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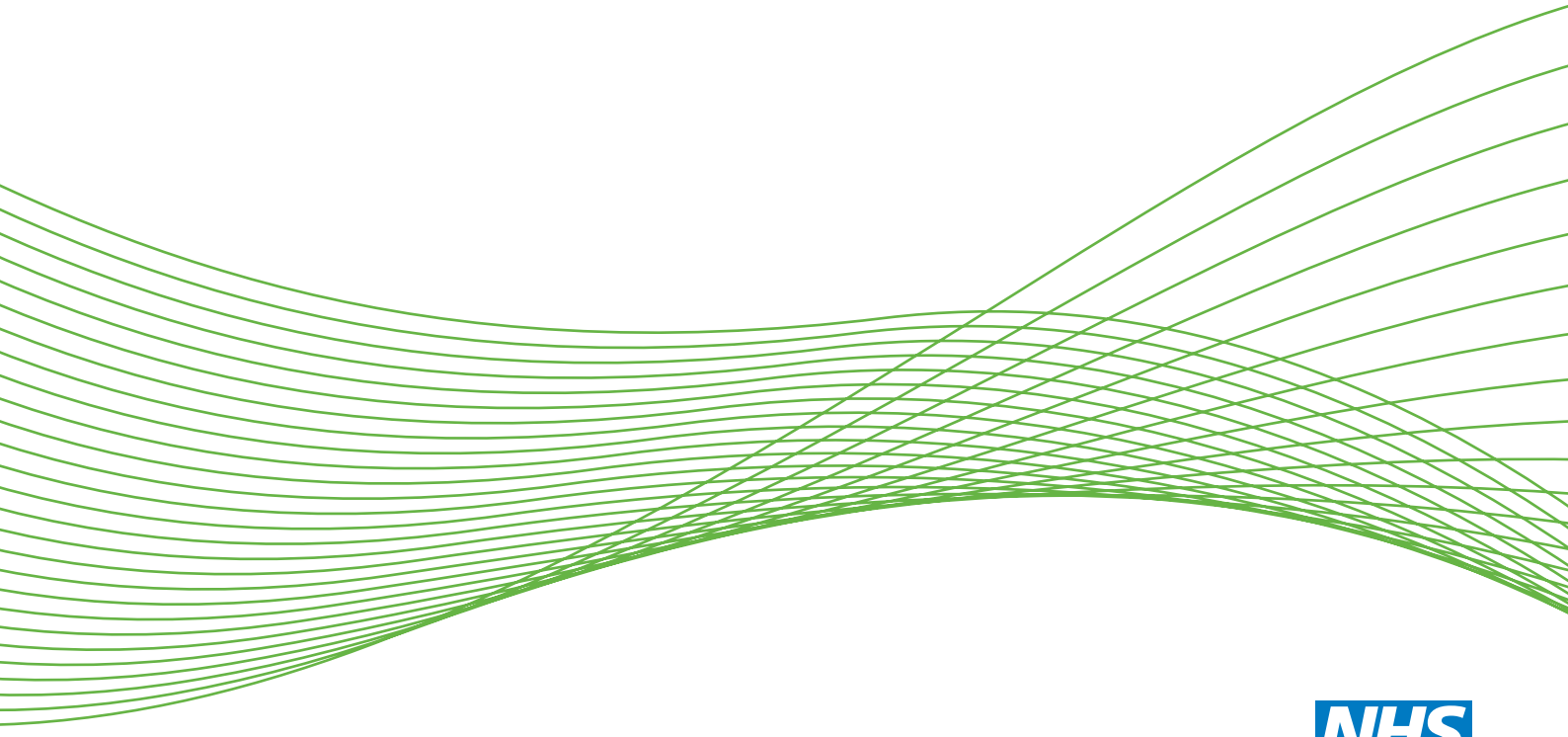

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Janette Greenhalgh,[1]* Adrian Bagust,[1] Angela Boland,[1] Kerry Dwan,[1] Sophie Beale,[1] Nigel Fleeman,[1] Joanne McEntee,[2] Yenal Dundar,[1] Marty Richardson[1] and Michael Fisher[3]

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Abstract

Prasugrel (Efient®) with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182): systematic review and economic analysis

Janette Greenhalgh,[1]* Adrian Bagust,[1] Angela Boland,[1] Kerry Dwan,[1] Sophie Beale,[1] Nigel Fleeman,[1] Joanne McEntee,[2] Yenal Dundar,[1] Marty Richardson[1] and Michael Fisher[3]

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Background: Acute coronary syndromes (ACSs) are life-threatening conditions associated with acute myocardial ischaemia. There are three main types of ACS: ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). One treatment for ACS is percutaneous coronary intervention (PCI) plus adjunctive treatment with antiplatelet drugs. Dual therapy antiplatelet treatment [aspirin plus either prasugrel (Efient®, Daiichi Sankyo Company Ltd UK/Eli Lilly and Company Ltd), clopidogrel or ticagrelor (Brilique®, AstraZeneca)] is standard in UK clinical practice. Prasugrel is the focus of this review.

Objectives: The remit is to appraise the clinical effectiveness and cost-effectiveness of prasugrel within its licensed indication for the treatment of ACS with PCI and is a review of National Institute for Health and Care Excellence technology appraisal TA182.

Data sources: Four electronic databases (MEDLINE, EMBASE, The Cochrane Library, PubMed) were searched from database inception to June 2013 for randomised controlled trials (RCTs) and to August 2013 for economic evaluations comparing prasugrel with clopidogrel or ticagrelor in ACS patients undergoing PCI.

Methods: Clinical outcomes included non-fatal and fatal cardiovascular (CV) events, adverse effects of treatment and health-related quality of life (HRQoL). Cost-effectiveness outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained. An independent economic model assessed four mutually exclusive subgroups: ACS patients treated with PCI for STEMI and with and without diabetes mellitus and ACS patients treated with PCI for UA or NSTEMI and with and without diabetes mellitus.

Results: No new RCTs were identified beyond that reported in TA182. TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38) compared prasugrel with clopidogrel in ACS patients scheduled for PCI. No relevant economic evaluations were identified. Our analyses focused on a key subgroup of patients: those aged < 75 years who weighed > 60 kg (no previous stroke or transient ischaemic attack). For the primary composite end point (death from CV causes, non-fatal myocardial infarction or non-fatal stroke) statistically significantly fewer events occurred in the prasugrel arm (8.3%) than in the clopidogrel arm (11%).

No statistically significant difference in major bleeding events was noted. However, there was a significant difference in favour of clopidogrel when major and minor bleeding events were combined (3.0 vs. 3.9%). No conclusions could be drawn regarding HRQoL. The results of sensitivity analyses confirmed that it is likely that, for all four ACS subgroups, within 5–10 years prasugrel is a cost-effective treatment option compared with clopidogrel at a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained. At the full 40-year time horizon, all estimates are < £10,000 per QALY gained.

Limitations: Lack of data precluded a clinical comparison of prasugrel with ticagrelor; the comparative effectiveness of prasugrel compared with ticagrelor therefore remains unknown. The long-term modelling exercise is vulnerable to major assumptions about the continuation of early health outcome gains.

Conclusion: A key strength of the review is that it demonstrates the cost-effectiveness of prasugrel compared with clopidogrel using the generic price of clopidogrel. Although the report demonstrates the cost-effectiveness of prasugrel compared with clopidogrel at a threshold of £20,000 to £30,000 per QALY gained, the long-term modelling is vulnerable to major assumptions regarding long-term gains. Lack of data precluded a clinical comparison of prasugrel with ticagrelor; the comparative effectiveness of prasugrel compared with ticagrelor therefore remains unknown. Well-audited data are needed from a long-term UK clinical registry on defined ACS patient groups treated with PCI who receive prasugrel, ticagrelor and clopidogrel.

Study registration: This study is registered as PROSPERO CRD42013005047.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

AC	Appraisal Committee
ACS	acute coronary syndrome
AG	Assessment Group
BCIS	British Cardiovascular Intervention Society
BNF	*British National Formulary*
CABG	coronary artery bypass grafting
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CURE	Clopidogrel in Unstable angina to prevent Recurrent Events
CURRENT-OASIS	Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes
CV	cardiovascular
DISPERSE-2	Dose conflrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non–ST segment Elevation myocardial infarction 2
DRG	diagnostic-related group
ECG	electrocardiograph
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
FDA	United States Food and Drug Administration
GDG	guideline development group
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IS	ischaemic stroke
ISAR-REACT	Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
JUMBO-TIMI	Joint Utilization of Medications to Block Platelets Optimally – Thrombolysis in Myocardial Infarction
MI	myocardial infarction
MINAP	Myocardial Ischaemia National Audit Project
MS	manufacturer submission
NICE	National Institute for Health and Care Excellence
NSTEMI	non-ST segment elevation myocardial infarction
OXVASC	Oxford Vascular Study
PCI	percutaneous coronary intervention
PLATO	PLATelet inhibition and patient Outcomes trial
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SIGN	Scottish Intercollegiate Guidelines Network
SPC	Summary of Product Characteristics
STA	single technology appraisal
STEMI	ST segment elevation myocardial infarction
TIA	transient ischaemic attack
TIMI	thrombolysis in myocardial infarction
TRITON-TIMI	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction
UA	unstable angina
UTVR	urgent target vessel revascularisation

Plain English summary

Acute coronary syndromes (ACSs) are life-threatening conditions associated with heart attacks. There are three main types of ACS: (1) ST segment elevation myocardial infarction, (2) non-ST segment elevation myocardial infarction and (3) unstable angina. These conditions are usually caused by a reduction in blood flow to the heart as a result of a coronary artery becoming narrow or blocked by a build-up of fatty deposits. The underlying cause of ACS is an erosion of the fatty deposit, which leads to the formation of a blood clot. One treatment for ACSs is percutaneous coronary intervention (PCI). In the PCI procedure, a balloon passed over a guidewire is inserted into the affected artery and inflated at the site of the blockage to restore blood flow to the heart. A stent is usually implanted to act as a scaffold and to hold open the artery wall. All PCI procedures include treatment with drugs to reduce further blood clotting (antiplatelets). In the UK, the recommended antiplatelet treatment is a combination of aspirin with either clopidogrel, prasugrel (Efient®, Daiichi Sankyo Company Ltd UK/Eli Lilly and Company Ltd) or ticagrelor (Brilique®, AstraZeneca). We considered the benefits and costs of prasugrel compared with clopidogrel or ticagrelor. There was only one study relevant to the review, and it compared prasugrel with clopidogrel. There were no studies that compared prasugrel with ticagrelor. We concluded that prasugrel is more beneficial than clopidogrel for all ACS patients and offers value to the NHS. We were unable to assess the benefits of prasugrel compared with ticagrelor as there was not enough evidence available.

Scientific summary

Background

Acute coronary syndromes (ACSs) are life-threatening conditions associated with acute myocardial ischaemia with or without infarction. These conditions usually result from a reduction in blood flow associated with a coronary artery becoming narrow or blocked through atherosclerosis (an accumulation of plaque containing fatty deposits or, less commonly, erosion of the endothelium) and atherothrombosis (a blood clot formed following the rupture of plaque).

There are three main types of ACS diagnosed by clinical history, electrocardiograph (ECG) and levels of cardiac enzymes: (1) ST segment elevation myocardial infarction (STEMI), (2) non-ST segment elevation myocardial infarction (NSTEMI) and (3) unstable angina (UA). A diagnosis of STEMI indicates that the affected artery is completely occluded, resulting in progressive necrosis of the area of heart muscle dependent on its blood supply. The most common cause of a STEMI is complete and persistent occlusion of a coronary artery by a blood clot (thrombus). A diagnosis of NSTEMI indicates partial or temporary blocking of an artery with limited tissue damage. In the case of UA, the clinical history suggests cardiac ischaemia, but without tissue death.

One treatment for ACS is percutaneous coronary intervention (PCI), also known as coronary angioplasty. Antiplatelet therapy is an established adjunct to PCI both before and for up to 12 months after the procedure. All PCI procedures include adjunctive treatment with antiplatelet drugs. The purpose of antiplatelet treatment is to inhibit the aggregation of platelets that can lead to thrombus formation and further vascular events. Dual therapy [aspirin plus either prasugrel (Efient®, Daiichi Sankyo Company Ltd UK/Eli Lilly and Company Ltd), clopidogrel or ticagrelor (Brilique®, AstraZeneca)] is the standard antiplatelet treatment in clinical practice in the UK. The antiplatelet drug prasugrel is the focus of this review.

Objectives

The remit of this update is to appraise the clinical effectiveness and cost-effectiveness of prasugrel within its licensed indication for the treatment of ACS with PCI and is a review of National Institute for Health and Care Excellence (NICE) technology appraisal TA182.

Methods

Four electronic databases were searched for randomised controlled trials (RCTs) and economic evaluations. Studies that compared prasugrel with clopidogrel or ticagrelor were considered in order to identity patients with ACS who were to be treated with PCI. Outcomes for clinical effectiveness included non-fatal and fatal cardiovascular (CV) events, mortality from any cause, atherothrombotic events, incidence of revascularisation procedures, adverse effects of treatment (including bleeding events) and health-related quality of life (HRQoL). For the assessment of cost-effectiveness, outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts, applied inclusion criteria to relevant publications and quality assessed the included studies. The results of the data extraction and quality assessment were summarised in structured tables and as a narrative description. No meta-analysis or network meta-analyses were undertaken.

Results

One good-quality RCT was identified for inclusion in the clinical review. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial compared prasugrel with clopidogrel in patients with ACS who were scheduled for PCI. No relevant economic evaluations were identified.

Summary of risks and benefits

This review focused on the health outcomes of the subgroup of patients discussed in TA182 and for whom the full dose of prasugrel is licensed, namely the core clinical cohort [i.e. patients without a history of transient ischaemic attach (TIA) or stroke, those with body weight of > 60 kg or those aged < 75 years]. For the primary composite end point of death from CV causes, non-fatal MI or non-fatal stroke, statistically significantly fewer events were recorded in the prasugrel arm (8.3%) than in the clopidogrel arm (11%) [hazard ratio (HR) = 0.74, 95% confidence interval (CI) 0.66 to 0.84; $p < 0.0001$]. No statistically significant difference in non-coronary artery bypass grafting (CABG)-related TIMI (thrombolysis in myocardial infarction) major bleeding was noted between the patients in the prasugrel and clopidogrel arms. However, there was a significant difference in favour of clopidogrel when major and minor bleeding events were combined (3.0% vs. 3.9%) (HR = 1.26, 95% CI 1.02 to 1.57; $p = 0.03$). The analysis of the net clinical benefit outcome (death from any cause, non-fatal MI, non-fatal stroke or non-CABG-related non-fatal TIMI major bleeding) favoured the use of prasugrel (12.5% in the clopidogrel group vs. 10.2% in the prasugrel group; HR = 0.80, 95% CI 0.71 to 0.89; $p < 0.001$). No conclusions could be drawn about the HRQoL of patients treated with prasugrel or clopidogrel owing to small numbers of trial respondents. In the absence of any direct trial evidence, no conclusions could be drawn about the comparative efficacy or safety of prasugrel and ticagrelor.

Summary of the assessment group's cost-effectiveness results

The economic evaluation submitted by the manufacturer met the NICE reference case criteria. However, the assessment group (AG) developed its own economic model for the following reasons: (1) the long-term model phase in the manufacturer's submitted economic model was considered to be unsatisfactory and potentially not sufficiently reliable to generate a realistic representation of 39 years of follow-up; (2) the manufacturer's decision model projects long-term (2–40 years) costs and outcomes solely in terms of mortality hazard rates fixed after 1 year, and takes no account of the effects of accumulating experience of CV events and disability; (3) the AG considered it appropriate to develop an economic model using the most reliable clinical evidence available and, therefore, preferred to use 3-year clinical data from the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial instead of 15-month data from the TRITON-TIMI 38 trial; and (4) to fulfil the remit stated by NICE and to review fully the guidance for prasugrel issued in TA182, the AG was required to compare four patient subgroups. The structure of the decision model submitted by the manufacturer did not readily facilitate modelling these four subgroups in terms of cost-effectiveness.

Independent economic model

The AG's decision model assessed four mutually exclusive subgroups of the core clinical cohort:

- ACS patients treated with PCI for STEMI and with diagnosed diabetes mellitus
- ACS patients treated with PCI for STEMI and without diagnosed diabetes mellitus
- ACS patients treated with PCI for UA or NSTEMI and with diagnosed diabetes mellitus
- ACS patients treated with PCI for UA or NSTEMI and without diagnosed diabetes mellitus.

The results of both the deterministic and probabilistic analyses confirmed that it appears likely that, for all four subgroups, within 5–10 years, prasugrel is a cost-effective treatment option when compared with clopidogrel at a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained. At the full 40-year time horizon, all estimated incremental cost-effectiveness ratios (ICERs) are less than £10,000 per QALY gained, indicating confidence in this interpretation of the available evidence.

Discussion

The remit of this review was to update the evidence underpinning TA182 NICE guidance for the use of prasugrel in the NHS. In TA182, only one RCT (TRITON-TIMI 38) compared prasugrel with clopidogrel in patients presenting with ACS who were intended to undergo treatment with PCI. No new trials were identified for inclusion in this update since the appraisal of prasugrel in 2009; this means that the present review is largely based on the clinical evidence available for TA182.

Clinical effectiveness

This review focused on the health outcomes of the subgroup of patients discussed in TA182 and for whom the full dose of prasugrel is licensed. In the core clinical cohort, all non-bleeding clinical outcomes of the TRITON-TIMI 38 trial favoured the use of prasugrel compared with clopidogrel. These findings held for the 15 months of trial follow-up and across subgroups of patients including those with STEMI and UA/NSTEMI. There was a statistically significant difference in event rates in favour of clopidogrel when major and minor bleeding rates were combined.

A clinical comparison of prasugrel with ticagrelor was not carried out by the AG (or the manufacturer of prasugrel). There were two reasons for this. First, there was no direct RCT evidence comparing prasugrel with ticagrelor; and, second, it was not possible to conduct an indirect comparison as there were irreconcilable differences between the two pivotal trials [including timing and dosing of clopidogrel and assessment of myocardial infarction (MI)]. Thus, the effectiveness and safety of prasugrel compared with ticagrelor remains unknown.

Cost-effectiveness

In the AG's independent economic model, the outcomes of the TRITON-TIMI 38 trial population were simulated as four mutually exclusive subgroups: (1) STEMI without diabetes mellitus, (2) STEMI with diabetes mellitus, (3) NSTEMI without diabetes mellitus and (4) NSTEMI with diabetes mellitus. This approach has allowed the AG to reconsider the strength of evidence underlying the previous NICE guidance, which excluded patients from treatment with prasugrel if they had not suffered a STEMI event, or had not been diagnosed with diabetes. The new model confirmed that, using a £20,000 to £30,000 per QALY gained threshold, within 5–10 years, it appears likely that prasugrel is a cost-effective treatment option when compared with clopidogrel for all four subgroups.

Strengths and limitations of the assessment

The main strength of this review is that, despite some remaining areas of uncertainty, the case for prasugrel compared with clopidogrel appears to have been strengthened. The results of the AG's independent economic model confirm the cost-effectiveness of prasugrel compared with clopidogrel, at a threshold of £20,000 to £30,000 per QALY gained, for key groups of patients with ACS who are to be treated with PCI. The structure of the AG's model differs from the model developed by the manufacturer in that it uses the most up-to-date clinical evidence available (from the CAPRIE trial) and compares four key patient subgroups. A particular strength of the AG's economic model is that is provides assessments at specific time periods within the modelled time horizon of 40 years.

Both the AG and the manufacturer demonstrate the cost-effectiveness of prasugrel compared with clopidogrel at a threshold of £20,000 to £30,000 per QALY gained. However, the AG acknowledges that any long-term modelling exercise is vulnerable to major assumptions about the continuation of early health outcome gains and it is noted that both the manufacturer's and the AG's models rely on extrapolating relatively short-term results from beyond the end of the trial to a further 40 years.

A key strength of the review is that the AG has been able to reassess the cost-effectiveness of prasugrel compared with clopidogrel using the generic price of clopidogrel in an independent economic model.

Uncertainties

The three areas of uncertainty noted by the Appraisal Committee for TA182 were reconsidered in this review. These centred on the generalisability of the TRITON-TIMI 38 trial results to patients in clinical practice in the UK. The AG is of the opinion that the clinical evidence for the equivalence of a 300-mg loading dose of clopidogrel (administered in TRITON-TIMI 38) with a 600-mg loading dose (often given in clinical practice in the UK) remains uncertain. Similarly, the AG considers that the importance of timing of the administration of the loading dose of clopidogrel on patient outcomes remains unresolved and differs between the TRITON-TIMI 38 trial and clinical practice in the NHS in England and Wales. The AG considers that the case for the effectiveness of prasugrel compared with clopidogrel in preventing MIs of all types and sizes appears to be robust.

A clinical comparison of prasugrel with ticagrelor was not carried out by the AG (or the manufacturer of prasugrel, Daiichi Sankyo Company Ltd UK/Eli Lilly and Company Ltd). Thus, the comparative effectiveness and safety of prasugrel compared with ticagrelor remain unknown.

Conclusions

Suggested research priorities

It would be most valuable to have well-audited data on defined ACS patient groups from a long-term clinical registry of all UK patients receiving prasugrel, ticagrelor and clopidogrel and who are treated with a PCI. Such a data source could provide a basis for research and audit to inform future assessments of these antiplatelet treatments.

It is suggested that any future trials in this area should focus on the comparison of prasugrel with ticagrelor and recruit patients with ACS who are to be treated with a PCI. It is anticipated that the results of the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial, if it is conducted well, could fill the current gap in evidence related to the comparative efficacy and safety of prasugrel compared with ticagrelor.

Study registration

This study is registered as PROSPERO CRD42013005047.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of health problem

Acute coronary syndromes (ACSs) are life-threatening conditions associated with acute myocardial ischaemia with or without infarction.[1] These conditions usually result from a reduction in blood flow associated with a coronary artery becoming narrow or blocked through atherosclerosis (an accumulation of plaque containing fatty deposits or, less commonly, erosion of the endothelium) and atherothrombosis (a blood clot formed following the rupture of plaque). The classic symptom of ACS is chest pain or tightness, although many people (particularly women, the elderly and those with diabetes mellitus) may present with atypical pain or no pain at all.[2–4] Other symptoms may include breathlessness, sweating and nausea.[2–4]

The underlying cause of ACS is build-up of atheroma within the wall of the coronary artery. This occurs over a number of years and is generally asymptomatic.[5] The risk factors for ACS are multifactorial and are the same as for cardiovascular (CV) disease. Among the non-modifiable risk factors are increasing age, sex (male) and a family history of premature coronary heart disease or premature menopause. Modifiable risk factors include smoking, diabetes mellitus (and impaired glucose tolerance), hypertension, dyslipidaemia, obesity and physical inactivity.[1,5] People with a history of myocardial infarction (MI) have an increased risk of recurrence or of other vascular events (e.g. stroke) when compared with the general population.[6]

There are three main types of ACS diagnosed by clinical history, electrocardiography (ECG) and levels of cardiac enzymes: (1) ST segment elevation myocardial infarction (STEMI), (2) non-ST segment elevation myocardial infarction (NSTEMI) and (3) unstable angina (UA). A diagnosis of STEMI indicates that the affected artery is completely occluded, resulting in progressive necrosis of the area of heart muscle dependent on its blood supply.[5,7] The most common cause of a STEMI is complete and persistent occlusion of a coronary artery by a blood clot (thrombus).[8] A diagnosis of NSTEMI indicates partial or temporary blocking of an artery with limited tissue damage.[5,7] In the case of UA, clinical history suggests cardiac ischaemia, but without tissue death.[5,7]

Over time, any damage sustained by the heart muscle results in scar tissue. The degree of the damage impacts on the overall ability of the heart to pump blood, which in turn impacts on the patient's longer-term survival.[8] The timely treatment of ACS is imperative as almost half of potentially salvageable heart muscle is lost within 1 hour of the coronary artery being occluded, and two-thirds is lost within 3 hours.[8] One treatment for ACS is percutaneous coronary intervention (PCI), also known as coronary angioplasty. In PCI, the affected coronary artery is dilated using a balloon catheter and a stent is usually implanted to act as a scaffold and to hold open the artery wall.[9] All PCI procedures are accompanied by adjunctive treatment with antiplatelet drugs. These drugs are the focus of this review.

Treatment pathway

ST segment elevation myocardial infarction

The objective of treatment for patients with STEMI is rapid and sustained revascularisation.[10] The recommended treatment for people with confirmed STEMI is immediate (primary) PCI to the occluded artery.[9,11] Clinical guidelines produced by National Institute for Health and Care Excellence (NICE) (CG167[8]) recommend coronary angiography with follow-on PCI (if indicated) as the preferred treatment for acute STEMI if presentation is within 12 hours of the onset of symptoms and primary PCI can be delivered within 120 minutes. When PCI facilities are not immediately available, treatment with thrombolysis (pharmacological reperfusion achieved through the use of 'clot-busting' drugs) should be considered.[12] When STEMI persists despite thrombolytic treatment, PCI (rescue) in an appropriately equipped unit should be considered.[8]

Unstable angina/non-ST segment elevation myocardial infarction

The objective of treatment for patients with UA/NSTEMI is to alleviate pain and anxiety, prevent recurrences of ischaemia and prevent, or limit, progression to further acute MI.[1] NICE Clinical Guideline CG94[13] recommends that people presenting with UA/NSTEMI are initially treated with aspirin and antithrombin therapy. Their risk of further cardiac events should then be assessed using a risk score measurement tool that predicts 6-month mortality, such as the Global Registry of Acute Cardiac Events (GRACE).[14] In addition to a GRACE[14] score, additional factors should be considered, including full clinical history [age, previous MI, previous coronary artery bypass grafting (CABG)], physical examination (including measurement of blood pressure and heart rate), and resting 12-lead ECG and blood tests (troponin I or T, creatinine, glucose and haemoglobin). *Table 1* is adapted from NICE CG94[13] and describes the risk categories of future CV events assigned to risk scores.

Patients considered to be at intermediate to high risk should be offered coronary angiography and follow-on PCI (if appropriate) within 96 hours of admission.[15] Patients with UA/NSTEMI who are clinically unstable or at high ischaemic risk should be offered angiography as soon as possible.[13] Patients at low risk should be treated medically; however, if ischaemia is subsequently experienced or is demonstrated on ischaemia testing, coronary angiography and delayed PCI (if appropriate) should be offered.[13]

Epidemiology

The Myocardial Ischaemia National Audit Project[5] (MINAP) is a national clinical audit of the management of heart attack. All hospitals in England, Wales and Belfast that admit patients with STEMI or NSTEMI contribute data (with the exception of Scarborough Hospital).

The most recent audit report[5] presents analyses for admissions between April 2012 and March 2013. The audit recorded 80,974 patients with a final diagnosis of MI; 40% (32,665) of cases were diagnosed as STEMI and 60% (48,309) were diagnosed as NSTEMI. The average age of patients with STEMI and NSTEMI was 65 years and 72 years, respectively.[5]

The authors of the report[5] emphasise that the audit records the majority of admissions for STEMI but that NSTEMI admissions are under-represented.

Of the total number of patient admissions for STEMI, MINAP[5] recorded that 68% (20,990) had primary PCI. The remaining patients received thrombolytic treatment (3%), no reperfusion treatment or treatment that was unclear (29%).[5]

TABLE 1 Categories of risk of future CV events

Predicted 6-month mortality	Risk of future adverse CV events
≤ 1.5%	Lowest
> 1.5–3.0%	Low
> 3.0–6.0%	Intermediate
> 6.0–9.0%	High
> 9.0%	Highest

The Assessment Group (AG) notes that the MINAP[5] data set does not include data for patients with UA as this condition does not fall under the audit's MI remit. However, the AG is aware that, in England in 2012 to 2013, there were 54,000 finished consultant episodes and 32,000 patient admissions for UA.[16]

British Cardiovascular Intervention Society Audit Data

The British Cardiovascular Intervention Society (BCIS) continuously audits interventional activity in the UK and the results are published annually. The most recent audit returns are for the year 2012.[17] The audit shows that there are currently 99 NHS PCI centres in the UK, almost double the number recorded in 2002. In 2012, 91,000 PCI procedures (for all indications) were carried out in the UK NHS, 27.4% in STEMI patients and 36.9% in UA/NSTEMI patients; the remainder were rescue or facilitated PCIs. A total of 24,631 PCIs for STEMI were conducted, the majority of which (23,842) were primary PCIs. The number of PCIs for STEMI has increased over time while the number of PCIs for UA/NSTEMI has remained stable.

Of patients referred for PCI in the UK in 2012, 74% were male and the average age was 64.9 years.[17] Approximately 20% had diabetes mellitus and 27% had had a previous MI.[17] One-quarter were current smokers and the majority (92%) were European.[17] It should be noted that these data are for an overall population of patients treated with PCI and, therefore, include patients other than those with ACS.

There are 85 NHS PCI centres in England and four in Wales. The total number of PCIs (all indications) performed in the NHS in England and Wales in 2012 was 75,217 and 3850, respectively. Almost 21,000 PCI procedures in England and 1000 in Wales were primary PCI procedures.

The BCIS audit data[17] show that the number of PCIs performed in England and Wales has increased annually, although the rate of increase has slowed. In 2002, fewer than 30,000 procedures were carried out and, in contrast, almost 80,000 PCIs were conducted in 2012. The BCIS data describe the use of the radial artery (guidewire inserted through the wrist) as the access point for PCI. Radial access has risen to 65% of PCIs conducted in 2012 from 10% in 2004.

Antiplatelet treatment

Treatment with antiplatelet therapy is an established adjunct to PCI both before and for up to 12 months after the procedure (NICE CG167[8] and NICE CG94).[13] The purpose of antiplatelet treatment is to inhibit the aggregation of platelets that can lead to thrombus formation and further vascular events including stent thrombosis. Dual antiplatelet therapy, aspirin plus prasugrel (Efient®, Daiichi Sankyo Company Ltd UK/Eli Lilly and Company Ltd), clopidogrel or ticagrelor (Brilique®, AstraZeneca), is the standard antiplatelet treatment in clinical practice in the UK.

Relevant national guidelines

A quality standard for ACS has been referred for consideration to NICE and, at the time of writing, was expected to be published in September 2014.[18,19] A treatment pathway for patients with ACS is also available on the NICE website.[20]

A number of NICE guidance documents and NICE guidelines are relevant to this review. These are described in *Table 2*.

TABLE 2 Relevant NICE documents

NICE documentation	Recommendation
TA182[21] (2009): prasugrel for the treatment of ACSs with PCI	Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with ACS having PCI, only when: • immediate primary PCI for STEMI is necessary • stent thrombosis has occurred during clopidogrel treatment • the patient has diabetes mellitus
CG94[13] (2010): UA and NSTEMI: the early management of UA and NSTEMI	Offer a 300-mg loading dose of clopidogrel to all patients with no contraindications who may undergo PCI within 24 hours of admission to hospital In line with Prasugrel for the treatment of ACSs with PCI (TA182), prasugrel in combination with aspirin is an option for patients undergoing PCI who have diabetes or have had stent thrombosis with clopidogrel treatment It is recommended that treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of NSTEMI. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended
TA236[22] (2011): ticagrelor for the treatment of ACSs	Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS, that is, people: • with STEMI-defined as ST elevation or new left bundle branch block on electrocardiography that cardiologists intend to treat with PCI • with NSTEMI • admitted to hospital with UA. Before ticagrelor is continued beyond the initial treatment, the diagnosis of UA should first be confirmed, ideally by a cardiologist
CG172[23] (2013): secondary prevention in primary and secondary care for patients following a MI (CG172 is an update of CG48)	Aspirin should be offered to all people after a MI and continued indefinitely, unless individuals are aspirin intolerant or have an indication for anticoagulation For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment Clopidogrel is a treatment option for up to 12 months for: • people who have had an NSTEMI, regardless of treatment • people who have had a STEMI and received a bare-metal or drug-eluting stent Ticagrelor is also recommended as per TA236 noted above Prasugrel for the treatment of ACS has not been incorporated in this guidance because this technology appraisal is currently scheduled for update There are special recommendations for antiplatelet therapy in people with an indication for anticoagulation

TABLE 2 Relevant NICE documents (*continued*)

NICE documentation	Recommendation
CG167[8] (2013): STEMI: the acute management of myocardial infarction with ST segment elevation	Following reperfusion therapy for STEMI, treatment with aspirin should be continued in line with CG48 MI secondary prevention[a] The Guideline Development Group considered that treatment with clopidogrel is an established option in the pharmacological treatment of people with acute STEMI including people undergoing primary PCI. The Guideline Development Group were aware that a clopidogrel loading dose of 600 mg is not licensed in the UK, but is used widely in current practice, especially in people undergoing primary PCI Prasugrel was noted as a recommended treatment from TA182 and is the subject of this current appraisal Ticagrelor is recommended as in TA236

a CG48 has been superseded by CG172.

Description of technology under assessment

Intervention

The oral antiplatelet prasugrel, used within its licensed indication, is the focus of this review. The Summary of Product Characteristics (SPC) for prasugrel is available from the Electronic Medicines Compendium.[24]

Prasugrel is a third-generation oral thienopyridine adenosine diphosphate receptor antagonist. It has a more rapid onset of action than clopidogrel as it requires only a single, relatively rapid metabolic step to produce the active agent (clopidogrel requires two steps). Prasugrel is prescribed as an adjunctive therapy to PCI to reduce platelet aggregation by irreversibly binding to $P2Y_{12}$ receptors. It is available as 5-mg or 10-mg film-coated tablets. Prasugrel is given (with aspirin) as a single 60-mg loading dose and then continued at 10 mg daily for up to 12 months.

Prasugrel is licensed in Europe[25] to be co-administered with aspirin, for the prevention of atherothrombotic events in patients with ACS (STEMI and UA/NSTEMI) undergoing primary or delayed PCI. As stated in the SPC, the use of prasugrel in patients with a history of stroke or transient ischaemic attack (TIA) is contraindicated, whereas in older ($\geq$ 75 years) patients prasugrel is generally not recommended. For patients who weigh $<$ 60 kg, the 60-mg loading dose of prasugrel should be used followed by a maintenance dose of 5 mg.[24] The SPC further states that, in patients with UA/NSTEMI in whom coronary angioplasty is performed within 48 hours after admission, the loading dose of prasugrel should be given only at the time of PCI.

NICE guidance (TA182[21]) limits the use of prasugrel (co-administered with aspirin) in the NHS to people with ACS having PCI only when:

- immediate primary PCI for STEMI is necessary
- stent thrombosis has occurred during clopidogrel treatment
- the patient has diabetes mellitus.

In TA182,[21] prasugrel was not recommended for patients with UA/NSTEMI who do not have diabetes mellitus or have not had a stent thrombosis following treatment with clopidogrel.

There is no patient access scheme in operation in the NHS for prasugrel.

The SPC for prasugrel highlights the increased bleeding risk for patients with ACS who are treated with prasugrel and aspirin. It is noted that the use of prasugrel in patients at increased risk of bleeding should be considered only when the benefits in terms of preventing ischaemic events are deemed to outweigh the risk of serious bleeding.[24]

Current usage in the NHS

The decision paper[26] presented to the Guidance Executive of NICE in June 2012 stated that the market share for prasugrel in terms of prescriptions had risen from 1% to 2% since 2011 and the monthly spend in the NHS had increased from approximately £400,000 to approximately £500,000. Data from the BCIS audit[18] illustrate that prasugrel use has increased marginally between 2011 and 2012 (*Table 3*).

The current *British National Formulary* (BNF)[27] list price of prasugrel for both 5-mg and 10-mg tablets is £47.56 per pack of 28 tablets. The current Drug Tariff[28] list price of aspirin 75 mg is 0.82 pence per pack of 28 tablets.

Comparators

The stated comparators to prasugrel in the final scope issued by NICE[7] are clopidogrel (generic) and ticagrelor, both in combination with low-dose aspirin.

Clopidogrel

Clopidogrel is a thienopyridine and is available as a 300-mg and 75-mg film-coated tablet. The 300-mg tablet is intended as a loading dose for patients with ACS and treatment should be continued at 75 mg daily with aspirin (75–325 mg). Clopidogrel has a marketing authorisation for use in several patient groups relevant to this appraisal:

- patients with MI (from a few days until < 35 days)
- patients with STEMI in combination with aspirin who are eligible for thrombolytic therapy
- patients with NSTEMI undergoing a stent placement following PCI, in combination with aspirin.

The AG notes that, according to its European Medicines Agency (EMA) licence, clopidogrel is not indicated for use in STEMI patients undergoing PCI. The patent for clopidogrel (Plavix, Sanofi) expired in 2010 and a number of generic versions are now licensed. This means that the cost of clopidogrel has substantially reduced since prasugrel was considered by NICE in 2009 (TA182).[21]

In the SPC, increased bleeding risk with clopidogrel use is noted, as is a possible interaction with proton pump inhibitors.[29]

The current Drug Tariff[28] list price for clopidogrel is £1.71 per pack of 28 tablets.

TABLE 3 British Cardiovascular Intervention Society estimate of usage of prasugrel in PCI (2011 to 2012)

Patient group	2011	2012
UA/NSTEMI	1.5%	2.6%
STEMI	22%	22.6%
UA/NSTEMI patients with diabetes mellitus	1.7%	2.8%

Ticagrelor

Ticagrelor is a direct-acting $P2Y_{12}$ receptor antagonist that has a different mechanism of action from the thienopyridines (prasugrel and clopidogrel). It has a rapid onset of action compared with clopidogrel and is a reversibly binding oral adenosine phosphate receptor antagonist. Ticagrelor is licensed in Europe[30] (co-administered with aspirin) for the prevention of atherothrombotic events in adult patients with ACS (UA/NSTEMI or STEMI), including patients managed medically and those who are managed with PCI or CABG. Ticagrelor is administered as a 90-mg film-coated tablet. Treatment should be started with a single 180-mg loading dose (two 90-mg tablets) and then continued at 90 mg twice daily. The recommended use of ticagrelor is a single course of treatment up to 12 months with aspirin.[31]

In the UK, NICE guidance (TA236[22]) recommends ticagrelor (with low-dose aspirin) for up to 12 months as a treatment option for adults with ACS:

- with STEMI or
- with NSTEMI or
- patients admitted to hospital with UA.

The SPC[31] for ticagrelor notes that patients treated with ticagrelor and aspirin are at increased risk of non-CABG major bleeding and are also more generally at risk of bleeds requiring medical attention but not fatal or life-threatening bleeds. Therefore, the SPC[31] recommends that the use of ticagrelor in patients at known increased risk for bleeding should be balanced against the expected benefit in terms of prevention of atherothrombotic events. It is further noted that co-administration of ticagrelor with strong CYP3A4 inhibitors is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor.[31]

Data from the 2012 BCIS audit report[18] indicate that in 2012 ticagrelor was used in 3.74% of PCI procedures in patients with UA/NSTEMI and in 7.04% of PCI procedures in patients with STEMI. The current BNF price[27] of ticagrelor is £54.60 per pack of 56 tablets.

In October 2013, AstraZeneca[32] reported that it had received a demand from the US Department of Justice, Civil Division, seeking documents and information regarding the PLATO (PLATelet inhibition and patient Outcomes)[33] trial, the pivotal trial that led to the regulatory authorisation of ticagrelor both in the US and in Europe. The AG is aware[34] that the EMA has also contacted AstraZeneca requesting further information about the PLATO[33] trial.

Chapter 2 Definition of the decision problem

Decision problem

The remit of this appraisal is to review and update (if necessary) the clinical effectiveness and cost-effectiveness evidence base described in TA182.[21] The key elements of the decision problem issued by NICE in the final scope[7] for this appraisal are set out in *Table 4*.

Within this report, reference to the use of prasugrel, clopidogrel or ticagrelor indicates that these treatments are given concomitantly with low-dose aspirin as per their licensed indications.

Overall aims and objectives of assessment

The remit of this review is to appraise the clinical effectiveness and cost-effectiveness of prasugrel within its licensed indication for the treatment of ACS with PCI (review of NICE technology appraisal TA182).[21]

TABLE 4 Key elements of the decision problem

Interventions	Prasugrel in combination with aspirin
Population	Patients with ACS undergoing primary or delayed PCI
Comparators	Clopidogrel in combination with low-dose aspirin
	Ticagrelor in combination with low-dose aspirin
Outcomes	The outcome measures to be considered include: • non-fatal and fatal CV events • mortality (from any cause) • atherothrombotic events • incidence of revascularisation procedures • adverse effects of treatment (including bleeding events) • health-related quality of life
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY gained
	The reference case stipulates that the time horizon for estimating clinical effectiveness and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared
	Costs should be considered from a NHS and Personal Social Services perspective
Other considerations	If the evidence allows, the following subgroups will be considered: people with STEMI, UA/NSTEMI, people with diabetes mellitus
	Guidance will be issued only in accordance with the marketing authorisation
	The availability of any patient access schemes for the interventions and comparators should be taken into account in the analysis

QALY, quality-adjusted life-year.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing the clinical effectiveness evidence are described in this chapter. The methods for reviewing the cost-effectiveness evidence are described in *Chapter 6*.

Methods for reviewing effectiveness

In addition to searching the manufacturer's submission for relevant references, the following databases were searched for studies of prasugrel:

- EMBASE (Ovid) 1974 to 18 June 2013.
- MEDLINE (Ovid) 1946 to Week 1 June 2013.
- The Cochrane Library June 2013.
- PubMed January 2010 to April 2013.

The results were entered into an EndNote X5 (Thomas Reuters, CA, USA) library and the references were deduplicated. Full details of the search strategies used are presented in *Appendix 1*.

The reference lists of included trials were searched for relevant trials. Information on trials in progress was sought from cardiology conference databases (European Society for Cardiology and the American College of Cardiology). The website clinicaltrials.gov was also searched for ongoing trials. In addition, advice was sought from the clinical advisor to the review.

Inclusion and exclusion criteria

Two reviewers (JG and NF) independently screened all titles and abstracts identified via searching and obtained full-paper manuscripts that were considered relevant by either reviewer (stage 1). The relevance of each study was assessed (JG/NF) according to the criteria set out below (stage 2), and studies that did not meet the criteria were excluded and their bibliographic details were listed alongside reasons for their exclusion. Any discrepancies were resolved by consensus and, when necessary, a third reviewer (AB) was consulted.

Study design

Only randomised controlled trials (RCTs) were included in the assessment of clinical effectiveness.

Interventions and comparators

The effectiveness of prasugrel within its licensed indication was assessed. Studies that compared prasugrel with clopidogrel or ticagrelor were considered for inclusion in the review.

Patient populations

Patients with ACSs who were to be treated with primary or delayed PCI constituted the relevant population.

Outcomes

Data on any of the following outcomes were included in the assessment of clinical effectiveness: non-fatal and fatal CV events, mortality from any cause, atherothrombotic events, incidence of revascularisation procedures, adverse effects of treatment (including bleeding events) and health-related quality of life (HRQoL).

Data extraction strategy

Data relating to both study design and quality were extracted by two reviewers (JG and KD) into an Excel spreadsheet (Microsoft Excel 2010; Microsoft Corporation, Redmond, WA, USA). The two reviewers cross-checked each other's data extraction and, when multiple publications of the same study were identified, data were extracted and reported as a single study.

Quality assessment strategy

The quality of the clinical effectiveness studies was assessed independently by two reviewers (JG and KD) according to the Centre for Reviews and Dissemination at the University of York's suggested criteria.[35] All relevant information is tabulated and summarised within the text of the report. Full details and results of the quality assessment strategy for clinical effectiveness studies are reported in *Appendix 2*.

Methods of data synthesis

The results of the clinical data extraction and clinical study quality assessment are summarised in structured tables and as a narrative description. An indirect treatment comparison of prasugrel with ticagrelor was planned.

Results

Quantity and quality of research available

A total of 1940 titles and abstracts were screened for inclusion in the review of clinical effectiveness evidence. The process of study selection is shown in *Figure 1*. Titles excluded at stage 2 ($n = 111$) are listed in *Appendix 3* along with reasons for their exclusion. The AG identified the pivotal trial (TRITON-TIMI 38[36]) discussed in TA182[21] but did not identify any new trials for inclusion in the review.

At stage 2, the AG excluded four clinical trials.[37–40] One of the trials[37] compared prasugrel with clopidogrel in a population of Asian patients with ACS undergoing PCI. This was excluded as it was considered to be a dose-ranging trial with a clopidogrel control. The trial recruited 719 patients and randomised them to one of three dosing regimens of prasugrel or standard clopidogrel according to patient weight and age

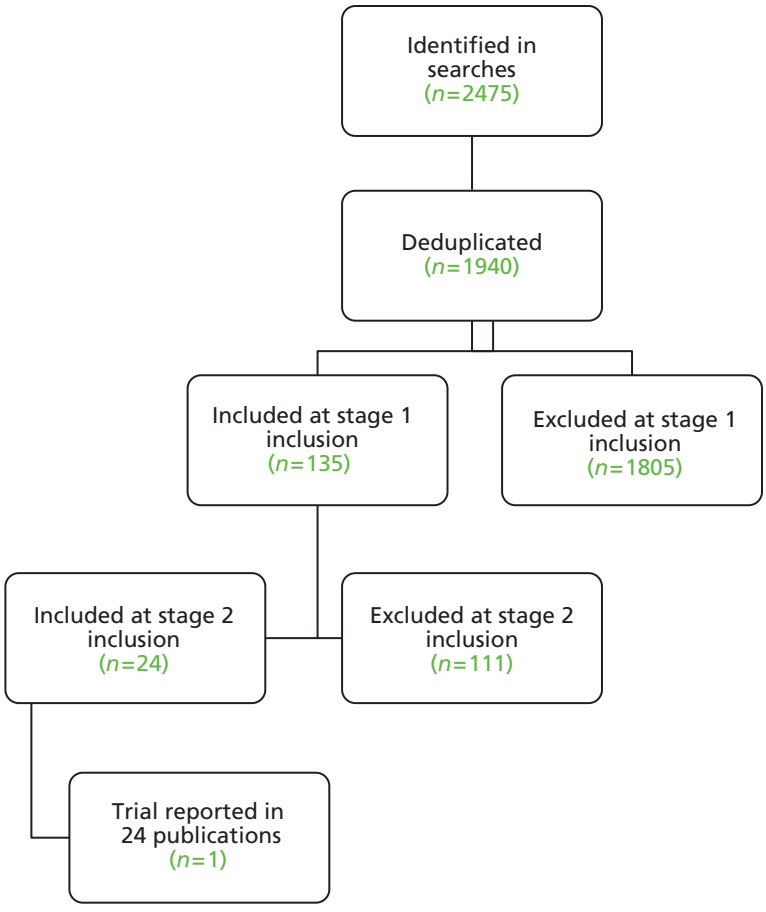

FIGURE 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

(< 60 kg and > 70 years or vice versa). The primary outcome was platelet aggregation at 4 hours after the loading dose. Secondary outcomes included major adverse cardiac events and CABG and non-CABG thrombolysis in myocardial infarction (TIMI) bleeding at 30 days and 90 days. The study was not powered to detect differences between treatments on the secondary outcomes. The JUMBO-TIMI (Joint Utilization of Medications to Block Platelets Optimally – Thrombolysis in Myocardial Infarction 26)[38] trial was similarly excluded. In this trial, patients ($n = 904$) undergoing PCI were randomised to one of three prasugrel dosing regimens or to clopidogrel and followed up for 30 days.

Two further excluded trials[39,40] included relevant comparators and patient populations but had pharmacodynamic (platelet aggregation) parameters. The AG considered that the trial populations were too small and the length of follow-up too short (5 days and 1 hour) to provide data relevant to this review.

Assessment of clinical effectiveness

The AG's systematic search of clinical effectiveness evidence yielded one relevant RCT (TRITON-TIMI 38[36]) for inclusion in the review. This trial was the pivotal trial discussed in TA182[21] and the key elements of this RCT are summarised in *Table 5*. The TRITON-TIMI 38[36] trial included 13,608 patients and was conducted in 30 countries. Patients received a loading dose of either prasugrel or clopidogrel (60 mg or 300 mg, respectively) followed by daily maintenance doses of 10 mg or 75 mg, respectively.

The results of the AG's quality assessment of the TRITON-TIMI 38[36] trial are presented in *Appendix 2*. Overall, the AG considers that the trial was robustly designed and of strong methodological quality.

TABLE 5 Summary of trial characteristics

Design	Intervention	Inclusion criteria (main)	Exclusion criteria (main)	Outcomes
International (30 countries) multicentre, Phase III double-blind, double-dummy RCT comparing prasugrel with clopidogrel in patients undergoing PCI. Patients ($n = 13,608$) were randomised in a 1 : 1 ratio and stratified according to presentation [i.e. UA/NSTEMI ($n = 10,074$) or STEMI ($n = 3534$)]. Duration of study: 15 months (median). A total of 73 patients were recruited from the UK	Prasugrel (LD 60 mg/MD 10 mg). Clopidogrel (LD 300 mg/MD 75 mg). Loading dose administered before, during or after PCI. Maintenance dose was continued for a median period of 14.5 months	Moderate- to high-risk UA or NSTEMI patients: ischaemic symptoms of 10 minutes or longer within 72 hours of randomisation. TIMI risk score of ≥ 3 and either ST segment deviation of ≥ 1 mm or an elevated cardiac biomarker of necrosis. Patients with STEMI could be enrolled within 12 hours of symptom onset if primary PCI was planned or within 14 days if delayed PCI was planned following initial pharmacotherapy for STEMI	Patients at increased risk of bleeding: anaemia, thrombocytopenia, intracranial pathology including TIA or stroke (within the last 3 months), severe hepatic dysfunction, oral anticoagulants, chronic non-steroidal anti-inflammatory drug use, or use of any thienopyridine within 5 days	Primary: composite of CV death, non-fatal MI or non-fatal stroke during follow-up period. Secondary: composite of death from CV causes, non-fatal MI, non-fatal stroke, rehospitalisation owing to cardiac ischaemic event. Composite of all-cause death, non-fatal MI, non-fatal stroke, stent thrombosis. At 30 days and 90 days: primary composite end point, composite of CV death, non-fatal MI, UTVR. Safety: non-CABG-related bleeding, TIMI life-threatening bleeding, TIMI major or minor bleeding

LD, loading dose; MD, maintenance dose; UTVR, urgent target vessel revascularisation.

As this report is an update of TA182,[21] the AG has reproduced the original summary information for TRITON-TIMI 38[36] in *Appendix 4*. The summary information presented includes:

- patient baseline characteristics (overall trial population)
- primary and secondary end point analyses (overall trial population)
- prespecified subgroup analyses for diagnosis, sex, age, diabetic status, type of stent implanted, use of glycoprotein IIb/IIIa receptor agonist, renal function (overall trial population)
- outcomes for STEMI patients (overall trial population)
- primary outcome for UA/NSTEMI, STEMI, all ACSs, patients with diabetes mellitus, patients with stents (overall trial population)
- outcomes for people with history of stroke/TIA
- outcomes for people > 70 years or weighing < 60 kg
- analyses of recurrent events following PCI (overall trial population).

A number of subgroup analyses relating to TRITON-TIMI 38[36] have been published; the key publications are listed, along with a brief description, in *Table 6*. A more comprehensive list of associated publications is presented in *Appendix 5* of this report. The paper by Wiviott (2011),[42] which is directly relevant to this appraisal, focuses on a sub-population of patients from the TRITON-TIMI 38[36] trial who are described as the 'core clinical cohort'. This sub-population is discussed in TA182[21] as the 'target population'. The core clinical cohort comprises patients for whom prasugrel is licensed and who may be treated with the full recommended dose of prasugrel (60-mg loading dose followed by 10 mg daily). These patients have no history of stroke or TIA, are younger than 75 years and weigh more than 60 kg. The AG focuses on the clinical evidence relevant to this subgroup. The rationale for this focus is presented in *Appendix 6*.

The core clinical cohort[42] comprised 10,804 patients (79%) from the randomised population of the TRITON-TIMI 38[36] trial. The characteristics of the patients in the core clinical cohort and the overall trial population are described in *Table 7*. The proportions of patients quoted in *Table 7* (taken from Wiviott *et al.*[42]) are not presented by trial arm. However, Wiviott *et al.*[42] states that patients in the core clinical cohort randomised to prasugrel and clopidogrel were well matched and that 50% of the core clinical cohort was randomised to prasugrel.[42] The AG notes that the patients in the overall trial population and the core clinical cohort appear to be similar in terms of baseline characteristics. In TA182,[21] the overall trial population of TRITON-TIMI 38[36] was considered to be younger and less likely to have experienced a prior MI than patients in clinical practice in England and Wales.

TABLE 6 The TRITON-TIMI 38 trial: main paper and associated publications

Reference	Title	Description
Wiviott *et al.* 2006[41]	Evaluation of prasugrel compared with clopidogrel in patients with ACSs: design and rationale for the TRITON-TIMI 38	Paper describing the design of the TRITON-TIMI 38 trial
Wiviott *et al.* 2007[36]	Prasugrel compared with clopidogrel in patients with ACSs	Primary publication of TRITON-TIMI 38 trial
Wiviott *et al.* 2011[42]	Efficacy and safety of intensive antiplatelet therapy with prasugrel from TRITON-TIMI 38 in a core clinical cohort defined by worldwide regulatory agencies	Paper describing outcomes of core clinical cohort of patients from TRITON-TIMI 38 trial: patients have no known history of stroke or TIA, are aged below 75 years and weigh more than 60 kg. The core clinical cohort represents 10,804 of the 13,608 patients included in the overall trial cohort

TABLE 7 Patient characteristics: core clinical cohort and overall trial population

Characteristic	Core clinical cohort, % ($n = 10,804$)	Overall trial population, % ($n = 13,608$)
Age (median)	NS	61 years (median)
UA/NSTEMI	73	74
Male	79	74
White	93	93
Region		
North America	32	32
South America	4	4
Western Europe	25	26
Eastern Europe	25	25
Africa/Asia/Middle East	14	14
Medical history		
Hypercholesterolaemia	56	56
Hypertension	62	64
Diabetes mellitus	22	23
Previous MI	17	18
Previous CABG	7	8
Creatinine clearance < 60 ml/minute	4	12
Multivessel coronary intervention	14	14
Glycoprotein IIb/IIIa inhibitor	56	55
ACE/ARB	75	76
Beta-blocker	89	88
Statin	93	92
CCB	16	18
ASA	100	99

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, aspirin; CCB, calcium channel blocker.

Clinical efficacy in the core clinical cohort

The manufacturer submission (MS; Daiichi Sankyo Company Ltd/Eli Lilly and Company Ltd, 2013) and the Wiviott *et al.*[42] paper report the clinical outcomes for the core clinical cohort of patients from the TRITON-TIMI 38[36] trial. It is emphasised by Wiviott *et al.*[42] that the core clinical cohort was identified in a post-hoc fashion defined by regulatory (EMA and the US Food and Drug Agency) criteria and should be considered as hypothesis generating.

The clinical efficacy outcomes for the core clinical cohort are presented in *Table 8*. For the primary composite end point of death from CV causes, non-fatal MI or non-fatal stroke, statistically significantly fewer events were recorded in the prasugrel arm (8.3%) than in the clopidogrel arm (11%) [hazard ratio (HR) = 0.74; 95% confidence interval (CI) 0.66 to 0.84; $p < 0.0001$]. Similarly, for the secondary composite end point (death from any cause, non-fatal MI, non-fatal stroke or non-CABG-related non-fatal TIMI major bleeding) statistically significantly fewer events were recorded in the prasugrel arm (10.2%) than in the clopidogrel arm (12.5%) (HR = 0.80; 95% CI 0.71 to 0.89; $p < 0.001$). The AG notes that the efficacy for both composite outcomes appears to be driven by the number of non-fatal MIs.

TABLE 8 Key clinical outcomes for the core clinical cohort from the TRITON-TIMI 38 trial

End point	Clopidogrel, *n*/*N* (%)	Prasugrel, *n*/*N* (%)	HR (95% CI)	*p*-value
Primary				
Death from CV causes, non-fatal MI or non-fatal stroke	569/5383 (11)[a]	433/5421 (8.3)[a]	0.74 (0.66 to 0.84)	< 0.001
Secondary				
Death from any cause, non-fatal MI, non-fatal stroke, or non-CABG-related non-fatal TIMI major bleeding (net clinical benefit)	641/5383 (12.5)[a]	522/5421 (10.2)[a]	0.80 (0.71 to 0.89)	< 0.001
CV death or MI	10.2%	7.7%	0.75 (0.66 to 0.85)	< 0.10
CV death	1.4%	1.4%	1.05 (0.75 to 1.46)	0.78
Death	2.0%	2.1%	1.03 (0.78 to 1.37)	0.82
MI	9.4%	6.7%	0.71 (0.62 to 0.81)	< 0.001
Stroke	1.0%	0.8%	0.75 (0.49 to1.15)	0.19
Stent thrombosis: definite	2.0%	0.8%	0.41 (0.29 to 0.60)	< 0.001
Stent thrombosis: definite/probable	2.3%	1.0%	0.44 (0.31 to 0.62)	< 0.001

CI, confidence interval.
a The percentages are Kaplan–Meier estimates of the rate of each end point at 15 months. As the Kaplan–Meier method takes into account censored data (i.e. sample losses before the final outcome occurs), each percentage does not correspond to the numerator divided by the denominator (because the denominator does not account for censored data).

Statistically significant differences in favour of prasugrel were also reported for the outcomes of definite stent thrombosis (HR = 0.41, 95% CI 0.29 to 0.60; $p < 0.001$) and definite or probable stent thrombosis (HR = 0.44; 95% CI 0.31 to 0.62; $p < 0.001$). There were also statistically significantly fewer MIs in the prasugrel arm (6.7%) than in the clopidogrel arm (9.4%) (HR = 0.71, 95% CI 0.62 to 0.81; $p < 0.001$).

Efficacy across subgroups within the core clinical cohort

Wiviott *et al.*[42] present a forest plot that displays the relative effectiveness of prasugrel compared with clopidogrel across a range of subgroups within the core clinical cohort, including diagnostic group (UA/NSTEMI or STEMI), sex, age and diabetic status. The published forest plot is reproduced in *Figure 2*. The clinical effectiveness of prasugrel appears to be consistent across subgroups.

Efficacy across time in the core clinical cohort

It is noted in Wiviott *et al.*[42] that, in the core clinical cohort, prasugrel was more effective than clopidogrel for the primary end point at 30 days as well as at the 15-month follow-up (*Table 9*).

Safety in the core clinical cohort

The key safety end point in the TRITON-TIMI 38[36] trial was the rate of non-CABG-related TIMI major bleeding in the overall trial cohort at 15 months. The data for the safety end points at 15 months in the core clinical cohort are presented in *Table 10*. No statistically significant difference in non-CABG-related TIMI major bleeding was noted between patients in the prasugrel and clopidogrel arms; however, there was a significant difference in favour of clopidogrel when major and minor bleeding events were combined (3.0% vs. 3.9%) (HR = 1.26, 95% CI 1.02 to 1.57; $p = 0.03$).

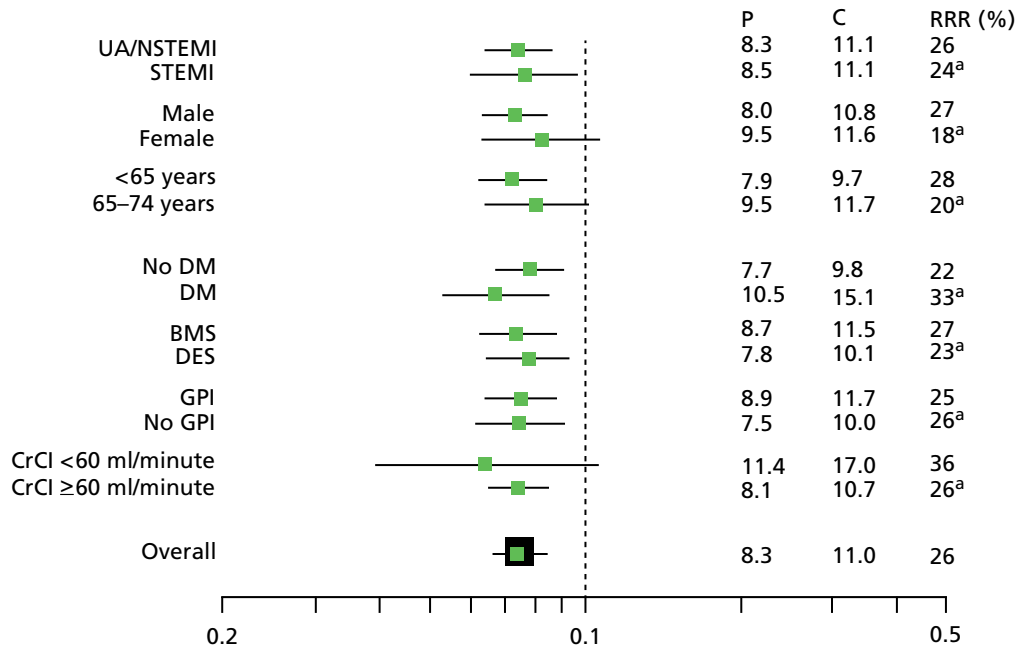

FIGURE 2 Key subgroups for primary efficacy end point (core clinical cohort). BMS, bare metal stent; CrCl, creatinine clearance; DES, drug-eluting stent; DM, diabetes mellitus; GPI, glycoprotein inhibitor; RRR, relative risk reduction. a, *p*-value was not significant. Reprinted from *Am J Cardiol*, vol. 108, Wiviott SD, Desai N, Murphy SA, Musumeci G, Ragosta M, Antman EM, *et al.*, Efficacy and safety of intensive antiplatelet therapy with prasugrel from TRITON-TIMI 38 in a core clinical cohort defined by worldwide regulatory agencies, pp. 905–11, 2011, with permission from Elsevier.

TABLE 9 Primary end point at 30 days and 15 months (proportion with event)

End point	Clopidogrel ($n = 5383$)	Prasugrel ($n = 5421$)	HR (95% CI)	*p*-value
Primary: death from CV causes, non-fatal MI or non-fatal stroke				
30 days	7.0%	5.0%	0.70 (0.60 to 0.82)	< 0.0001
30 days to 15 months	4.5%	3.6%	0.80 (0.65 to 0.97)	0.027

TABLE 10 Safety end points in the core clinical cohort

End point	Clopidogrel, *n*/*N* (%)	Prasugrel, *n*/*N* (%)	HR (95% CI)	*p*-value
Non-CABG-related TIMI major bleeding	73/5337 (1.5)	91/5390 (1.9)	1.24 (0.91 to 1.69)	0.17
TIMI major or minor bleed	3.0%	3.9%	1.26 (1.02 to 1.57)	0.03
Fatal TIMI major	0.1%	0.2%	2.65 (0.70 to 9.97)	0.14
Intracranial haemorrhage	0.3%	0.2%	0.69 (0.30 to 1.62)	0.39
TIMI major or minor bleeding				
30 days	1.6%	1.9%	1.21 (0.91 to 1.62)	0.19
30 days to 15 months	1.5%	2.1%	1.31 (0.95 to 1.79)	0.97

Net clinical benefit

The analysis of the net clinical benefit outcome (death from any cause, non-fatal MI, non-fatal stroke or non-CABG-related non-fatal TIMI major bleeding) favoured the use of prasugrel in the core clinical cohort (12.5% in the clopidogrel group vs. 10.2% in the prasugrel group; HR 0.80, 95% CI 0.71 to 0.89; $p < 0.001$).

Health-related quality of life

Data relevant to HRQoL are available only for the TRITON-TIMI 38[36] overall trial population and are not specific to the core clinical cohort. The HRQoL substudy was open to all TRITON-TIMI 38[36] patients at participating sites in eight countries: the USA, Australia, Canada, Germany, Italy, Spain, the UK and France. HRQoL was evaluated using three instruments: (1) the Angina Frequency and Physical Limitations scales of the Seattle Angina Questionnaire; (2) the London School of Hygiene Dyspnoea Questionnaire; and (3) the European Quality of Life-5 Dimensions (EQ-5D) self-report questionnaire and the European Quality visual analogue scale. Assessments were taken at baseline and at days 30, 180, 360 and 450 (or last visit).

The HRQoL study recruited a much smaller sample than was initially planned (475 patients, compared with 3000 patients), and in TA182[21] the representativeness of the substudy sample was considered to be unclear, as was the clinical utility of the results. Therefore, the AG was unable to draw any conclusions as to the HRQoL of patients treated with prasugrel or clopidogrel in the TRITON-TIMI 38[36] trial. The results from the HRQoL study are presented in the MS.

Data relevant to key patient groups of the core clinical cohort

Specific clinical data relating to patients with STEMI, NSTEMI or diabetes mellitus in the core clinical cohort were not available from the MS. The AG notes from the forest plot in *Figure 2* that the clinical effectiveness of prasugrel compared with clopidogrel was in evidence across the range of subgroups including STEMI, UA/NSTEMI and patients with and without diabetes. The manufacturer's model enabled economic data pertaining to these patient groups to be extracted.

Overall summary of findings

All of the outcomes listed in the final scope issued by NICE were reported in the MS.

The clinical outcomes for the core clinical cohort of the TRITON-TIMI 38[42] trial demonstrate statistically significant differences in favour of prasugrel compared with clopidogrel across a range of outcomes and clinical subgroups. In terms of safety (bleeding events), one statistically significant difference between prasugrel and clopidogrel was noted. The exception was for the combined outcome of TIMI major and minor bleeding, for which significantly more events occurred with prasugrel than with clopidogrel. No conclusions regarding HRQoL could be drawn owing to lack of data.

Clinical discussion points from TA182

It is noted in this report that the TRITON-TIMI 38[36] trial was a well-designed trial. However, three key areas of uncertainty were raised at the time of TA182[21] by the Appraisal Committee (AC) in respect of the TRITON-TIMI 38[36] trial. The AC was concerned that the results of the TRITON-TIMI 38[36] trial may not be generalisable to patients in England and Wales for the following reasons:

- The loading dose of clopidogrel administered in the trial was 300 mg whereas a loading dose of 600 mg may be administered in clinical practice in England and Wales.
- The majority of patients (74%) in the trial received the clopidogrel loading dose during the PCI procedure. In clinical practice in England and Wales, patients undergoing planned PCI receive the clopidogrel loading dose before the PCI procedure.

- Clinical efficacy in the trial was largely driven by statistically significant differences in non-fatal MIs. Non-fatal MIs included both clinical MIs (symptoms) and non-clinical MIs (biomarkers and ECG readings). If only the incidence of clinical MIs were compared between treatment arms, there may be no differences in outcomes between the arms.

Clopidogrel loading dose: size

Manufacturer comments

The difference in size of the clopidogrel loading dose given to patients in the TRITON-TIMI 38[36] trial (300 mg) and the dose (600 mg) most often used in clinical practice in England and Wales is addressed in the MS. The manufacturer acknowledges that there is variation in UK clinical practice as to whether 300 mg or 600 mg of clopidogrel is used in PCI treatment.

The manufacturer points out the inconsistency between clinical guidelines as to the recommended loading dose of clopidogrel (300 mg or 600 mg). For example, in NICE CG94,[13] published in 2010, NICE recommends 300 mg while acknowledging that evidence exists to support the use of 600 mg. The Scottish Intercollegiate Guidelines Network (SIGN)[43] guidelines recommend the use of a 300-mg loading dose, whereas the European Society for Cardiology (ESC) advocates both 300-mg and 600-mg loading doses.[10,11,44]

The manufacturer states that the case for the additional benefit of 600 mg rather than 300 mg is not proven and cites the results of the CURRENT-OASIS (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes 7)[45] trial, published in 2010. In this trial, patients with ACS ($n = 25{,}806$) who were scheduled for early angiography and PCI were randomised to receive a loading dose of 300 mg or 600 mg of clopidogrel and either high- or low-dose aspirin. The patients who received a 600-mg loading dose of clopidogrel and had a PCI continued with 150 mg of clopidogrel for the first 7 days and on day 8 received the standard 75-mg maintenance dose. Patients who received the 300-mg loading dose of clopidogrel and had a PCI continued on 75 mg of clopidogrel following the PCI procedure. The MS reports that in the overall trial population (which also includes the patients who did not undergo the scheduled PCI), the primary composite end point of death from CV causes, MI or stroke at 30 days was not statistically significantly different between the 600-mg arm (4.2%) and the 300-mg arm (4.4%) (HR = 0.94, 95% CI 0.83 to 1.06; $p < 0.61$); however, there was a statistically significant increase in bleeding events in the 600-mg arm (2.5%) compared with the 300-mg arm (2.0%) (HR = 1.24, 95% CI: 1.05 to 1.46; $p < 0.01$). This finding was consistent for subgroups of patients regardless of diagnosis (STEMI or NSTEMI).

The outcomes for the 69% of patients randomised to the CURRENT-OASIS 7[46] trial and who received PCI treatment after randomisation only are also reported in the MS. A statistically significant difference in the occurrence of the primary composite end point in favour of the 600-mg arm (3.9%) compared with the 300-mg arm (4.5%) is noted (HR 0.86, 95% CI 0.74 to 0.99; $p = 0.039$). However, the MS states that no statistical differences were noted for either the STEMI subgroup (HR 0.83, 95% CI 0.66 to 1.05; $p < 0.117$) or NSTEMI subgroup (HR 0.87, 95% CI 0.72 to 1.06; $p < 0.167$).

The manufacturer concludes that the results of the overall CURRENT-OASIS[45] trial do not demonstrate any clear benefit associated with the use of a 600-mg loading dose of clopidogrel compared with a 300-mg dose and thus it is unlikely that the use of 600 mg of clopidogrel in the TRITON-TIMI 38[36] trial would have changed the efficacy results, although it may have resulted in an increase in the number of bleeding events in the clopidogrel arm.

Assessment Group comments

The AG is aware that the licensed loading dose of clopidogrel is 300 mg and that this was the established loading dose in routine clinical practice in the USA when the TRITON-TIMI 38[36] trial commenced. The AG notes that, in TA182,[21] the manufacturer supported the case for the use of 300 mg of clopidogrel in the UK by reporting data from the Eli Lilly-sponsored AntiPlatelet Treatment Observational Registry[47] and

the IMS Health Acute Cardiovascular Analyser study.[48,49] These data indicated that, in 2007, 60–79% of ACS patients in the UK received the 300 mg licensed dose. Clinical advice to the AG is that clinical practice differs between PCI centres as to the loading dose of clopidogrel.

The AG agrees with the manufacturer that there are differences in the stated recommendations in the available clinical guidelines. The manufacturer correctly states that that the SIGN[43] guidelines recommend a 300-mg loading dose of clopidogrel whereas the ESC[10,11,44] guidelines recommend both 300 mg and 600 mg.

The most recent NICE guidelines for UA/NSTEMI (CG94[13]) state that most people admitted with UA/NSTEMI should be treated with a loading dose of 300 mg of clopidogrel. However, the guidelines further state that, if very early (< 24 hours) invasive intervention is planned, a higher loading dose should be considered, particularly in cases for which the procedure will be carried out within 6 hours. The guideline development group (GDG) responsible for CG94[13] has stated in the guideline that as they were not able to formally review all the evidence for a 600-mg loading dose, they were not able to recommend this at the time of publication.

The recently published (July 2013) NICE guidelines CG167[8] for patients with STEMI simply state that treatment with clopidogrel is an established option in the pharmacological treatment of people with acute STEMI, including people undergoing primary PCI. The GDG for CG167[8] noted that a clopidogrel loading dose of 600 mg is not licensed in the UK but is used widely in current practice, especially in people undergoing PCI.

The AG agrees with the manufacturer's conclusion that the results from the overall population of the CURRENT-OASIS 7[45] trial do not appear to support the use of a 600-mg loading dose of clopidogrel over a 300-mg dose. However, the AG considers that the results of the subgroup analysis[45] of the 69% (17,263) of patients treated with PCI suggest that the trial protocol clopidogrel regimen of a 600-mg loading dose followed by 7 days at 150 mg and then 75 mg daily statistically significantly reduces CV events (including stent thrombosis) when compared with a loading dose of 300 mg followed by 75 mg daily. However, the AG also notes that the prevalence of bleeding events was statistically significantly greater in the 600-mg arm than in the 300-mg arm. In addition, the trial follow-up was for a period of 30 days and, therefore, longer-term outcomes are unknown. The AG notes that the findings of the PCI subgroup analysis of the CURRENT-OASIS 7[46] trial are based on subgroup analyses that are subject to statistical caveats; however, the findings are consistent with those of a meta-analysis comprising trials with PCI-treated patients.[50]

In summary, the AG considers that the loading dose of clopidogrel given in the TRITON-TIMI 38[36] trial may be inconsistent with the majority of clinical practice in England and Wales. Data to determine whether or not there is any difference in clinical efficacy between a 300-mg and 600-mg loading dose of clopidogrel are limited.

Timing of the clopidogrel loading dose

Manufacturer comments

In the MS, the manufacturer notes that the timing of the clopidogrel loading dose administered to patients in the TRITON-TIMI 38[36] trial (79% of patients received treatment at the time of PCI) is different to the timing of the loading dose in clinical practice (clopidogrel is given prior to PCI whenever possible) in England and Wales.[21] However, the manufacturer also points out, citing data from the MINAP report,[5] that door-to-treatment time in the UK is decreasing annually, thereby reducing the opportunity for preloading with clopidogrel.

The manufacturer restates the arguments put forward in their MS for TA182[21] that changing the timing of the loading dose of clopidogrel in the trial would not have greatly impacted on the clinical efficacy

outcomes of the trial. The manufacturer cites numerous sources of evidence derived from the analysis of the TRITON-TIMI 38[36] trial to support their argument:

- The effects of prasugrel were consistent over time. For the overall study period, the HR (0.81, 95% CI 0.73 to 0.90) is similar to the HR for the 0–3 days time period (HR 0.82, 95% CI 0.71 to 0.96) and the period from 3 days to the end of the study period (HR 0.80, 95% CI 0.70 to 0.93). An additional landmark analysis examining occurrence of MI, stent thrombosis and urgent target vessel revascularisation (UTVR) at 0–3 days and beyond 3 days confirmed sustained benefit over time.
- In the case of patients treated with glycoprotein IIb/IIIa inhibitors, there was no evidence that the relative benefit of prasugrel compared with clopidogrel was reduced or that there was an excess need for bail-out glycoprotein IIb/IIIa inhibitor use during PCI in those patients randomised to clopidogrel in the study.
- A group of patients received pretreatment up to 24 hours before PCI. The percentage of patients in this pretreated subgroup reaching the composite end point of CV death, non-fatal MI, or non-fatal stroke from randomisation through study end was 9.94% and 11.29% (unadjusted crude event rates) for patients pretreated with prasugrel and clopidogrel, respectively. Although the difference is not statistically significant for this subgroup, the difference supports the theory that, to a large extent, the timing of the loading dose did not influence overall efficacy.

Assessment Group comments

The AG considers that the evidence to support or refute the benefits of preloading with clopidogrel compared with clopidogrel at the time of PCI is equivocal; this means that whether or not patients in the trial would benefit more from clopidogrel compared with patients in the NHS in England and Wales remains unclear.

Clinical compared with non-clinical myocardial infarctions

Manufacturer's comments

A point of discussion during the previous appraisal[21] of prasugrel was that the definition of MI used in TRITON-TIMI 3836 included non-clinically detected MIs. The manufacturer states that the definition of MI in the TRITON-TIMI 3836 trial was based on the American College of Cardiology Task Force on Clinical Data Standards published in 2001.[51] This definition was prespecified and agreed with the regulatory agencies [United States Food and Drug Administration (FDA) and EMA] prior to the start of the trial. The AC and the Evidence Review Group (ERG) were concerned that, if the non-clinical MIs were excluded from the analyses, the resultant clinical difference in non-fatal MIs alone may not be statistically significant when comparing prasugrel with clopidogrel. In response, the manufacturer cited evidence from a reanalysis[52] of the TRITON-TIMI 3836 trial MI ($n = 1218$ MIs). These MIs were reassessed according to the 2007 criteria of the Universal Definition of Myocardial Infarction (*Table 11*) developed by the European Society of Cardiology, the American College of Cardiology, the American Heart Association and the World Heart Federation

TABLE 11 Universal definition of MI

Type	Description
Type 1	Spontaneous MI caused by a primary coronary event, such as a plaque rupture in a coronary artery with less blood then flowing to the muscle
Type 2	Secondary MI owing to either increased oxygen demand or decreased supply owing to other conditions such as spasm of the coronary artery or low blood oxygen from anaemia
Type 3	Sudden cardiac death with evidence of MI but occurring before blood samples could be obtained or before the appearance of cardiac biomarkers in the blood
Type 4	MI related to a PCI
Type 4a	MI associated with a PCI procedure
Type 4b	MI associated with stent thrombosis as documented by an angiography or at autopsy
Type 5	MI associated with CABG

Task Force.[53] Reviewers, who were blinded to treatment allocation, assessed the size and timing of all MIs and whether or not the MI was STEMI or NSTEMI. Of the 1218 MIs considered, 1163 had biomarker data to indicate the size. In the MS, the manufacturer reports that, when analysed according to non-clinical and clinical MIs, compared with clopidogrel, prasugrel demonstrated a significant reduction in MIs that was consistent across the spectrum of MIs of varying type, size and timing.

The manufacturer also points to a further analysis[54] of the TRITON-TIMI 38[36] data in which the rate of CV death within 180 days was compared in people who had experienced a new MI and those who had not. Among patients who experienced a new MI of any type, the rate of CV death was significantly higher (6.5% vs. 1.3%; $p < 0.001$). This was the case even after adjustment for other risk factors (adjusted HR 5.2, 95% CI 3.8 to 7.1; $p = 0.001$). The manufacturer argues that these findings suggest that all MIs have prognostic implications.

In summary, the manufacturer claims that the results of the reanalysis[52,54] of the MIs from the TRITON-TIMI 38[36] trial demonstrate that treatment with prasugrel significantly reduces the risk of all MIs when compared with clopidogrel. The manufacturer also states that further evidence suggests that any type of MI is associated with a significantly increased risk of CV death, with a consistent relationship across all MI types as defined[53] by the universal classification system.

Assessment Group comments

The AG considers that the manufacturer has provided a convincing case to support the hypothesis that prasugrel is effective across all types of MI when compared with clopidogrel. The AG also notes the finding that the reductions in MIs associated with small enzyme releases were not significantly different in the prasugrel-treated and clopidogrel-treated arms of the trial. This suggests that the clinical efficacy results were unlikely to have been driven by reductions in non-clinical MIs.

In summary, of the three key issues raised in TA182[21] and discussed in this section, the AG considers that the size and timing of the loading dose of clopidogrel and the impact these factors have on the primary outcome of the TRITON-TIMI 38[36] trial remain unclear. However, the reanalysis[52,54] of the MIs by the manufacturer demonstrates that prasugrel was more effective than clopidogrel in preventing occurrence of MIs.

Stent thrombosis

In TA182,[21] prasugrel is recommended for patients who have had a stent thrombosis during the course of treatment with clopidogrel. In the MS for the present review, the manufacturer describes the outcomes of related research conducted in collaboration with Professor Gershlick (Consultant Cardiologist, University Hospital of Leicester, Leicester, UK). The purpose of the research is to develop a method to identify patients at risk of stent thrombosis. The manufacturer reports that 20 risk factors for stent thrombosis have been identified, nine relating to patient factors, three relating to the lesion and eight relating to the PCI. These risk factors are presented in table 26 of the MS. The risk scores have subsequently been validated by the manufacturer using data from patients in the TRITON-TIMI 38[36] trial. It is suggested in the MS that the risk scores could be used in clinical practice to identify patients at risk of stent thrombosis and thereby guide treatment decisions.

Comparison of prasugrel with ticagrelor

At the time of TA182,[21] the standard comparator to prasugrel was clopidogrel. However, in 2010, NICE approved the use of ticagrelor as an antiplatelet treatment for patients with ACS (TA236).[22] The pivotal clinical trial assessing ticagrelor is the PLATO[33] trial, in which ticagrelor is compared with clopidogrel in a population of ACS patients. Further information pertaining to the PLATO[33] trial is presented in *Appendix 7*. In the MS (for ticagrelor), the manufacturer of ticagrelor (AstraZeneca) put forward a convincing case that

a formal indirect treatment comparison between the TRITON-TIMI 38[36] and PLATO[33] trials would be inappropriate. The manufacturer's case was accepted by both the ERG and the AC at the time of the ticagrelor appraisal (TA236).[22]

Since the appraisal of ticagrelor, no new relevant RCTs have been conducted with either prasugrel or ticagrelor, nor is there any new direct evidence comparing prasugrel with ticagrelor. However, a number of authors have published indirect treatment comparisons using data from the TRITON-TIMI 38[36] and PLATO[33] trials. The AG considers that any comparison of the results of the TRITON-TIMI 38[36] and PLATO[33] trials is both problematic and inappropriate. Consequently, the AG has not conducted an indirect treatment comparison in this update of TA182.[21] The AG is of the opinion that the issues that mitigate against conducting such an indirect comparison remain unchanged from those presented and accepted during TA236 (ticagrelor).[22] Specifically, these refer to differences in the target populations, the usage of clopidogrel (loading dose and timing of administration) and differences in MI assessment. The AG notes that there is no indirect comparison presented in the MS and that the manufacturer agreed with the AC and the ERG in TA236 (ticagrelor)[22] that such an indirect comparison would be inappropriate.

Problems with an indirect comparison of the TRITON-TIMI 38

The key features of the TRITON-TIMI 38[36] and PLATO[33] trials are described in *Table 12* (reproduced from the MS for TA236).[22] Both trials were conducted in an ACS population, use clopidogrel as a comparator and report the same primary composite efficacy end point (death from CV causes, non-fatal MI, or non-fatal stroke during the follow-up period).

TABLE 12 Comparison of TRITON-TIMI 38 and PLATO RCTs

Characteristic	TRITON-TIMI 38	PLATO
Number of patients	13,608	18,624
Patient population	Patients with early invasively managed ACS scheduled for PCI (including STEMI and NSTEMI patients undergoing same admission PCI). Symptom onset within 72 hours	Broad ACS population (including STEMI). Symptom onset within 24 hours
Prior clopidogrel	Excluded	Allowed (including in-hospital prior to randomisation)
% STEMI	Capped at 26% (18% undergoing primary PCI)	40.5% (all intended for primary PCI)
Clopidogrel load	Only 300 mg allowed	300 mg or 600 mg
Timing of randomisation	Later: after angiography; after decision to perform PCI	Earlier: usually before angiography (if done)
Randomisation	Prasugrel 60-mg load and 10 mg once daily or clopidogrel 300-mg load and 75 mg once daily	Ticagrelor 180-mg load and 90 mg twice daily or clopidogrel 300- to 600-mg load and 75 mg once daily
Administration of study drug	Started in the time interval from randomisation up to 1 hour after PCI	Started immediately after randomisation
Primary efficacy end point	CV death/MI/stroke	CV death/MI/stroke
Primary safety end point	Non-CABG TIMI major bleeding	PLATO major bleeding
PCI	99% (all at randomisation)	61% (49% within 24 hours of randomisation)
CABG	3.2% (0.35% on primary admission)	10.2% (4.5% on primary admission)
Medical management only	1.1%	34%
Glycoprotein IIb/IIIa use	54%	27%
Follow-up	Up to 15 months	Up to 12 months

Reproduced from MS.

Differences in the target population

The TRITON-TIMI 38[36] trial recruited patients with ACS who were intended to be managed with PCI and were randomised just prior to the PCI. A more diverse range of patients was randomised to the PLATO[33] trial; patients in PLATO[33] were randomised at presentation and then investigators decided whether patients were to receive revascularisation treatment or medical therapy.

A TRITON-TIMI trial publication[55] describes the results of a subgroup of patients with STEMI; however, this group included patients who were treated with primary or planned PCI. In the PLATO[33] trial, all patients with STEMI were treated with primary PCI.

A subgroup analysis[56] of the PLATO[33] trial has also been published. This analysis describes the results of ACS patients who were intended for invasive treatment. However, as only 77% of this cohort actually underwent PCI it cannot be considered as a PCI-only cohort.

Differences in clopidogrel loading

The two trials[33,36] differed as to the dosing and timing of administration of clopidogrel (the common comparator). The loading dose of clopidogrel administered in the TRITON-TIMI 38 trial[36] was 300 mg, but, in the PLATO trial,[33] loading doses of 300 mg or 600 mg were allowed. A total of 19.6% of clopidogrel-treated patients in the overall PLATO[33] cohort, 26.8% in the cohort intended for invasive management and 38.6% in the STEMI cohort received 600 mg of clopidogrel.

In the TRITON-TIMI 38[36] trial, most patients received their loading dose of clopidogrel in the time interval between the insertion of the guidewire for PCI up to 1 hour after the procedure, whereas, in the PLATO[33] trial, most patients received their loading dose of clopidogrel before randomisation.

The issue of the size of loading dose and timing of administration of clopidogrel was discussed in detail earlier in this report (see *Clinical discussion points from TA182*). The AG is of the opinion that the differences in clopidogrel usage across the two trials must be considered problematic. The AG remains convinced that, for the reasons previously outlined, there are no reliable clinical data to permit a robust comparison of prasugrel with ticagrelor.

Differences in myocardial infarction assessment

The assessment of MIs across the two trials requires consideration. It was noted in TA236[22] that determining whether or not a patient has a non-clinical MI during the angioplasty procedure is difficult, as any enzymatic changes observed may be wholly due to the original MI that triggered the procedure. A more definitive assessment can be made if multiple measurements of cardiac enzymes are taken between the initial event and the PCI procedure as it is then possible to differentiate a gradually falling pattern of enzymes and a subsequent rise after the PCI (consistent with a further MI having occurred at the time of the procedure). It was further noted in TA236[22] that, in the TRITON-TIMI 38[36] trial (with the exception of the STEMI primary PCI cohort), there was time for at least two preprocedure enzyme measurements to be taken, whereas, in the PLATO[33] trial, only one preprocedure enzyme measurement was taken and any elevated enzymes could not be reliably attributed to either the index event or a new MI. The impact of the differences in MI assessment means that in the PLATO[33] trial the majority of MIs included in the primary end point were clinical MIs, whereas almost half of those included in the TRITON-TIMI 38[36] trial results were non-clinical only.

Differences in duration of trials

There was a difference in the length of follow-up of the two trials. The PLATO[33] trial involved a median follow-up of 9 months, whereas the TRITON-TIMI 38[36] trial followed patients for a median of 15 months. The AG is of the opinion that it is not appropriate to indirectly compare outcomes at 9 months with those at 15 months as the proportion of participants experiencing CV death, MI or stroke is likely to increase as the length of follow-up increases.

Differences in the primary analysis of the trials

The two trials[33,36] also used different measures for the primary analysis. In anticipation of a lack of proportionality of hazards in the TRITON-TIMI 38[36] trial, assessment of the primary outcome was made using the Gehan–Wilcoxon test for the primary analysis rather than the log-rank test. (The Gehan–Wilcoxon test assigns greater weight to earlier time points than the log-rank test.) The log-rank test was then used in a prespecified sensitivity analysis. In contrast, the Cox proportional hazards model was used for the primary analysis in the PLATO trial.[33] The AG is concerned about the impact that the different assumptions stated in these trials would have on the results of an indirect comparison.

Summary and critique of published indirect comparisons of prasugrel and ticagrelor

Four published indirect comparisons[57–60] of prasugrel compared with ticagrelor were identified by the AG and the manufacturer during searching; the key features of these studies are described in *Appendix 8*. The quality of the four published indirect comparisons[57–60] identified by the AG (and the manufacturer) was assessed using the assessment of multiple systematic reviews (AMSTAR)[61] tool. The results are presented in *Appendix 9*.

The published indirect comparison of ticagrelor and prasugrel in patients with ACS conducted by Biondi-Zoccai *et al.*[57,62] was based on the results of the PLATO[33] and TRITON-TIMI 38[36] trials as well as on data from a 12-week dose-ranging trial that compared ticagrelor with clopidogrel in 990 patients with NSTEMI [Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST segment Elevation myocardial infarction 2 (DISPERSE 2)].[63] The total number of patients in the indirect comparison was 32,893. The results of the indirect comparison of prasugrel and ticagrelor demonstrated no statistically significant differences in overall death, non-fatal MI, non-fatal stroke, or their composite.[57] Prasugrel was associated with a significantly lower risk of stent thrombosis, and ticagrelor was associated with a significantly lower risk of any major bleeding and major bleeding associated with cardiac surgery. However, the risk of non-CABG-related major bleeding was similar for prasugrel and ticagrelor. The authors concluded that prasugrel and ticagrelor are superior to clopidogrel for ACS. The results of the indirect comparison suggest similar efficacy and safety of prasugrel compared with ticagrelor, whereas prasugrel appears more protective of stent thrombosis but causes more bleeding.

The AG's main criticism of the indirect comparison in Biondi-Zoccai *et al.*[57] is that the findings are largely based on the outcomes of the TRITON-TIMI 38[36] and PLATO[33] trials. The substantial differences between the two trials (see *Problems with an indirect comparison of TRITON-TIMI 38*) render the results of the indirect comparison unreliable. The AG considers that results from the dose-ranging DISPERSE-2[63] trial make a negligible contribution to the results presented by Biondi-Zoccai *et al.*[57] as the length of follow-up was very short. The AG also notes that the published indirect comparison considered overall death (not CV death) as part of the primary composite end point.

The publication by Passaro *et al.*[59] presented a simplified network meta-analysis graph to improve the communicative value of the analysis undertaken by Biondi-Zoccai *et al.*[57] The analysis excluded the dose-ranging DISPERSE-2[63] trial and instead included the outcomes from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE)[64] trial in which clopidogrel was compared with placebo in 12,562 patients with NSTEMI who were largely managed medically (only 21% of patients were treated with PCI). No rationale was given for the inclusion of the CURE[64] trial. The AG assumes that the reason for inclusion was to enable the authors to expand the treatment network. The conclusions of this analysis concurred with those of Biondi-Zoccai *et al.*,[57] with the exception that no difference in major bleeding between prasugrel and ticagrelor was indicated.[59]

As stated previously, the AG does not consider it appropriate to compare the results of the TRITON-TIMI 38[36] and PLATO[33] trials owing to their inherent differences.

The meta-analysis conducted by Chatterjee *et al.*[58] was intended to compare prasugrel and ticagrelor in patients with ACS or those undergoing coronary intervention for the same, or for significant coronary artery disease, by conducting a network meta-analysis.[58] Four studies, comprising a total of 34,126 patients, were included: PLATO,[33] TRITON-TIMI 38,[36] DISPERSE-2[63] and JUMBO-TIMI 26.[38] The JUMBO-TIMI 26[38] trial was a dose-ranging Phase II trial comparing prasugrel with clopidogrel in 900 patients intended for PCI. The follow-up was limited to 30 days. Chatterjee *et al.*[58] found no difference in CV mortality or rates of MI among patients undergoing PCI but stated that CABG-related bleeding was lower with prasugrel than with ticagrelor. The authors concluded that prasugrel may be more effective than ticagrelor for preventing stent thrombosis and recurrent ischaemic events and warn that the credibility of any indirect comparison hinges on the similarity of the included trials and point to the differences in the patient populations included in the TRITON-TIMI 38[36] and PLATO[33] trials (randomised at presentation for PCI and randomised at presentation to the treatment centre, respectively). The authors acknowledge that this increases the likelihood of heterogeneity and recommend that a head-to-head trial of prasugrel and ticagrelor should be carried out.

The AG is of the opinion that the results of the TRITON-TIMI 38[36] and PLATO[33] trials have made a major contribution to the Chatterjee *et al.*[58] analysis and do not consider it appropriate to compare these two trials. The AG also considers that the length of follow-up of the DISPERSE-2[38] and JUMBO-TIMI 26[38] trials was too short to provide data relevant to the current appraisal.

The work published by Steiner *et al.*[60] was intended to indirectly compare prasugrel, ticagrelor, high-dose clopidogrel and standard-dose clopidogrel in patients scheduled for PCI by undertaking a network meta-analysis from 14 eligible studies (48,982 patients). All studies are described in *Appendix 7*. The three largest studies are TRITON-TIMI 38,[36] a substudy from the PLATO trial (PLATO-INVASIVE[56]) and CURRENT-OASIS 7 PCI.[45] These trials included patients with ACS and contributed almost 90% of patients in the analysis, whereas the other studies included stable or mixed study populations. A subgroup analysis was conducted on patients with ACS and treated with PCI using data from five studies: TRITON-TIMI 38,[36] PLATO,[33] CURRENT-OASIS 7,[45] Han *et al.*[65] and DOSER.[66] This subgroup analysis corroborated the overall findings of the review which were that, for the majority of outcomes, there was no superiority of either prasugrel or ticagrelor and that prasugrel was associated with a significantly lower risk than ticagrelor for stent thrombosis but an increased risk of major or minor bleeding.

The AG is of the opinion that the overall network meta-analysis is not relevant to this review as the majority of included trials comprise stable or mixed study populations and are of short duration with primarily pharmacodynamics outcomes. The results of the ACS PCI subgroup are largely based on the comparison of the TRITON-TIMI 38[36] and PLATO[33] trials; the AG has previously stated this comparison to be inappropriate. The three other trials included in the subgroup analysis (CURRENT-OASIS 7,[46] Han *et al.*[65] and DOSER[66]) compare high-dose clopidogrel with standard-dose clopidogrel and are of too short a duration to be of relevance to the current appraisal.

Discussion

One relevant RCT was identified for inclusion in this review, namely the TRITON-TIMI 38[36] trial. This was an international, double-blind trial that recruited a large number of patients. The trial was robustly designed to demonstrate the clinical efficacy of prasugrel compared with clopidogrel in a population of patients with ACS who were treated with PCI. The outcomes for the core clinical cohort were considered relevant to this appraisal. Although the core clinical cohort comprised 79% of the overall trial population, this subgroup analysis was not prespecified in the original trial protocol[42] and should, therefore, be considered as exploratory and hypothesis generating. Searching did not identify any trials of prasugrel compared with ticagrelor.

In the core clinical cohort, prasugrel was favoured over clopidogrel for the primary composite end point of death from CV causes, non-fatal MI, or non-fatal stroke. This effect appeared to be consistent across subgroups (including STEMI, UA/STEMI and patients with and without diabetes mellitus) and for the duration of the trial. Likewise, the benefit of prasugrel was statistically significantly greater for the secondary composite end point (death from any cause, non-fatal MI, non-fatal stroke, or non-CABG-related non-fatal TIMI major bleeding). The efficacy for both composite end points was driven by the reduced number of non-fatal MIs in the prasugrel arm. Other statistically significant differences in favour of prasugrel were reported for the outcomes of definite stent thrombosis and definite or probable stent thrombosis. There were no statistically significant differences noted between trial arms for the majority of the safety outcomes related to bleeding; however, there was a statistically significant difference in favour of clopidogrel when TIMI major and minor bleeds were combined. The calculated net clinical benefit also statistically significantly favoured prasugrel over clopidogrel. No reliable HRQoL outcome data for the patients in the TRITON-TIMI 38 trial were available.

No detailed clinical data were identified by the AG that related to key patient groups within the core clinical cohort, patients with STEMI or UA/NSTEMI or patients with diabetes mellitus.

The three areas of concern noted during TA182[21] were reconsidered in this review. These centred around the generalisability of the TRITON-TIMI 38[36] trial results to patients in clinical practice in England and Wales. The AG considers that the clinical evidence for the equivalence of a 300-mg loading dose of clopidogrel (administered in the trial) with the 600-mg loading dose often given in clinical practice remains uncertain. Similarly, the AG is of the opinion that the importance of timing of the administration of the clopidogrel loading dose on patient outcomes remains an issue. However, the AG considers that the case for the effectiveness of prasugrel compared with clopidogrel in preventing MIs of all types and sizes appears to be robust and indicates that prasugrel is more effective than clopidogrel at preventing MIs.

No indirect comparison of prasugrel with ticagrelor was conducted by the AG or the manufacturer. The AG did not conduct an indirect treatment comparison using data from the TRITON-TIMI 38[36] and PLATO[33] trials owing to irreconcilable differences between the trials. These differences were discussed in the appraisal of ticagrelor during TA236.[22] Four published indirect comparisons[57–60] were considered to provide unreliable conclusions as they were based largely on data derived from the TRITON-TIMI 38[36] and PLATO[33] trials. The comparative effectiveness and safety of prasugrel compared with ticagrelor remains unknown.

Chapter 4 Assessment of cost-effectiveness

There are three distinct elements to this section on cost-effectiveness. First, the methods and results of a literature search for economic evidence describing prasugrel since the publication of the previous NICE guidance[21] is presented. Second, a summary and critique of the economic model submitted by Daiichi Sankyo Company Ltd/Eli Lilly and Company Ltd is described (the AG notes that no other manufacturer submitted an economic model). Third, the AG's independent economic model is described alongside comprehensive interpretation of the model's results.

Systematic review of existing cost-effectiveness evidence

Search strategy

This review is an update of an existing review; however, searching was not date limited. In addition to searching the MS for relevant references, the following databases were searched for economic evaluations of prasugrel:

- Ovid MEDLINE(R) (1946 to August Week 3 2013)
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (searched 30 August 2013)
- NHS EED (searched 30 August 2013)
- EMBASE (1974 to 30 August 2013).

The results were entered into an EndNote X5 library (and the references were deduplicated electronically). Full details of the search strategy are presented in *Appendix 1*.

Inclusion and exclusion criteria

At stage 1, two reviewers (ABol and SB) independently screened all titles and abstracts. Full paper manuscripts of any titles and abstracts that were considered relevant by either reviewer were obtained when possible. At stage 2, the relevance of each study was assessed (ABol and SB) according to the criteria set out in *Table 13*. Studies that did not meet the criteria were excluded. Any discrepancies were resolved by consensus and, when necessary, a third reviewer was consulted.

TABLE 13 Inclusion and exclusion criteria

Variable	Inclusion criteria	Exclusion criteria
Intervention or comparator	Prasugrel	Not prasugrel
Study design	Full economic evaluation	Methodological paper, letter,[a] abstract[b]
Perspective	UK or European perspective	Non-European perspective
Source of publication	Unrelated to previous appraisal	Related to previous appraisal (e.g. NICE/ERG/manufacturer)

a Letters were included if they were related to a study already included in the review.
b Abstracts were judged for inclusion at the very end of the inclusion process in order to ascertain whether or not sufficient information was available for the abstract to be included in the review.

Data extraction and quality assessment strategy

In the AG's review protocol,[67] data relating to both study design and quality were planned to be extracted by two reviewers (ABol and SB) into an Excel spreadsheet (Microsoft Excel 2010; Microsoft Corporation, Redmond, WA, USA). It was also planned that all economic evaluations identified for inclusion in the review would be quality assessed according to the Drummond *et al.*[68] 10-point checklist. However, no studies were identified for inclusion in the AG's review.

Results: quantity and quality of research available

After deduplication of 1449 references, a total of 1230 titles and abstracts were screened for inclusion at stage 1. Of these 1230 references, 1117 were immediately excluded because they did not include prasugrel as an intervention or a comparator. At stage 2, inclusion criteria were applied to 113 references. During stage 2, 98 references were excluded, leaving a possible 15 references available for potential inclusion and these are listed *Table 14*. Of the 15 potentially eligible references, none of the papers met the full inclusion criteria that were set by the AG.

The review carried out by the AG picked up the three studies[69,72,73] that the manufacturer had identified for inclusion in the review of cost-effectiveness evidence presented in the MS. Two of these studies[69,73] were carried out from a US perspective and the third study[72] employed the model that was submitted to NICE for the evaluation of prasugrel in 2009 (TA182[21]); all three studies[69,72,73] were therefore excluded from the review by the AG.

Studies by Davies *et al.*[72,74–76]

The AG notes that, of the 15 potentially eligible studies identified via electronic searching, four of the references were authored by Davies *et al.*; one was a full paper[72] and three were abstracts.[74–76] In the MS (p. 87), the manufacturer comments that the results of the analyses described in the full paper[72] were generated by the same model as that submitted to NICE for the evaluation of prasugrel in 2009 (TA182).[21] This reference was therefore excluded from the review by the AG as the economic model described therein has been previously fully discussed and critiqued. However, as the full paper[72] reports model results using costs and rehospitalisation rates specific to Germany, Sweden, the Netherlands and Turkey, the AG has reproduced the table of results from the main study[72] and also the results of a sensitivity analysis where the price of clopidogrel has been set to zero (*Table 15*). The results of the Spanish model-based cost-effectiveness analysis presented in one of the abstracts have not been presented here as the abstract[76] did not include sufficient population data to allow comparison with the other published model results. In summary, all of the individual country incremental cost-effectiveness ratio (ICER) estimates demonstrate the cost-effectiveness of prasugrel compared with clopidogrel in the overall licensed population and in four patient subgroups (UA/NSTEMI, STEMI, ACS diabetes and the core clinical cohort); when the price of clopidogrel is set to zero, prasugrel remains cost-effective compared with clopidogrel in the overall licensed population.

Conclusions of the Assessment Group's cost-effectiveness literature review

The AG did not identify any published papers that met the inclusion criteria for the review.

TABLE 14 List of 15 excluded studies

Study	Title	Comment
Mahoney *et al.*[69]	Cost-effectiveness of prasugrel versus clopidogrel in patients with ACSs and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in MI TRITON-TIMI 38	Non-European perspective
Serebruany[70]	Letter by Serebruany regarding article "Cost-effectiveness of prasugrel versus clopidogrel in patients with ACSs and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in MI TRITON-TIMI 38"	Letter/linked to Mahoney[69]
Mahoney *et al.*[71]	Response to letter regarding article "Cost-effectiveness of prasugrel versus clopidogrel in patients with ACSs and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in MI TRITON-TIMI 38"	Letter/linked to Mahoney[69]
Davies *et al.*[72]	Prasugrel vs. clopidogrel in patients with ACSs undergoing percutaneous coronary intervention: a model-based cost-effectiveness analysis for Germany, Sweden, the Netherlands and Turkey	Related to previous appraisal (same economic model – TA182)
Mauskopf *et al.*[73]	Cost-effectiveness of prasugrel in a US managed care population	Non-European perspective
Davies *et al.*[74]	Is prasugrel cost-effective relative to clopidogrel in patients with ACSs undergoing percutaneous coronary intervention from the perspective of the UK national health service? A model-based analysis	Abstract
Davies *et al.*[75]	Is prasugrel cost-effective relative to clopidogrel in patients with ACSs undergoing percutaneous coronary intervention from the perspective of the German health care system? A model-based analysis	Abstract
Davies *et al.*[76]	Prasugrel vs. clopidogrel in patients with ACSs undergoing percutaneous coronary intervention: A Spanish model-based cost-effectiveness analysis	Abstract
Greenhalgh *et al.*[15]	Prasugrel for the treatment of acute ACSs with percutaneous coronary intervention	NICE
Hill *et al.*[77]	Prasugrel for the treatment of ACSs with percutaneous coronary intervention: NICE technology appraisal guidance	NICE/ERG
Keast *et al.*[78]	Cost-effectiveness of prasugrel and clopidogrel for ACSs in a medicaid population	Abstract/non-European perspective
Mahoney *et al.*[79]	Cost-effectiveness of prasugrel versus clopidogrel in patients with ACSs and planned PCI: Results from the TRITON-TIMI 38 trial from the German perspective	Abstract
Mondragon *et al.*[80]	Cost-effectiveness of prasugrel versus clopidogrel in patients with ACSs undergoing percutaneous coronary intervention in the private sector in Mexico	Abstract/non-European perspective
Mondragon *et al.*[81]	Cost-effectiveness of prasugrel versus clopidogrel in patients with ACSs undergoing percutaneous coronary intervention in the public health care system in Mexico	Abstract/non-European perspective
Rao *et al.*[82]	A decision modelling approach to evaluate the cost-effectiveness of prasugrel versus clopidogrel in patients with planned percutaneous coronary intervention	Abstract

TABLE 15 Cost-effectiveness results for the overall licensed population and specific subgroups from four European countries

Per patient costs, QALYs and ICER	Licensed population ($n = 13,090$)		UA/NSTEMI ($n = 9669$)		STEMI ($n = 3421$)		ACS diabetes ($n = 2947$)		Core cohort ($n = 10,804$)	
	CLOP	PRA	CLOP	PRA	CLOP	PRA	CLOP	PRA	CLOP	PRA
Germany										
Total costs (€)	19,942	20,725	19,990	20,751	19,804	20,652	18,995	19,817	21,428	22,220
QALYs	10.657	10.712	10.661	10.702	10.647	10.740	9.972	10.109	11.524	11.547
ICER (€)	14,350		18,530		9131		6025		14,487	
Sweden										
Total costs (€)	27,003	27,345	27,020	27,330	26,954	27,388	25,633	26,021	29,128	29,481
QALYs	10.945	10.997	10.930	10.968	10.988	11.080	10.214	10.347	11.870	11.923
ICER (€)	6520		8016		4738		2910		6711	
Netherlands										
Total costs (€)	13.646	14,147	13,667	14,152	13,587	14,132	13,049	13,566	14,626	15,132
QALYs	12.919	12.987	12.907	12.959	12.952	13.065	11.988	12.156	14.053	14.122
ICER (€)	7369		9378		4788		3080		7342	
Turkey										
Total costs (€)	3789	4167	3796	4171	3769	4158	3591	3975	4074	4455
QALYs	9.521	9.573	9.518	9.558	9.531	9.616	8.810	8.937	10.366	10.419
ICER	7294		9371		4552		3036		7207	
Licensed population: clopidogrel drug cost set at zero										
ICER (€)	Germany (18,494)			Sweden (7058)			Netherlands (7634)		Turkey (14,251)	

CLOP, clopidogrel; PRA, prasugrel; QALY, quality-adjusted life-year.

Review of the Eli Lilly and Company Ltd/Daiichi Sankyo Company Ltd economic model

Overview of manufacturer's submitted model

Table 16 describes NICE's reference case checklist and provides the manufacturer's assessment of how the submitted economic model matches NICE's checklist.

In summary, the manufacturers have submitted the same economic model that they previously presented during the original appraisal of prasugrel for the treatment of ACS with PCI (TA182).[21] However, some aspects of the submitted model have been updated in the light of feedback generated during the original appraisal of prasugrel (TA182).[21] These revised aspects are:

- use of sensitivity analysis encompassing the entire population as opposed to a 'typical' patient profile
- removal of the functionality that allowed the user to choose to model 15 months of treatment (as the licence is only for 12 months)

TABLE 16 The NICE reference case checklist

NICE reference case requirements	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by the Institute	Yes but timing and dose of comparator in UK does not match that used in the trial
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	Economic evaluation was carried out from the perspective of the NHS – no PSS costs are described in the MS
Perspective on costs	NHS and PSS	Yes
Perspective on outcomes	All health effects on individuals	Time horizon chosen was a lifetime horizon so all relevant benefits are accounted for in the economic model; only in-trial drug and hospital costs are considered
Type of economic evaluation	Cost-effectiveness analysis	All outcome data up to 12 months are derived from a single Phase III RCT (TRITION-TIMI 38), which was appropriate. Four clinical studies were identified via ad hoc literature searches and used to estimate long-term risks up to 40 years
Synthesis of evidence on outcomes	Based on a systematic review	Although quality-of-life data were collected during the TRITON-TIMI 38 trial they were not used owing to small number of responses. Instead, published US EQ-5D scores were used
Measure of health benefits	QALYs	Valuations within the EQ-5D scores were calculated using time trade-off techniques
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Not stated in the MS
Source of preference data for valuation of changes in HRQoL	Representative sample of general public	Yes
Discount rate	An annual rate of 3.5% on both costs and QALYs	Yes
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes, equal weighting regardless of characteristics

PSS, Personal Social Services; QALY, quality-adjusted life-year.

- conduct of scenario analysis using the ERG's suggestions for utility values, amended long-term relative risk (RR) of mortality and reduced incidence of non-fatal MI
- use of the generic (reduced) price of clopidogrel
- updated costs.

The model was developed with the principle of simulating the TRITON-TIMI 38[36] trial outcomes as closely as possible. There are two main phases to the model: the active treatment phase, which spans the duration of the clinical trial, and the post-treatment phase, which extrapolates outcomes and costs beyond events that took place during the treatment phase, up until death or lifetime horizon (base case 40 years). Within the trial period, there is an opening 3-day period, modelled using a decision tree, followed by 12 cycles, each of 1 month, up to 12 months. The transitions were time dependent. Long-term mortality was based on adjustment of population life tables to reflect prognostic implications of the events modelled over the short term. The model also permits some costs to accumulate after the end of the trial period.

Figure 3 shows the state transition diagram for the Markov model element of the TRITON-TIMI 38[36] study. Patients enter the model at the point of the index ACS event, immediately prior to undergoing PCI. Exit occurs at death, or at completion of the model time horizon.

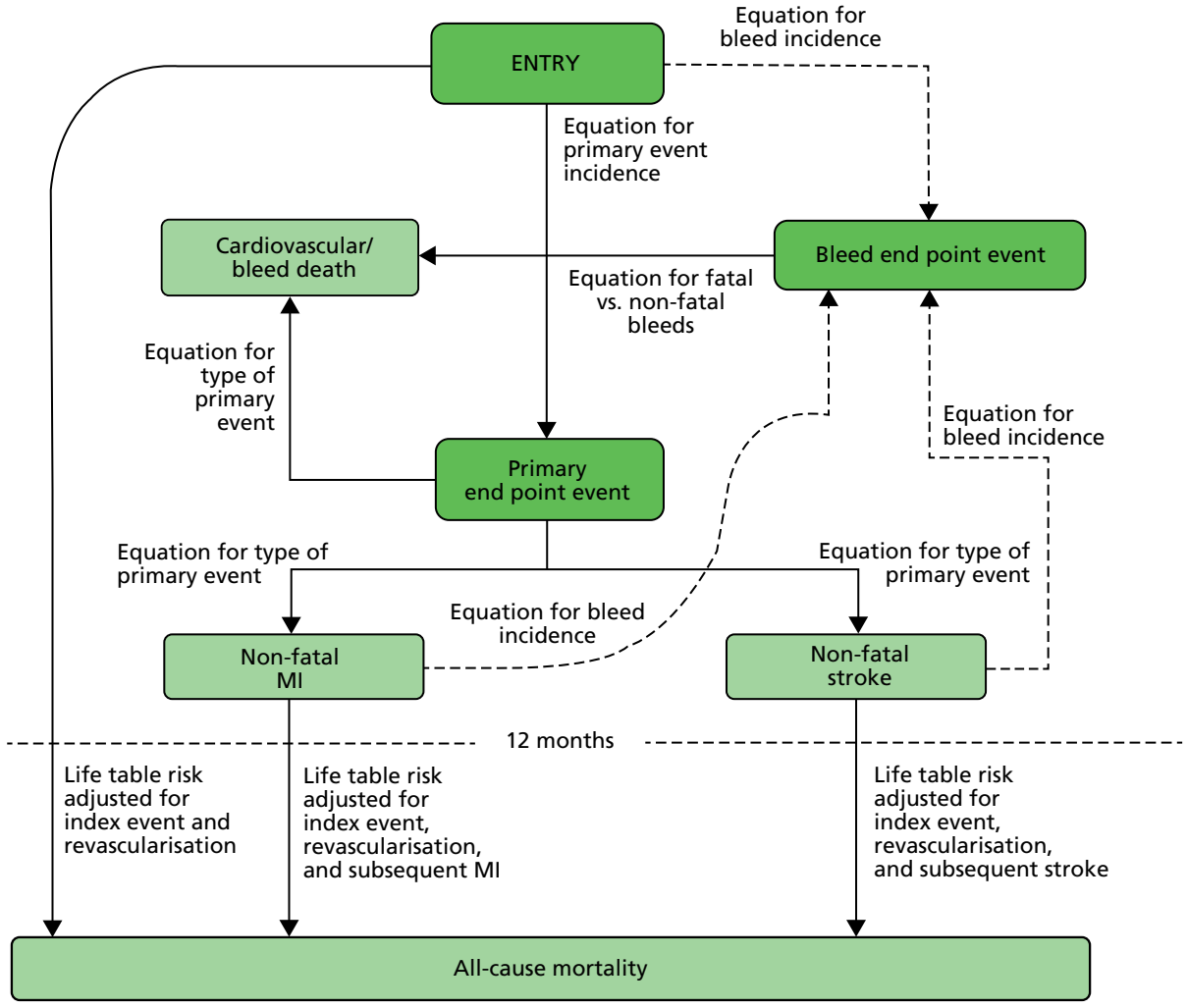

FIGURE 3 Schema of manufacturer's model. Note: the lightly dashed lines leading to 'bleed end point event' are intended to highlight that these do not represent transitions to health states that continue to impart prognostic effects in terms of long-term mortality, or permanent utility decrements. Patients remain in their origin states following bleed events, except when the event is fatal. Temporary utility decrements are applied at the time of major non-fatal bleeds. Rehospitalisation occurs in all states at rates determined by current and past clinical events. MI, myocardial infarction. Reproduced from MS.

Parameters and values

The parameters and values used in the economic model are displayed in *Table 17*.

Sources of evidence used to inform and develop the model

The TRITON-TIMI 38[36] trial was the key source of clinical evidence described in the MS. Non-trial sources of clinical evidence were also identified via literature reviews to inform assumptions regarding additional clinical inputs, long-term extrapolation of mortality and HRQoL.

TABLE 17 Key parameters used in the model

Parameter	Data	Source
General		
Treatment duration	12 months	SPC, treatment guidelines
Time horizon	40 years	NICE reference case
Discounting	3.5%	NICE reference case
Risk equations for transition probabilities		
Primary events	Logistic regression for 3-day risk (OR) Weibull regression for longer-term risk (HR)	Modelling working group based on TRITON baseline characteristics and end points results
Fatal bleeds, major bleeds, minor bleeds	Logistic regression for 3-day risk (OR) Weibull regression for longer term risk (HR)	Modelling working group based on TRITON baseline characteristics and end points results
RRs for post-trial all-cause mortality [RR (95% CI)]		
Angina	1.21 (1.03 to 1.43)	Rosengren *et al.* (1998)[83]
UA/NSTEMI	1.55 (1.31 to 1.84)	Allen *et al.* (2006)[84]
STEMI	1.84 (1.52 to 2.20)	Allen *et al.* (2006)[84]
Reinfarcted NSTEMI	2.93 (2.34 to 3.66)	Mueller *et al.* (1995)[85]
Reinfarcted STEMI	3.48 (2.77 to 4.37)	Mueller *et al.* (1995)[85]
Stroke	2.39 (1.44 to 3.97)	Taneja *et al.* (2004)[86]
Utility decrements compared with general population [EQ-5D time-trade-off utility scores (SE)]		
ACS	0.0409 (± 0.0002)	Sullivan *et al.* (2006)[87]
Stroke	0.0524 (± 0.0001)	Sullivan *et al.* (2006)[87]
Major bleed	25% decrement to population norm for 14 days	Assumption
Cost per hospitalisation (weighted)		
Clopidogrel	£3070	MS
Prasugrel	£3081	MS
Drug acquisition costs		
Clopidogrel	£0.24, loading dose £0.07/day, maintenance dose	NHS Drug Tariff[28] 75 mg (28 tablets) £1.83
Prasugrel	£10.20, loading dose £1.70/day, maintenance dose	MIMS August 13 (based on £47.56 per pack of 28 tablets)[88]

OR, odds ratio; SE, standard error.
Reproduced from MS.

Baseline treatment strategy

The base case model uses a maximum treatment duration of 12 months, which matches the SPC[24] and clinical practice in England and Wales. Aspirin use is continued up to 15 months for modelling purposes.

Baseline and relative risks of disease progression

There are two main phases to the model: the active treatment phase (duration of the trial) and the post-treatment phase, which extrapolates outcomes and costs beyond the duration of the trial up until death.

Separate risk equations for the primary end point events were modelled for UA/NSTEMI and STEMI populations. These analyses used logistic models for events occurring within 3 days, and Weibull models over the remainder of the trial period. Both primary efficacy and safety (bleed) end points predicted by these equations were disaggregated from their combinations into specific event types (e.g. CV death, non-fatal MI and stroke).

The primary end point risk equations played no part in predicting survival beyond the trial. RRs for all-cause mortality were applied to general population (life table-based) mortality rates adjusted to exclude deaths from CV causes. The RRs reflected the index ACS status and revascularisation of all patients in the trial, and the prognostic implications of a further MI or stroke within the trial period.

The estimation of transition probabilities and hospitalisation rates can be split into a number of sections. *Table 18* provides an overview of these sections; further detail is provided beneath the table.

Risk of a primary end point

Probabilities of primary end point events were estimated from TRITON-TIMI 38[36] trial data. Logistic regression was used to predict the occurrence of events during the initial (acute) 3-day period. Standard parametric time to event (survival) analysis (Weibull functions) was used to estimate the risk of events from day 4 to the end of treatment period (12 months).

The AG notes that, despite available clinical trial evidence, the model uses multinomial logistic regression analysis to derive risk equations to predict the probability that having experienced an event, the event is fatal MI, non-fatal MI, or a non-fatal stroke (MS, p. 98). The risk equations in the model focus on time to first event only, although, if a non-fatal event precedes a fatal event, primacy is given to the fatal event.

Risk of major and minor bleeds and mortality following a bleed

The risk of major and minor bleed was estimated using risk equations (MS, p. 98). The model definition of bleeds does not exclude CABG-related bleeds. Non-fatal bleeds are not treated as on-going health states within the model [such events incur only temporary reductions (14 days) in HRQoL and resource use consequences]; however, prognostic implications were captured by the events that occurred up to the end of the trial follow-up period.

TABLE 18 Transition probabilities, duration and event description

Section	Period	Incident event	Type of event
Risk of primary end point event (CV death, MI, stroke) following PCI	3 days	Logistic	Multinomial logistic for CV death, non-fatal MI and non-fatal stroke
	4 days to 12 months	Weibull	
Risk of major and minor bleeds (including fatal)	3 days	Logistic	Logistic for fatal bleeds, logistic for major vs. minor (no distinction between time periods)
	4 days to 12 months	Weibull	
Risk of events and mortality following treatment phase	12 months to 40 years	Cause elimination life tables adjusted for trial events RRs	Mortality and hospitalisations

Multiple events

Patients who experience a trial end point in some cases experienced multiple events. The risk equations focus on the time to first event only, although, if a non-fatal event preceded a fatal event, primacy was given to the fatal event. Long-term utility and life expectancy implications of clinical events were driven by the occurrence of a first event and were deemed to be unaffected by multiple occurrences. These events were recognised within the model in terms of associated rehospitalisations.

Extrapolation beyond the trial period

Based on treatment follow-up of 15 months in TRITON-TIMI 38,[36] risk equations were developed in order to estimate the risk of primary efficacy and safety events for the cohorts of patients receiving prasugrel and clopidogrel. After the maximum treatment duration of 12 months, no additional treatment effect was accrued in either of the two treatment arms.

Patients who reached the end of the trial without suffering prognostic events could be expected to face a lower risk of mortality than patients who did suffer prognostic events. A literature review was conducted in order to identify potential sources for studies reporting long-term mortality rates in ACS PCI patients. As no studies that reported on long-term follow-up of revascularised ACS patients were identified, RRs from four studies[83–85,89] of patients who had undergone revascularisation were used. Indirect comparisons were used to derive RRs of mortality compared with coronary heart disease-free patients for each health state included in the model.

The manufacturer adjusted actuarial life tables by RRs calculated by comparing life table mortality rates over the appropriate age ranges with cause elimination life tables for the UK. The MS states that 'actuarial life tables were taken from the Government Actuarial Department and cause elimination life tables were calculated using Office for National Statistics data (excluding cause of death codes ICD-1-100-199)' (MS, p. 101).

The RRs used to model the period beyond 12 months are shown in *Table 19*.

Population

The populations described in the economic model reflect the patients enrolled in TRITON-TIMI 38[36] (details presented in *Table 20*).

TABLE 19 Indirect RRs of mortality compared with coronary heart disease-free mortality in patients with the health states included in the manufacturer's model

			Indirect RR (95% CI) vs. CHD-free mortality	
Health state	Source	Details of study	Non-revascularised	Revascularised
Angina	Rosengren *et al.* (1998)[83]	Pooled RR for angina mortality 4–16 years after onset	1.59 (1.16 to 2.20)	1.21 (1.03 to 1.43)
NSTEMI	Allen *et al.* (2006)[84]	Multivariate adjusted RR estimates for mortality in patients with NSTEMI (RR 1.28) or STEMI (RR 1.52) compared with patients with angina during 10-year follow-up	2.04 (1.73 to 2.41)	1.55 (1.31 to 1.84)
STEMI			2.42 (2.03 to 2.88)	1.84 (1.54 to 2.20)
Reinfarcted NSTEMI	Mueller *et al.* (1995)[85]	RR for mortality in patients with reinfarction within 42 days (RR 1.89)	3.85 (3.09 to 4.81)	2.93 (2.34 to 3.66)
Reinfarcted STEMI			4.58 (3.65 to 5.75)	3.48 (2.77 to 4.37)
Stroke	Taneja *et al.* (2004)[86]	RR for mortality in patients with a prior stroke at baseline during a 4-year follow-up of PRAIS-UK	–	2.39 (1.44 to 3.97)

CHD, coronary heart disease.

TABLE 20 Modelled patient populations

Population	Description
All ACS	All patients other than those with prior stroke or TIA and including patients who are now recommended to be treated with a 5-mg maintenance dose
ACS core	Core clinical cohort, patients without prior TIA/stroke, aged < 75 years and weigh ≥ 60 kg
UA/NSTEMI	UA/NSTEMI licensed population (excluding prior TIA/stroke)
STEMI	STEMI licensed population (excluding prior TIA/stroke)
ACS diabetes	ACS licensed population with diabetes (excluding prior TIA/stroke)

Interventions and comparators

The economic evaluation compares prasugrel in combination with aspirin and clopidogrel in combination with aspirin, at licensed doses. Consistent with both the TRITON-TIMI 38[36] trial and the SPC,[24] prasugrel is initiated with a single 60-mg loading dose and then continued at 10 mg once a day for up to 12 months in combination with aspirin (75–325 mg). Clopidogrel was initiated with a single 300-mg loading dose and then continued at 75 mg once a day in combination with aspirin for 12 months.

The manufacturer considered that a formal indirect comparison between prasugrel and ticagrelor was inappropriate and no economic analysis of this comparison has been presented in the MS.

Perspective, time horizon and discounting

The perspective for outcomes reflects all the direct health effects, whereas the perspective used for costs is that of the NHS. Outcomes are expressed in terms of life-years and quality-adjusted life-years (QALYs) gained. The time horizon is set at 40 years and, in line with the NICE *Guide to the Methods of Technology Appraisal*,[90] both costs and benefits are discounted at 3.5%. A half-cycle adjustment was performed for both costs and outcomes (attributing events on the basis of average patient exposure over the course of each cycle).

Health-related quality of life

Although the TRITON-TIMI 38[36] trial included a HRQoL substudy, the manufacturer reports that it was not possible to provide robust HRQoL estimates owing to the very small numbers of patients with events included within the analysis. The manufacturer, therefore, conducted a systematic review of the literature to identify HRQoL studies relevant to the modelled trial population. The MS (p. 102) includes details of the methods used in the systematic review. Mean utility decrements for ACS (0.049) and stroke/MI (0.052) were taken directly from a US study,[87] which was designed to produce a specific list of preference weights for use in economic evaluations; the study used the US version of the EQ-5D.

To calculate utility weights for use in the economic evaluation, background UK population norms (free of disease) which vary by age and sex, as described by Kind *et al.*,[91] were applied to all patients in the trial. The utility decrements for ACS and stroke/MI were then used alongside these background utility estimates. Finally, the MS assumed that, for a major bleed, a decrement of 25% of the population (utility) norm was applicable for a 14-day period (25% decrement equates to a 0.007 utility toll).

Resources and costs

The key categories of cost estimates in the MS are related to (1) hospitalisations and (2) drug costs. Key cost parameter assumptions are presented in *Table 21*.

TABLE 21 Key cost parameter assumptions

Parameter	Assumption	Justification
Resource utilisation at index PCI	The costs of index ACS episodes and index hospitalisations were not included in the analyses	The costs of index hospitalisation were common to both arms
Costs of repeat hospitalisations	Only hospitalisations related to end points or to serious adverse events requiring rehospitalisation and potentially related to the ACS condition or the PCI intervention were included in the cost analysis	These represent all rehospitalisations clinically adjudicated as relevant to the trial population and intervention irrespective of adjudicated end points. Regression (Poisson) methods were used to predict rates of rehospitalisation conditional on clinical event histories
	Rehospitalisations were valued at a weighted average unit cost per hospitalisation (using NHS reference costs)	DRGs were allocated to 2487 individual hospitalisations by clinical reviewer and then UK HRG4 codes matched by a UK clinical cardiologist
Geographical variation in hospitalisation rates	Underlying differences in hospitalisation rates were applied by geographic location (based on economic substudy across eight countries)	Observed hospitalisation rates in the UK were lower than in the trial as a whole. The regression reflects this lesser propensity to hospitalise in the UK within the trial
Drug costs	Miscellaneous drug acquisition costs were included within the NHS reference costs applied to hospitalisations within the model. These may include antiplatelet costs (e.g. clopidogrel), but the acquisition cost continued to be applied during hospitalisations in the model, potential double counting	Double counting of antiplatelet drug acquisition costs would have no material effect on the ICER as these would constitute tiny proportions of hospital episode costs, apply to both arms, and leave average hospitalisation costs unaffected

DRG, diagnostic-related group; HRG, health-related group.

Drug acquisition costs

Patients were assumed to be treated with either aspirin and clopidogrel or aspirin and prasugrel for 12 months. The acquisition costs of prasugrel, clopidogrel and aspirin are shown in *Table 22*. No drug costs were applied beyond 12 months.

TABLE 22 Drug acquisition costs

	Cost of loading dose (per day)	Cost of maintenance dose (per day)	Source
Prasugrel	£10.20	£1.70	MS
Clopidogrel	£0.24	£0.07	MS
Aspirin	NA	£0.01	MS

NA, not applicable.

Cost of hospitalisations in TRITON-TIMI 38

The TRITON-TIMI 38[36] trial included a preplanned economic substudy which recorded the occurrence of rehospitalisations associated with serious adverse events over a 12-month period in eight countries: Australia, Canada, the USA, France, Germany, the UK, Spain and Italy. The hospitalisation substudy covered the trial period and focused on 2487 hospitalisations from 6705 patients. Individual US diagnostic-related groups (DRGs) were then assigned to each hospitalisation to facilitate a cost estimation for each episode. The assignments of DRGs were carried out by an expert who was blinded to the treatment arm of the study in which they occurred. Poisson regression was used to predict the rate of hospitalisations within the trial period according to clinical event history and geographical location to estimate the rates in the overall population. Patients who remained alive at the end of the trial continued to accrue life-years, QALYs and costs. No further incidence of clinical events was modelled during the extrapolation phase and the hospitalisation rates were estimated at the same constant rate per living patient in both arms.

For the UK economic evaluation, each DRG code was matched to a corresponding UK 'NHS reference costs' HRG4 code by a consultant cardiologist. The allocated unit costs were then used to calculate an average weighted unit cost per hospital episode for patients in the prasugrel and clopidogrel arms of TRITON-TIMI 38.[36] The manufacturer stated that a conservative approach was adopted as the average cost of hospitalisation in the clopidogrel arm was used for both treatment arms, despite evidence to suggest that the weighted average unit cost per hospitalisation episode may be more expensive in the prasugrel arm. Hospitalisation costs are presented in *Table 23*.

Cost-effectiveness results

Five different subgroups are considered, namely (1) the whole ACS licensed population (excluding prior stroke/TIA), (2) the ACS core population (excluding those with prior stroke/TIA and patients weighing < 60 kg or aged ≥ 75 years), (3) the UA/NSTEMI licensed population (excluding those with prior stroke/TIA), (4) the STEMI licensed population (excluding those with prior stroke or TIA) and (5) the ACS–diabetes licensed population (excluding those with prior stroke or TIA). The base case ICERs generated by the manufacturer's model for these five subgroups are presented in *Table 24*.

Sensitivity analyses

A probabilistic sensitivity analysis was not undertaken. Univariate (one-way) sensitivity analysis was conducted by the manufacturer for selected model parameters, namely discounting, haemorrhage utility decrement, MI and stroke utility decrements, hospitalisation episodes, treatment duration, RR for all-cause mortality (post-trial phase) and time horizon. The results of the one-way sensitivity analysis are shown in *Table 25*.

TABLE 23 Summary of hospitalisation resource use and unit costs

Economic substudy sample	Clopidogrel ($n = 3332$)	Prasugrel ($n = 3373$)
Total hospitalisations (*n*)	1259	1228
Rate of rehospitalisation per month	0.0256	0.0245
Weighted average unit cost per hospitalisation episode (from trial)	£3070	£3081
Weighted average unit cost per hospitalisation (base case)	£3070	£3081

TABLE 24 Cost-effectiveness of prasugrel compared with clopidogrel evaluated by subgroup > 40 years. Percentages are event probabilities

Population	Whole ACS licensed population (excluding prior stroke/TIA)			ACS core (excluding prior stroke/TIA and patients weighing < 60 kg or aged ≥ 75 years)			UA/NSTEMI licensed population (excluding prior stroke/TIA)			STEMI licensed population (excluding prior stroke/TIA)			ACS diabetes, licensed population (excluding prior stroke/TIA)		
Treatment	**CLOP**	**PRA**	**Effect**	**CLOP**	**PRA**	**Effect**	**CLOP**	**PRA**	**Effect**	**CLOP**	**PRA**	**Effect**	**CLOP**	**PRA**	**Effect**
Event probabilities			***Ratio***			***Ratio***			***Ratio***			***Ratio***			***Ratio***
CV death	2.05%	1.76%	0.86	1.58%	1.36%	0.86	1.80%	1.66%	0.92	2.76%	2.05%	0.74	3.59%	2.73%	0.76
MI	8.49%	6.43%	0.76	8.15%	6.20%	0.76	8.60%	6.61%	0.77	8.17%	5.91%	0.72	10.64%	6.72%	0.63
Stroke	0.74%	0.69%	0.93	0.64%	0.58%	0.90	0.72%	0.54%	0.74	0.79%	1.12%	1.42	1.23%	1.01%	0.82
Total combined end point	11.28%	8.87%	0.79	10.37%	8.14%	0.79	11.13%	8.80%	0.79	11.71%	9.08%	0.78	15.46%	10.46%	0.68
Fatal bleed	0.00%	0.11%	NA	0.00%	0.05%	NA	0.00%	0.11%	NA	0.00%	0.12%	NA	0.00%	0.15%	NA
Major bleed	1.71%	2.19%	1.28	1.50%	1.95%	1.30	1.49%	2.07%	1.39	2.32%	2.52%	1.09	2.21%	2.35%	1.06
Minor bleed	1.93%	2.51%	1.30	1.49%	1.98%	1.33	1.69%	2.40%	1.42	2.61%	2.82%	1.08	2.70%	2.93%	1.08
Total bleed	3.64%	4.81%	1.32	2.99%	3.97%	1.33	3.18%	4.58%	1.44	4.93%	5.46%	1.11	4.91%	5.42%	1.11
Results			***Increment***			***Increment***			***Increment***			***Increment***			***Increment***
Life-years	13.14	13.21	0.07	14.14	14.20	0.07	13.16	13.21	0.05	13.09	13.20	0.11	12.35	12.52	0.17
QALYs	10.16	10.21	0.05	10.97	11.02	0.05	10.16	10.20	0.04	10.16	10.25	0.09	9.50	9.63	0.13
Costs	£5469	£6062	£593	£5867	£6463	£596	£5480	£6067	£587	£5437	£6046	£609	£5209	£5809	£600
Cost per life-year			£8847			£8,979			£11,661			£5,337			£3,550
Cost per QALY			£11,660			£11,796			£15,452			£6,987			£4,675

CLOP, clopidogrel; NA, not applicable; PRA, prasugrel.

TABLE 25 One-way sensitivity analyses for ACS core clinical cohort[a]

Model factor adjusted		Clopidogrel			Prasugrel			ICERs				
		LYs	QALYs	Costs (£)	LYs	QALYs	Costs (£)	Δ LYs	Δ QALYs	Δ Costs (£)	£/LY	£/QALY
Base case		14.14	10.97	5867	14.20	11.02	6463	0.07	0.05	596	8979	11,796
Discounting rates	0.00% pa	21.56	16.65	8917	21.68	16.74	9546	0.12	0.09	628	5147	6787
	6.00% pa	11.11	8.64	4622	11.16	8.68	5203	0.05	0.04	581	12,574	16,475
Haemorrhage disutility (120 days)	× 8	14.14	10.96	5864	14.20	11.01	6461	0.07	0.05	596	8979	11,851
MI/stroke disutility	× 0.5	14.14	10.97	5864	14.20	11.02	6461	0.07	0.05	596	8979	11,966
	× 1.5	14.14	10.96	5864	14.20	11.01	6461	0.07	0.05	596	8979	11,630
Mortality RR	× 0.5	14.27	11.06	5916	14.30	11.09	6501	0.04	0.03	584	15,775	20,619
	× 1.5	14.05	10.90	5827	14.13	10.96	6431	0.09	0.07	605	6919	9096
Clopidogrel preloading adjustment	70%	14.15	10.97	5867	14.20	11.02	6461	0.06	0.04	593	10,631	13,959
NHS reference costs (HRG)	× 0.5	14.14	10.97	2945	14.20	11.02	3535	0.07	0.05	590	8892	11,682
	× 0.8	14.14	10.97	4696	14.20	11.02	5290	0.07	0.05	594	8944	11,750
	× 1.2	14.14	10.97	7032	14.20	11.02	7631	0.07	0.05	599	9014	11,841
	× 1.5	14.14	10.97	8784	14.20	11.02	9386	0.07	0.05	602	9066	11,909

HRG, Healthcare Resource Group; LY, life-years; pa, per annum.
a The core clinical cohort is defined as ACS patients without prior TIA/stroke, aged <75 years and weighing ≥ 60 kg.
Numbers may not compute owing to rounding.

Critique of submitted economic model

The AG's critique of the manufacturer's submitted economic model is the same as the original critique presented by the ERG during the original appraisal of prasugrel (TA182).[21] The AG and the ERG are the same academic research group.

As outlined in section 8.2.4.1 of the MS, at the time of the original appraisal, the ERG suggested amendments to the manufacturer's economic model in the following six main areas:

- life table calculations, which need to allow for competing risks
- differences in discounting approaches
- treatment costs, which should reflect usage and pack wastage
- alternative utility values (i.e. those derived from the HODAR database)
- reduced incidence of non-fatal MIs such that the underlying rate of MIs is 50% that recorded in the TRITON-TIMI[36] trial
- amended long-term RRs of mortality by ignoring the initial impact of ACS prior to TRITON-TIMI-related events (i.e. ignoring the sources from Rosengren *et al.*[83]).

The AG agrees with the manufacturer that the first three points mentioned above lead to non-significant changes in the size of the ICER. The manufacturer carried out a scenario analysis to determine the effect of the remaining three amendments suggested by the ERG.

The impact of this scenario analysis on the results for the relevant subgroups is presented in *Table 26*.

The results of the manufacturer's scenario analysis show that, when comparing prasugrel with clopidogrel, all relevant ICERs remained within the £20,000 to £30,000 per QALY gained threshold.

However, the AG is of the opinion that the basic structure of the manufacturer's economic model still requires further refinement. The main focus of the AG's critique is the manufacturer's projection of long-term survival. The AG's specific concerns are outlined in detail in *Independent economic assessment: results* and *Independent economic assessment: discussion*.

In summary, the AG developed its own economic model for the following reasons:

- The long-term model phase in the manufacturer's submitted economic model was considered to be unsatisfactory and potentially not sufficiently reliable to generate a realistic representation of 39-years of follow-up.
- The manufacturer's decision model projects long-term (years 2–40) costs and outcomes solely in terms of mortality hazard rates fixed after 1 year, and takes no account of the effects of accumulating experience of CV events and disability.
- The AG considered it appropriate to develop an economic model using the most reliable clinical evidence available and, therefore, preferred to use 3-year clinical data from the CAPRIE[92] (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial instead of 15-month data from the TRITON-TIMI 38[36] trial.
- To fulfil the remit stated by NICE and to review fully the guidance for prasugrel issued in TA182,[21] the AG was required to compare four patient subgroups (STEMI without diabetes mellitus, STEMI with diabetes mellitus, NSTEMI without diabetes mellitus and NSTEMI with diabetes mellitus). The structure of the decision model submitted by the manufacturer does not readily facilitate modelling these four subgroups in terms of cost-effectiveness.

TABLE 26 Scenario analysis results altering utility values, RR for mortality and rate of MI

Population	UA/NSTEMI		STEMI		ACS–diabetes		ACS core	
Treatment	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel
Life-years	14.64	14.68	15.04	15.14	13.97	14.12	15.74	15.79
QALYs	9.74	9.76[a]	10.04	10.11	9.26	9.36	10.51	10.54
Costs (£)	6047	6644	6203	6825	5809	6430	6487	7092
Cost per life-year (£)		16,713		5834		3952		11,509
Cost per QALY (£)		25,504		8827		6002		17,439
Base case cost/QALY (£)		15,542		6987		4675		11,796

a The AG altered the QALY value to enable the ICER to equal £25,504, probably a transcription error by the manufacturer.

Independent economic assessment: methods

Background and modelling rationale

The manufacturer of prasugrel has chosen to resubmit the same decision model previously employed for the NICE single technology appraisal (STA) of prasugrel in 2009.[21] This model comprised two distinct phases:

- a short-term statistical model of the data from the TRITON-TIMI 38[36] clinical trial (up to 15 months follow-up)
- a long-term model projecting survival and hospitalisation of patients alive at the end of the first phase up to a maximum of 40 years.

In the ERG's report prepared as part of the STA process, particular concern was expressed about the structure of this model. The ERG concluded that the initial phase of the model generated reliable outcome estimates:

> *Comparison of the mortality rate (all causes) obtained by Kaplan–Meier analysis of TRITON-TIMI 38 data (supplied by the manufacturer) with corresponding rates generated by the model at 30 days and 12 months indicate a good correspondence for treatment with clopidogrel and with prasugrel for all specified populations.*
>
> *Greenhalgh* et al. *2009, section 5.5.2*[93]

However, the long-term model phase was considered by the ERG to be less satisfactory and potentially not sufficiently reliable to generate a realistic representation of a further 39 years of follow-up:

> *In the long-term component of the submitted model there is an assumption that differences established between the prasugrel and clopidogrel arms of the TRITON-TIMI 38 trial will be preserved indefinitely at the level observed at the end of the trial. However, there is no reason to believe that further serious nonfatal events will not continue to occur to patients in both cohorts, and if events occurring during the trial are presumed to influence later survival, then it is also likely that any such events in subsequent periods will also have important effects. Since active treatment with clopidogrel or prasugrel will have ceased, it can be expected that event rates will be similar in both arms. As a result of this process it is likely that over time the disease history of patients will converge, and therefore any initial advantage for either treatment will be progressively attenuated. This effect would have become evident in the model results if the long-term model had been structured to reflect changes in health states over time.*
>
> *Greenhalgh* et al. *2009, section 5.5.3*[93]

As these serious concerns have not been addressed by the manufacturer in the model submitted for this reappraisal of prasugrel, the AG has developed a new decision model. The AG's model accepts the manufacturer's statistical model for the initial phase (up to 12 months), but replaces the long-term projection with a more detailed structure that provides an improved representation of subsequent CV events, accumulating patient histories, alteration in health states and associated care costs, as well as patient HRQoL.

Patient populations

The AG has structured its decision model to accommodate four mutually exclusive subgroups of the core clinical cohort population (i.e. all ACS patients excluding those with a history of TIA or stroke, those with body weight of < 60 kg or those aged > 75 years):

- ACS patients treated with PCI for STEMI and with diagnosed diabetes
- ACS patients treated with PCI for STEMI and without diagnosed diabetes
- ACS patients treated with PCI for UA or NSTEMI and with diagnosed diabetes
- ACS patients treated with PCI for UA or NSTEMI and without diagnosed diabetes.

These were the groups considered by the ERG to be important in the development of the final 2009 guidance related to prasugrel (TA182[21]) and they therefore form an appropriate basis for this review of the existing guidance.

Treatment options

No suitable clinical evidence has been identified that can provide the basis for a reliable comparison between prasugrel and ticagrelor. The AG model, therefore, has been developed as a simple comparison between dual antiplatelet therapy for 12 months from index PCI with either clopidogrel in combination with low-dose aspirin or prasugrel in combination with low-dose aspirin.

Model design and structure

The AG for this review also acted as AG for the reappraisal of clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. That reappraisal was an update of NICE guidance TA90[94] and resulted in the publication of TA210,[95] which was issued in December 2010. In TA210,[95] NICE made recommendations concerning the use of clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. As part of the TA210[95] guidance development process, the AG developed a detailed decision model to estimate the long-term health care and outcomes expected for patients receiving different strategies of long-term preventative treatment. The model took the form of an individual patient simulation. It was calibrated mainly using data provided by the manufacturer of clopidogrel from the CAPRIE[92] clinical trial, supplemented with data provided by the manufacturer of dipyridamole from the PROFESS[96] clinical trial and some additional published trial results. The additional data included follow-up results for 3 years from the start of preventative therapy. Supplementary details are provided in *Appendix 6*.

The AG has concluded that the MI subpopulation model used in the development of TA210[95] (the TA210[95] model), which was based largely on CAPRIE[92] trial data, addresses very similar issues to those that are of concern to this review of TA182.[21] The AG's clinical advisor has confirmed that CAPRIE[92] data are an appropriate trial source for extrapolating long-term vascular events and that no better source has become available since 2010.

However, there is a significant practical drawback to using the individual patient simulation approach that was employed in the TA210[95] model, namely the extended run times involved in generating model results, especially when carrying out probabilistic sensitivity analyses. The AG has therefore re-engineered the TA210[95] model, and the current AG model for prasugrel employs a long-term Markov chain, which operates for up to 39 years of follow-up beyond the first 12 months of treatment with clopidogrel or prasugrel. This re-engineering has necessitated some compromises to the fully flexible logic of the TA210[95] model, which allowed each patient to experience any number of occlusive vascular events at any time in any year. However, the frequency of these events is low, and restricting the Markov model to 12-month cycles and allowing only one event per cycle is unlikely to have a noticeable effect on the

evaluation of treatments. In theory, the number of events per patient may be marginally understated, along with the related treatment costs and disutilities; however, as these apply in the same way to both arms of the evaluation, the impact on the assessment of comparative cost-effectiveness is believed to be negligible.

The annual transition matrix for the AG model is shown in *Table 27.* The matrix shows how the health state of a patient is altered depending on the type of vascular event suffered during the year and the most severe previous event experienced, including whether or not the patient had suffered a severely disabling stroke (modified Rankin Scale score 3–5).

Patients enter the long-term model with the average number of vascular events experienced in the first 12 months following the index PCI event, estimated by the manufacturer's short-term statistical model, apportioned between the first four states [None, MI(1)ND, Stroke(1)ND and Stroke(1)D] (see *Table 27*). The model then traces the long-term accumulating event history separately for males and females within each of the four subpopulations, using sex-specific parameter values (*Table 28*).

Assessment of uncertainty

A univariate sensitivity analysis has been performed on all model variables subject to uncertainty, and results are presented in the form of 'torpedo' diagrams ranking the 20 variables subject to greatest uncertainty in terms of influence on the deterministic estimated ICER per QALY gained for prasugrel compared with clopidogrel, as measured after 40 years' follow-up.

A probabilistic sensitivity analysis has been carried out, using 1000 simulations and employing a standardised set of random variables selected to ensure full coverage of the uncertainty domain (sometimes referred to as orthogonal sampling), and incorporating correlated random variables as necessary.

TABLE 27 Annual transition matrix between health states owing to events occurring during the year[a]

	Health state at beginning of year									
Worst event	None	MI	Stroke	Stroke	MI	Stroke	Stroke	MI	Stroke	Stroke
Prior events	0	1	1	1	2	2	2	3 +	3 +	3 +
Disabled	ND	ND	ND	D	ND	ND	D	ND	ND	D
Event in year										
No event	None (0) ND	MI (1) ND	Stroke (1) ND	Stroke (1) D	MI (2) ND	Stroke (2) ND	Stroke (2) D	MI (3 +) ND	Stroke (3 +) ND	Stroke (3 +) D
Fatal MI	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead
Non-fatal MI	MI (1) ND	MI (2) ND	Stroke (2) ND	Stroke (2) D	MI (2) ND	Stroke (3 +) ND	Stroke (3+) D	MI (3 +) ND	Stroke (3 +) ND	Stroke (3 +) D
Fatal HS	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead
Non-fatal HS not disabling	Stroke (1) ND	Stroke (2) ND	Stroke (2) ND	Stroke (2) D	Stroke (3+) ND	Stroke (3 +) ND	Stroke (3 +) D	Stroke (3 +) ND	Stroke (3 +) ND	Stroke (3 +) D
Non-fatal HS disabling	Stroke (1) D	Stroke (2) D	Stroke (2) D	Stroke (2) D	Stroke (3 +) D	Stroke (3 +) D	Stroke (3 +) D	Stroke (3 +) D	Stroke (3 +) D	Stroke (3 +) D
Fatal IS/TIA	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead
Non-fatal IS/TIA not disabling	Stroke (1) ND	Stroke (2) ND	Stroke (2) ND	Stroke (2) D	Stroke (3 +) ND	Stroke (3 +) ND	Stroke (3 +) D	Stroke (3 +) ND	Stroke (3 +) ND	Stroke (3 +) D
Non-fatal IS/TIA disabling	Stroke (1) D	Stroke (2) D	Stroke (2) D	Stroke (2) D	Stroke (3 +) D	Stroke (3 +) D	Stroke (3+) D	Stroke (3 +) D	Stroke (3 +) D	Stroke (3 +) D
OVD	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead
NVD	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead

D, disabled (Rankin 3–5); HS, haemorrhagic stroke; IS, ischaemic stroke/transient ischaemic attack; ND, not disabled (Rankin 0–2); NVD, non-vascular death; OVD, other vascular death.
a Columns show the initial health state, rows show in-year events and the table body shows the end of year health state.

TABLE 28 Patients estimated in each health state from manufacturer's short-term statistical model, used as starting values for Liverpool Reviews and Implementation Group long-term Markov model

				Clopidogrel				Prasugrel			
Subgroup	Sex	Number of patients	Mean age (years) (at 1 year)	No event	Non-fatal MI only	Non-fatal stroke ± MI	Dead	No event	Non-fatal MI only	Non-fatal stroke ± MI	Dead
STEMI diabetes	Females	126	61.9	106.4	12.9	1.4	5.3	113.1	7.4	1.7	3.8
	Males	387	59.0	327.6	42.7	2.7	14.0	348.2	23.9	4.8	10.1
STEMI no diabetes	Females	358	60.1	323.5	23.8	2.6	8.2	329.3	19.0	2.7	7.1
	Males	1876	56.5	1692.7	141.9	6.3	35.1	1724.0	109.7	12.0	30.4
UA/NSTEMI diabetes	Females	559	62.5	484.8	53.3	5.9	15.2	507.1	34.6	3.8	13.4
	Males	1229	60.3	1067.2	118.7	13.1	30.1	1117.2	77.2	8.4	26.3
UA/NSTEMI no diabetes	Females	1138	61.1	1028.6	86.2	5.8	17.4	1044.5	71.0	4.6	18.0
	Males	4641	58.1	4204.4	350.8	23.4	62.4	4269.4	288.9	18.6	64.1

Parameter sources and values

All the parameter values used in the Markov model for event incidence risk (*Table 29*), event fatality rates (*Table 30*) and RRs remain unchanged from those previously described in the AG report for the development of NICE guidance TA 210,[95] with the exception of the RR applying to patients with/without diabetes (*Table 31*).

Cost of medication

The cost of dual antiplatelet therapy in the first year, and the cost of continuing low-dose aspirin thereafter, is detailed in *Table 32*. Both clopidogrel and prasugrel usage has been adjusted to reflect actual usage in the clinical trial. The cost of a loading dose of 300-mg clopidogrel or 60-mg prasugrel is included.

TABLE 29 Event incident risks

Parameter	Sex	Mean[a]	LCL	UCL
Risk of IS in year 1	Male and female	0.609% and 1.086%	0.406% and 0.560%	0.853% and 1.780%
Risk of HS in year 1	Male and female	0.096%	0.033%	0.191%
Proportion of stroke survivors disabled (modified Rankin Scale 3+)	Male and female	35%	33%	37%
IS risk multiplier for stroke survivors not disabled (modified Rankin Scale 0–2)	Male and female	0.945	0.851	1.039
IS risk multiplier for stroke survivors disabled (modified Rankin Scale 3+)	Male and female	1.201	1.031	1.370
Annual risk of first MI in event-free ACS population treated with aspirin	Male and female	2.052% and 2.393%	2.010% and 2.255%	2.095% and 2.530%
Annual risk of first IS in event-free ACS population treated with aspirin	Male and female	0.300% and 0.774%	0.251% and 0.694%	0.349% and 0.854%
Annual risk of first HS in event-free ACS population treated with aspirin	Male and female	0.096%	0.033%	0.191%
Annual risk of OVD in event-free ACS population treated with aspirin	Male and female	0.646% and 0.863%	0.609% and 0.594%	0.683% and 1.132%
Short-term extra risk of MI after first MI event in ASC population treated with aspirin	Male and female	3.287%	3.272%	3.303%
Long-term annual risk of MI after first MI event in ACS population treated with aspirin	Male and female	5.787%	5.766%	5.809%
Short-term extra risk of IS after first MI event in ACS population treated with aspirin	Male and female	1.608%	1.598%	1.618%
Long-term annual risk of IS after first MI event in ACS population treated with aspirin	Male and female	1.837%	1.827%	1.847%
Long-term annual risk of HS after first MI event in ACS population treated with aspirin	Male and female	0.190%	0.189%	0.191%

HS, haemorrhagic stroke; IS, ischaemic stroke; LCL, lower 95% confidence limit, OVD, occlusive vascular disease; UCL, upper 95% confidence limit.

a When one percentage only is given, the relevant data source did not indicate a significant difference by sex for some risks.

TABLE 30 Event fatality rates

Parameter	Sex	Mean	LCL	UCL
MI fatality odds model: constant	Male	0.00986	0.00553	0.01755
MI fatality odds model: age coefficient	Male	0.0455	0.0368	0.0541
MI fatality odds model: constant	Female	0.00801	0.00125	0.05124
MI fatality odds model: age coefficient	Female	0.0538	–0.0192	0.1269
MI subgroup odds multiplier for MI fatality	Male	0.574	0.361	0.913
	Female	0.584	0.269	1.267
IS fatality odds model: constant	Male	0.00212	0.00040	0.011117
IS fatality odds model: age coefficient	Female	0.0520	0.0269	0.0770
MI subgroup odds multiplier for IS fatality	Male and female	1.673	0.772	3.626
HS fatality	Male	32.6%	20.6%	45.9%
	Female	59.9%	37.7%	80.1%
Event (MI/stroke) order odds multiplier				
First event	Male and female	0.791	0.693	0.904
Second event	Male and female	1.931	1.593	2.342
Third event	Male and female	4.398	2.936	6.587

HS, haemorrhagic stroke; IS, ischaemic stroke; LCL, lower 95% confidence limit; UCL, upper 95% confidence limit.

TABLE 31 Relative risk of key events for patients with diabetes compared with no diabetes

Event	RR	Standard error	LCL	UCL	Source
MI	1.339	0.082	1.141	1.571	Malmberg (2000);[97] see table 3
Stroke	1.446	0.144	1.091	1.921	Malmberg (2000);[97] see table 3
OVD	2.121	0.262	1.269	3.544	Kleinman (1988);[98] see table 3, weighted average of males and females
NVD	1.242	0.233	0.787	1.960	Kleinman (1988);[98] see table 3, weighted average of males and females

LCL, lower 95% confidence limit; NVD, non-vascular death; OVD, occlusive vascular event; UCL, upper 95% confidence limit.

TABLE 32 Calculation of antiplatelet therapy costs

Detail	Clopidogrel	Prasugrel	Low-dose aspirin
Pack price (28 tablets)	£1.71 (Drug Tariff November 2013)[28]	£47.56 (BNF October 2013)[27]	£0.82 (Drug Tariff November 2013)[28]
Cost of loading dose	£0.24	£10.19	–
Cost of 12 months' supply[a]	£18.43[a]	£511.67[a]	£10.70
Total dual antiplatelet therapy cost (year 1)	£29.37	£532.56	–
Annual maintenance cost	–	–	£10.70

a Adjusted for treatment duration.

Resource use estimation

Health-care costs and health-related utility values are applied for both time spent in each health state and as discrete single-event costs and disutilities.

Unit cost estimation

Unit costs used in the AG's report for TA182[21] have been uplifted using the Hospital and Community Health Services (HCHS) inflation index[99] to 2012 prices. The revised costs are shown in *Table 33*.

Health-related utility estimation

Utility parameter values are shown in *Table 34*.

Continuing utility on health states

The continuing health state EQ-5D utility value for patients who were event-free or suffered a non-fatal MI (but no strokes) and who were alive 12 months after the index PCI was derived from the economic substudy of the PLATO[33] clinical trial and based on a weighted average of patients with no event or non-fatal MI after 12 months of follow-up.[100]

Four separate utility parameters for patients suffering at least one stroke/TIA were sourced from a study of EQ-5D observations as part of the Oxford Vascular Study (OXVASC).[101] These reflect sex differences and mild compared with severe strokes (grades 0–2 vs. 3–5 in the modified Rankin Scale).

Age-related annual utility decrement and baseline adjustment

An annual loss of utility was estimated from the UK population EQ-5D norms by fitting a linear regression trendline to all participants aged > 35 years.[91] The decrement was used to adjust the initial health state utilities of each subgroup for the differences in mean age between the TRITON-TIMI 38[42] cohort and the OXVASC[101] patient sample. It was also applied annually to the results of the AG's Markov model to reflect the average decline of utility score with advancing age.

TABLE 33 Unit costs for events and treatment in model health states

Cost component	Mean	Standard error	LCL	UCL
Event				
Fatal MI	£2373.68	£121.11	£2136.31	£2611.05
Non-fatal MI	£6165.21	£314.55	£5548.69	£6781.73
Fatal stroke	£9381.43	£478.64	£8443.29	£10,319.57
Non-fatal non-disabling stroke	£6858.64	£349.93	£6172.77	£7544.50
Non-fatal disabling stroke	£14,602.70	£754.04	£13,142.43	£16,062.97
OV death	£2407.50	£122.83	£2166.75	£2648.25
NV death	£2407.50	£122.83	£2166.75	£2648.25
Annual cost in health state				
Event free/MI only	£618.03	£31.53	£556.23	£679.84
Non-disabling stroke	£1804.06	£92.04	£1623.66	£1984.47
Disabling stroke	£5537.72	£282.54	£4983.95	£6091.50

LCL, lower 95% confidence limit; NV, non-vascular; OV, other vascular; UCL, upper 95% confidence limit.

TABLE 34 Utility values assigned to model events, health states and advancing age

Utility component	Mean	Standard error	LCL	UCL
Event				
Fatal MI	–0.100	–	0.000	–0.200
Non-fatal MI	–0.037	0.056	–0.147	0.073
Fatal stroke	–0.100	–	0.000	–0.200
Non-fatal non-disabling stroke	0.000	–	0.000	–0.200
Non-fatal disabling stroke	0.000	–	0.000	–0.200
OV death	–0.100	–	0.000	–0.200
NV death	–0.100	–	0.000	–0.200
Utility in health state				
Event free/MI only	0.874	0.003	0.869	0.880
Non-disabling stroke (female)	0.769	0.009	0.751	0.786
Disabling stroke (female)	0.418	0.013	0.392	0.443
Non-disabling stroke (male)	0.838	0.009	0.821	0.855
Disabling stroke (male)	0.487	0.013	0.463	0.512
Annual age decrement				
All patients (male and female)	–0.0044	0.0004	–0.0052	–0.0035

LCL, lower 95% confidence limit; NV, non-vascular; OV, other vascular; UCL, upper 95% confidence limit.

Initial event disutility

Seven model events (four fatal and three non-fatal) can be expected to result in an additional utility decrement in the first year of follow-up during early recovery. For only one of these events (non-fatal MI) has it been possible to source a specific value, using an analysis of UK Prospective Diabetes Study trial results, which compares utility values for events occurring within 12 months with those occurring earlier.[102] Sources for non-fatal stroke parameters (mild and severe) gave contradictory figures, suggesting that there is no clear additional early disutility effect beyond the long-term continuing effect of a stroke. These parameters were therefore set to zero and made subject to a univariate sensitivity analysis. No sources could be found for disutility associated with the four types of fatal events (fatal MI, fatal stroke, other vascular death and non-vascular death). A notional value of –0.1 was assigned to each parameter, and a sensitivity analysis was conducted.

Discounting costs and outcomes

Both costs and outcomes were discounted annually at 3.5%. Univariate sensitivity analyses were carried out using discount rates of 0% and 6% for both costs and outcomes.

Time horizon

The model generates results annually at the end of each year from trial randomisation. However, deterministic results are reported at 1, 5, 10, 20 and 40 years, and probabilistic results at 5 and 40 years.

Key modelling assumptions

Long-term accumulating risks

The main objective of the AG's model of prasugrel is to assess whether or not modelling the accumulation of risk-bearing disease events has the effect of causing the long-term experience of patients in both the comparator arms to converge. In this context, the AG considered that this objective could be mainly served through the explicit incorporation of strokes, and their associated elevated event risks and larger ongoing

care costs, into the model. The AG also considered that some more marginal issues could be omitted so as to achieve modelling efficiency by generating rapid feedback of results to the user.

Main source of parameter values

The model employed in this appraisal is a simplified version of the individual patient simulation model developed for the NICE appraisal of clopidogrel and modified release dipyridamole which resulted in NICE guidance TA210.[95] The event risk and fatality risk parameters for that model have been preserved in the new formulation and were sourced primarily from analyses of results from the CAPRIE[92] trial, which were kindly made available to the AG by the manufacturer of clopidogrel.

The AG sought clinical advice as to the suitability of using the CAPRIE[92] data. This advice indicated that the CAPRIE[92] trial results were the most appropriate basis for estimating long-term risk probabilities in the follow-up of ACS patients treated with PCI in the UK.

Annual cycles

The AG's model involves annual cycles for 39 years beyond the index PCI event. This cycle length was adopted for convenience, recognising that it risks some inaccuracy in the number of events occurring each year. In the TA210[95] model, individual patients may suffer multiple events in any year, and each contributes to modifying the future risk profile of the patient. By contrast, the AG's model assumes that such events occur to separate individuals and the risk profile is only updated annually. The extent of any inaccuracy introduced as a result of this change is unclear, and could, in principle, either increase or decrease overall event rates. However, as the same risks apply to both prasugrel and clopidogrel patients, it is unlikely that incremental costs and outcomes will be affected.

Time horizon

The maximum time horizon (40 years) of the AG's model could be considered to be excessively long, as the duration of the primary trial (TRITON-TIMI 38[36]) was no more than 15 months, and the CAPRIE trial,[92] which was used for populating the risk parameters, had only 3 years of follow-up data. In particular, the stability of the risk equations used for advancing age might be called into question. With this in mind, model results are reported at various time points from 5 years, which represents a more cautious extrapolation.

Follow-up secondary prophylaxis is limited to low-dose aspirin in the model, partly for convenience but also to avoid the possibility of obscuring the primary comparison between prasugrel and clopidogrel use for the primary PCI. Similarly, no attempt has been made to incorporate various other aspects of guidance relating to post-stroke and post-MI care (including surgery and other medication options).

Secondary prophylaxis

No attempt has been made to incorporate the adverse effects of aspirin therapy, or the possibility of non-adherence to continuing aspirin treatment. In addition, the risk of bleeding events associated with long-term prophylaxis was not considered. For all these issues, patients in both arms will be similarly affected throughout follow-up, so that the net effect on incremental differences should be marginal.

Stroke-related disability

In line with the TA210[95] model, the representation of stroke-related disability has been limited to two categories based on the modified Rankin Scale. The available data to calibrate the model with greater precision are not available and this approximation works well with a natural distinction between mild and severe dependency.

Validation and quality assurance

The AG's long-term model has been cross-matched against the original individual patient model to ensure all formulae have been correctly implemented. In addition, check totals have been incorporated into each annual application to ensure that any discrepancies in patient totals, health state totals and event totals are readily identifiable. The starting values for the long-term model have been matched to the manufacturer's model at 12 months for accuracy.

Independent economic assessment: results

Results from the AG's model are presented separately for each of the four patient subgroups that were previously considered by the AC when formulating NICE guidance TA182.[21]

For each subgroup, detailed deterministic cost-effectiveness estimates are presented across a range of time periods, namely 1, 5, 10, 20 and 40 years after the index PCI. A univariate sensitivity analysis is presented for the 40 years' follow-up scenario. Probabilistic cost-effectiveness results are presented for 5 and 40 years' follow-up, with a scatterplot of random replications and a cost-effectiveness acceptability curve (CEAC) for the 40 years' follow-up scenario.

ST segment elevation myocardial infarction: diabetes subgroup

Deterministic results are detailed in *Table 35* (life-years), *Table 36* (QALYs), *Table 37* (costs) and *Table 38* (ICERs). The ICER at the end of the first year is high, owing to the inclusion of the full additional cost of treatment with prasugrel, while only modest health gains have accrued from the reduced incidence of MIs. Over time the estimated ICER decreases steadily, suggesting that incremental benefit continues to accrue over subsequent decades while incremental cost increases at a slower rate. The ICER for prasugrel compared with clopidogrel falls below £30,000 per QALY gained after 5 years.

TABLE 35 Mean deterministic estimated life-years for STEMI patients with diabetes

Follow-up	Mean time in health state				Life-years	
Treatment	Event free	MI(s) only	Mild stroke(s) +/– MI(s)	Severe stroke(s) +/– MI(s)	Total	Total discounted
1 year						
Clopidogrel	0.923	0.054	0.003	0.001	0.981	0.981
Prasugrel	0.950	0.031	0.004	0.002	0.986	0.986
Difference	+0.027	–0.024	+0.001	+0.001	+0.005	+0.005
5 years						
Clopidogrel	3.953	0.557	0.066	0.037	4.612	4.320
Prasugrel	4.171	0.397	0.073	0.040	4.681	4.383
Difference	+0.218	–0.160	+0.007	+0.004	+0.069	+0.063
10 years						
Clopidogrel	6.865	1.250	0.234	0.134	8.483	7.375
Prasugrel	7.268	1.010	0.238	0.137	8.653	7.517
Difference	+0.403	–0.241	+0.005	+0.002	+0.170	+0.142
20 years						
Clopidogrel	10.429	2.339	0.640	0.373	13.780	10.664
Prasugrel	11.059	2.067	0.643	0.372	14.141	10.924
Difference	+0.630	–0.272	+0.003	–0.001	+0.361	+0.260
40 years						
Clopidogrel	12.151	2.894	0.925	0.529	16.499	11.823
Prasugrel	12.890	2.637	0.936	0.530	16.994	12.140
Difference	+0.739	–0.257	+0.012	+0.001	+0.495	+0.316

TABLE 36 Mean deterministic estimated QALYs for STEMI patients with diabetes

Follow-up	Mean QALYs in health state				Event disutility (QALYs)			QALYs	
Treatment	Event free	MI(s) only	Mild stroke +/– MI(s)	Severe stroke +/– MI(s)	MI	Stroke	Death	Total	Total discounted
1 year									
Clopidogrel	0.837	0.049	0.002	0.001	–0.005	0.000	–0.003	0.882	0.882
Prasugrel	0.861	0.028	0.004	0.001	–0.003	0.000	–0.002	0.889	0.889
Difference	+0.024	–0.021	+0.001	0.000	+0.002	0.000	+0.001	+0.007	+0.007
5 years									
Clopidogrel	3.554	0.500	0.056	0.019	–0.011	–0.001	–0.011	4.104	3.846
Prasugrel	3.750	0.356	0.062	0.021	–0.009	–0.001	–0.011	4.168	3.904
Difference	+0.196	–0.144	+0.006	+0.002	+0.003	0.000	+0.001	+0.064	+0.059
10 years									
Clopidogrel	6.108	1.108	0.197	0.066	–0.020	–0.003	–0.022	7.434	6.475
Prasugrel	6.467	0.893	0.201	0.067	–0.017	–0.002	–0.022	7.587	6.603
Difference	+0.358	–0.215	+0.004	+0.001	+0.003	0.000	0.000	+0.153	+0.129
20 years									
Clopidogrel	9.126	2.029	0.525	0.175	–0.036	–0.006	–0.043	11.768	9.171
Prasugrel	9.676	1.787	0.528	0.175	–0.033	–0.006	–0.044	12.083	9.400
Difference	+0.550	–0.241	+0.003	+0.000	+0.003	0.000	0.000	+0.314	+0.228
40 years									
Clopidogrel	10.499	2.473	0.742	0.240	–0.046	–0.009	–0.070	13.828	10.054
Prasugrel	11.136	2.243	0.751	0.241	–0.044	–0.008	–0.072	14.247	10.326
Difference	+0.637	–0.229	+0.009	+0.001	+0.003	0.000	–0.002	+0.419	+0.272

TABLE 37 Mean deterministic estimated costs for STEMI patients with diabetes

Follow-up		Mean costs in health state				Event costs			Cost	
Treatment	Drug costs	Event free	MI(s) only	Mild stroke +/– MI(s)	Severe stroke +/– MI(s)	MI	Stroke	Death	Total	Total discounted
1 year										
Clopidogrel	29	570	33	5	8	683	68	69	1465	1465
Prasugrel	533	587	19	7	12	386	101	51	1695	1695
Difference	+503	+16	–15	+3	+4	–297	+33	–18	+230	+230
5 years										
Clopidogrel	68	2443	344	119	204	1529	838	272	5817	5454
Prasugrel	572	2578	245	131	224	1169	915	257	6090	5723
Difference	+504	+135	–99	+13	+20	–361	+77	–16	+273	+269
10 years										
Clopidogrel	110	4243	773	422	744	2543	2589	528	11951	10277
Prasugrel	615	4492	624	430	756	2149	2646	519	12231	10552
Difference	+505	+249	–149	+9	+12	–394	+56	–9	–280	+275
20 years										
Clopidogrel	166	6446	1445	1154	2063	4040	6523	1041	22878	17013
Prasugrel	673	6835	1277	1160	2060	3651	6580	1050	23287	17363
Difference	+507	+389	–168	+6	–3	–390	+58	+9	+409	+351
40 years										
Clopidogrel	195	7510	1789	1668	2930	4801	9129	1681	29702	19904
Prasugrel	704	7966	1630	1689	2938	4437	9259	1723	30345	20351
Difference	+508	+457	–159	+21	+8	–364	+130	+42	+643	+447

TABLE 38 Mean deterministic ICER for STEMI patients with diabetes

	Total cost		Total QALYs		Incremental		
Follow-up	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	ICER (£ per QALY)
1 year	£1465	£1695	0.882	0.889	+£230	+0.007	£31,915
5 years	£5454	£5723	3.846	3.904	+£269	+0.059	£4603
10 years	£10,277	£10,552	6.475	6.603	+£275	+0.129	£2139
20 years	£17,013	£17,363	9.171	9.400	+£350	+0.228	£1537
40 years	£19,904	£20,351	10.054	10.326	+£447	+0.272	£1640

Figure 4 displays the results of univariate sensitivity analysis, indicating that uncertainty from individual model parameters has a modest influence on the magnitude of the ICER in this subgroup: the discount rates for costs and outcomes cause the largest changes, but the ICER remains within the range £1000 to £2500 per QALY gained.

Probabilistic analysis at the 40-year follow-up horizon for this subgroup yields a higher estimated ICER (£1732 per QALY gained) derived from very small incremental cost and QALY estimates (+£515 and +0.297, respectively). The scatterplot (*Figure 5*) and CEAC for this subgroup (*Figure 6*) indicate the relative cost-effectiveness of prasugrel despite the long-term erosion of incremental differences over time.

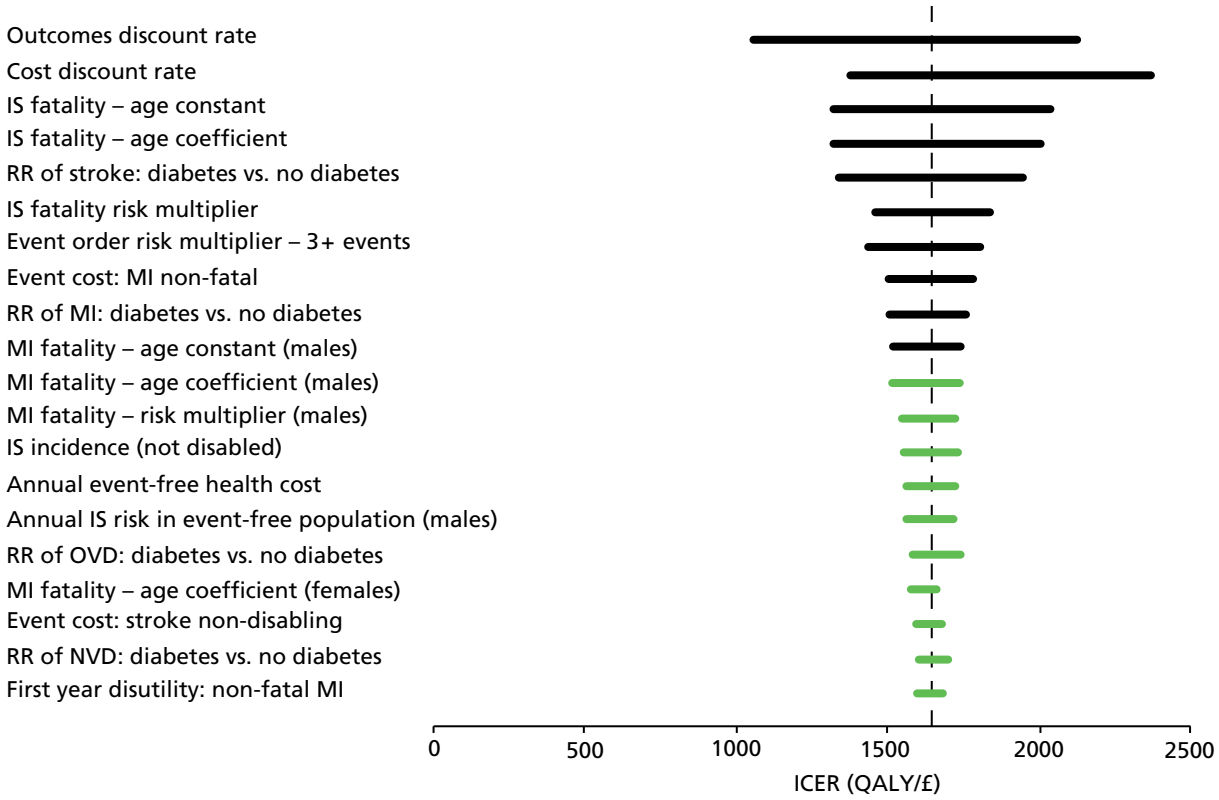

FIGURE 4 Univariate sensitivity analysis: 20 most important parameters in determining the ICER for STEMI patients with diabetes.

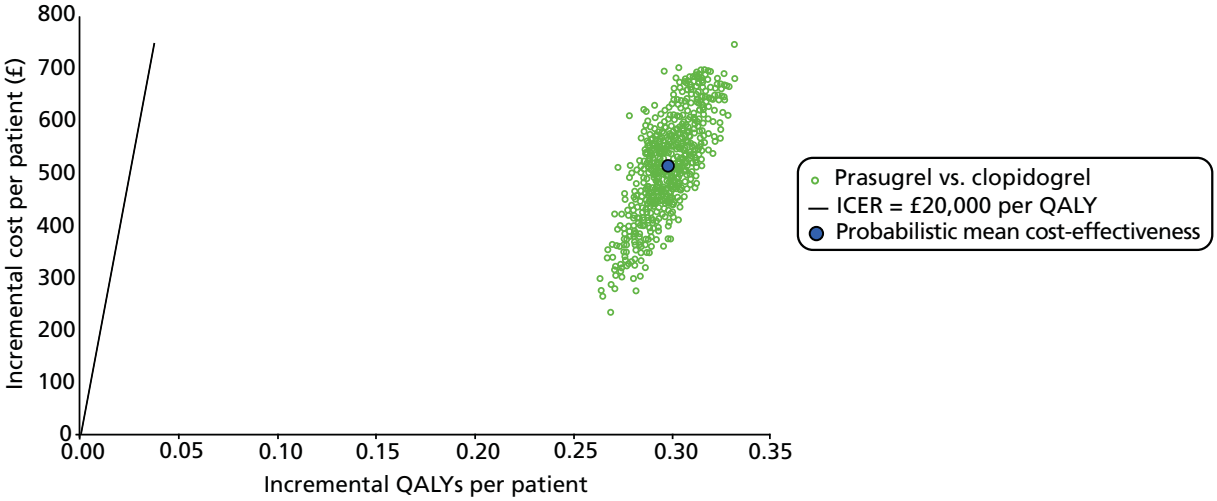

FIGURE 5 Probabilistic sensitivity analysis scatterplot of prasugrel compared with clopidogrel for STEMI patients with diabetes.

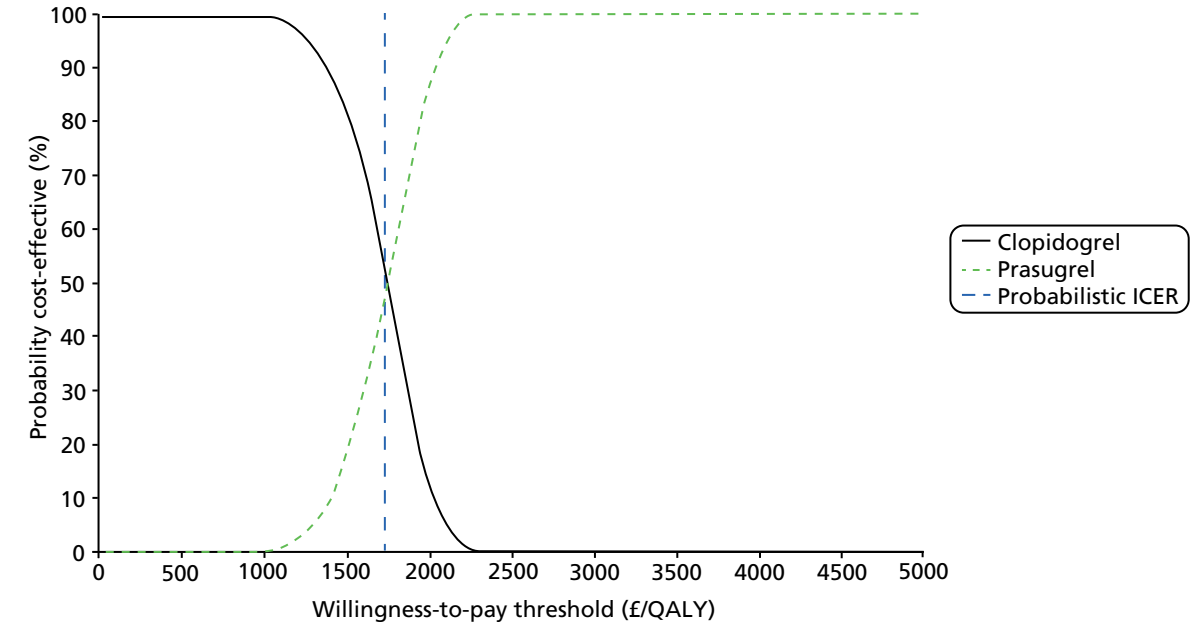

FIGURE 6 Cost-effectiveness acceptability curve of prasugrel compared with clopidogrel for STEMI patients with diabetes.

ST segment elevation myocardial infarction: no diabetes subgroup

Deterministic results are detailed in *Table 39* (life-years), *Table 40* (QALYs), *Table 41* (costs) and *Table 42* (ICERs). The ICER at the end of the first year is high, owing to the inclusion of the full additional cost of treatment with prasugrel, whereas only modest health gains have accrued from the reduced incidence of MIs. Over time the estimated ICER decreases steadily, suggesting that incremental benefit continues to accrue over subsequent decades while incremental cost increases at a slower rate. The ICER for prasugrel compared with clopidogrel falls below £30,000 per QALY gained at 10 years.

Figure 7 displays the results of univariate sensitivity analyses, which indicate that uncertainty from the discounting rate for outcomes has the largest impact on the estimated ICER (ranging between £4000 and £9000 per QALY gained). Other individual model parameters have only a modest influence on the magnitude of the ICER in this subgroup.

TABLE 39 Mean deterministic estimated life-years for STEMI patients without diabetes

Follow-up	Mean time in health state				Life-years	
Treatment	Event free	MI(s) only	Mild stroke(s) +/– MI(s)	Severe stroke(s) +/– MI(s)	Total	Total discounted
1 year						
Clopidogrel	0.951	0.037	0.001	0.001	0.990	0.990
Prasugrel	0.960	0.029	0.002	0.001	0.992	0.992
Difference	+0.008	–0.008	+0.001	0.000	+0.001	+0.001
5 years						
Clopidogrel	4.201	0.439	0.050	0.028	4.717	4.417
Prasugrel	4.269	0.382	0.055	0.031	4.736	4.434
Difference	+0.068	–0.057	+0.005	+0.003	+0.019	+0.017
10 years						
Clopidogrel	7.364	1.095	0.200	0.115	8.775	7.617
Prasugrel	7.491	1.008	0.205	0.118	8.823	7.657
Difference	+0.127	–0.087	+0.005	+0.003	+0.048	+0.040
20 years						
Clopidogrel	11.363	2.272	0.612	0.360	14.607	11.230
Prasugrel	11.564	2.171	0.617	0.363	14.714	11.307
Difference	+0.201	–0.101	+0.005	+0.002	+0.107	+0.076
40 years						
Clopidogrel	13.585	3.012	0.971	0.565	18.133	12.711
Prasugrel	13.827	2.916	0.979	0.568	18.291	12.808
Difference	+0.242	–0.096	+0.008	+0.003	+0.158	+0.097

TABLE 40 Mean deterministic estimated QALYs for STEMI patients without diabetes

Follow-up	Mean QALYs in health state				Event disutility (QALYs)			QALYs	
Treatment	Event free	MI(s) only	Mild stroke +/– MI(s)	Severe stroke +/– MI(s)	MI	Stroke	Death	Total	Total discounted
1 year									
Clopidogrel	0.874	0.034	0.001	0.000	–0.003	0.000	–0.002	0.905	0.905
Prasugrel	0.882	0.026	0.002	0.001	–0.002	0.000	–0.001	0.907	0.907
Difference	+0.008	–0.008	+0.001	+0.000	+0.001	0.000	–0.000	+0.002	+0.002
5 years									
Clopidogrel	3.825	0.398	0.044	0.015	–0.009	–0.001	–0.009	4.262	3.992
Prasugrel	3.887	0.347	0.048	0.016	–0.008	–0.001	–0.009	4.279	4.008
Difference	+0.062	–0.052	+0.004	+0.001	+0.001	0.000	0.000	+0.017	+0.016
10 years									
Clopidogrel	6.636	0.982	0.172	0.059	–0.018	–0.002	–0.019	7.809	6.792
Prasugrel	6.751	0.903	0.177	0.060	–0.017	–0.002	–0.019	7.852	6.828
Difference	+0.114	–0.079	+0.005	+0.002	+0.001	0.000	0.000	+0.043	+0.036
20 years									
Clopidogrel	10.067	1.990	0.512	0.175	–0.034	–0.005	–0.040	12.664	9.805
Prasugrel	10.245	1.899	0.516	0.176	–0.033	–0.005	–0.040	12.758	9.872
Difference	+0.178	–0.091	+0.005	+0.001	+0.001	0.000	0.000	+0.094	+0.067
40 years									
Clopidogrel	11.861	2.588	0.791	0.263	–0.047	–0.009	–0.069	15.378	10.950
Prasugrel	12.072	2.502	0.798	0.265	–0.046	–0.009	–0.070	15.512	11.033
Difference	+0.211	–0.087	+0.007	+0.002	+0.001	0.000	–0.001	+0.133	+0.084

TABLE 41 Mean deterministic estimated costs for STEMI patients without diabetes

Follow-up		Mean costs in health state				Event costs			Cost	
Treatment	Drug costs	Event free	MI(s) only	Mild stroke +/– MI(s)	Severe stroke +/– MI(s)	MI	Stroke	Death	Total	Total discounted
1 year										
Clopidogrel	29	588	23	2	4	463	36	37	1183	1183
Prasugrel	533	593	18	3	6	360	59	33	1605	1605
Difference	+503	+5	–5	+1	+2	–103	+22	–4	+422	+422
5 years										
Clopidogrel	69	2596	271	91	155	1263	725	228	5398	5045
Prasugrel	573	2638	236	99	170	1137	790	224	5867	5510
Difference	+503	+42	–35	+8	+15	–126	+65	–4	+468	+465
10 years										
Clopidogrel	113	4551	677	361	637	2293	2517	469	11617	9931
Prasugrel	616	4630	623	370	654	2153	2595	466	12108	10414
Difference	+504	+78	–54	+9	+17	–139	+78	–2	+490	+482
20 years										
Clopidogrel	175	7022	1404	1104	1994	3951	7095	957	23702	17354
Prasugrel	679	7147	1342	1113	2008	3810	7192	959	24249	17870
Difference	+504	+124	–63	+9	+13	–141	+96	+3	+546	+515
40 years										
Clopidogrel	213	8396	1861	1752	3129	4967	10868	1664	32850	21167
Prasugrel	718	8546	1802	1767	3146	4836	11002	1678	33493	21722
Difference	+505	+150	–59	+15	+17	–132	+134	+13	+643	+555

TABLE 42 Mean deterministic ICER for STEMI patients without diabetes

	Total cost		Total QALYs		Incremental		
Follow-up	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	ICER (£ per QALY)
1 year	£1183	£1605	0.905	0.907	+£422	+0.002	£224,302
5 years	£5044	£5510	3.992	4.008	+£465	+0.016	£29,607
10 years	£9931	£10,414	6.792	6.828	+£482	+0.036	£13,370
20 years	£17,354	£17,870	9.805	9.872	+£516	+0.067	£7670
40 years	£21,167	£21,722	10.950	11.033	+£555	+0.084	£6626

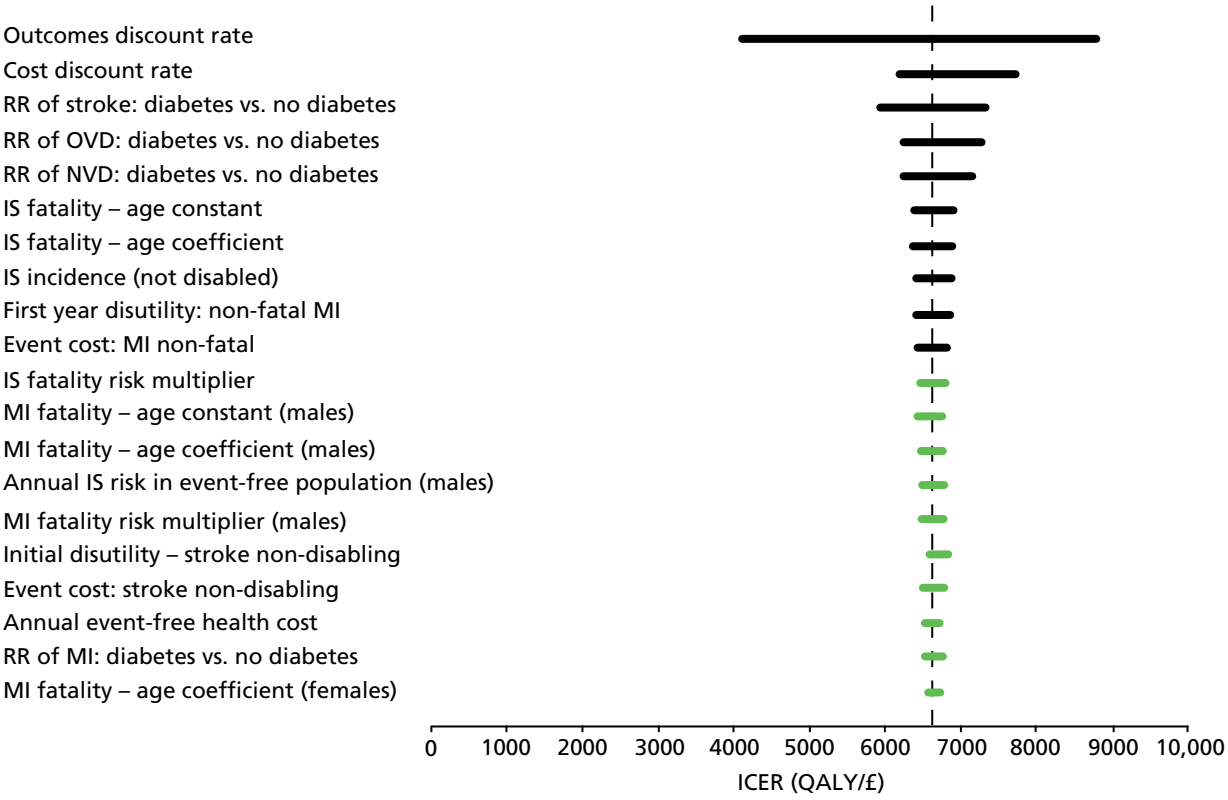

FIGURE 7 Univariate sensitivity analysis: 20 most important parameters in determining the ICER for STEMI patients without diabetes.

Probabilistic analysis at the 40-year follow-up horizon for this subgroup yields a higher estimated ICER (£7073 per QALY gained) derived from small incremental cost and QALY estimates (+£609 and +0.086, respectively). The scatterplot (*Figure 8*) and CEAC for this subgroup (*Figure 9*) indicate the relative cost-effectiveness of prasugrel despite the long-term erosion of incremental differences over time.

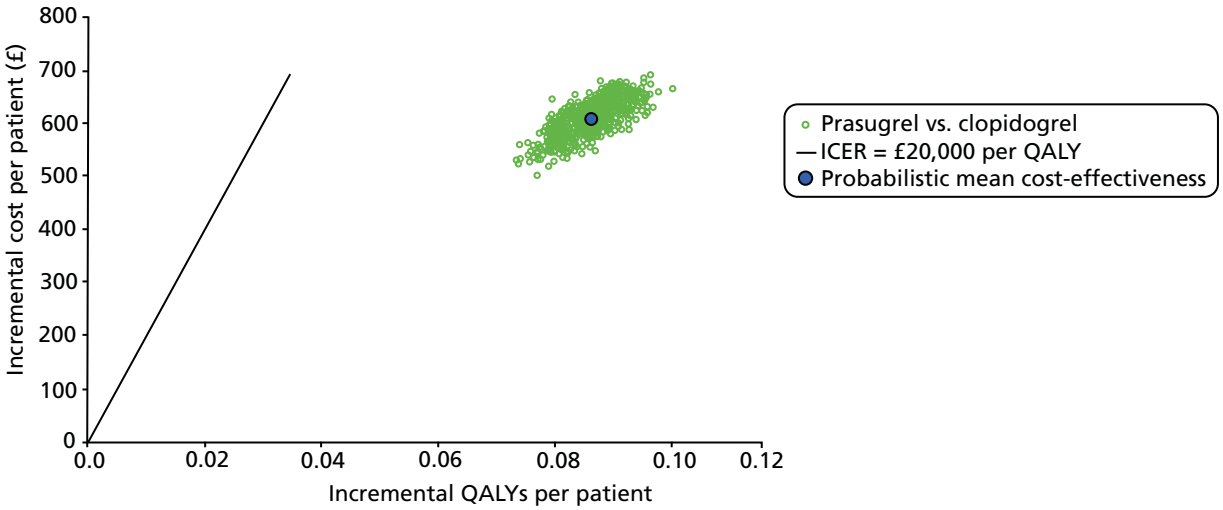

FIGURE 8 Probabilistic sensitivity analysis scatterplot of prasugrel compared with clopidogrel for STEMI patients without diabetes.

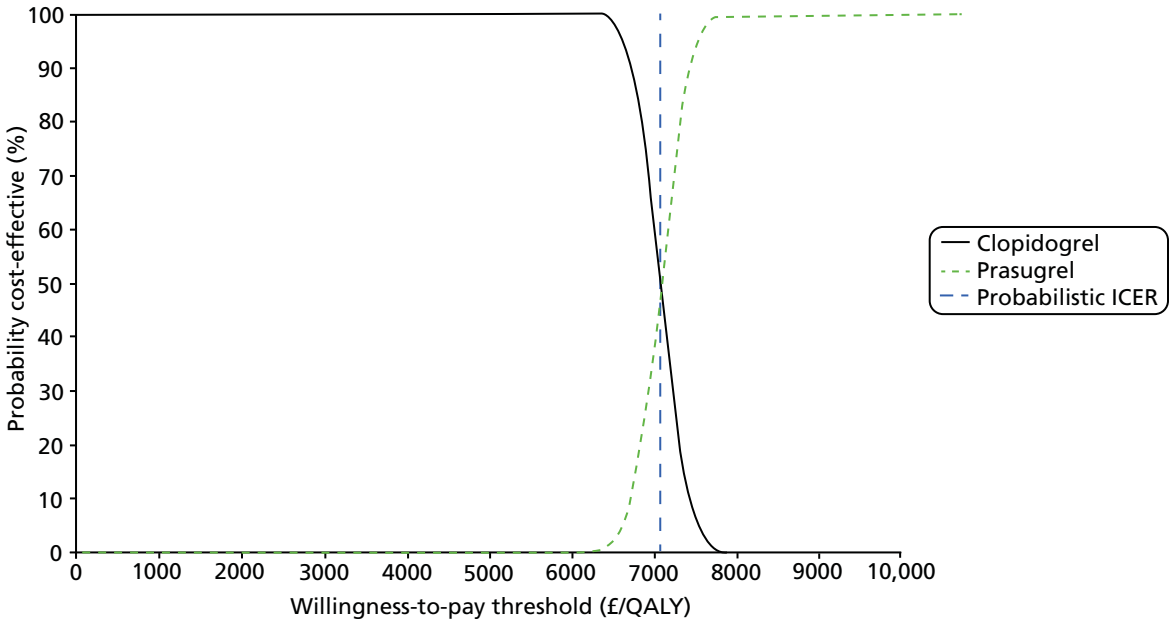

FIGURE 9 Cost-effectiveness acceptability curve of prasugrel compared with clopidogrel for STEMI patients without diabetes.

Unstable angina/non-ST segment elevation myocardial infarction: diabetes subgroup

Deterministic results are detailed in *Table 43* (life-years), *Table 44* (QALYs), *Table 45* (costs) and *Table 46* (ICERs). The ICER at the end of the first year is high, owing to the inclusion of the full additional cost of treatment with prasugrel, whereas only modest health gains have accrued from the reduced incidence of MIs. Over time, the estimated ICER decreases steadily, suggesting that incremental benefit continues to accrue over subsequent decades, while incremental cost increases at a slower rate. The ICER for prasugrel compared with clopidogrel falls below £30,000 per QALY gained after 5 years.

Figure 10 displays the results of univariate sensitivity analyses, which indicate that uncertainty from event incidence and fatality rates have the largest effect on the estimated ICER (ranging between –£1000 and £400 per QALY gained). Other individual model parameters have only a modest influence on the magnitude of the ICER in this subgroup.

TABLE 43 Mean deterministic estimated life-years for UA/NSTEMI patients with diabetes

Follow-up	Mean time in health state				Life-years	
Treatment	Event free	MI(s) only	Mild stroke(s) +/– MI(s)	Severe stroke(s) +/– MI(s)	Total	Total discounted
1 year						
Clopidogrel	0.934	0.048	0.003	0.002	0.987	0.987
Prasugrel	0.954	0.031	0.002	0.001	0.989	0.989
Difference	+0.020	–0.017	–0.001	–0.000	+0.002	+0.002
5 years						
Clopidogrel	4.032	0.513	0.071	0.040	4.656	4.361
Prasugrel	4.198	0.400	0.060	0.035	4.692	4.394
Difference	+0.166	–0.113	–0.012	–0.005	+0.036	+0.033
10 years						
Clopidogrel	6.986	1.172	0.242	0.139	8.540	7.426
Prasugrel	7.291	1.004	0.060	0.126	8.639	7.508
Difference	+0.305	–0.168	–0.012	–0.013	+0.099	+0.083
20 years						
Clopidogrel	10.536	2.202	0.645	0.371	13.754	10.667
Prasugrel	11.009	2.015	0.606	0.349	13.980	10.827
Difference	+0.473	–0.186	–0.038	–0.022	+0.226	+0.161
40 years						
Clopidogrel	12.127	2.690	0.907	0.510	16.233	11.733
Prasugrel	12.675	2.515	0.870	0.487	16.547	11.930
Difference	+0.548	–0.176	–0.037	–0.023	+0.313	+0.197

TABLE 44 Mean deterministic estimated QALYs for UA/NSTEMI patients with diabetes

Follow-up	Mean QALYs in health state				Event disutility (QALYs)			QALYs	
Treatment	Event free	MI(s) only	Mild stroke +/– MI(s)	Severe stroke +/– MI(s)	MI	Stroke	Death	Total	Total discounted
1 year									
Clopidogrel	0.842	0.043	0.003	0.001	–0.004	0.000	–0.002	0.883	0.883
Prasugrel	0.860	0.028	0.002	0.001	–0.003	0.000	–0.002	0.887	0.887
Difference	+0.018	–0.015	–0.001	0.000	+0.001	0.000	0.000	+0.003	+0.003
5 years									
Clopidogrel	3.602	0.457	0.061	0.020	–0.011	–0.001	–0.011	4.118	3.858
Prasugrel	3.750	0.356	0.050	0.017	–0.009	–0.001	–0.011	4.154	3.892
Difference	+0.148	–0.101	–0.010	–0.003	+0.002	0.000	0.000	+0.037	+0.034
10 years									
Clopidogrel	6.178	1.032	0.202	0.067	–0.020	–0.002	–0.022	7.434	6.477
Prasugrel	6.447	0.883	0.181	0.061	–0.017	–0.002	–0.022	7.530	6.557
Difference	+0.270	–0.149	–0.021	–0.006	+0.002	0.000	0.000	+0.095	+0.080
20 years									
Clopidogrel	9.164	1.897	0.522	0.171	–0.035	–0.006	–0.045	11.668	9.114
Prasugrel	9.575	1.733	0.490	0.160	–0.033	–0.006	–0.045	11.874	9.261
Difference	+0.411	–0.165	–0.032	–0.011	+0.002	0.000	0.000	+0.205	+0.147
40 years									
Clopidogrel	10.426	2.285	0.719	0.227	–0.044	–0.009	–0.071	13.533	9.919
Prasugrel	10.896	2.129	0.688	0.216	–0.042	–0.008	–0.072	13.806	10.095
Difference	+0.470	–0.156	–0.031	–0.011	+0.002	0.000	–0.002	+0.273	+0.176

TABLE 45 Mean deterministic estimated costs for UA/NSTEMI patients with diabetes

Follow-up		Mean costs in health state				Event costs			Cost	
Treatment	Drug costs	Event free	MI(s) only	Mild stroke +/– MI(s)	Severe stroke +/– MI(s)	MI	Stroke	Death	Total	Total discounted
1 year										
Clopidogrel	29	577	30	6	10	603	80	47	1383	1383
Prasugrel	533	590	19	4	8	393	52	43	1642	1642
Difference	+503	+13	–10	–2	–3	–210	–27	–4	+259	+259
5 years										
Clopidogrel	69	2492	317	129	222	1436	829	262	5755	5391
Prasugrel	572	2594	247	107	195	1171	691	259	5837	5487
Difference	+504	+103	–70	–21	–27	–265	–138	–3	+82	+96
10 years										
Clopidogrel	110	4318	724	437	770	2421	2430	533	11743	10102
Prasugrel	614	4506	621	392	698	2129	2149	535	11644	10054
Difference	+504	+189	–104	–46	–72	–292	–281	+1	–99	–47
20 years										
Clopidogrel	166	6512	1361	1163	2055	3848	5891	1075	22071	16476
Prasugrel	672	6804	1246	1094	1933	3557	5478	1090	21872	16362
Difference	+506	+292	–115	–69	–122	–292	–413	+15	–199	–114
40 years										
Clopidogrel	192	7495	1663	1636	2822	4519	7987	1706	28019	19015
Prasugrel	699	7834	1554	1569	2697	4243	7575	1743	27915	18939
Difference	+507	+339	–108	–67	–125	–275	–412	+37	–105	–77

TABLE 46 Mean deterministic ICER for UA/NSTEMI patients with diabetes

	Total cost		Total QALYs		Incremental		
Follow-up	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	ICER (£ per QALY)
1 year	£1383	£1642	0.883	0.887	+£259	+0.003	£76,856
5 years	£5391	£5487	3.858	3.892	+£96	+0.034	£2846
10 years	£10,102	£10,054	6.477	6.557	–£47	+0.080	Dominant
20 years	£16,476	£16,362	9.114	9.261	–£114	+0.147	Dominant
40 years	£19,015	£18,939	9.919	10.095	–£77	+0.176	Dominant

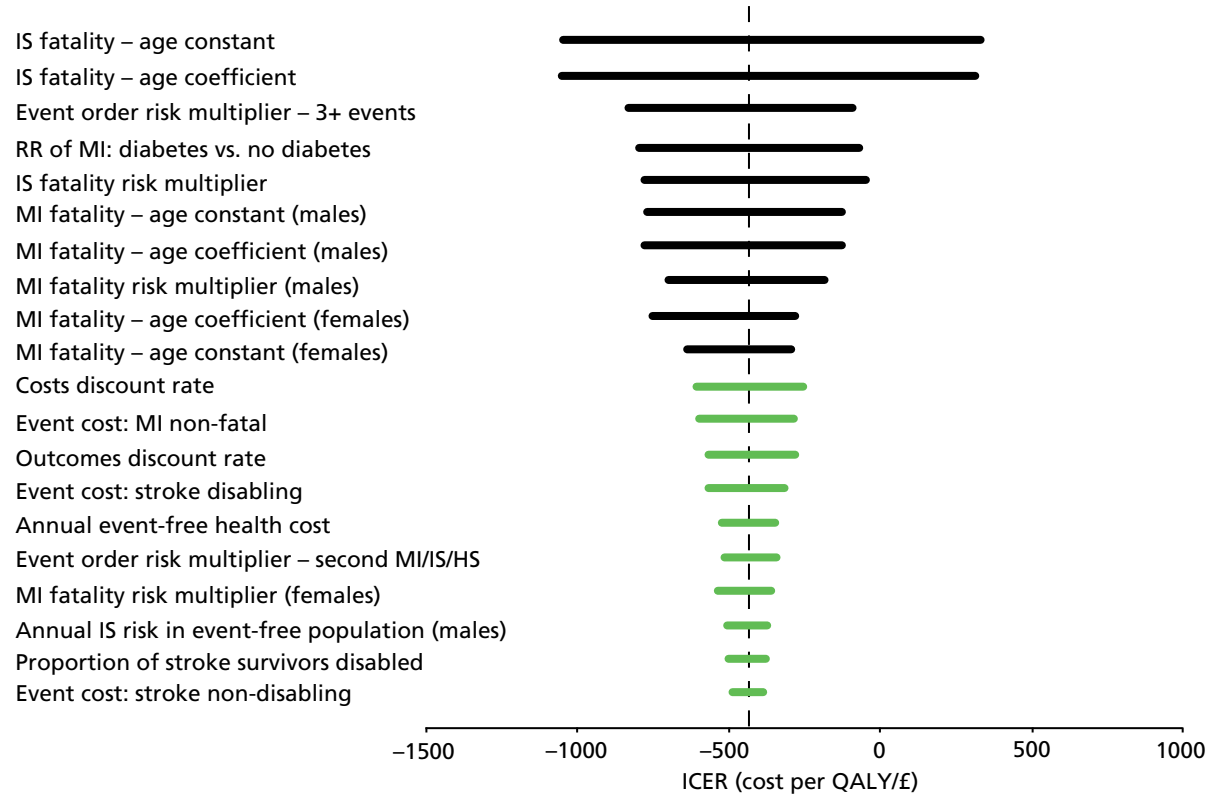

FIGURE 10 Univariate sensitivity analysis: 20 most important parameters in determining the ICER for UA/NSTEMI patients with diabetes.

Probabilistic analysis at the 40-year follow-up horizon for this subgroup confirms that prasugrel dominates clopidogrel with a small net cost saving and positive incremental benefit (–£120 and +0.191, respectively). The scatterplot (*Figure 11*) and CEAC for this subgroup (*Figure 12*) indicate the cost-effectiveness of prasugrel despite the long-term erosion of incremental differences over time.

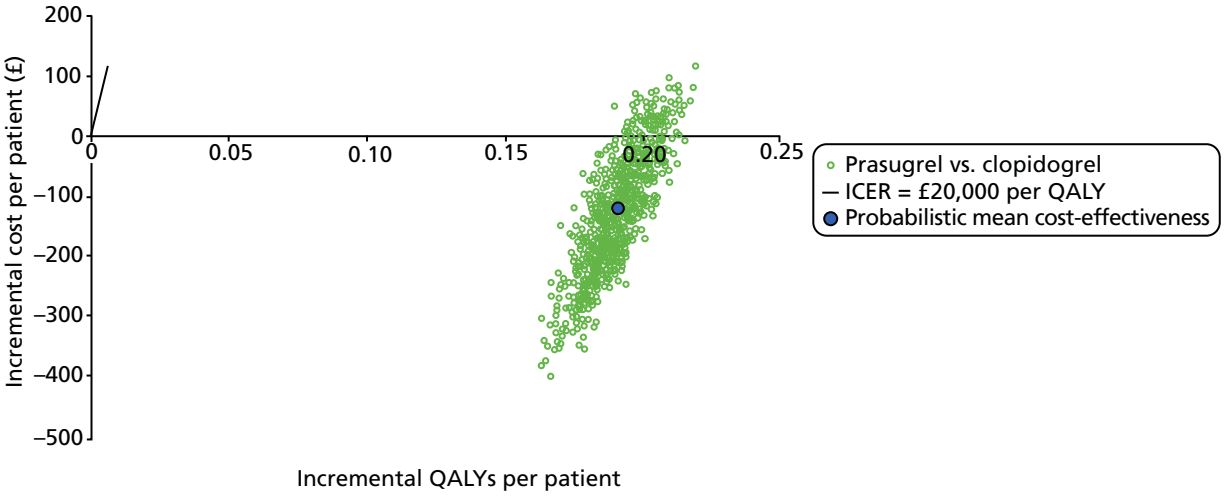

FIGURE 11 Probabilistic sensitivity analysis scatterplot of prasugrel compared with clopidogrel for UA/NSTEMI patients with diabetes.

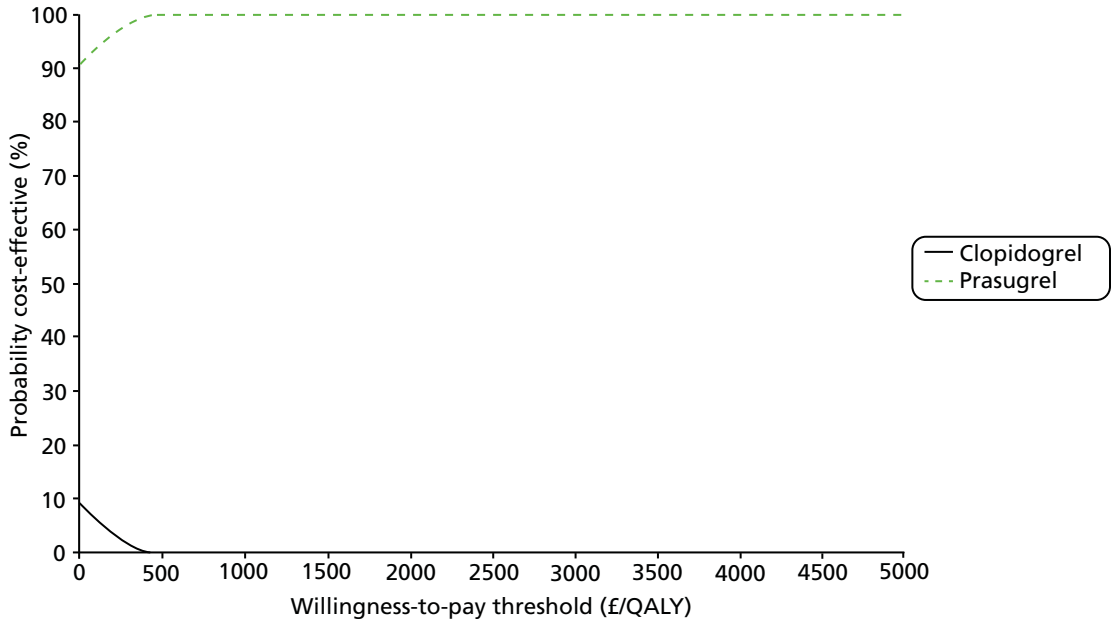

FIGURE 12 Cost-effectiveness acceptability curve of prasugrel compared with clopidogrel for UA/NSTEMI patients with diabetes.

Unstable angina/non-ST segment elevation myocardial infarction: no diabetes subgroup

Deterministic results are detailed in *Table 47* (life-years), *Table 48* (QALYs), *Table 49* (costs) and *Table 50* (ICERs). The ICER at the end of the first year is high, owing to the inclusion of the full additional cost of treatment with prasugrel, whereas only modest health gains have accrued from the reduced incidence of MIs. Over time the estimated ICER decreases steadily, suggesting that incremental benefit continues to accrue over subsequent decades while incremental cost increases at a slower rate. The ICER for prasugrel compared with clopidogrel falls below £30,000 per QALY gained after 10 years.

TABLE 47 Mean deterministic estimated life-years for UA/NSTEMI patients without diabetes

Follow-up	Mean time in health state				Life-years	
Treatment	Event free	MI(s) only	Mild stroke(s) +/– MI(s)	Severe stroke(s) +/– MI(s)	Total	Total discounted
1 year						
Clopidogrel	0.953	0.038	0.002	0.001	0.993	0.993
Prasugrel	0.960	0.031	0.001	0.001	0.993	0.993
Difference	+0.007	–0.007	–0.000	0.000	0.000	0.000
5 years						
Clopidogrel	4.204	0.443	0.053	0.030	4.730	4.429
Prasugrel	4.262	0.398	0.051	0.028	4.737	4.435
Difference	+0.058	–0.046	–0.004	–0.002	+0.007	+0.006
10 years						
Clopidogrel	7.348	1.092	0.206	0.118	8.764	7.611
Prasugrel	7.454	1.023	0.197	0.113	8.787	7.630
Difference	+0.106	–0.069	–0.009	–0.005	+0.024	+0.019
20 years						
Clopidogrel	11.249	2.219	0.607	0.354	14.429	11.125
Prasugrel	11.417	2.139	0.593	0.345	14.494	11.169
Difference	+0.167	–0.079	–0.015	–0.009	+0.064	+0.044
40 years						
Clopidogrel	13.248	2.863	0.924	0.530	17.565	12.454
Prasugrel	13.446	2.788	0.909	0.520	17.663	12.512
Difference	+0.198	–0.075	–0.015	–0.010	+0.099	+0.058

TABLE 48 Mean deterministic estimated QALYs for UA/NSTEMI patients without diabetes

Follow-up	Mean QALYs in health state				Event disutility (QALYs)			QALYs	
Treatment	Event free	MI(s) only	Mild stroke +/– MI(s)	Severe stroke +/– MI(s)	MI	Stroke	Death	Total	Total discounted
1 year									
Clopidogrel	0.869	0.034	0.001	0.000	–0.003	0.000	–0.001	0.901	0.901
Prasugrel	0.875	0.028	0.001	0.000	–0.002	0.000	–0.001	0.901	0.901
Difference	+0.006	–0.006	0.000	0.000	+0.001	0.000	0.000	0.000	0.000
5 years									
Clopidogrel	3.799	0.399	0.046	0.015	–0.009	–0.001	–0.009	4.241	3.972
Prasugrel	3.851	0.358	0.043	0.014	–0.008	–0.001	–0.010	4.248	3.979
Difference	+0.052	–0.041	–0.003	–0.001	+0.001	0.000	–0.000	+0.007	+0.007
10 years									
Clopidogrel	6.571	0.971	0.175	0.059	–0.018	–0.002	–0.020	7.736	6.732
Prasugrel	6.666	0.909	0.167	0.057	–0.017	–0.002	–0.020	7.760	6.751
Difference	+0.095	–0.062	–0.008	–0.002	+0.001	0.000	0.000	+0.024	+0.020
20 years									
Clopidogrel	9.892	1.929	0.502	0.169	–0.034	–0.005	–0.042	12.411	9.637
Prasugrel	10.039	1.859	0.490	0.164	–0.033	–0.005	–0.042	12.471	9.678
Difference	+0.147	–0.071	–0.013	–0.005	+0.001	0.000	0.000	+0.060	+0.042
40 years									
Clopidogrel	11.494	2.446	0.746	0.243	–0.046	–0.008	–0.070	14.804	10.655
Prasugrel	11.666	2.379	0.733	0.238	–0.045	–0.008	–0.071	14.892	10.708
Difference	+0.172	–0.067	–0.013	–0.005	+0.001	0.000	–0.001	+0.087	+0.053

TABLE 49 Mean deterministic estimated costs for UA/NSTEMI patients without diabetes

Follow-up		Mean costs in health state				Event costs			Cost	
Treatment	Drug costs	Event free	MI(s) only	Mild stroke +/– MI(s)	Severe stroke +/– MI(s)	MI	Stroke	Death	Total	Total discounted
1 year										
Clopidogrel	29	589	23	3	5	471	45	26	1192	1192
Prasugrel	533	593	19	2	4	388	37	28	1604	1604
Difference	+503	+4	–4	–1	–1	–83	–8	+1	+413	+413
5 years										
Clopidogrel	69	2598	274	96	165	1274	743	228	5447	5091
Prasugrel	573	2634	246	90	156	1168	693	229	5787	5437
Difference	+503	+36	–28	–7	–10	–106	–50	+1	+340	+346
10 years										
Clopidogrel	112	4541	675	371	654	2287	2467	482	11590	9920
Prasugrel	616	4607	632	355	627	2169	2357	485	11848	10200
Difference	+503	+66	–43	–16	–27	–119	–111	+2	+257	+280
20 years										
Clopidogrel	173	6952	1371	1096	1961	3870	6680	1000	23103	17002
Prasugrel	677	7056	1322	1069	1911	3748	6505	1006	23293	17239
Difference	+504	+103	–49	–27	–50	–122	–175	+6	+190	+237
40 years										
Clopidogrel	207	8188	1769	1667	2934	4753	9799	1693	31010	20328
Prasugrel	711	8310	1723	1640	2880	4637	9622	1707	31230	20576
Difference	+504	+123	–46	–27	54	–116	–178	+14	+220	+248

TABLE 50 Mean deterministic ICER for UA/NSTEMI patients without diabetes

	Total cost		Total QALYs		Incremental		
Follow-up	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	ICER (£ per QALY)
1 year	£1192	£1604	0.90097	0.90134	+£413	+0.00037	£1,101,662
5 years	£5091	£5437	3.972	3.979	+£346	+0.007	£52,288
10 years	£9920	£10,200	6.732	6.751	+£280	+0.020	£14,276
20 years	£17,002	£17,239	9.637	9.678	+£237	+0.042	£5688
40 years	£20,328	£20,576	10.655	10.708	+£248	+0.053	£4667

Figure 13 displays the results of univariate sensitivity analyses, which indicate that uncertainty from discounting rates, and event incidence and fatality rates have the largest effect on the estimated ICER (ranging between £2500 and £6500 per QALY gained). Other individual model parameters have only a modest influence on the magnitude of the ICER in this subgroup.

Probabilistic analysis at the 40-year follow-up horizon for this subgroup yields a lower estimated ICER of £4154 per QALY gained, derived from small incremental cost and QALY estimates (+£212 and +0.051, respectively). The scatterplot (*Figure 14*) and CEAC for this subgroup (*Figure 15*) indicate the relative cost-effectiveness of prasugrel despite the long-term erosion of incremental differences over time.

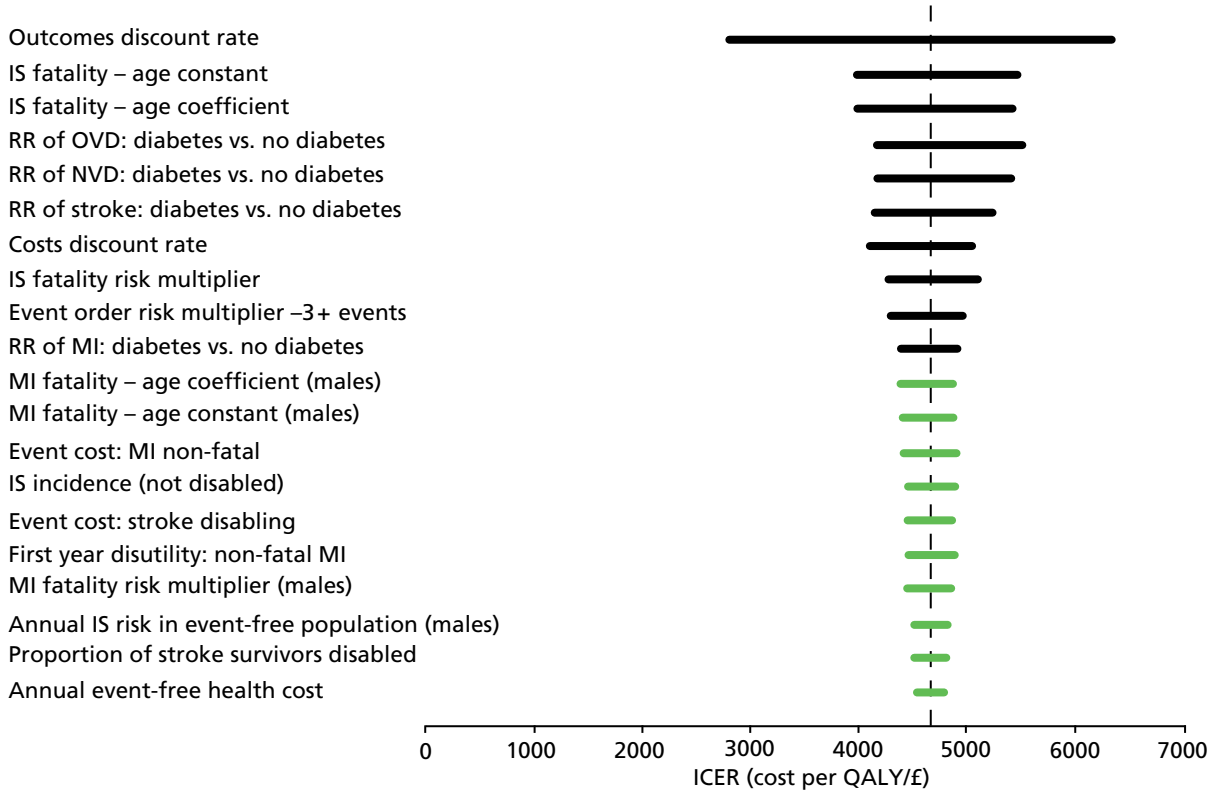

FIGURE 13 Univariate sensitivity analysis: 20 most important parameters in determining the ICER for UA/NSTEMI patients without diabetes.

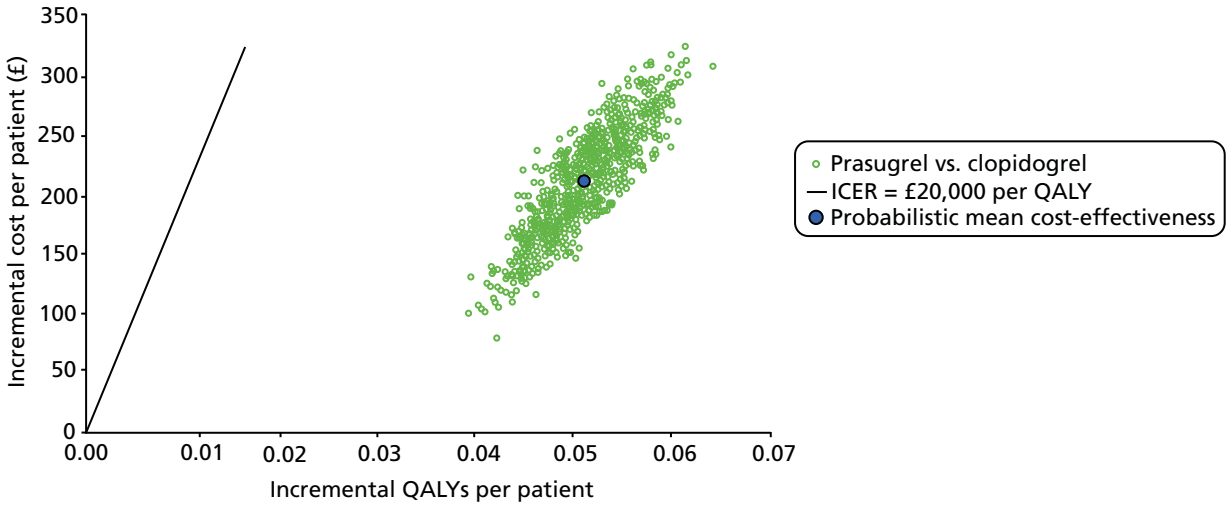

FIGURE 14 Probabilistic sensitivity analysis scatterplot of prasugrel compared with clopidogrel for UA/NSTEMI patients without diabetes.

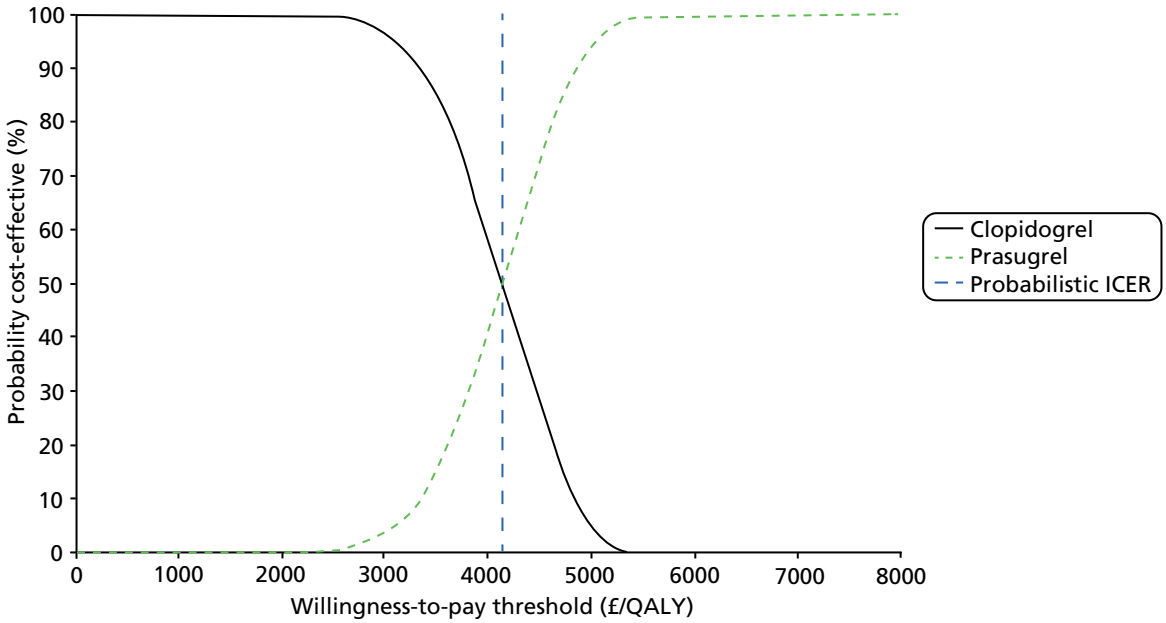

FIGURE 15 Cost-effectiveness acceptability curve of prasugrel compared with clopidogrel for UA/NSTEMI patients without diabetes.

Independent economic assessment: discussion of cost-effectiveness evidence

The main concern expressed by the ERG in its critique of the manufacturer's original submission in 2009 was that the very basic nature of projecting patient survival beyond the short follow-up period of the TRITON-TIMI 38[36] trial perpetuated a small effectiveness advantage over a period of 40 years. This projection method failed to allow the possibility of initial health gain being progressively attenuated and thus worsened the apparent economic comparison of prasugrel compared with clopidogrel. The application of the findings of the CAPRIE[92] trial in a similar patient population over a longer follow-up period to populate a long-term model has allowed the issue of clinical and economic benefit to be reassessed in a structured manner. The results from the AG's model suggest that attenuation of the initial benefits is indeed likely to occur, but that it is closely matched by narrowing of the initial cost difference so that estimated ICERs tend to reduce progressively rather than increase.

Simulation of the TRITON-TIMI 38[36] trial population within the AG's decision model as four mutually exclusive subgroups has facilitated a reconsideration of the strength of evidence underlying the previous NICE guidance[21] which excluded patients from treatment with prasugrel if they had not suffered from a STEMI event, or been diagnosed with diabetes. Both the deterministic and probabilistic analyses have confirmed that, within 5–10 years, and in all four subgroups, it appears likely that prasugrel is a cost-effective treatment option when compared with clopidogrel at a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained. At the full 40-year time horizon, all estimated ICERs are less than £10,000 per QALY gained, indicating confidence in this interpretation of the available evidence.

This economic analysis has developed beyond the previous assessment, using results from a large study (CAPRIE[92] data) over a longer period (3 years) and, therefore, serves to strengthen the case that was previously presented for consideration. However, any long-term modelling exercise is vulnerable to major assumptions about the continuation of early outcome gains, far beyond any possibility of experimental validation through an extended clinical trial. It is likely that the only viable approach to obtaining corroborative evidence would be from an extended patient register, tracing patients' subsequent health and health-care careers over decades.

Assessment of factors relevant to the NHS and other parties

The AG considers that any changes to the patient population eligible for prasugrel made as a result of this appraisal would not substantially affect resource use in the NHS in England and Wales.

Chapter 5 Discussion

The remit of this review was to update the evidence underpinning TA182[21] NICE guidance for the use of prasugrel in the NHS. In TA182,[21] only one RCT (TRITON-TIMI 38[36]) compared prasugrel with clopidogrel in patients presenting with ACS who were intended for treatment with PCI. No new trials were identified for inclusion in this update, which means that the present review is largely based on the clinical evidence available for TA182.[21]

Statement of principal findings

Clinical effectiveness

This review focused on the health outcomes of the subgroup of patients discussed in TA182[21] and for whom the full dose of prasugrel is licensed, namely the core clinical cohort (i.e. patients without a history of TIA or stroke, those with body weight of < 60 kg or those aged > 75 years). This group of patients constituted 79% of the overall population of TRITON-TIMI 38.[36] In the core clinical cohort, all non-bleeding clinical outcomes of the TRITON-TIMI 38[36] trial favoured the use of prasugrel compared with clopidogrel. These findings held over time and across subgroups of patients, including those with STEMI and UA/NSTEMI. There was a statistically significant difference in event rates in favour of clopidogrel when major and minor bleeding rates were combined.

A clinical comparison of prasugrel with ticagrelor was not carried out by the AG (or the manufacturer of prasugrel). There were two reasons for this. First, there was no direct RCT evidence comparing prasugrel with ticagrelor and, second, it was not possible to conduct an indirect comparison as there were irreconcilable differences between the two pivotal trials[33,36] (including timing and dosing of clopidogrel and assessment of MI). Thus, the comparative effectiveness and safety of prasugrel compared with ticagrelor still remain unknown.

Cost-effectiveness

In the AG's independent economic model, the outcomes of the TRITON-TIMI 38[36] trial population were simulated as four mutually exclusive subgroups: STEMI without diabetes mellitus, STEMI with diabetes mellitus, NSTEMI without diabetes mellitus and NSTEMI with diabetes mellitus. This approach has allowed the AG to reconsider the strength of evidence underlying the previous NICE guidance[21] that excluded patients from treatment with prasugrel if they had not suffered a STEMI event, or had not been diagnosed with diabetes. The new model confirmed that, using a £20,000 to £30,000 per QALY gained threshold, within 5–10 years, it appears likely that prasugrel is a cost-effective treatment option when compared with clopidogrel for all four subgroups.

Strengths and limitations of the assessment

The main strength of this review is that, despite some remaining areas of uncertainty, the case for prasugrel compared with clopidogrel appears to have been strengthened. The results of the AG's independent economic model confirm the cost-effectiveness of prasugrel compared with clopidogrel, at a threshold of £20,000 to £30,000 per QALY gained, for key groups of patients with ACS who are to be treated with PCI. The structure of the AG's model differs from the model developed by the manufacturer in that it uses the most up-to-date clinical evidence available (from the CAPRIE[92] trial) and compares four patient subgroups (STEMI without diabetes mellitus, STEMI with diabetes mellitus, NSTEMI without diabetes mellitus and NSTEMI with diabetes mellitus). A particular strength of the AG's economic model is that is provides assessments at specific time periods within the modelled time horizon of 40 years.

Both the AG and the manufacturer demonstrate the cost-effectiveness of prasugrel compared with clopidogrel at a threshold of £20,000 to £30,000 per QALY gained. However, the AG acknowledges that any long-term modelling exercise is vulnerable to major assumptions about the continuation of early health outcome gains, and it is noted that both the manufacturer's and the AG's models rely on extrapolating relatively short-term results from beyond the end of the trial to a further 40 years.

Since TA182,[21] the patent for clopidogrel has expired. In TA182,[21] the assessment of the cost-effectiveness of prasugrel was based on the non-generic price of clopidogrel using the economic model submitted by the manufacturer of prasugrel. A key strength of this update is that the AG has been able to reassess the cost-effectiveness of prasugrel compared with clopidogrel using the generic price of clopidogrel in an independent economic model.

The clinical effectiveness and cost-effectiveness findings of the report are limited by the nature of the available clinical evidence. Since TA182,[21] no new clinical evidence has become available to support the use of prasugrel compared with clopidogrel. In the short-term, all clinical effectiveness data used in the model were derived from a single RCT (TRITON-TIMI 38).[36] In the longer term, all clinical effectiveness data used in the model were primarily derived from a single RCT (CAPRIE).[92] The AG notes that both RCTs recruited large numbers of patients and were well conducted and well reported.

The AG notes that, although the TRITON-TIMI-38[36] trial was considered to be of a robust design, the majority (93%) of the trial population was white Caucasian. This does not negate the findings of this report, but it must be considered as a limitation to the applicability of the recommendations.

Uncertainties

The three areas of uncertainty noted by the AC for TA182[21] were reconsidered in this review. These centred on the generalisability of the TRITON-TIMI 38[36] trial results to patients in clinical practice in the UK. The AG is of the opinion that the clinical evidence for the equivalence of a 300-mg loading dose of clopidogrel (administered in TRITON-TIMI 38[36]) with a 600-mg loading dose (often given in clinical practice in the UK) remains uncertain. Similarly, the importance of timing of the administration of the loading dose of clopidogrel on patient outcomes remains unresolved and differs between the TRITON-TIMI 38[36] trial and clinical practice in the NHS in England and Wales. The AG considers that the case for the clinical effectiveness of prasugrel compared with clopidogrel in preventing MIs of all types and sizes appears to be robust.

Part of the remit for this review was to consider the efficacy of prasugrel compared with ticagrelor for patients with ACS who are to be treated with PCI. As no head-to-head trial has been conducted comparing these two treatments, the AG considered the possibility of an indirect treatment comparison using data from the TRITON-TIMI 38[36] and PLATO[33] trials; however, the AG concluded that the key differences between the two trials made any comparison unreliable. Thus, the comparative clinical effectiveness and safety of prasugrel compared with ticagrelor remains unknown. However, the AG is aware of a RCT that commenced recruiting patients in September 2013.[103,104] The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5[103,104] trial is designed to assess whether or not ticagrelor is superior to prasugrel in patients with ACS and planned invasive strategy. The primary outcome is the composite of death, MI or stroke at 12 months in a planned patient population of 4000. The results of the ISAR-REACT 5[103,104] trial will allow a formal comparison of the efficacy of prasugrel compared with ticagrelor.

Chapter 6 Conclusions

Suggested research priorities

It would be most valuable to have well-audited data on defined ACS patient groups from a long-term clinical registry of all UK patients receiving prasugrel, ticagrelor and clopidogrel and who are treated with a PCI. Such a data source could provide a basis for research and audit to inform future assessments of these antiplatelet treatments.

A database that allows comparison of populations or regions within the UK NHS in which all patients are uniformly treated with one or other of the antiplatelet agents would be a useful and informative resource.

It is suggested that any future trials in this area should focus on the comparison of prasugrel with ticagrelor and recruit patients with ACS who are to be treated with a PCI. It is anticipated that the results of the ISAR-REACT 5[103,104] trial, if conducted well, could fill the current gap in evidence related to the comparative efficacy and safety of prasugrel compared with ticagrelor.

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Contributions of authors

Janette Greenhalgh was the project lead and conducted the review of clinical evidence.

Adrian Bagust conducted the critical appraisal of manufacturers' economic model and development of de novo economic model.

Angela Boland supported the review process (clinical and economics).

Kerry Dwan conducted the clinical quality assessment and data extraction and was the statistical advisor.

Sophie Beale supported the review process (economics).

Nigel Fleeman conducted the literature selection and data management.

Joanne McEntee was the pharmacy advisor.

Yenal Dundar conducted the literature searching.

Marty Richardson conducted the data extraction and was the statistical advisor.

Michael Fisher was the clinical advisor.

All authors read and commented on draft versions of the report.

References

1. Egton Medical Information Systems Ltd. *Acute Coronary Syndromes*. 2013. URL: www.patient.co.uk/doctor/acute-coronary-syndrome (accessed April 2013).
2. Arslanian-Engoren C, Engoren M. Physiological and anatomical bases for sex differences in pain and nausea as presenting symptoms of acute coronary syndromes. *Heart Lung* 2010;**39**:386–93. http://dx.doi.org/10.1016/j.hrtlng.2009.10.013
3. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, *et al.* Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart* 2009;**95**:20–6. http://dx.doi.org/10.1136/hrt.2007.138537
4. Hasin T, Hochadel M, Gitt AK, Behar S, Bueno H, Hasin Y. Comparison of treatment and outcome of acute coronary syndrome in patients with versus patients without diabetes mellitus. *Am J Cardiol* 2009;**103**:772–8. http://dx.doi.org/10.1016/j.amjcard.2008.11.034
5. MINAP. *How the NHS Cares for Patients with Heart Attack. Annual Public Report April 2012–March 2013*. 2013. URL: www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2013-14/MINAP-Audit-Report-2013-LOW.pdf (accessed November 2013).
6. Greenhalgh J, Bagust A, Boland A, Martin Saborido C, Oyee J, Blundell M, *et al.* Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis. *Health Technol Assess* 2011;**15**(31). http://dx.doi.org/10.3310/hta15310
7. NICE. *Prasugrel with Percutaneous Coronary Intervention for Treating Acute Coronary Syndrome (Review of TA182): Final Scope*. 2013. URL: http://guidance.nice.org.uk/TA/WaveR/141 (accessed 2013 October).
8. NICE. *Myocardial infarction with ST-segment-elevation (STEMI): The Acute Management of Myocardial Infarction with ST-segment-elevation (STEMI): NICE Clinical Guideline CG167*. 2013 URL: http://publications.nice.org.uk/myocardial-infarction-with-st-segment-elevation-cg167 (accessed November 2013).
9. National Institute for Cardiovascular Outcomes Research. *National Audit of Percutaneous Coronary Interventional Procedures Public Report 2011*. London: National Institute for Cardiovascular Outcomes Research (NICOR). 2011. URL: www.ucl.ac.uk/nicor/audits/adultcardiacintervention/publicreports/documents/pcireport2012 (accessed April 2013).
10. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2011; **32**:2999–3054. http://dx.doi.org/10.1093/eurheartj/ehr236
11. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, *et al.*, ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33**:2569–619. http://dx.doi.org/10.1093/eurheartj/ehs215
12. Egton Medical Information Systems Ltd. *Percutaneous Coronary Intervention*. 2013. URL: www.patient.co.uk/doctor/percutaneous-coronary-intervention (accessed April 2013).
13. NICE. *The Early Management of Unstable Angina and Non-ST-segment-Elevation Myocardial Infarction: NICE Clinical Guideline 94*. 2010. URL: www.nice.org.uk/guidance/cg94/evidence/cg94-unstable-angina-and-nstemi-full-guidance-and-appendices2 (accessed November 2013).

14. Global Registry of Acute Coronary Events. *GRACE ACS Risk Model*. 2013. URL: www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html (accessed May 2013).
15. Greenhalgh J, Bagust A, Boland A, Saborido CM, Fleeman N, McLeod C, *et al.* Prasugrel for the treatment of acute coronary artery syndromes with percutaneous coronary intervention. *Health Technol Assess* 2010;**14**(Suppl. 1). http://dx.doi.org/10.3310/hta14Suppl1/05
16. Health and Social Care Information Centre. *Hospital Episode Statistics: Admitted Patient Care 2012–13. Diagnosis*. 2012–13 URL: www.hscic.gov.uk/catalogue/PUB12566/hosp-epis-stat-admi-summ-rep-2012-13-rep.pdf (accessed November 2013).
17. British Cardiovascular Intervention Society. *BCIS Audit Returns – Adult Interventional Procedures*. 2012. URL: www.bcis.org.uk/pages/page_box_contents.asp?pageid=780&navcatid=11 (accessed November 2013).
18. NICE. *NICE Quality Standards: QS forward planner*. 2013. URL: www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp?domedia=1&mid=6D55F322-CBF6-F672–00B5C83632967E35 (accessed December 2013).
19. NICE quality standards [QS68]. *Acute Coronary Syndromes (Including Myocardial Infarction)*. URL: www.nice.org.uk/guidance/qs68 (accessed November 2013).
20. NICE. *NICE Pathways: Acute Coronary Syndrome Overview*. 2013. URL: http://pathways.nice.org.uk/pathways/acute-coronary-syndrome (accessed December 2013).
21. NICE. *Prasugrel for the Treatment of Acute Coronary Syndromes with Percutaneous Coronary Intervention: TA182*. 2009. URL: http://publications.nice.org.uk/prasugrel-for-the-treatment-of-acute-coronary-syndromes-with-percutaneous-coronary-intervention-ta182 (accessed October 2013).
22. NICE. *Ticagrelor for the Treatment of Acute Coronary Syndromes (ACS): TA236*. 2011. URL: http://publications.nice.org.uk/ticagrelor-for-the-treatment-of-acute-coronary-syndromes-ta236 (accessed November 2013).
23. NICE. *MI – Secondary Prevention. Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction: NICE Clinical Guideline CG172*. 2013. URL: http://publications.nice.org.uk/mi-secondary-prevention-cg172 (accessed November 2013).
24. Electronic Medicines Compendium. *Efient – SPC*. 2014; URL: www.medicines.org.uk/emc/medicine/21504 (accessed February 2014).
25. EMEA. *European Public Assessment Report for Efient*. 2009. URL: www.emea.europa.eu/humandocs/PDFs/EPAR/Efient/H-984-en6.pdf (accessed November 2013).
26. NICE. *Acute Coronary Syndrome – Prasugrel. Appendix A: Decision Paper Presented to the Institute's Guidance Executive*. 2012. URL: http://guidance.nice.org.uk/TA182/ReviewDecisionJune12/ReviewDecisionAppendix/pdf/English (accessed 2013 October).
27. Joint Formulary Committee. *British National Formulary* (online). London: BMJ Group and Pharmaceutical Press. URL: www.medicinescomplete.com (accessed December 2013).
28. NHS Prescription Services. *Electronic Drug Tariff 2013*. URL: www.ppa.org.uk/edt/November_2013/mindex.htm (accessed November 2013).
29. Electronic Medicines Compendium. *Clopidogrel – SPC*. 2013. URL: www.medicines.org.uk/emc/medicine/24206/SPC/Plavix+300mg+tablets/#CONTRAINDICATIONS (accessed October 2013)
30. European Medicines Agency. *Brilique*. 2013. URL: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001241/human_med_001398.jsp&mid=WC0b01ac058001d124 (accessed December 2013).

31. Electronic Medicines Compendium. *Brilique – SPC*. 2013. URL: www.medicines.org.uk/emc/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/ (accessed October 2013).

32. AstraZeneca PLC. *Third Quarter and Nine Months Results (2013)*. 2013. URL: www.astrazeneca.com/cs/Satellite?blobcol=urldata&blobheader=application%2Fpdf&blobheadername1=Content-Disposition&blobheadername2=MDT-Type&blobheadervalue1=inline%3B+filename%3DPress-release.pdf&blobheadervalue2=abinary%3B+charset%3DUTF-8&blobkey=id&blobtable=MungoBlobs&blobwhere=1285660598284&ssbinary=true (accessed November 2013).

33. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–57. http://dx.doi.org/10.1056/NEJMoa0904327

34. FiercePharma. *EU Watchdogs Demand Info on AstraZeneca's Disputed Brilinta Trial*. 2013. URL: www.fiercepharma.com/story/eu-watchdogs-demand-info-astrazenecas-disputed-brilinta-trial/2013–11–08?utm_medium=nl&utm_source=internal (accessed November 2013).

35. Centre for Reviews and Dissemination. *CRD's Guidance for Undertaking Reviews in Healthcare: Systematic Reviews*. 3rd edn. University of York, York: Centre for Reviews and Dissemination; 2009.

36. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–15. http://dx.doi.org/10.1056/NEJMoa0706482

37. Ge J, Zhu J, Hong BK, Boonbaichaiyapruck S, Goh YS, Hou CJ, *et al.* Prasugrel versus clopidogrel in Asian patients with acute coronary syndromes: design and rationale of a multi-dose, pharmacodynamic, phase 3 clinical trial. *Curr Med Res Opin* 2010; **26**:2077–85. http://dx.doi.org/10.1185/03007995.2010.502048

38. Wiviott SD, Antman EM, Winters KJ, Weerakkody G, Murphy SA, Behounek BD, *et al.* Investigators J-T. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. *Circulation* 2005;**111**:3366–73. http://dx.doi.org/10.1161/CIRCULATIONAHA.104.502815

39. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, *et al.* Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circulation Cardiovasc Interv* 2012;**5**:797–804. http://dx.doi.org/10.1161/CIRCINTERVENTIONS.112.972323

40. Xanthopoulou I, Theodoropoulos KF, Kassimis G, Gizas V, Tsigkas G, Koutsogiannis N, *et al.* Ticagrelor vs prasugrel in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Eur Heart J* 2012;**33**:41.

41. Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G, *et al.* Investigators T-T. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J* 2006;**152**:627–35. http://dx.doi.org/10.1016/j.ahj.2006.04.012

42. Wiviott SD, Desai N, Murphy SA, Musumeci G, Ragosta M, Antman EM, Braunwald E. Efficacy and safety of intensive antiplatelet therapy with prasugrel from TRITON-TIMI 38 in a core clinical cohort defined by worldwide regulatory agencies. *Am J Cardiol* 2011;**108**:905–11. http://dx.doi.org/10.1016/j.amjcard.2011.05.020

43. SIGN. *Acute Coronary Syndromes*. 2007. URL: www.sign.ac.uk/pdf/sign93.pdf (accessed October 2013).

44. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, *et al.* Guidelines on myocardial revascularization. *Eur Heart J* 2010; **31**:2501–55. http://dx.doi.org/10.1093/eurheartj/ehq277

45. Mehta SR, Bassand JP, Chrolavicious S, Diaz R, Eikelboom J, Fox KAA, *et al.* Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010;**363**:930–42. http://dx.doi.org/10.1056/NEJMoa0909475

46. Mehta SR, Tanguay J-F, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, *et al.* Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 2010;**376**:1233–43. http://dx.doi.org/10.1016/S0140-6736(10)61088-4

47. Bakhai A, Iñiguez A, Ferrieres J, Needs N, Schmitt C, Sartral M, *et al.* International comparison of health care resources and quality of life in acute coronary syndrome patients in 2007: results from the AntiPlatelet Treatment Observational Registry (APTOR). *Value Health* 2008;**11**:A209–10.

48. McCollam P, Bae J, Nasuti P, Anger C. *Clopidogrel Patterns of Use in Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention in 5 European Countries*. PCV107. Poster presented at the International Society of Pharmacoeconomics and Outcomes Research 11th Annual European Congress, Athens, 2008.

49. McCollam P, Bae J, Nasuti P, Yeung E, Hamad B. *Clopidogrel Patterns of Use in Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention in 5 European Countries*. P01294. Presentation presented at the European Society of Cardiology Congress, Vienna, 2007.

50. Lotrionte MMD, Biondi-Zoccai GGLMD, Agostoni PMD, Abbate AMD, Angiolillo DJMDP, Valgimigli MMDP, *et al.* Meta-Analysis Appraising High Clopidogrel Loading in Patients Underqoinq Percutaneous Coronary Intervention(dagger). *Am J Cardiol* 2007;**100**:1199–206. http://dx.doi.org/10.1016/j.amjcard.2007.05.048

51. Cannon CP, Battler A, Grindis RG, Cox JL, Ellis SG, Every NR, *et al.* American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. *J Am Coll Cardiol* 2001;**38**:2114–30. http://dx.doi.org/10.1016/S0735-1097(01)01702-8

52. Morrow DA, Wiviott SD, White HD, Nicolau JC, Bramucci E, Murphy SA, *et al.* Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation* 2009;**119**:2758–64. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.833665

53. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, *et al.* Universal definition of myocardial infarction. *Eur Heart J* 2007;**28**:2525–38. http://dx.doi.org/10.1093/eurheartj/ehm355

54. Bonaca MP, Wiviott SD, Braunwald E, Murphy SA, Ruff CT, Antman EM, *et al.* American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation universal definition of myocardial infarction classification system and the risk of cardiovascular death: observations from the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38). *Circulation* 2012;**125**:577–83. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.041160

55. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, *et al.* Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009; **373**:723–31. http://dx.doi.org/10.1016/S0140-6736(09)60441-4

56. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, *et al.* Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010;**375**:283–93. http://dx.doi.org/10.1016/S0140-6736(09)62191-7

57. Biondi-Zoccai G, Lotrionte M, Agostoni P, Abbate A, Romagnoli E, Sangiorgi G, *et al.* Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. *Int J Cardiol* 2011;**150**:325–31. http://dx.doi.org/10.1016/j.ijcard.2010.08.035

58. Chatterjee S, Ghose A, Sharma A, Guha G, Mukherjee D, Frankel R. Comparing newer oral anti-platelets prasugrel and ticagrelor in reduction of ischemic events-evidence from a network meta-analysis. *J Thromb Thrombolysis* 2013;**36**:223–32. http://dx.doi.org/10.1007/s11239-012-0838-z

59. Passaro D, Fadda V, Maratea D, Messori A. Anti-platelet treatments in acute coronary syndrome: simplified network meta-analysis. *Int J Cardiol* 2011;**150**:364–7. http://dx.doi.org/10.1016/j.ijcard.2011.05.083

60. Steiner S, Moertl D, Chen L, Coyle D, Wells GA. Network meta-analysis of prasugrel, ticagrelor, high- and standard-dose clopidogrel in patients scheduled for percutaneous coronary interventions. *Thromb Haemost* 2012;**108**:318–27. http://dx.doi.org/10.1160/TH11-08-0586

61. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al.* Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;**7**:10. http://dx.doi.org/10.1186/1471-2288-7-10

62. Biondi-Zoccai G, D'Ascenzo F, Abbate A, Agostoni P, Modena MG. Agreement between adjusted indirect comparison and simplified network meta-analyses on prasugrel and ticagrelor. (Reply to Passaro *et al. Int J Cardiol* 2011;**150**:364–7.) *Int J Cardiol* 2011;**151**:228–9. http://dx.doi.org/10.1016/j.ijcard.2011.06.036

63. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, *et al.* Investigators D-. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* 2007;**50**:1844–51. http://dx.doi.org/10.1016/j.jacc.2007.07.053

64. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Clopidogrel in unstable angina to prevent recurrent events trial I. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502. http://dx.doi.org/10.1056/NEJMoa010746

65. Han YL, Wang B, Li Y, Xu K, Wang SL, Jing QM, *et al.* A high maintenance dose of clopidogrel improves short-term clinical outcomes in patients with acute coronary syndrome undergoing drug-eluting stent implantation. *Chin Med J (Engl)* 2009;**122**:793–7.

66. Aradi D, Vorobecsuk A, Pinter T. Doubling the maintenance dose of clopidogrel in patients with high post-clopidogrel platelet reactivity after percutaneous coronary intervention: the DOSER randomized placebo-controlled trial. *Eur Heart J* 2010;**31**(Suppl. 1):971.

67. Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Fleeman N, *et al. Prasugrel With Percutaneous Coronary Intervention for Treating Acute Coronary Syndromes (Review of TA182)*. 2013. URL: www.nice.org.uk/nicemedia/live/13908/64290/64290.pdf (accessed 2013 December).

68. Drummond M, Stoddart G, Torrance G. *Methods for the Economic Evaluation of Health Care Programmes*. 2nd edn. Oxford: Oxford University Press; 1997.

69. Mahoney EM, Wang K, Arnold SV, Proskorovsky I, Wiviott S, Antman E, *et al.* Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocadial infarction TRITON-TIMI 38. *Circulation* 2010;**121**:71–9. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.900704

70. Serebruany VL. Letter by Serebruany regarding article 'Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction TRITON-TIMI 38'. *Circulation* 2010;**122**:e436. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.936757

71. Mahoney EM, Wang K, Arnold SV, Cohen DJ, Proskorovsky I, Wiviott S, *et al.* Response to letter regarding article 'Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction TRITON-TIMI 38'. *Circulation* 2010;**122**:e146. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.951889

72. Davies A, Bakhai A, Schmitt C, Barrett A, Graham-Clarke P, Sculpher M. Prasugrel vs clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a model-based cost-effectiveness analysis for Germany, Sweden, the Netherlands and Turkey. *J Med Econ* 2013; **16**:510–21. http://dx.doi.org/10.3111/13696998.2013.768998

73. Mauskopft JA, Graham JB, Ramaswamy K, Zagar AJ, Magnuson EA, Cohen DJ, *et al.* Cost-effectiveness of prasugrel in a US managed care population. *J Med Econ* 2011;**15**:166–74. http://dx.doi.org/10.3111/13696998.2011.637590

74. Davies A, Sculpher M, Schmitt C, Barrett A, Baird J, Zanotti G, *et al.* Prasugrel cost-effective relative to clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention from the perspective of the UK national health service? A model-based analysis. *Value Health* 2009;**12**:A329. http://dx.doi.org/10.1016/S1098-3015(10)74616-7

75. Davies A, Sculpher M, Schmitt C, Barrett A, Clouth J, McCollam PL, *et al.* Is prasugrel cost-effective relative to clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention from the perspective of the German health care system? A model-based analysis. *Value Health* 2009;**12**:A331. http://dx.doi.org/10.1016/S1098-3015(10)74628-3

76. Davies A, Sculpher MJ, Barrett A, Valladares A, Huete T, Dilla T. Prasugrel vs. clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a Spanish model-based cost-effectiveness analysis. *Value Health* 2010;**13**:A357. http://dx.doi.org/10.1016/S1098-3015(11)72428-7

77. Hill RA, Chung H, George E, Longson C, Stevens A. Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention: NICE technology appraisal guidance. *Heart* 2010;**96**:1407–8. http://dx.doi.org/10.1136/hrt.2010.202853

78. Keast S, Burns CF, Harrison D, Nesser N, Lambert T. Cost-effectiveness of prasugrel and clopidogrel for acute coronary syndrome in a medicaid population. *J Manag Care Pharm* 2010;**16**:146.

79. Mahoney EM, Wang K, McCollam PL, Schmitt C, Cohen DJ. Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned PCI: Results from the triton-timi 38 trial from the German perspective. *Value Health* 2009;**12**:A328–9. http://dx.doi.org/10.1016/S1098-3015(10)74614-3

80. Mondragon R, Arrieta-Maturino E, Vargas-Valencia JJ, Ramirez-Gamez J, Martinez-Fonseca J, Guzman-Sotelo M. Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention in the private sector in Mexico. *Value Health* 2011;**14**:A535. http://dx.doi.org/10.1016/j.jval.2011.08.1515

81. Mondragon R, Arrieta-Maturino E, Vargas-Valencia JJ, Martinez-Fonseca J, Guzman-Sotelo M, Galindo-Suarez RM, *et al.* Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention in the public health care system in Mexico. *Value Health* 2011;**14**:A545. http://dx.doi.org/10.1016/j.jval.2011.08.1579

82. Rao S, Lin FJ, Ojo O, Patel V, Yu S, Zhan L, *et al.* A decision modeling approach to evaluate the cost-effectiveness of prasugrel versus clopidogrel in patients with planned percutaneous coronary intervention. *Value Health* 2011;**14**:A39–40. http://dx.doi.org/10.1016/j.jval.2011.02.229

83. Rosengren A, Wilhelmsen L, Hagman M, Wedel H. Natural history of myocardial infarction and angina pectoris in a general population sample of middle-aged men: a 16 year follow up of the Primary Prevention Study, Goteberg, Sweden. *J Intern Med* 1998;**244**:495–505. http://dx.doi.org/10.1111/j.1365-2796.1998.00394.x

84. Allen L, O' Donnell C, Camargo CJ, Giugliano R, Lloyd-Jones D. Comparison of long-term mortality across the spectrum of acute coronary syndromes. *Am Heart J* 2006;**151**:1065–71. http://dx.doi.org/10.1016/j.ahj.2005.05.019

85. Mueller H, Forman S, Menegus M, Cohen L, Knatterud G, Braunwald E. Prognostic significance of nonfatal reinfarction during 3-year follow up: results of the Thrombolysis in Myocardial Infarction (TIMI) phase II clinical trial. The TIMI Investigators. *J Am Coll Cardiol* 1995;**26**:900–7. http://dx.doi.org/10.1016/0735-1097(95)00270-1

86. Taneja A, Collinson J, Flather M, Bakhai A, de Arenaza D, Wang D, *et al.* Mortality following non-ST elevation acute coronary syndrome: 4 years follow up of the PRAIS UK Registry (Prospective Registry of Acute Ischaemic Syndromes in the UK). *Eur Heart J* 2004;**25**:2013–18. http://dx.doi.org/10.1016/j.ehj.2004.08.009

87. Sullivan P, Ghushchyan V. Preference based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006;**26**:410–20. http://dx.doi.org/10.1177/0272989X06290495

88. MIMS. *Prescription Drug Database: MIMS*. 2013. URL: www.mims.co.uk/ (accessed November 2014).

89. Mehta S, Cannon C, Fox K. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *J Am Med Assoc* 2005;**293**:2908–17. http://dx.doi.org/10.1001/jama.293.23.2908

90. NICE. *Guide to the Methods of Technology Appraisal*. London: NICE; 2013. URL: http://publications.nice.org.uk/pmg9 (accessed April 2013).

91. Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D*. Centre for Health Economics Discussion Paper (172). York: University of York; 1999.

92. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39. http://dx.doi.org/10.1016/S0140-6736(96)09457-3

93. Greenhalgh J, Bagust A, Boland A, Martin Saborido C, Fleeman N, McLeod C, *et al. Prasugrel for the Treatment of Acute Coronary Syndromes with Percutaneous Coronary Intervention: A Single Technology Appraisal*. Liverpool: Liverpool Reviews and Implementation Group, University of Liverpool; 2009.

94. NICE. *Clopidogrel and Modified-Release Dypiridamole in the Prevention of Occlusive Vascular Events: TA90 (replaced by TA210)*. 2005. URL: www.nice.org.uk/TA090 (accessed December 2013).

95. NICE. *Vascular Disease – Clopidogrel and Dipyridamole (TA210)*. 2010. URL: http://guidance.nice.org.uk/TA210 (accessed December 2013).

96. Diener H-C, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, *et al.* Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol* 2008;**7**:875–84. http://dx.doi.org/10.1016/S1474-4422(08)70198-4

97. Malmberg K, Yusuf S, Gerstein H, Brown J, Zhao F, Humt D, *et al.* Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction. *Circulation* 2000;**102**:1014–19. http://dx.doi.org/10.1161/01.CIR.102.9.1014

98. Kleinman J, Donahue R, Harris M, Finucane F, Madans J, Brock D. Mortality among diabetics in a national sample. *Am J Epidemiol* 1988;**128**:389–401.

99. Curtis L. *Unit Costs of Health and Social Care 2012 (PSSRU)*. 2012. URL: www.pssru.ac.uk/project-pages/unit-costs/2012/ (accessed November 2014).

100. AstraZeneca. *Ticagrelor for the Treatment of Acute Coronary Syndromes: Manufacturer Submission*. 2010. URL: www.nice.org.uk/nicemedia/live/12169/55171/55171.pdf (accessed November 2014).

101. Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin Scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. *Med Decis Making* 2010;**30**:341–54. http://dx.doi.org/10.1177/0272989X09349961

102. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Med Decis Making* 2002;**22**:340–9. http://dx.doi.org/10.1177/027298902400448902

103. ClinicalTrials.gov. *Prospective, Randomised Trial of Ticagrelor Versus Prasugrel in Patients with Acute Coronary Syndrome (ISAR-REACT 5)*. 2013. URL: http://clinicaltrials.gov/ct2/show/NCT01944800?term=ticagrelor&rank=41 (accessed November 2014).

104. Schulz S, Angiolillo D, Antoniucci D, Bernlochner I, Hamm C, Jaitner J, *et al.* Randomized Comparison of Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndrome and Planned Invasive Strategy—Design and Rationale of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 Trial. *J Cardiovasc Transl Res* 2014;**7**:91–100. http://dx.doi.org/10.1007/s12265-013-9527-3

105. Antman EM, Wiviott SD, Murphy SA, Voitk J, Hasin Y, Widimsky P, *et al.* Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 2008;**51**:2028–33. http://dx.doi.org/10.1016/j.jacc.2008.04.002

106. Hochholzer W, Wiviott SD, Antman EM, Contant CF, Guo J, Giugliano RP, *et al.* Predictors of bleeding and time dependence of association of bleeding with mortality: Insights from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38 (TRITON-TIMI 38). *Circulation* 2011;**123**:2681–9. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.002683

107. Laynez A, Sardi G, Torguson R, Xue Z, Suddath WO, Satler LF, *et al.* Safety and efficacy of prasugrel use in patients undergoing percutaneous coronary intervention and anticoagulated with bivalirudin. *Am J Cardiol* 2013;**111**:516–20. http://dx.doi.org/10.1016/j.amjcard.2012.10.035

108. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, *et al.* Cytochrome p-450 polymorphisms and response to clopidogrel. *New Engl J Med* 2009;**360**:354–62. http://dx.doi.org/10.1056/NEJMoa0809171

109. Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, *et al.* Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet* 2010;**376**:1312–19. http://dx.doi.org/10.1016/S0140-6736(10)61273-1

110. Michelson AD, Frelinger AL 3rd, Braunwald E, Downey WE, Angiolillo DJ, Xenopoulos NP, *et al.* Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. *Eur Heart J* 2009;**30**:1753–63. http://dx.doi.org/10.1093/eurheartj/ehp159

111. Murphy SA, Antman EM, Wiviott SD, Weerakkody G, Morocutti G, Huber K, *et al.* Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. *Eur Heart J* 2008;**29**:2473–9. http://dx.doi.org/10.1093/eurheartj/ehn362

112. O'Donoghue M, Antman EM, Braunwald E, Murphy SA, Steg PG, Finkelstein A, *et al.* The efficacy and safety of prasugrel with and without a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) analysis. *J Am Coll Cardiol* 2009;**54**:678–85. http://dx.doi.org/10.1016/j.jacc.2009.05.025

113. O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, *et al.* Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;**374**:989–97. http://dx.doi.org/10.1016/S0140-6736(09)61525-7

114. Pride YB, Wiviott SD, Buros JL, Zorkun C, Tariq MU, Antman EM, *et al.* Effect of prasugrel versus clopidogrel on outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention without stent implantation: a TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel (TRITON)-Thrombolysis in Myocardial Infarction (TIMI) 38 substudy. *Am Heart J* 2009;**158**:e21–6. http://dx.doi.org/10.1016/j.ahj.2009.06.021

115. Pride YB, Tung P, Mohanavelu S, Zorkun C, Wiviott SD, Antman EM, *et al.* Angiographic and clinical outcomes among patients with acute coronary syndromes presenting with isolated anterior ST-segment depression: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) substudy. *JACC Cardiovasc Interv* 2010;**3**:806–11. http://dx.doi.org/10.1016/j.jcin.2010.05.012

116. Riesmeyer JS, Salazar DE, Weerakkody GJ, Ni L, Wrishko RE, Ernest CS 2nd, *et al.* Relationship between exposure to prasugrel active metabolite and clinical outcomes in the TRITON-TIMI 38 substudy. *J Clin Pharmacol* 2012;**52**:789–97. http://dx.doi.org/10.1177/0091270011406280

117. Ruff CT, Giugliano RP, Antman EM, Murphy SA, Lotan C, Heuer H, *et al.* Safety and efficacy of prasugrel compared with clopidogrel in different regions of the world. *Int J Cardiol* 2012;**155**:424–9. http://dx.doi.org/10.1016/j.ijcard.2010.10.040

118. Scirica B, Morrow D, Antman E, Bonaca M, Murphy S, Braunwald E, *et al.* Timing and clinical setting of cardiovascular death or myocardial infarction following PCI for ACS-observations from the TRITON-TIMI 38 trial. *J Am Coll Cardiol* 2012;**1**:E340. http://dx.doi.org/10.1016/S0735-1097(12)60341-6

119. Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ, *et al.* Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. *J Am Coll Cardiol* 2012;**60**:388–96. http://dx.doi.org/10.1016/j.jacc.2012.03.030

120. Udell JA, Braunwald E, Antman EM, Murphy SA, Montalescot G, Wiviott SD. Benefit of prasugrel in ST-elevation myocardial infarction according to timing of percutaneous coronary intervention: Insight from the triton-TIMI 38 study. *Circulation* 2011;**124**:A9309. http://dx.doi.org/10.1016/j.jcin.2014.01.160

121. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, Verheugt FW, *et al.* Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation* 2008;**118**:1626–36. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.791061

122. Wiviott SD, Braunwald E, McCabe CH, Horvath I, Keltai M, Herrman JP, *et al.* Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet* 2008;**371**:1353–63. http://dx.doi.org/10.1016/S0140-6736(08)60422-5

123. Wrishko RE, Ernest CS, Small DS, Li YG, Weerakkody GJ, Riesmeyer JR, *et al.* Population pharmacokinetic analyses to evaluate the influence of intrinsic and extrinsic factors on exposure of prasugrel active metabolite in TRITON-TIMI 38. *J Clin Phamacol* 2009;**49**:984–98. http://dx.doi.org/10.1177/0091270009337942

124. Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Fleeman N, *et al. The Clinical and Cost-Effectiveness of Prasugrel with Percutaneous Coronary Intervention for Treating Acute Coronary Syndromes (Review of TA182)*. Liverpool: Liverpool Reviews and Implementation Group, University of Liverpool; 2013.

125. Abuzahra M, Pillai M, Caldera A, Hartley WB, Gonzalez R, Bobek J, *et al.* Comparison of higher clopidogrel loading and maintenance dose to standard dose on platelet function and outcomes after percutaneous coronary intervention using drug-eluting stents. *Am J Cardiol* 2008;**102**:401–3. http://dx.doi.org/10.1016/j.amjcard.2008.03.073

126. Angiolillo DJ, Bernardo E, Palazuelos J, Desai B, Weisberg I, Alfonso F, *et al.* Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions. Results of a randomized study. *Thromb Haemost* 2008;**99**:161–8. http://dx.doi.org/10.1160/TH07-09-0562

127. Palmerini T, Barozzi C, Tomasi L, Sangiorgi D, Marzocchi A, De Servi S, *et al.* A randomised study comparing the antiplatelet and antiinflammatory effect of clopidogrel 150 mg/day versus 75 mg/day in patients with ST-segment elevation acute myocardial infarction and poor responsiveness to clopidogrel: results from the DOUBLE study. *Thromb Res* 2010;**125**:309–14. http://dx.doi.org/10.1016/j.thromres.2009.06.016

128. Price MJ, Berger PB, Teirstein PS, Tanguay J-F, Angiolillo DJ, Spriggs D, *et al.* Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;**305**:1097–105. [Erratum published in *JAMA* 2011;**305**;2174.] http://dx.doi.org/10.1001/jama.2011.290

129. Aleil B, Jacquemin L, De Poli F, Zaehringer M, Collet J-P, Montalescot G, *et al.* Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary intervention: results from the VASP-02 (Vasodilator-Stimulated Phosphoprotein-02) randomized study. *JACC Cardiovasc Interv* 2008;**1**:631–8. http://dx.doi.org/10.1016/j.jcin.2008.09.004

130. von Beckerath N, Kastrati A, Wieczorek A, Pogatsa-Murray G, Sibbing D, Graf I, *et al.* A double-blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days. *Eur Heart J* 2007;**28**:1814–19. http://dx.doi.org/10.1093/eurheartj/ehl489

131. Alexopoulos D, Xanthopoulou I, Davlouros P, Plakomyti T-E, Panagiotou A, Mavronasiou E, *et al.* Prasugrel overcomes high on-clopidogrel platelet reactivity in chronic coronary artery disease patients more effectively than high dose (150 mg) clopidogrel. *Am Heart J* 2011;**162**:733–9. http://dx.doi.org/10.1016/j.ahj.2011.07.026

132. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann F-J, Michelson AD, *et al.* Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;**116**:2923–32. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.740324

Appendix 1 Literature search strategies

OvidSP MEDLINE(R)

1946 to June Week 1 2013

1	exp Acute Coronary Syndrome/
2	(coronary adj syndrome$).ti,ab.
3	exp Angina, Unstable/
4	(unstable adj2 angina).ti,ab.
5	exp Myocardial Infarction/
6	(myocard$ adj infarct$).ti,ab.
7	heart infarct$.ti,ab.
8	exp Myocardial Ischemia/
9	(myocard$ adj isch?emi$).ti,ab.
10	(isch?emic adj3 heart).ti,ab.
11	or/1-10
12	(Prasugrel or Effient or Efient).af
13	11 and 12
14	animal/ not (animal/ and human/)
15	13 not 14
16	Limit 15 to (English language)

OvidSP EMBASE

1974 to 2013 June 18

1	exp unstable angina pectoris/ or exp acute coronary syndrome/ or heart infarction/ or heart muscle ischemia/ or ischemic heart disease/
2	(coronary adj syndrome$).ti,ab.
3	(unstable adj2 angina).ti,ab.
4	(myocard$ adj infarct$).ti,ab.
5	heart infarct$.ti,ab.
6	(myocard$ adj isch?emi$).ti,ab.
7	(isch?emic adj3 heart).ti,ab.
8	or/1-7
9	(Prasugrel or Effient or Efient).af
10	8 and 9
11	limit 10 to (human and english language)

The Cochrane Library Searches

Prasugrel or Effient or Efient:ti,ab,kw (word variations have been searched).

Appendix 2 Quality assessment of included trial

	Randomisation			Baseline comparability				Blinding				Withdrawals			
Trial	Truly random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	> 80% in final analysis	Reasons stated	ITT	Other outcomes
Wiviott *et al.* 2007[36]	✓	✓	✓	✓	✓	✓	✓[a]	✓	✓	✓	NS	✓	✓	✓	✗

✗, no; ✓, yes; ITT, intention to treat; NS, not stated.
a Included use of stents, use of glycoprotein IIb/IIIa inhibitors, aspirin, statins, beta-blockers, etc.

Appendix 3 Table of excluded studies with rationale

Paper	Reason for exclusion
National Horizon Scanning Centre. *Prasugrel for Acute Coronary Artery Syndrome with Percutaneous Coronary Intervention: Horizon Scanning Technology Briefing*. Birmingham: National Horizon Scanning Centre (NHSC); 2007, issue 2, page 6. URL: www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32007000470&UserID=0#.VKwJkdKDl8E (accessed July 2013)	Abstract of review
NICE. *Prasugrel for the Treatment of Acute Coronary Syndromes with Percutaneous Coronary Intervention.* Health Technology Assessment Database. URL: www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32011000084&UserID=0 (accessed November 2013)	Abstract of TA182
Canadian Agency for Drugs and Technologies in Health. Clopidogrel, Prasugrel and Ticagrelor in Adults with Acute Coronary Syndrome: A Review of the Clinical Effectiveness. Health Technology Assessment Database, 2011. URL: www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32011001503&UserID=0 (accessed November 2013)	Abstract of systematic reviews
National Horizon Scanning Centre. *Prasugrel (Efient) for the Prevention of Atherothrombotic Events in Patients with Acute Coronary Syndromes who will be Managed Without Acute Coronary Revascularisation in Combination with Aspirin*. Birmingham: National Horizon Scanning Centre (NHSC); 2011	Horizon scanning document
British Journal of Cardiology. News from the ESC Congress 2012. *Br J Cardiol* 2012;**19**:152–5	Meeting report
American Journal for Cardiology, 18th Annual Interventional Vascular Therapeutics Angioplasty Summit-Transcatheter Cardiovascular Therapeutics Asia Pacific Symposium, TCTAP Hong Kong, 23–6 April 2013	Meeting report
Journal of American College of Cardiology. *JACC Official Highlights from the ACC. 13 62nd Annual Scientific Session and Expo: MD Conference Express*. March 9–12 2013. URL: www.nxtbook.com/nxtbooks/md_conference_express/acc2013/#/0 (accessed November 2013)	Meeting report
Society for Cardiovascular Angiography and Interventions' 36th Annual Scientific Sessions. Catheterization and Cardiovascular Interventions 2013;**81**:S1. Orlando, Florida, 8–11 May 2013	Meeting report
Aalbers J. Prasugrel study addresses timing of thienopyridine loading dose in NSTEMI patients pre-PCI (the ACCOAST study). *Cardiovasc J Afr* 2011;**22**:168	Letter
Abdel-Latif A, Moliterno DJ. Prasugrel versus clopidogrel in primary PCI: Considerations of the TRITON-TIMI 38 substudy. *Curr Cardiol Rep* 2009;**11**:323–4	Report of a TRITON-TIMI 38 substudy
Alexander W. TRITON-TIMI 38: Clopidogrel and prasugrel. *Pharm Ther* 2008;**33**:51	Report of a TRITON-TIMI 38
Alexander W. FDA advisory committee meeting on prasugrel for acute coronary syndromes. *Pharm Ther* 2009;**34**:155–6	FDA discussion of prasugrel
Alexander W. Cardiovascular research technologies 2012. *Pharm Ther* 2012;**37**:186–9	Discussion document
Alexander W. Transcatheter cardiovascular therapeutics 2012. *Pharm Ther* 2012;**37**:709–10	Meeting review
Alexopoulos D, Theodoropoulos KC, Stavrou EF, Xanthopoulou I, Kassimis G. Tsigkas G, *et al.* Prasugrel versus high dose clopidogrel to overcome early high on clopidogrel platelet reactivity in patients with ST elevation myocardial infarction. *Cardiovasc Drugs Ther* 2012;**26**:393–400	Platelet reactivity trial. 30-day outcomes
Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, *et al.* Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2012;**5**:797–804	Platelet reactivity trial. 30-day outcomes
Aradi D, Komocsi A, Price M, Cuisset T, Ari H, Hazarbasanov D, *et al.* Efficacy and safety of intensified antiplatelet therapy on the basis of platelet reactivity testing in patients after PCI: systematic review and meta-analysis. *EuroIntervention* 2012;**8**:N109	Platelet function studies
Aradi D, Komocsi A, Price M, Cuisset T, Ari H, Hazarbasanov D, *et al.* Efficacy and safety of intensified antiplatelet therapy on the basis of platelet reactivity testing in patients after percutaneous coronary intervention: Systematic review and meta-analysis. *J Am Coll Cardiol* 2012;**60**:B218	Abstract of systematic review

Paper	Reason for exclusion
Aradi D, Komocsi A, Vorobcsuk A, Serebruany VL. Impact of clopidogrel and potent P2Y12-inhibitors on mortality and stroke in patients with acute coronary syndrome or undergoing percutaneous coronary intervention: A systematic review and meta-analysis. *Thromb Haemost* 2013;**109**:93–101	Systematic review
Aradi D, Pinter T, Magyari B, Konyi A, Vorobcsuk A, Horvath IG, *et al.* Optimizing P2Y12-receptor inhibition in acute coronary syndrome patients after PCI using platelet function testing: Impact of prasugrel versus high-dose clopidogrel. *J Am Coll Cardiol* 2013;**1**:E1922	Registry study
Aradi D, Serebruany VL. No benefit of new-generation antiplatelet agents on stroke compared to clopidogrel. *Eur Heart J* 2011;**32**:555	Abstract of systematic review
Armero S, Bonello L, Berbis J, Camoin-Jau L, Lemesle G, Jacquin L, *et al.* Rate of nuisance bleedings and impact on compliance to prasugrel in acute coronary syndromes. *Am J Cardiol* 2011;**108**:1710–13	Not RCT
Arnesen H. Thrombocardiology: an update. *Expert Rev Cardiovasc Ther* 2010;**8**:331–3	Meeting review
Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. *N Engl J Med* 2013;**368**:2113–24	Review
Beigel R, Fefer P, Fink N, Grupper A, Varon D, Hod H, *et al.* The immediate antiplatelet effect of prasugrel versus clopidogrel in patients undergoing primary angioplasty for ST-elevation myocardial infarction-implications for reperfusion. *J Am Coll Cardiol* 2012;**1**:E503	Platelet function study
Bellemain-Appaix A, Brieger D, Beygui F, Silvain J, Pena A, Cayla G, *et al.* New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention: A meta-analysis. *J Am Coll Cardiol* 2010;**56**:1542–51	Systematic review discussed in main report
Biondi-Zoccai G, D'Ascenzo F, Abbate A, Agostoni P, Modena MG. Agreement between adjusted indirect comparison and simplified network meta-analyses on prasugrel and ticagrelor. *Int J Cardiol* 2011;**151**:228–9. [Reply to Passaro *et al. Int J Cardiol* 2011;**150**:364–7]	Letter
Biondi-Zoccai G, Lotrionte M, Agostoni P, Abbate A, Romagnoli E, Sangiorgi G, *et al.* Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. *Int J Cardiol* 2011;**150**:325–31	Abstract of indirect treatment comparison discussed in main report
Biondi-Zoccai G, Lotrionte M, Moretti C, Sciuto F, Omede P, Abbate A, *et al.* Comparing ticagrelor versus prasugrel for the treatment of patients with acute coronary syndromes: Evidence from a 32,983-patient adjusted indirect comparison meta-analysis. *EuroIntervention* 2010;**6**(Suppl. H)	Indirect treatment comparison discussed in main report
Canadian Agency for Drugs and Technologies in Health. *Clopidogrel, Prasugrel and Ticagrelor in Adults with Acute Coronary Syndrome: a Review of the Clinical Effectiveness*. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2011	Various systematic reviews
Canadian Agency for Drugs and Technologies in Health. *Clopidogrel, Prasugrel and Ticagrelor in Adults with Acute Coronary Syndrome: A Review of the Clinical Effectiveness, Cost Effectiveness and Guidelines*. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2012	Systematic review but not relevant to review
Capodanno D, Tamburino C. Cyphering the statistical and clinical significance of prasugrel in the TRITON-TIMI 38 trial. *Int J Cardiol* 2011;**146**:242–3	Theoretical paper
Cattaneo M. New P2Y12 inhibitors. *Circulation* 2010;**121**:171–9	Discussion
Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, *et al.* Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;**367**:2100–9	Platelet function and tailored treatment trial
De Servi S, Savonitto S. How to explain the reduced cardiovascular mortality in the ticagrelor arm of the PLATO trial? *Int J Cardiol* 2011;**149**:265–7	Discussion
Dowdall M. Clopidogrel treatment prior to percutaneous coronary intervention questioned by results of recent analysis. *Intervent Cardiol* 2013;**5**:13–14	Discussion
Dridi NP, Johansson PI, Clemmensen P, Engstrom T, Radu M, Pedersen F, *et al.* Thrombocytes and individualization of oral antiplatelet treatment after percutaneous coronary intervention (tailor). *J Am Coll Cardiol* 2012;**60**:B215	Platelet function study

Paper	Reason for exclusion
Erlinge D, Ten Berg J, Foley D, Angiolillo DJ, Wagner H, Brown PB, *et al.* Reduction in platelet reactivity with prasugrel 5 mg in low-body-weight patients is noninferior to prasugrel 10 mg in higher-body-weight patients: results from the FEATHER trial. *J Am Coll Cardiol* 2012;**60**:2032–40	Crossover study
Floyd JS, Serebruany VL. Prasugrel as a potential cancer promoter: review of the unpublished data. *Arch Int Med* 2010;**170**:1078–80	Review
Freeman MK. Thienopyridine antiplatelet agents: focus on prasugrel. *Consult Pharm* 2010;**25**:241–257	Review
Garrett AD. Ticagrelor tops prasugrel in pharmacodynamic study. *Drug Top* 2012;**156**:P43.	News article
Ge J, Zhu J, Hong BK, Boonbaichaiyapruck S, Goh YS, Hou CJ, *et al.* Prasugrel versus clopidogrel in Asian patients with acute coronary syndromes: design and rationale of a multi-dose, pharmacodynamic, phase 3 clinical trial. *Curr Med Res Opin* 2010;**26**:2077–85	Dose-ranging trial
Giugliano RP, Braunwald E. The year in non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 2010;**56**:2126–38	Review of guidelines
Giugliano RP, Braunwald E. The year in non ST-segment elevation acute coronary syndrome. *JAm Coll Cardiol* 2011;**58**:2342–54	Review of guidelines
Giugliano RP, Braunwald E. The year in non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 2012;**60**:2127–39	Review of guidelines
Goodwin MM, Desilets AR, Willett KC. Thienopyridines in acute coronary syndrome. *Ann Pharmacother* 2011;**45**:207–17	Review
Greenhalgh J, Bagust A, Boland A, Saborido CM, Fleeman N, McLeod C, *et al.* Prasugrel for the treatment of acute coronary artery syndromes with percutaneous coronary intervention. *Health Technol Assess* 2010;**14**(Suppl. 1)	Short version of TA182 ERG report
Hamilos M, Kochiadakis G, Skalidis E, Igoumenidis N, Saloustros I, Psathakis E, *et al.* Prasugrel is associated with higher levels of P2Y12 blockade and less periprocedural myonecrosis than clopidogrel in patients undergoing coronary angioplasty for stable coronary artery disease. *Eur Heart J* 2012;**33**:41	Not patient group
Hill RA, Chung H, George E, Longson C, Stevens A. Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention: NICE technology appraisal guidance. *Heart* 2010;**96**:1407–8	Discussion of NICE decision
IQWiG. Prasugrel bei akutem Koronarsyndrom. [Prasugrel in the treatment of acute coronary syndrome] Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). IQWiG-Berichte 89; 2011	German HTA
Jakubowski JA, Riesmeyer JS, Close SL, Leishman AG, Erlinge D. TRITON and beyond: new insights into the profile of prasugrel. *Cardiovasc Ther* 2012;**30**:e174–82	Review of prasugrel studies to 2007
Jakubowski JA, Winters KJ, Naganuma H, Wallentin L. Prasugrel: a novel thienopyridine antiplatelet agent. A review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. *Cardiovasc Drug Rev* 2007;**25**:357–74	Review of prasugrel studies up to 2012
Jeong YH, Tantry US, Gurbel PA. Importance of potent P2Y(12) receptor blockade in acute myocardial infarction: focus on prasugrel. *Expert Opin Pharmacother* 2012;**13**:1771–96	Review
Lange CG. Is prasugrel more effective than clopidogrel at preventing future cardiac events? *JAAPA* 2011;**24**:52, 55	Review
Lee DH, Kim MH, Park TH, Park JS, Park K, Zhang HZ, *et al.* Comparison of prasugrel and clopidogrel reloading on high platelet reactivity in clopidogrel-loaded patients undergoing percutaneous coronary intervention (PRAISE-HPR): a study protocol for a prospective randomized controlled clinical trial. *Trials* 2013;**14**:62	Platelet function study
Lopes RD, Becker RC, Alexander JH, Armstrong PW, Califf RM, Chan MY, *et al.* Highlights from the III International Symposium of Thrombosis and Anticoagulation (ISTA), October 14–16, 2010, Sao Paulo, Brazil. *J Thromb Thrombolysis* 2011;**32**:242–66	Meeting review
Lopes RD, Becker RC, Newby LK, Peterson ED, Hylek EM, Granger CB, *et al.* Highlights from the IV International Symposium of Thrombosis and Anticoagulation (ISTA), October 20–21, 2011, Salvador, Bahia, Brazil. *J Thromb Thrombolysis* 2012;**34**:143–63	Meeting review

Paper	Reason for exclusion
Lopes RD, Granger CB. Interpreting the TRITON results in light of the event adjudication process. *Cardiology* 2010;**115**:89–90	Commentary
Lynch DR Jr, Dantzler DM Jr, Zhao D. Prasugrel versus clopidogrel for acute coronary syndromes. *N Engl J Med* 2013;**368**:188	Letter
Manolis AS, Manolis TA, Papadimitriou P, Koulouris S, Melita H. Combined antiplatelet therapy: still a sweeping combination in cardiology. *Cardiovasc Hematol Agents Med Chem* 2013;**1**:136–67	Not RCT
Mariani M, Mariani G, De Servi S. Efficacy and safety of prasugrel compared with clopidogrel in patients with acute coronary syndromes: results of TRITON-TIMI 38 trials. *Expert Rev Cardiovasc Ther* 2009;**7**:17–23	Expert review
Martin MT, Spinler SA, Nutescu EA. Emerging antiplatelet therapies in percutaneous coronary intervention: a focus on prasugrel. *Clin Ther* 2011;**33**:425–42	Review
Mauri L, Kereiakes DJ, Normand SL, Wiviott SD, Cohen DJ, Holmes DR, *et al.* Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. *Am Heart J* 2010;**160**:1035–41	Not comparators of interest
Mohammad RA, Goldberg T, Dorsch MP, Cheng JW. Antiplatelet therapy after placement of a drug-eluting stent: a review of efficacy and safety studies. *Clin Ther* 2010;**32**:2265–81	Review
Montalescot, G. Benefits for specific subpopulations in TRITON-TIMI 38. *Eur Heart J* 2009[Suppl. 11(G)]:G18–24	Discussion
Montalescot G, Collet JP, Vicaut E, Cayla G, Cuisset T, Elhadad S, *et al.* A randomized trial of bedside platelet function monitoring to adjust antiplatelet therapy versus standard of care in patients undergoing drug eluting stent implantation: the ARCTIC study. *Circulation* 2012;**126**:2777	ARCTIC platelet function study
Montalescot G, Sideris G, Cohen R, Meuleman C, Bal dit Sollier C, Barthelemy O, *et al.* Prasugrel compared with high-dose clopidogrel in acute coronary syndrome. The randomised, double-blind ACAPULCO study. *Thromb Haemost* 2010;**103**:213–23	Not patient population
Motovska Z, Kala P. Benefits and risks of clopidogrel use in patients with coronary artery disease: evidence from randomized studies and registries. *Clin Ther* 2008;**30**(part 2):2191–202	Review
Navarese EP, Verdoia M, Schaffer A, Suriano P, Kozinski M, Castriota F, *et al.* Ischaemic and bleeding complications with new, compared to standard, ADP-antagonist regimens in acute coronary syndromes: a meta-analysis of randomized trials. *QJM* 2011;**104**:561–9	Meta-analysis
Neumann FJ. Balancing efficacy and safety in the TRITON-TIMI 38 trial. *Eur Heart J* 2009(Suppl. 11)(G): G14–17	Review
Oberhansli M, Lehner C, Puricel S, Lehmann S, Togni M, Stauffer JC, *et al.* A randomized comparison of platelet reactivity in patients after treatment with various commercial clopidogrel preparations: the CLO-CLO trial. *Arch Cardiovasc Dis* 2012;**105**:587–92	Clopidogrel dosing study
Oh EY, Abraham T, Saad N, Rapp JH, Vastey FL, Balmir E. A comprehensive comparative review of adenosine diphosphate receptor antagonists. *Expert Opin Pharmacother* 2012;**13**:175–91	Systematic review
Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, *et al.* Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol* 2013;**61**:1601–6	Platelet function study
Passaro D, Fadda V, Maratea D, Messori A. Anti-platelet treatments in acute coronary syndrome: simplified network meta-analysis. *Int J Cardiol* 2011;**150**:364–7	Discussed in main body of this AG report
Rabasseda X. A report from the 60th Annual Scientific Session & Expo and I2 (Innovation and Intervention) Summit of the American College of Cardiology April 2–5, 2011 – New Orleans, Louisiana USA). *Drugs Today* 2011;**47**:381–400	Meeting review
Rabasseda X. Highlights from the American College of Cardiology 2012 Annual Meeting: March 24–27, 2012 – Chicago, Illinois, USA. *Drugs Future* 2012;**37**:379–87	Meeting review

Paper	Reason for exclusion
Ramanakumar A, Bajaj R, Singh A, Dani S, Basheer Z, Hannan J. Comparison of prasugrel 60 Mg vs. clopidogrel 600 Mg loading doses in patients undergoing primary PCI for acute STEMI. *Cardiovasc Interv* 2013;**1**:S7	Not randomised
Scott DM, Norwood RM, Parra D. P2Y12 inhibitors in cardiovascular disease: focus on prasugrel. *Ann Pharmacother* 2009;**43**:64–76	Review
Serebruany VL. Excess rates of nonfatal myocardial infarction in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel (preventing clinical events or chasing enzymatic ghosts?). *Am J Cardiol* 2008;**101**:1364–6	Comment
Serebruany VL. Delays of event adjudication in the TRITON trial. *Cardiology* 2010;**115**:217–20	Comment
Serebruany VL. Mortality in the TRITON trial: update from the FDA prasugrel action package. *Am J Cardiol* 2010;**105**:1356–7.	Comment
Serebruany VL. The TRITON versus PLATO trials: differences beyond platelet inhibition. *Thromb Haemost* 2010;**103**:259–61	Comment
Serebruany VL. Timing of thienopyridine loading and outcomes in the TRITON trial: the FDA Prasugrel Action Package outlook. *Cardiovasc Revasc Med* 2011;**12**:94–8	Comment
Serebruany VL, Midei MG, Meilman H, Malinin AI, Lowry DR. Platelet inhibition with prasugrel (CS-747) compared with clopidogrel in patients undergoing coronary stenting: the subset from the JUMBO study. *Postgrad Med J* 2006;**82**:404–10	Comment
Siller-Matula JM, Francesconi M, Dechant C, Jilma B, Maurer G, Delle-Karth G, *et al.* Personalized antiplatelet treatment after percutaneous coronary intervention: The MADONNA study. *Eur Heart J* 2012;**33**:41	Not RCT
Silvain J, Bellemain-Appaix A, Barthelemy O, Beygui F, Collet JP, Montalescot G. Optimal use of thienopyridines in Non-ST-elevation acute coronary syndrome following CURRENT-OASIS 7. *Circulation Cardiovasc Interv* 2011;**4**:95–103	Review
Singh T, Cuomo L, Cohen M, Ahmad HA, Aronow WS. Use of antiplatelet therapy after percutaneous coronary intervention with bare-metal stents and different types of drug-eluting stents. *Curr Clin Pharmacol* 2013;**8**:59–66	Not relevant comparators
Skalli S, Garcia Palop B, Faudel A, Nouvel M, Parat S, Jacob X, *et al.* Are prasugrel and clopidogrel equally effective and safe? *Int J Clin Pharm* 2012;**34**:258	Review
Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ, *et al.* Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. *J Am Coll Cardiol* 2012;**60**:388–96	Subgroup analysis from TRITON-TIMI 38
Sorich MJ, Vitry A, Ward MB, Horowitz JD, McKinnon RA. Prasugrel vs. clopidogrel for cytochrome P450 2C19-genotyped subgroups: integration of the TRITON-TIMI38 trial data. *J Thrombos Haemost* 2010;**8**:1678–84	Genotype study
Spinler SA, Rees C. Review of prasugrel for the secondary prevention of atherothrombosis. *J Manag Care Pharm* 2009;**15**:383–95	Review
Steiner S, Chen L, Coyle D, Wells GA. Indirect treatment comparison of novel antiplatelet drugs directed against the ADP receptor compared to placebo-evaluation by three different statistical approaches. *J Cardio Rehab Prev* 2011;**31**:E8	Abstract of network meta-analysis discussed in present report
Steiner, S, Chen L, Coyle D and Wells GW. Effects of prasugrel, ticagrelor and high dose clopidogrel compared to placebo evaluated by three different statistical approaches for indirect treatment comparisons. *Eur Heart J* 2011;**32**:252	Abstract of network meta-analysis discussed in present report
Steiner S, Chen L, Coyle D, Wells GW. Effects of prasugrel, ticagrelor and high dose clopidogrel compared to placebo evaluated by three different statistical approaches for indirect treatment comparisons. *Eur Heart J* 2011;**32**:252	Network meta-analysis discussed in present report
Steiner S, Moertl D, Chen L, Coyle D, Wells GA. Network meta-analysis of prasugrel, ticagrelor, high- and standard-dose clopidogrel in patients scheduled for percutaneous coronary interventions (provisional abstract). 2012;**108**;318–27	Abstract of network meta-analysis discussed in present report
Storey RF. Pharmacology and clinical trials of reversibly-binding P2Y12 inhibitors. *Thromb Haemost* 2011;**105**(Suppl. 1):75–81	Not RCT

Paper	Reason for exclusion
Storey RF, Bliden KP, Patil SB, Karunakaran A, Ecob R, Butler K, *et al.* Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol* 2010;**56**:185–93	Not intervention
Testa L, Bhindi R, Van Gaal WJ, Latini RA, Pizzocri S, Lanotte S, *et al.* What is the risk of intensifying platelet inhibition beyond clopidogrel? A systematic review and a critical appraisal of the role of prasugrel. *QJM* 2010;**103**:367–77	Systematic review
Ukena C, Bohm M, Schirmer SH. Hot topics in cardiology: Data from IABP-SHOCK II, TRILOGY-ACS, WOEST, ALTIDUDE, FAME II and more. *Clin Res Cardiol* 2012;**101**:861–74	Meeting review
Unger EF. Weighing benefits and risks – the FDA's review of prasugrel. *N Engl J Med* 2009;**361**:942–5	Summary of FDA review
Veverka A, Hammer JM. Prasugrel: a new thienopyridine inhibitor. *J Pharm Pract* 2009;**22**:158–65	Review
Wiviott SD. Intensity of antiplatelet therapy in patients with acute coronary syndromes and percutaneous coronary intervention: the promise of prasugrel? *Cardiol Clin* 2008;**26**:629–37	Discussion
Wiviott SD. Prasugrel: TRITON-TIMI 38 stent trial. *Clin Res Cardiol* 2008;**97**:410	Abstract of TRITON-TIMI 38 substudy
Wiviott SD, Antman EM, Braunwald E. Mortality in the TRITON trial: update from the FDA prasugrel action package. *Am J Cardiol* 2010;**106**:293–4	Response to letter
Wiviott SD, Antman EM, Braunwald E. Prasugrel. *Circulation* 2010;**122**:394–403	Review
Wiviott SD, Antman EM, Winters KJ, Weerakkody G, Murphy SA, Behounek BD, *et al.* Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. *Circulation* 2005;**111**:3366–73	Dose-ranging trial
Wiviott SD, Braunwald E, Murphy SA, Antman EM, Investigators T-T. A perspective on the efficacy and safety of intensive antiplatelet therapy in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38. *Am J Cardiol* 2008;**101**:1367–70	Response to letter
Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, *et al.* Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;**116**:2923–32	Crossover trial
Wouter Jukema J, Collet JP, De Luca L. Antiplatelet therapy in patients with ST-elevation myocardial infarction undergoing myocardial revascularisation: beyond clopidogrel. *Curr Med Res Opin* 2012;**28**:203–11	Review
Xanthopoulou I, Theodoropoulos KF, Kassimis G, Gizas V, Tsigkas G, Koutsogiannis N, *et al.* Ticagrelor vs prasugrel in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Eur Heart J* 2012;**33**:41	Platelet function study
Yokoi H, Kimura T, Isshiki T, Ogawa H, Ikeda Y. Pharmacodynamic assessment of a novel P2Y12 receptor antagonist in Japanese patients with coronary artery disease undergoing elective percutaneous coronary intervention. *Thrombos Res* 2012;**129**:623–8	Not patient group

ARCTIC, The Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting.

Appendix 4 Selected data taken from Evidence Review Group report for TA182 appraisal

All data are for the overall population unless otherwise stated.

Summary of baseline characteristics of patients in TRITON-TIMI 38

Characteristic	Prasugrel ($n = 6813$)	Clopidogrel ($n = 6795$)
UA or NSTEMI (%)	74	74
STEMI (%)	26	26
Age (median) (years)	61	61
≥ 75 years (%)	13	13
Female (%)	25	27
White race (%)	92	93
Region of enrolment (%)		
North America	32	32
Western Europe	26	26
Eastern Europe	24	25
Middle East, Africa, Asia-Pacific	14	14
South America	4	4
Medical history (%)		
Hypertension	64	64
Hypercholesterolaemia	56	56
Diabetes mellitus	23	23
Tobacco use	38	38
Previous MI	18	18
Previous CABG	8	7
Creatinine clearance < 60 ml/minute	11	12
Index procedure (%)		
PCI	99	99
CABG	1	1
Stent	94	95
Bare-metal stent only	48	47
≥ 1 drug-eluting stent	47	47
Multivessel PCI	14	14

Characteristic	Prasugrel ($n = 6813$)	Clopidogrel ($n = 6795$)
Timing of study drug administration (%)[a]		
Before PCI	26	25
During PCI	73	74
After PCI	1	1

a Administration of the study drug before PCI occurred before the first coronary guidewire was placed during the index PCI; administration during PCI occurred after the first coronary guidewire was placed or within 1 hour after the patient was taken from the cardiac catheterisation laboratory; and administration after PCI occurred more than 1 hour after the patient was taken from the cardiac catheterisation laboratory.
Patients could have had more than one type of medical history, undergone more than one type of index procedure, or received more than one type of pharmacotherapy during index hospitalisation.

Primary end point analysis

These results are for the overall trial population ($n = 13,608$), which includes patients with a history of stroke or TIA. At the end of the trial period, there was a statistically significant reduction in the primary end point in the prasugrel arm compared with the clopidogrel arm. This result was largely attributable to differences in the occurrence of non-fatal MI. The ERG notes that there are no statistically significant differences in mortality (CV death or death from all causes) or non-fatal stroke between the groups.

TRITON-TIMI 38: efficacy results at 15 months (overall cohort)

End point	Clopidogrel ($N = 6795$) *n* (%)	Prasugrel ($N = 6813$) *n* (%)	HR (95% CI)	*p*-value[a]
Primary				
Death from CV causes, non-fatal MI or non-fatal stroke	781 (12.1)	643 (9.9)	0.81 (0.73 to 0.90)	< 0.001
Death from CV causes	150 (2.4)	133 (2.1)	0.89 (0.70 to 1.12)	0.31
Non-fatal MI	620 (9.5)	475 (7.3)	0.76 (0.67 to 0.85)	< 0.001
Non-fatal stroke	60 (1.0)	61 (1.0)	1.02 (0.71 to 1.45)	0.93
Secondary				
Death from any cause	197 (3.2)	188 (3.0)	0.95 (0.78 to 1.16)	0.64
Death from CV causes, non-fatal MI or UTVR	798 (12.3)	652 (10.0)	0.81 (0.73 to 0.89)	< 0.001
Death from CV causes	150 (2.4)	133 (2.1)	0.89 (0.70 to 1.12)	0.31
Non-fatal MI	620 (9.5)	475 (7.3)	0.76 (0.67 to 0.85)	< 0.001
UTVR	233 (3.7)	156 (2.5)	0.66 (0.54 to 0.81)	< 0.001
Stent thrombosis[b]	142 (2.4)	68 (1.1)	0.48 (0.36 to 0.64)	< 0.001
Death from CV causes, non-fatal MI, non-fatal stroke or rehospitalisation for ischaemia	938 (14.6)	797 (12.3)	0.84 (0.76 to 0.92)	< 0.001

a Taken from published paper.[36]
b Stent thrombosis defined as definite or probable according to the Academic Research Consortium.
p-values were calculated using the log-rank test. The analysis for the primary end point used the Gehan–Wilcoxon test for which the *p*-value was < 0.
The percentages are Kaplan–Meier estimates of the rate of each end point at 15 months. As the Kaplan–Meier method takes into account censored data (i.e. sample losses before the final outcome occurs), each percentage does not correspond to the numerator divided by the denominator (because the denominator does not account for censored data).
Patients could have had more than one type of end point.

Secondary end points

Statistically significant reductions in favour of prasugrel were found for three secondary clinical end points: (1) composite end point of CV death, non-fatal MI or UTVR; (2) composite end point of death from CV causes, non-fatal MI, non-fatal stroke or rehospitalisation for ischaemia; and (3) stent thrombosis.

Results of the secondary analyses in respect of the primary composite end point were presented at 3 days, 30 days, 90 days and day 4 to day 90. The CEs all show a statistically significant benefit of prasugrel over time.

TRITON-TIMI: primary efficacy outcomes at 3 days, 30 days, 90 days and day 4 to day 90 (overall cohort)

End point	Time	Clopidogrel (*N* = 6795) (%)	Prasugrel (*N* = 6813) (%)	HR for prasugrel (95% CI)	*p*-value
Death from CV causes, non-fatal MI, non-fatal stroke	3 days	5.6	4.7	0.82 (0.71 to 0.96)	< 0.01
	30 days	7.4	5.7	0.77 (0.67 to 0.88)	< 0.01
	90 days	8.4	6.8	0.80 (0.71 to 0.90)	< 0.001
	Day 4 to 90	6.9	5.6	0.80 (0.70 to 0.93)	< 0.003
Death from CV causes, non-fatal MI, UTVR	30 days	7.4	5.9	0.78 (0.69 to 0.89)	< 0.01
	90 days	8.7	6.9	0.79 (0.70 to 0.90)	< 0.01

Patients could have had more than one type of end point.

Prespecified subgroup analyses

The subgroups included in the MS are as follows: UA/NSTEMI, STEMI, males, females, < 65 years, 65–74 years, ≥ 75 years, diabetes mellitus, type of stent, use of glycoprotein IIb/IIIa receptor antagonist, and renal function. The MS presents a forest plot showing the primary efficacy end point results within selected subgroups for the overall trial cohort. The forest plot shows a statistically significant benefit of prasugrel for all subgroups with the exception of females, patients aged ≥ 65 years and patients with creatinine clearance of < 60 ml/minute.

ST segment elevation myocardial infarction patient subgroup

The MS presents data relevant to the STEMI cohort. The relevant text can be found on page 53 of the MS. It is emphasised in the MS that the trial was not powered to compare the effects of prasugrel with clopidogrel in the STEMI population. A total of 3534 STEMI patients were randomised. The primary end point (CV death, non-fatal MI or non-fatal stroke) was statistically significantly reduced with prasugrel at 30 days (HR 0.68, $p = 0.002$) and 15 months (HR 0.79, 95% CI 0.65 to 0.97; $p = 0.02$). The secondary end point (CV death, MI or UTVR) was also statistically significantly reduced with prasugrel at 30 days ($p = 0.02$) and 15 months ($p = 0.03$). Stent thrombosis and the composite of CV death or non-fatal MI were reported to be statistically significantly reduced with prasugrel at 30 days and 15 months.

At 15 months, no statistically significant difference was reported between the prasugrel arm and the clopidogrel arm of the trial for non-CABG-related TIMI major bleeding (HR 1.11, 95% CI 0.70 to 1.77; $p = 0.65$). The MS concludes that for STEMI patients who are treated with PCI, prasugrel offers a greater reduction in ischaemic events without an excess risk in major bleeding.

Primary efficacy results for the unstable angina/non-ST segment elevation myocardial infarction, ST segment elevation myocardial infarction and all acute coronary syndrome groups in the TRITON-TIMI 38 trial

TRITON-TIMI 38: primary efficacy for unstable angina/non-ST segment elevation myocardial infarction, ST segment elevation myocardial infarction and all acute coronary syndrome groups (European Public Assessment Report)

Primary efficacy end point and components at study end

Event	Prasugrel, *n* (%)[a]	Clopidogrel, *n* (%)[a]	HR (95% CI)[b]	*p*-value[c]
UA/NSTEMI	**N = *5044***	**N = *5030***		
CV death, non-fatal MI or non-fatal stroke	469 (9.30)	565 (11.23)	0.820 (0.726 to 0.927)	0.002
CV death	90 (1.78)	92 (1.83)	0.979 (0.732 to 1.309)	0.885
Non-fatal MI	357 (7.08)	464 (9.22)	0.761 (0.663 to 0.873)	< 0.001
Non-fatal stroke	40 (0.79)	41 (0.82)	0.979 (0.633 to 1.513)	0.922
All cause death	130 (2.58)	121 (2.41)	1.076 (0.840 to 1.378)	0.563
All MI	366 (7.26)	476 (9.46)	0.760 (0.663 to 0.871)	< 0.001
All stroke	49 (0.97)	46 (0.91)	1.068 (0.714 to 1.597)	0.748

Event	Prasugrel, *n* (%)[a]	Clopidogrel, *n* (%)[a]	HR (95% CI)[b]	*p*-value[c]
STEMI	**N = *1769***	**N = *1765***		
CV death, non-fatal MI or non-fatal stroke	174 (9.84)	216 (12.24)	0.793 (0.649 to 0.968)	0.019
CV death	43 (2.43)	58 (3.29)	0.738 (0.497 to 1.094)	0.129
Non-fatal MI	118 (6.67)	156 (8.84)	0.746 (0.588 to 0.948)	0.016
Non-fatal stroke	21 (1.19)	19 (1.08)	1.097 (0.590 to 2.040)	0.770
All cause death	58 (3.28)	76 (4.31)	0.759 (0.539 to 1.068)	0.113
All MI	119 (6.73)	157 (8.90)	0.748 (0.589 to 0.949)	0.016
All stroke	26 (1.47)	25 (1.42)	1.032 (0.596 to 1.787)	0.911
All ACS	**N = *6813***	**N = *6795***		
CV death, non-fatal MI or non-fatal stroke	643 (9.44)	781 (11.49)	0.812 (0.732 to 0.902)	< 0.001
CV death	133 (1.95)	150 (2.21)	0.886 (0.701 to 1.118)	0.307
Non-fatal MI	475 (6.97)	620 (9.12)	0.757 (0.672 to 0.853)	< 0.001
Non-fatal stroke	61 (0.90)	60 (0.88)	1.016 (0.712 to 1.451)	0.930
All cause death	188 (2.76)	197 (2.90)	0.953 (0.781 to 1.164)	0.639
All MI	485 (7.12)	633 (9.32)	0.757 (0.673 to 0.852)	< 0.001
All stroke	75 (1.10)	71 (1.04)	1.055 (0.763 to 1.460)	0.745

a Percentage of randomly assigned subjects reaching the primary end point.
b HR and a 95% CI used as an estimate of overall RR, prasugrel compared with clopidogrel, over the course of the study.
c Two-sided *p*-values are based on Gehan–Wilcoxon test comparing event free survival distributions of prasugrel and clopidogrel for the composite primary end point. The individual components of the end points were tested using log-rank test. Clinical presentation, UA/NSTEMI compared with STEMI, was used as a stratification factor in analysis involving all ACS subjects.

Patients with diabetes mellitus

TRITON-TIMI 38: clinical events by diabetic status

End point	Clopidogrel (%)	Prasugrel (%)	HR (95% CI)	*p*-value	*p*-value for the subgroup analyses that compare diabetes with no diabetes
Patients without diabetes mellitus	**N = *5225***	**N = *5237***			
Primary efficacy end point of death from CV causes, non-fatal MI or non-fatal stroke	10.6	9.2	0.86 (0.76 to 0.98)	0.02	
Death from CV causes or MI	10.0	8.5	0.85 (0.75 to 0.97)	0.01	
Fatal or non-fatal MI	8.7	7.2	0.82 (0.72 to 0.95)	0.006	
Death from CV causes	1.9	1.7	0.91 (0.68 to 1.23)	0.53	
Stent thrombosis	2.0	0.9	0.45 (0.31 to 0.65)	< 0.001	
Death from CV causes, non-fatal MI, non-fatal stroke or major bleeding event	12.3	11.5	0.92 (0.82 to 1.03)	0.16	
Patients with diabetes mellitus	**N = *1570***	**N = *1576***			
Primary efficacy end point of death from CV causes, non-fatal MI or non-fatal stroke	17.0	12.2	0.70 (0.58 to 0.85)	< 0.001	0.09
Death from CV causes or MI	15.4	10.8	0.68 (0.56 to 0.84)	< 0.001	0.08
Fatal or non-fatal MI	13.2	8.2	0.60 (0.48 to 0.76)	< 0.001	0.02
Death from CV causes	4.2	3.4	0.85 (0.58 to 1.24)	0.40	0.78
Stent thrombosis	3.6	2.0	0.52 (0.33 to 0.84)	0.007	0.63
Death from CV causes, non-fatal MI, non-fatal stroke or major bleeding event	19.2	14.6	0.74 (0.62 to 0.89)	0.001	0.05

Event rates are reported using Kaplan–Meier estimates at 450 days. Comparisons are expressed as HRs and 95% CIs including the entire duration of follow-up. Testing for an interaction between the efficacy of prasugrel compared with clopidogrel and diabetic status was performed by constructing a Cox proportional-hazards model using terms for both the main effect and the interaction.
Reproduced from MS.

TRITON-TIMI 38: bleeding rates by diabetes mellitus status

End point	Patients with diabetes mellitus ($n = 3146$) %	Patients without diabetes mellitus ($n = 10,462$) %	HR (95% CI)	*p*-value
Major non-CABG-related bleeding event	2.6	2.0	1.28 (0.97 to 1.68)	0.08
Major non-CABG-related or minor bleeding event	4.8	4.2	1.15 (0.95 to 1.41)	0.15

Reproduced from MS.

TRITON-TIMI 38: bleeding rates for prasugrel compared with clopidogrel by diabetes mellitus status

End point	Clopidogrel %	Prasugrel %	HR (95% CI)	*p*-value	*p*-value for the subgroup analyses that compare diabetes with no diabetes
Patients without diabetes mellitus	**N = *5225***	**N = *5237***			
Major non-CABG-related bleeding event	1.6	2.4	1.43 (1.07 to 1.91)	0.02	
Major non-CABG-related or minor bleeding event	3.6	4.9	1.32 (1.08 to 1.61)	0.006	
Patients with diabetes mellitus	**N = *1570***	**N = *1576***			
Major non-CABG-related bleeding event	2.6	2.5	1.06 (0.66 to 1.69)	0.81	0.29
Major non-CABG-related or minor bleeding event	4.3	5.3	1.30 (0.92 to 1.82)	0.13	0.93

Reproduced from MS.

Patients with stents

In this group, 6461 patients received bare-metal stents, 5743 patients received drug-eluting stents and 640 patients received both types of stent. In the 'stented' group as a whole, the occurrence of the primary end point was reduced in the prasugrel arm compared with the clopidogrel arm (9.7% compared with 11.9%, HR 0.81; $p = 0.0001$). Similar results were reported for drug-eluting stents and bare-metal stents.

Efficacy and bleeding and net clinical benefit in selected subpopulations

TRITON-TIMI 38: efficacy, bleeding and net clinical benefit in selected populations

End point	Clopidogrel *n/N* (%)	Prasugrel *n/N* (%)	HR for prasugrel (95% CI)	*p*-value
History of stroke or TIA				
Death from CV causes, non-fatal MI, non-fatal stroke (primary efficacy end point)	35/256 (14.4)	47/262 (19.1)	1.37 (0.89 to 2.13)	0.15
Non-CABG-related TIMI major bleeding	6/252 (2.9)	14/257 (5.0)	2.46 (0.94 to 6.42)	0.06
Death from any cause, non-fatal MI, non-fatal stroke, or non-CABG-related non-fatal TIMI major bleeding	39/256 (16.0)	57/262 (23.0)	1.54 (1.02 to 2.32)	0.04
Aged ≥ 75 years, body weight < 60 kg, or history of stroke or TIA				
Death from CV causes, non-fatal MI, non-fatal stroke (primary efficacy end point)	199/1347 (16.0)	198/1320 (16.1)	1.02 (0.84 to 1.24)	0.83
Non-CABG-related TIMI major bleeding	38/1328 (3.3)	52/1305 (4.3)	1.42 (0.93 to 2.15)	0.10
Death from any cause, non-fatal MI, non-fatal stroke, non-CABG-related non-fatal TIMI major bleeding	239/1347 (19.0)	249/1320 (20.2)	1.07 (0.90 to 1.28)	0.43

The percentages are Kaplan–Meier estimates of the rate of each end point at 15 months. As the Kaplan–Meier method takes into account censored data (i.e. sample losses before the final outcome occurs), each percentage does not correspond to the numerator divided by the denominator (because the denominator does not account for censored data). Reproduced from MS.

TRITON-TIMI 38 recurrent events analysis

This analysis compared the number of subsequent events (after the first event within the primary end point) that occurred within each arm of the trial. More subsequent events were recorded in the clopidogrel arm than in the prasugrel arm (115 compared with 58; $p < 0.001$).

Appendix 5 Publications related to the TRITON-TIMI 38 trial

Author/year	Title	Description
Wiviott *et al.* 2006[41]	Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimising platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38)	Paper describing the design of the TRITON-TIMI 38 trial
Wiviott *et al.* 2007 [36]	Prasugrel versus clopidogrel in patients with acute coronary syndromes	Primary publication of TRITON-TIMI 38 trial
Wiviott *et al.* 2011[42]	Efficacy and safety of intensive antiplatelet therapy with prasugrel from TRITON-TIMI 38 in a core clinical cohort defined by worldwide regulatory agencies	Paper describing outcomes of 'core clinical cohort' of patients from TRITON-TIMI 38 trial: patients no known history of stroke or TIA, aged below 75 years and weighing more than 60 kg. The core clinical cohort represent 10,804 of the 13,608 patients included in the overall trial cohort
Antman *et al.* 2008[105]	Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis	Paper reporting on the effects of both the loading dose and the maintenance dose of prasugrel in the TRITON-TIMI 38 trial ($n = 13,608$)
Bonaca *et al.* 2012[54]	American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation universal definition of myocardial infarction classification system and the risk of cardiovascular death: observations from the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38)	Paper reporting the risk of CV death for patients in the TRITON-TIMI 38 trial according to the individual MI subtypes defined in the universal definition of MI classification system
Hochholzer *et al.* 2011[106]	Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI-38)	Paper reporting the major predictors of serious bleeding in patients in the TRITON-TIMI 38 trial
Laynez *et al.* 2011[107]	Safety and efficacy for the use of prasugrel in patients undergoing percutaneous coronary intervention and anticoagulated with bivalirudin	Paper presenting the results of a study that compared prasugrel and clopidogrel antiplatelet therapy in patients with ACS undergoing PCI with bivalirudin, rather than heparin, anticoagulation
[a]Mega *et al.* 2009[108]	Cytochrome *p*-450 polymorphisms and response to clopidogrel	Paper reporting an analysis of clinical outcomes for clopidogrel-treated patients who could be classified as carriers or non-carriers of the reduced function CYP2C19 allele ($n = 1459$)
Mega *et al.* 2010[109]	Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis	Paper reporting an analysis of the association between ABCB1 3435C->T and reduced function alleles of CYP2C19 ($n = 2932$ patients) and clinical outcomes in the TRITON-TIMI 38 trial
Michelson *et al.* 2009[110]	Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial	Paper reporting the outcome of analyses of platelet function between prasugrel- and clopidogrel-treated patients ($n = 125$) in the TRITON-TIMI 38 trial

Author/year	Title	Description
Montalescot *et al.* 2009[55]	Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial	Paper reporting the clinical outcomes for the STEMI subgroup of patients ($n = 3534$) from the TRITON-TIMI 38 trial
Morrow *et al.* 2009[52]	Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction	Paper reporting the reassessment of the MIs recorded in the TRITON-TIMI 38 trial using a new universal definition of MI developed by the Joint task force of the ESC, American College of Cardiology Foundation, American Heart Association and World Heart Federation
Murphy *et al.* 2008[111]	Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial	Paper reporting on the efficacy of prasugrel compared with clopidogrel in reducing the occurrence of subsequent ischaemic events (following a non-fatal trial event) in the Reduction in recurrent CV events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial
O'Donoghue *et al.* 2009[112]	The efficacy and safety of prasugrel with and without a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) analysis	Paper reporting clinical outcomes for patients who did and did not receive treatment with glycoprotein IIb/IIIa inhibitors during the PCI procedure in the TRITON-TIMI 38 trial
[a]O'Donoghue *et al.* 2009[113]	Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials	Paper reporting clinical outcomes for patients who were treated with proton-pump inhibitors in the PRINCIPLE-TIMI 44 trial ($n = 201$) and the TRITON-TIMI 38 trial ($n = 4529$)
Pride *et al.* 2009[114]	Effect of prasugrel versus clopidogrel on outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention without stent implantation: a TRial to assess Improvement in Therapeutic Outcomes by optimising platelet inhibitioN with prasugrel (TRITON)-Thrombolysis in Myocardial Infarction (TIMI) 38 substudy	Paper reporting the clinical outcomes of patients ($n = 569$) who did not receive stents as part of the PCI procedure in the TRITON-TIMI 38 trial
Pride *et al.* 2010[115]	Angiographic and clinical outcomes among patients with acute coronary syndromes presenting with isolated anterior ST-segment depression: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) substudy	Paper reporting clinical outcomes for a subgroup of patients ($n = 1198$) with isolated anterior ST-segment depression on 12-lead electrocardiogram in the TRITON-TIMI 38 trial
Riesmeyer *et al.* 2012[116]	Relationship between exposure to prasugrel active metabolite and clinical outcomes in the TRITON-TIMI 38 substudy	Paper reporting the outcomes of a study designed to identify the effect of increased exposure to the prasugrel active on bleeding risk
Ruff *et al.* 2012[117]	Safety and efficacy of prasugrel compared with clopidogrel in different regions of the world	To determine whether or not there were differential effects of prasugrel compared with clopidogrel in the TRITON-TIMI 38 study according to geographical region

Author/year	Title	Description
Scirica *et al.* 2012[118]	Timing and clinical setting of cardiovascular death or myocardial infarction following PCI for ACS-observations from the TRITON-TIMI 38 trial	Paper reporting the outcomes of an analysis from the TRITON-TIMI 38 study of the time of occurrence of new cardiac events (MI/stent thrombosis) and the setting of those events (peri procedural/procedural/spontaneous)
Smith *et al.* 2012[119]	Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis	The objective of this study was to characterise the bleeding, transfusion and other outcomes of patients related to the timing of prasugrel or clopidogrel withdrawal before CABG
Udell *et al.* 2011[120]	Benefit of prasugrel in ST-elevation myocardial infarction according to timing of percutaneous coronary intervention: Insight from the TRITON-TIMI 38 study	Conference abstract reporting the clinical outcomes of the STEMI subgroup of patients ($n = 3534$) from the TRITON-TIMI 38 trial. A sensitivity analysis that after the exclusion of procedural MIs
Wiviott *et al.* 2008[121]	Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38	Paper reporting the clinical outcomes for the subgroup of patients with diabetes mellitus ($n = 3146$) from the TRITON-TIMI 38 trial
Wiviott *et al.* 2008[122]	Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a sub-analysis of a randomised trial	Paper reporting the outcomes for the subgroup of patients from the TRITON-TIMI 38 trial who were treated with stents ($n = 12,844$)
Wrishko *et al.* 2009[123]	Population pharmacokinetic analyses to evaluate the influence of intrinsic and extrinsic factors on exposure of prasugrel active metabolite in TRITON-TIMI 38	Pharmacodynamic substudy of TRITON-TIMI 38

PRINCIPLE-TIMI, Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation – Thrombolysis in Myocardial Infarction.
a Excluded at stage 1 but included here for completeness.

Appendix 6 Definition of the decision problem and patient populations and details of the independent economic model

Definition of the decision problem and patient populations

This section is relevant to Sections 4.1 and 6.3.2 of the Assessment Report[124] and is intended to provide the rationale for the specific patient populations considered by the AG in the Assessment Report.

The final scope[7] issued by NICE (described in table 4 of the Assessment Report) for this appraisal identifies the relevant population as patients with ACS undergoing primary or delayed PCI. It further states that if the evidence allows, subgroups of patients will be considered, including people with UA/NSTEMI, STEMI and people with diabetes mellitus. Finally, the scope specifies that guidance will only be issued in accordance with the marketing authorisation.

The remit of the AG was to appraise the clinical effectiveness and cost-effectiveness of prasugrel within its licensed indication for the treatment of ACS with PCI and was a review of an existing technology appraisal, TA182.[21]

No new RCT evidence for prasugrel has been published and the clinical evidence base for the effectiveness of prasugrel remains unchanged from that considered for TA182.[21] The AG has therefore taken its starting position for this multiple technology appraisal as a reassessment of the evidence from TA182.[21]

Core clinical cohort

The evidence for TA182[21] was based on a single RCT, the TRITON-TIMI-3836 trial. The TRITON-TIMI-38[36] trial included 13,608 patients with ACS who were to be treated with PCI. The relevance of the evidence from the overall TRITON-TIMI 38[36] trial population was constrained by the marketing authorisation, which excludes patients with prior stroke or TIA and patients with active peptic ulcer disease, and restricts use in patients over the age of 75 years and in those weighing < 60 kg to a lower 5-mg dose to limit the risk of severe bleeding.

In their evidence submission for TA182,[21] the manufacturer identified a reduced population from the TRITON-TIMI-38[36] trial that they referred to as the 'target population', and the manufacturer considered the 'target population' to be the most relevant for providing data for the development of the economic model. The ERG and the AC agreed with this selection, as the excluded patients were either explicitly excluded from the marketing authorisation or were not supported by trial evidence (as the trial was based on the full 10-mg dose). It is therefore this 'target population' that is the focus of the Assessment Report and is described as the 'core clinical cohort' in the manufacturer's latest evidence submission (review of TA182[2]). This cohort comprised 10,804 (79%) patients from the overall trial population.

Specific subpopulations identified in the Assessment Report

During the process of TA182,[2] an appraisal consultation document was issued (June 2009) that restricted the use of prasugrel to patients undergoing PCI as primary treatment for patients with a STEMI event, as well as those suffering stent thrombosis while under treatment with clopidogrel. In a response to the appraisal consultation document, the manufacturer of prasugrel suggested that several other high-risk patient groups should also be considered, in particular those diagnosed with diabetes.

In preparation for the second meeting of the AC, the Chairperson requested that the ERG should provide cost-effectiveness estimates relating to four mutually exclusive subgroups defined by the type of index event (STEMI compared with UA/NSTEMI) and whether or not patients were diagnosed with diabetes mellitus. These results were provided by the ERG and then considered by the AC. The AC concluded that prasugrel could be recommended for three of the four subgroups, but that the results for UA/NSTEMI non-diabetic patients did not support a positive recommendation.

As the evidence base has not changed since the publication of TA182,[2] the AG has taken the view that the review of the existing guidance should involve a reassessment of the same subgroups of the same trial cohort and has developed its economic model on this basis.

Independent economic model

The purpose of this section is to provide further information relevant to the independent economic model in respect of the model design and structure (section 6.3.4 of the Assessment Report), the data source for the key patient groups of the core clinical cohort (page 36 of the Assessment Report) and parameter sources and values (section 6.3.6 of the Assessment Report).

The manufacturer's decision model comprises two parts:

- a statistical model to represent the main clinical outcomes of the trial during the first 12 months of follow-up until the trial treatments clopidogrel or prasugrel have finished
- a long-term model based on modified life table data to represent survival for up to an additional 39 years.

The AG found the short-term statistical model to be an accurate representation of the reported trial outcomes and was content to employ the results of this part of the manufacturer's model unaltered. The specifications of the statistical outcome functions are shown in table 17 of the AG report. However, the AG considers that the long-term life table extrapolation is unrealistically simple and does not adequately represent the likelihood of patients suffering multiple additional CV events in their lifetime and the associated disutility and costs associated with such events.

The AG has therefore extracted the outcomes from the manufacturer's short-term model for the four mutually exclusive subgroups of the 'core clinical cohort' and employed these as the initial conditions for surviving patients entering the AG's long-term state-transition model.

The details of these outcome data from the manufacturer's short-term model are fully described in table 28 of the AG report, covering 10,314 patients in the original 'core clinical cohort' (but excluding additionally those with peptic ulcer disease who had been previously included in the manufacturer's analysis despite the explicit contraindication shown in the SPC). Costs, survival time and utility/disutility values during the first year (short term) are estimated on the same basis as in the AG's long-term model. Specific clinical data relating to patients with STEMI, UA/NSTEMI or diabetes mellitus in the core clinical cohort were not available from the MS or the most recent publication.

The possible interstate transitions from year to year in the AG's long-term model are represented in detail in table 27 of the AG report. *Figure 16* provides a graphic representation.

The main source of data used to populate the AG's long-term model is the CAPRIE[92] clinical trial. This was a double-blind placebo comparison of clopidogrel with aspirin involving 19,185 patients with atherosclerotic vascular diseases manifested as either ischaemic stroke (IS), MI or symptomatic peripheral arterial disease. Only CAPRIE[92] data from 5741 MI patients without prior history of other vascular events were used to populate the AG's long-term model. Follow-up of patients continued for up to 3 years

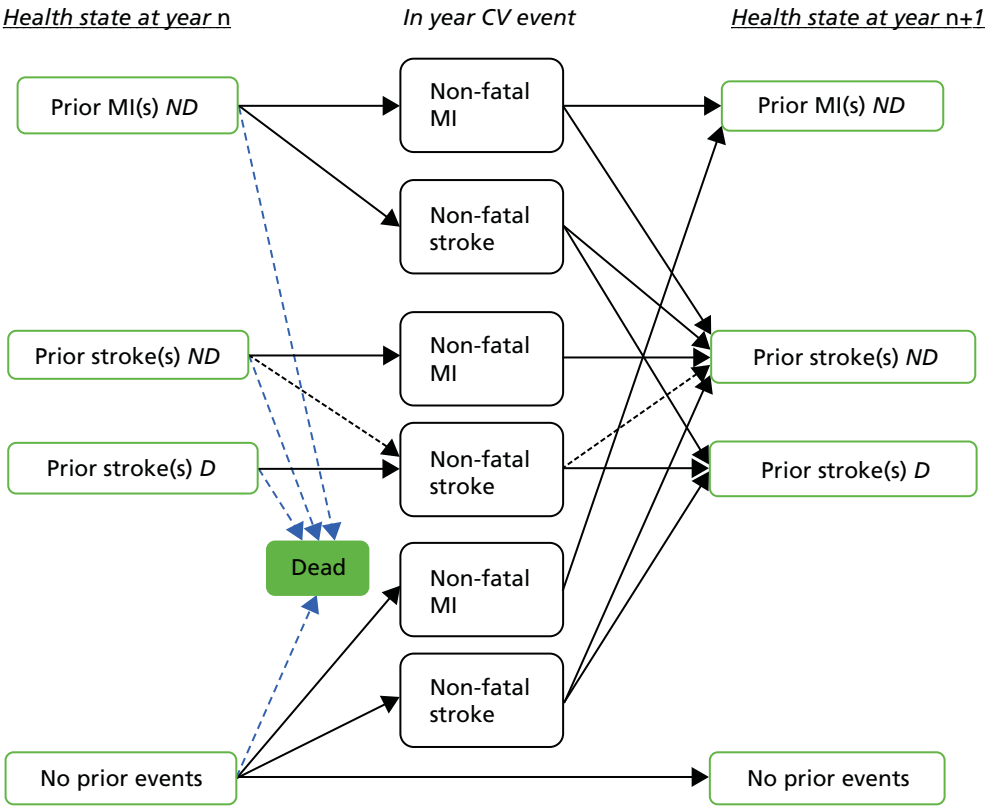

FIGURE 16 If no event occurs in year, the patient remains in the same health state. D, disabled; ND, not disabled. Boxes with green edges represent health states; boxes with black edges represent events. Green shading represents a 'sink state' and boxes without shading represent temporal states. The dashed lines linking 'prior stroke ND' states at the beginning and end of a year indicate that a new non-disabling stroke event can occur. The blue dashed lines represent the transition to death. The solid lines linking 'prior stroke D' states at the beginning and end of a year indicate that this pathway is mandatory for any patient who suffered a prior disabling stroke, regardless of the severity of stroke suffered during the year.

(mean 1.9 years). The primary outcome was the first occurrence of IS, MI or vascular death. Secondary outcomes included: the first occurrence of IS, MI, amputation or vascular death; vascular death; overall net benefit; any stroke (including primary intracranial haemorrhage), MI or death from any cause; and death from any cause.

The manufacturer of clopidogrel kindly carried out extensive reanalyses of the CAPRIE[92] trial data as specified by the AG, in order to estimate independent event hazards adjusted to age, sex and event history. Full details of the estimated event rates (appendix 10) and event fatality rates (appendix 11) are provided in the full AG report for TA210.

Appendix 7 Details of the PLATelet inhibition and patient Outcomes trial

Key trial characteristics

The recommendations made in the NICE guidance TA236[22] were based on a single RCT known as the PLATO[33] trial. The PLATO[33] trial was an international, multicentre, double-blind, double-dummy Phase III trial comparing ticagrelor plus aspirin with clopidogrel plus aspirin in 18,624 patients admitted to hospital with ACS with or without STEMI. It is important to note that patients were randomised to the trial irrespective of planned intervention and, therefore, the patient population included ACS patients who were to be medically managed as well as those who were to undergo PCI. The trial follow-up was for 12 months, however, the AG notes that the trial protocol stipulated that once the requisite number of events (1780) had accrued, patients were required to leave the trial after their 6-month or 9-month visit. The key trial characteristics are described in the table below.

PLATO trial key characteristics

PLATO trial design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes

• RCT, Phase III, international, double-blind, double-dummy
• 43 countries including UK (18 centres, 281 patients)
• 18,624 patients admitted to hospital with ACS, with or without ST-segment elevation
	• Ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) + ASA
	• Clopidogrel (300-mg to 600-mg loading dose, 75-mg daily thereafter) + ASA
	
	ASA dosing
	
	• Most patients received 75–100 mg daily unless they could not tolerate the drug. For those who had not previously been receiving ASA, 325 mg was the preferred loading dose; 325 mg was also permitted as the daily dose for 6 months after stent placement
		• Patients hospitalised for an ACS, with ST-segment elevation or new LBBB during previous 24 hours
		• Patients hospitalised without ST-segment elevation during the previous 24 hours with at least two of the following:
		• ST-segment changes indicative of ischaemia
		• a positive test for a biomarker indicative of myocardial necrosis
		• one of several risk factors (age > 60 years; previous MI or CABG; coronary artery disease with stenosis ≥ 50%; previous IS, TIA, carotid stenosis ≥ 50% or previous cerebral revascularisation; diabetes mellitus; peripheral vascular disease; or renal dysfunction)
			• Any contraindication against the use of clopidogrel
			• Fibrinolytic therapy within 24 hours before randomisation
			• Need for oral anticoagulation therapy
			• Increased risk of bradycardia without an implanted pacemaker
			• Concomitant therapy with a strong cytochrome P450 3A inhibitor or inducer
				• 12-month planned follow-up or until 1780 events had occurred
				• Primary
				  ○ Composite end point of death from vascular causes, MI or stroke
				• Secondary
				  ○ Primary end point in patients for who early invasive management was planned at randomisation
				  ○ Composite end point of death from vascular causes, MI, stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemic, TIA or other arterial thrombotic events
				  ○ MI
				  ○ Death from vascular causes
				  ○ Stroke
				  ○ Death from any cause

ASA, aspirin; LBBB, left bundle branch block; TIA, transitory ischaemic attack.

PLATelet inhibition and patient Outcomes trial outcomes

The results of the PLATO[33] trial for the overall trial population at 12 months showed a statistically significant benefit of ticagrelor was found for the primary composite end point [9.8% compared with 11.67% (HR 0.84, 95% CI 0.77 to 0.92; $p < 0.001$)]. When the individual components of the composite end point are disaggregated, the reduction in the primary end point is driven by statistically significant reductions in death from vascular causes (HR 0.79, 95% CI 0.69 to 0.91; $p = 0.001$) and MI (HR 0.84, 95% CI 0.75 to 0.95; $p = 0.005$).

A novel system for categorising bleeding events was utilised in the PLATO[33] trial. There were no statistically significant differences between the two arms of the trial for the end points of PLATO major bleed (primary safety end point) and PLATO major fatal/life-threatening bleed; however, statistically significant differences in favour of clopidogrel are in evidence for the end points of PLATO total major + minor bleed (HR 1.11, 95% CI 1.03 to 1.20; p=0.008) and PLATO non-CABG major bleed (HR 1.19, 95% CI 1.02 to 1.38; $p = 0.03$).

PLATelet inhibition and patient Outcomes trial subgroup analyses

The results of analyses that assess the clinical effectiveness of ticagrelor compared with clopidogrel in the range of patient populations included in the PLATO[33] trial are summarised in the table below. The patient populations include people intended for early angiography, people managed medically, people with STEMI, people who were treated with CABG and people with diabetes. With the exception of the subgroup of patients treated with CABG and people with diabetes, a statistically significant benefit for ticagrelor compared with clopidogrel is recorded.

PLATelet inhibition and patient Outcomes trial subgroup analyses (primary efficacy end point)

Trial name	Patient group (*n*)	Ticagrelor (KM%/12 months)	Clopidogrel (KM%/ 12 months)	HR (95% CI)	*p*-value
PLATO	All ACS (18,624)	9.8	11.7	0.84 (0.77 to 0.92)	< 0.001
PLATO-INVASIVE	Intended for early angiography (13,408)	9.0	10.7	0.84 (0.75 to 0.94)	0.0025
PLATO-MEDICAL	Conservative management (5216)	12.0	14.3	0.85 (0.73 to 1.00)	0.04
PLATO-STEMI	STEMI with PCI				
	STEMI or LBBB at presentation (7544)	9.4	10.8	0.87 (0.75 to 1.01)	0.07
	LBBB/STEMI at presentation or STEMI at discharge (8430)	9.3	11.0	0.85 (0.74 to 0.97)	0.02
PLATO-CABG	CABG (1261)	10.6	13.1	0.84 (0.60 to 1.16)	0.29
PLATO-DIABETES	With diabetes mellitus (4622)	14.1	16.2	0.88 (0.76 to 1.03)	NR
	Without diabetes mellitus (13,951)	8.4	10.2	0.83 (0.74 to 0.93)	NR

PLATO health-related quality of life

The PLATO[33] trial included a Health Economics and Quality of Life substudy. This substudy employed the paper version of the EQ-5D questionnaire and the manufacturer converted the EQ-5D scores to utility values to inform the cost-effectiveness analyses presented in the manufacturer's submission for TA236 using the UK tariff weightings.

Of the total number of 18,624 patients, 15,212 (82%) had a utility score calculated at discharge from the index hospitalisation (visit 1). At visit 4 (6 months) and visit 6 (12 months) the percentage of patients in the full cohort with a utility score was 80% and 79%, respectively. Of the 10,686 patients who were eligible for a 12-month follow-up (referred to as the 12-month cohort), 8840 (83%) had a utility score calculated at visit 1. The corresponding percentage of patients in the 12-month cohort with utility score at visit 4 and visit 6 was 81% and 80%, respectively.

No differences were found between ticagrelor and clopidogrel for any of the items on the EQ-5D.

Appendix 8 Key characteristics of identified indirect comparisons of prasugrel and ticagrelor

Publication	Objective	Trials included; length of follow-up	Comparator 1	Comparator 2	Patient group (*n*)	Primary outcomes of the meta-analysis
Biondi-Zoccai *et al.* 2011[57]	To perform an indirect comparison meta-analysis of prasugrel *vs.* ticagrelor in patients with ACS	TRITON-TIMI 38 2007;[36] 15 months	Prasugrel; 60-mg LD/ 10 mg daily	Clopidogrel 300-mg LD/ 75 mg daily	All ACS (13,608)	• Death, MI or stroke • TIMI major bleeding
		PLATO 2009;[33] 9 months	Ticagrelor; 180-mg LD/ 90 mg twice daily	Clopidogrel 300- to 600-mg LD/75 mg daily	All ACS (18,624)	
		DISPERSE-2 2007;[63] 3 months	Ticagrelor; 90 mg twice daily[a]	Clopidogrel 300-mg LD/ 75 mg daily	NSTEMI (661)	
Passaro *et al.* 2011[59]	Presentation of a simplified network meta-analysis graph to improve the communicative value of the analysis by Biondi-Zoccai	TRITON-TIMI 38 2007;[36] 15 months	Prasugrel	Clopidogrel 300-mg LD/ 75 mg daily	All ACS (13,608)	• Death from any cause • Death from CV causes, MI or stroke • Major bleeding
		PLATO 2009;[33] 9 months	Ticagrelor	Clopidogrel 300- to 600-mg LD/75 mg daily	All ACS (18,624)	
		CURE 2001;[64] 3–12 months	Clopidogrel 300-mg LD/ 75mg daily	Placebo	NSTEMI (12,562)	
Chatterjee *et al.* 2013[58]	To compare the relative efficacies of prasugrel and ticagrelor in the reduction of meaningful clinical end points in patients with ACS or CAD intended for PCI treatment using a network meta-analysis of published data	TRITON-TIMI 38 2007;[36] 15 months	Prasugrel	Clopidogrel 300-mg LD/ 75 mg daily	All ACS (13,608)	• Overall death • Probable/definite stent thrombosis, MI, TVR, recurrent ischaemia, serious recurrent ischaemia • TIMI non-CABG major bleeding
		PLATO 2009;[33] 9 months	Ticagrelor	Clopidogrel 300- to 600-mg LD/75 mg daily	All ACS (18,624)	
		DISPERSE-2 2007;[63] 3 months	Ticagrelor; 90 mg twice daily[a]	Clopidogrel 300-mg LD/ 75 mg daily	NSTEMI (661)	
		JUMBO-TIMI 26 2005;[38] 30 days	Prasugrel; three different dosing regimens	Clopidogrel 300-mg LD/ 75 mg daily	ACS intended for PCI (904)	
Steiner *et al.* 2012[60]	To compare the efficacy and safety of prasugrel, ticagrelor and high-dose clopidogrel in patients undergoing PCI	Abuzahra 2008;[125] 30 days	Clopidogrel 600-mg LD/ 150 mg daily	Clopidogrel 300-mg LD/ 75 mg daily	ACS: 44%, SCAD: 56% (119)	• All cause death • Major bleeding
		Angiolillo 2008;[126] 30 days	Clopidogrel 600-mg LD/ 150 mg daily	Clopidogrel 300-mg LD/ 75 mg daily	SCAD (40)	
		DOSER 2010;[66] 30 days	Clopidogrel 600-mg LD/ 150 mg daily	Clopidogrel 300-mg LD/ 75 mg daily	SCAD, HTPR (74)	
		DOUBLE 2010;[127] 1 month	Clopidogrel 300mg LD/ 150 mg daily	Clopidogrel 300mg LD/ 75 mg daily	STEMI (54)	

Publication	Objective	Trials included; length of follow-up	Comparator 1	Comparator 2	Patient group (*n*)	Primary outcomes of the meta-analysis
		GRAVITAS 2011;[128] 6 months	Clopidogrel 300- to 600-mg LD/150 mg daily	Clopidogrel 300- to 600-mg LD/75 mg daily	ACS: 40%, SCAD: 60%, HTPR: 100% (2214)	
		Han *et al.* 2009;[65] 30 days	Clopidogrel 600-mg LD/ 150 mg daily	Clopidogrel 600-mg LD/ 75 mg daily	ACS (813)	
		OASIS 7 PCI 2010;[46] 30 days	Clopidogrel 600-mg LD/ 150 mg daily	Clopidogrel 300-mg LD/ 75 mg daily	ACS (17,263)	
		VASP-02 2008;[129] 14 days	Clopidogrel 300- to 600-mg LD/150 mg daily	Clopidogrel 300- to 600-mg LD/75 mg daily	Stable CAD (153)	
		Von Beckerath *et al.* 2007;[130] 30 days	Clopidogrel 600-mg LD/ 150 mg daily	Clopidogrel 300- to 600 mg LD/75 mg daily	Stable CAD (60)	
		JUMBO-TIMI 26 2005;[38] 30 days	Prasugrel; three different dosing regimens	Clopidogrel 300-mg LD/ 75 mg daily	ACS intended for PCI (904)	
		TRITON-TIMI 38 2007;[36] 15 months	Prasugrel	Clopidogrel 300-mg LD/ 75 mg daily	All ACS (13,608)	
		Alexopolous 2011;[131] 30 days	Clopidogrel 600-mg LD/ 10 mg prasugrel daily	Clopidogrel 300- to 600-mg LD/150 mg daily	ACS: 70%, Stable CAD: 30%, HTPR: 100% (71)	
		PRINCIPLE-TIMI 44 2007;[132] 15 days	Prasugrel 60-mg LD/ 10 mg daily	Clopidogrel 600-mg LD/ 150 mg daily	Stable CAD (201), 55% PCI	
		PLATO INVASIVE 2009;[56] 9 months	Ticagrelor 180-mg LD/ 180 mg daily	Clopidogrel 300- to 600-mg LD/75 mg daily	ACS (13,408), 77% PCI	

HTPR, High on-Treatment Platelet Reactivity; LD, loading dose; PRINCIPLE-TIMI, Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation – Thrombolysis in Myocardial Infarction; SCAD, stable coronary artery disease.
a Does not include 323 patients treated with ticagrelor 180 mg twice daily.

Appendix 9 Quality assessment of identified indirect comparisons of prasugrel and ticagrelor

None of the indirect comparisons stated whether or not the design was a priori. Biondi-Zoccai *et al.*[57] did not perform a comprehensive search strategy, assess the quality of included studies or assess publication bias. Chatterjee *et al.*[58] did not state whether or not there was duplicate selection or data extraction and did not provide a list of excluded studies or study characteristics. They also did not provide a breakdown of results of the quality assessment or use it in formulating conclusions, although they did state that all included studies were judged to be at a low risk of bias. The assessment was not applicable to the article by Passaro *et al.*[59] as the primary aim of this was to present a simplified network meta-analysis graph based on the review by Biondi-Zoccai *et al.*[57] The review by Steiner *et al.*[60] did not provide a list of excluded studies, assess publication bias or use the quality assessment in formulating conclusions.

Quality of the identified indirect comparisons

Review	A priori design provided?	Duplicate selection/data extraction?	Comprehensive literature search?	Publication status used as an inclusion criterion?	List of studies provided?	Study characteristics provided?	Scientific quality of included studies assessed?	Scientific quality of included studies used appropriately?	Appropriate methods used to combine findings?	Publication bias assessed?	COIs stated?
Biondi-Zoccai *et al.* 2011[57]	NS	NS	No	Yes	Yes	Yes	No	No	Yes	No	Yes
Chatterjee *et al.* 2013[58]	NS	NS	Yes	Yes	No, excluded studies not given	No	Yes[a]	No	Yes	Yes	Yes
Passaro *et al.* 2011[59]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Steiner *et al.* 2012[60]	NS	Yes	Yes	Yes	No, excluded studies not given	Yes	Yes	No	Yes	No	Yes

COI, conflict of interest; NA, not applicable; NS, not stated.
a But no results given, only stated studies were low risk of bias.

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