MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182)

This report was commissioned by the NIHR HTA Programme as project number 12/62/01

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Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182)

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1 LIST OF ABBREVIATIONS

AC	Appraisal Committee
ACS	acute coronary syndromes
AG	Assessment Group
BCIS	British Cardiovascular Intervention Society
CABG	coronary artery bypass grafting
CEAC	cost- effectiveness acceptability curve
CE	composite endpoint
CI	confidence interval
CV	cardiovascular
ECG	electrocardiograph
DRG	Diagnostic Related Group
DM	diabetes mellitus
EMC	electronic medicines compendium
EMA	European Medicines Agency
ERG	Evidence Review Group
GDG	guidelines development group
HRQoL	health-related quality of life
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LD	loading dose
LYG	life year gained
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
PCI	percutaneous coronary intervention
PLATO	PLATelet inhibition and patient Outcomes trial
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
QoL	quality of life
RCT	randomised controlled trial
SA	sensitivity analysis
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 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction
UA	unstable angina
vs	Versus
WTP	willingness to pay

2 SCIENTIFIC SUMMARY

2.1 Background

Acute coronary syndromes (ACS) 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, electrocardiogram (ECG) and levels of cardiac enzymes: ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and 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, 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, clopidogrel or ticagrelor) is the standard antiplatelet treatment in clinical practice in the UK. The antiplatelet drug prasugrel is the focus of this review.

2.2 Objectives

The remit of this update is to appraise the clinical and cost effectiveness of prasugrel within its licensed indication for the treatment of ACS with PCI and is a review of NICE technology appraisal TA182.

2.3 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 nonfatal 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 (LY) 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.

2.4 Results

One good quality randomised controlled trial (RCT) was identified for inclusion in the clinical review. The TRITON-TIMI 38 trial compared prasugrel with clopidogrel in patients with ACS who were scheduled for PCI. No relevant economic evaluations were identified.

2.5 Summary of risks and benefits

This review focussed 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 less than 60kg or those aged over 75 years. For the primary composite endpoint of death from CV causes, nonfatal MI, or nonfatal stroke, statistically significantly fewer events were recorded in the prasugrel arm (8.3%) compared with the clopidogrel arm (11%) (HR=0.74; 95% CI: 0.66 to 0.84; p<0.0001). No statistically significant difference in non-CABG-related TIMI 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, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding) favoured the use of prasugrel (12.5% in the clopidogrel group vs10.2% 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 due 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.

2.6 Summary of the Assessment Group's cost-effectiveness results

The economic evaluation submitted by the manufacturer met the NICE reference case criteria. However, the AG developed its own economic model for the following reasons: (i) 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 (ii) 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 (iii) 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 trial instead of 15 month data from the TRITON-TIMI 38 trial (iv) to fulfil the remit stated by NICE and to fully review 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

Both the results of the deterministic and probabilistic analyses confirmed that it appears likely that, for all four subgroups, within 5 to 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.

2.7 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 for 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.

2.7.1 Clinical effectiveness

This review focussed 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 i.e. 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. 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 MI). Thus, the comparative effectiveness and safety of prasugrel vs ticagrelor still remain unknown.

2.7.2 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: 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 which excluded patients from treatment with prasugrel if they had not suffered from 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 to10 years, it appears likely that prasugrel is a cost-effective treatment option when compared with clopidogrel for all four subgroups.

2.7.3 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 vs 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 vs 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 out to 40 years.

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

2.7.4 Uncertainties

The three areas of uncertainty noted by the AC for TA182 were re-considered 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 300mg loading dose of clopidogrel (administered in TRITON-TIMI 38) with a 600mg 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). Thus, the comparative effectiveness and safety of prasugrel vs ticagrelor still remain unknown.

2.8 Conclusions

2.8.1 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 5 trial, if conducted well, could fill the current gap in evidence related to the comparative efficacy and safety of prasugrel vs ticagrelor.

3 BACKGROUND

3.1 Description of health problem

Acute coronary syndromes (ACS) 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 or 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 risk factors as for cardiovascular (CV) disease. Among the non-modifiable risk factors are increasing age, gender (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 other vascular event (e.g. stroke) when compared to the general population.[6]

There are three main types of ACS diagnosed by clinical history, electrocardiogram (ECG) and levels of cardiac enzymes: ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and 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 patients' 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 include adjunctive treatment with antiplatelet drugs. These drugs are the focus of this review.

3.2 Treatment pathway

STEMI

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 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. Where PCI facilities are not immediately available, treatment with thrombolysis (pharmacological reperfusion achieved through the use of 'clot-busting' drugs should be considered).[12] Where STEMI persists despite thrombolytic treatment, PCI (rescue) in an appropriately equipped unit should be considered.[8]

UA/NSTEMI

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] The 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 graft [CABG]), physical examination (including measurement of blood pressure and heart rate); resting 12-lead ECG and blood tests (troponin I or T, creatinine, glucose and haemoglobin). Table 1 is reproduced from NICE CG94[13] and describes the risk categories of future CV events assigned to risk scores.

Table 1 Categories of risk of future cardiovascular events

Predicted 6-month mortality	Risk of future adverse cardiovascular events
1.5% or below	Lowest
>1.5 to 3.0%	Low
>3.0 to 6.0%	Intermediate
>6.0 to 9.0%	High
Over 9.0%	Highest

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.[16]

3.3 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) 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 ratio should be 1 to 3 rather than 2 to 3.

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]

The Assessment Group (AG) notes that the MINAP[5] dataset 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.[17]

British Cardiovascular Intervention Society Audit Data

The British Cardiovascular Intervention Society (BCIS) continuously audits interventional activity in the UK and results are published annually. The most recent audit returns are for the year 2012.[18] 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 these (23,842) were primary PCIs. The number of PCIs for STEMI has increased over time whilst the number of PCIs for UA/NSTEMI has remained stable.

Of patients referred for PCI in the UK in 2012, 74% were male with an average age of 64.9 years.[18] Approximately 20% had diabetes mellitus and 27% had had a previous MI.[18] One quarter were current smokers and the majority (92%) were European.[18] 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[18] 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; 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.

3.4 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, clopidogrel or ticagrelor is the standard antiplatelet treatment in clinical practice in the UK.

3.5 Relevant national guidelines

A quality standard for ACS has been referred for consideration to NICE and is expected to be published in September 2014.[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 acute coronary syndromes with percutaneous coronary intervention	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 or • stent thrombosis has occurred during clopidogrel treatment or • the patient has diabetes mellitus
CG94[13] (2010) Unstable angina and NSTEMI: the early management of unstable angina and non-ST segment elevation myocardial infarction	Offer a 300mg 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 acute coronary syndromes with percutaneous coronary intervention' (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 acute coronary syndromes (ACS)	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 electrocardiogram-that cardiologists intend to treat with PCI or • NSTEMI or • admitted to hospital with unstable angina. 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 myocardial infarction (CG172 is an update of CG48)	Aspirin should be offered to all people after an 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-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
CG167[8] (2013) Myocardial infarction with ST segment elevation (STEMI): the acute management of myocardial infarction with ST segment elevation (STEMI)	Following reperfusion therapy for STEMI, treatment with aspirin should be continued in line with CG48 MI secondary prevention* 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 600mg 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

*CG48 has been superseded by CG172

3.6 Description of technology under assessment

3.6.1 Intervention

The oral antiplatelet, prasugrel (Efient ®; Daiichi Sankyo UK/Eli Lilly and Company Ltd), 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 (EMC).[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 5mg or 10mg film-coated tablets. Prasugrel is given (with aspirin) as a single 60mg loading dose and then continued at 10mg 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, whilst in older (≥75 years) patients prasugrel is generally not recommended. For patients who weigh less than 60kg, the 60mg loading dose of prasugrel should be used followed by a maintenance dose of 5mg.[24]

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 or
- stent thrombosis has occurred during clopidogrel treatment or
- 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 (PAS) 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 only be considered when the benefits in terms of preventing ischaemic events are deemed to outweigh the risk of serious bleeding.[24]

3.6.2 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).

Table 3 BCIS 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%

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

3.6.3 Comparators

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

Clopidogrel

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

- patients with MI (from a few days until less than 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) 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.

Ticagrelor

Ticagrelor is a direct-acting $P2Y_{12}$ receptor antagonist that has a different mechanism of action than 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 coronary artery bypass grafting (CABG). Ticagrelor is administered as a 90mg film-coated tablet. Treatment should be started with a single 180mg loading dose (two 90mg tablets) and then continued at 90mg 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 (for example, ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) 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 reported[32] that they had received a demand from the US Department of Justice, Civil Division, seeking documents and information regarding the PLATO[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.

4 DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

The remit of this appraisal is to review and update (if necessary) the clinical 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.

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: • nonfatal and fatal cardiovascular 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 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 an 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 only be issued 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

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.

4.2 Overall aims and objectives of assessment

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

5 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.

5.1 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 2013 June 18
- Medline (Ovid) 1946 to 2013 June Week 1
- The Cochrane Library to 2013 June
- PUBMED 2013 January 2010 to 2013 April 28

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

5.1.1 Inclusion and exclusion criteria

Two reviewers JG/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). 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, where necessary, a third reviewer 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 ACS who were to be treated with primary or delayed PCI comprised the relevant population.

Outcomes

Data on any of the following outcomes were included in the assessment of clinical effectiveness: nonfatal 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/KD) into an Excel spreadsheet. The two reviewers cross-checked each other's data extraction and where multiple publications of the same study were identified, data were extracted and reported as a single study.

5.1.2 Quality assessment strategy

The quality of the clinical-effectiveness studies was assessed independently by two reviewers (JG/KD) according to the Centre for Reviews and Dissemination at York University'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.

5.1.3 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.

5.2 Results

5.2.1 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 (below 60kgs and older than 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 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.

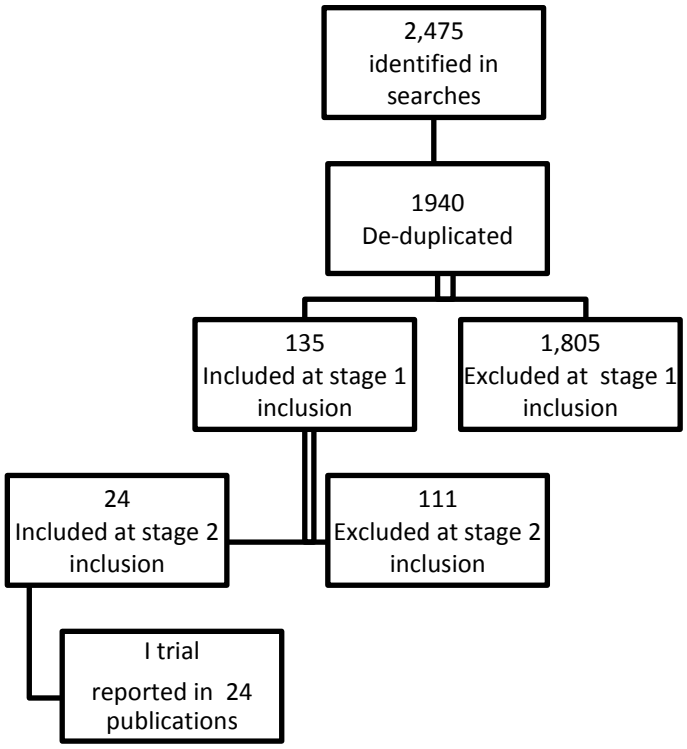


Figure 1 PRISMA flowchart

5.2.2 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 (60mg or 300mg respectively) followed by daily maintenance doses of 10mg or 75mg respectively.

The results of the AG's quality assessment of the TRITON-TIMI 38[36] trial are presented in Appendix 2 of this report. 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 (10,074) or STEMI (3,534). Duration of study: 15 months (median) 73 patients were recruited from the UK	Prasugrel (LD 60mg/MD 10mg) Clopidogrel (LD 300mg/MD 75mg) 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 ≥1mm 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	<u>Primary:</u> Composite of CV death, nonfatal MI or nonfatal stroke during follow-up period <u>Secondary:</u> Composite of death from CV causes, nonfatal MI, nonfatal stroke, rehospitalisation due to cardiac ischaemic event Composite of all cause death, nonfatal MI, nonfatal stroke; stent thrombosis <u>At 30 days and 90 days:</u> Primary composite endpoint; Composite of CV death, nonfatal MI, urgent target vessel revascularisation <u>Safety:</u> Non CABG-related bleeding TIMI life-threatening bleeding TIMI major or minor bleeding

CABG=coronary artery bypass graft; CV=cardiovascular; LD=loading dose; MD=maintenance dose NSAID=non-steroidal anti-inflammatory drug; RCT=randomised controlled trial; TIMI=Thrombolysis In Myocardial Infarction

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 endpoint analyses (overall trial population)
- forest plot displaying pre-specified 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 ACS, patients with diabetes mellitus, patients with stents (overall trial population)
- outcomes for people with history of stroke/TIA
- outcomes for people older than 70 years or weighing less than 60kg
- 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)[41] that is directly relevant to this appraisal focusses 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 (60mg loading dose followed by 10mg daily). These patients have no history of stroke or TIA, are younger than 75 years and weigh more than 60kg. The AG focusses on the clinical evidence relevant to this subgroup.

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

Author/Year	Title	Description
Wiviott 2006[42]	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)	Paper describing the design of the TRITON-TIMI 38 trial
Wiviott 2007[36]	Prasugrel versus clopidogrel in patients with acute coronary syndromes	Primary publication of TRITON-TIMI 38 trial
Wiviott 2011[41]	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 60kg. The core clinical cohort represents10,804 of the 13,608 patients included in the overall trial cohort

The core clinical cohort[41] 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 the Wiviott et al paper[41]) are not presented by trial arm. However, the Wiviott et al paper[41] 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.[41] 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 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%
Hypertension	62%	64%
Hypercholesterolemia	56%	56%
Diabetes mellitus	22%	23%
Previous MI	17%	18%
Previous CABG	7%	8%
Creatinine clearance <60ml/min	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; CABG=coronary artery bypass grafting; CCB=calcium channel blocker

5.3 Clinical efficacy in the core clinical cohort

The manufacturer's submission (MS) and the Wiviott et al (2011) paper[41] 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[41] 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 endpoint of death from CV causes, nonfatal MI, or nonfatal stroke, statistically significantly fewer events were recorded in the prasugrel arm (8.3%) compared with the clopidogrel arm (11%) (HR=0.74; 95% CI: 0.66 to 0.84; p<0.0001). Similarly, for the secondary composite endpoint (death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding) statistically significantly fewer events were

recorded in the prasugrel arm (10.2%) compared with 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 nonfatal MIs.

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%) compared with the clopidogrel arm (9.4%) (HR=0.71; 95% CI: 0.62 to 0.81; p<0.001).

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

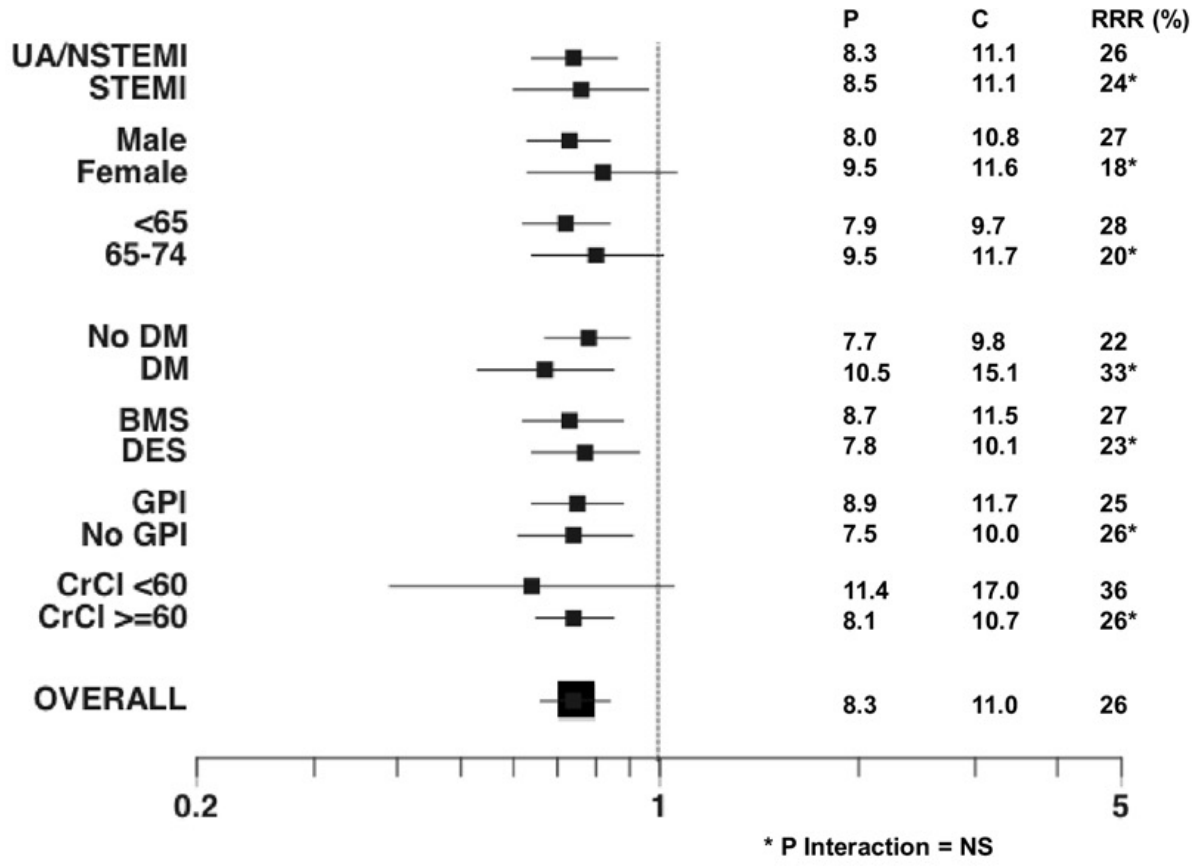
Endpoint	**Prasugrel n/N (%)**	**Clopidogrel n/N (%)**	**Hazard ratio 95% CI**	***p* value**
Primary				
Death from CV causes, nonfatal MI, or nonfatal stroke	433/5421 8.3%	569/5383 11%	0.74 (0.66 to 0.84)	<0.001
Secondary				
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal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

CABG=coronary artery bypass grafting; CI=confidence interval; CV=cardiovascular; MI=myocardial infarction; TIMI = Thrombosis In Myocardial Infarction

Note: The percentages are Kaplan-Meier estimates of the rate of each endpoint 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)

Efficacy across subgroups within the core clinical cohort

The 2011 published paper[41] presents 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), gender, age and diabetic status. The published forest plot is reproduced in Figure 2. The clinical effectiveness of prasugrel appears to be consistent across subgroups.



CrCl=creatinine clearance; DM=diabetes mellitus; BMS=bare metal stent; GPI=glycoprotein inhibitor

Figure 2 Key subgroups for primary efficacy endpoint (core clinical cohort)

Efficacy across time for the core clinical cohort

It is noted in the 2011 published paper[41] that for the core clinical cohort, prasugrel was more effective than clopidogrel for the primary endpoint at 30 days as well as at the 15 month follow-up (Table 9).

Table 9 Primary endpoint at 30 days and 15 months

Endpoint	Prasugrel	Clopidogrel	Hazard ratio 95% CI	*p* value
Primary: death from CV causes, nonfatal MI, or nonfatal stroke				
30 days	5.0%	7.0%	0.70 (0.60 to0.82)	<0.0001
30 days to 15 months	3.6%	4.5%	0.80 (0.65 to0.97)	0.027

CV=cardiovascular; MI=myocardial infarction

Safety in the core clinical cohort

The key safety endpoint 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 endpoints 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).

Table 10 Safety endpoints in the core clinical cohort

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

CABG=coronary artery bypass graft; TIMI=Thrombolysis In Myocardial Infarction

Net clinical benefit

The analysis of the net clinical benefit outcome (death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal 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 only available for the TRITON-TIMI 38[36] overall trial population and are not specific to the core clinical cohort. The HRQoL sub-study was open to all

TRITON-TIMI 38[36] patients at participating sites in eight countries: USA, Australia, Canada, Germany, Italy, Spain, UK and France. Health-related QoL was evaluated using three instruments: i) Angina Frequency and Physical Limitations Scores scales of the Seattle Angina Questionnaire; ii) London School of Hygiene Dyspnoea Questionnaire score; iii) EQ-5D self-report questionnaire and the EQ visual analogue scale. Assessments were taken at baseline, day 30, day 180, day 360, and day 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 sub-study 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.

5.3.1 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 to 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.

5.4 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[41] 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 due to lack of data.

5.5 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 in respect of the TRITON-TIMI 38[36] trial. The Appraisal Committee 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 300mg whereas a loading dose of 600mg may be administered in clinical practice in England and Wales

- the majority (74%) of patients 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 nonfatal MIs. Nonfatal 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.

5.5.1 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 (300mg) and the dose (600mg) 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 300mg or 600mg of clopidogrel is used in PCI treatment. Results of a market research survey conducted in June 2013 amongst UK clinicians on behalf of the manufacturer are reported in the MS. These results demonstrate that, of the ACS-PCI patients who received a loading dose of clopidogrel [redacted].

The manufacturer points out the inconsistency between clinical guidelines as to the recommended loading dose of clopidogrel (300mg or 600mg). For example, in NICE CG94[13] published in 2010 (Unstable angina and NSTEMI: the early management of unstable angina and non-ST segment elevation myocardial infarction) NICE recommends 300mg whilst acknowledging that evidence exists to support the use of 600mg. The SIGN[43] guidelines recommend the use of a 300mg loading dose, whilst the European Society for Cardiology (ESC) advocates both 300mg and 600mg loading doses.[10,44,45]

The manufacturer states that the case for the additional benefit of 600mg rather than 300mg is not proven and cites the results of the CURRENT-OASIS 7[46] 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 300mg or 600mg of clopidogrel and either high- or low-dose aspirin. The patients who received a 600mg loading dose of clopidogrel **and** had a PCI continued with 150mg of clopidogrel for the first 7 days and on day 8 received the standard 75mg maintenance dose. Patients who received the 300mg loading dose of clopidogrel **and** had a PCI continued on 75mg 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 endpoint of death from CV causes, MI or stroke at 30 days was not statistically significantly different between the 600mg arm (4.2%) and the 300mg 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 600mg arm (2.5%) compared with the 300mg 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[47] 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 endpoint in favour of the 600mg arm (3.9%) compared with the 300mg 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[46] trial do not demonstrate any clear benefit associated with the use of a 600mg loading dose of clopidogrel compared with a 300mg dose and thus it is unlikely that the use of 600mg of clopidogrel in the TRITON-TIMI 38[36] trial would have changed the efficacy results but 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 300mg and that this was the established loading dose in routine clinical practice in the United States when the TRITON-TIMI 38[36] trial commenced. The AG notes that in TA182,[21] the manufacturer supported the case for the use of 300mg of clopidogrel in the UK by reporting data from the Lilly sponsored AntiPlatelet Treatment Observational Registry and the IMS Health Acute Cardiovascular Analyzer study. These data indicated that in 2007 60% to 79% of ACS patients in the UK received the 300mg licensed dose. The AG notes the contrast between clopidogrel 300mg

use in 2007 (at the time of TA182[21] it was approximately 33%) and more recent clopidogrel use (approximately [redacted]) reported in the manufacturer's survey described in the MS. 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 300mg loading dose of clopidogrel whilst the ESC[10,45,48] guidelines recommend both 300mg and 600mg.

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 300mg of clopidogrel. However, the guidelines further state that if early (<24 hours) invasive intervention is planned a higher loading dose should be considered, particularly in cases where the procedure will be carried out within 6 hours. The guideline development group (GDG) responsible for CG94[13] has stated in the guideline that since they were not able to formally review all the evidence for a 600mg 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 600mg 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[46] trial do not appear to support the use of a 600mg loading dose of clopidogrel over a 300mg dose. However, the AG considers that the results of the subgroup analysis[46] of the 69% (17,263) of patients treated with PCI suggest that that the trial protocol clopidogrel regimen of a 600mg loading dose followed by 7 days at 150mg and then 75mg daily, statistically significantly reduces CV events (including stent thrombosis) when compared with a loading dose of 300mg followed by 75mg daily. However, the AG also notes that bleeding events were statistically significantly greater in the 600mg arm than in the 300mg 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[47] trial are consistent with the findings of a meta-analysis comprising trials with PCI-treated patients.[49]

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 there is any difference in clinical efficacy between a 300mg and 600mg loading dose of clopidogrel are limited.

5.5.2 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. 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 pre-loading with clopidogrel.

The manufacturer re-states 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 namely that:

- the effects of prasugrel were consistent over time. For the overall study period the hazard ratio (0.81 [95% CI: 0.73 to 0.90]) is similar to the hazard ratios for the 0 to 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 at 0 to 3 days and beyond 3 days confirmed sustained benefit over time

- for patients treated with GPIIb/IIIa inhibitors, there was no evidence that the relative benefit of prasugrel vs clopidogrel was reduced or that there was an excess need for bail out GPIIb/IIIa inhibitor use during PCI in those patients randomised to clopidogrel in the study

- a group of patients received pre-treatment up to 24 hours before PCI. The percentage of patients in this pre-treated subgroup reaching the composite endpoint of CV death, nonfatal MI, or nonfatal stroke from randomisation through study end was 9.94% and 11.29% (unadjusted crude event rates) for patients pre-treated with prasugrel and clopidogrel respectively. While 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 there is currently limited evidence to support or refute the benefits of pre-loading with clopidogrel vs clopidogrel at the time of PCI; this means that whether patients in the trial would benefit more from clopidogrel compared with patients in the NHS in England and Wales remains unclear.

5.5.3 Clinical vs non-clinical MIs

Manufacturer's comments

A point of discussion during the previous appraisal[21] of prasugrel was that the definition of MI used in TRITON-TIMI 38[36] included non-clinically detected MIs. The manufacturer states that the definition of MI in the TRITON-TIMI 38[36] trial was based on the American College of Cardiology Task Force on Clinical Data Standards published in 2001.[50] This definition was pre-specified and agreed with the regulatory agencies (FDA and EMA) prior to the start of the trial. The Appraisal Committee and the ERG were concerned that if the non-clinical MIs were excluded from the analyses, the resultant clinical difference in nonfatal MIs alone may not be statistically significant when comparing prasugrel with clopidogrel. In response, the manufacturer cited evidence from a re-analysis[51] of the TRITON-TIMI 38[36] trial MI (n=1218 MIs). These MIs were re-assessed according to the 2007 criteria of the Universal Definition of Myocardial Infarction (varying type, size, and timing.

Table 11) developed by the European Society of Cardiology, the American College of Cardiology, The American Heart Association and the World Heart Federation Task Force.[52] Reviewers, who were blinded to treatment allocation, assessed the size and timing of all MIs and whether 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.

Table 11 Universal definition of myocardial infarction

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 due to either increased oxygen demand or decreased supply due 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

The manufacturer also points to a further analysis (Bonaca et al[53]) of the TRITON-TIMI 38[36] data in which the rate of CV death within 180 days was compared for people who had experienced a new MI with those who had not. Patients who experienced a new MI of any type had a significantly higher rate of CV death (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 re-analysis[51,53] 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[52] 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 re-analysis[51,53] of the MIs by the manufacturer demonstrates that prasugrel was more effective than clopidogrel in preventing occurrence of MIs.

5.6 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). The purpose of the research is to develop a method to identify patients at risk of stent thrombosis. According to the MS, the methodology and results of the research are to be published at the end of 2013. 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.

5.7 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. 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 Evidence Review Group (ERG) and the Appraisal Committee 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 Appraisal Committee and the ERG in TA236 (ticagrelor)[22] that such an indirect comparison would be inappropriate.

5.7.1 Problems with an indirect comparison of the TRITON-TIMI 38 and PLATO trials

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 endpoint (death from CV causes, nonfatal MI, or nonfatal stroke during the follow-up period).

Table 12 Comparison of TRITON-TIMI 38 and PLATO RCTs

Characteristic	TRITON-TIMI 38	PLATO
Number patients	13,608	18,624
Patient population	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 300mg allowed	300mg or 600mg
Timing of randomisation	**Later** After angiography After decision to perform PCI	**Earlier** Usually before angiography (if done)
Randomisation	Prasugrel 60mg load 10mg once daily Or Clopidogrel 300mg load 75mg once daily	Ticagrelor 180mg load 90 mg twice daily Or Clopidogrel 300mg to 600mg load 75mg 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 endpoint	CV death/MI/stroke	CV death/MI/stroke
Primary safety endpoint	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

CABG=coronary artery bypass graft; TIMI=Thrombolysis In Myocardial Infarction

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[54] 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[55] 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 300mg. In the PLATO trial[33] loading doses of 300mg or 600mg were allowed; 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 600mg 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 guide-wire 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 Section 5.5.1 of this report. 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 MI assessment

The assessment of MIs across the two trials requires consideration. It was noted in TA236[22] that determining whether 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 pre-procedure enzyme measurements to be taken, whereas in the PLATO[33] trial, only one pre-procedure 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 endpoint were clinical MIs whilst almost half 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 to 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 compared to the log-rank test.) The log-rank test was then used in a pre-specified 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.

5.7.2 Summary and critique of published indirect comparisons of prasugrel and ticagrelor

Four published indirect comparisons[56-59] of prasugrel vs ticagrelor were identified by the AG and the manufacturer during searching; the key features of these studies are described in Appendix 6. The quality of the four published indirect comparisons[56-59] identified by the AG (and the manufacturer) was assessed using the 'assessment of multiple systematic reviews' (AMSTAR)[60] tool. The results are presented in Appendix 7.

The published indirect comparison of ticagrelor vs prasugrel in patients with ACS conducted by Biondi-Zoccai et al[56,61] 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 (DISPERSE 2).[62] The total number of patients in the indirect comparison was 32,893. The results of the indirect comparison of prasugrel vs ticagrelor demonstrated no statistically significant differences in overall death, nonfatal MI, nonfatal stroke, or their composite.[56] 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 vs ticagrelor, whilst prasugrel appears more protective of stent thrombosis but causes more bleeding.

The AG's main criticism of the Biondi-Zoccai[56] indirect comparison 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 (as previously described by the AG in Section 5.7.1) render the results of the indirect comparison unreliable. The AG considers that results from the dose ranging DISPERSE-2[62] trial make a negligible contribution to the results presented in the Biondi-Zoccai et al[56] paper 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 endpoint.

The publication by Passaro et al[58] presented a simplified network meta-analysis graph to improve the communicative value of the analysis undertaken by Biondi-Zoccai et al.[56] The analysis excluded the dose-ranging DISPERSE-2[62] trial and instead included the outcomes from the CURE[63] 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[63] trial. The AG assumes that the reason for inclusion was that doing so enabled the authors to expand the treatment network. The conclusions of this analysis concurred with those of Biondi-Zoccai et al,[56] with the exception that no difference in major bleeding between prasugrel and ticagrelor was indicated.[58]

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

The meta-analysis conducted by Chatterjee et al[57] 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.[57] Four studies, comprising a total of 34,126 patients were included: PLATO,[33] TRITON-TIMI 38,[36] DISPERSE-2[62] and JUMBO-TIMI 26.[38] The JUMBO-TIMI 26[38] trial was a dose-ranging phase 2 trial comparing prasugrel with clopidogrel in 900 patients intended for PCI. The follow-up was limited to 30 days. Chatterjee et al[57] found no difference in CV mortality or rates of MI among patients undergoing PCI but stated that CABG-related bleeding was lower with prasugrel compared with ticagrelor. The authors[57] concluded that prasugrel may be more effective than ticagrelor for preventing stent thrombosis and recurrent ischemic events. The authors of the Chatterjee et al publication[57] 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 analysis[57] 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[59] 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 sub-study from the PLATO trial (PLATO-INVASIVE[55]) and CURRENT-OASIS 7 PCI.[46] 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,[46] Han[64] and DOSER.[65] 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 compared to 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,[47] Han[64] and DOSER[65]) compare high dose clopidogrel to standard dose clopidogrel and are of too short a duration to be of relevance to the current appraisal.

5.8 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 pre-specified in the original trial protocol[41] and should therefore be considered as exploratory and hypothesis generating. Searching did not identify any trials of prasugrel vs ticagrelor.

In the core clinical cohort prasugrel was favoured over clopidogrel for the primary composite endpoint of death from CV causes, nonfatal MI, or nonfatal 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 endpoint (death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding). The efficacy for both composite endpoints was driven by the reduced number of nonfatal 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 compared with 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 re-considered 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 300mg loading dose of clopidogrel (administered in the trial) with the 600mg loading dose often given in clinical practice remains uncertain. Similarly, the AG is of the opinion that the importance of the 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 vs 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 due to irreconcilable differences between the trials. These differences were discussed in the appraisal of ticagrelor during TA236.[22] Four published indirect comparisons[56-59] 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 vs ticagrelor remains unknown.

6 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/Eli Lilly and Company Limited 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.

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 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 August 30, 2013)
- NHS EED (searched August 30, 2013)
- EMBASE (1974 to 2013 August 30)

The results were entered into an ENDNOTE X5 library (Thomas Reuters, CA, USA) and the references were de-duplicated electronically. Full details of the search strategy are presented in Appendix 1.

6.1.2 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 where possible. At Stage 2, the relevance of each study was assessed (ABol and SB) according to the criteria set out in third reviewer was consulted.

Table 13. Studies that did not meet the criteria were excluded. Any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted.

Table 13 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Intervention or comparator	Prasugrel	
Study design	Full economic evaluation	Methodological paper, letter,* abstract**
Perspective	U.K or European perspective	Non-European perspective
Source of publication	Unrelated to previous appraisal	Related to previous appraisal (e.g. NICE/ERG/Manufacturer)

* Letters were included if they were related to a study already included in the review;**Abstracts were judged for inclusion at the very end of the inclusion process in order to ascertain whether sufficient information was available for the abstract to be included in the review

6.1.3 Data extraction and quality assessment strategy

In the AG's review protocol,[66] data relating to both study design and quality were planned to be extracted by two reviewers (ABol and SB) into an Excel spreadsheet (Excel software, Henderson, NV, 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[67]10-point checklist. However, no studies were identified for inclusion in the AG's review.

6.1.4 Results: quantity and quality of research available

After de-duplication 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[68-70] that the manufacturer had identified for inclusion in the review of cost-effectiveness evidence presented in the MS. Two of these studies[68,70] were carried out from a US perspective and the third study[69] employed the model that was submitted to NICE for the evaluation of prasugrel in 2009 (TA182[21]) – all three studies[68-70] were therefore excluded from the review by the AG.

Table 14 List of 15 excluded studies

Study	Title	Comment
Excluded studies		
Mahoney[68]	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	Non-European perspective
Serebruany[71]	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"	Letter/linked to Mahoney[68]
Mahoney[72]	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"	Letter/linked to Mahoney[68]
Davies[69]	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	Related to previous appraisal (same economic model – TA182)
Mauskopf[70]	Cost-effectiveness of prasugrel in a US managed care population	Non-European perspective
Davies[73]	Is 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	Abstract
Davies[74]	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	Abstract
Davies[75]	Prasugrel vs clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A Spanish model-based cost-effectiveness analysis	Abstract
Greenhalgh[15]	Prasugrel for the treatment of acute coronary artery syndromes with percutaneous coronary intervention	NICE
Hill[76]	Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention: NICE technology appraisal guidance	NICE/ERG
Keast[77]	Cost-effectiveness of prasugrel and clopidogrel for acute coronary syndrome in a medicaid population	Abstract/non-European perspective
Mahoney[78]	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	Abstract
Mondragon[79]	Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention in the private sector in Mexico	Abstract/non-European perspective
Mondragon[80]	Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention in the public health care system in Mexico	Abstract/non-European perspective
Rao[81]	A decision modelling approach to evaluate the cost-effectiveness of prasugrel versus clopidogrel in patients with planned percutaneous coronary intervention	Abstract

Studies by Davies et al

The AG notes that, of the 15 potentially eligible studies identified via electronic searching, four of the references were authored by Davies and colleagues; one was a full paper[69] and three were abstracts.[73-75] In the MS (pg 87), the manufacturer comments that the results of the analyses described in the full paper[69] 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[69] reports model results using costs and rehospitalisation rates specific to Germany, Sweden, Netherlands and Turkey, the AG has reproduced the table of results from the main study[69] 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[75] 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 to 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.

6.1.5 Conclusions of the AG's cost-effectiveness literature review

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

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

	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		9,131		6,025		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 (€)	6,520		8,016		4,738		2,910		6,711	
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 (€)	7,369		9,378		4,788		3,080		7,342	
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	7,294		9,371		4,552		3,036		7,207	
Licensed population: clopidogrel drug cost set at zero										
ICER (€)	Germany (18,494)		Sweden (7,058)		Netherlands (7,634)				Turkey (14,251)	

CLOP=clopidogrel; PRA=prasugrel; QALY=quality adjusted life year; ICER=incremental cost-effectiveness ratio

6.2 Review of the Lilly/Daiichi-Sankyo economic model

6.2.1 Overview of manufacturer's submitted model

Table 16 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).This 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 due to small number of responses. Instead, published US EuroQol EQ-5D scores were used
Measure of health benefits	QALYs	Valuations within the EuroQol 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

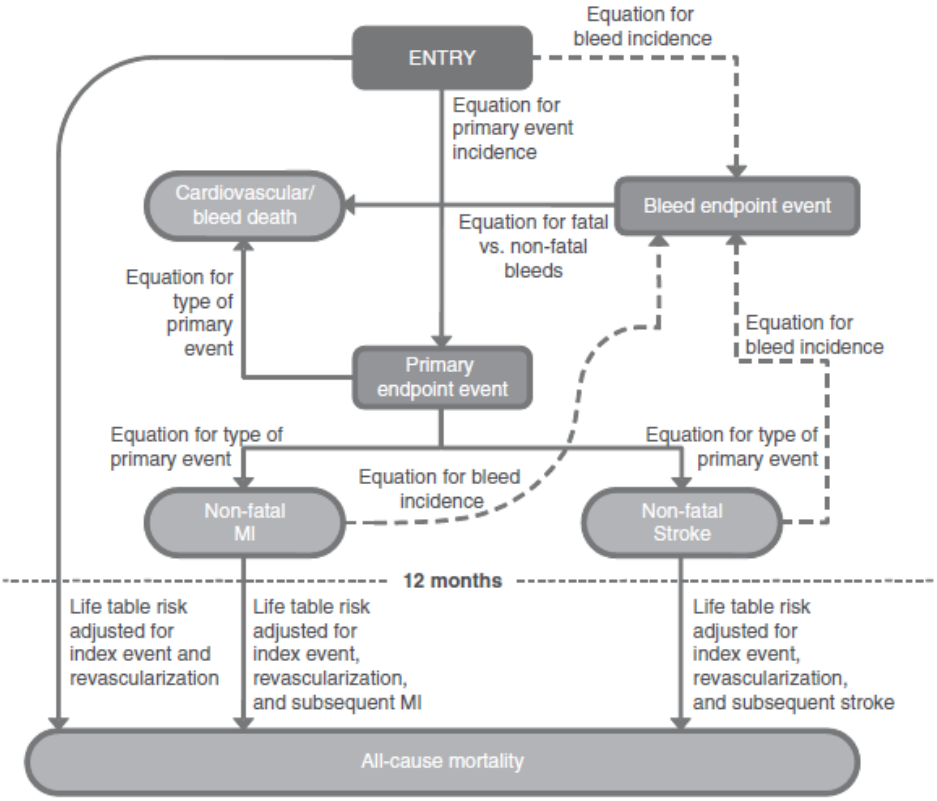
HRQoL=health related quality of life; MS=Manufacturer's submission; NICE=National Institute for Health and Care Excellence; PSS=personal social services; QALY= quality adjusted life year; RCT= randomised controlled trial

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 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 which allowed the user to choose to model 15 months of treatment (as the licence is only for 12 months)
- conduct of scenario analysis using the ERG's suggestions for utility values, amended long-term relative risk of mortality and reduced incidence of nonfatal 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.



The lightly dashed lines leading to 'bleed endpoint 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 where the event is fatal. Temporary utility decrements are applied at the time of major nonfatal bleeds. Re-hospitalisation occurs in all states at rates determined by current and past clinical events.

MI=myocardial infarction

Figure 3 Schema of manufacturer's model

6.2.2 Parameters and values

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

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)	Modelling working group based on TRITON baseline characteristics and end points results
	Weibull regression for longer term risk (HR)	
Fatal, major, minor bleeds	Logistic regression for 3 day risk (OR)	Modelling working group based on TRITON baseline characteristics and end points results
	Weibull regression for longer term risk (HR)	
RRs for post-trial all-cause mortality		
Angina	1.21 (1.03 to 1.43)	Rosengren et al (1998)[82]
UA/NSTEMI	1.55 (1.31 to 1.84)	Allen et al (2006)[83]
STEMI	1.84 (1.52 to 2.20)	Allen et al (2006)[83]
Re-infarcted NSTEMI	2.93 (2.34 to 3.66)	Mueller et al (1995)[84]
Re-infarcted STEMI	3.48 (2.77 to 4.37)	Mueller et al (1995)[84]
Stroke	2.39 (1.44 to 3.97)	Taneja et al (2004)[85]
Utility decrements compared to general population		
ACS	0.0409 (±0.0002)	Sullivan et al (2006)[86]
Stroke	0.0524 (±0.0001)	Sullivan et al (2006)[86]
Major bleed	25% decrement to population norm for 14 days	Assumption
Cost per hospitalisation (weighted)		
Clopidogrel	£3,070	Manufacturer submission
Prasugrel	£3,081	Manufacturer submission
Drug acquisition costs		
Clopidogrel	£0.24, loading dose £0.07/day, maintenance dose	NHS Drug Tariff[28] 75mg (28 tab) £1.83
Prasugrel	£10.20, loading dose £1.70/day, maintenance dose	MIMS August 13 (based upon £47.56 per pack of 28 tablets)[87]

ACS=acute coronary syndrome; HR=hazard ratio; NSTEMI=non-STsegment elevation myocardial infarction; OR=odds ratio; RR=relative risk; STEMI=ST segment elevation myocardial infarction; SPC=Summary of Product Characteristics; UA=unstable angina

6.2.3 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 health related quality of life.

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 endpoint 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) endpoints predicted by these equations were disaggregated from their combinations into specific event types (e.g. CV death, nonfatal MI and stroke).

The primary endpoint risk equations played no part in predicting survival beyond the trial. Relative risks for all-cause mortality were applied to general population (life table based) mortality rates adjusted to exclude deaths from CV causes. The relative risks 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.

Table 18 Transition probabilities, duration and event description

Section	Period	Incident event	Type of event
Risk of primary endpoint event (CV death, MI, stroke) following PCI	3 days	Logistic	Multinomial logistic for CV death, nonfatal MI and nonfatal stroke
	4 days - 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 - 12 months	Weibull	
Risk of events and mortality following treatment phase	12 months - 40 years	Cause elimination life tables adjusted for trial events RRs	Mortality and hospitalisations

CV=cardiovascular; MI=myocardial infarction; PCE=percutaneous coronary stent

Risk of a primary end point

Probabilities of primary endpoint 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, nonfatal MI, or a nonfatal stroke (MS, pg 98). The risk equations in the model focus on time to first event only; although where a nonfatal 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, pg 98). The model definition of bleeds does not exclude CABG-related bleeds. Nonfatal bleeds are not treated as on-going health states within the model (such events only incur 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.

Multiple events

Patients who experience a trial endpoint in some cases experienced multiple events. The risk equations focus on the time to first event only, although, where a nonfatal 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 re-hospitalisations.

Extrapolation beyond the trial period

Based on treatment follow-up of 15 months in TRITON-TIMI[36] 38, 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 lower risks for 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, relative risks from four studies[82-84,88] of patients who had undergone revascularisation were used. Indirect comparisons were used to derive relative risks of mortality compared with coronary heart disease-free patients for each health state included in the model.

The manufacturer adjusted actuarial life tables by relative risks 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 ICD-1- 100-199) (MS, pg 101).

The relative risks used to model the period beyond 12 months are shown in Table 19.

Table 19 Indirect relative risks of mortality compared with coronary heart disease–free mortality in patients with the health states included in the manufacturer's model

Health State	Source	Details of study	Indirect relative risk (95% CI) vs CHD-free mortality	
			Non-revascularised	Revascularised
Angina	Rosengren et al (1998)[82]	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) [83]	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)[84]	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)[85]	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; CI=confidence interval; NSTEMI=non-ST segment elevation myocardial infarction; RR=relative risk; STEMI=ST segment elevation myocardial infarction

6.2.4 Population

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

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 5mg maintenance dose
ACS core	Core clinical cohort, patients without prior TIA/stroke, aged <75 years and ≥60kg
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)

ACS=acute coronary syndrome; NSTEMI=non-ST segment elevation myocardial infarction; STEMI=ST segment elevation myocardial infarction; UA=unstable angina

6.2.5 Interventions and comparators

The economic evaluation compares prasugrel in combination with aspirin to 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 60mg loading dose and then continued at 10mg once a day for up to 12 months in combination with aspirin (75-325mg). Clopidogrel was initiated with a single 300mg loading dose and then continued at 75mg 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.

6.2.6 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,[89] 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).

6.2.7 Health related quality of life

Although the TRITON-TIMI 38[36] trial included a HRQoL sub-study, the manufacturer reports that it was not possible to provide robust HRQoL estimates due 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 (pg 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[86] 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,[90] 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).

6.2.8 Resources and costs

The key categories of cost estimates in the MS are related to (i) hospitalisations and (ii) 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 endpoints or to serious adverse events requiring re-hospitalisation and potentially related to the ACS condition or the PCI intervention were included in the cost analysis.	These represent all re-hospitalisations clinically adjudicated as relevant to the trial population and intervention irrespective of adjudicated endpoints. Regression (Poisson) methods were used to predict rates of re-hospitalisation conditional on clinical event histories
	Re-hospitalisations were valued at a weighted average unit cost per hospitalisation (using NHS reference costs)	DRGs were allocated to 2,487 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 sub-study across 8 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 anti-platelet costs (e.g. clopidogrel) but the acquisition cost continued to be applied during hospitalisations in the model, potential double counting.	Double counting of anti-platelet 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.

ACS=acute coronary syndrome; DRG=diagnostic related group; HRG=health related group; ICER=incremental cost-effectiveness ratio; PCI=percutaneous coronary intervention

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	MIMS August 13 (based upon £47.56 per pack of 28 tablets)[87]
Clopidogrel	£0.24	£0.07	NHS Drug Tariff[28] 75mg (28 tab) £1.83
Aspirin		£0.01	

Cost of hospitalisations in TRITON-TIMI 38

TRITON-TIMI 38[36] included a pre-planned economic sub-study which recorded the occurrence of re-hospitalisations associated with serious adverse events over a 12-month period in eight countries: Australia, Canada, US, France, Germany, UK, Spain and Italy. The hospitalisation sub-study covered the trial period and focussed on 2,487 hospitalisations from 6,705 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.

Table 23 Summary of hospitalisation resource use and unit costs

Economic sub-study sample	Clopidogrel (n=3,332)	Prasugrel (n=3,373)
Total hospitalisations (n)	1,259	1,228
Rate of re-hospitalisation per month	0.0256	0.0245
Weighted average unit cost per hospitalisation episode (from trial)	£3,070	£3,081
Weighted average unit cost per hospitalisation (base case)	**£3,070**	**£3,081**

6.2.9 Cost-effectiveness results

Five different subgroups are considered, namely (i) all ACS licensed population (excluding prior stroke/TIA), (ii) ACS Core (excluding prior stroke/TIA and patients <60kg or ≥ 75 years), (iii) UA/NSTEMI, licensed population (excluding prior stroke/TIA), (iv) STEMI, licensed population (excluding prior stroke or TIA), and (v) ACS diabetes, licensed population (excluding prior stroke or TIA). The base case ICERS generated by the manufacturer's model for these five subgroups are presented in Table 24.

Table 24 Cost effectiveness of prasugrel compared with clopidogrel evaluated by subgroup over 40 years

	All ACS licensed population (excluding prior stroke/TIA)			ACS Core (excluding prior stroke/TIA and patients <60kg or ≥ 75 years)			UA/NSTEMI, licensed population (excluding prior stroke/TIA)			STEMI, licensed population (excluding prior stroke or TIA)			ACS diabetes, licensed population (excluding prior stroke or TIA)		
	CLOP	**PRA**	**Ratio or Δ**	**CLOP**	**PRA**	**Ratio or Δ**	**CLOP**	**PRA**	**Ratio or Δ**	**CLOP**	**PRA**	**Ratio or Δ**	**CLOP**	**PRA**	**Ratio or Δ**
Event probabilities															
Cardiovascular 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
Myocardial infarction	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 endpoint	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
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	£5,469	£6,062	£593	£5,867	£6,463	£596	£5,480	£6,067	£587	£5,437	£6,046	£609	£5,209	£5,809	£600
Cost per life year			£8,847			£8,979			£11,661			£5,337			£3,550
Cost per QALY			£11,660			£11,796			£15,452			£6,987			£4,675

CLOP=clopidogrel; PRA=prasugrel; QALY=quality adjusted life year; ACS=acute coronary syndromes; UA=unstable angina; NSTEMI=non-ST segment elevation myocardial infarction; STEMI=ST segment elevation myocardial infarction

6.2.10 Sensitivity analyses

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

Table 25 One-way sensitivity analyses for ACS core clinical cohort

		Clopidogrel			Prasugrel			Incremental				
		LYs	QALYs	Costs	Lys	QALYs	Costs	∆ LYs	∆ QALYs	∆ Costs	£ / LY	£ / QALY
Base case		14.14	10.97	5,867	14.20	11.02	6,463	0.07	0.05	596	8,979	11,796
Discounting	0.00%	21.56	16.65	8,917	21.68	16.74	9,546	0.12	0.09	628	5,147	6,787
	6.00%	11.11	8.64	4,622	11.16	8.68	5,203	0.05	0.04	581	12,574	16,475
Haemorrhage disutility	(120 days) x 8	14.14	10.96	5,864	14.20	11.01	6,461	0.07	0.05	596	8,979	11,851
MI / stroke disutility	x 0.5	14.14	10.97	5,864	14.20	11.02	6,461	0.07	0.05	596	8,979	11,966
	x 1.5	14.14	10.96	5,864	14.20	11.01	6,461	0.07	0.05	596	8,979	11,630
Mortality RR	x 0.5	14.27	11.06	5,916	14.30	11.09	6,501	0.04	0.03	584	15,775	20,619
	x 1.5	14.05	10.90	5,827	14.13	10.96	6,431	0.09	0.07	605	6,919	9,096
Clopidogrel pre-loading adjustment	70%	14.15	10.97	5,867	14.20	11.02	6,461	0.06	0.04	593	10,631	13,959
NHS Reference costs (HRG)	x 0.5	14.14	10.97	2,945	14.20	11.02	3,535	0.07	0.05	590	8,892	11,682
	x 0.8	14.14	10.97	4,696	14.20	11.02	5,290	0.07	0.05	594	8,944	11,750
	x 1.2	14.14	10.97	7,032	14.20	11.02	7,631	0.07	0.05	599	9,014	11,841
	x 1.5	14.14	10.97	8,784	14.20	11.02	9,386	0.07	0.05	602	9,066	11,909

* The core clinical cohort is defined as ACS patients without prior TIA/stroke, aged <75 years and ≥60kg. Numbers may not compute due to rounding; HRG=health care resource group; LY=life years; MI=myocardial infarction; CLOP=clopidogrel; PRA=prasugrel; QALY=quality adjusted life years; RR=relative risk

6.2.11 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 need to allow for competing risks
- Differences in discounting approaches
- Treatment costs reflecting usage and pack wastage
- Alternate utility values, i.e. those derived from the HODAR database
- Reduced incidence of nonfatal MIs such that the underlying rate of MIs is 50% that recorded in the TRITON-TIMI[36] trial
- Amended long-term relative risks of mortality by ignoring the initial impact of ACS prior to TRITON-TIMI related events, i.e. ignoring the sources from Rosengren et al.[82]

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.

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

	UA/NSTEMI		STEMI		ACS diabetes		ACS Core	
	CLOP	PRA	CLOP	PRA	CLOP	PRA	CLOP	PRA
Life years	14.64	14.68	15.04	15.14	13.97	14.12	15.74	15.79
QALYs	9.74	9.76*	10.04	10.11	9.26	9.36	10.51	10.54
Costs	6,047	6,644	6,203	6,825	5,809	6,430	6,487	7,092
Cost per life-year		£16,713		£5,834		£3,952		£11,509
Cost per QALY		£25,504		£8,827		£6,002		£17,439
Base case cost/QALY		£15,542		£6,987		£4,675		£11,796

ACS=acute coronary syndrome; MI=myocardial infarction; NSTEMI=non-ST segment elevation myocardial infarction; STEMI= ST segment elevation myocardial infarction; QALY=quality adjusted life year; RR=relative risk; UA=unstable angina; * the AG altered the QALY value to enable the ICER to equal £25,504, probably a transcription error by the manufacturer

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 Section 6.3.1.

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 cardiovascular 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[91] trial instead of 15 month data from the TRITON-TIMI 38[36] trial

- to fulfil the remit stated by NICE and to fully review 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.

6.3 Independent economic assessment: Methods

6.3.1 Background and modelling rationale

The manufacturer of prasugrel has chosen to resubmit the same decision model previously employed for the NICE 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)

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)

Since these serious concerns have not been addressed by the manufacturer in the model submitted for this re-appraisal 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 health-related quality of life.

6.3.2 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 less than 60kg or those aged over 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.

6.3.3 Treatment options

No suitable clinical evidence has been identified which 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.

6.3.4 Model design and structure

The AG for this review also acted as AG for the re-appraisal of clopidogrel and modified release dipyridamole for the prevention of occlusive vascular events. That re-appraisal was an update of NICE guidance TA90[92] and resulted in the publication of TA210[93] which was issued in December 2010. In TA210[93] NICE made recommendations concerning the use of

clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. As part of the TA210[93] 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 preventive 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[91] clinical trial, supplemented with data provided by the manufacturer of dipyridamole from the PROFESS[94] clinical trial and some additional published trial results. The additional data included follow-up results for 3 years from the start of preventive therapy.

The AG has concluded that the MI sub-population model used in the development of TA210[93] (the TA210[93] model), which was based largely on CAPRIE[91] 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[91] data is 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[93] 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[93] 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[93] 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 the patient had suffered a severely disabling stroke (modified Rankin Scale 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) (Table 27). The model then traces the long-term accumulating event history separately for males and females within each of the four sub-populations, using gender specific parameter values (Table 28).

6.3.5 Assessment of uncertainty

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 vs clopidogrel as measured after 40 years follow-up.

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 due to events occurring during the year.

(Columns show the initial health state, rows show in-year events and the table body shows the end of year health state)

	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
Nonfatal 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
Nonfatal 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
Nonfatal 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	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead	Dead
Nonfatal IS 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
Nonfatal IS 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

MI=myocardial infarction; HS=haemorrhagic stroke; IS=ischaemic stroke/transient ischaemic attack; D=disabled (Rankin 3-5); ND=not disabled (Rankin 0-2); OVD=other vascular death; NVD=non-vascular death

Table 28 Patients estimated in each health state from manufacturer's short-term statistical model, used as starting values for LRiG long-term Markov model

				Clopidogrel				Prasugrel			
Subgroup	Gender	Number of patients	Mean Age (at 1 year)	No event	Nonfatal MI only	Nonfatal stroke +/- MI	Dead	No event	Nonfatal MI only	Nonfatal 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

6.3.6 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 relative risks remain unchanged from those previously described in the AG report for the development of NICE guidance TA 210,[93] with the exception of the relative risk applying to patients with/without diabetes (Table 31).

Table 29 Event incident risks

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

LCL=lower confidence limit; UCL=upper confidence limit; IS=ischaemic stroke; HS=haemorrhagic stroke; OVD=occlusive vascular disease

Table 30 Event fatality rates

Parameter	Gender	Mean	LCL	UCL
MI fatality odds model – constant	M	0.00986	0.00553	0.01755
MI fatality odds model – age coefficient	M	0.0455	0.0368	0.0541
MI fatality odds model – constant	F	0.00801	0.00125	0.05124
MI fatality odds model – age coefficient	F	0.0538	-0.0192	0.1269
MI subgroup odds multiplier for MI fatality	M	0.574	0.361	0.913
	F	0.584	0.269	1.267
IS fatality odds model – constant	M	0.00212	0.00040	0.011117
IS fatality odds model – age coefficient	F	0.0520	0.0269	0.0770
MI subgroup odds multiplier for IS fatality	M&F	1.673	0.772	3.626
HS fatality	M	32.6%	20.6%	45.9%
	F	59.9%	37.7%	80.1%
Event (MI/stroke) order odds multiplier :				
1st event	M&F	0.791	0.693	0.904
2nd event	M&F	1.931	1.593	2.342
3rd event	M&F	4.398	2.936	6.587

LCL=lower confidence limit; UCL=upper confidence limit; IS=ischaemic stroke; HS=haemorrhagic stroke

Table 31 Relative risk of key events for patients with diabetes vs no diabetes

Event	Relative risk	Standard error	LCL	UCL	Source
MI	1.339	0.082	1.141	1.571	Malmberg (2000)[95] Table 3
Stroke	1.446	0.144	1.091	1.921	Malmberg (2000)[95] Table 3
OVD	2.121	0.262	1.269	3.544	Kleinman (1988)[96] Table 3 weighted average of males & females
NVD	1.242	0.233	0.787	1.960	Kleinman (1988)[96] Table 3 weighted average of males & females

MI=myocardial infarction; OVD=occlusive vascular event; NVD=non-vascular death; LCL=lower confidence limit; UCL=upper confidence limit

6.3.7 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 300mg clopidogrel or 60mg prasugrel is included.

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 (*adjusted for treatment duration)	£18.43*	£511.67*	£10.70
Total dual antiplatelet therapy cost (year 1)	**£29.37**	**£532.56**	-
Annual maintenance cost	-	-	**£10.70**

6.3.8 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[97] to 2012 prices. The revised costs are shown in

Table 33.

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

	Mean	Standard error	LCL	UCL
Event				
Fatal MI	£2,373.68	£121.11	£2,136.31	£2,611.05
Nonfatal MI	£6,165.21	£314.55	£5,548.69	£6,781.73
Fatal stroke	£9,381.43	£478.64	£8,443.29	£10,319.57
Nonfatal non-disabling stroke	£6,858.64	£349.93	£6,172.77	£7,544.50
Nonfatal disabling stroke	£14,602.70	£754.04	£13,142.43	£16,062.97
OV death	£2,407.50	£122.83	£2,166.75	£2,648.25
NV death	£2,407.50	£122.83	£2,166.75	£2,648.25
Annual cost in health state				
Event free / MI only	£618.03	£31.53	£556.23	£679.84
Non-disabling stroke	£1,804.06	£92.04	£1,623.66	£1,984.47
Disabling stroke	£5,537.72	£282.54	£4,983.95	£6,091.50

MI=myocardial infarction; OV=other vascular; NV=non-vascular; LCL=lower confidence limit; UCL=upper confidence limit

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 nonfatal MI (but no strokes) and who were alive 12 months after the index PCI was derived from the economic sub-study of the PLATO[33] clinical trial, and based on a weighted average of patients with no event or nonfatal MI after 12 months of follow-up.[98]

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).[99] These reflect gender differences and mild vs 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 or over.[90] 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[41] cohort and the OXVASC[99] 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.

Initial event disutility

Seven model events (four fatal and three nonfatal) 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 (nonfatal 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.[100] Sources for nonfatal 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 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.

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

	Mean	Standard error	LCL	UCL
Event				
Fatal MI	-0.100	-	0.000	-0.200
Nonfatal MI	-0.037	0.056	-0.147	+0.073
Fatal stroke	-0.100	-	0.000	-0.200
Nonfatal non-disabling stroke	0.000	-	0.000	-0.200
Nonfatal 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

MI=myocardial infarction; OV=other vascular; NV=non-vascular; LCL=lower confidence limit; UCL=upper confidence limit

6.3.9 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.

6.3.10 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.

6.3.11 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 on-going 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.[93] 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[91] 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[91] data. This advice indicated that the CAPRIE[91] 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 events occurring each year. In the TA210[93] 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, since the duration of the primary trial (TRITON-TIMI 38[36]) was no more than 15 months, and the CAPRIE trial,[91] 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[93] 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.

6.3.12 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.

6.4 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 Appraisal Committee 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. 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.

6.4.1 STEMI - 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, due to the inclusion of the full additional cost of treatment with prasugrel, whilst 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 whilst 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 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 £1,000 to £2,500 per QALY gained.

Probabilistic analysis at the 40 year follow-up horizon for this subgroup yields a higher estimated ICER (£3,363 per QALY gained) derived from very small incremental cost and QALY estimates (+£1.19 and +0.00035 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.

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 dis-counted
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

QALY=quality adjusted life year

Table 37 Mean deterministic estimated costs for STEMI patients with diabetes

Follow-up	Drug costs	Mean costs in health state				Event costs			Cost	
Treatment		Event free	MI(s) only	Mild stroke +/- MI(s)	Severe stroke +/- MI(s)	MI	Stroke	Death	Total	Total dis-counted
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

Follow-up	Total cost		Total QALYs		Incremental		ICER (£ per QALY)
	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	
1 year	£1,465	£1,695	0.882	0.889	+£230	+0.007	£31,915
5 years	£5,454	£5,723	3.846	3.904	+£269	+0.059	£4,603
10 years	£10,277	£10,552	6.475	6.603	+£275	+0.129	£2,139
20 years	£17,013	£17,363	9.171	9.400	+£350	+0.228	£1,537
40 years	£19,904	£20,351	10.054	10.326	+£447	+0.272	£1,640

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

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

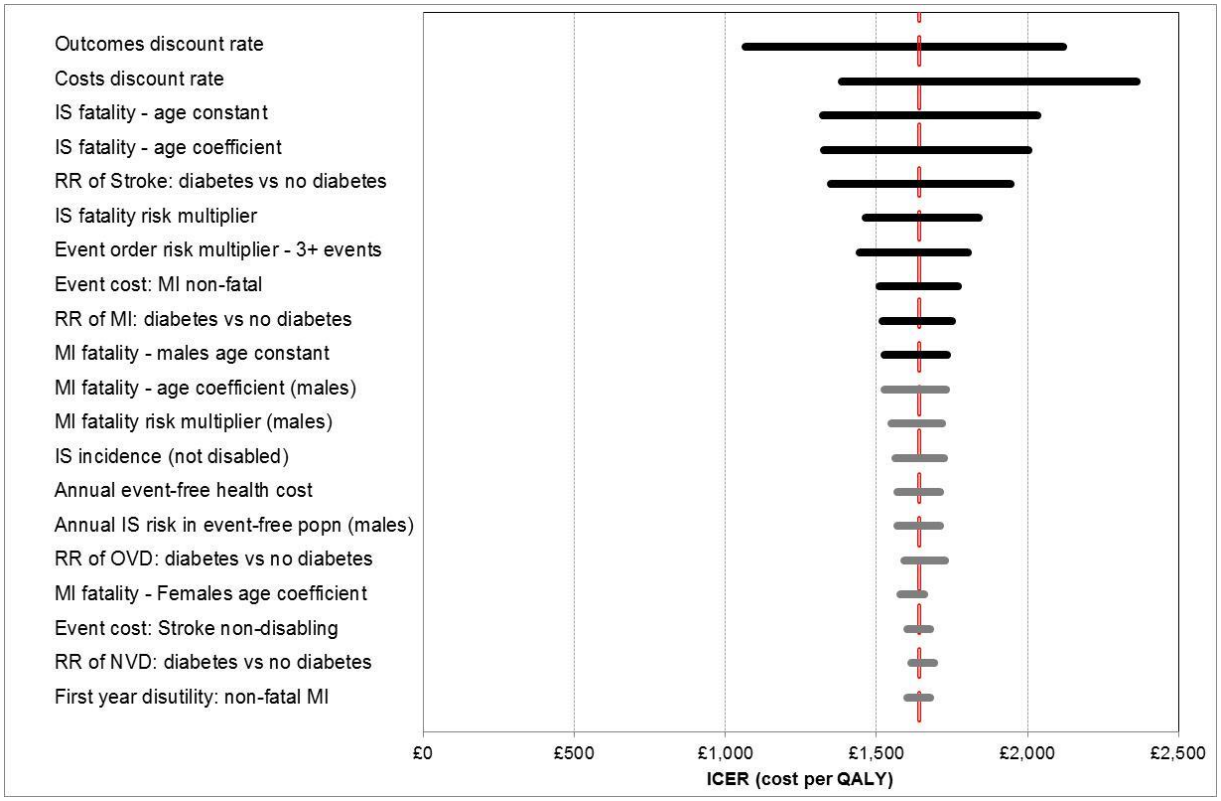


Figure 5 PSA scatterplot of prasugrel vs clopidogrel for STEMI patients with diabetes

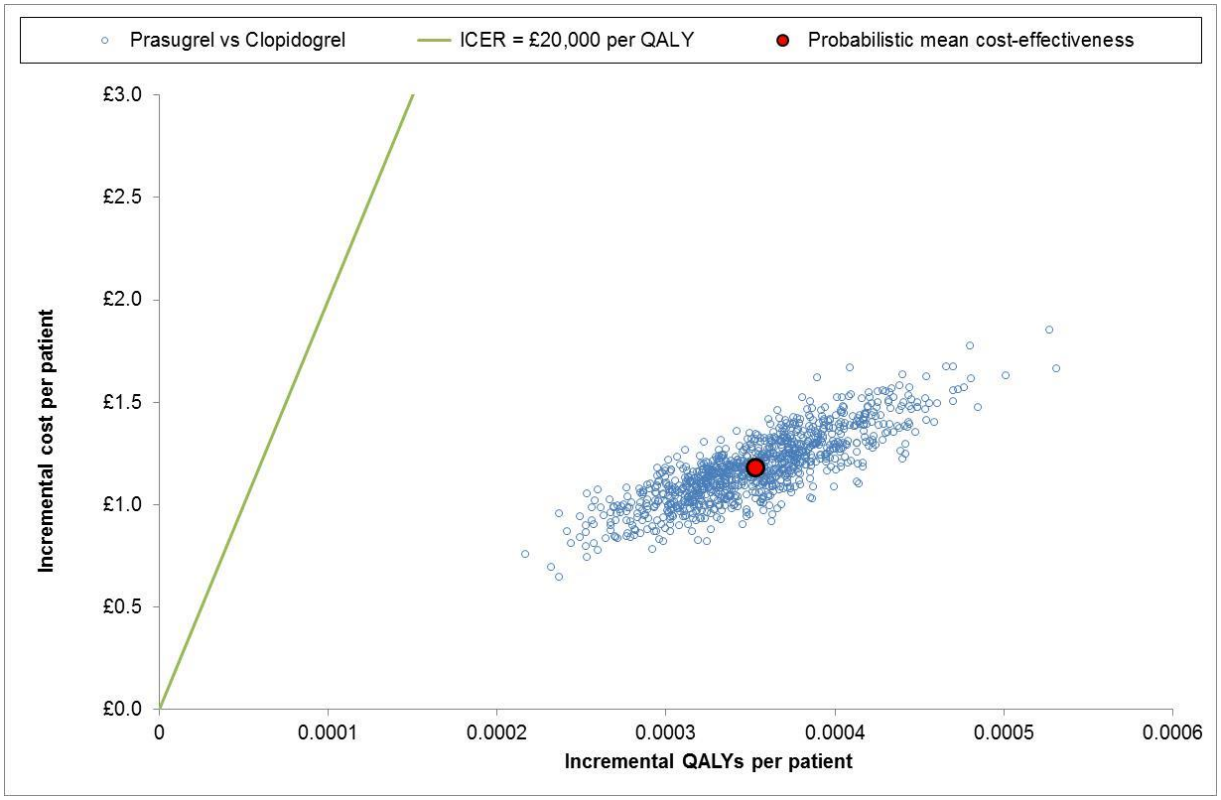
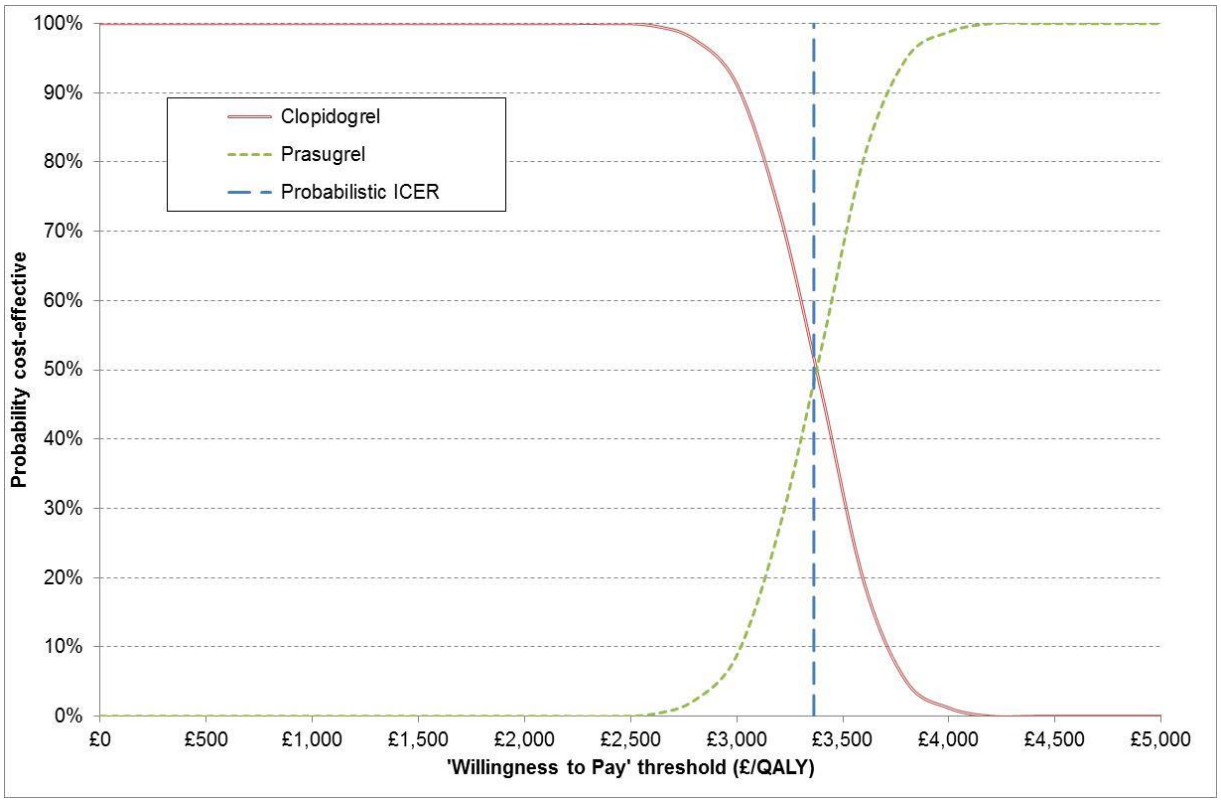


Figure 6 CEAC of prasugrel vs clopidogrel for STEMI patients with diabetes



6.4.2 STEMI - 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, due to the inclusion of the full additional cost of treatment with prasugrel, whilst 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 whilst 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 £4,000 and £9,000 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 (£3,303 per QALY gained) derived from very small incremental cost and QALY estimates (+£0.64 and +0.00019 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.

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 dis-counted
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

QALY=quality adjusted life year

Table 41 Mean deterministic estimated costs for STEMI patients without diabetes

Follow-up	Drug costs	Mean costs in health state				Event costs			Cost	
Treatment		Event free	MI(s) only	Mild stroke +/- MI(s)	Severe stroke +/- MI(s)	MI	Stroke	Death	Total	Total dis-counted
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

Follow-up	Total cost		Total QALYs		Incremental		ICER (£ per QALY)
	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	
1 year	£1,183	£1,605	0.905	0.907	+£422	+0.002	£224,302
5 years	£5,044	£5,510	3.992	4.008	+£465	+0.016	£29,607
10 years	£9,931	£10,414	6.792	6.828	+£482	+0.036	£13,370
20 years	£17,354	£17,870	9.805	9.872	+£516	+0.067	£7,670
40 years	£21,167	£21,722	10.950	11.033	+£555	+0.084	£6,626

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

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

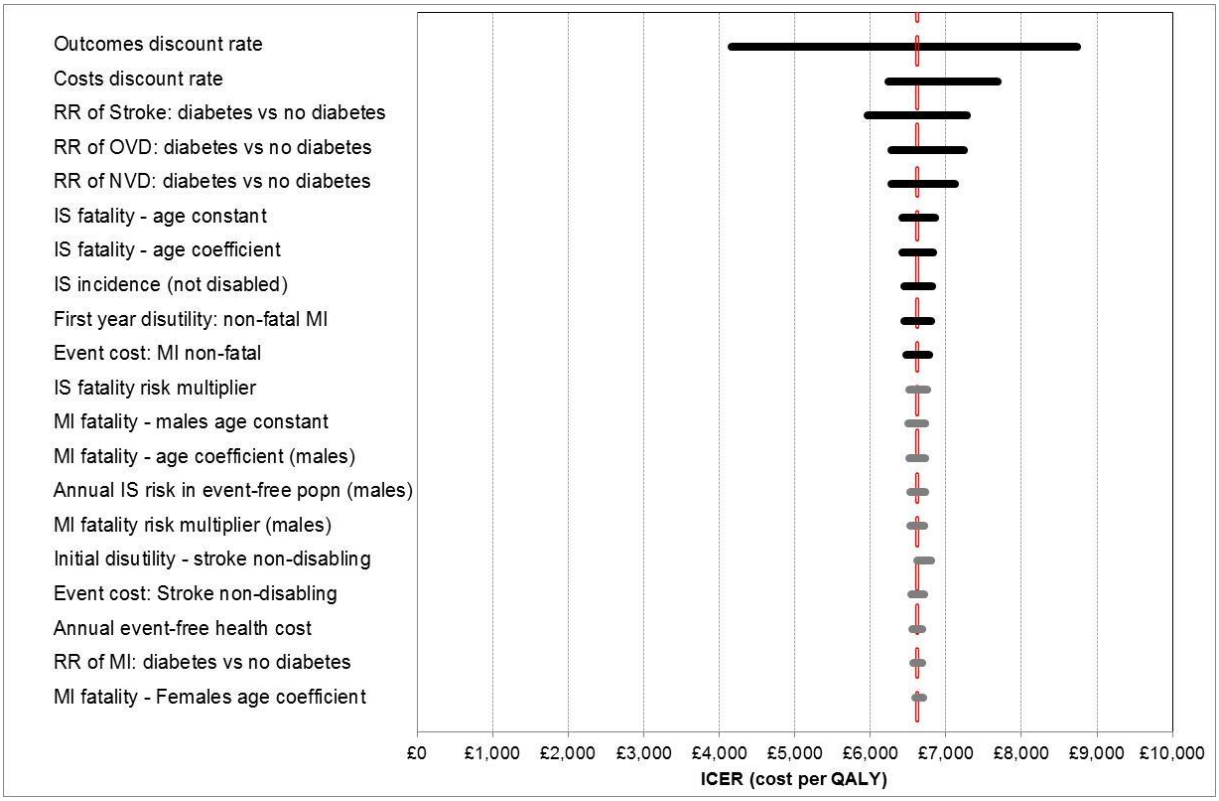


Figure 8 PSA scatterplot of prasugrel vs clopidogrel for STEMI patients without diabetes

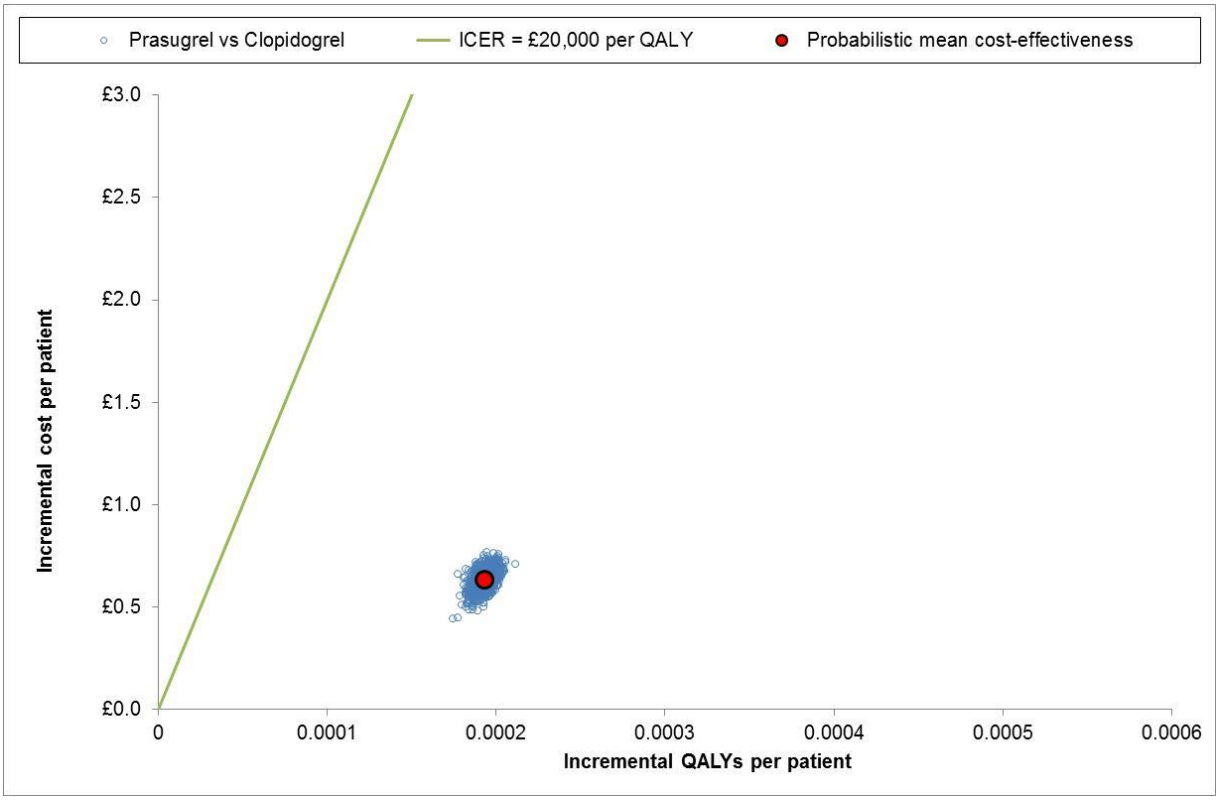
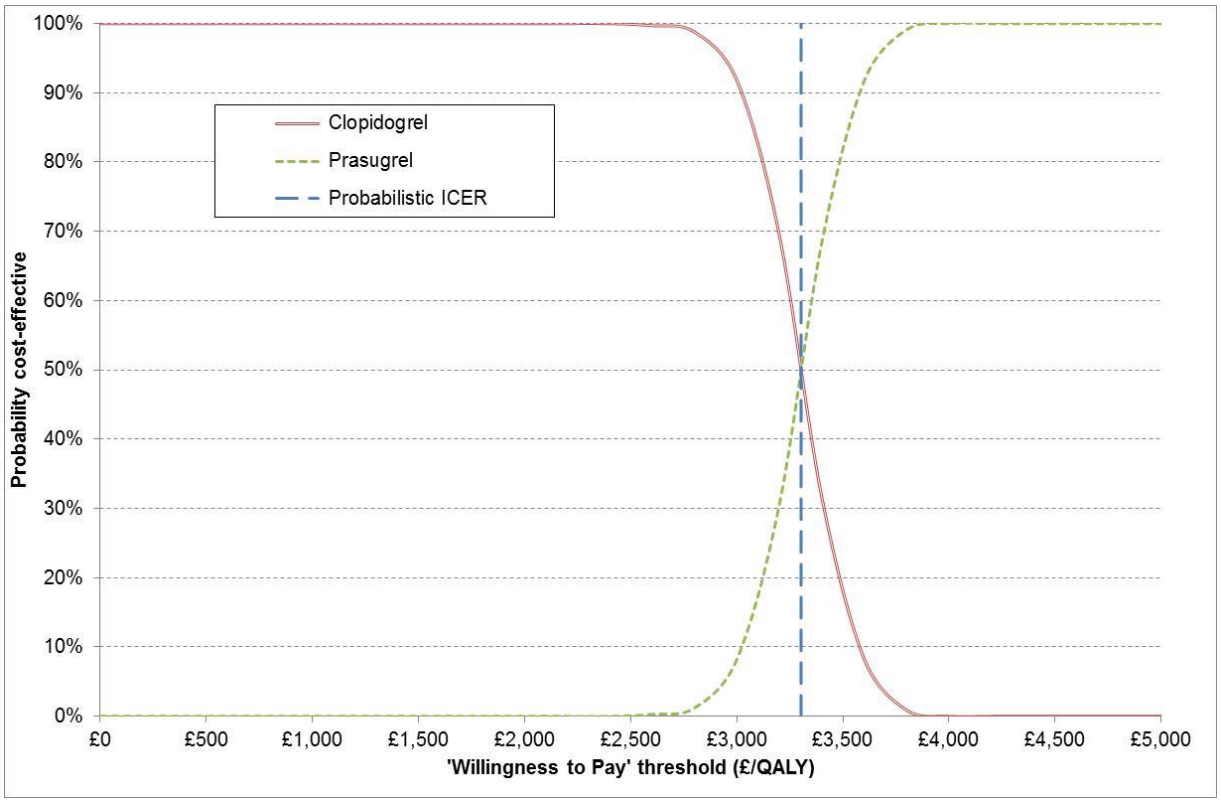


Figure 9 CEAC of prasugrel vs clopidogrel for STEMI patients without diabetes



6.4.3 UA/NSTEMI - 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, due to the inclusion of the full additional cost of treatment with prasugrel, whilst 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 whilst 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 -£1,000 and +£400 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 £2,792 per QALY gained, derived from very small incremental cost and QALY estimates (+£0.53 and +0.00019 respectively). The scatterplot (Figure 11) and CEAC

for this subgroup (Figure 12) indicate the relative cost effectiveness of prasugrel despite the long-term erosion of incremental differences over time.

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 dis-counted
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

QALY=quality adjusted life year

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

Follow-up	Drug costs	Mean costs in health state				Event costs			Cost	
Treatment		Event free	MI(s) only	Mild stroke +/- MI(s)	Severe stroke +/- MI(s)	MI	Stroke	Death	Total	Total dis-counted
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

Follow-up	Total cost		Total QALYs		Incremental		ICER (£ per QALY)
	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	
1 year	£1,383	£1,642	0.883	0.887	+£259	+0.003	£76,856
5 years	£5,391	£5,487	3.858	3.892	+£96	+0.034	£2,846
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

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

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

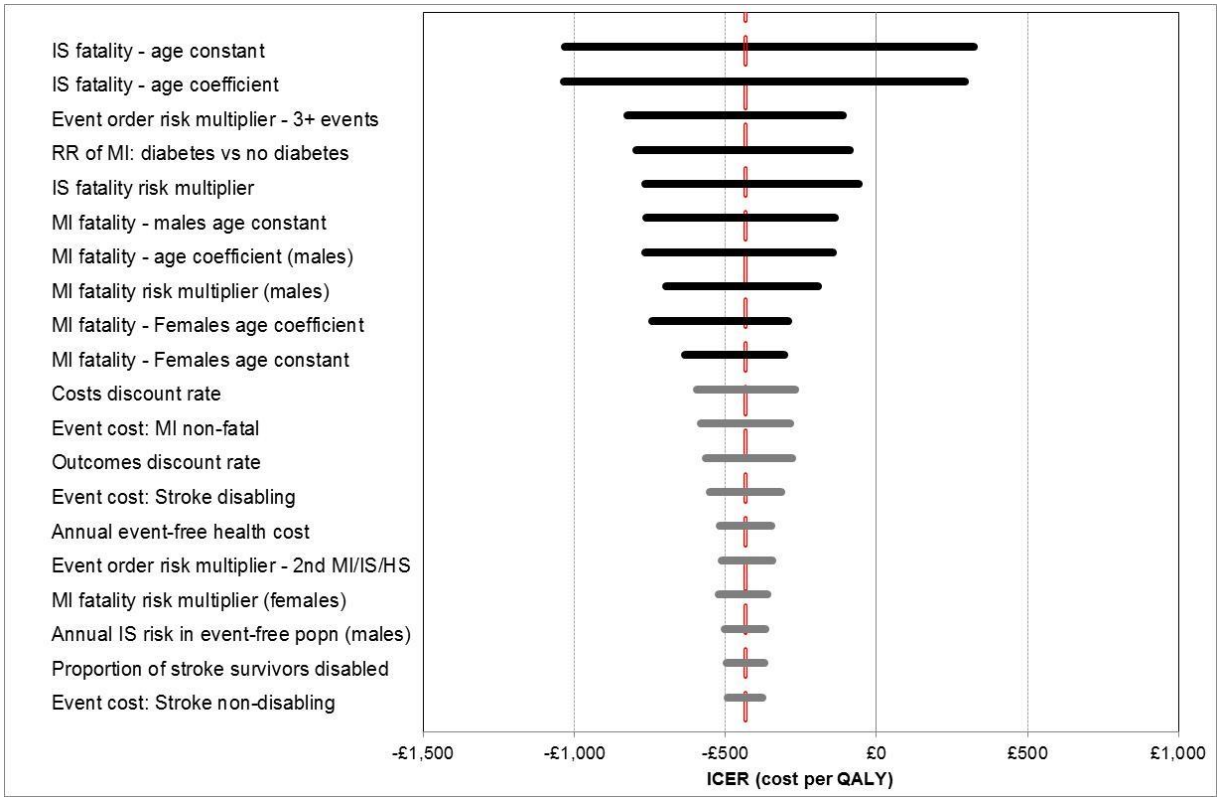


Figure 11 PSA scatterplot of prasugrel vs clopidogrel for UA/NSTEMI patients with diabetes

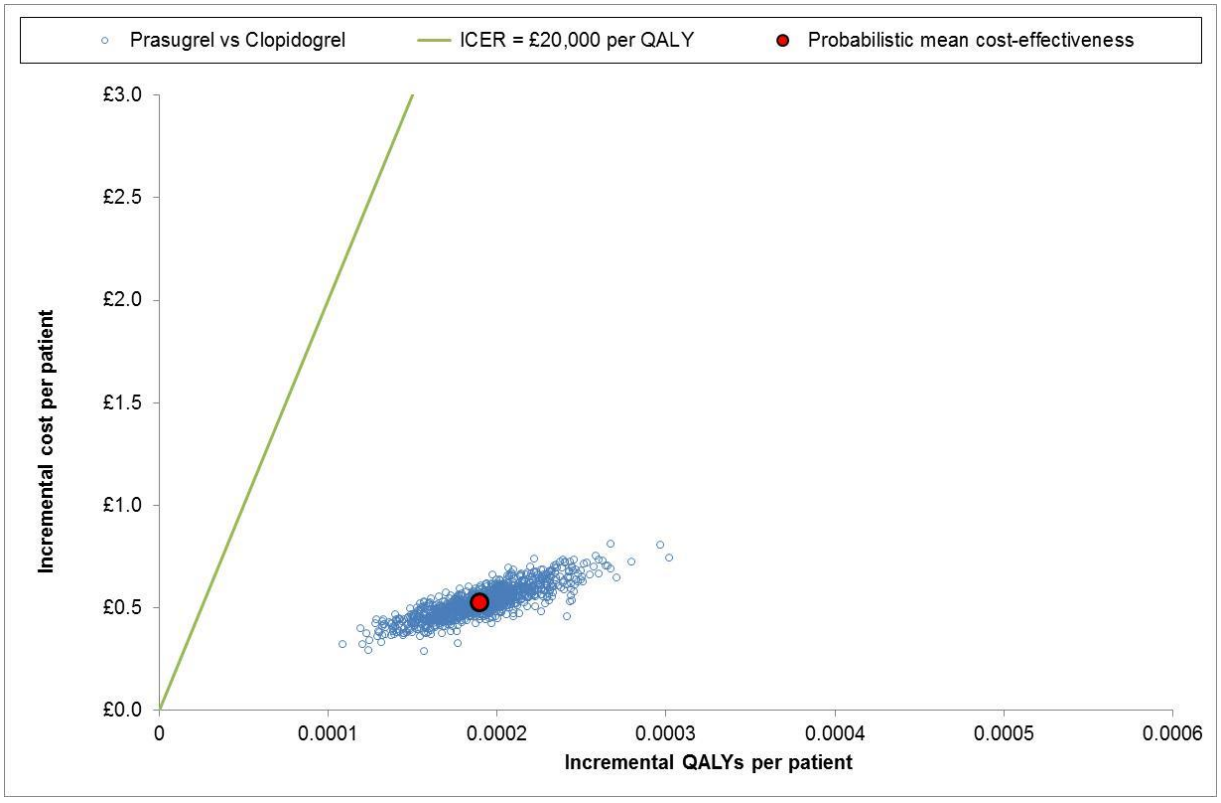
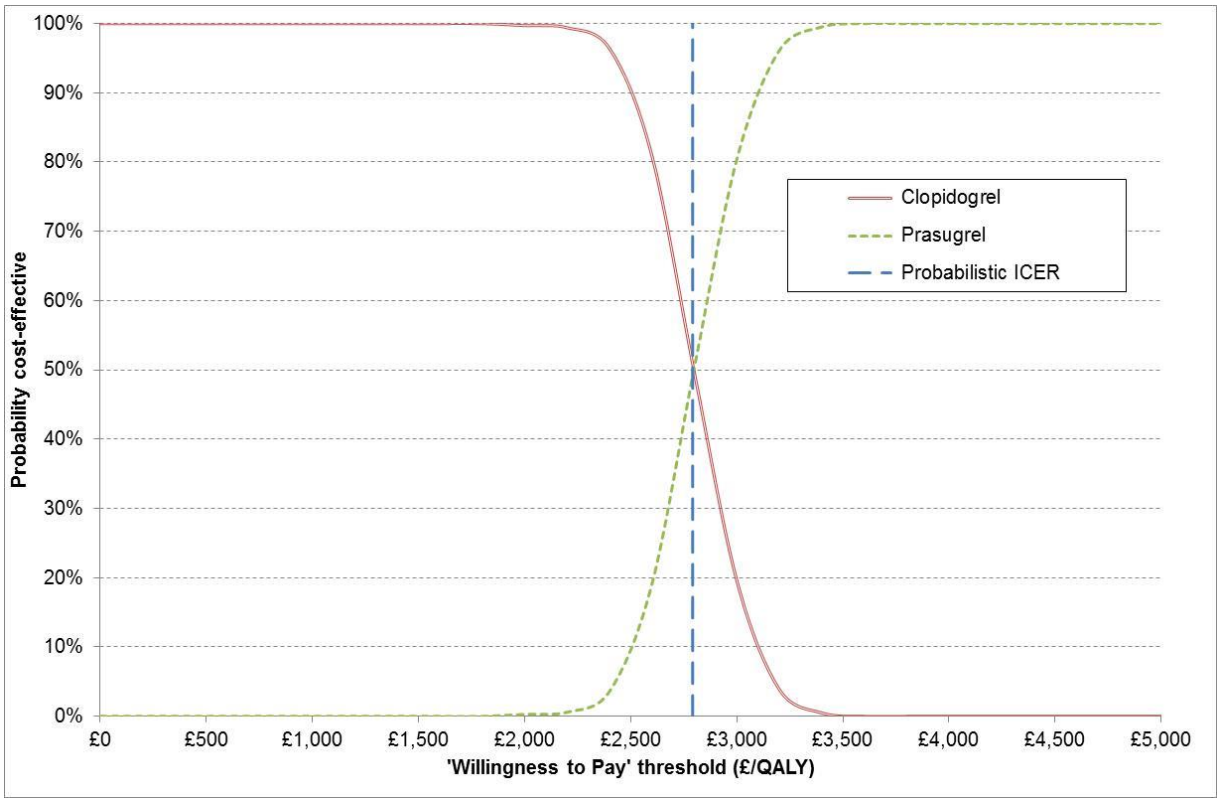


Figure 12 CEAC of prasugrel vs clopidogrel for UA/NSTEMI patients with diabetes



6.4.4 UA/NSTEMI – 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, due to the inclusion of the full additional cost of treatment with prasugrel, whilst 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 whilst incremental cost increases at a slower rate. The ICER for prasugrel compared with clopidogrel falls below £30,000 per QALY gained after 10 years.

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 £2,500 and +£6,500 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 low estimated ICER of £2,158 per QALY gained, derived from very small incremental cost and QALY estimates (+£0.24 and +0.00011 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.

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 dis-counted
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

QALY=quality adjusted life year

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

Follow-up	Drug costs	Mean costs in health state				Event costs			Cost	
Treatment		Event free	MI(s) only	Mild stroke +/- MI(s)	Severe stroke +/- MI(s)	MI	Stroke	Death	Total	Total dis-counted
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

Follow-up	Total cost		Total QALYs		Incremental		ICER (£ per QALY)
	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	
1 year	£1,192	£1,604	0.90097	0.90134	+£413	+0.00037	£1,101,662
5 years	£5,091	£5,437	3.972	3.979	+£346	+0.007	£52,288
10 years	£9,920	£10,200	6.732	6.751	+£280	+0.020	£14,276
20 years	£17,002	£17,239	9.637	9.678	+£237	+0.042	£5,688
40 years	£20,328	£20,576	10.655	10.708	+£248	+0.053	£4,667

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

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

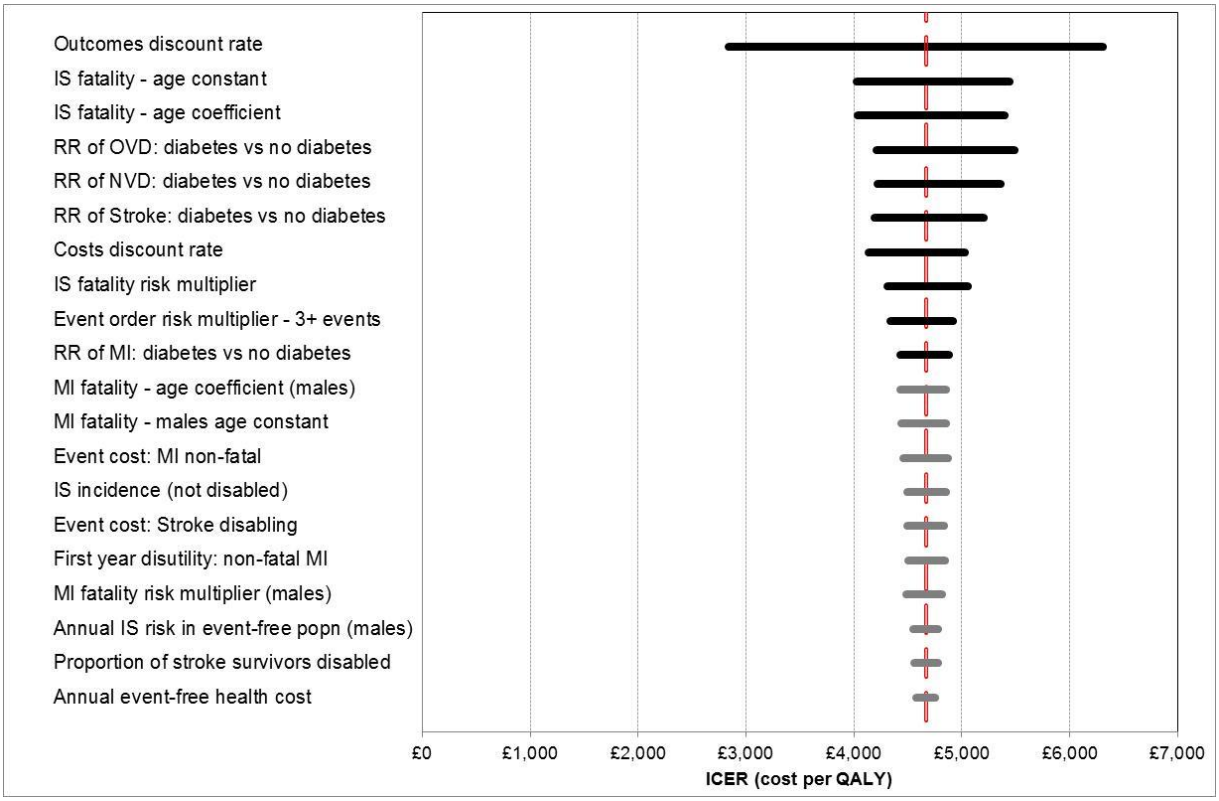


Figure 14 PSA scatterplot of prasugrel vs clopidogrel for UA/NSTEMI patients without diabetes

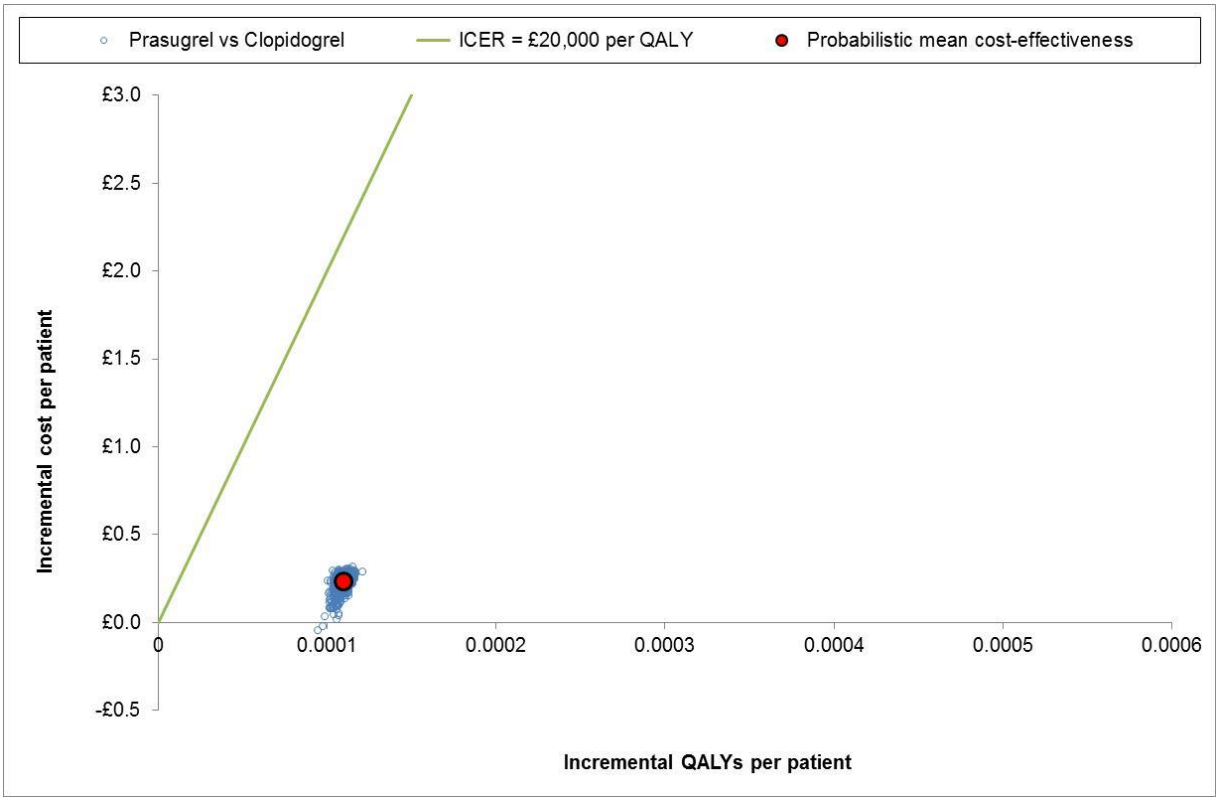
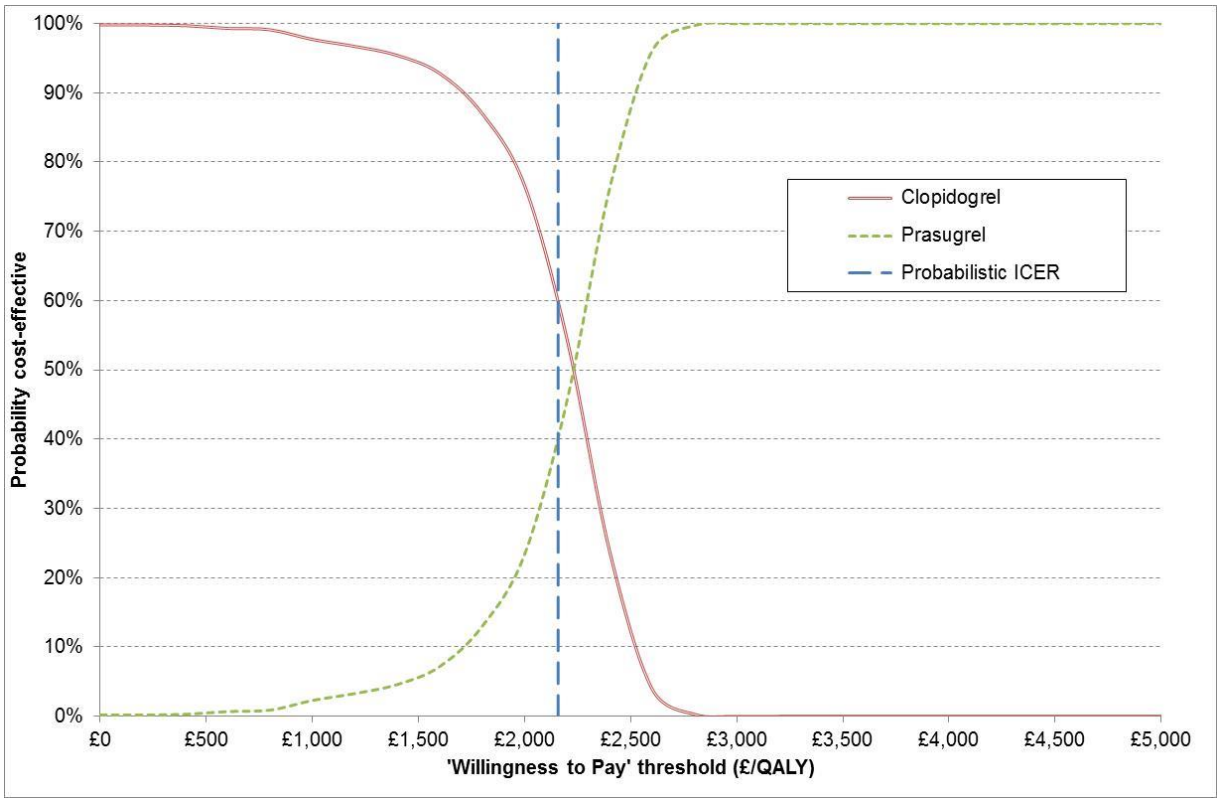


Figure 15 CEAC of prasugrel vs clopidogrel for UA/NSTEMI patients without diabetes



6.5 Independent economic assessment: Discussion of cost-effectiveness evidence

The main concern expressed by the ERG in their 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[91] 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 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 to 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[91] 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.

7 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.

8 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; this means that the present review is largely based on the clinical evidence available for TA182.[21]

8.1 Statement of principle findings

8.1.1 Clinical effectiveness

This review focussed 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 less than 60kg or those aged over 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. 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 vs ticagrelor still remain unknown.

8.1.2 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] which excluded patients from treatment with prasugrel if they had not suffered from 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 to10 years, it appears likely that prasugrel is a cost-effective treatment option when compared with clopidogrel for all four subgroups.

8.1.3 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 vs 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[91] 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 vs 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 out to 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 to 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 model were primarily derived from a single RCT (CAPRIE).[91] The AG notes that both RCTs recruited large numbers of patients and were well conducted and well reported.

8.1.4 Uncertainties

The three areas of uncertainty noted by the AC for TA182[21] were re-considered 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 300mg loading dose of clopidogrel (administered in TRITON-TIMI 38[36]) with a 600mg 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 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 effectiveness and safety of prasugrel vs ticagrelor remains unknown. However, the AG is aware of an RCT[101] that commenced recruiting patients in September 2013. The ISAR-REACT 5[101] trial is designed to assess whether 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[101] trial will allow a formal comparison of the efficacy of prasugrel vs ticagrelor.

9 CONCLUSIONS

9.1 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 5[101] trial, if conducted well, could fill the current gap in evidence related to the comparative efficacy and safety of prasugrel vs ticagrelor.

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110. 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: Cardiovascular Interventions. 2010; 3:806-11.
111. 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. JClP. 2012; 52:789-97.
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113. 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.
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116. 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. 2008a; 118:1626-36.
117. 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. 2008b; 371:1353-63.
118. 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. JClP. 2009; 49:984-98.

11 APPENDICES

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

Trial	Randomisation			Baseline Comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		ITT	Other outcomes
	Truly random	Allocation concealment	Number stated	Presented	Achieved*			Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated		
Wiviott 2007	✔	✔	✔	✔	✔	✔	✔ a	✔	✔	✔	NS	✔	✔	✔	×

a included use of stents, use of GPIIb/IIIa inhibitors, aspirin, statins, beta-blockers etc; NS=not stated

Appendix 3: Table of excluded studies with rationale

	Paper	Reason for exclusion
1.	(2007) Prasugrel for acute coronary artery syndrome with percutaneous coronary intervention: horizon scanning technology briefing (Structured abstract). Health Technology Assessment Database, 6.	Abstract of review
2.	(2009) Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention (Structured abstract). Health Technology Assessment Database.	Abstract of TA182
3.	(2011) Clopidogrel, Prasugrel and Ticagrelor in adults with acute coronary syndrome: a review of the clinical effectiveness (Structured abstract). Health Technology Assessment Database.	Abstract of Systematic Reviews
4.	(2011) 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 (Structured abstract). Health Technology Assessment Database.	Horizon scanning document
5.	(2012). News from the ESC Congress 2012. British Journal of Cardiology 19(4): 152-155.	Meeting report
6.	(2013).18th Annual Interventional Vascular Therapeutics Angioplasty Summit-Transcatheter Cardiovascular Therapeutics Asia Pacific Symposium, TCTAP 2013. American Journal of Cardiology 1).	Meeting report
7.	(2013). American College of Cardiology's 62nd Annual Scientific Session and i2 Summit: Innovation in Intervention, ACC.13. Journal of the American College of Cardiology 1).	Meeting report
8.	(2013). Society for Cardiovascular Angiography and Interventions' 36th Annual Scientific Sessions. Catheterization and Cardiovascular Interventions 81.	Meeting report
9.	Aalbers, J. (2011). Prasugrel study addresses timing of thienopyridine loading dose in NSTEMI patients pre-PCI (the ACCOAST study). Cardiovascular Journal of Africa 22(3): 168.	Letter
10.	Abdel-Latif, A. and D. J. Moliterno (2009). Prasugrel versus clopidogrel in primary PCI: Considerations of the TRITON-TIMI 38 substudy. Current Cardiology Reports 11(5): 323-324.	Report of a TRITON-TIMI 38 substudy
11.	Alexander, W. (2008). TRITON-TIMI 38: Clopidogrel and prasugrel. Pharmacy and Therapeutics 33(1): 51.	Report of a TRITON-TIMI 38
12.	Alexander, W. (2009). FDA advisory committee meeting on prasugrel for acute coronary syndromes. Pharmacy and Therapeutics 34(3): 155-156.	FDA discussion of prasugrel
13.	Alexander, W. (2012). Cardiovascular research technologies 2012. Pharmacy and Therapeutics 37(3): 186-189.	Discussion document
14.	Alexander, W. (2012). Transcatheter cardiovascular therapeutics 2012. Pharmacy and Therapeutics 37(12): 709-710.	Meeting review
15.	Alexopoulos D, Theodoropoulos KC, Stavrou EF, Xanthopoulou I, Kassimis G. Tsigkas G, et al (2012). Prasugrel versus high dose clopidogrel to overcome early high on clopidogrel platelet reactivity in patients with ST elevation myocardial infarction. Cardiovascular Drugs & Therapy 26(5): 393-400.	Platelet reactivity trial. 30 day outcomes
16.	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: Cardiovascular Interventions. 2012; 5:797-804.	Platelet reactivity trial. 30 day outcomes
17.	Aradi D, Komocsi A, Price M, Cuisset T, Ari H, Hazarbasanov D,	Platelet function

	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.	studies
18.	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. Journal of the American College of Cardiology. 2012; 60:B218..	Abstract of systematic review
19.	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. Thrombosis and Haemostasis. 2013; 109:93-101.	Systematic review
20.	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. Journal of the American College of Cardiology. 2013; 1):E1922.	Registry study
21.	Aradi D, Serebruany VL. No benefit of new-generation antiplatelet agents on stroke compared to clopidogrel. European Heart Journal. 2011; 32:555.	Abstract of systematic review
22.	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. American Journal of Cardiology. 2011; 108:1710-3	Not RCT
23.	Arnesen, H. (2010). Thrombocardiology: An update. Expert Review of Cardiovascular Therapy 8(3): 331-333.	Meeting review
24.	Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. New England Journal of Medicine. 2013; 368:2113-24.	Review
25.	Beigel R, Fefer P, Fink N, Grupper A, Varon D, Hod H, et al. The immidiate antiplatelet effect of prasugrel versus clopidogrel in patients undergoing primary angioplasty for st-elevation myocardial infarction-implications for reperfusion. Journal of the American College of Cardiology. 2012; 1):E503.	Platelet function study
26.	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. Journal of the American College of Cardiology. 2010; 56:1542-51.	Systematic review discussed in main report
27.	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). International Journal of Cardiology. 2011; 151:228-9.	letter
28.	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 (Structured abstract). International Journal of Cardiology. 2011; 150(3	Abstract of indirect treatment comparison discussed in main report
29.	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.	Indirect treatment comparison discussed in main report
30.	CADTH (211-12) A number of Canadian reports. Health Technology Assessment Database, 5.	Various systematic reviews

31.	CADTH (2012) Clopidogrel, prasugrel and ticagrelor in adults with acute coronary syndrome: a review of the clinical effectiveness, cost effectiveness and guidelines (Structured abstract). Health Technology Assessment Database.	Systematic review but not relevant to review
32.	Capodanno D, Tamburino C. Cyphering the statistical and clinical significance of prasugrel in the TRITON-TIMI 38 trial. International Journal of Cardiology. 2011; 146:242-3.	Theoretical paper
33.	Cattaneo M. (2010). New P2Y12 inhibitors. Circulation 121(1): 171-179.	Discussion
34.	Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. New England Journal of Medicine. 2012; 367:2100-9.	Platelet function and tailored treatment trial
35.	De Servi S, Savonitto S. How to explain the reduced cardiovascular mortality in the ticagrelor arm of the PLATO trial? International Journal of Cardiology. 2011; 149:265-7.	Discussion
36.	Dowdall M. Clopidogrel treatment prior to percutaneous coronary intervention questioned by results of recent analysis. Interventional Cardiology (London). 2013; 5:13-4.	Discussion
37.	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). Journal of the American College of Cardiology. 2012; 60:B215.	Platelet function study
38.	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. Journal of the American College of Cardiology. 2012; 60:2032-40. .	Cross-over study
39.	Floyd JS, Serebruany VL. Prasugrel as a potential cancer promoter: review of the unpublished data. Archives of Internal Medicine. 2010; 170:1078-80.	Review
40.	Freeman MK. (2010). Thienopyridine antiplatelet agents: focus on prasugrel. Consultant Pharmacist 25(4): 241-257.	review
41.	Garrett AD. (2012). Ticagrelor tops prasugrel in pharmacodynamic study. Drug Topics 156(9): 20120915.	News article
42.	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. Current Medical Research & Opinion. 2010; 26:2077-85.	Dose-ranging trial
43.	Giugliano, R. P. and E. Braunwald (2010). The year in non-st-segment elevation acute coronary syndrome. Journal of the American College of Cardiology 56(25): 2126-2138.	Review of guidelines
44.	Giugliano, R. P. and E. Braunwald (2011). The year in non ST-segment elevation acute coronary syndrome. Journal of the American College of Cardiology 58(22): 2342-2354.	Review of guidelines
45.	Giugliano, R. P. and E. Braunwald (2012). The year in non-ST-segment elevation acute coronary syndrome. Journal of the American College of Cardiology 60(21): 2127-2139.	Review of guidelines
46.	Goodwin MM, Desilets AR, Willett KC. Thienopyridines in acute coronary syndrome. Annals of Pharmacotherapy. 2011; 45:207-17.	review
47.	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 Technology Assessment (Winchester, England). 2010; 14 Suppl 1:31-8.	Short version of TA182 ERG report

48.	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. European Heart Journal. 2012; 33:41.	Not patient group
49.	Hill, R. A., H. Chung, E. George, C. Longson and A. Stevens (2010). Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention: NICE technology appraisal guidance. Heart 96(17): 1407-1408.	Discussion of NICE decision
50.	IqwiG (2011) Prasugrel in the treatment of acute coronary syndrome (Structured abstract). Health Technology Assessment Database.	German HTA
51.	Jakubowski JA, Riesmeyer JS, Close SL, Leishman AG, Erlinge D. TRITON and beyond: new insights into the profile of prasugrel. Cardiovascular therapeutics. 2012; 30:e174-82.	Review of prasugrel studies to 2007
52.	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. Cardiovascular Drug Reviews. 2007; 25:357-74.	Review of prasugrel studies up to 2012
53.	Jeong YH, Tantry US, Gurbel PA. Importance of potent P2Y(12) receptor blockade in acute myocardial infarction: focus on prasugrel. Expert Opinion on Pharmacotherapy. 2012; 13:1771-96.	Review
54.	Lange, C. G. (2011). Is prasugrel more effective than clopidogrel at preventing future cardiac events? JAAPA 24(2): 52, 55.	Review
55.	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.	Platelet function study
56.	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. Journal of Thrombosis and Thrombolysis. 2011; 32:242-66.	Meeting review
57.	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. Journal of Thrombosis and Thrombolysis. 2012; 34:143-63.	Meeting review
58.	Lopes RD, Granger CB. Interpreting the TRITON results in light of the event adjudication process. Cardiology. 2010; 115:89-90	Commentary
59.	Lynch DR, Jr., Dantzler DM, Jr., Zhao D. Prasugrel versus clopidogrel for acute coronary syndromes. New England Journal of Medicine. 2013; 368:188.	Letter
60.	Manolis AS, Manolis TA, Papadimitriou P, Koulouris S, Melita H. Combined antiplatelet therapy: still a sweeping combination in cardiology. Cardiovascular & Hematological Agents in Medicinal Chemistry. 2013; 11:136-67. .	Not RCT
61.	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 Review of Cardiovascular Therapy. 2009; 7:17-23.	Expert review
62.	Martin MT, Spinler SA, Nutescu EA. Emerging antiplatelet therapies in percutaneous coronary intervention: a focus on	Review

	prasugrel. Clinical Therapeutics. 2011; 33:425-42.	
63.	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. American Heart Journal. 2010; 160:1035-41.	Not comparators of interest
64.	Mohammad RA, Goldberg T, Dorsch MP, Cheng JW. Antiplatelet therapy after placement of a drug-eluting stent: a review of efficacy and safety studies. Clinical Therapeutics. 2010; 32:2265-81.	Review
65.	Montalescot, G. (2009). Benefits for specific subpopulations in TRITON-TIMI 38. European Heart Journal, Supplement 11(G): G18-G24.	Discussion
66.	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
67.	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. Thrombosis & Haemostasis. 2010; 103:213-23.	Not patient population
68.	Motovska Z, Kala P. Benefits and risks of clopidogrel use in patients with coronary artery disease: evidence from randomized studies and registries. Clinical Therapeutics. 2008; 30 Pt 2:2191-202.	Review
69.	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
70.	Neumann, F. J. (2009). Balancing efficacy and safety in the TRITON-TIMI 38 trial. European Heart Journal, Supplement 11(G): G14-G17.	Review
71.	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. Archives of Cardiovascular Diseases. 2012; 105:587-92.	Clopidogrel dosing study
72.	Oh EY, Abraham T, Saad N, Rapp JH, Vastey FL, Balmir E. A comprehensive comparative review of adenosine diphosphate receptor antagonists. Expert Opinion on Pharmacotherapy. 2012; 13:175-91.	Systematic review
73.	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. Journal of the American College of Cardiology. 2013; 61:1601-6.	Platelet function study
74.	Passaro D, Fadda V, Maratea D, Messori A. Anti-platelet treatments in acute coronary syndrome: simplified network meta-analysis. International Journal of Cardiology. 2011; 150:364-7.	Comment on Biondi Zoccai – discussed in main report
75.	Rabasseda X. A report from the 60th Annual Scientific Session & Expo and I2 (Innovation and Intervention) Summit of the	Meeting review

	American College of Cardiology April 2-5, 2011 - New Orleans, Louisiana USA). Drugs of Today. 2011; 47:381-400.	
76.	Rabasseda X. Highlights from the American College of Cardiology 2012 Annual Meeting: March 24-27, 2012 - Chicago, Illinois, USA. Drugs of the Future. 2012; 37:379-87.	Meeting review
77.	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. JACC: Cardiovascular Interventions. 2013; 1):S7.	Not randomised
78.	Scott DM, Norwood RM, Parra D. P2Y12 inhibitors in cardiovascular disease: focus on prasugrel. Annals of Pharmacotherapy. 2009; 43:64-76.	Review
79.	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?). American Journal of Cardiology. 2008; 101:1364-6.	Comment
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Appendix 4: Selected data taken from ERG 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)
Unstable angina or NSTEMI (%)	74	74
STEMI (%)	26	26
Age (median) yr	61	61
≥ 75 yr (%)	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/min (%)	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
Timing of study-drug administration (%) ¶		
Before PCI	26	25
During PCI	73	74
After PCI	1	1

* 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. NSTEMI = non-ST-segment elevation myocardial infarction (MI), STEMI=ST-segment elevation MI; CABG=coronary artery bypass grafting; PCI =percutaneous coronary intervention.¶ 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.

Primary endpoint 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 endpoint in the prasugrel arm compared to the clopidogrel arm. This result was largely due to differences in the occurrence of nonfatal MI. The ERG notes that there are no statistically significant differences in mortality (CV death or death from all causes) or nonfatal stroke between the groups.

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

Endpoint	**Prasugrel (n = 6,813)**	**Clopidogrel (n = 6,795)**	**HR (95% CI)**	***p*-value***
	n (%)	n (%)		
Primary				
Death from CV causes, nonfatal MI, or nonfatal stroke	643 (9.9)	781 (12.1)	0.81 (0.73 to 0.90)	< 0.001
Death from CV causes	133 (2.1)	150 (2.4)	0.89 (0.70 to 1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67 to 0.85)	< 0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71 to 1.45)	0.93
Secondary				
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78 to 1.16)	0.64
Death from CV causes, nonfatal MI, or UTVR	652 (10.0)	798 (12.3)	0.81 (0.73 to 0.89)	< 0.001
Death from CV causes	133 (2.1)	150 (2.4)	0.89 (0.70 to 1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67 to 0.85)	< 0.001
UTVR*	156 (2.5)	233 (3.7)	0.66 (0.54 to 0.81)	< 0.001
Stent thrombosis[a]	68 (1.1)	142 (2.4)	0.48 (0.36 to 0.64)	< 0.001
Death from CV causes, nonfatal MI, nonfatal stroke, or rehospitalisation for ischaemia	797 (12.3)	938 (14.6)	0.84 (0.76 to 0.92)	< 0.001

HR =hazard ratio; MI = myocardial infarction; CV = cardiovascular; MI = myocardial infarction; UTVR = urgent target vessel revascularisation; p-values were calculated using the log-rank test. The analysis for the primary endpoint used the Gehan-Wilcoxon test for which the p-value was less than 0; stent thrombosis defined as definite or probable according to the Academic Research Consortium;*taken from published paper[36]

Secondary endpoints

Statistically significant reductions in favour of prasugrel were found for three secondary clinical endpoints: i) CE of cardiovascular death, nonfatal MI or UTVR; ii); CE of death from cardiovascular causes, nonfatal MI, nonfatal stroke or rehospitalisation for ischaemia iii) stent thrombosis (Table 4.8).

Results of the secondary analyses in respect of the primary CE 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.

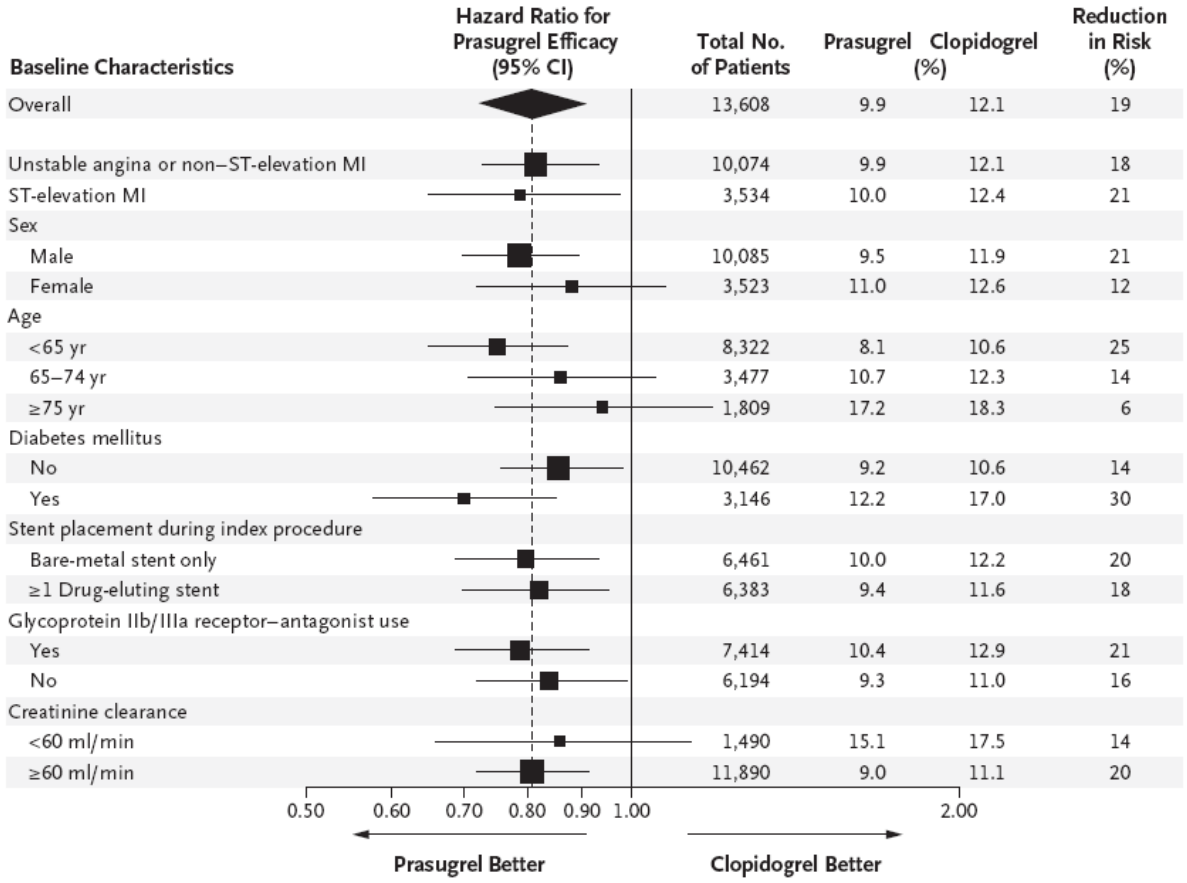
TRITON-TIMI 38: Primary efficacy outcomes at 3 days, 30 days, 90 days and day 4 to day 90 (overall cohort)

Endpoint	**Time**	**Prasugrel (n = 6,813) %**	**Clopidogrel (n = 6,795) %**	**HR for prasugrel (95% CI)**	***p-value***
Death from CV causes, nonfatal MI, nonfatal stroke	3 days	4.7	5.6	0.82 (0.71 to 0.96)	<0.01
	30 days	5.7	7.4	0.77 (0.67 to0.88)	<0.01
	90 days	6.8	8.4	0.80 (0.71 to 0.90)	<0.001
	day 4 to 90	5.6	6.9	0.80 (0.70 to 0.93)	<0.003
Death from CV causes, nonfatal MI, UTVR	30days	5.9%	7.4%	0.78 (0.69 to 0.89)	<0.01
	90 days	6.9%	8.7%	0.79 (0.70 to 0.90)	<0.01

CV = cardiovascular; MI = myocardial infarction; UTVR = urgent target vessel revascularisation; CI=confidence interval; HR=hazard ratio

Pre-specified subgroup analyses

The subgroups included in the MS are as follows: UA/NSTEMI; STEMI; males; females, <65 years; 65-74 years; ≥ 75 years; DM; type of stent; use of glycoprotein IIb/IIIa receptor antagonist; renal function. The MS presents a forest plot showing the primary efficacy endpoint 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 <60ml/min.



STEMI 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 versus clopidogrel in the STEMI population. A total of 3,534 STEMI patients were randomized. The primary endpoint (cardiovascular death, nonfatal MI or nonfatal 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 endpoint of cardiovascular death, MI or urgent target vessel revascularisation 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 cardiovascular death or nonfatal 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 UA/NSTEMI, STEMI and all ACS groups in the TRITON-TIMI 38 trial

TRITON-TIMI 38 Primary efficacy for: UA/NSTEMI, STEMI, all ACS patient groups (EPAR)

Primary efficacy endpoint and components at study end				
Event	Prasugrel	Clopidogrel	Hazard Ratio	p-value[c]
	n (%)[a]	n (%)[a]	(95% CI)[b]	
UA/NSTEMI	**N=5,044**	**N=5,030**		
CV Death, Nonfatal MI, or Nonfatal Stroke	469 (9.30)	565 (11.23)	0.820 (0.726,0.927)	0.002
CV Death	90 (1.78)	92 (1.83)	0.979 (0.732,1.309)	0.885
Nonfatal MI	357 (7.08)	464 (9.22)	0.761 (0.663,0.873)	<0.001
Nonfatal Stroke	40 (0.79)	41 (0.82)	0.979 (0.633,1.513)	0.922
All Cause Death	130 (2.58)	121 (2.41)	1.076 (0.840,1.378)	0.563
All MI	366 (7.26)	476 (9.46)	0.760 (0.663,0.871)	<0.001
All Stroke	49 (0.97)	46 (0.91)	1.068 (0.714,1.597)	0.748
STEMI	**N=1,769**	**N=1,765**		
CV Death, Nonfatal MI, or Nonfatal Stroke	174 (9.84)	216 (12.24)	0.793 (0.649,0.968)	0.019
CV Death	43 (2.43)	58 (3.29)	0.738 (0.497,1.094)	0.129
Nonfatal MI	118 (6.67)	156 (8.84)	0.746 (0.588,0.948)	0.016
Nonfatal Stroke	21 (1.19)	19 (1.08)	1.097 (0.590,2.040)	0.770
All Cause Death	58 (3.28)	76 (4.31)	0.759 (0.539,1.068)	0.113
All MI	119 (6.73)	157 (8.90)	0.748 (0.589,0.949)	0.016
All Stroke	26 (1.47)	25 (1.42)	1.032 (0.596,1.787)	0.911
All ACS	**N=6,813**	**N=6,795**		
CV Death, Nonfatal MI, or Nonfatal Stroke	643 (9.44)	781 (11.49)	0.812 (0.732,0.902)	<.001
CV Death	133 (1.95)	150 (2.21)	0.886 (0.701,1.118)	0.307
Nonfatal MI	475 (6.97)	620 (9.12)	0.757 (0.672,0.853)	<0.001
Nonfatal Stroke	61 (0.90)	60 (0.88)	1.016 (0.712,1.451)	0.930
All Cause Death	188 (2.76)	197 (2.90)	0.953 (0.781,1.164)	0.639
All MI	485 (7.12)	633 (9.32)	0.757 (0.673,0.852)	<0.001
All Stroke	75 (1.10)	71 (1.04)	1.055 (0.763,1.460)	0.745

ACS = acute coronary syndromes; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; N = number of randomly assigned subjects; n = number of subjects in sub-category; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

a Percentage of randomly assigned subjects reaching the primary endpoint

b Hazard ratio and a 95% CI used as an estimate of overall relative risk, prasugrel versus 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 endpoint. The individual components of the endpoints were tested using log-rank test. Clinical presentation, UA/NSTEMI versus 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

Endpoint	Prasugrel %	Clopidogrel %	HR (95% CI)	*p* value	$P_{interaction}$ versus no diabetes
Patients without DM	5237	5225			
Primary efficacy endpoint of death from CV causes, nonfatal MI, or nonfatal stroke	9.2	10.6	0.86 (0.76 to 0.98)	0.02	
Death from CV causes or MI	8.5	10.0	0.85 (0.75 to 0.97)	0.01	
Fatal or nonfatal MI	7.2	8.7	0.82 (0.72 to 0.95)	0.006	
Death from CV causes	1.7	1.9	0.91 (0.68 to 1.23)	0.53	
Stent thrombosis	0.9	2.0	0.45 (0.31 to 0.65)	< 0.001	
Death from cv causes, nonfatal MI, nonfatal stroke, or major bleeding event	11.5	12.3	0.92 (0.82 to 1.03)	0.16	
Patients with DM	1,576	1,570			
Primary efficacy endpoint of death from CV causes, nonfatal MI, or nonfatal stroke	12.2	17.0	0.70 (0.58 to 0.85)	< 0.001	0.09
Death from CV causes or MI	10.8	15.4	0.68 (0.56 to 0.84)	< 0.001	0.08
Fatal or nonfatal MI	8.2	13.2	0.60 (0.48 to 0.76)	< 0.001	0.02
Death from CV causes	3.4	4.2	0.85 (0.58 to 1.24)	0.40	0.78
Stent thrombosis	2.0	3.6	0.52 (0.33 to 0.84)	0.007	0.63
Death from CV causes, nonfatal MI, nonfatal stroke, or major bleeding event	14.6	19.2	0.74 (0.62 to 0.89)	0.001	0.05

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction

Event rates are reported using Kaplan-Meier estimates at 450 days. Comparisons are expressed as hazard ratios (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. Source: Wiviott et al 2008[102]

TRITON-TIMI 38 bleeding rates by DM status

Endpoint	Patients with DM (n = 3,146) %	Patients without DM (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

CABG = coronary artery bypass grafting; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; Source: Wiviott et al 2008[102]

TRITON-TIMI 38 bleeding rates for prasugrel versus clopidogrel by DM status

Endpoint	Clopidogrel %	Prasugrel %	HR (95% CI)	p-value	P interaction versus No Diabetes
Patients without DM	5,225	5,237			
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 DM	1,570	1,576			
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

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; CABG=coronary artery bypass grafting. Source: Wiviott et al 2008[102]

Patients with stents

In this group 6,461 received bare-metal stents, 5,743 received drug-eluting stents, and 640 received both types of stent. In the 'stented' group as a whole, the occurrence of the primary endpoint was reduced in the prasugrel arm compared to the clopidogrel arm (9.7% versus 11.9%, HR=0.81, p=0.0001). Similar results were reported for drug eluting stents and bare metal stents.

TRITON-TIMI 38 rates of stent thrombosis in patients who received stents

Endpoint	Clopidogrel (n = 6,422) %	Prasugrel (n = 6,422) %	HR (95% CI)	p-value
Stent thrombosis				
All patients receiving stents	2.35	1.13	0.48 (0.36 to 0.64)	< 0.0001
Patients receiving only DES	2.31	0.84	0.36 (0.22 to 0.58)	< 0.0001
Patients receiving only BMS	2.41	1.27	0.52 (0.35 to 0.77)	0.0009
Early stent thrombosis				
All patients receiving stents	1.56	0.64	0.41 (0.29 to 0.59)	< 0.0001
Patients receiving only DES	1.44	0.42	0.29 (0.15 to 0.56)	0.0001
Patients receiving only BMS	1.66	0.75	0.45 (0.28 to 0.73)	0.0009
Late stent thrombosis				
All patients receiving stents	0.82	0.49	0.60 (0.37 to 0.97)	0.03
Patients receiving only DES	0.91	0.42	0.46 (0.22 to 0.97)	0.04
Patients receiving only BMS	0.78	0.53	0.68 (0.35 to 1.31)	0.24

CI = confidence interval; HR = hazard ratio; DES= drug-eluting stent; BMS= bare metal stent
Note: Stent thrombosis was defined based on Academic Research Consortium [ARC] definitions: Definite stent thrombosis was defined as the total occlusion originating in or within 5 mm of the stent, or visible thrombus within the stent or within 5 mm of the stent in the presence of an acute ischaemic clinical syndrome within 48 hours; probable stent thrombosis was defined as any unexpected death within the first 30 days or any MI, which was related to documented acute ischaemic in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
Note: Early stent thrombosis was defined as occurring within 30 days of randomisation; late stent thrombosis was defined as occurring more than 30 days after randomisation.
Note: All endpoint rates were rounded in Wiviott et al., 2008. This publication provides the percentage of patients (but not the number of patients) who experienced each endpoint; the above numbers therefore are percentages, as indicated in the column headings. Event rates are reported with Kaplan-Meier failure estimates at 450 days and were compared by the log-rank test. Comparisons are expressed as univariate hazard ratios and 95% CIs including the entire duration of follow-up. Note: Each patient received at least one coronary stent.
Note: Data do not include patients who had mixed stent types. Source: Wiviott et al 2008[103]

Efficacy and bleeding and net clinical benefit in selected subpopulations

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

Endpoint	Clopidogrel n/N (%)	Prasugrel n/Na (%)	HR for Prasugrel (95% CI)	p-value
History of stroke or transient ischaemic attack				
Death from CV causes, nonfatal MI, nonfatal stroke (primary efficacy endpoint)	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, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal 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 transient ischaemic attack				
Death from CV causes, nonfatal MI, nonfatal stroke (primary efficacy endpoint)	199/1,347 (16.0)	198/1,320 (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, nonfatal MI, nonfatal stroke, non-CABG-related nonfatal TIMI major bleeding	239/1347 (19.0)	249/1320 (20.2)	1.07 (0.90 to 1.28)	0.43

CABG = coronary artery bypass grafting; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; n = number of treated patients experiencing endpoint; N = total number of patients treated. Note: The percentages are Kaplan-Meier estimates of the rate of each endpoint 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). Source: Wiviott et al 2007[36]

TRITON-TIMI 38 recurrent events analysis

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

Appendix 5: Publications related to the TRITON-TIMI 38 trial

Author/Year	Title	Description
Wiviott 2006[42]	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)	Paper describing the design of the TRITON-TIMI 38 trial
Wiviott 2007[36]	Prasugrel versus clopidogrel in patients with acute coronary syndromes	Primary publication of TRITON-TIMI 38 trial
Wiviott 2011[41]	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 60kg. The core clinical cohort represent 10,804 of the 13,608 patients included in the overall trial cohort
Antman 2008[104]	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	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 2012[53]	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)	Paper reporting the risk of cardiovascular 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 2011[105]	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)	Paper reporting the major predictors of serious bleeding in patients in the TRITON-TIMI 38 trial
Laynez 2011[106]	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.
Mega 2009[107]$	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 2010[108]	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 2009[109]	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
Montalescot 2009[54]	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 2009[51]	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	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, ACCF, AHA and WHF
Murphy 2008[110]	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 cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial
O'Donoghue 2009a[111]	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	Paper reporting clinical outcomes for patients who did and did not receive treatment with GP IIb/IIIa inhibitors during the PCI procedure in the TRITON-TIMI 38 trial
O'Donoghue 2009b[112] $	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 2009[113]	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	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 2010[114]	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	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 2012[115]	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 2012[116]	Safety and efficacy of prasugrel compared with clopidogrel in different regions of the world.	To determine whether there were differential effects of prasugrel compared with clopidogrel in the TRITON-TIMI 38 study according to geographical region
Scirica 2012[117]	Timing and clinical setting of cardiovascular	Paper reporting the outcomes of an analysis

	death or myocardial infarction following PCI for ACS-observations from the TRITON-TIMI 38 trial	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 2012[118]	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 2011[119]	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 2008a[102]	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 2008b[103]	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 2009[120]	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

$ excluded at stage 1 but included here for completeness

Appendix 6 Key characteristics of identified indirect comparisons of prasugrel and ticagrelor

Publication	Objective	Trials included Length of follow-up	Comparator 1	Comparator 2	Patient group Number of patients (N)	Primary outcomes of the meta-analysis
Biondi-Zoccai[56]	To perform an indirect comparison meta-analysis of prasugrel vs ticagrelor in patients with ACS	TRITON-TIMI 38[36] 2007 15 months	Prasugrel 60mg LD/10mg daily	Clopidogrel 300mg LD/75mg daily	All ACS (13,608)	• Death, MI or stroke • TIMI major bleeding
		PLATO[33] 2009 9 months	Ticagrelor 180mg LD/90mg twice daily	Clopidogrel 300 to 600mg LD/75mg daily	All ACS (18,624)	
		DISPERSE-2[62] 2007 3 months	Ticagrelor 90mg twice daily*	Clopidogrel 300mg LD/75mg daily	NSTEMI (661)	
Passaro[58]	Presentation of a simplified network meta-analysis graph to improve the communicative value of the analysis by Biondi-Zoccai	TRITON-TIMI 38[36] 2007 15 months	Prasugrel	Clopidogrel 300mg LD/75mg 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 600mg LD/75mg daily	All ACS (18,624)	
		CURE[121] 2001 3 to 12 months	Clopidogrel 300mg LD/75mg daily	Placebo	NSTEMI (12,562)	
Chatterjee[57]	To compare the relative efficacies of prasugrel and ticagrelor in the reduction of meaningful clinical endpoints in patients with ACS or CAD intended for PCI treatment using a network meta-analysis of published data	TRITON-TIMI 38[36] 2007 15 months	Prasugrel	Clopidogrel 300mg LD/75mg 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 600mg LD/75mg daily	All ACS (18,624)	
		DISPERSE-2[62] 2007 3 months	Ticagrelor 90mg twice daily*	Clopidogrel 300mg LD/75mg daily	NSTEMI (661)	
		JUMBO-TIMI 26[38] 2005 30 days	Prasugrel 3 different dosing regimens	Clopidogrel 300mg LD/75mg daily	ACS intended for PCI (904)	

Steiner[59]	To compare the efficacy and safety of prasugrel, ticagrelor and high-dose clopidogrel in patients undergoing PCI	Abuzahra[122] 2008 30 days	Clopidogrel 600mg LD/150mg daily	Clopidogrel 300mg LD/75mg daily	(119) ACS :44% SCAD:56%	• All cause death • Major bleeding
		Angiolillo#197}[123] 2008 30 days	Clopidogrel 600mg LD/150mg daily	Clopidogrel 300mg LD/75mg daily	(40) SCAD	
		DOSER[65] 2010 30 days	Clopidogrel 600mg LD/150mg daily	Clopidogrel 300mg LD/75mg daily	(74) SCAD HTPR	
		DOUBLE[124] 2010 1 month	Clopidogrel 300mg LD/150mg daily	Clopidogrel 300mg LD/75mg daily	STEMI (54)	
		GRAVITAS[125] 2011 6 months	Clopidogrel 300mg to 600mg LD/150mg daily	Clopidogrel 300mg to 600mg LD/75mg daily	(2214) ACS:40% SCAD:60% HTPR:100%	
		Han[64] 2009 30 days	Clopidogrel 600mg LD/150mg daily	Clopidogrel 600mg LD/75mg daily	ACS (813)	
		OASIS 7 PCI [47] 2010 30 days	Clopidogrel 600mg LD/150mg daily	Clopidogrel 300mg LD/75mg daily	ACS (17,263)	
		VASP-02[126] 2008 14 days	Clopidogrel 300mg to 600mg LD/150mg daily	Clopidogrel 300mg to 600mg LD/75mg daily	Stable CAD (153)	
		Von Beckerath[127] 2007 30 days	Clopidogrel 600mg LD/150mg daily	Clopidogrel 300mg to 600mg LD/75mg daily	Stable CAD (60)	
		JUMBO-TIMI 26[38] 2005 30 days	Prasugrel 3 different dosing regimens	Clopidogrel 300mg LD/75mg daily	ACS intended for PCI (904)	
		TRITON-TIMI 38[36] 2007	Prasugrel	Clopidogrel 300mg LD/75mg daily	All ACS (13,608)	

		15 months				
		Alexopolous [128] 2011 30 days	Clopidogrel 600mg LD/10mg prasugrel daily	Clopidogrel 300mg to 600mg LD/150mg daily	(71) ACS:70% Stable CAD:30% HTPR:100%	
		PRINCIPLE-TIMI 44[129] 2007 15 days	Prasugrel 60mg LD/10mg daily	Clopidogrel 600mg LD/150mg daily	(201) Stable CAD 55% PCI	
		PLATO INVASIVE[55] 2009 9 months	Ticagrelor 180mg LD/180mg daily	Clopidogrel 300mg to 600mg LD/75mg daily	ACS (13,408) 77% PCI	

* Does not include 323 patients treated with ticagrelor 180mg twice daily
LD=loading dose; HTPR=High on-Treatment Platelet Reactivity; SCAD=stable coronary artery disease

Appendix 7

Quality assessment of identified indirect comparisons of prasugrel and ticagrelor

None of the indirect comparisons stated whether the design was 'a priori'. Biondi-Zoccai[56] did not perform a comprehensive search strategy, assess the quality of included studies or assess publication bias. Chatterjee[57] did not state whether there was duplicate selection or data extraction, 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[58] as the primary aim of this was to present a simplified network meta-analysis graph based on the review by Biondi-Zoccai.[56] The review by Steiner[59] 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[56]	NS	NS	No	Yes	Yes	Yes	No	No	Yes	No	Yes
Chatterjee[57]	NS	NS	Yes	Yes	No, excluded studies not given	No	Yes[b]	No	Yes	Yes	Yes
Passaro[58]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Steiner[59]	NS	Yes	Yes	Yes	No, excluded studies not given	Yes	Yes	No	Yes	No	Yes

NS= Not stated; NA =applicable; COI=conflicts of interest
a however no formal scoring system was used and no results presented
b but no results given, only stated studies were low risk of bia