bleeding: arterial puncture	–	–	–	–	–	–	–	–	36 (0.5)	22 ()
Bleeding: surgical site	–	–	–	–	–	–	–	–	56 (0.9)	53 (0.8)
Major bleeding: TIMI	1 (0.1)	0	12 (0.2)[a]	11 (0.2)[a]	36 (0.6)[a]	36 (0.6)[a]	33 (0.5)[a]	37 (0.6)[a]	68 (1.1)	73 (1.2)
Major bleeding: GUSTO	0	2 (0.05)	13 (0.2)[a]	13 (0.2)[a]	44 (0.7)[a]	36 (0.6)[a]	35 (0.6)[a]	35 (0.6)[a]	78 (1.3)	70 (1.1)
Minor bleeding	–	–	–	–	–	–	–	–	322 (5.1)	153 (2.4)

–, data not available in published reports; GUSTO, global utilisation of streptokinase and tPA for occluded coronary arteries; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.
a Extrapolated from graph.

TABLE 3 *Incidence, and absolute and relative risk reductions for composite outcome of cardiovascular death, non-fatal MI or stroke, using data from the CURE trial as reported in the SIGN guidelines*[85]

Time interval, months	Clopidogrel, %	Placebo, %	ARR, % (95% CI)	RRR, % (95% CI)	NNT, per interval (95% CI)	NNT, per month
0–1	4.35	5.54	1.19 (0.43–1.95)	21.5 (8.39–32.76)	84 (51–231)	84
> 1–3	1.84	2.67	0.83 (0.30–1.37)	31.2 (12.47–45.88)	120 (73–333)	240
> 3–6	1.73	1.79	0.06 (–0.42 to 0.54)	3.2 (–27.01 to 26.28)	1725 (186–∞)	5174
> 6–9	1.27	1.36	0.09 (–0.37 to 0.56)	6.9 (–32.22 to 34.50)	1057 (179.59–∞)	3171
> 9–12	1.09	1.28	0.19 (–0.32 to 0.69)	14.7 (–30.69 to 44.282)	534 (144.72–∞)	1601
0–12	9.30	11.41	2.11 (1.04–3.17)	18.5 (9.59–26.50)	47 (32–96)	508

ARR, absolute risk reduction; NNT, number needed to treat; RRR, relative risk reduction.

TABLE 4 *Risk of cardiovascular death, MI or stroke, and bleeding, in patients stratified by risk as reported in the CURE trial*[19]

	Low risk (TIMI 0–2)		Intermediate risk (TIMI 3–4)		High risk (TIMI 5–7)	
	Clopidogrel (n = 1602)	Placebo (n = 1674)	Clopidogrel (n = 3671)	Placebo (n = 3626)	Clopidogrel (n = 986)	Placebo (n = 1003)
Cardiovascular death, MI or stroke	4.1%	5.4%	9.8%	11.4%	15.9%	20.7%
	$p < 0.04$		$p < 0.03$		$p < 0.004$	
	RR 0.77 (95% CI 0.56–1.04)[a]		RR 0.86 (95% CI 0.75–0.98)[a]		RR 0.77 (95% CI 0.64, 0.93)[a]	
	NNT = 63		NNT = 63		NNT = 21	
Major bleeding	2.6%	1.9%	3.8%	2.6%	5.1%	4.1%
	RR 1.34 (95% CI 0.85–2.11)		RR 1.44 (95% CI 1.12–1.86)		RR 1.24 (95% CI 0.83–1.86)	
	$p = 0.21$		$p = 0.005$		$p = 0.30$	

MI, myocardial infarction; NNT, number needed to treat; RR, relative risk; TIMI, thrombolysis in myocardial infarction.
a Calculated by the reviewers using estimated numbers of patients calculated from the rates of events and total number of patients as reported in the publication.[19]

received a 300 mg loading dose of clopidogrel followed by 75 mg daily for 36 weeks plus 325 mg aspirin for 1 week followed by 100 mg aspirin. The placebo group of 43 patients received aspirin alone at the same regimen as those receiving clopidogrel. *Table 5* shows the incidence of MACEs over a 1-year period and *Table 6* reports the cumulative incidence; these data were extracted from the Kaplan–Meier graph presented in the published paper. *Table 7* provides the number of patients requiring hospitalisation due to ACS and the number who died from cardiovascular causes; the time point at which the latter data were measured is uncertain.[39] This trial showed that treatment with clopidogrel reduced the incidence of MACEs and the proportion of patients requiring hospital admission for ACS over the 12-month period. Using data extracted, the RR for MACEs was 0.56 (95% CI 0.28–1.13) and the relative risk reduction (RRR) was 44% (95% CI –13.13 to 72.03); the RR for requiring hospitalisation was 0.67 (95% CI 0.37–1.21) and the RRR was 33% (95% CI –20.96–63.26). None of these results were statistically significant, possibly indicating that the study was underpowered. The hazard ratio calculated from the Kaplan–Meier graph is 0.79 (95% CI 0.31–2.04).

Duration of clopidogrel therapy

No studies that directly compared the effect of different durations of clopidogrel therapy for patients with NSTE-ACS were identified. Yusuf *et al.*[18] used the results from the CURE trial to assess the early and late effects of clopidogrel use. Results from Yusuf *et al.* were reported in the original HTA report,[12] but do not compare different durations of clopidogrel use.

TABLE 5 *Number of patients experiencing a MACE over a 12-month period (n = 43 per treatment arm) (extrapolated from a Kaplan–Meier graph)[39]*

	Time point								
	2 months	**3 months**	**5 months**	**6 months**	**7.5 months**	**8 months**	**9 months**	**11 months**	**12 months**
Clopidogrel	1	0	0	1	0	2	4	0	1
Placebo	1	1	1	1	3	1	2	3	3

TABLE 6 *Cumulative number of patients (%) experiencing a MACE over a 12-month period (extrapolated from a Kaplan–Meier graph)[39]*

	Time point								
	2 months	**3 months**	**5 months**	**6 months**	**7.5 months**	**8 months**	**9 months**	**11 months**	**12 months**
Clopidogrel	1 (2.3)	1 (2.3)	1 (2.3)	2 (4.7)	2 (4.7)	4 (9.3)	8 (18.6)	8 (18.6)	9 (20.9)
Placebo	1 (2.3)	2 (4.7)	3 (7.0)	4 (9.3)	7 (16.3)	8 (18.6)	10 (23.3)	13 (30.2)	16 (37.2)

TABLE 7 *Number (%) of patients requiring hospitalisation for ACS or who died from cardiovascular causes (time point unclear)[39]*

Outcome	Clopidogrel	Placebo
Requiring hospitalisation	12 (28)	18 (42)
Cardiovascular mortality	1 (2)	1 (2)

When the inclusion criteria were widened to include participants with STEMI, PAD, stroke and PCI, four RCTs across six publications were identified (*Table 8*).[40–45] These RCTs compared the effect of different durations of clopidogrel therapy following PCI, with three studies comparing 1 month with 6 months of therapy, and one study comparing 1 month with 12 months of therapy. Two of these studies[42,43-45] reported statistically significant reductions in ischaemic events for participants taking clopidogrel for longer periods following PCI, and a third[41] reported significantly fewer incidents of restenosis and the need for revascularisation with longer durations of clopidogrel treatment. These studies indicate that a longer duration of antiplatelet therapy may be beneficial in patients after stent implantation. The fourth study[40] reported no significant differences between 1 and 6 months of clopidogrel therapy post-stent implantation.

Rebound in patients with NSTE-ACS

Two small RCTs reported across three publications[47–49] assessed the changes in biomarkers following clopidogrel or ticlopidine initiation and withdrawal for patients with NSTE-ACS. Patients were prescribed clopidogrel 300 mg on day 1 then 75 mg a day for a further 6 days ($n = 10$), or ticlopidine 500 mg twice daily for 2 days then 250 mg twice daily for a further 5 days ($n = 19$). These groups were compared with patients who were not prescribed clopidogrel ($n = 9$) or ticlopidine ($n = 18$). To investigate the potential for rebound, only data from the treatment arms were extracted. Adenosine diphosphate (ADP)-induced platelet aggregation (PA), spontaneous PA, prothrombin fragment 1+2 (F1+2), thrombin–antithrombin complex (TAT), von Willebrand factor (VWF), fibrinogen, tissue-type plasminogen activator antigen (tPA), plasminogen activator inhibitor (PAI) activity, D-dimer, and platelet count (*Table 9*) were measured at baseline, 7 days and 14 days (1 week after withdrawal).

The trial reported no significant difference in results between the three time points and does not provide any evidence in support of rebound effects following clopidogrel withdrawal.[47–49] However, this was a very small trial with only 10 patients taking

TABLE 8 *Number of patients experiencing adverse cardiovascular events, mortality or revascularisation post-PCI (p-value where statistical significance was reported)*

Study	Pekdemir (2003)[40]	Akbulut (2004)[41]	Bernardi (2007)[42]	CREDO trial[43–46]
Clopidogrel dose	300 mg loading dose; 75 mg daily	75 mg starting at least 3 days before procedure	300 mg loading dose; appears to be 75 mg daily	300 mg loading dose; 75 mg daily
Duration of treatment	1 month ($n = 140$); 6 months ($n = 138$)	4 weeks ($n = 39$); 24 weeks ($n = 39$)	30 days ($n = 502$); 180 days ($n = 502$)	4 weeks ($n = 1053$); 12 months ($n = 1063$)
Follow-up	6 months	24 weeks	180 days	1 year
All-cause death	2 vs 1	Not reported	12 vs 4 ($p < 0.05$)	24 vs 18
Cardiovascular death	Not reported	0 vs 0	8 vs 4	Not reported
MI	3 vs 3	3 vs 1	13 vs 7	90 vs 70
Stroke	Not reported	0 vs 0	1 vs 0	12 vs 9
Death, MI, stroke	Not reported	Not reported	23 vs 8 ($p < 0.05$)	122 vs 89 ($p < 0.05$)
Revascularisation	16 vs 17	4 vs 1 ($p < 0.05$)	26 vs 18	223 vs 225
MACE	18 vs 19	Not reported	40 vs 25	Not reported
Stent occlusion	8 vs 5	Not reported	Not reported	Not reported
Restenosis	29 vs 33	4 vs 2 ($p < 0.05$)	Not reported	Not reported

MACE, major adverse cardiovascular event; MI, myocardial infarction.

TABLE 9 *Study assessing biomarkers following discontinuation of clopidogrel and ticlopidine [mean (SD)]* [47–49]

Outcome measure	Baseline	7 days	14 days
Clopidogrel			
Levels of F1+2[47]	1.57 (0.4)	1.52 (0.47)	1.4 (0.32)
TAT (ng/ml)[47]	3.19 (1.0)	3.18 (1.4)	2.89 (0.87)
VWF (%)[47,49]	158 (39)	141 (30)	145 (30)
Fibrinogen (g/l)[47]	3.51 (0.76)	3.46 (0.76)	4.59 (1.7)
(tPA) (ng/m)[48,49]	15.8 (9.8)	26.5 (3.8)	24.6 (3.2)
PAI activity (U/l)[48]	23.8 (9.1)	21.3 (5.5)	20.6 (5.1)
D-dimer (ng/ml)[48,49]	761 (284)	970 (378)	806 (177)
Platelet count (fl)[49]	Not reported	9.6 (not reported)	9.4 (not reported)
Ticlopidine			
F1+2[47]	1.42 (0.47)	1.48 (0.43)	1.42 (0.38)
TAT (ng/ml)[47,49]	3.12 (0.8)	3.03 (1.0)	2.77 (0.92)
VWF (%)[47,49]	162 (20)	155 (20)	144 (22)
Fibrinogen (g/l)[47,49]	2.94 (0.79)	3.44 (0.9)	3.16 (0.78)
tPA (ng/ml)[48]	15.3 (5.5)	17.0 (5.9)	17.2 (4.5)
PAI activity (U/l)[48,49]	20.8 (11.4)	13.6 (7.2)	10.0 (10.7)
D-dimer (ng/ml)[48,49]	595 (267)	515 (254)	435 (179)

F1+2, prothrombin fragment 1+2; fl, femtolitre; PAI, plasminogen activator inhibitor; TAT, thrombin–antithrombin complex; tPA, tissue-type plasminogen activator antigen; VWF, von Willebrand factor.

clopidogrel and 19 patients taking ticlopidine. In addition, these therapies were prescribed for only 1 week, which is not comparable to the use of clopidogrel or ticlopidine in patients with NSTE-ACS in clinical practice.

A retrospective cohort of 3137 patients (1568 medical and 1569 PCI patients over an 18-month period) with acute MI, unstable angina or other evidence of ACS, who were discharged on clopidogrel therapy and did not experience an adverse event while taking clopidogrel, assessed the incidence, timing and clustering of mortality and acute MI after stopping clopidogrel treatment, and the association between the duration of clopidogrel treatment and event rates after cessation of treatment.[38] The median duration of follow-up for the cohort of medical patients was 155 days [interquartile range (IQR) 98; 254 days]. Of the 1568 medical patients, 268 (17.1%) suffered an acute MI or died, with 163 (60.8%) of these incidents occurring within the first 90 days post withdrawal of clopidogrel. This translates into an incidence rate per 1000 patient days of follow-up of 1.31 (95% CI 1.12–1.53) for the first 90 days, 0.69 (95% CI 0.53–0.89) for 91–180 days and 0.64 (95% CI 0.44–0.94) for 181–270 days' follow-up. Using multivariate analysis, a significantly increased risk of adverse events was demonstrated in the 0–90 day post-withdrawal period compared with the 91–180 day period [incidence rate ratio (IRR) 1.98; 95% CI 1.46–2.69). The finding was similar when only acute MI was considered (IRR 1.98; 95% CI 1.46–2.69). In addition, the increased risk for acute MI and all-cause mortality in the 0–90 day period was found for all durations of clopidogrel after hospital discharge: 3 months or less (IRR 2.13; 95% CI 1.36–3.32), 6 months or less (IRR 2.20; 95% CI 1.49–3.26), 9 months or less (IRR 2.00; 95% CI 1.41–2.85) or over 9 months (IRR 1.79; 95% CI 0.96–3.34).

Rebound in other patient populations

For completeness, studies of rebound with clopidogrel were sought for populations other than those with NSTE-ACS, namely patients with PAD, stroke, post-PCI and MI. A detailed summary of the findings from these studies is provided in Appendix 2. In brief, these studies provide no evidence to suggest that a rebound effect is associated with clopidogrel withdrawal. There is some indication that long-term antiplatelet therapy is required in patients fitted with a coronary stent.

Summary

Overall, there is evidence that clopidogrel is effective in reducing adverse cardiovascular events in patients with NSTE-ACS; this benefit may be most evident in the first 3 months. There is some evidence that there is an increased risk of bleeding with clopidogrel when compared with aspirin. When stratified by the TIMI risk score, patients of intermediate risk had a significant reduction in the risk of cardiovascular death, MI or stroke, but a significant increase in the risk of major bleeding.

There were no direct comparisons of the effectiveness of different durations of clopidogrel treatment in patients with NSTE-ACS. The evidence available relating to the potential rebound effect on withdrawal of clopidogrel therapy in patients with NSTE-ACS was limited: two very small RCTs provide no suggestion of rebound effects following either clopidogrel or ticlopidine withdrawal. Results from one small case series, measuring platelet biomarkers after withdrawal of clopidogrel[56] in patients with PCI, showed significant increases in some biomarkers 1 month post-withdrawal, but that in itself is not evidence of rebound. The strongest evidence came from a retrospective cohort study indicating that the risk of acute MI or mortality was higher in the first 90 days following withdrawal of clopidogrel than in later periods. This finding held for all durations of clopidogrel therapy and for both medically-treated and PCI-treated patients.

Discussion of the clinical evaluation

Effectiveness and safety

Since the previous HTA report,[12] only one RCT has been conducted in the patients with NSTE-ACS for whom data are available.[39] This RCT recruited only 43 patients per treatment arm and therefore was likely to be underpowered. Furthermore, it reported a limited number of outcomes, and results were primarily extrapolated from a Kaplan–Meier graph. Data from this trial show that the rate of non-fatal MI, recurrent ischaemia and cardiovascular-related death over a 12-month period was nearly twice as high for patients on placebo (16 patients; 37.2%) as for patients on clopidogrel (9 patients; 20.9%). However, the CURE trial is still the primary source of data in the NSTE-ACS population. Results from the CURE trial show clopidogrel to be significantly more effective than placebo at reducing the risk of the composite outcome, cardiovascular death, non-fatal MI or stroke, for a treatment duration of 1 month (and possibly treatment durations of up to 3 months) and across the whole 12-month follow-up period.

Previous systematic reviews evaluating clopidogrel included trials conducted in various patient populations: patients with ischaemic stroke, MI or symptomatic atherosclerotic PAD;[87–92] stable coronary heart disease (CHD);[93] planned PCI or coronary angiogram;[43–46] documented MI, with or without ST elevation;[94] acute STEMI, left bundle branch block or ST depression;[95,96] and multiple atherothrombotic risk factors or documented coronary, cerebrovascular or symptomatic PAD disease.[97–99] In our review of clopidogrel plus aspirin in NSTE-ACS, these trials did not meet our inclusion criteria, and the results of these other systematic reviews are not comparable with those of our review. Given that there are so few data to inform our review, it might be argued that a broader range of trials ought to be drawn upon. However, a comparison between these other studies and the CURE trial found that, in addition to being conducted in non-ACS populations, the trials were not comparable with the CURE trial in terms of study size, treatment regimen, time to follow-up and outcomes reported. Where similar outcomes were measured across the trials, results varied greatly in magnitude and sometimes direction of effect. This reflects the clinical heterogeneity between the trials, and demonstrates that results from these populations are not generalisable to the NSTE-ACS population. The details of these trials and their results, on which this comparison was made, are provided in Appendix 3.

Duration of treatment and rebound

There were no studies that directly compared different durations of clopidogrel treatment. There was some evidence from the CURE trial that benefits of clopidogrel treatment, such as a reduction in MI, stroke and death, may be most apparent within the first 3 months of treatment. An exhaustive search for evidence to support the suggestion that clopidogrel withdrawal is associated with a rebound effect in patients with NSTE-ACS yielded few studies. One retrospective cohort study reported an increased risk of adverse events within the first 90 days post withdrawal of clopidogrel. However, the cohort was obtained from Veterans Affairs hospital discharges, consisting predominantly of male veterans (99%; mean age 66 years), and the generalisability of these results to a wider population is uncertain.[38] Furthermore, even if reliable, these data cannot confirm whether the risk of acute MI or mortality following clopidogrel withdrawal is higher or lower than that in patients not treated with clopidogrel. Much of the evidence available showed that, as expected, the time lag between withdrawal and increases in biomarkers reflects the lifespan of platelets, which is approximately 10 days.[100] This would reflect the

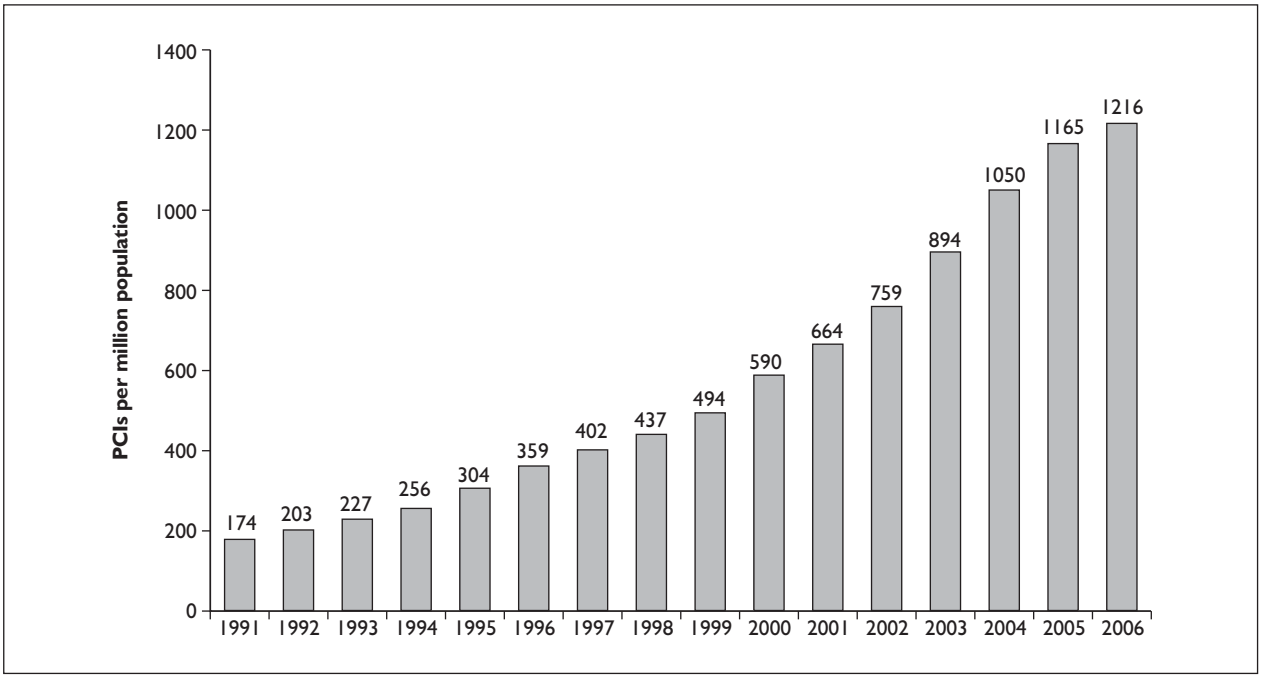

FIGURE 1 *Increase in the number of PCIs conducted per million population between 1991 and 2006, using data from the British Cardiac Intervention Society audit reports.*[101]

expected physiological process rather than any adverse effect of clopidogrel therapy.

Changes in service provision

Since the CURE trial was conducted, there has been a substantial increase in the use of PCI in the UK. This rise in PCI use over 16 years is demonstrated in *Figure 1*, constructed from data from the British Cardiac Intervention Society (BCIS) audit reports.[101] According to the BCIS audit reports, 73,612 PCI procedures were undertaken across 91 UK centres (1216 per million) in 2006, compared with 20,511 PCI procedures across 53 UK centres in 1996 (359 per million). Of those undertaken in 2006, 94.4% involved stent placement, compared with approximately 45% in 1996.[101] It is likely that many of the higher-risk patients included in the CURE trial would now undergo an early PCI rather than prolonged medical management or a late PCI procedure. Given this, it seems appropriate to determine the effectiveness of clopidogrel treatment in patients at intermediate risk of ACS, rather than in the entire ACS population. Results from the CURE trial show that patients with intermediate risk do benefit from clopidogrel treatment in terms of cardiovascular death, MI or stroke, but that they have an increased risk of major bleeding.[19]

Further factors for consideration regarding future service provision are the expiry of the patent for clopidogrel in 2013, the associated availability of cheaper generic brands and the emergence of new, possibly more effective, drugs such as prasugrel. It may be argued that if clopidogrel is to be superseded by a more effective or safer drug in the near future, a trial of clopidogrel may not be advisable or cost-effective. However, if the cost of clopidogrel is likely to decrease markedly, this will make its use in both a future trial and clinical practice more cost-effective.

Conclusions

There is evidence that clopidogrel is effective in reducing adverse cardiovascular events in patients with NSTE-ACS, and that this benefit may be most evident in the first 3 months. There is insufficient evidence to determine the effectiveness of different durations of clopidogrel treatment, or the presence or absence of a rebound effect on withdrawal of clopidogrel therapy, in these patients.

Chapter 4

Assessment of cost-effectiveness evidence

Summary of approach

The search strategy outlined in Chapter 3 was used to identify published cost-effectiveness studies, in order to assist in updating an existing decision model evaluating alternative durations of clopidogrel treatment in patients with NSTE-ACS.[12] The objective was to examine other published decision models evaluating the cost-effectiveness of clopidogrel in NSTE-ACS, with the aim of identifying alternative structural assumptions, parameter estimates and key areas of uncertainty. These studies were not subject to a formal review, but were used to inform the overall development of the existing model in relation to structural assumptions and parameter estimates. These findings were used in conjunction with the results of the clinical effectiveness review to provide a basis for updating the existing decision model and the assumptions and parameter inputs applied therein.

The assessment of cost-effectiveness evidence starts with an overview of the existing decision model,[12] in order to highlight the main issues and the assumptions adopted in the existing approach used to evaluate the cost-effectiveness of alternative durations of clopidogrel. The wider cost-effectiveness evidence is then considered in more detail. This provides the context for the updated cost-effectiveness model and the VOI analysis presented in Chapter 5.

Overview of existing decision model

Main and colleagues[12] developed a decision model to assess the long-term cost-effectiveness of 12 months of treatment with clopidogrel in addition to aspirin in comparison with aspirin alone in the UK NHS. This model forms the basis of the updated analyses presented in Chapter 5. The model comprised two parts: a short-term element, which relates to a period of 12 months after a patient presents with NSTE-ACS, and a long-term element which extrapolates a patient's lifetime costs and outcomes conditional on surviving the first 12 months after the acute episode. It was developed to estimate costs from the perspective of the NHS and health outcomes in terms of QALYs. For the base-case analysis, a lifetime time horizon was used.

To avoid excessive duplication, only a brief overview of the data sources and input parameters is reported here. Full details are published elsewhere.[12] The model is probabilistic in that all input parameters are entered as probability distributions to reflect their imprecision, and Monte Carlo simulation is used to reflect this uncertainty in the model's results. A 2001–2 price base was used, and annual discount rates of 6% for costs and 1.5% for benefits were applied.

In the base-case analysis, two alternative strategies were considered:

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

A range of sensitivity analyses were also undertaken to assess the robustness of the results of the base-case model to the use of alternative assumptions and parameter inputs. Two of these analyses have particular relevance to the question being addessed within this review. The first element is related to risk stratification, exploring the impact of heterogeneity in baseline event data between higher-risk (defined as the presence of one or more of the following characteristics: age 70 years or more; ST depression and diabetes) and lower-risk patients (absence of all of these). The second element considered a range of alternative strategies representing shorter durations of clopidogrel, in addition to the two main strategies included in the base-case analysis.

The following section summarises the main structural issues and assumptions related to the short- and long-term models.

Short-term model

The short-term model was developed using a decision tree and characterised the period up

to 12 months following an episode of ACS. The structure of this model is outlined in *Figure 2*. Baseline probabilities of death, non-fatal MI and revascularisation as well as resource use data were taken from the Prospective Registry of Acute Ischaemic Syndrome in the UK (PRAIS-UK).[102] This is an observational cohort registry of 1046 patients admitted to 56 UK hospitals with ACS between 23 May 1998 and 3 February 1999. Baseline data reported in PRAIS-UK were

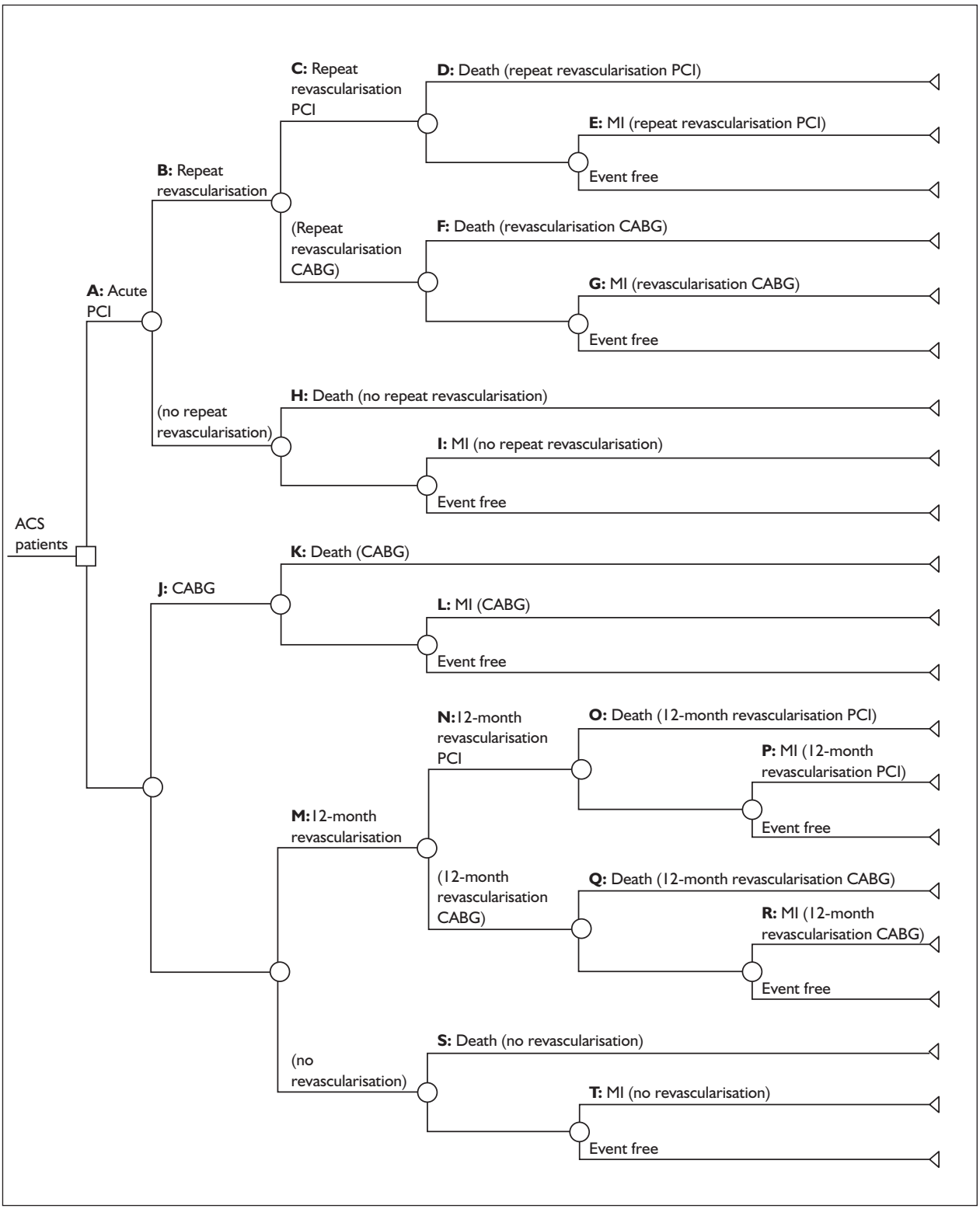

FIGURE 2 *Structure of the short-term model. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.*

only reported at 6 months' follow-up. In order to provide input parameters for the short-term model, these data were extrapolated to 12 months to reflect the follow-up period reported in the CURE trial. These data were used to represent the probabilities of these events associated with Strategy 2.

For patients who experience a non-fatal MI during the 6-month period, resource use and cost were based on costs estimated in NHS hospitals in England.[102] In addition, the costs of adverse events related to major bleeding and stroke were incorporated into the short-term model with the respective probabilities of incurring these events taken from PRAIS-UK. The drug costs were based on undiscounted prices from the *British National Formulary*. Other data used to evaluate resource use were taken from the literature.

Three mutually exclusive outcomes were modelled: non-fatal MI, death (cardiovascular and non-cardiovascular) and IHD without non-fatal MI during the 12-month period. These outcomes also represented the starting health states for the long-term model. The RRs for the use of clopidogrel in addition to aspirin compared with aspirin alone were taken from the CURE trial. Separate RRs for each of the major end points in the short-term model (as well as those for the adverse events) were modelled as log-normal distributions. These RRs were applied to the baseline probabilities to estimate the respective probabilities of the outcomes (and adverse events) associated with Strategy 1 (12 months of clopidogrel treatment).

Long-term model

A long-term (extrapolation) model estimated the subsequent prognosis for patients who finished the short-term (12-month) model in one of two disease states: those having experienced a non-fatal MI and those who have not (well but with IHD and hereafter referred to as IHD). This was used to quantify the remaining quality-adjusted life expectancy and costs of patients exiting the short-term model in the two non-fatal states. It took the form of a four-state Markov process as illustrated in *Figure 3*.

Depending on progress through the short-term model, patients entered the long-term model in either the IHD state or the non-fatal MI state. Patients entering the IHD state could subsequently experience a non-fatal MI, in which case they moved to the non-fatal MI state for 1 year, after which they could die or move to the post-MI state. Patients experiencing any subsequent non-fatal MIs remained in the post-MI state, although the costs of such events were reflected in the model. The transitions from the IHD, non-fatal MI and post-MI states to death reflected the all-cause mortality risk (including both cardiovascular and non-cardiovascular mortality). These transitions were estimated from data on two cohorts from the Nottingham Heart Attack Register (NHAR) from 1992 ($n = 979$) and 1998 ($n = 300$).

Based on a cycle of 1 year, the annual percentage probability of non-fatal MI and death for IHD patients was estimated to be 1.8% and 7.2% respectively. The probability of death in the first year following non-fatal MI was 19%, and for subsequent years was 7%. The uncertainty associated with each transition probability was characterised by assigning a normal distribution to the (log) hazard.

Health-state costs were incorporated into the Markov model by attaching a mean annual cost to the IHD, non-fatal MI and post-MI states. An additional (one-off) transition cost was also

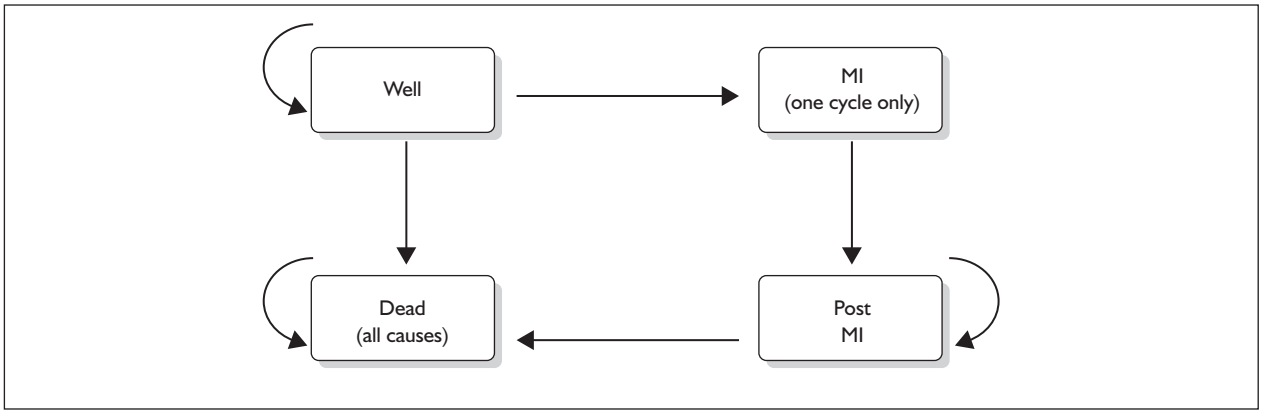

FIGURE 3 *Structure of the long-term model. MI, myocardial infarction.*

added when a patient died, based on resource data obtained from the NHAR. These state and transition costs related to hospital resource use only, and were based on data collected as part of the 1998 cohort of the NHAR. Average annual health-state costs were calculated by aggregating the resources consumed by each patient in the 1998 NHAR cohort according to whether they would have fallen into the three non-dead states in the model: IHD, non-fatal MI or post-MI. As in the short-term model, the uncertainty in resource use in the long-term model was characterised by beta distributions (to reflect the proportion of patients utilising a particular resource item) and log-normal distributions (to reflect the intensity of use).

In order to quality-adjust survival (and hence to estimate QALYs), it was assumed that the health states of all patients who were alive were valued, on average, at the same utility, regardless of which health state they were in. For the base-case analysis, this was assumed to be 0.8 with a standard deviation (SD) of 0.09. A range of alternative estimates were considered in the sensitivity analysis.

The overall model was run for a period of 40 cycles (equivalent to 40 years), after which the vast majority of patients had died. The model was developed in EXCEL with the Crystal Ball 'add-on'. The Monte Carlo simulation was run for 1000 iterations. The model was run several times – once for a base-case analysis and then for a number of alternative sensitivity analyses.

Base-case results

The base-case results are presented in *Table 10*. The ICER of clopidogrel plus aspirin, compared with treatment with aspirin alone, was estimated to be £6078 per QALY gained. At a threshold willingness to pay of £30,000 per QALY, the probability that clopidogrel in combination with aspirin was cost-effective was 0.79.

Sensitivity analysis exploring alternative treatment durations and risk stratification

As previously stated, a series of sensitivity analyses was also undertaken to explore the potential robustness of the base-case results to the inclusion of alternative strategies (representing alternative durations of treatment with clopidogrel of less than 12 months) and to variations in the baseline risk by re-estimating these risks according to higher- and lower-risk categories.

The original model was populated on the assumption that the relative treatment effect of clopidogrel remained constant over the follow-up period reported in the CURE trial. This assumption was applied at the time because of the lack of robust data on the RR estimates, for the separate outcomes considered in the model, over alternative follow-up durations. For the strategies considering shorter treatment durations with clopidogrel, patients were assumed to follow the same event risks associated with Strategy 1 (12 months of clopidogrel treatment) over the duration of treatment. At the point at which treatment was stopped, patients were assumed to revert back to the same event risks associated with Strategy 2 (aspirin alone). After 12 months, all patients followed the same set of transition probabilities, although clearly each strategy differed according to the probability that patients entered the long-term model in the non-fatal MI and IHD states.

Assuming that the RR remains constant with time, then the absolute benefit of treatment with clopidogrel will clearly be greatest when the baseline event risk is highest.

TABLE 10 *Base-case estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis*

				Probability cost-effective for maximum WTP[a]		
Strategy	**Cost (£)**	**QALYs**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
1: Clopidogrel –12 months	12,695	8.2795	6078	0.68	0.79	0.81
2: Standard therapy	12,225	8.2022		0.32	0.21	0.19

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; WTP, willingness to pay.
a The probability that each strategy is more cost-effective than the others is conditional on a different maximum willingness to pay for an additional QALY.

While patients with ACS remain at continued risk of death and non-fatal MI over the 12-month period of the short-term model, the majority of these events occur early after the acute event. Evidence from observational sources indicates that the highest risk of cardiac death is at the time of presentation, and that after 2 months this risk declines to the same level as for patients with chronic stable angina.[103] A similar decline in the risk of non-fatal cardiac events (MI, recurrent angina) has been reported after the initial hospitalisation. From an efficiency perspective, this was considered to have important implications concerning the optimal duration of treatment with clopidogrel. Treatment with clopidogrel for shorter durations was thus considered to represent relevant alternative strategies to those included in the base-case analysis.

A series of three separate strategies, representing alternative treatment durations with clopidogrel, was considered in addition to the main strategies included in the base-case analysis. The five strategies evaluated in this sensitivity analysis were as follows:

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

Table 11 reports the cost-effectiveness of different durations of treatment with clopidogrel calculated in the sensitivity analysis. The use of clopidogrel over longer periods is associated with both increased costs and increased QALYs in comparison with shorter durations, such that the ICER rises as the duration of treatment with clopidogrel increases. The ICER of Strategy 4 (1 month of treatment with clopidogrel) compared with Strategy 5 (standard care alone) is £895 per QALY. The ICER of Strategy 3 compared with Strategy 4 is £5625. The ICER of Strategy 2 compared with Strategy 3 is £6951. Finally, the ICER of Strategy 1 compared with Strategy 2 is £13,988. Hence, the results of this analysis indicate that a decision concerning the optimal duration of treatment with clopidogrel is dependent upon the amount the NHS is prepared to pay per additional QALY. As the amount the NHS is prepared to pay increases, the more cost-effective treatment with clopidogrel for longer durations becomes. At a threshold of £30,000 per QALY, Strategy 1 (12 months' duration) was cost-effective with an associated probability of 0.74, making it the optimal strategy.

The effect of patient heterogeneity using risk stratification in baseline events was investigated to explore the potential impact this had on the relative cost-effectiveness of alternative treatment durations with clopidogrel. The expected costs and QALYs and the ICER of the alternative strategies, based on this approach for the high-risk and low-risk groups, are reported in *Tables 12*

TABLE 11 *Estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis*

				Probability cost-effective for maximum WTP		
Strategy	**Cost (£)**	**QALYs**	**ICER (£)**	**£10,000**	**£30,000**	**£50,000**
1: Clopidogrel – 12 months	13,090	8.3972	13,988	0.28	0.74	0.81
2: Clopidogrel – 6 months	12,869	8.3814	6951	0.36	0.09	0.04
3: Clopidogrel – 3 months	12,752	8.3645	5625	0.07	0.01	0.00
4: Clopidogrel – 1 month	12,673	8.3506	895	0.21	0.08	0.06
5: Standard therapy	12,648	8.3222		0.08	0.09	0.09

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; WTP, willingness to pay.

TABLE 12 *Estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis (higher-risk patients)*

				Probability cost-effective for maximum WTP		
Strategy	**Cost (£)**	**QALYs**	**ICER (£)**	**£10,000**	**£30,000**	**£50,000**
1: Clopidogrel – 12 months	12,637	7.9972	8756	0.55	0.80	0.83
2: Clopidogrel – 6 months	12,418	7.9723	4852	0.19	0.03	0.02
3: Clopidogrel – 3 months	12,301	7.9479	4281	0.03	0.01	0.00
4: Clopidogrel – 1 month	12,213	7.9275	588	0.15	0.07	0.06
5: Standard therapy	12,189	7.8864		0.09	0.09	0.09

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; WTP, willingness to pay.

TABLE 13 *Estimates of mean lifetime costs and QALYs for clopidogrel (in combination with standard therapy) and standard therapy alone, together with incremental analysis (lower-risk patients)*

				Probability cost-effective for maximum WTP		
Strategy	**Cost (£)**	**QALYs**	**ICER (£)**	**£10,000**	**£30,000**	**£50,000**
1: Clopidogrel – 12 months	13,928	8.9964	34,629	0.01	0.31	0.57
2: Clopidogrel – 6 months	13,705	8.9899	30,786	0.03	0.16	0.13
3: Clopidogrel – 3 months	13,597	8.9864	11,816	0.31	0.30	0.15
4: Clopidogrel – 1 month	13,528	8.9805	1732	0.54	0.14	0.07
5: Standard therapy	13,506	8.9680	NA	0.11	0.08	0.08

ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-years; WTP, willingness to pay.

and *13* respectively. In both risk groups, none of the five strategies was ruled out on the grounds of dominance/extended dominance. Again, the use of clopidogrel over longer periods was associated with both increased costs and increased QALYs in comparison with shorter durations. However, the ICERs between the various strategies were markedly different among the separate risk groups.

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

The differences between the high- and low-risk groups was also evident in the probability that each strategy was cost-effective at various threshold willigness-to-pay values. At £10,000 per QALY, the probability that 12 months of treatment with clopidogrel was cost-effective was 55% in the high-risk group and only 1% in the low-risk group. At £30,000 per QALY, the probabilities were 80% and 31% respectively.

While these results indicated that the optimal duration of clopidogrel appears sensitive to the risk stratification applied, the authors noted at the time that it was important to treat these results with some caution owing to the assumptions applied in the model. Two major issues were highlighted: (1) in the absence of appropriate RR data for these

separate risk groups and the separate time periods, a common RR was applied throughout the model; and (2) no systematic evaluation of the extent of any possible rebound effect due to early withdrawal from clopidogrel was undertaken. As such, the conclusions that could be drawn were considered to be tentative, and were seen primarily as generating hypotheses to be explored more robustly with a more rigorous approach or by conducting an additional trial.

Review of published cost-effectiveness analyses

The following section provides an overview of published studies on the cost-effectiveness of clopidogrel in patients with NSTE-ACS. The searches identified two economic models analysing cost per life-year gained[104,105] and three additional cost–utility models.[106–108] The studies were also included in a recent comprehensive pharmacoeconomic review that was identified during the search process.[109]

The models were reviewed in relation to the assumptions and parameter inputs applied. In particular, close attention was paid to aspects related to the assumption of a constant RR or to issues that may be related to a rebound effect.

Input parameters

All studies were consistent in the use of RRs from the CURE or the PCI–CURE trial to populate the relative treatment effects applied in the model. Similarly, all models assumed a constant relative treatment effect over time. No study was identified that assumed a rebound effect after withdrawal of clopidogrel.

Baseline risks were taken consistently from epidemiological databases specific to the countries under investigation. Costs were assessed from the perspective of a health-care payer and/or society and were obtained from the CURE study, published sources and/or expert opinion.

The three cost–utility analyses identified applied different utility values for health states which are of limited comparability. The only study consistent with the health states represented by the model developed by Main *et al.*[12] applied differential utilities to the respective states according to the time they were experienced.[106] A utility of 0.8 (95% CI 0.72–0.88) was applied for the ACS event-free, year 1 and MI, year 1 stages. For subsequent years in the ACS event-free and post-MI stages, a utility weight of 0.93 (95% CI 0.89–0.97) was applied.

Structural assumptions and results

The analyses of cost per life-year gained for both Spain[104] and Sweden,[105] as well as additional studies included in the pharmacoeconomic review[109] based on conference abstracts, are homogeneous in approaches and assumptions. Both studies assessed a treatment duration with clopidogrel of 1 year and included health states representing 'individuals at risk', non-fatal MI, stroke and death. These studies concluded that, in comparison with commonly-accepted thresholds of cost-effectiveness, the addition of clopidogrel to aspirin compared with aspirin alone provided good value for money in all countries or was cost saving from a societal perspective; no estimate of cost-effectiveness exceeded a value of €11,000 per additional life-year gained.

Despite some differences in the structure and inputs of the cost–utility analyses, these studies appeared to follow similar principles to those based on cost per life-year gained. They concluded that, in comparison with commonly applied thresholds of cost-per-QALY estimates, clopidogrel provided good value for money in the base-case analyses and, in particular, across different parameter assumptions as part of the sensitivity analyses. The recent pharmacoeconomic review[109] provides a more comprehensive overview of the different studies' structural assumptions and parameter inputs. In the context of our review, only issues related specifically to the aim of this study are reported.

Apart from the previous HTA report, only one other study has evaluated the cost-effectiveness of alternative treatment durations of clopidogrel,[108] evaluating the cost-effectiveness of different durations of clopidogrel as part of a deterministic sensitivity analysis. Treatment durations for periods both less than and greater than the 12-month duration assumed in the base-case analysis were considered. For the first 12 months, the additional costs and effects of administering clopidogrel were assessed in monthly increments. Each additional month of clopidogrel treatment added approximately 0.005 QALYs and an additional cost of US$140 (ICER = US$26,100 per QALY) relative to the next-shortest duration of therapy. This approach assumed both constant relative treatment

effects and constant baseline event rates over the initial 12 months. Given this, the ICER remained constant over the first 12 months.

However, after the initial 12 months, the authors assumed a declining event rate for MI, cardiovascular death and revascularisation which led to a decrease in effectiveness. As a consequence, the ICER of continuing treatment with clopidogrel beyond 1 year increased to US$31,600 per QALY in the second year and to US$730,000 per QALY in the fifth year. For longer durations of clopidogrel, the impact of bleeding, in terms of its impact on cost-effectiveness, appeared to offset the effect of clopidogrel in reducing other events.

Implications of other published studies

The previous HTA report was largely consistent with other studies in this area; all studies assumed constant relative treatment effects over a 12-month duration, based on data from the CURE trial. Resource utilisation, costs and baseline event risks were typically taken from country-specific data. The main difference between the models relates to the utility values applied to the health states of the various models, with considerable variation between studies.

With respect to modelling alternative treatment durations of clopidogrel, none of the assumptions employed in the separate models contradicted the basis of the approach used in our earlier model. All studies assumed that the RR of clopidogrel remained constant over the duration of treatment. However, only one other study explicitly considered the cost-effectiveness of alternative durations of clopidogrel treatment. The approach employed was largely consistent with our previous work. As such, the variation in cost-effectiveness reported was a function of changes in the baseline events over time associated with standard care as opposed to any variation in the relative treatment effect of clopidogrel. This study found that treatment durations beyond 12 months became markedly less cost-effective as the underlying event rate reduced over time. In addition, the impact of adverse events (e.g. bleeding) became more important in the cost-effectiveness estimates for durations of clopidogrel therapy of longer than 12 months.

Although there have been a number of previous cost-effectiveness analyses evaluating the cost-effectiveness of clopidogrel, only two studies[104,105] have explicitly considered the cost-effectiveness of alternative durations in patients with NSTE-ACS. Both of these studies evaluated alternative durations as part of a sensitivity analysis, and neither attempted to systematically identify relevant literature to inform this specific question. Similarly, neither of these studies attempted to quantify the impact of uncertainty surrounding the decision regarding the optimal treatment duration of clopidogrel in terms of whether additional research (e.g. a trial) may itself be cost-effective in providing further information. Chapter 5 reports on the revisions made to the existing cost-effectiveness model, based on the findings of the clinical effectiveness and cost-effectiveness reviews, and extends the original work to consider an explicit assessment of the costs of decision uncertainty using VOI approaches.

Chapter 5

Economic model and value of information analysis

Introduction

The existing economic model was revised, based on the updated review of clinical effectiveness data reported in Chapter 3 and the review of economic studies in Chapter 4. The changes made to the original model are reported in the following sections. The objective was to update the model inputs and assumptions, and to extend the previous work to address two related analyses concerning the optimal duration of clopidogrel treatment:

1. A revised assessment of the relative cost-effectiveness of alternative treatment durations based on the updated reviews of clinical effectiveness and cost-effectiveness data. This requires an estimation of mean lifetime costs and QALYs of the different strategies and their cost-effectiveness to be compared using ICERs as appropriate. Uncertainty in the cost-effectiveness of the alternative strategies will be reflected by means of cost-effectiveness acceptability curves (CEACs). These show the probability that each strategy is cost-effective, using alternative values for the maximum (or threshold) value the health service is willing to pay for an additional QALY in these patients.
2. A formal assessment of the potential value of further research using VOI analyses. Bayesian VOI analysis is used to estimate the expected costs of decision uncertainty predicted by the model and the maximum value that can be placed on additional research aimed at reducing this uncertainty. This analysis will be used as the basis for identifying research priorities in this area and to establish an upper bound on the value of a future trial in this area. This will provide a necessary condition for establishing whether a trial is likely to provide value for money for the HTA programme.

Methods

The existing decision model was updated and extended, based on the clinical and cost-effectiveness reviews, to provide the vehicle for the revised cost-effectiveness estimates and the VOI analysis.

Cost-effectiveness

The existing decision model provides the basis for estimating the costs and cost-effectiveness of alternative durations of treatment with clopidogrel. The analysis compares five different strategies based on alternative treatment durations with clopidogrel compared with standard care with aspirin. The previous model assumed that the relative treatment effect was constant across different time periods and hence only the baseline risk was varied in the cost-effectiveness analysis. This assumption is revisited on the basis of the updated clinical effectiveness review, and alternative scenarios are explored. The study was conducted from an NHS perspective with a discount rate of 3.5% for both costs and effects (as opposed to 6% for costs and 1.5% for effects in the previous model). Costs were updated to reflect 2005–6 prices.

The model is probabilistic; that is, each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this *parameter uncertainty* is then translated into uncertainty in the overall results. This ultimately helps decision-makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision, i.e. *decision uncertainty*. This is to be presented graphically using CEACs[110] which show the probability that each intervention is cost-effective, conditional on a range of possible threshold values that NHS decision-makers attach to an additional QALY. The Monte Carlo simulation was conducted using 5000 simulations.

Value of information

A VOI framework is used to provide an explicit measure of the cost associated with uncertainty surrounding the decision related to the optimal duration of clopidogrel, through formal consideration and valuation of the consequences associated with this uncertainty. This analysis

is used as the basis to inform future research priorities and, in particular, is used to establish the potential value of a future trial. A similar approach to informing research priorities using a VOI framework has recently been applied to several case studies in the NHS HTA programme and for NICE.[111,112] VOI analyses have also been conducted in related areas, such as the use of glycoprotein IIb/IIIa antagonists in ACS[113] and the use of clopidogrel in the secondary prevention of occlusive vascular events.[112]

In probabilistic modelling, the expected cost of uncertainty surrounding the adoption decision can be determined using the expected value of perfect information (EVPI). The expected costs of uncertainty represent the consequences in terms of costs incurred and lost benefits that would have occurred should it later transpire that the adoption decision was not correct. VOI analysis involves establishing the difference between the expected value of a decision made on the basis of existing evidence and, following the collection of further information, the expected value of a decision made on the basis of new evidence. The EVPI values the resolution of all uncertainty, through the provision of perfect information, and provides a measure of the maximum return to further research. The EVPI represents the maximum a decision-maker should be willing to pay for additional evidence to inform this decision in the future. If the EVPI exceeds the expected costs of additional research, then it is potentially cost-effective to acquire more information by conducting such research.

Within the framework, the EVPI for the decision can be determined directly from the results of the probabilistic analysis, with each iteration representing a possible future resolution of the existing uncertainty for which the optimal decision (the intervention which maximises net benefit) can be identified. For a decision involving j interventions, where net benefit is dependent upon a set of unknown parameters θ, the EVPI is simply the difference between the expected value of the decision made on the basis of existing information ($\max_j [E_\theta \{NB(j, \theta)\}]$) and the value of the decision made with perfect information ($\max_j \{NB(j,)\}$), averaged over all possible realisations of uncertainty ($E_\theta [\max_j \{NB(j, \theta)\}]$):

$$EVPI = E_\theta [\max_j \{NB(j, \theta)\}] - \max_j [E_\theta \{NB(j, \theta)\}]$$

As information is a public good, generation of perfect information for one instance of a decision ensures that the information is available for other instances of the decision. Hence, the overall value of perfect information surrounding a health-care policy decision depends upon the number of times that the decision is faced over the lifetime of the technology.[111] The population-level EVPI is determined by scaling up the individual EVPI according to the number of people who would be affected by the information over the anticipated lifetime of the technology:

where I = incidence in period, t = period, T = total number of periods for which information

$$EVPI * \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}$$

from research would be useful and r = discount rate.

In addition to determining the EVPI surrounding the decision as a whole, VOI approaches can also be used for particular elements of the decision in order to direct and focus research towards the areas where the elimination of uncertainty has the most value. The EVPPI can be calculated for individual or subsets of parameters. The process involves determining the expected value of a decision made with and without perfect information for the subset of parameters of interest. For a subset of parameters φ, the expected value of partial perfect information (EVPPI) is simply the difference between the expected value of the decision made on the basis of existing information ($\max_j [E_\theta \{NB(j,)\}]$) (as with the calculation of decision EVPI) and the value of the decision made with perfect information about φ ($\max_j [E_{\theta|\varphi} \{NB(j, \theta)\}]$). Where perfect information about the subset of parameters has no impact on the decision, the information has no value. The value of the decision made with perfect information about φ is averaged over all possible realisations of uncertainty ($E_\varphi [\max_j (E_{\theta|\varphi} \{NB(j, \theta)\}]]$) to reflect the fact that the subset of parameters can resolve at any point within the distributions:

$$EVPPI_\varphi = E_\varphi [\max_j (E_{\theta|\varphi} \{NB(j, \theta)\})] - \max_j [E_\theta \{NB(j, \theta)\}]$$

On the basis of EVPI and EVPPI calculations, the potential value of a future trial (or other research designs) will be evaluated. The VOI which could be acquired by conducting further research depends crucially on the number of future patients who could benefit from it, i.e. the time horizon over which the information would be useful. It has

recently been suggested that selecting a value for the time horizon is essentially a proxy for a more complex and uncertain process of future changes to the decision problem which impact on the EVPI.[114] One future change that is likely will be the price of clopidogrel when it comes off patent. The potential impact on EVPI estimates of this change was therefore an important consideration.

Assumptions and data inputs

Treatment strategies

In line with the previous model, five separate strategies were assessed, including four strategies that reflected alternative durations of clopidogrel:

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

Epidemiological parameters (baseline events)

In common with the existing model, baseline probabilities of death, non-fatal MI and revascularisation were taken from PRAIS-UK[102] and extrapolated to a duration of 12 months.[12] Data on baseline events were also stratified by risk group. As reported by Main and colleagues,[12] high risk was defined by age ≥ 70, ST depression or diabetes (and low risk was defined as the absence of all of these), on the basis of discussion with clinical collaborators and the results of a previous analysis of the relationship between prognostic indicators and outcomes based on the PRAIS-UK data. Fifty-eight per cent of all patients belonged to the high-risk group.

The data reported at 6 months from PRAIS-UK were extrapolated to 12 months using the observed relationship between these periods reported in the CURE trial illustrated in the previous report.[12] This approach was employed as a result of the more consistent findings that this approach provided, as opposed to the alternatives considered.[12]

The probabilities of death, non-fatal MI and IHD (i.e. no event) occurring during each interval were modelled using the Dirichlet distribution. This is the multidimensional generalisation of the beta distribution and can be used to represent polychotomous (i.e. more than two events) transition probabilities to ensure that the sum of probabilities across multiple events equals 1. During the first 30 days in PRAIS-UK (*Table 14*), a total of 33 patients died, 41 patients had a non-fatal MI and the remainder (959 patients) were classified as IHD. The probabilities of each event were thus modelled using a Dirichlet (33,41,959) distribution. Of the 959 patients with IHD at 1 month, the probabilities of death, non-fatal MI or remaining in the IHD state during the next interval (1–3 months) were then modelled using a Dirichlet (21,4,934) distribution, reflecting the number of observed events in PRAIS-UK during this interval. A similar process was used to determine the probabilities between 3 and 6 months. The event rates between 6 and 12 months were then estimated, based on the percentage of additional events reported in the CURE trial. These probabilities were used to represent the transition probabilities for standard care alone (i.e. Strategy 5) across each time period.

The transition probabilities used in the long-term model are shown in *Table 15* and are based on a cycle length of 1 year. These data determine how patients move between the states outlined in *Figure 2* and are based on the same analysis of the NHAR as applied in the earlier model. The uncertainty associated with each transition probability was characterised by assigning a normal distribution to the (log) hazard. The estimates of the (log) hazard were then exponentiated and converted to probabilities.

Relative treatment effects

The earlier model was populated using estimates of the relative treatment effect of clopidogrel from the CURE trial.[17–22] Although the updated clinical effectiveness review reported in Chapter 3 identified one additional trial that provided information on the clinical effectiveness of clopidogrel in patients with NSTE-ACS, this trial was considered to be underpowered, and reported limited results.[39] Thus the CURE trial remains the primary source of data used in the updated model.

TABLE 14 *Distribution of events in PRAIS-UK across separate time periods during the 6-month follow-up period*

	Time period			
Event	**1 month, *n* (%)**	**1–3 months, *n* (%)**	**3–6 months, *n* (%)**	**Total (0–6 months), *n***
Death (all cause)	33 (43.4)	21 (27.6)	22 (28.9)	76
Non-fatal MI	41 (74.5)	4 (7.3)	10 (18.2)	55
Stroke	8 (53.3)	3 (20)	4 (26.7)	15
Major bleed	9 (69.2)	2 (15.4)	2 (15.4)	13
MI (fatal/non-fatal)	54 (71.1)	8 (10.5)	12 (15.8)	74

MI, myocardial infarction.

TABLE 15 *Annual transition probabilities used in the long-term model [95% CI (range)]*

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

IHD, ischaemic heart disease; MI, myocardial infarction.

The RRs taken from the CURE trial that were applied in the previous model are shown in *Table 16* for the use of clopidogrel in addition to aspirin compared with aspirin alone. Separate RRs for each of the major end points in the short-term model are reported. To account for uncertainty in these estimates, the (log) RRs were modelled as normal distributions. These results were then exponentiated to provide estimates of the RRs applied in the probabilistic analysis. The RRRs were assumed to remain constant throughout the duration of the clopidogrel treatment period.

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

The updated clinical effectiveness review identified a more recent analysis of the CURE data presented in the SIGN guidelines (No. 93).[85] Post hoc analysis of different time periods indicated that the treatment effect in the first 3 months of treatment may be greater than in later periods. While it was noted that this was a post hoc, exploratory analysis and hence comprises non-randomised comparisons, these data do provide a level of evidence which may question the validity of assuming that the treatment effect of clopidogrel remains constant over time. Additional exploratory work was therefore undertaken to examine the robustness of the model results and the VOI estimates to this alternative assumption.

The data reported in the SIGN guidelines were based on the composite end point of cardiovascular death, non-fatal MI and stroke. Disaggregated data for the individual end points of the decision model were not reported. Similarly, the time intervals reported in the SIGN guidance were not consistent

TABLE 16 *Relative risks of outcomes applied in decision model: clopidogrel plus aspirin vs aspirin alone*

Outcome	RR mean (95% CI)	RR, log RR (SE)
All-cause mortality	0.93 (0.81–1.07)	–0.08 (0.07)
Non-fatal MI	0.71 (0.60–0.84)	–0.34 (0.09)
Non-fatal stroke	0.73 (0.50–1.09)	–0.31 (0.20)
Major bleed	1.38 (1.13–1.67)	0.32 (0.10)

CI, confidence interval; MI, myocardial infarction; RR, relative risk; SE, standard error.

with the separate strategies considered in the model. Consequently, it was not possible to apply these data directly to the existing structure of the decision model. In order to include the relative treatment effect on the composite end point, the model structure and parameterisation had to be altered. Instead of using a Dirichlet distribution to estimate the probability of each individual end point (to which the RR associated with each individual end point was subsequently applied), a beta distribution was assigned to estimate the probability of the composite end point in the model at each time interval. The RR associated with the combined end point was applied to this probability for the clopidogrel strategies. A separate Dirichlet distribution was then used to apportion the events into the separate health states of the model. This approach assumes that the effect of clopidogrel is equivalent in terms of reducing the probability of the individual end points that constitute the composite end point. As bleeding events were not part of the composite end point, a separate analysis was undertaken, assuming that the risk of these particular events remained constant over the period of treatment being evaluated.

In addition to the structural problems, another issue was that the time intervals reported in the SIGN guidance did not match up completely with the time intervals represented by the separate strategies. However, it was noted that variation in the RR estimates were most evident in the first 3-month period, which was also the period for which these RRs were reported to be statistically significant. In the intervals reported after 3 months, there was less variation and none of the differences were reported to be statistically significant. As such, it was decided to pool the time intervals after 3 months to estimate one single treatment effect to be applied to these separate intervals. In the absence of the patient-level data, these calculations were re-estimated assuming no loss to follow-up. While this approach will tend to overestimate the precision of this estimate, it will not affect the central estimate.

Table 17 reports the RR estimates for the composite outcome considered as a separate scenario to the base-case assumption of constant relative effects. Log-normal distributions were applied to these varying RRs as to the constant RRs for differing health outcomes. To account for uncertainty in these estimates, the (log) RRs were modelled as normal distributions.

Rebound assumptions

The updated clinical effectiveness review concluded that existing evidence available that related to the potential rebound effect on withdrawal of clopidogrel therapy in patients with NSTE-ACS was limited. In the absence of robust data identified from the clinical effectiveness review, the potential impact of rebound was modelled by assuming that patients who withdrew from clopidogrel reverted

TABLE 17 *Relative risks of the composite outcome based on SIGN guidance: clopidogrel plus aspirin vs aspirin alone*

Composite outcome	RR, mean (95% CI)	RR , Log RR (SE)
0–1 month	0.78 (0.67–0.92)	–0.24 (0.08)
1–3 months	0.69 (0.54–0.88)	–0.37 (0.12)
3–12 months	0.92 (0.78–1.10)	–0.08 (0.09)

CI, confidence interval; RR, relative risk; SE, standard error.

back instantaneously to the equivalent risk faced by patients on aspirin alone. That is, any additional treatment effect conferred by clopidogrel was assumed to cease immediately at the time of withdrawal and hence patients were assumed to rebound to the same prognosis as an equivalent patient on aspirin alone. Patients were assumed to continue with long-term aspirin therapy in all strategies. However, in those strategies of less than 12 months' duration, patients faced a higher risk of subsequent events for the remainder of the 12-month period than in the strategy in which clopidogrel was given for the entire 12-month duration.

Costs and utility estimates

Unit costs reported for the previous model were updated to reflect 2005–6 prices. A number of minor changes were required to deal with the revised structure of the model, although none of these made any significant difference to the main results.

Owing to the resources and time available for the short report, it was not considered feasible to update the existing utility estimates using systematic approaches. We therefore proposed to use the existing utility estimates applied in the current model as the basis for estimating quality of life. However, assuming that each health state has the same underlying quality of life was acknowledged as a potential limitation. The review of existing models in Chapter 4 identified one study which was considered to provide a reasonable alternative source of utility values that could partially address the limiting assumption that health states had the same underlying utility value. Hence the values for this study which applied differential utility weights for first and subsequent years for the separate states were utilised.[106] The utility estimates were modelled as beta distributions (with alpha and beta parameters). *Table 18* shows the mean utility values and the resulting parameters of the beta distribtution.

Value of information and patent expiry

As previously noted, the VOI estimates that could be acquired by conducting further research will depend on the time horizon considered to reflect the lifespan of the decision under investigation. The analysis reported here is undertaken on the assumption of a 10-year time horizon. A finite time horizon is conventionally applied in order to represent a period of time over which it is anticipated that there will not be substantial changes which will significantly alter the nature of the decision problem under investigation (e.g. the emergence of new comparators, etc.). However, one future change that is known is that clopidogrel will come off patent in 2011, and hence it was considered important to reflect this in the EVPI estimates.

The EVPI calculations were undertaken assuming an annual incidence of 60,000.[113] Assuming a time horizon of 10 years and a discount rate of effects of 3.5%, the total population multiplier amounts to approximately 515,000. The population multiplier for high-risk patients equates to 58% of this, i.e. 298,478 (and 217,983 for low-risk patients).

Clearly, the price of generic clopidogrel is subject to considerable uncertainty. The only direct evidence available for the potential future price of generic clopidogrel is from the US, where generic clopidogrel was temporarily supplied by Apotex in 2006 at a price of 80% of the branded product.[115] However, it is unlikely that this figure can be generalised to a UK context for two reasons:

1. In general, generic prices are highly dependent on policy environment[116] and it has been shown that generic prices differ substantially across countries.[117]
2. In the event of generic competition, prices can be expected to fall over time as generic prices typically depend on the time since the patent expired. The case in the US reflected an off-patent period of 1 month only with one single generic market entrant.

The impact factors on generic prices identified in the literature included the following:[117,118]

- average revenue per brand name extended unit
- number of extended units sold before patent loss
- age of market in terms of time the brand-name product was sold
- time since the patent expired
- average revenue per generic extended unit.

As clopidogrel is among the world's best-selling drugs and as the Apotex case proved that there are already manufacturers of generics who are prepared for market entry, substantial generic competition can be expected. It therefore seems highly likely that the price of generic clopidogrel in

TABLE 18 *Parameters for the distribution of utility values*

Health state	Mean utility	Alpha	Beta
IHD year 1	0.8	76.03	19.01
Post-IHD	0.93	144.43	10.87
MI year 1	0.8	76.03	19.01
Post-MI	0.93	144.43	10.87

IHD, ischaemic heart disease; MI, myocardial infarction.

the UK will be below the level charged by Apotex. As such, a price of 25% of the original product, corresponding with the ratio of the average price of generic (£4.83) to branded (£19.33) drugs in the UK, was considered to be more appropriate.

Scenarios

Cost-effectiveness and VOI estimates are presented for a number of scenarios. All scenarios consider a cohort of non-ST-elevation ACS patients (at a starting age of 60) over a time horizon of 40 years. The base-case analysis (Scenario 1) assumes a constant treatment for the different durations of clopidogrel. Separate analyses are presented for all patients and also for high- and low-risk groups. Two further individual scenarios are then considered:

- Scenario 2: Applying separate treatment effects for the different durations of clopidogrel based on the data reported in the SIGN guidelines. As in Scenario 1, results are presented for all patients and for the high- and low-risk groups.
- Scenario 3: Investigating the impact of the introduction of generic clopidogrel. This scenario is undertaken only for the VOI analysis, as the implementation decision about the cost-effectiveness of clopidogrel should be based on prevailing prices, and a separate decision should be taken following the emergence of generic clopidogrel. However, while the decision about a potential trial can be made on the basis of current information, given that the delay in the arrival of this information is likely to be after the introduction to the market of a generic version of clopidogrel, it seems pertinent to consider the potential implications of this future change.

Results

Cost-effectiveness of different treatment durations of clopidogrel assuming constant effects

Base-case scenario (Scenario 1)

Table 19 presents the analysis of the ICER for the base-case scenario assuming constant relative treatment effects for clopidogrel in all patients. Where more than two programmes are being compared, the ICERs are calculated using the following process:

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

In this scenario, none of the 5 strategies is ruled out on the grounds of dominance/extended dominance. The use of clopidogrel over longer periods is associated with both increased costs and increased QALYs in comparison with shorter durations, such that the ICER rises as the duration of treatment with clopidogrel increases. The ICER of Strategy 4 (1-month treatment with clopidogrel) compared with Strategy 5 (standard care alone) is £4790 per QALY. The ICER of Strategy 3 compared with Strategy 4 is £9489. The

TABLE 19 *Cost-effectiveness results for all patients (Scenario 1)*

Mean values from simulation				% of results cost-effective at threshold		
Strategy	**QALYs**	**Cost (£)**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
1: Clopidogrel – 12 months	8.1236	19,758	18,712	51.7	67.5	73.8
2: Clopidogrel – 6 months	8.1094	19,493	10,482	18.9	9.9	6.4
3: Clopidogrel – 3 months	8.0954	19,347	9489	2.0	0.7	0.2
4: Clopidogrel – 1 month	8.0835	19,233	4790	7.5	5.0	4.0
5: Standard therapy	8.0642	19,141	NA	15.7	16.8	15.7

ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-years.

ICER of Strategy 2 compared with Strategy 3 is £10,482. The ICER of Strategy 1 compared with Strategy 2 is £18,712. Hence, the results of this analysis indicate that a decision concerning the optimal duration of treatment with clopidogrel is dependent upon the amount the NHS is prepared to pay per additional QALY. As the amount the NHS is prepared to pay increases, the more cost-effective treatment with clopidogrel for longer durations becomes. At conventional thresholds of between £20,000 and £30,000 per QALY, the optimal duration of clopidogrel appears to be 12 months.

In comparison with the earlier model, the ICERs associated with the clopidogrel strategies are higher in the updated model. The reasons for this are: (1) the increase in costs due to applying current prices, and (2) the changes to the discount rates, employing 3.5% for both costs and outcomes (as opposed to 1.5% for outcomes and 6% for costs in the previous model). However, despite the less favourable ICERs, the conclusions arising from the updated model are consistent with those reported previously.

Figures 4 and *5* present the CEACs and associated frontier for Scenario 1. The CEACs demonstrate that the probability that Strategy 1 is cost-effective increases as the maximum willingness to pay increases: if society is prepared to pay £20,000 for an additional QALY, the probability that Strategy 1 is cost-effective is approximately 52%, increasing to 74% if the maximum willingness to pay is £40,000.

Although the CEAC provides a useful graphical representation of the uncertainty associated with the probability that individual strategies are cost-effective over a range of threshold values, the results of the CEAC can only be used to identify

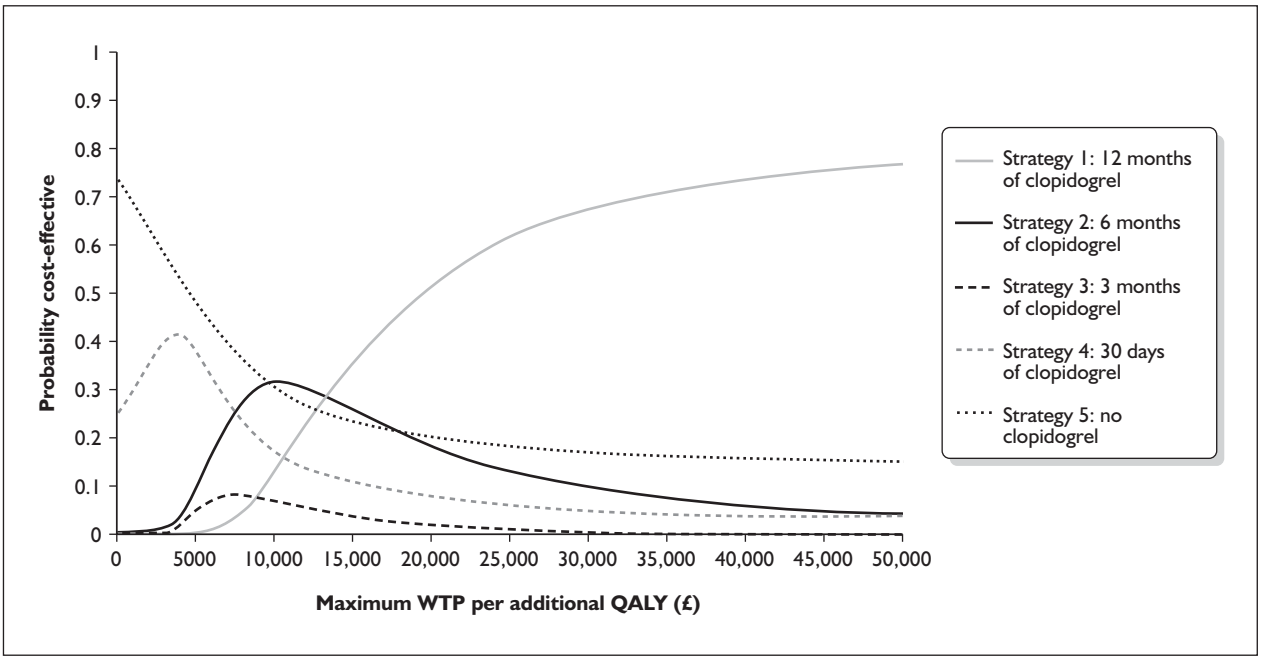

FIGURE 4 *CEAC of different clopidogrel strategies (Scenario 1, all patients). QALY, quality-adjusted life-year; WTP, willingness to pay.*

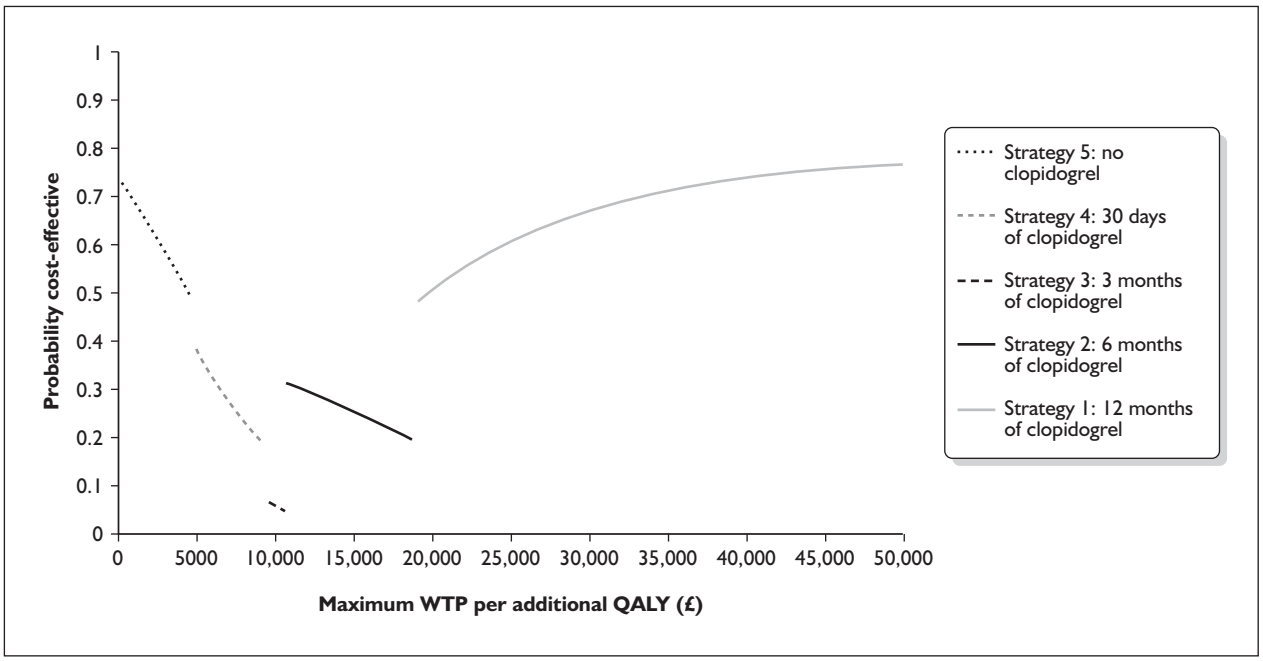

FIGURE 5 *Cost-effectiveness frontier for the different strategies (Scenario 1, all patients). QALY, quality-adjusted life-year; WTP, willingness to pay.*

the optimal implementation decision under a restrictive set of assumptions. This is because the strategy with the highest probability of being cost-effective does not necessarily have the highest expected pay-off (i.e. net benefit), and will only have this when the distribution of these pay-offs is symmetrical. This limitation can be overcome by using a cost-effectiveness frontier to indicate which strategy is optimal (and the associated probability that this strategy is the most cost-effective) across the range of values representing the maximum amount the NHS is prepared to pay for an additional QALY. The frontier for this analysis is provided in *Figure 5*.

The expected costs and QALYs and the ICER of the alternative strategies based on the high-risk and low-risk groups are reported in *Tables 20* and *21* respectively. In both risk groups, none of the five strategies were ruled out on the grounds of dominance/extended dominance. As before, the use of clopidogrel over longer periods was associated with both increased costs and increased QALYs in comparison with shorter durations. However, the ICER between the various strategies was markedly different between the two risk groups.

In high-risk patients, the ICER of Strategy 1 (12-month duration of clopidogrel) was more favourable than in the combined analysis of all patients. This was to be expected as the number of events represented by the baseline was higher, and as such the application of the same treatment effect would result in proportionally more absolute benefit. Hence, the ICER was decreased to £13,380 per QALY and, at conventional thresholds, Strategy 1 appears cost-effective. In turn, the lower number of baseline events in low-risk patients had a less favourable effect on the cost-effectiveness of longer durations of clopidogrel. At conventional thresholds of cost-effectiveness, Strategy 3 (3 months of clopidogrel) appears to be the optimal decision and longer durations do not appear cost-effective.

Cost-effectiveness of different durations of clopidogrel treatment assuming varying treatment effects

Scenario 2

Table 22 reports the ICER estimates employing the composite outcome based on the data reported in the SIGN guidelines. As shown in *Table 17*, the RRs assigned in this analysis do not assume a constant treatment effect, with more favourable estimates assigned to months 0–1 and 1–3 compared with periods beyond 3 months' duration. The results show less favourable ICER estimates, although these do not vary significantly from those reported in Scenario 1. The resulting ICER increased marginally to £20,661 per QALY (compared with £18,712 in Scenario 1). As expected, the associated ICERs of the shorter durations (Strategy 3 = 3

TABLE 20 *Cost-effectiveness in high-risk patients (Scenario 1)*

Mean values from simulation				% of results cost-effective at threshold		
Strategy	**QALYs**	**Cost (£)**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
1: Clopidogrel – 12 months	7.7710	19,187	13,380	65.8	75.1	78.9
2: Clopidogrel – 6 months	7.7496	18,900	7971	9.3	4.2	2.1
3: Clopidogrel – 3 months	7.7300	18,744	7930	0.7	0.2	0.0
4: Clopidogrel – 1 month	7.7123	18,604	4846	4.8	3.2	2.5
5: Standard therapy	7.6882	18,487	NA	16.5	17.3	16.5

ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-years.

TABLE 21 *Cost-effectiveness in low-risk patients (Scenario 1)*

Mean values from simulation				% of results cost-effective at threshold		
	QALYs	**Cost (£)**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
1: Clopidogrel – 12 months	8.6850	21,244	49,436	4.9	16.7	28.7
2: Clopidogrel – 6 months	8.6802	21,005	36,226	14.8	20.2	22.8
3: Clopidogrel – 3 months	8.6769	20,886	17,826	31.3	30.0	23.7
4: Clopidogrel – 1 month	8.6713	20,786	4891	31.6	20.2	13.7
5: Standard therapy	8.6600	20,731	NA	11.1	13.0	11.1

ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-years.

TABLE 22 *Cost-effectiveness estimates for all patients (Scenario 2)*

Mean values from simulation				% of results cost-effective at threshold		
Strategy	**QALYs**	**Cost (£)**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
1: Clopidogrel – 12 months	8.2019	20,094	20,661	42.9	56.3	62.6
2: Clopidogrel – 6 months	8.1887	19,820	11,917	32.5	26.6	23.0
3: Clopidogrel – 3 months	8.1753	19,661	4095	24.6	17.1	14.4
4: Clopidogrel – 1 month	8.1236	19,449	3632	0.1	0.0	0.0
5: Standard therapy	8.0686	19,250	NA	0.0	0.0	0.0

ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-years.

months, Strategy 4 = 1 month) improved markedly owing to the more favourable RR estimates applied to the earlier periods of treatment with clopidogrel. However, assuming a threshold of between £20,000 and £30,000 per QALY, Strategy 1 appeared to remain the optimal strategy in all patients.

It should be recognised that the structural alterations required to model the composite end point, will have a potentially important effect on the results if there are differences between the effect of clopidogrel on the composite end point and its effect on individual end points. The constant effects model assumes a larger treatment effect for non-fatal MI (RR 0.70) and stroke (RR 0.73), while the effect on mortality was comparatively low (RR 0.93). In contrast, the use of the composite end point assumes that the effects on mortality, non-fatal MI and stroke are equal (although these vary with time), with RRs of 0.78 (0–1 month), 0.69 (months 1–3) and 0.92 (after month 3). Consequently, while the impact

of applying the composite end points results in less favourable RRs across each of the time intervals beyond 1 month for stroke and non-fatal MI, the estimate for mortality remains higher at each interval. While these two effects are likely to counter each other to some degree, the impact of assuming a higher treatment effect on mortality could be important. However, it is unclear whether this was sufficient to markedly bias the results.

Figures 6 and 7 report the CEACs and associated frontier for Scenario 2 and demonstrate that there is higher decision uncertainty related to the use of clopidogrel over 12 months compared with Scenario 1. This may have important implications for the VOI estimates reported separately, as while Strategy 1 appears to remain cost-effective in this scenario, the uncertainty surrounding this was no higher and, assuming all other things remain equal, should result in a higher value associated with obtaining further information.

The expected costs and QALYs and the ICER of the alternative strategies based on the high-risk and low-risk groups are reported in *Tables 23* and *24* respectively. In the high-risk group, none of the five strategies were ruled out on the grounds of dominance/extended dominance. As before, the use of clopidogrel over longer periods was associated with both increased costs and increased QALYs in comparison with shorter durations. Similarly, the ICERs for longer durations of clopidogrel were less favourable for durations of longer than 3 months (and vice versa for durations of 3 months or less), although the ICER for Strategy 1 was below conventional thresholds.

In contrast, in the low-risk group, Strategy 2 was ruled out by extended dominance by Strategy 1. The ICER for Strategy 1 was considerably higher (£58,691 per QALY) than conventional thresholds. The results reinforced the findings from Scenario 1 in low-risk patients, that durations of clopidogrel treatment of longer than 3 months do not appear to be cost-effective.

Value of information associated with the decision problem

Separate estimates of total EVPI and EVPPI were estimated for Scenarios 1 and 2. A third scenario was considered based on the VOI following patent expiry. As the patent of clopidogrel is due to expire in 2011,[115] a price reduction of 75% was assumed, which corresponds with the average price of a generic compared with a branded drug in the UK. Rather than reporting the results of the third scenario separately, EVPI results are presented for Scenarios 1 and 2, applying the current price of clopidogrel ('on patent' results) and applying the potential generic price of clopidogrel ('off patent' results). These results are reported across a range of potential thresholds of cost-effectiveness.

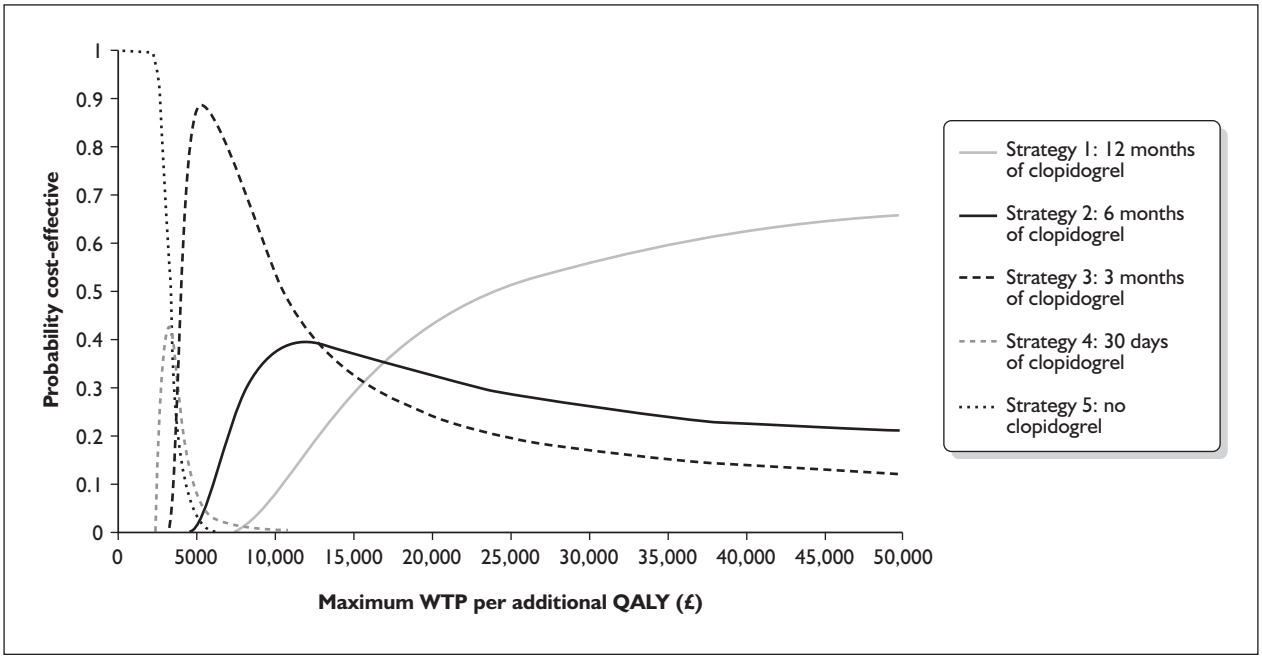

FIGURE 6 *CEAC for clopidogrel strategies (Scenario 2, all patients). QALY, quality-adjusted life-year; WTP, willingness to pay.*

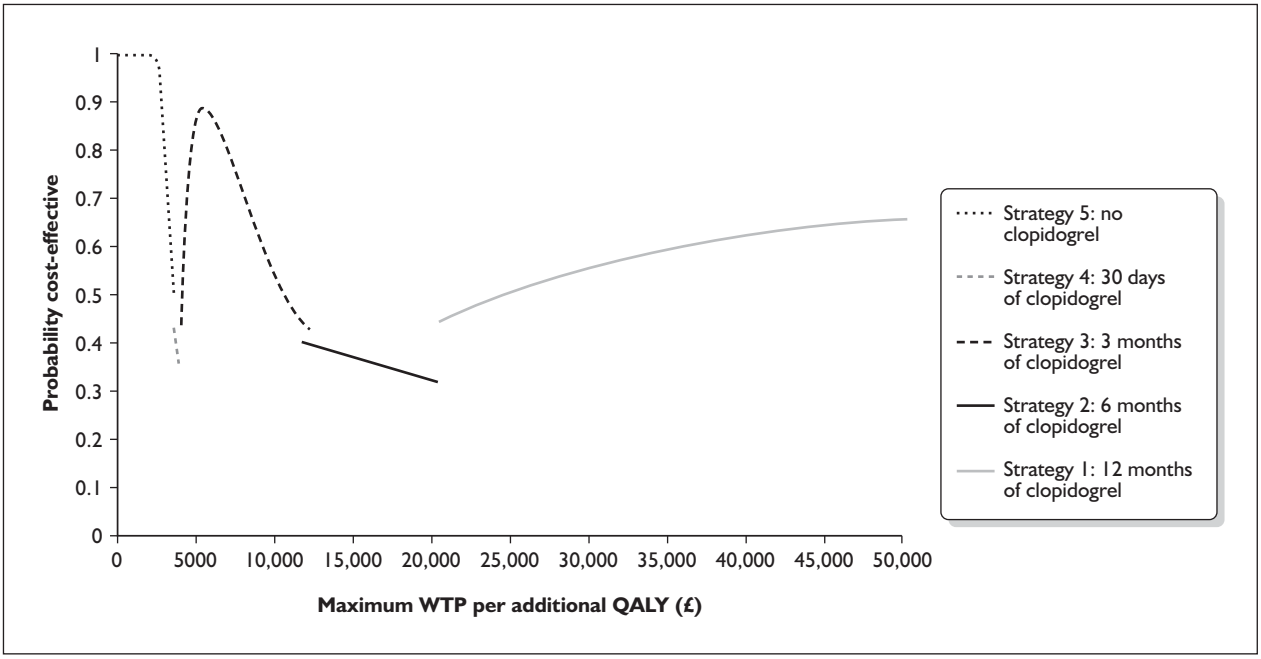

FIGURE 7 *Cost-effectiveness frontier for clopidogrel strategies (Scenario 2, all patients). QALY, quality-adjusted life-year; WTP, willingness to pay.*

TABLE 23 *Cost-effectiveness based on Scenario 2, high-risk patients*

Mean values from simulation				% of results cost-effective at threshold		
Strategy	**QALYs**	**Cost (£)**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
1: Clopidogrel – 12 months	7.8783	19.664	15,063	59.3	69.2	73.0
2: Clopidogrel – 6 months	7.8586	19.368	9144	11.9	6.4	4.3
3: Clopidogrel – 3 months	7.8400	19.197	3809	28.7	24.4	22.6
4: Clopidogrel – 1 month	7.7653	18.913	3615	0.1	0.1	0.1
5: Standard therapy	7.6906	18.643	NA	0.0	0.0	0.0

ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-years.

TABLE 24 *Cost-effectiveness based on Scenario 2, low-risk patients*

Mean values from simulation				% of results cost-effective at threshold		
Strategy	**QALYs**	**Cost (£)**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
1: Clopidogrel – 12 months	8.7079	21,065	58,691	4.6	13.8	23.5
2: Clopidogrel – 6 months	8.7037	20,821	ED	6.0	8.7	10.1
3: Clopidogrel – 3 months	8.7018	20,695	6780	81.9	74.8	65.2
4: Clopidogrel – 1 month	8.6825	20,564	3936	6.1	2.3	1.1
5: Standard therapy	8.6589	20,471	NA	0.2	0.4	0.2

ED, extendedly dominated; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-years.

Total EVPI

Tables 25 and *26* report the total population EVPI for a range of cost-effectiveness thresholds for Scenarios 1 and 2 respectively. Estimates of total EVPI ranged between £3.27 million and £123.17 million across the different scenarios, risk groups and range of thresholds. The calculation demonstrates that there was significant variability in the potential value of research, depending upon the scenario (and risk group) or threshold considered most relevant to the particular decision-maker. At a more conventional threshold of cost-effectiveness between £20,000 and £30,000 per QALY, the range was reduced to between £3.27 million and £108.45 million. However, the potential value of a trial to address the current decision problem clearly remains highly uncertain and may be considered to be potentially worthwhile at the top end of the scale and not at the lower end.

The estimates of total EVPI for the high- and low-risk groups differed markedly. At a threshold of cost-effectiveness between £20,000 and £30,000 per QALY, total EVPI ranged from £34.11 million to £77.10 million in high-risk patients (and from £3.27 million to £20.38 million in low-risk patients). As expected, for the majority of analyses, estimates of total EVPI based on the scenario of

TABLE 25 *Total EVPI for Scenario 1 (constant treatment effects)*

	EVPI at a willingness to pay per QALY (£)		
	£20,000	**£30,000**	**£40,000**
EVPI while on patent			
All patients	102,442,841	108,454,348	123,171,826
High-risk patients	65,803,244	77,100,300	92,043,666
Low-risk patients	15,007,631	20,376,578	28,264,558
EVPI while off patent			
All patients	50,691,302	66,929,942	84,945,937
High-risk patients	42,274,257	57,936,239	74,972,484
Low-risk patients	11,597,014	10,762,438	11,385,255

EVPI, expected value of perfect information; QALY, quality-adjusted life-year.

TABLE 26 *Total EVPI for Scenario 2 (varying treatment effects)*

	EVPI at a willingness to pay per QALY (£)		
	£20,000	**£30,000**	**£40,000**
EVPI while on patent			
All patients	77,630,538	84,699,365	92,810,082
High-risk patients	57,425,624	68,493,740	82,069,534
Low-risk patients	3,265,709	7,917,239	16,148,398
EVPI while off patent			
All patients	50,413,420	69,988,782	90,072,197
High-risk patients	34,107,321	48,687,162	63,485,715
Low-risk patients	11,903,071	11,705,540	12,525,800

EVPI, expected value of perfect information; QALY, quality-adjusted life-year.

generic clopidogrel (EVPI while off patent) reduced the total EVPI range to between £50.41 million and £69.99 million in all patients (and between £34.11 million and £57.94 million in high-risk patients and £10.76 million and £11.90 million in low-risk patients).

The separation of the results according to different risk groups, and the subsequent variability in the total EVPI estimates, may have important policy implications, particularly in relation to a future trial. As the cost-effectiveness estimates have demonstrated, the cost-effectiveness of alternative durations of clopidogrel differed markedly between the risk groups. While a strategy of 12 months of clopidogrel treatment appeared potentially cost-effective compared with shorter durations in all patients and in the subgroup of patients at high risk, strategies of treating beyond 3 months were not considered cost-effective for patients at low risk. It should also be recognised that since the CURE trial has been published, routine clinical practice has shifted towards greater use of invasive investigation in medium- to high-risk patients.[85] Given this, recent guidance from SIGN has suggested that the benefits of clopidogrel are likely to be overestimated in the case of more widespread application invasive investigation. The implications of this remain somewhat unclear. While, it is apparent that this may have an effect on the cost-effectiveness of longer treatment durations and potentially alter the conclusions based on cost-effectiveness regarding the optimal duration of clopidogrel in high-risk patients, it is also possible that this in itself could increase the decision uncertainty and hence the associated VOI. However, if routine clinical practice has shifted markedly in the UK to the extent that the CURE trial itself (or the model presented here) is no longer considered to be representative of current practice, then the results for this group of patients may be misleading.

Given the uncertainty surrounding changing practice, the result for the lower-risk group may be considered more reliable in terms of informing a future trial on the basis of the current model and the data inputs. At a threshold of £20,000–£30,000 per QALY, total EVPI ranged between £3.27 million and £20.38 million. These results are considerably lower than the EVPI results for all patients or the high-risk group. A separate analysis of EVPI in low-risk patients was also undertaken that looked at various combinations of strategies. This may assist in informing the potential design of any future trial, as it may not be feasible to run a trial with the five strategies outlined.

Figure 8 reports the EVPI estimates for different combinations of strategies in low-risk patients. The combinations of strategies with the highest EVPI were Strategies 1 (12 months of clopidogrel) versus 5 (standard care alone) and Strategies 1 (12 months of clopidogrel) versus 4 (1 month of clopidogrel). While the results of the cost-effectiveness analysis suggest that the question of most apparent interest would be a comparison of Strategies 1 (12 months of treatment based on current NICE guidelines) and 3 (3 months of treatment based on the results of the cost-effectiveness analysis and the recent SIGN guidelines), the value of a trial to inform this question appears to be markedly lower than other combinations (£8.13 million).

EVPPI

Although estimates of the total EVPI provide a useful global estimate of the uncertainty surrounding the adoption decision, they do not provide an indication of where further research would be of most value. EVPPI can be used to consider particular elements of the decision problem in order to direct and focus research towards the specific areas where the elimination of uncertainty has the most value. The EVPPI can be calculated for individual or subsets of parameters. This can be particularly relevant to the design of any future research, as subsets of parameters can be grouped according to related areas, and may also be used to separate out parameters for which a randomised design is necessary and those where this may not be essential (e.g. effectiveness parameters are likely to need a randomised design to minimise bias; however, issues of bias are likely to be less critical for obtaining epidemiological or cost data and observational design may be more appropriate). Given the computational time required to perform these calculations, they were undertaken using an assumption of constant relative effect (Scenario 1) at a threshold of £30,000 per QALY.

Parameters in the model were separated into three distinct areas:

1. effectiveness parameters – comprising the RR estimates applied in the model
2. epidemiology – comprising the baseline events and long-term prognosis parameters
3. costs – comprising the short- and longer-term cost inputs applied in the model.

Table 27 reports the results for EVPPI (also represented graphically in *Figure 9*). The results indicate the uncertainty surrounding the effectiveness parameters (hence the requirement

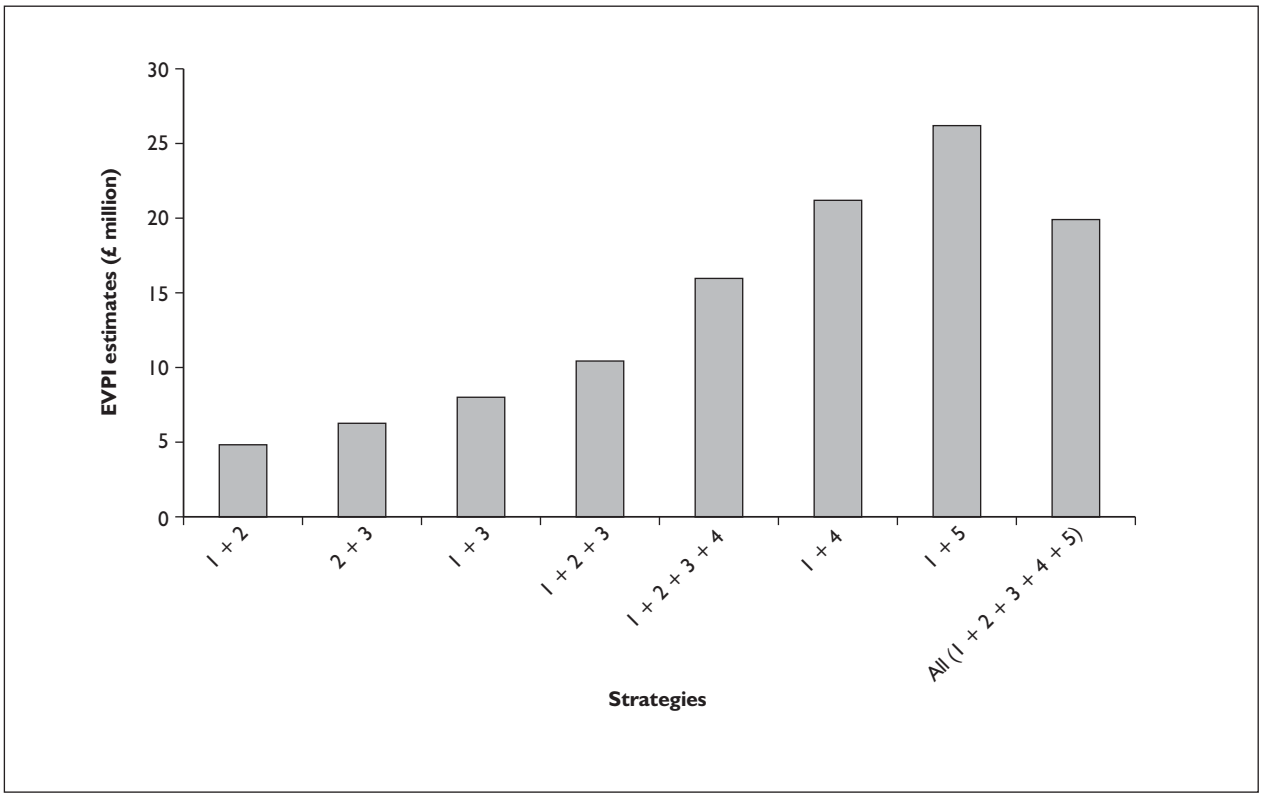

FIGURE 8 *Expected value of perfect information (EVPI) for different combinations of strategies, low-risk patients, on patent.*

for a randomised trial) contribute much more significantly to all patients and the high-risk group. In both of these groups, the effectiveness parameters account for the majority of the uncertainty surrounding the total EVPI estimates. However, for the low-risk group, the effectiveness parameters constitute less than 50% of the total EVPI estimates. Consequently, while the total EVPI (Scenario 1) ranges between £10.76 million and £20.38 million for the low-risk group, the VOI associated with the effectiveness parameters ranges between £4.25 million and £8.80 million.

Conclusions

From a cost-effectiveness perspective, the optimal duration of clopidogrel is clearly an important consideration, particularly in relation to issues of risk stratification. The updated model reinforced the conclusions from the earlier analysis. That is, a policy of 12 months of clopidogrel for patients with NSTE-ACS appears to be cost-effective both in 'average' patients (i.e. based on the average across all patient risks considered) and in the subgroup of higher-risk patients, compared with shorter-

TABLE 27 *EVPPI results (at a threshold of £30,000 per QALY) (£)*

	All patients, on patent	All patients, off patent	High risk, on patent	High risk, off patent	Low risk, on patent	Low risk, off patent
Total EVPI	108,454,348	66,929,942	77,100,300	57,936,239	20,376,578	10,762,438
Effectiveness	89,113,472	62,599,024	77,346,725	52,717,491	8,795,492	4,246,111
Epidemiology	1,326,024	0	25,558	0	7,112,372	1,129,651
Cost	3,269,190	477,875	498,879	228,462	3,097,121	1,046,485

EVPI, expected value of perfect information.

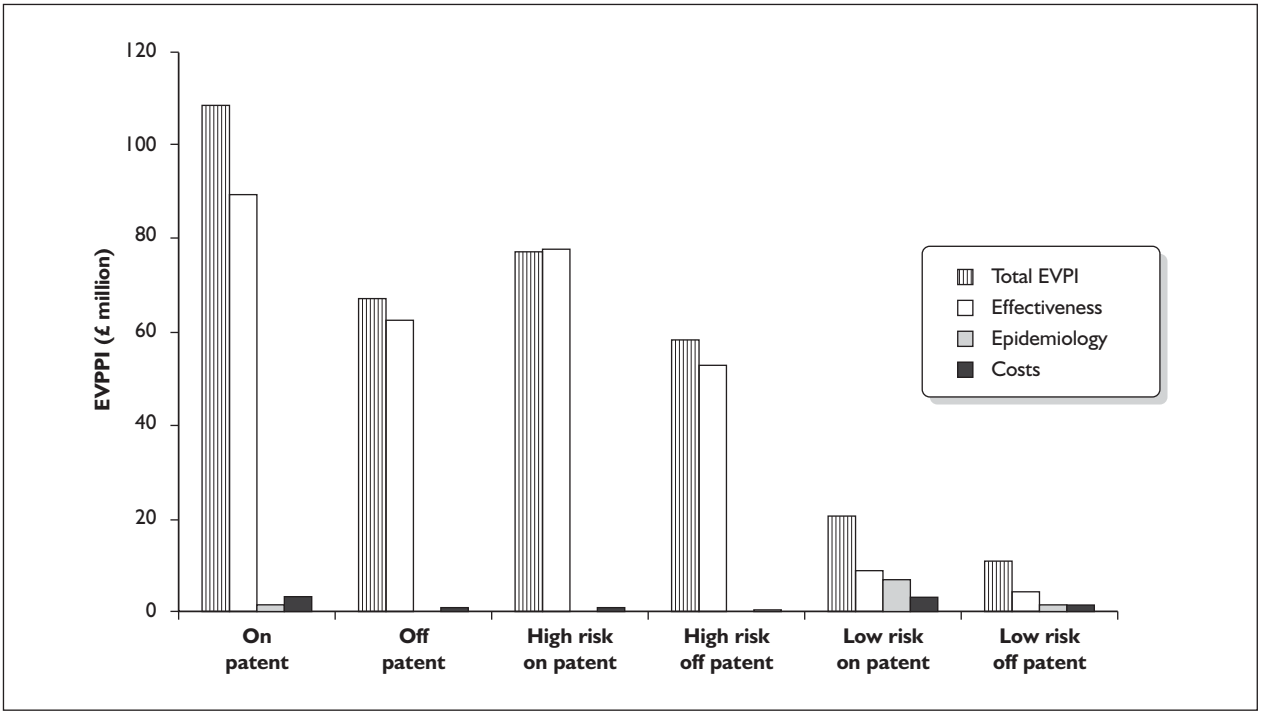

FIGURE 9 *Partial expected value of perfect information (EVPI) results (at a threshold of £30,000 per QALY).*

term durations. However, for lower-risk patients, treatment with clopidogrel beyond 3 months does not appear to be cost-effective. These conclusions appeared robust to alternative assumptions related to whether the relative effect of clopidogrel was assumed to remain constant over time or whether the treatment effect in the first 3 months was assumed to be greater than in later periods.

The major extension to the earlier work was a formal consideration of the VOI surrounding the decision problem. This was undertaken to assist in identifying future research priorities and, in particular, is used to establish the potential value of a future trial. This was done by estimating the EVPI associated with various scenarios in order to provide an upper bound to the amount a decision-maker should be willing to pay to obtain further information (and also assuming that this information will resolve all remaining uncertainty). Account was also taken of the potential impact when a generic version of clopidogrel becomes available. The analysis revealed considerable variation in the EVPI estimates. Estimates of EVPI were markedly higher for an 'average' patient and for high-risk patients compared with those for lower-risk patients. Similarly, consideration of the EVPI for parameter groups revealed that the contribution of the relative effectiveness parameters was less significant in the lower-risk patients. It was also acknowledged that if routine clinical practice has shifted markedly in the UK to the extent that the CURE trial itself (or the model presented here) is no longer considered to be representative of current practice for groups at high risk, then the results for this group of patients may be misleading.

At a threshold of £20,000–£30,000 per QALY, total EVPI ranged from £3.27 million to £20.38 million in the low-risk group. Given that a trial is unlikely to be able to report until after the market entry of generic clopidogrel; equivalent EVPI estimates for this scenario ranged between £10.8 million and £11.9 million. The EVPPI calculations demonstrated that approximately 40–45% of this value related to the relative effectiveness parameters (i.e. those for which an RCT would be required). Given that the estimates of EVPI represent upper bounds to further research and that some uncertainty will remain, then the true economic value will be even lower than those reported here.

Chapter 6
Discussion

Statement of principal findings

Clinical evaluation

There is evidence that clopidogrel is effective in reducing adverse cardiovascular events in patients with NSTE-ACS, with some indication that this benefit may be most evident in the first 3 months. There is some evidence that clopidogrel increases the risk of bleeding when compared with aspirin.[17–22] When stratified by the TIMI risk score, there was a significant reduction in the risk of the composite outcome cardiovascular death, MI or stroke in patients with low, intermediate and high risk of ACS, and a significant increase in the risk of major bleeding in patients classified as intermediate risk.[19] There was no direct evidence relating to the effectiveness of different durations of clopidogrel treatment in patients with NSTE-ACS.

Two small RCTs provided no suggestion of rebound effects following either clopidogrel or ticlopidine withdrawal in patients with NSTE-ACS.[47–49] One retrospective cohort suggested an increased risk of adverse events in the first 90 days after the withdrawal of clopidogrel. One small case series showed significant increases in some biomarkers 1 month after clopidogrel withdrawal in patients with PCI, but this was not evidence of rebound.[56]

Economic evaluation

In terms of the cost-effectiveness of alternative durations of clopidogrel, the updated model reinforced the conclusions from the earlier analysis. That is, a policy of 12 months of clopidogrel for patients with NSTE-ACS appears cost-effective both in 'average' patients (i.e. based on the average across all patient risks considered) and in the subgroup of higher-risk patients (the presence of any of the following: age > 70, ST depression or diabetes) compared with shorter-term durations. The ICER of 12 months' duration ranged from £13,380 to £20,661 per additional QALY across the different scenarios considered. However, for lower-risk patients (absence of any of the risk factors), treatment with clopidogrel beyond 3 months did not appear to be cost-effective. The ICER of 12 months of treatment with clopidogrel varied between £49,436 and £58,691 per QALY). These conclusions appeared robust to alternative assumptions related to whether the relative effect of clopidogrel was assumed to remain constant over time or was one in which the treatment effect in the first 3 months was assumed to be greater than in later periods.

Estimates of EVPI were markedly higher for an 'average' patient (i.e. based on all patients) and for high-risk patients than for those for lower-risk patients (ranging between £48.69 million and £108.4 million at a threshold of £30,000 per QALY). It was also acknowledged that more recent changes in routine clinical practice in the UK have shifted markedly in the UK to the extent that the CURE trial itself (or the model presented here) may no longer be considered to be representative of current practice for groups at high risk, and as such the EVPI results for this group of patients may be overstated.

At a threshold of £20,000–£30,000 per QALY, total EVPI ranged from £3.27 million to £20.38 million in the low-risk group. Given that a trial is unlikely to be able to report until after the market entry of generic clopidogrel, equivalent EVPI estimates for this scenario ranged between £10.8 million and £11.9 million. The EVPPI calculations demonstrated that approximately 40–45% of this value related to the treatment effectiveness parameters for clopidogrel (i.e. those for which an RCT would be required).

Strengths and limitations of the assessment

Strengths

We conducted an extensive search to locate appropriate published and unpublished research in any language to address a clear research question using predefined inclusion criteria. The study selection, data extraction, and quality assessment were conducted in duplicate, reducing the potential for error and bias. Efforts were made to obtain additional data on clinical effectiveness by contacting the authors of included studies.

The search was used to assist in the development of the updated decision model. The updated cost-effectiveness results represent the most systematic approach to date to address the cost-effectiveness of alternative durations of treatment with clopidogrel. The analysis was also extended to consider the cost of decision uncertainty to assist in identifying priorities (and equally importantly the potential value) for further research.

Limitations

From necessity, our review was limited by the available data. Only one additional RCT was identified that provided information on the clinical effectiveness of clopidogrel in patients with NSTE-ACS. However, this trial was likely to be underpowered, and reported limited results, with these being extrapolated primarily from a Kaplan–Meier graph. Therefore, the CURE trial remains the primary source of effectiveness and safety data in the NSTE-ACS population.

There were no studies that directly compared different durations of clopidogrel treatment. Despite the lack of evidence directly comparing different durations of clopidogrel it should be recognised that trials in related patient populations may provide additional evidence which could be considered in relation to the benefits of longer durations of clopidogrel treatment. As part of the inclusion criteria applied in our review, only studies evaluating clopidogrel in patients with unstable angina or non-ST-elevation myocardial infarction were considered. Consequently, RCTs in patients with stable CHD were excluded. However, clearly the natural history of CHD is characterised by periods of stability (asymptomatic or stable angina) and periods of acute instability (ACS). Hence, for durations of clopidogrel over 3 months, during which time many patients will be back in the stable state, evidence of the effectiveness of clopidogrel in stable patients may be relevant. The CHARISMA trial in patients with stable CHD failed to find a significant additional benefit associated with the use of clopidogrel plus aspirin versus aspirin alone (RR of primary end point 0.93; 95% CI 0.86–0.995; $p = 0.04$).[97–99] Interestingly, the RR estimate reported in the CHARISMA trial was very similar to the RR estimate applied in Scenario 2 of the model (RR 0.92; 95% CI 0.78–1.10). Hence, it is unlikely that the inclusion of the CHARISMA trial would significantly alter the conclusions based on this particular scenario. However, a more detailed consideration of the full range of evidence from trials in stable CHD may be a useful approach in future research.

With regard to the perceived rebound effect on the withdrawal of clopidogrel, there was only limited evidence in medically-treated patients to support this. Despite extensive searches for evidence in NSTE-ACS, there were no studies reporting events or levels in biomarkers before and after thienopyridine treatment withdrawal. The strongest evidence came from one retrospective cohort, indicating an increased risk of adverse events (acute MI or all-cause mortality) in the first 90 days after the withdrawal of clopidogrel. However, these data cannot confirm if the risk of adverse events following clopidogrel withdrawal was higher or lower than that in patients not treated with clopidogrel. Additional evidence relating to rebound following clopidogrel withdrawal came from studies of populations other than medically-treated NSTE-ACS reported cardiovascular event rates. This included the same retrospective cohort that reported an increased risk of adverse events in medically-treated patients, which also found an increased risk of adverse events in the first 90 days after the withdrawal of clopidogrel in patients who had undergone PCI.

The cost-effectiveness and VOI analyses are subject to a number of potential limitations. These relate both to the limitations noted in relation to the effectiveness parameters and to the limited evidence on the potential rebound effect, but also to the uncertainty surrounding a range of other factors. Firstly, the issue of risk stratification is clearly an important consideration. However, it should be noted that the pragmatic approach to risk stratification applied in the decision model (due to limited patient numbers and data available in the epidemiological data used) dichotomised the population into two separate risk categories (higher- and lower-risk patients). This meant that consideration could not be given to a wider categorisation (i.e. including a third group to represent patients at intermediate risk). Secondly, these definitions are not directly comparable with other risk stratification approaches that have been applied elsewhere. Indeed, it should be recognised that the sample of patients included in the epidemiological data set were all hospitalised for NSTE-ACS and hence are likely to be more representative of patients at intermediate to high risk using conventional classifications. Hence, the interpretation of the results in low- and high-risk groups should be seen in this context.

The results of the VOI demonstrate considerable variation in the potential value of further research. While the potential impact of the emergence of a generic version of clopidogrel was considered, there remains significant uncertainty about the actual price difference that will be realised, given that generic prices are highly dependent on regulatory environment, which is currently under reform in the UK. While a 10-year time horizon was chosen for the VOI calculations, there is clearly uncertainty in relation to the typical duration of health technology life cycles.

More importantly, the EVPI results present an upper bound to further research and hence do not provide both a necessary and sufficient condition, even if the cost of a trial fell below this amount. This is because a trial will resolve only a proportion of the uncertainty and as such the amount of uncertainty that is likely to be resolved would have to be assessed against the cost of the trial to ensure that any further research was considered an efficient use of resources. Finally, it is worth noting that even should research appear to provide a worthwhile use of NHS resources, the true opportunity cost of this research remains unclear. Indeed, there may be numerous other research areas, for which comparable EVPI estimates are not available, which would provide greater value for money than the specific application presented here. Hence, the more widespread use of VOI approaches to a broader range of applications would provide additional benchmarks with which to evaluate the value for money associated with research into a range of alternative decision problems.

Uncertainties

There is still a large degree of uncertainty surrounding both the optimal duration of clopidogrel treatment and the impact of withdrawal of clopidogrel treatment, which can only be addressed by further research. The most appropriate study design would be an RCT that directly compared different durations of clopidogrel treatment in patients with NSTE-ACS. Such a trial would compare the effects of 3 months' and 12 months' treatment with clopidogrel and would follow patients up after discontinuation of clopidogrel. Ideally, in order to definitively answer the possibility of a rebound effect with clopidogrel, outcomes would include with the measurement of biomarkers for platelet activity before, during and after clopidogrel treatment.

The proportion of patients who would have been treated with thienopyridines at the time of the CURE trial, who would now routinely undergo early PCI, is unclear. Since the completion of the CURE trial in 2000 and 2006, there was over a 100% increase in the number of PCIs conducted in the UK (see *Figure 1*).[101] It is not unreasonable to presume that many of the higher-risk patients that were included in the CURE trial would undergo an early PCI if treated today, rather than prolonged medical management or a late PCI procedure.

Changes in routine clinical practice (particularly for the high-risk group) may mean that the cost-effectiveness and VOI results may be less generalisable in particular risk groups. The implications of this remain uncertain. While it may clearly impact on the cost-effectiveness of longer-treatment durations and potentially alter the conclusions based on cost-effectiveness regarding the optimal duration of clopidogrel in high-risk patients, it is also possible that this itself could increase the decision uncertainty and hence the associated VOI. However, if routine clinical practice has shifted markedly in the UK to the extent that the CURE trial itself (or the model presented here) is no longer considered to be representative of current practice, then the results for this group of patients may be inaccurate.

Feasibility of further research

Ideally, an adequately powered, well-conducted RCT that directly compares different durations of clopidogrel treatment in patients with NSTE-ACS would be required to provide more robust evidence in relation to the impact of clopidogrel withdrawal. The use of an RCT would minimise possible biases associated with establishing causality of any potential rebound effect, and provide robust estimates of the relative effect of alternative durations of treatment. Such an RCT would also address the question of a possible rebound effect associated with clopidogrel withdrawal. However, the design and cost of this trial need to be evaluated carefully, both in relation to the VOI estimates reported here and to issues that may affect the feasibility of such research.

Clearly, an RCT which was sufficiently powered to address alternative durations of clopidogrel would inevitably have to be at least as large as the CURE study ($n = 12,562$), if not several times greater in magnitude, owing to the smaller effect sizes that would be predicted between different durations

of clopidogrel. The feasibility and timeliness of such a trial would therefore need to be questioned. Even if such a trial could be undertaken, it appears unlikely that such a study would be able to report prior to the market entry of a generic version of clopidogrel. As such, the off-patent results from the VOI analysis suggest that the value of further research would be markedly lower than research which would be available currently. Furthermore, should investigation of the physiological basis of any rebound effect be considered to be warranted, this could be accommodated by including assessment of biomarkers as one of the trial outcomes. Realistically, such additional demands would further militate against the feasibility of such a trial.

In addition to the costs and logistics of undertaking such an RCT, other considerations would also need to be taken into account. Owing to the potential for a lengthy delay between commissioning an RCT and the availability of the results, other factors relevant to the current decision problem may have markedly altered which could further limit the 'realisable' value of such research. Clearly, the emergence of alternative treatments which could represent relevant comparators to clopidogrel may significantly alter both the cost-effectiveness and VOI estimates presented here. In addition, practice could also significantly change during this period. Indeed, the use of coronary intervention is increasing markedly. If such a trend continues, then the VOI results presented here could significantly over-estimate the value of research, as these results related primarily to the use of clopidogrel in patients who are managed without coronary intervention. The EVPI estimates are likely to decline as the population multiplier applied in the calculations will become smaller as a higher proportion of patients are managed with coronary interventions. It should also be recognised that the more widespread use of coronary interventions and, in particular, the greater use of drug-eluting stents may mean that patients will not be eligible for earlier clopidogrel withdrawal owing to the risk of stent thrombosis.[119]

Chapter 7
Conclusions

Implications for service provision

- Clopidogrel combined with aspirin is more effective in reducing adverse cardiovascular events than aspirin alone in patients with NSTE-ACS.
- Clopidogrel combined with aspirin may increase the risk of bleeding compared with aspirin alone.
- The optimal duration of clopidogrel treatment in patients with NSTE-ACS is uncertain.
- There was some evidence that a rebound effect occurs following the withdrawal of clopidogrel, but its clinical significance was unclear.
- Cost-effectiveness results suggest that longer durations of clopidogrel (greater than 3 months) do not appear cost-effective in patients at lower risk. However, for an average-risk patient (and in higher-risk patients), 12 months' treatment of clopidogrel appears to be more cost-effective than shorter durations.

Recommendations for research

To determine optimal duration of clopidogrel treatment, a large, well-conducted RCT that directly compares different durations of clopidogrel treatment in patients with NSTE-ACS is ideally required. However, both the design and cost of this trial need to be evaluated carefully in relation to the VOI estimates reported here. In lower-risk groups, for which shorter durations of clopidogrel appear more cost-effective, it would seem unlikely that an adequately powered RCT would be considered to provide value for money owing to the significant cost that would be required to undertake such a study and the cost of the uncertainty that such a trial might resolve. In addition, to the potential value of such research, there remains a number of other issues which could affect the feasibility and timeliness of such research.

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Contribution of authors

Wolf Rogowski (Visiting Research Fellow) was involved in the cost-effectiveness section, study selection, development of the economic model and report writing. Jane Burch (Research Fellow) was responsible for study selection, data extraction, validity assessment, data analysis and writing the report. Stephen Palmer (Senior Research Fellow) was involved in the cost-effectiveness section, study selection, development of the economic model and report writing and took overall responsibility for the economic component. Cheryl Craigs (Research Fellow) was involved in study selection, data extraction, validity assessment, data analysis and writing of the report. Su Golder (Information Officer) devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. Nerys Woolacott (Senior Research Fellow) provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the review.

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Appendix 1

Search strategy

Searches for systematic reviews of clopidogrel

Cochrane Database of Systematic Reviews (CDSR)

Searched via The Cochrane Library, www.thecochranelibrary.com
Version: 2007 Issue 1
Date searched: 27/02/07

#1. (clopidogrel or ticlopidine or plavix):ti,ab,kw
#2. MeSH descriptor Ticlopidine
#3. (#1 OR #2), from 2002 to 2007
#4. (myocard* near/4 (infarct* or acute)) or (without near/2 st near/2 elevation*) or (non near/2 st near/2 elevation*) or nstemi or (non next stemi) or (heart next attack*) or (acute next coronary next syndrome*) or acs or (unstable near/2 angina) or pci or (percutaneous next coronary next intervention*) or (coronary next heart next disease*) or chd or (myocard* near/2 (isch?emia)) or ptca or (percutaneous next transluminal next coronary next angioplasty)
#5. MeSH descriptor Myocardial Infarction explode all trees
#6. MeSH descriptor Angina, Unstable, this term only
#7. MeSH descriptor Coronary Disease, this term only
#8. MeSH descriptor Myocardial Ischemia, this term only
#9. MeSH descriptor Angioplasty, Transluminal, Percutaneous Coronary, this term only
#10. (#4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11. (#3 AND #10)

This retrieved six records.

Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) Database

Searched via www.crd.york.ac.uk/crdweb/
Date searched: 01/03/07

#1. clopidogrel or ticlopidine or plavix
#2. MeSH descriptor Ticlopidine
#3. (#1 OR #2), from 2002 to 2007

This retrieved 43 records in DARE, and 14 records in the HTA database.

Searches for randomised controlled trials of clopidogrel

CENTRAL

Searched via The Cochrane Library
Version: 2007 Issue 1
Date searched: 27/02/07

#1. clopidogrel or ticlopidine or plavix
#2. MeSH descriptor Ticlopidine
#3. (#1 OR #2), from 2002 to 2007
#4. (myocard* near/4 (infarct* or acute)) or (without near/2 st near/2 elevation*) or (non near/2 st near/2 elevation*) or nstemi or (non next stemi) or (heart next attack*) or (acute next coronary next syndrome*) or acs or (unstable near/2 angina) or pci or (percutaneous next coronary next intervention*) or (coronary next heart next disease*) or chd or (myocard* near/2 (isch?emia)) or ptca or (percutaneous next transluminal next coronary next angioplasty)
#5. MeSH descriptor Myocardial Infarction explode all trees
#6. MeSH descriptor Angina, Unstable, this term only
#7. MeSH descriptor Coronary Disease, this term only
#8. MeSH descriptor Myocardial Ischemia, this term only
#9. MeSH descriptor Angioplasty, Transluminal, Percutaneous Coronary, this term only
#10. (#4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11. (#3 AND #10)

This retrieved 184 records.

CINAHL – Cumulative Index to Nursing & Allied Health Literature

Date range: 1982 to February week 3 2007
Searched via OVID Biomed
Date searched: 27/02/07
Search strategy:

1. exp Myocardial Infarction/(9236)
2. mi.ti. (646)
3. (myocard$adj4 (infarct$or acute)).ti,ab. (5971)
4. (without adj2 st adj2 elevation$).ti,ab. (24)
5. (non adj2 st adj2 elevation$).ti,ab. (233)
6. nstemi.ti,ab. (19)
7. non-stemi.ti,ab. (4)

8. heart attack$.ti,ab. (947)
9. acute coronary syndrome$.ti,ab. (949)
10. acs.ti,ab. (381)
11. (unstable adj2 angina).ti,ab. (545)
12. unstable angina/(797)
13. pci.ti,ab. (250)
14. percutaneous coronary intervention$.ti,ab. (629)
15. Coronary Disease/(6847)
16. coronary heart disease$.ti,ab. (3000)
17. chd.ti,ab. (1216)
18. (myocard$adj2 ischaemia).ti,ab. (72)
19. (myocard$adj2 ischemia).ti,ab. (484)
20. myocardial ischemia/(1337)
21. ptca.ti,ab. (241)
22. percutaneous transluminal coronary angioplasty.ti,ab. (301)
23. Angioplasty, Transluminal, Percutaneous Coronary/(1655)
24. or/1–23 (20664)
25. Ticlopidine/(109)
26. Ticlopidine.ti,ab. (59)
27. clopidogrel.ti,ab. (263)
28. plavix.ti,ab. (15)
29. Clopidogrel Bisulfate/(343)
30. 2007$.ew. (37438)
31. 2006$.ew. (164153)
32. 2005$.ew. (151990)
33. 2004$.ew. (130980)
34. 2003$.ew. (107909)
35. or/30–34 (592470)
36. 24 and (or/26–29) and 35 (216)
37. exp random sample/(28663)
38. random assignment/(14687)
39. exp prospective studies/(53768)
40. exp Clinical Trials/(42343)
41. clinical trial.pt. (19954)
42. (clin$adj25 trial$).ti,ab. (12803)
43. ((singl$or doubl$or tripl$or trebl$) adj25 (blind$or mask$)).ti,ab. (6121)
44. placebos/(3376)
45. placebo$.ti,ab. (8367)
46. random$.ti,ab. (40555)
47. rct.ti,ab. (637)
48. Research Methodology/(6574)
49. quantitative studies/(3075)
50. or/37–49 (131546)
51. 36 and 50 (92)

EMBASE

Date range: 1996 to 2007 week 8
Searched via OVID Biomed
Date searched: 27/02/07
Search strategy:

1. exp Heart Infarction/(62298)
2. mi.ti. (561)
3. (myocard$adj4 (infarct$or acute)).ti,ab. (44006)
4. (without adj2 st adj2 elevation$).ti,ab. (404)
5. (non adj2 st adj2 elevation$).ti,ab. (1139)
6. nstemi.ti,ab. (222)7 non-stemi.ti,ab. (30)
7. heart attack$.ti,ab. (1060)
8. acute coronary syndrome$.ti,ab. (6236)
9. acs.ti,ab. (2979)
10. (unstable adj2 angina).ti,ab. (4882)
11. exp Unstable Angina Pectoris/(6153)
12. pci.ti,ab. (3478)
13. percutaneous coronary intervention$.ti,ab. (4500)
14. Ischemic Heart Disease/(27358)
15. coronary artery disease/(34422)
16. coronary heart disease$.ti,ab. (14352)
17. chd.ti,ab. (6083)
18. (myocard$adj2 ischaemia).ti,ab. (1533)
19. (myocard$adj2 ischemia).ti,ab. (7078)
20. heart muscle ischemia/(24337)
21. ptca.ti,ab. (3349)
22. percutaneous transluminal coronary angioplasty.ti,ab. (2999)
23. Transluminal Coronary Angioplasty/(9877)
24. or/1–24 (140029)
25. Ticlopidine/(5381)
26. Ticlopidine.ti,ab. (1272)
27. clopidogrel.ti,ab. (2143)
28. Clopidogrel/(8373)
29. plavix.ti,ab. (72)
30. or/26–30 (11249)
31. 2007$.em. (85039)
32. 2006$.em. (630103)
33. 2005$.em. (563462)
34. 2004$.em. (535805)
35. 2003$.em. (509598)
36. or/32–36 (2324007)
37. prasugrel.af. (85)
38. cs-747.af. (48)
39. LY640315.af. (7)
40. or/38–40 (103)
41. Randomized Controlled Trial/(100635)
42. randomization/(19605)
43. Double-Blind Procedure/(44058)
44. single-blind procedure/(5460)
45. Crossover Procedure/(14358)
46. rct$.ti,ab. (2887)
47. randomi?ed control$trial$.ti,ab. (20969)
48. (clin$adj2 trial$).ti,ab. (71951)
49. *clinical trial/(1280)
50. random allocation.ti,ab. (318)
51. randomly allocated.ti,ab. (5381)
52. (random adj2 allocated).ti,ab. (139)
53. ((single or double or treble or triple) adj blind$).ti,ab. (43118)
54. placebo$.ti,ab. (56566)
55. 25 and 31 and 41 (4117)
56. or/42–55(218594)

57. 56 and 57 (791)

MEDLINE
Date range: 1996 to February week 2 2007
Searched via OVID Biomed
Date searched: 27/02/07
Search strategy:

1. exp Myocardial Infarction/(38787)
2. mi.ti. (420)
3. (myocard$adj4 (infarct$or acute)).ti,ab. (43643)
4. (without adj2 st adj2 elevation$).ti,ab. (383)
5. (non adj2 st adj2 elevation$).ti,ab. (1077)
6. nstemi.ti,ab. (167)
7. non-stemi.ti,ab. (25)
8. heart attack$.ti,ab. (1413)
9. acute coronary syndrome$.ti,ab. (5990)
10. acs.ti,ab. (2947)
11. (unstable adj2 angina).ti,ab. (4840)
12. unstable angina/(4427)
13. pci.ti,ab. (3118)
14. percutaneous coronary intervention$.ti,ab. (4219)
15. Coronary Disease/(33355)
16. coronary heart disease$.ti,ab. (14431)
17. chd.ti,ab. (5972)
18. (myocard$adj2 ischaemia).ti,ab. (1367)
19. (myocard$adj2 ischemia).ti,ab. (7033)
20. myocardial ischemia/(16399)
21. ptca.ti,ab. (3129)
22. percutaneous transluminal coronary angioplasty.ti,ab. (2950)
23. Angioplasty, Transluminal, Percutaneous Coronary/(13792)
24. or/1–23 (112235)
25. Ticlopidine/(2305)
26. Ticlopidine.ti,ab. (1119)
27. clopidogrel.ti,ab. (1842)
28. plavix.ti,ab. (64)
29. or/25–28 (3204)
30. 2007$.ed. (88626)
31. 2006$.ed. (633206)
32. 2005$.ed. (595731)
33. 2004$.ed. (584307)
34. 2003$.ed. (531876)
35. or/30–34 (2433746)
36. randomized controlled trial.pt. (133677)
37. 24 and 29 and 35 and 36 (140)

MEDLINE In-Process & Other Non-Indexed Citations
Date range: up to 26 February 2007
Searched via OVID Biomed
Date searched: 27/02/07
Search strategy:

1. mi.ti. (81)
2. (myocard$adj4 (infarct$or acute)).ti,ab. (1957)
3. (without adj2 st adj2 elevation$).ti,ab. (16)
4. (non adj2 st adj2 elevation$).ti,ab. (70)
5. nstemi.ti,ab. (16)
6. non-stemi.ti,ab. (12)
7. heart attack$.ti,ab. (65)
8. acute coronary syndrome$.ti,ab. (383)
9. acs.ti,ab. (245)
10. (unstable adj2 angina).ti,ab. (167)
11. pci.ti,ab. (328)
12. percutaneous coronary intervention$.ti,ab. (355)
13. coronary heart disease$.ti,ab. (668)
14. chd.ti,ab. (350)
15. (myocard$adj2 ischaemia).ti,ab. (57)
16. (myocard$adj2 ischemia).ti,ab. (285)
17. ptca.ti,ab. (59)
18. percutaneous transluminal coronary angioplasty.ti,ab. (57)
19. Ticlopidine.ti,ab. (30)
20. clopidogrel.ti,ab. (180)
21. plavix.ti,ab. (8)
22. ((singl$or doubl$or tripl$or trebl$) adj25 (blind$or mask$)).ti,ab. (1692)
23. placebo$.ti,ab. (2300)
24. rct.ti,ab. (189)
25. random$.af. (17010)
26. trial$.af. (11217)
27. or/1–18 (3620)
28. or/19–21 (208)
29. or/22–26 (24568)
30. 27 and 28 and 29 (33)

Searches for systematic reviews of prasugrel

Cochrane Database of Systematic Reviews (CDSR)

Searched via The Cochrane Library
Version: 2007 Issue 1
Date searched: 27/02/07

There was no need to limit by disease terms as so few records were retrieved with the following search strategy.

#1. prasugrel
#2. cs-747
#3. LY640315
#4. #1 or #2 or #3 or #4

This retrieved no records in CDSR and four in CENTRAL.

Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) Database

Searched via www.crd.york.ac.uk/crdweb/
Date searched: 27/02/07

#1. prasugrel
#2. cs-747
#3. LY640315
#4. #1 or #2 or #3 or #4

This retrieved one record in HTA.

Searches for randomised controlled trials of prasugrel

CENTRAL

Searched via The Cochrane Library
Version: 2007 Issue 1
Date searched: 27/02/07

There was no need to limit by disease terms as so few records were retrieved with the following search strategy.

#1. prasugrel
#2. cs-747
#3. LY640315
#4. #1 or #2 or #3 or #4

This retrieved 4 records.

CINAHL – Cumulative Index to Nursing & Allied Health Literature

Date range: 1982 to February week 3 2007
Searched via OVID Biomed
Date searched: 27/02/07
Search strategy:

1. prasugrel.af. (1)
2. cs-747.af. (1)
3. LY640315.af. (1)
4. or/1–3 (1)

EMBASE

Date range: 1996 to 2007 week 8
Searched via OVID Biomed
Date searched: 27/02/07
Search strategy:

1. exp Heart Infarction/(62298)
2. mi.ti. (561)
3. (myocard$adj4 (infarct$or acute)).ti,ab. (44006)
4. (without adj2 st adj2 elevation$).ti,ab. (404)
5. (non adj2 st adj2 elevation$).ti,ab. (1139)
6. nstemi.ti,ab. (222)
7. non-stemi.ti,ab. (30)
8. heart attack$.ti,ab. (1060)
9. acute coronary syndrome$.ti,ab. (6236)
10. acs.ti,ab. (2979)
11. (unstable adj2 angina).ti,ab. (4882)
12. exp Unstable Angina Pectoris/(6153)
13. pci.ti,ab. (3478)
14. percutaneous coronary intervention$.ti,ab. (4500)
15. Ischemic Heart Disease/(27358)
16. coronary artery disease/(34422)
17. coronary heart disease$.ti,ab. (14352)
18. chd.ti,ab. (6083)
19. (myocard$adj2 ischaemia).ti,ab. (1533)
20. (myocard$adj2 ischemia).ti,ab. (7078)
21. heart muscle ischemia/(24337)
22. ptca.ti,ab. (3349)
23. percutaneous transluminal coronary angioplasty.ti,ab. (2999)
24. Transluminal Coronary Angioplasty/(9877)
25. or/1–24 (140029)
26. prasugrel.af. (85)
27. cs-747.af. (48)
28. LY640315.af. (7)
29. or/26–28 (103)
30. Randomized Controlled Trial/(100635)
31. randomization/(19605)
32. Double-Blind Procedure/(44058)
33. single-blind procedure/(5460)
34. Crossover Procedure/(14358)
35. rct$.ti,ab. (2887)
36. randomi?ed control$trial$.ti,ab. (20969)
37. (clin$adj2 trial$).ti,ab. (71951)
38. *clinical trial/(1280)
39. random allocation.ti,ab. (318)
40. randomly allocated.ti,ab. (5381)
41. (random adj2 allocated).ti,ab. (139)
42. ((single or double or treble or triple) adj blind$).ti,ab. (43118)
43. placebo$.ti,ab. (56566)
44. or/30–43 (218594)
45. 25 and 29 and 44 (21)

MEDLINE

Date range: 1996 to February week 2 2007
Searched via OVID Biomed
Date searched: 27/02/07
Search strategy:

1. prasugrel.af. (26)
2. cs-747.af. (11)
3. LY640315.af. (6)
4. or/1–3 (28)

MEDLINE In-Process & Other Non-Indexed Citations

Date range: up to 26 February 2007
Searched via OVID Biomed
Date searched: 27/02/07
Search strategy:

1. prasugrel.af. (8)
2. cs-747.af. (0)
3. LY640315.af. (0)
4. or/1–3 (8)

Searches for economic evaluations of clopidogrel

NHS Economic Evaluation Database (NHS EED)

Searched via www.crd.york.ac.uk/crdweb/
Date searched: 01/03/07

#1. clopidogrel or ticlopidine or plavix
#2. MeSH descriptor Ticlopidine
#3. (#1 OR #2), from 2002 to 2007

This retrieved 45 records.

Health Economic Evaluations Database (HEED)

March 2007
Date searched: 01/03/07

clopidogrel or ticlopidine or plavix

This retrieved 97 records.

Searches for economic evaluations of prasugrel

NHS Economic Evaluation Database (NHS EED)

Searched via www.crd.york.ac.uk/crdweb/
Date searched: 27/02/07

#1. prasugrel
#2. cs-747
#3. LY640315
#4. #1 or #2 or #3 or #4

This retrieved one record in HTA.

Health Economic Evaluations Database (HEED)

March 2007
Date searched: 01/03/07

Prasugrel or cs-747 or LY640315

This retrieved no records.

Searches for withdrawal/rebound/ discontinuation of clopidogrel

CINAHL – Cumulative Index to Nursing & Allied Health Literature

Date range: 1982 to May week 1 2007
Searched via OVID Biomed
Date searched: 09/05/07
Search strategy:

1. exp myocardial infarction/(9476)
2. mi.ti. (663)
3. (myocard$adj4 (infarct$or acute)).ti,ab. (6108)
4. (without adj2 st adj2 elevation$).ti,ab. (24)
5. (non adj2 st adj2 elevation$).ti,ab. (238)
6. nstemi.ti,ab. (20)
7. non-stemi.ti,ab. (5)
8. heart attack$.ti,ab. (966)
9. acute coronary syndrome$.ti,ab. (983)
10. acs.ti,ab. (395)
11. (unstable adj2 angina).ti,ab. (550)
12. unstable angina/(821)
13. pci.ti,ab. (261)
14. percutaneous coronary intervention$.ti,ab. (651)
15. coronary disease/(6993)
16. coronary heart disease$.ti,ab. (3059)
17. chd.ti,ab. (1240)
18. (myocard$adj2 ischaemia).ti,ab. (73)
19. (myocard$adj2 ischemia).ti,ab. (496)
20. myocardial ischemia/(1376)
21. ptca.ti,ab. (244)
22. percutaneous transluminal coronary angioplasty.ti,ab. (305)
23. angioplasty, transluminal, percutaneous coronary/(1716)
24. stroke$.ti,ab. (11870)
25. Cerebrovascular Accident/(11975)
26. (cerebrovascular adj2 accident$).ti,ab. (423)
27. cva.ti,ab. (244)
28. Ischemic Attack, Transient/(0)
29. (transient adj2 (ischemic or ischaemic)).ti,ab. (415)
30. tia.ti,ab. (209)
31. Peripheral Vascular Diseases/(1027)
32. ((peripheral adj (arter$or vascular) adj disease) or PAD).ti,ab. (1314)
33. or/1–32 (36570)
34. ticlopidine/(111)
35. ticlopidine.ti,ab. (59)
36. clopidogrel.ti,ab. (276)
37. plavix.ti,ab. (18)
38. clopidogrel bisulfate/(362)
39. or/34–38 (502)

40. 33 and 39 (352)
41. rebound.ti,ab. (251)
42. withdraw$.ti,ab. (3500)
43. discontinu$.ti,ab. (2759)
44. or/41–43 (6311)
45. 40 and 44 (5)

EMBASE

Date range: 1996 to 2007 week 18
Searched via OVID Biomed
Date searched: 08/05/07
Search strategy:

1. exp heart infarction/(64253)
2. mi.ti. (570)
3. (myocard$adj4 (infarct$or acute)).ti,ab. (45144)
4. (without adj2 st adj2 elevation$).ti,ab. (419)
5. (non adj2 st adj2 elevation$).ti,ab. (1192)
6. nstemi.ti,ab. (230)
7. non-stemi.ti,ab. (35)
8. heart attack$.ti,ab. (1084)
9. acute coronary syndrome$.ti,ab. (6489)
10. acs.ti,ab. (3120)
11. (unstable adj2 angina).ti,ab. (4941)
12. exp unstable angina pectoris/(6270)
13. pci.ti,ab. (3676)
14. percutaneous coronary intervention$.ti,ab. (4752)
15. ischaemic heart disease/(28100)
16. coronary heart disease/(28100)
17. coronary heart disease$.ti,ab. (14674)
18. chd.ti,ab. (6243)
19. (myocard$adj2 ischaemia).ti,ab. (1557)
20. (myocard$adj2 ischemia).ti,ab. (7242)
21. heart muscle ischemia/(24916)
22. ptca.ti,ab. (3372)
23. percutaneous transluminal coronary angioplasty.ti,ab. (3019)
24. transluminal coronary angioplasty/(10027)
25. Stroke/(42540)
26. stroke$.ti,ab. (50200)
27. Cerebrovascular Accident/(13500)
28. (cerebrovascular adj2 accident$).ti,ab. (1638)
29. cva.ti,ab. (612)
30. Transient Ischemic Attack/(5784)
31. (transient adj2 (ischemic or ischaemic)).ti,ab. (3428)
32. tia.ti,ab. (1907)
33. Peripheral Vascular Disease/(4030)
34. ((peripheral adj (arter$or vascular) adj disease) or PAD).ti,ab. (8221)
35. or/1–34 (188519)
36. ticlopidine/(5530)
37. ticlopidine.ti,ab. (1291)
38. clopidogrel/(8879)
39. clopidogrel.ti,ab. (2255)
40. plavix.ti,ab. (77)
41. or/36–40 (11794)
42. 35 and 41 (7418)
43. rebound.ti,ab. (3286)
44. drug treatment failure/or drug withdrawal/or rebound/(26343)
45. withdraw$.ti,ab. (32781)
46. discontinu$.ti,ab. (28240)
47. or/43–46 (77342)
48. 42 and 47 (346)

MEDLINE

Date range: 1996 to April week 4 2007
Searched via OVID Biomed
Date searched: 09/05/07
Search strategy:

1. exp myocardial infarction/(39803)
2. mi.ti. (428)
3. (myocard$adj4 (infarct$or acute)).ti,ab. (44780)
4. (without adj2 st adj2 elevation$).ti,ab. (394)
5. (non adj2 st adj2 elevation$).ti,ab. (1118)
6. nstemi.ti,ab. (171)
7. non-stemi.ti,ab. (31)
8. heart attack$.ti,ab. (1456)
9. acute coronary syndrome$.ti,ab. (6228)
10. acs.ti,ab. (3075)
11. (unstable adj2 angina).ti,ab. (4907)
12. unstable angina/(4516)
13. pci.ti,ab. (3281)
14. percutaneous coronary intervention$.ti,ab. (4453)
15. coronary disease/(33867)
16. coronary heart disease$.ti,ab. (14790)
17. chd.ti,ab. (6154)
18. (myocard$adj2 ischaemia).ti,ab. (1397)
19. (myocard$adj2 ischemia).ti,ab. (7198)
20. myocardial ischemia/(16745)
21. ptca.ti,ab. (3143)
22. percutaneous transluminal coronary angioplasty.ti,ab. (2970)
23. angioplasty, transluminal, percutaneous coronary/(14170)
24. stroke$.ti,ab. (48243)
25. Cerebrovascular Accident/(21784)
26. (cerebrovascular adj2 accident$).ti,ab. (1637)
27. cva.ti,ab. (606)
28. Ischemic Attack, Transient/(4891)
29. (transient adj2 (ischemic or ischaemic)).ti,ab. (3219)
30. tia.ti,ab. (1800)
31. Peripheral Vascular Diseases/(3892)
32. ((peripheral adj (arter$or vascular) adj disease) or PAD).ti,ab. (8295)
33. or/1–32 (171966)

34. ticlopidine/(2396)
35. ticlopidine.ti,ab. (1136)
36. clopidogrel.ti,ab. (1939)
37. plavix.ti,ab. (71)
38. or/34–37 (3337)
39. 33 and 38 (2089)
40. rebound.ti,ab. (3131)
41. withdraw$.ti,ab. (31006)
42. discontinu$.ti,ab. (27225)
43. or/40–42 (59032)
44. 39 and 43 (112)

MEDLINE In-Process & Other Non-Indexed Citations

Date range: up to 8 May 2007
Searched via OVID Biomed
Date searched: 09/05/07
Search strategy:

1. [exp myocardial infarction/] (0)
2. mi.ti. (88)
3. (myocard$adj4 (infarct$or acute)).ti,ab. (1914)
4. (without adj2 st adj2 elevation$).ti,ab. (18)
5. (non adj2 st adj2 elevation$).ti,ab. (70)
6. nstemi.ti,ab. (16)
7. non-stemi.ti,ab. (8)
8. heart attack$.ti,ab. (61)
9. acute coronary syndrome$.ti,ab. (411)
10. acs.ti,ab. (267)
11. (unstable adj2 angina).ti,ab. (166)
12. unstable angina/(0)
13. pci.ti,ab. (351)
14. percutaneous coronary intervention$.ti,ab. (356)
15. coronary disease/(0)
16. coronary heart disease$.ti,ab. (623)
17. chd.ti,ab. (336)
18. (myocard$adj2 ischaemia).ti,ab. (52)
19. (myocard$adj2 ischemia).ti,ab. (290)
20. myocardial ischemia/(0)
21. ptca.ti,ab. (61)
22. percutaneous transluminal coronary angioplasty.ti,ab. (55)
23. angioplasty, transluminal, percutaneous coronary/(0)
24. stroke$.ti,ab. (2496)
25. Cerebrovascular Accident/(0)
26. (cerebrovascular adj2 accident$).ti,ab. (69)
27. cva.ti,ab. (37)
28. Ischemic Attack, Transient/(0)
29. (transient adj2 (ischemic or ischaemic)).ti,ab. (129)
30. tia.ti,ab. (81)
31. Peripheral Vascular Diseases/(0)
32. ((peripheral adj (arter$or vascular) adj disease) or PAD).ti,ab. (433)
33. or/1–32 (6225)
34. ticlopidine/(0)
35. ticlopidine.ti,ab. (30)
36. clopidogrel.ti,ab. (184)
37. plavix.ti,ab. (6)
38. or/34–37 (205)
39. 33 and 38 (100)
40. rebound.ti,ab. (157)
41. withdraw$.ti,ab. (1952)
42. discontinu$.ti,ab. (1833)
43. or/40–42 (3849)
44. 39 and 43 (6)

All results were saved to rebound.enl.

Database	Results	After deduplication	Custom 4 field
EMBASE	346	344	EMBASE 09/05/07
MEDLINE	112	38	MEDLINE 09/05/07
MEDLINE In-Process	6	4	MEDLINE In-Process 09/05/07
CINAHL	5	1	CINAHL 09/05/07
Total	469	387	

Results were then deduplicated against RCTs main library (as these have already been screened) and saved as rebound minus rcts main library.enl (345 results).

Appendix 2

Investigation of a rebound effect following clopidogrel withdrawal: results of studies evaluating withdrawal of thienopyridine treatment in populations other than NSTE-ACS

Most of the additional studies retrieved were of patients who had undergone stent implantation; therefore, given the introduction of a foreign body into the cardiovascular system, the risk of adverse clinical events was thought not likely to be comparable to that of the general ACS population, or more generally of cardiovascularly compromised patients. Results from the few studies of patients with PAD, stroke or MI, or who had discontinued therapy to undergo surgery other than PCI, were thought most likely to be more representative of the NSTE-ACS population and are therefore discussed first; however, these do not offer any conclusive evidence of a rebound effect following withdrawal of clopidogrel.

PAD, stroke, MI and discontinuation for non-PCI surgery

Only three studies reported event rates in patients who had not undergone PCI.[82–84] One reported a case series of 23 patients who were to undergo lithotripsy and who were taking antiplatelet therapy, owing to previous MI, coronary artery bypass graft (CABG), TIA, chronic atrial fibrillation or PAD.[83] Antiplatelet therapy was discontinued 8 days before lithotripsy and haemorrhagic and thromboembolic events were reported. Of these 23 patients, three received ticlopidine (the remaining patients received either aspirin or dipyridamole), none of whom showed any thromboembolic complications. A second case series comprised 320 patients hospitalised after a TIA or stroke; the drugs administered to the patients during the month prior to admission were recorded.[82] Of the 22 patients who had been administered clopidogrel during the month prior to admission, one had discontinued antiplatelet therapy 10 days prior to an ischaemic stroke. Finally, there were two case reports; both patients discontinued therapy 1 week prior to Mohs micrographic surgery (a technique using a microscope to ensure the complete removal of cancerous skin cells).[84] One patient with prior stroke and MI receiving ticlopidine suffered a deep vein thrombosis 36 hours post-surgery. The second patient had a history of atherosclerosis, CABG, aortic valve replacement and breast cancer and suffered a clotted prosthetic aortic valve 3 days post-surgery. These reports do not provide any evidence to confirm or reject the existence of rebound following clopidogrel withdrawal.

PCI

RCTs

Five RCTs compared clopidogrel and ticlopidine therapy for patients undergoing a PCI. One RCT administered clopidogrel ($n = 355$) or ticlopidine ($n = 345$) for 1 month following PCI; the incidence of cardiovascular death and ischaemic events was recorded at long-term follow-up.[50] The trial reported that, approximately 2 years after the PCI, 40 (11.3%) participants in the clopidogrel group and 19 (5.5%) participants in the ticlopidine group either died due to cardiovascular problems or experienced a non-fatal MI. While this result shows a significantly lower risk of cardiovascular mortality or non-fatal MI in the ticlopidine group than in the clopidogrel group, it does not provide any evidence for rebound effects. The four remaining trials described occurrences of stent thrombosis following the unplanned discontinuation of clopidogrel or ticlopidine therapy (*Table 28*); these trials also offer no evidence of a rebound effect.

Cohort studies

One observational cohort study evaluated 2226 consecutive patients who had undergone a successful stent implantation, and then received either clopidogrel or ticlopidine for 3–6 months.[55] Of these, 17 discontinued their treatment prematurely, five of whom went on to develop a stent thrombosis (29.4%). This rate of thrombosis was higher than that for the study population as a whole, with 49 (2.2%) patients developing a

TABLE 28 *Number of patients experiencing stent occlusion following unplanned/premature discontinuation of clopidogrel after PCI*

	Juergens (2004)[51]	Biondi-Zoccai (2006)[52]	Bertrand (2000)[53]	Berger (1999)[54]
Intervention and its duration				
Clopidogrel	150 mg loading dose; 75 mg daily (*n* = 154)	Dose not stated (*n* = 393)	75 mg daily (*n* = 335) or 300 mg loading dose; 75 mg daily (*n* = 345)	300 mg loading dose; 75 mg daily (*n* = 500)
Ticlopidine	500 mg loading dose; 250 mg twice daily (*n* = 153)	Dose not stated (*n* = 112)	250 mg twice daily (*n* = 340).	500 mg loading dose; 250 mg twice daily (*n* = 827)
Duration of treatment	2 weeks	8 months	28 days	2 weeks
Number of cases of premature discontinuation				
Clopidogrel	1	Not reported	17 and 7	Not reported
Ticlopidine	2	Not reported	28	Not reported
Number of cases of stent occlusion				
Clopidogrel	0	0	0 and 0	1
Ticlopidine	1	2	0	None reported

stent thrombosis. Premature discontinuation of thienopyridine therapy was identified as a risk factor for subsequent stent thrombosis.

The retrospective cohort study described in Chapter 3 provided results for patients who had undergone PCI as well as for those who were treated medically.[38] Of the 1569 patients who received PCI for ACS and discontinued clopidogrel therapy during the follow-up period, 984 received bare metal stents and 585 received drug-eluting stents. Of these, 124 (7.9%) suffered an acute MI or died, with 73 (58.9%) of these incidents occurring within the first 90 days post withdrawal of clopidogrel. This translates into an incidence rate per 1000 patient days of follow-up of 0.57 (95% CI 0.45–0.72) for the first 90 days, 0.33 (95% CI 0.23–0.47) for 91–180 days and 0.19 (95% CI 0.09–0.37) for 181–270 days' follow-up. Using multivariate analysis, a significantly increased risk of adverse events was demonstrated in the 0–90 day post-withdrawal period compared with the 91–180 day period (IRR 1.82; 95% CI 1.17–2.83). When analysed separately, the result for patients whose PCI involved a bare metal stent was IRR 2.14; 95% CI 1.23–3.74.

Case series

Eight case series provided information relating to outcomes after discontinuation of thienopyridine therapy (five of clopidogrel, two of ticlopidine and one not specified). One case series of 54 long-term clopidogrel users reported the results of biomarkers 1 month after clopidogrel withdrawal.[56] This study showed significant increases in some biomarkers 1 month post-withdrawal, most notably increases in ADP-induced percentage platelet aggregation. However, there were no significant increases in the platelet count or volume (*Table 29*).[56] This study was conducted in diabetic patients who were considered to be more susceptible to atherothrombotic events due to increased platelet reactivity and proinflammatory status.

The remaining four case series evaluating clopidogrel reported clinical outcomes between 5 months and 2.5 years post-withdrawal (*Table 30*).[57–60] One trial reported outcomes for 13 patients who discontinued treatment prematurely.61 This study reported a higher rate of stent occlusion in these patients (3/13; 23.1%) than that reported in the overall study population (6/404; 1.5%), and concluded that the discontinuation of clopidogrel was associated with a poorer outcome.

Three studies reported outcomes for ticlopidine,[63,120] or data for thienopyridine therapy generally (*Table 31*).[64] Two studies compared the clinical outcomes for those who completed the prescribed regimen with those who discontinued early;[74,120] both showed a much higher rate of reported events in the patients that discontinued therapy early, and concluded that premature discontinuation of thienopyridine therapy was strongly associated with an increased mortality[64] or stent thrombosis.[120] The third reported outcomes

TABLE 29 *Comparison of mean (SD) levels of biomarkers for 54 long-term clopidogrel users at baseline and 1 month after clopidogrel withdrawal*[56]

Outcome	Baseline vs 1 month post-withdrawal	
hs-CRP (mg/dl)	30 vs 40[a]	$p < 0.05$
P-selectin resting: % positive platelets	16 vs 28[a]	$p < 0.001$
P-selectin ADP stimulated: % positive platelets	31 vs 58[a]	$p < 0.0001$
% Platelet aggregation following ADP stimuli		
6 μmol/l ADP	45 vs 69[a]	$p < 0.0001$
20 mol/l ADP	55 vs 77[a]	$p < 0.0001$
HbA1C levels, % (SD)	7.1 (1.3) vs 7.1(1.9)	$p > 0.05$
Haematocrit, % (SD)	40.5 (3.8) vs 41.2 (3.3)	$p > 0.05$
Platelet count, 10^9/ml (SD)	222.3 (58.9) vs 232.2 (51.5)	$p > 0.05$
Mean platelet volume, fl (SD)	8.9 (1.0) vs 8.8 (1.2)	$p > 0.05$

ADP, adenosine diphosphate; HbA1C, glycosylated haemoglobin; fl, femtolitre; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation.
a Extrapolated from a graph.

TABLE 30 *Number of patients (%) experiencing adverse cardiac events, stent thrombosis or occlusion, or revascularisation at follow-up after discontinuation of clopidogrel post-PCI*

Study	Pfisterer (2006)[57]	Han (2007)[58]	Rau (2005)[59]	Carlsson (2007)[60]
Intervention – clopidogrel dose	300 mg loading dose; 75 mg daily ($n = 743$)	300–600 mg loading dose; 75 mg daily ($n = 200$)	300 mg loading dose; 75 mg daily ($n = 62$)	600 mg loading dose; 75 mg daily ($n = 1377$)
Duration of treatment	6 months	4 months	6 months	1–12 months
Follow-up	1 year	150–340 days	6 months	1 month to 2.5 years
Cardiovascular death	6 (0.8)	1 (0.5)	Not reported	Not reported
MI	23 (3.1)	1 (0.5)	Not reported	Not reported
Revascularisation	Not reported	18 (9.0)	Not reported	Not reported
MACE	Not reported	21 (10.5)	Not reported	Not reported
Stent occlusion	16 (2.2)	Not reported	Not reported	Not reported
Late thrombosis	65 (8.7)	Not reported	1 (1.6)	9 (0.65)

MACE, major adverse cardiovascular event; MI, myocardial infarction.

at 1 month, 2 weeks after discontinuing a 2-week course of ticlopidine; although two patients were reported to have died, neither death was ischaemia-related.[63]

Case reports

Thirty-three case reports relating to patients receiving antiplatelet therapy post-stenting, across 17 publications, were identified (*Table 32*). Where reported, the duration of antiplatelet treatment ranged from 2 days to 31 months, and the time lapse post discontinuation of the event ranged from 4 days to 4 years. Of the 27 events where the lapse between discontinuation and the event was reported, four occurred within 7 days of discontinuation, 13 within 14 days, and 17 within 21 days; 10 events occurred after 21 days. The most common event was stent thrombosis (30 events), with 17 cardiovascular events reported. When considering the occurrence of MI, the most common cardiovascular event, 12 of the 15 MIs reported occurred within 14 days

TABLE 31 *Outcomes for non-clopidogrel therapies following PCI*

Study	Spertus (2006)[64]	Pascual Figal (2000)[120]	Berger (1999)[63]
Intervention	Unspecified thienopyridine for 3–6 months ($n = 500$) vs discontinuation before 1 month ($n = 68$)	250 mg ticlopidine twice daily for 4 weeks ($n = 226$) vs discontinuation before 4 weeks ($n = 18$)	250mg ticlopidine twice daily for 14 days (n = 827)
Follow-up	12 months	1 month	30 days
Results	All-cause death 7.5% vs 0.7% ($p < 0.05$) Cardiac re-hospitalisation 23% vs 14% (NS)	Subacute stent thrombosis 3 (17%) vs 4 (1.8%)	All-cause death 2 (0.2%) Cardiovascular death 0 Stent thrombosis 0

NS, not significant.

after discontinuation of therapy; there seemed to be no relationship between the duration of thienopyridine treatment and the period of time between discontinuation and the MI.

The only case study to report changes in biomarkers, and therefore provide a direct assessment of any potential rebound effect, was that of the patient with angina who withdrew from both prasugrel (a newer thienopyridine than clopidogrel) and aspirin treatment.[73] This patient was reported to have had at least a twofold increase in all platelet measures, with platelet activation biomarkers being higher than those observed at presentation of acute vascular event, suggesting a rebound effect in this patient.[73]

DOI: 10.3310/hta13310

TABLE 32 *Case reports of adverse outcomes following discontinuation of antiplatelet therapy prescribed after PCI*

Study	Duration of antiplatelet treatment	Time lapse between discontinuation and event	No adverse outcomes	Stent thrombosis	MI	Cardiogenic shock	Clotted prosthetic aortic valve	Pulmonary embolism	High platelet biomarkers
Clopidogrel									
Ten Berg (2006)[77]	Discontinued 'in hospital'	8 days		✓	✓				
Ten Berg (2006)[77]	2 days	6 days		✓	✓				
Puri (2006)[72]	2 weeks	13 months		✓					
Yang (2006)[80]	2 weeks	20 months		✓					
Helft (2003)[67]	2 weeks	Unknown	✓						
Kerner (2003)[70]	1 month	14 days			✓				
Ten Berg (2006)[77]	1 month	4 years		✓	✓				
Ten Berg (2006)[77]	1 month	8 days		✓	✓				
Zimarino (2004)[81]	3 months	15 days		✓					
Waters (2005)[79]	6 months	14 days		✓					
Cassin (2007)[65]	6 months	5 months		✓					
Stabile (2004)[74]	6 months	6.5 months		✓					
Ten Berg (2006)[77]	7–8 months	4 weeks		✓		✓			
Waters (2005)[79]	8 months	7 days		✓	✓	✓			
Ten Berg (2006)[77]	9 months	14 days		✓	✓				
Stabile (2004)[74]	11 months	4 days		✓					
Ten Berg (2006)[77]	12 months	14 days		✓	✓				
Chrissoheris (2006)[66]	12 months	4 weeks		✓	✓				
Ten Berg (2006)[77]	13 months	15 days		✓	✓				
Chrissoheris (2006)[66]	13 months	7 weeks		✓					
Jimenez-Quevedo (2004)[68]	15 months	17 days		✓					
Waters (2005)[79]	16 months	13 days		✓	✓				
Kereiakes (2002)[69]	31 months	10 days		✓	✓				

continued

TABLE 32 *Case reports of adverse outcomes following discontinuation of antiplatelet therapy prescribed after PCI (continued)*

Study	Duration of antiplatelet treatment	Time lapse between discontinuation and event	No adverse outcomes	Stent thrombosis	MI	Cardiogenic shock	Clotted prosthetic aortic valve	Pulmonary embolism	High platelet biomarkers
van Werkum (2006)[78]	Unknown	Unknown		✓					
van Werkum (2006)[78]	Unknown	Unknown		✓					
van Werkum (2006)[78]	Unknown	Unknown		✓					
van Werkum (2006)[78]	Unknown	Unknown		✓					
Prasugrel									
Serebruany (2006)[73]	Non-compliant	3–4 weeks							✓
Ticlopidine									
Naber (2001)[71]	1 month	14 days		✓	✓				
Cassin (2007)[65]	2 months	14 days		✓					
Tabuchi (1998)[75]	2 months	7 days							
Takeda (2007)[76]	3 months	2.5 months		✓	✓				
Unspecified thienopyridine									
Kereiakes (2002)[69]	6 months	10 months		✓	✓				
Total number of cases			2	30	15	2	0	0	1

MI, myocardial infarction.

Appendix 3

Details of clopidogrel efficacy RCTs conducted in populations other than patients with NSTE-ACS

Our searches identified a number of trials that evaluated the effectiveness of clopidogrel compared with aspirin in populations other than NSTE-ACS (patients with ischaemic stroke, MI or symptomatic atherosclerotic PAD;[87–92] stable CHD;[93] planned PCI or coronary angiogram;[43–46] documented MI, with or without ST elevation;[94] acute STEMI, left bundle branch block or ST depression;[95,96] multiple atherothrombotic risk factors or documented coronary, cerebrovascular or symptomatic PAD disease[97–99]). One of these trials provided data for the rebound section of the current review.[43–46] As well as being conducted in a different population, none of these trials are directly comparable with the CURE trial in terms of study size, treatment regime, time to follow-up and outcomes reported:

- CAPRIE:[87–92] aspirin was not prescribed in conjunction with clopidogrel, with 325 mg aspirin prescribed to the placebo arm (only 33% of patients in the CURE trial were prescribed > 200 mg); mean follow-up was longer than the CURE trial, at 1.9 years.
- ASCET:[93] a small trial ($n = 206$); 160 mg or less of aspirin prescribed to all patients (67% of patients were prescribed < 200 mg aspirin in the CURE trial); only reported changes in biomarkers (outcomes which were not reported in the CURE trial).
- CREDO:[43–46] the placebo group were prescribed clopidogrel for 28 days post-PCI (clopidogrel not administered to placebo group in the CURE trial); 325 mg aspirin prescribed to all patients (33% of patients in the CURE trial prescribed > 200 mg).
- CADET:[94] a small trial ($n = 184$); aspirin was not prescribed in conjunction with clopidogrel, and only 75 mg aspirin was prescribed to the placebo group (42% received < 100 mg aspirin in the CURE trial); only reported changes in biomarkers (outcomes which were not reported in the CURE trial); follow-up was shorter than the CURE trial, at 6 months.
- COMMIT:[95,96] 162 mg aspirin prescribed to all patients (67% of patients were prescribed < 200 mg aspirin in the CURE trial); follow-up was substantially shorter than the CURE trial, at only 28 days.
- CHARISMA:[97–99] 75–160 mg aspirin prescribed to all patients (33% of patients in the CURE trial were prescribed > 200 mg); follow-up was longer than the CURE trial, at 22 months.

Table 33 provides the results reported in each of the trials. *Table 34* shows the results of outcome measures comparable across the five trials that reported clinical outcomes as reported in the trials, and *Table 35* shows these converted to RRs, RRRs or relative risk increases (RRIs). Across all the trials, clopidogrel reduces the risk of the composite outcomes of MI/stroke/(all-cause or cardiovascular) death, and where reported reduces the risk of fatal and non-fatal MI and stroke; however, the magnitude of these effects varies. There is less consistency across trials for the other comparative outcomes. These differences are likely to be due to the clinical heterogeneity seen between the trials as outlined above. Other clopidogrel trials identified did not compare clopidogrel with aspirin, but were considered for inclusion in the rebound section of the review: TRUE (ticlopidine versus clopidogrel);[52] CLASSICS (ticlopidine versus two clopidogrel regimes; included in the rebound section of the current review);[53] JUMBO (prasugrel versus clopidogrel);[121] MATCH (aspirin plus clopidogrel versus placebo plus clopidogrel).[122]

TABLE 33 *Results of outcome measures comparable across the six trials that reported clinical outcome*

Trial	Population and design	Interventions	Results
CAPRIE[87–92]	19,185 patients with ischaemic stroke, MI or symptomatic atherosclerotic PAD Randomised; double-blinded Follow-up: mean 1.91 years Complete for 99% of patients in both arms of the trial Sample size calculation: yes ITT analysis: yes	Clopidogrel 75 mg plus aspirin placebo daily ($n = 9599$) vs Clopidogrel placebo plus 325 mg aspirin daily ($n = 9586$)	*2 years: RRR (95% CI)* Ischaemic stroke, MI or vascular death: RRR 8.7% (95% CI 0.3–16.5) Ischaemic stroke, MI, amputation or vascular death: RRR 7.67% (95% CI –0.8 to 15.3) Vascular death: RRR 7.6% (95% CI –6.9 to 20.1) Any stroke, MI or death: RRR 7.0% (95% CI –0.9 to 14.2) All-cause mortality: RRR 2.2% (95% CI –9.9 to 12.9) *2 years:* n Non-fatal ischaemic stroke: clopidogrel: 472; aspirin: 504 Non-fatal MI: clopidogrel: 255; aspirin: 301 Non-fatal primary intracranial haemorrhage: clopidogrel: 14; aspirin: 24 Amputation: clopidogrel: 52; aspirin: 47 Fatal ischaemic stroke: clopidogrel: 37; aspirin: 42 Fatal MI: clopidogrel: 53; aspirin: 75 Haemorrhagic death: clopidogrel: 23; aspirin: 27 Other vascular death: clopidogrel: 260; aspirin: 261 Non-vascular death: clopidogrel: 187; aspirin: 166
ASCET[93]	206 patients with stable coronary heart disease verified with coronary angiography not responding to aspirin Randomised; laboratory staff blinded Follow-up: 1 year Appears complete Sample size calculation: no ITT analysis: appear to have compete follow-up	Clopidogrel 75 mg plus 160 mg aspirin daily ($n = 101$) vs 160 mg aspirin daily ($n = 105$)	*1 month: median (25, 75 percentiles)* CRP (mg/l): clopidogrel: 3.10 (1.45, 6.25); aspirin: 3.72 (1.68, 7.14) TNF-α (pg/ml): clopidogrel: 1.05 (0.84, 1.56); aspirin: 1.07 (0.88, 1.57) IL-6 (pg/ml): clopidogrel: 2.5 (1.5,0 4.30); aspirin: 2.60 (2.00, 3.80) IL-10 (pg/ml): clopidogrel: 2.11 (1.30, 3.56); aspirin: 2.26 (1.34, 3.73) MCP-I (pg/ml): clopidogrel: 264 (222, 321); aspirin: 277 (228, 350) P-SEL (ng/ml): clopidogrel: 37.7 (31.8, 44.6); aspirin: 37.6 (31.2, 43.8) *1 year: median (25, 75 percentiles)* CRP (mg/l): clopidogrel: 3.46 (1.77, 6.40); aspirin: 3.02 (1.63, 6.57) TNF-α (pg/ml): clopidogrel: 0.99 (0.78, 1.34); aspirin: 1.00 (0.75, 1.36) IL-6 (pg/ml): clopidogrel: 2.60 (1.50, 3.80); aspirin: 2.60 (1.70, 3.80) IL-10 (pg/ml): clopidogrel: 1.75 (1.14, 3.43); aspirin: 1.77 (1.17, 2.98) MCP-I (pg/ml): clopidogrel: 241 (2.02, 3.03); aspirin: 245 (196, 298) P-SEL (ng/ml): clopidogrel: 37.3 (30.5, 46.6); aspirin: 37.4 (30.5, 46.4) CD40L (pg/ml): clopidogrel: 468 (318, 859); aspirin: 515 (347, 863) TGF-β (pg/ml): clopidogrel: 1003 (548, 1404); aspirin: 1105 (592, 1543)

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Trial	Population and design	Interventions	Results
CREDO[43–46]	2116 patients referred for planned PCI or coronary angiogram Randomised; double-blinded Follow-up: 1 year Complete for 63% and 61% of patients in the clopidogrel and placebo groups respectively Sample size calculation: yes ITT analysis: yes	Clopidogrel 300 mg then clopidogrel 75 mg plus 325 mg aspirin daily ($n = 1053$) vs Placebo prior to PCI, then 75 mg clopidogrel for 28 days, then placebo for up to 1 year; 325 mg aspirin was prescribed throughout ($n = 1063$)	*28 days: RRR (95% CI)* Death, MI, stroke: RRR 19.7% (95% CI –13.3 to 43.1) Any major bleeding: clopidogrel: 4.7%; aspirin: 3.6% Non-procedural major bleeding: clopidogrel: 0.18%; aspirin: 0.3% Procedural major bleeding: clopidogrel: 4.7%; aspirin: 3.37% Any minor pleading: clopidogrel: 3.1%; aspirin: 2.3% Non-procedural minor bleeding: clopidogrel: 0.3%; aspirin: 0.1% Procedural minor bleeding: clopidogrel: 2.9%; aspirin: 2.2% *1 year (RRR (95% CI)* Death, MI, stroke: RRR 37.4% (95% CI 1.8–60.1) Any major bleeding: clopidogrel: 8.8%; aspirin: 6.7% Non-procedural major bleeding: clopidogrel: 1.2%; aspirin: 0.8% Procedural major bleeding: clopidogrel: 7.7%; aspirin: 5.9% Any minor pleading: clopidogrel: 4.7%; aspirin: 3.6% Non-procedural minor bleeding: clopidogrel: 0.3%; aspirin: 0.1% Procedural minor bleeding: clopidogrel: 2.9%; aspirin: 2.2%
CADET[94]	184 patients aged at least 21 years with documented MI (with or without ST elevation) within the previous 3–7 days Randomised; double-blinded Follow-up: 6 months Complete for 82% of patients Sample size calculation: yes ITT analysis: yes	Clopidogrel 75 mg daily ($n = 94$) vs Aspirin 75 mg daily ($n = 90$)	*6 months: difference from baseline (first quartile, third quartile)* Fibrinogen – Clauss (g/l): clopidogrel: 0.70 (0.09, 2.40); aspirin: 1.01 (0, 2.16) Fibrinogen – nephelometric (g/l): clopidogrel: 0.58 (–0.13, 1.91); aspirin: 0.60 (–0.10, 1.80) CRP (mg/l): clopidogrel: 21.0 (5.5, 55.1); aspirin: 17.8 (8.5, 42.1) D-dimer (ng/ml): clopidogrel: 35 (0, 120); aspirin: 21 (–18, 103) VWF (IU/dl): clopidogrel: 64 (38, 99); aspirin: 55 (31, 83) Factor VIII (IU/dl): clopidogrel: 43 (16, 75); aspirin: 50 (27, 76) Plasma viscosity (mPa.s): clopidogrel: 0.03 (–0.02, 0.10); aspirin: 0.06 (–0.01, 0.10) Tissue plasma activator (ng/ml): clopidogrel: 1.1 (–1.9, 4.4); aspirin: 1.4 (–2.7, 4.5) *Adverse events: patients ever reporting* Chest pain: clopidogrel: 14; aspirin: 13 Surgical intervention: clopidogrel: 11; aspirin: 13 Angina: clopidogrel: 9; aspirin: 11 Coughing: clopidogrel: 5; aspirin: 11 Dizziness: clopidogrel: 6; aspirin: 10

continued

TABLE 33 *Results of outcome measures comparable across the six trials that reported clinical outcome (continued)*

Trial	Population and design	Interventions	Results
			Dyspnoea: clopidogrel: 9; aspirin: 8 Diarrhoea: clopidogrel: 4; aspirin: 6 MI: clopidogrel: 1; aspirin: 6 Indigestion: clopidogrel: 5; aspirin: 5 Lower respiratory tract infection: clopidogrel: 2; aspirin: 5 Other: clopidogrel: 58; aspirin: 49 *Serious (fatal or life-threatening) adverse events occurring* Chest pain: clopidogrel: 2; aspirin: 5 Surgical intervention: clopidogrel: 4; aspirin: 2 Angina: clopidogrel: 3; aspirin:6 Dizziness: clopidogrel: 1; aspirin: 0 Dyspnoea: clopidogrel: 1; aspirin: 0 Diarrhoea: clopidogrel: 1; aspirin: 0 MI: clopidogrel: 1; aspirin: 6 Other: clopidogrel: 11; aspirin: 13
COMMIT[95,96]	45,852 patients hospitalised within 24 hours of onset of symptoms of acute STEMI, left bundle branch block or ST depression Randomised; triple-blinded Follow-up: 28 days Complete for over 99% of patients Sample size calculation: no ITT analysis: yes	Clopidogrel 75 mg plus 162 mg aspirin daily ($n = 22,961$) vs Placebo plus 162 mg aspirin ($n = 22,891$)	*28 days: RRR (95% CI); NNT (95% CI)* Death, reinfarction or stroke: RRR 8.2% (95% CI 2.7–13); NNT 122 (95% CI 78–367) Death: RRR 6.5 (95% CI 0.9–12); NNT 192 (95% CI 103–1349) Reinfarction: RRR 14 (95% CI 2.9–24); NNT 302 (95% CI 176–1413) Stroke: RRR 14 (95% CI –3.0 to 28); NNT Not significant Major bleeding: RRR 6.9 (95% CI –16 to 36); NNT Not significant

Trial	Population and design	Interventions	Results
CHARISMA[97–99]	At least 45 years of age with either multiple atherothrombotic risk factors or documented coronary, cerebrovascular or symptomatic PAD disease Randomised; double-blinded Follow-up: Median 22 months Complete for over 99% of patients in both arms Sample size calculation: yes ITT analysis: yes	Clopidogrel 75 mg plus 75–162 mg aspirin daily ($n = 7802$) vs Placebo plus 75–162 mg aspirin daily ($n = 7801$)	*22 months: RR (95% CI)* First occurrence MI, stroke, cardiovascular death: RR 0.93 (95% CI 0.83–1.05) All-cause mortality: RR 0.99 (95% CI 0.86–1.14) Cardiovascular mortality: RR 1.04 (95% CI 0.87–1.25) MI: RR 0.94 (95% CI 0.75–1.18) Ischaemic stroke (non-fatal): RR 0.81 (95% CI 0.64–1.02) Stroke (non-fatal): RR 0.79 (95% CI 0.64–0.98) First occurrence MI, stroke, cardiovascular death, hospitalisation for unstable angina, TIA or revascularisation: RR 0.92 (95% CI 0.86–0.995) Hospitalisation for unstable angina, TIA or revascularisation: RR 0.90 (95% CI 0.82–0.98) Severe bleeding: RR 1.25 (95% CI 0.97–1.61) Fatal bleeding: RR 1.53 (95% CI 0.83–2.82) Primary intracranial haemorrhage: RR 0.96 (95% CI 0.56–1.65) Moderate bleeding: RR 1.62 (95% CI 1.27–2.08)

CD40L, CD40 ligand; CI, confidence interval; CRP, C-reactive protein; IL, interleukin; ITT, intention to treat; MCP, member cofactor protein; MI, myocardial infarction; NNT, number needed to treat; P-SEL, P-selectin; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RR, relative risk; RRR, relative risk reduction; STEMI, ST-elevation myocardial infarction; TGF, transforming growth factor; TIA, transient ischaemic attack; TNF, tumour necrosis factor; VWF, von Willebrand factor.

TABLE 34 *Results of outcome measures comparable across the five trials evaluating clopidogrel and aspirin as reported in the papers*

	Time point									
	CAPRIE[87–92] (2 years)		**CREDO[43-46] (1 year)**		**COMMIT[95,96] (28 days)**		**CHARISMA[97–99] (22 months)**		**CURE[17–22] (1 year)**	
Outcome	**Clopidogrel**	**Aspirin**	**Clopidogrel**	**Aspirin**	**Clopidogrel**	**Aspirin**	**Clopidogrel**	**Aspirin**	**Clopidogrel**	**Aspirin**
MI/stroke/(all-cause or cardiovascular) death	RRR 7.0% (95% CI –0.9 to14.2)		RRR 37.4% (95% CI 1.8–60.1)		RRR 8.2% (95% CI 2.7–13)		RR 0.93 (95% CI 0.83–1.05)		582 (9.3%)	719 (11.4%)
	All death		All death		All death		Cardiovascular death		Cardiovascular death	
MI (fatal/non fatal unspecified)	–		–		RRR 14% (95% CI 2.9–24)		RR 0.94 (95% CI 0.75–1.18)		324 (5.2%)	419 (6.6%)
Stroke (fatal/non-fatal unspecified)	509 (5.3%)	546 (5.7%)	–		RRR 14% (95% CI –3.0 to 28)		–		75 (1.2%)	87 (1.4%)
Mortality (cardiovascular)	RRR 7.6% (95% CI –6.9 to 20.1)		–		–		RR 1.04 (95% CI 0.87–1.25)		318 (5.1%)	345 (5.5%)
Major bleeding	–		93 (8.8%)	71 (6.7%)	RRR 6.9% (95% CI –16 to 36)		RR 1.25 (95% CI 0.97–1.61)		231 (3.7%)	169 (2.7%)
Bleeding (fatal)	–		–		–		RR 1.53 (95% CI 0.83–2.82)		11 (0.2%)	15 (0.2%)
Minor bleeding	–		50 (4.7%)	38 (3.6%)	–		–		322 (5.1%)	153 (2.4%)

CI, confidence interval; MI, myocardial infarction; RR, relative risk; RRR, relative risk reduction.

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TABLE 35 *Results of outcome measures comparable across the five trials evaluating clopidogrel and aspirin expressed as RRs and/or RRRs or RRIs with 95% CIs where provided or calculable*

	Trial (follow-up)				
	CAPRIE[87–92] (2 years)	**CREDO[43–46] (1 year)**	**COMMIT[95,96] (28 days)**	**CHARISMA[97–99] (22 months)**	**CURE[17–22] (1 year)**
MI/stroke/ cardiovascular death	RRR 7.0% (95% CI –0.9 to 14.2)	RRR 37.4% (95% CI 1.8–60.1)	RRR 8.2% (95% CI 2.7–13)	RR 0.93 (95% CI 0.83–1.05); RRR 7% (95% CI –5.0 to 17.0)	RR 0.82 (95% CI 0.73–0.90); RRR 18.5% (95% CI 9.6–26.5)
MI (fatal/non-fatal unspecified)	–	–	RRR 14% (95% CI 2.9–24)	RR 0.94 (95% CI 0.75–1.18); RRR 6% (95% CI –18.0 to 25.0)	RR 0.78 (95% CI 0.68–0.90); RR 22% (95% CI 10.4–32.4)
Stroke (fatal/non-fatal unspecified)	RR 0.93 (95% CI 0.83–1.05); RRR 7% (95% CI –4.69 to 17.22)	–	RRR 14% (95% CI –3.0 to 28)	–	RR 0.87 (95% CI 0.64–1.18); RRR 13% (95% CI –18.0 to 36.1)
Mortality (cardiovascular)	RRR 7.6% (95% CI –6.9 to 20.1)	–	–	RR 1.04 (95% CI 0.87–1.25); RRI 4% (95% CI –13.0 to 25.0)	RR 0.93 (95% CI 0.80–1.08); RRR 7% (95% CI –7.7 to 20.0)
Major bleeding	–	RR 1.32 (95% CI 0.98–1.78); RRI 32% (95% CI 1.74–78.0)	RRR 6.9% (95% CI –16 to 36)	RR 1.25 (95% CI 0.97–1.61); RRI 25% (95% CI –3.0 to 61.0)	RR 1.38 (95% CI 1.13–1.67); RRI 38% (95% CI 13.2–67.3)
Bleeding (fatal)	–	–	–	RR 1.53 (95% CI 0.83–2.82); RRI 53% (95% CI –17.0 to 182)	RR 0.74 (95% CI 0.34–1.61); RRR 26% (95% CI –60.7 to 66.1)
Minor bleeding	–	RR 1.33 (95% CI 0.88–2.01); RRI 33% (95% CI 12.1–100.8)	–	–	RR 2.12 (95% CI 1.75–2.56); RRI 112% (95% CI 75.4–156.1)

CI, confidence interval; MI, myocardial infarction; RR, relative risk; RRI, relative risk increase; RRR, relative risk reduction.

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We look forward to hearing from you.

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