STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ticagrelor for the treatment of acute coronary syndromes

This report was commissioned by the NIHR HTA Programme as project number 08/240

Completed February 4th 2011

CONTAINS IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title:	Ticagrelor for the treatment of acute coronary syndromes
Produced by:	Liverpool Reviews and Implementation Group (LRiG)
Authors:	Adrian Bagust, Professor of Modelling in Health, Liverpool Reviews and Implementation Group, University of Liverpool Angela Boland, Associate Director, Liverpool Reviews and Implementation Group, University of Liverpool Michaela Blundell, Research Fellow (Medical Statistician) Liverpool Reviews and Implementation Group, University of Liverpool Michael Fisher, Consultant Cardiologist, Royal Liverpool University Hospital, Liverpool Yenal Dundar, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool Janette Greenhalgh, Research Fellow (Clinical Effectiveness), Liverpool Reviews and Implementation Group, University of Liverpool Monica Lai, Research Fellow (Economic Modelling), Liverpool Reviews and Implementation Group, University of Liverpool Gerlinde Massey, Research Assistant (Clinical Effectiveness), Liverpool Reviews and Implementation Group, University of Liverpool Chris Proudlove, Director, North West Medicines Information Centre, Pharmacy Practice Unit, Liverpool
Correspondence to:	Dr Janette Greenhalgh, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, Brownlow Hill, Liverpool L69 3GB
Date completed:	4th February 2011

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 08/240

Declared competing interests of the authors:

Michael Fisher has received remuneration from Astra Zeneca for symposium attendance and speaker fees from Sanofi-Aventis.

Acknowledgements:

The authors are pleased to acknowledge Dr Rod Stables, (Liverpool Heart and Chest Hospital NHS Trust), Dr Raphael Perry (Liverpool Heart and Chest Hospital NHS Trust) Professor Dyfrig Hughes (Bangor University) and Dr Ameet Bakhai (Barnet and Chase Farm Hospitals NHS Trust, Royal Free Hampstead NHS Trust) who provided feedback on the clinical (RS, RP) and economic sections (DH, AB) of the ERG report. Catrin Tudur-Smith provided feedback on the statistical sections of the report.

Rider on responsibility for report:

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Greenhalgh J, Bagust A, Boland A, Blundell M, Lai M, Dundar Y, Massey G, Proudlove C, Fisher M. Ticagrelor for the treatment of acute coronary syndromes: A Single Technology Appraisal. LRiG, The University of Liverpool, 2011.

Contributions of authors:

Janette Greenhalgh	Project lead, drafted the clinical results section and supervised the production of the final report
Adrian Bagust	Critical appraisal of the economic model
Angela Boland	Critical appraisal of the economic evidence
Michaela Blundell	Critical appraisal of clinical statistical approach
Monica Lai	Critical appraisal of the economic model
Yenal Dundar	Cross checking of manufacturer's search strategies
Gerlinde Massey	Cross checking of clinical data
Chris Proudlove	Critical appraisal of the manufacturer's submission
Michael Fisher	Critical appraisal of the clinical sections of the manufacturer's submission

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

Table of contents

Abbreviations

AC	Appraisal Committee
ACS	acute coronary syndromes
AE(s)	adverse event(s)
AMI	acute myocardial infarction
ASA	aspirin
BMS	bare metal stent
CABG	coronary artery bypass grafting
CI	confidence interval
CSR	clinical study report
CV	cardiovascular
DES	drug eluting stent
EMA	European Medicines Agency
EQ-5D	EuroQol 5D (a standardised instrument used as a measure of health outcome)
ERG	Evidence Review Group
ESC	European Society of Cardiology
FDA	Food and Drug Administration of America
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost-effectiveness ratio
KM	Kaplan Meier
ITT	intention to treat
LBBB	left bundle branch block
LYG	life years gained
MI	myocardial infarction
MS	manufacturer's submission
MVD	multivascular disease
NICE	National Institute for Health and Clinical Excellence
NSTEMI	non ST segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PLATO trial	The Study of Platelet Inhibition and Patient Outcomes
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life years
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
UA	unstable angina
vs	versus
WTP	willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE from AstraZeneca UK Ltd in support of the use of ticagrelor (Brilique^{TM}) as a treatment for patients with acute coronary syndromes (ACS). The manufacturer's submission (MS) describes the use of ticagrelor in combination with aspirin (ASA) compared with clopidogrel in combination with ASA in patients with ACS. In the ERG report, the treatment comparison of interest is referred to as ticagrelor versus clopidogrel. The manufacturer considers that there is no credible evidence to enable a comparison of ticagrelor with prasugrel.

Ticagrelor has a marketing authorisation in Europe. It is licensed for use (co-administered with ASA) for the prevention of atherothrombotic events in adult patients with ACS (unstable angina [UA], non-ST-elevation myocardial infarction [NSTEMI] or ST-elevation myocardial infarction [STEMI]); including patients managed medically and those who are managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

1.2 Summary of submitted clinical-effectiveness evidence

The clinical effectiveness evidence described in the MS is derived from a single phase III double-blind, double dummy randomised controlled trial (RCT) which compares the use of ticagrelor with clopidogrel. The PLATO trial was conducted in 43 countries and includes 18,624 patients with ACS. After 1878 events had occurred, the manufacturer demonstrated that ticagrelor was superior in the prevention of thrombotic events in the composite endpoint of vascular death, myocardial infarction (MI), or stroke compared to clopidogrel (9.8% vs 11.7%, HR= 0.84; 95% CI 0.77 to 0.92; $p<0.001$). The reduction in primary events was driven primarily by significant reductions in the rates of MI (5.8% vs 6.9%, HR= 0.84; 95% CI 0.75 to 0.95; p=0.005) and vascular death (4.0% vs 5.1%, HR= 0.79; 95% CI 0.69 to 0.91; p=0.001). The number of strokes was greater in the ticagrelor arm (125/9333, 1.5%) compared to the clopidogrel arm (106/9291, 1.3%), but this did not reach statistical significance. No difference was found between the ticagrelor and clopidogrel arms for any of the items on the health-related quality of life measure used in the trial (EQ-5D). Trial-defined major bleeding events were similar in both arms, but there were statistically significantly more trial-defined (combined) major and minor bleeding events in the ticagrelor arm compared with the clopidogrel arm (16.1% vs 14.6%, HR=1.11; 95% CI 1.03 to 1.20;

p=0.008) and more non-CABG related major bleeding (4.5% vs 3.8%, HR=1.19; 95% CI 1.02 to 1.38; p=0.03). Statistically significantly increased rates of dyspnoea and, in the first week ventricular pauses of length≥3 seconds detected by Holter monitoring were noted in the ticagrelor arm, in addition to increases in serum uric acid and serum creatinine from baseline values from the beginning to the end of the trial.

In the absence of any head-to-head trial data comparing ticagrelor to prasugrel, the manufacturer has appropriately identified an indirect analysis published by an independent third party. The manufacturer puts forward a convincing case that the differences in design and procedures between the two main trials included in the analysis render the comparison difficult and inappropriate. According to the manufacturer, there is therefore no credible indirect evidence of comparative effectiveness of ticagrelor vs prasugrel in the treatment of ACS.

1.3 Summary of submitted cost-effectiveness evidence

In the absence of any relevant UK economic evaluations, the manufacturer submitted a *de novo* economic evaluation comparing ticagrelor vs clopidogrel for patients with ACS (STEMI, NSTEMI, UA) including patients managed medically, and those who are managed with PCI or CABG as per the licensed indication. The manufacturer constructed an EXCEL-based cost-utility model and is a two-part construct with a one-year decision tree, based on data from the PLATO study, and a Markov model for long term extrapolation. The model was designed to ensure capture of all major clinical and resource generating events that a patient may experience throughout the course of their remaining life. There are four mutually exclusive health states in the one-year decision tree: no further event, non-fatal MI, non-fatal stroke and death from any cause. At the end of the one-year period represented by the decision tree, patients are allocated to one of four of the six mutually exclusive health states in the Markov model: no further event, non-fatal MI, post MI, non-fatal stroke, post stroke and dead. The perspective adopted in the economic evaluation was that of the NHS and Personal Social Services (PSS) and costs and benefits were discounted at 3.5% per annum. Clinical-effectiveness data from the PLATO trial were used to populate the submitted economic model. Quality adjusted life years (QALYs) were estimated using EQ-5D data collected in the PLATO trial. The mean age, as well as the proportion, of older patients in England and Wales, differs from the mean age and proportion of older patients in the PLATO study. The manufacturer took account of these differences by using age adjusted event rates to ensure that the cost-effectiveness analysis would be generalisable to the UK ACS population. In summary, the manufacturer's base case (40 years) incremental cost effectiveness ratio (ICER) for ticagrelor vs clopidogrel for ACS patients is £3,696 per QALY

gained; other estimates are £2,825 per QALY gained (STEMI), £5,230 per QALY gained (NSTEMI) and £5,374 per QALY gained (UA). The manufacturer showed the ICER to be robust when subjected to extensive deterministic and probabilistic sensitivity analysis (PSA). The manufacturer also presented cost effectiveness results for ticagrelor vs prasugrel based on the results of a published indirect analysis; the manufacturer is of the opinion that the results are not credible.

1.3.1 Commentary on the robustness of submitted evidence

The ERG is of the opinion that ticagrelor is cost effective compared with clopidogrel for UA and NSTEMI patients with ACS.

However, in line with published NICE guidance (TA152) and NICE guidelines (CG48), the ERG distinguishes between groups of STEMI patients: STEMI without stenting, STEMI with BMS, STEMI with DES and STEMI with other (e.g. CABG). The ERG is therefore unable to ascertain the cost effectiveness of ticagrelor compared with clopidogrel in STEMI subgroups as all STEMI patients in the cost-effectiveness analysis had received 12 months clopidogrel+ASA; in England and Wales patients with STEMI without stenting are recommended to receive at least 4 weeks treatment and STEMI patients with BMS are recommended to receive 3 months treatment. Patients treated with DES are included in the overall STEMI subgroup but only the ICER for the overall STEMI subgroup is presented in the MS.

1.3.2 Strengths

The manufacturer provides evidence from a well-designed trial (PLATO) of the clinical benefit of ticagrelor vs clopidogrel. The trial recruited a large number of patients who reflect the case-mix of patients likely to be seen in clinical practice in the UK. The trial demonstrated a mortality benefit associated with ticagrelor; this is unusual in cardiovascular trials. In the assessment of MI events, mainly clinical MIs were included in the analysis, adding robustness to this measure. The manufacturer has reported the results of a substantial quality of life (QoL) sub-study; the results demonstrate that there is no difference in the QoL (based on EQ-5D scores) of patients receiving treatment with ticagrelor compared with clopidogrel. However, it is noted that EQ-5D is a generic instrument and would usually be complimented in a clinical trial with the use of a disease specific instrument.

1.3.3 Weaknesses

The PLATO trial was planned to continue for up to 12 months; however, when the number of events (1780) that were required to show a statistically significant difference between the two arms had been reached, the protocol required patients to leave the trial at 6 months or 9 months. Since one-year mortality is a key endpoint in most trials of cardiovascular disease, the ERG considers that all patients should have been followed up to 12 months.

As discussed above, duration of antiplatelet treatments administered to patients in the PLATO trial may not reflect clinical practice in England and Wales.

There are no head-to-head trial data comparing the clinical efficacy of ticagrelor with prasugrel. The evidence presented in a published indirect comparison is considered by the manufacturer and the ERG to be inappropriate as it compares the outcomes of two trials that are inherently different.

The ERG has several important criticisms of the submitted economic evaluation in addition to concerns about the comparator. Firstly, the limited proportion of patients followed-up for 12 months in the trial increases the uncertainty in the estimates of the final disposition of patients at the conclusion of the trial which is the prime driver of long-term patient benefits in the Markov model. Secondly, the structure of the Markov model is such that it does not represent real world patient experience as it does not explicitly allow patients to suffer multiple cardiovascular events in their lifetime. The consequence of this is that future costs and benefits, in both groups may not be estimated accurately. The model also assumes that all patients receive ASA as a long-term preventative treatment; in England and Wales cardiovascular patients with multivascular disease go on to receive long-term clopidogrel treatment. Finally, the model applies an average utility score for each health state regardless of time spent in the state, when experience shows that ACS patients suffer from an initial utility decrement which steadily diminishes, and the ERG is of the opinion that the effect of applying an average score is to underestimate the size of the ICER at 12 months.

Currently in England and Wales patients with multivascular disease (MVD) are treated with long-term clopidogrel plus ASA; in the submitted economic model it is assumed that all patients are treated with long-term ASA (i.e. including patients with MVD). The ERG notes that NICE guidance (TA210) for patients with MVD was released after the MS was submitted.

1.3.4 Areas of uncertainty

Patients were (appropriately) excluded from the key trial if clopidogrel was contraindicated for any reason. There will be a small number of patients in UK clinical practice for whom clopidogrel is contraindicated and it is therefore unclear whether ticagrelor is a treatment option for these patients.

As the PLATO trial population did not reflect the experience of those ACS patients who, according to NICE guidelines (CG48) and NICE guidance (TA152), require treatment for at least 4 weeks (STEMI without stenting) and 3 months (STEMI with BMS), the cost effectiveness of ticagrelor vs clopidogrel for these groups of patients is unknown. The true cost effectiveness of ticagrelor vs clopidogrel for STEMI patients with DES is also uncertain as only a single ICER for the whole STEMI group is presented.

1.4 Key issues

The manufacturer reports that European guidelines state that all STEMI patients with ACS should receive clopidogrel+ASA for 12 months. NICE guidelines and NICE guidance differ from European guidelines in that they recommend at least 4 weeks of clopidogrel+ASA for STEMI patients without stenting and 3 months of clopidogrel+ASA for STEMI patients with BMS. A key issue for debate is whether clinical practice in the UK reflects European guidelines or NICE recommendations. In addition, recent evidence from clinical practice shows that in the UK a not insignificant number of patients discontinue dual antiplatelet treatment after approximately 90 days.

The manufacturer presents an ICER for a homogenous STEMI subgroup. The ERG considers that it is appropriate to divide this subgroup into four smaller groups: STEMI without stenting, STEMI with BMS, STEMI with DES and STEMI with other. Consequently a key issue is whether or not a single ICER is valid and reflects the incremental costs and benefits for the STEMI subgroup as a whole or whether four individual effectiveness and cost-effectiveness estimates are required before informed decision making can take place. Although not specified in the final scope issued by NICE, the ERG considers that it is important to discuss the four subgroups within the STEMI population.

The manufacturer presents the ICER for a homogeneous UA subgroup. The ERG considers that it would have been informative to explore the size of the individual ICERs for patients with low, medium and high risks of a future event.

The annual cost of ticagrelor per patient is substantially more expensive than generic clopidogrel, and the financial impact on the NHS of a recommendation for use of ticagrelor would be considerable.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

In the context section of the MS, the manufacturer appropriately describes the key issues related to the decision problem as set out by NICE. A summary of this section of the MS is presented in Boxes 1-7. All information is taken directly from the MS. In Box 1, the aetiology and epidemiology of ACS are described.

Box 1 Aetiology and epidemiology of ACS

Acute coronary syndrome (ACS) is a syndrome caused by acute myocardial ischaemia (a critical reduction in blood flow to the heart muscle) precipitated by atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis, vascular constriction and coronary occlusion. The precipitating symptom that triggers the diagnostic and therapeutic cascade is chest pain but many patients especially women and those with diabetes can present with ACS with atypical pain or no pain at all.[1-3] In the UK, approximately 16% of patients with ACS die before admission to a hospital.[4]

Acute coronary syndromes including unstable angina (UA) and acute myocardial infarction (AMI) are a major cause of morbidity and mortality in the developed world.[4] In 2006/7 there were 70,000 cases of UA, and 113,000 cases of AMI with 24,000 subsequent MIs in the UK.[5] Acute coronary syndrome is one of the most common causes of death in the UK and survivors often suffer persistent angina symptoms, heart failure and have a high risk of further ACS episodes.[6]

The ERG notes that ACS refers to a group of clinical syndromes associated with acute myocardial ischaemia.

2.2 Critique of manufacturer's overview of current service provision

The Executive Summary presented in the MS (MS, p11) states that the aim of treatment for ACS is to restore normal coronary blood flow, reverse ischaemia and limit damage from infarction. Prevention of further coronary thrombosis with antiplatelet therapy is a key component of acute management in this patient population.

The manufacturer has summarised relevant NICE guidance in the MS and this is replicated in Table 1.The ERG has added NICE guidance TA210[7] (TA210[7]was issued after the submission date of the MS) and the relevant section of TA152[8] to Table 1. The ERG is aware that the text taken from TA152[8] in not a NICE recommendation, but considers it to be of relevance to patients who receive coronary stents as part of their PCI treatment.

Table 1 Relevant NICE recommendations

NICE Guidance/guidelines	Recommendation
TA182[9] Prasugrel for the treatment of ACS with PCI 2009	Prasugrel (with ASA) is recommended as an option for preventing atherothrombotic events in patient 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.
CG48[10] Secondary prevention in primary and secondary care for patients following a MI 2007	Clopidogrel (with ASA) should be continued for 12 months after the most recent acute episode of a NSTEMI. Clopidogrel + ASA should be continued for at least 4 weeks after a STEMI event.
CG94[11] The early management of unstable angina and non-ST-segment elevation MI 2010	**ASA** ASA should be offered to all patients (if ASA is contraindicated, clopidogrel) starting with a single 300 mg loading dose; treatment continued indefinitely. **Clopidogrel** A 300 mg loading dose is recommended for: • patients with a predicted 6-month mortality of more than 1.5% and no contraindications (such as excessive bleeding risk) • all patients with no contraindications who may undergo PCI within 24 hours of admission Continued treatment with the standard dose for 12 months is recommended. In CABG consider stopping clopidogrel 5 days* before in those patients with low risk. For patients at intermediate or higher risk, discuss continuation of clopidogrel before CABG with the cardiac surgeon and base the decision on the balance of ischaemic and bleeding risk.
TA210[7] 2010 Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of TA90)	**Clopidogrel** Clopidogrel is recommended for: • patients who have had an ischaemic stroke or who have peripheral arterial disease or multivascular disease or • patients who have had an MI only if ASA is contraindicated **Modified-release dipyridamole** Modified-release dipyridamole plus ASA is recommended for: • patients who have had a transient ischaemic attack or • patients who have had an ischaemic stroke only if clopidogrel is contraindicated or not tolerated Modified-release dipyridamole alone is recommended for: • patients who have had an ischaemic stroke only if ASA and clopidogrel are contraindicated or not tolerated or • patients who have had an ischaemic attack only if ASA is contraindicated or not tolerated
TA152[8] 2008 Drug eluting stents for the treatment of coronary heart disease	There is a risk of stent thrombosis associated with the use of both types of stent (DESs and BMSs). To prevent thrombosis occurring, patients are required to use an antiplatelet drug, such as clopidogrel, in addition to aspirin during and after the implantation of a stent. The American College of Cardiologists/American Heart Association PCI guidelines (also endorsed by the Society for Cardiovascular Angiography Interventions) and the BCIS have recommended that for patients receiving DESs the duration of clopidogrel use should be increased to at least 12 months, after which time continuation of clopidogrel should be reviewed taking into account the risk for further events on an individual patient basis. The Committee noted the current UK recommendation that clopidogrel should be given for an additional 9 months in patients receiving a DES [compared with BMS] and it therefore considered it appropriate that this should be taken account of in the cost-effectiveness analysis."

*Five days is specified in the NICE guideline and varies from the SPC specified duration of seven days.
TA= technology appraisal; CG= clinical guideline

The ERG notes that CG48[11] also states that the duration of treatment with dual antiplatelet therapy depends upon other indications. The ERG is aware that in respect of patients with

STEMI, CG48[11] recommendations may not always be followed and that CG48[11] is due to be reviewed.

The manufacturer provides an adequate description of the treatment pathways for patients with ACS. These are presented in Box 2, Box 3 and Box 4.

Box 2 Early classification of patients with ACS

Early diagnosis and classification determine ongoing treatment and morbidity and mortality outlook. Classification is based on the characteristics of the presenting electrocardiogram and levels of cardiac enzymes:

- The presence of acute chest pain and persistent ST segment elevation indicates the total occlusion of an affected coronary artery and is classified as ST-elevation MI (STEMI).
- The presence of chest pain without ST segment elevation is classified as NSTE-ACS (non ST elevation ACS). NSTE-ACS is further sub classified into UA or non-ST-segment myocardial infarction (NSTEMI) based on the absence or presence of myocardial damage as evidence by the presence of elevated cardiac troponins.[12]

Box 3 Clinical pathway for patients with STEMI

Patients assessed by the paramedical team and found to have ECG changes consistent with STEMI are admitted directly to the cardiac unit/cardiac catheterisation labs. The recommended treatment for patients with confirmed STEMI (presenting within 12 hours of symptom onset) is immediate primary percutaneous coronary intervention (PCI) consisting of angioplasty to the occluded coronary artery and placement of a stent, or if PCI facilities are not immediately available pharmacological reperfusion (thrombolysis).[13] Primary PCI should be performed as soon as possible and in any case within 2 hours of first medical contact. Where this is not possible, patients should receive thrombolysis followed by either rescue PCI within 12 hours if ischaemic symptoms do not resolve or later pre-discharge angiography if fibrinolysis is successful. All patients undergoing PCI for STEMI are recommended to receive aspirin and clopidogrel loading doses followed by maintenance treatment with combination antiplatelet therapy.[13]

It should be noted that ASA and/or clopidogrel are recommended in the early management of patients with STEMI.[11] The ERG further notes that as described in Table 1, NICE guidance[9] recommends antiplatelet treatment with prasugrel as an alternative to clopidogrel for specific subgroups of patients who are to undergo PCI (i.e. when immediate primary PCI for STEMI is necessary, or stent thrombosis has occurred during clopidogrel treatment or the patient has diabetes mellitus) .

Box 4 Clinical pathway for patients with UA or NSTEMI

For all patients admitted with NSTEMI, in line with the NICE guideline on UA and NSTEMI[11] first-line treatment should include a single loading dose of ASA and anticoagulation (e.g. heparin). For patients with hypersensitivity to ASA, clopidogrel monotherapy should be considered as an alternative. Patients should be assessed using an established scoring system to predict six month mortality and the risk of future adverse cardiovascular events to guide clinical management in particular the need for early angiography and PCI.
With regard to management strategies, patients assessed to be at low risk of early recurrent coronary events should be considered for a conservative non-invasive (or medical) strategy. Patients of medium to high risk are recommended to have early coronary angiography and revascularisation if appropriate.[11]

In addition to the manufacturer's description of treatments for patients with NSTEMI, the ERG notes that all patients undergoing PCI for UA/NSTEMI should receive ASA and clopidogrel loading doses followed by maintenance treatment with dual antiplatelet therapy.[13] The ERG is aware that medical management of ACS patients will include antiplatelet therapy and that, in addition to the treatments outlined by the manufacturer, some patients with ACS will be referred for CABG.

The ERG notes that recent guidelines published by the European Society of Cardiology (ESC)[14] endorse the treatment pathways described in the MS.

The MS describes current antiplatelet treatments and the place of ticagrelor. This is presented in Box 5 and Box 6. The ERG notes that co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor.[15]

Box 5 Current antiplatelet treatment options for ACS

Antiplatelet therapy is an integral part of ACS care. Aspirin, a mainstay of current practice, irreversibly blocks platelet activation via inhibition of thromboxane synthesis. More recently, dual antiplatelet therapy, in which a second antiplatelet drug is added to aspirin, has emerged as the standard of care in ACS. Clopidogrel, a thienopyridine, irreversibly binds to the platelet ADP receptor ($P2Y_{12}$), a mechanism distinct from aspirin. Prasugrel differs from clopidogrel in its metabolism and activation, with greater potency and a faster onset of activity.

Clopidogrel is indicated for both UA/NSTEMI and STEMI, but for STEMI it is only indicated for medically treated patients eligible for thrombolytic therapy with a recommended 12 month treatment period. Clopidogrel is also widely used in patients undergoing PCI (including primary PCI).

Prasugrel is indicated for both NSTEMI and STEMI, but only for patients undergoing primary or delayed PCI (Prasugrel SPC 2009). Prasugrel has not been assessed in patients that would be managed medically. In addition there are a number of specific patient parameters (e.g. age and weight) which need to be taken into account before prescribing prasugrel. Prasugrel is also used in UK clinical practice in line with recent NICE guidance[9] for a narrow group of patients.

Box 6 Ticagrelor

Even with the current standard of care (i.e. dual antiplatelet therapy with clopidogrel and ASA) serious cardiovascular (CV) events recur, most of them within months of the index ACS event.[16] The GRACE (Global Registry of Acute Coronary Events) study showed that the 5 year morbidity and mortality are just as high in patients with NSTEMI and UA as those with STEMI.[17] There remains a need for antiplatelet therapy that provides greater efficacy in terms of improved cardiovascular mortality over current treatments preferably without an increased risk of serious bleeding.

Existing oral antiplatelet treatments (clopidogrel and prasugrel) while effective, have limitations that do not enable simple decision making at the point of initiation of treatment in an emergency setting. Consideration of these factors adds an additional level of complexity to the prescribing decision making process.

Ticagrelor is a direct-acting $P2Y_{12}$ receptor antagonist that has a different mechanism of action than the thienopyridines (clopidogrel and prasugrel). Ticagrelor, one of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines, is the first reversibly binding oral adenosine diphosphate (ADP) receptor antagonist. It is a selective ADP-receptor antagonist acting on the $P2Y_{12}$ ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor does not interact with the ADP binding site itself, but interacts with platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction. Unlike clopidogrel and prasugrel, ticagrelor does not require metabolic activation. Ticagrelor has a rapid onset of action compared with clopidogrel and is the first reversibly-binding oral ADP receptor antagonist.

Ticagrelor represents a new treatment option for ACS. It provides an advance over the current standard of care clopidogrel, regardless of presenting diagnosis (e.g. STEMI, NSTEMI, UA) and management strategy (invasive or non invasive). Ticagrelor has been included as an antiplatelet treatment option in the ESC guidelines for invasively managed patients with UA/NSTEMI and STEMI although it is not currently approved in any jurisdiction.[14]

The manufacturer has estimated the number of patients presenting with ACS in England and Wales who are likely to be eligible for treatment with ticagrelor in Box 7.

Box 7 Number of patients eligible for treatment with ticagrelor

It is estimated that all patients (approximately 144,000 annually) in England and Wales presenting with ACS will be eligible for treatment with ticagrelor. From recent Hospital Episode Statistics data approximately 136,000 patients presented with ACS in England for the period 2009/2010.[18] (Based on the incidence of ACS in England together with 2009 based population projections for England and Wales (National Population Projections 2009), it is estimated that there are 7,900 ACS patients in Wales.

The ERG is of the opinion that the manufacturer's summary of the disease context and available treatments for patients with ACS is reasonable.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

In the MS, the manufacturer presents the decision problem issued by NICE[5] and the manufacturer's rationale for any deviation from this.

Table 2 Decision problem and manufacturer's responses

	Final scope issued by NICE	Decision problem addressed in the MS	Rationale if different from scope
Population	Patients presenting with ACS irrespective of whether they have undergone revascularisation	As scope	
Intervention	Ticagrelor +ASA	Ticagrelor +ASA	
Comparator(s)	For people who are to be managed with PCI: • Clopidogrel + ASA • Prasugrel +ASA For people who are not to be managed with PCI: • Clopidogrel+ASA	For all ACS patients including those medically managed and those to be managed with PCI (as per the full PLATO population). • Clopidogrel +ASA Data on the following subgroups: STEMI, NSTEMI and UA will also be presented. For people who are to be managed with PCI: • Prasugrel +ASA	The PLATO study included a broad spectrum ACS patient population; no distinction was made between the UA/NSTEMI patients intended to be managed invasively and medically and the inclusion of STEMI patients intended for primary PCI. The PLATO-INVASIVE substudy investigated the effect of ticagrelor in patients identified at randomisation with investigator intent for invasive strategy undergoing early angiography; however as only 77% of this cohort actually underwent PCI this subgroup is not representative of a pure PCI-only cohort.
Outcomes	Mortality Thrombotic cardiovascular events Need for revascularisation Adverse effects of treatment Health-related quality of life	Mortality (all cause) Thrombotic cardiovascular events Adverse effects of treatment Health-related quality of life <u>Additional outcomes</u> Recurrent ischaemia	The pivotal phase III study PLATO will provide efficacy and adverse event data. The primary endpoint for this study is the time to first occurrence of composite of death from vascular causes, MI or stroke. Secondary endpoints include: incidences of MI alone, vascular death alone, stroke alone, stent thrombosis, and death from any cause. Data on the need for revascularisation will not be presented. In the PLATO study (in line with clinical practice) nearly all patients with STEMI received revascularisation; for patients with NSTEMI or UA it was left to investigators as to whether the patient was medically managed or revascularised.
Economic analysis	The reference case stipulates that : the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY; time horizon for estimation clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness presented as incremental cost per quality-adjusted life year (QALY). The time horizon for the modelling is a lifetime which is assumed to be 40 years. Perspective: NHS and Personal Social Services	
Other considerations	If the evidence allows, the following subgroups will be considered: people with UA, NSTEMI and STEMI.	Results will be presented for each of the subgroups specified in the scope.	

3.1 Population

The ERG notes that ACS is an umbrella term for three patient subgroups, STEMI, NSTEMI and UA; antiplatelet treatment recommendations for each group fall under the remit of differing NICE guidelines[10-11] and guidance.[8]

The relevant population described in the decision problem is patients presenting with ACS irrespective of whether they have undergone revascularisation. This is consistent with the population of the key trial cited by the manufacturer and used as the main source of clinical evidence in the MS.

The ERG notes however that all patients in the key trial received treatment for at least six months. NICE clinical guideline CG48[10] recommends that patients with NSTEMI should receive dual antiplatelet treatment for 12 months following the index event. In contrast, patients with an STEMI who are treated with a combination of aspirin and clopidogrel during the first 24 hours after the MI should continue this treatment for at least 4 weeks. The subgroup of STEMI patients who are treated for 4 weeks with dual antiplatelet therapy is not represented in the key trial. The manufacturer acknowledges the CG48[10] recommendations, but adds that the European guidelines[14] for the management of STEMI recommend dual antiplatelet therapy for 12 months (MS, p12). The ERG is aware that CG48[10] may not always be followed in clinical practice and that CG48[10] is due for review.

The ERG considers that NICE guidance TA152[8], recognises that following treatment with a BMS patients receive dual antiplatelet therapy for 3 months. The ERG notes that treatment with dual antiplatelet therapy for 3 months will only apply to patients who have a STEMI as CG94[11] (noted earlier) recommends that patients with NSTEMI receive dual antiplatelet therapy for 12 months. In the key trial all patients with STEMI receive at least 6 months dual antiplatelet treatment regardless of the type of stent they received.

3.2 Intervention

Ticagrelor has a UK marketing authorisation and is licensed for use (co-administered with ASA) for the prevention of atherothrombotic events in adult patients with ACS (UA angina NSTEMI or STEMI); including patients managed medically and those who are managed with PCI or CABG. Ticagrelor is administered as 90mg film-coated tablets. Treatment should be initiated with a single 180mg loading dose (two 90mg tablets) and then continued at 90mg twice daily. The recommended use of ticagrelor is for a single course of treatment up to 12 months with aspirin. The manufacturer does not expect that patients will receive repeated courses of ticagrelor (MS, p12).

3.3 Comparators

Two main treatment strategies are included in the final scope issued by NICE.[5] For patients who are to be managed with PCI, the two comparators are prasugrel and clopidogrel. For patients who are not to be managed with PCI, clopidogrel is the comparator. The manufacturer (MS, p26) asserts that there is low usage of prasugrel in the NHS in England and Wales and states that [redacted] The clinical advisor to the ERG has verified that recent use of prasugrel in UK clinical practice is low.

The pivotal trial in the MS directly compares ticagrelor with clopidogrel in a cohort of patients who are to be managed with and without PCI. In the absence of any direct RCT evidence of the relative efficacy of ticagrelor compared with prasugrel, the manufacturer cites data from a paper[19] (recently published independently by a third party) that describes the results of an indirect analysis between ticagrelor and prasugrel. The manufacturer is highly critical of the indirect analysis (MS, p61 to p66) and maintains that the two main RCTs included are too different in patient population and design to be appropriately compared. Similar criticisms have been voiced by independent reviewers.[20] The ERG agrees that the indirect analysis is inappropriate and its results should therefore be interpreted with caution.

3.4 Outcomes

The outcomes listed in the scope issued by NICE include mortality, thrombotic cardiovascular events, need for revascularisation, adverse effects of treatment and health-related quality of life (HRQoL). The manufacturer has addressed all these outcomes, with the exception of 'need for revascularisation'. The manufacturer has justified the omission of 'need for revascularisation' with the following statement (MS, pg30): '...nearly all patients with STEMI received revascularisation whilst for patients with NSTEMI or UA it was left to the investigators' discretion as to whether the patient was medically managed or revascularised.' The ERG considers that the scope is ambiguous and the manufacturer's explanation is acceptable if the scope is interpreted as referring to changing the immediate mode of treatment (i.e. revascularisation) within the trial. However, it is the opinion of the ERG that this outcome was intended to refer to additional, unplanned revascularisation following any index procedure; this has not been addressed by the manufacturer.

The manufacturer states that outcome data for recurrent ischaemia are provided; however the ERG notes that these data are not presented in the clinical section of the MS but are presented in the published trial paper.[21] The ERG has included the recurrent ischaemia data from the published paper in this report.

The manufacturer reports the results of a HRQoL study carried out as part of the key trial. The patient responses to the EQ-5D questionnaires are presented as utility scores in the cost-effectiveness section of the MS.

3.5 Economic analysis

The manufacturer's economic analysis is in line with that stipulated in the final scope issued by NICE. The manufacturer has presented its economic assessment in terms of QALYs and has modelled outcomes using a lifetime horizon of 40 years. Costs are considered from an NHS and Personal Social Services perspective.

3.6 Other considerations

In the decision problem NICE has suggested that if the evidence allows, the clinical and cost-effectiveness outcomes for subgroups of patients with STEMI, NSTEMI and UA should be considered. In the clinical effectiveness section of the MS, the manufacturer describes the outcomes for the following subgroups of patients from the key trial: patients who were identified at randomisation as being intended for early invasive strategy (angiography followed by PCI/CABG [i.e from all ACS subgroups]); patients who were identified at randomisation as being intended for early conservative strategy (UA and NSTEMI patients); patients with STEMI (treated with primary or planned PCI). The ERG notes that in the MS, there is a mismatch between subgroups of interest in the economic evaluation and the clinical subgroups in the clinical section. In the clinical effectiveness section, outcomes are presented for a combined UA and NSTEMI patient group; in the economic evaluation, ICERs are presented the UA patient group and the NSTEMI patient group.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

Table 3 provides an outline of the key background/clinical information and its location within the MS. Its purpose is to signpost the reader to the main areas of background/clinical information within the MS.

Table 3 Key clinical information in the MS

Key information	**Pages in the MS**
Description of the technology	16
Context	19-27
Equity and equality	28
Statement of decision problem	29-31
Literature search	32
Search strategies	260-264
Study selection: direct evidence	33-35
indirect evidence	59-60
Clinical-effectiveness evidence:	
Trial information	34-45
Results: main and subgroups	45-57
Results: safety	69-75
Results: quality of life	148-150

4.1.1 Critique of search

The results of two clinical literature reviews are reported in the MS; one to inform the review of clinical effectiveness and the second to identify studies for inclusion in the indirect analysis. The first of these is described here while the results of the second are included in the summary and critique of the indirect comparison exercise discussed in Section 4.8.1.

In the MS, the information describing the systematic reviews of the literature undertaken does not reveal the number of reviewers involved in the review activities. There is no indication that review decisions (e.g. application of inclusion criteria) or data extraction tables were cross checked by a second reviewer.

All major electronic databases were searched including the Cochrane Library, Medline PubMed,, Medline In Process, Ovid EMBASE. The searches were conducted for each database up to 9th April 2010 with no limit on the starting date. There was no evidence in the MS that international conferences were searched.

There are conflicting statements made in the MS regarding studies that were additional to those identified from the database searches described above. In the main body of the MS (MS, p32) it is said that 'three additional studies, unpublished at the time of search, previously presented at international cardiology congresses and expected to be published during this appraisal were included from AstraZeneca's internal database.' In Appendix 2 of the MS (MS, p256) it is said that 'one study was included from the AstraZeneca clinical trial database. The study was unpublished at the time of search but was expected to be published by the time of the STA review.' In the flow diagram (MS, p34) that depicts the study selection process, two studies are said to have been identified through sources other than the Medline database search.

The ERG conducted its own searches and is confident that no relevant published studies have been excluded.

4.1.2 Critique of the inclusion/exclusion criteria

The explicit inclusion/exclusion criteria used in the review are described in the MS (MS, p33) and are reproduced in Table 4.

Table 4 Inclusion/Exclusion criteria (direct analysis)

	Clinical effectiveness
Inclusion criteria	Population - patients with acute coronary syndromes or coronary artery disease Interventions - involving licensed dose of ticagrelor Outcomes - clinical efficacy and safety Study design - randomised, double-blind controlled trials Language restrictions - none
Exclusion criteria	Population - healthy volunteers Interventions - involving unlicensed dose of ticagrelor Outcomes - non-clinical/experimental outcomes Study design - methodological papers Language restrictions - none

4.1.3 Table of identified studies

The search conducted by the manufacturer identified one study for inclusion in the review. The PLATO[21] trial is a phase III RCT published in 2009. Six subgroup analyses[21-26] resulting from the PLATO[21] trial were also identified by the manufacturer.

An appropriate PRISMA[27] flow diagram, describing the review process is provided by the manufacturer (MS, p34). As noted previously, this confirms that additional studies were identified through sources other than the Medline databases; it is uncertain whether this number should be one, two or three.

4.1.4 Details of relevant studies not included in the submission

The ERG is confident that the PLATO[21] trial is the only relevant trial to the decision problem issued by NICE.

4.2 Description of the included study

The PLATO[21] trial was powered to detect superiority in the primary endpoint and is

> *a large randomised controlled clinical trial that enrolled adult ACS patients (STEMI, NSTEMI and UA, including a UK population) irrespective of planned intervention (e.g. PCI). PLATO[21] compared ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) with clopidogrel (300 or 600 mg loading dose, 75 mg thereafter) in 18,624 patients with ACS over a 12 month period (MS, p12).*

Key outcome definitions (clinical efficacy and bleeding) are described in Table 5. For a comparison of bleeding definitions between those utilised in the PLATO[21] trial with the TIMI definitions, the reader is referred to page 70 of the MS. The characteristics of the PLATO[21] trial are described in Table 6.

Table 5 PLATO clinical efficacy outcome definitions

Clinical outcome	Definition
Death from vascular causes	Death from vascular causes or cerebrovascular causes and any death without another known cause
Myocardial infarction	Universal definition.[28] The MIs reported in the MS appropriately exclude silent MIs (defined as development of a new or presumed pathological Q waves in the absence of cardiac ischaemic symptoms)
Stroke	Focal loss of neurologic function caused by an ischaemic or haemorrhagic event, with residual symptoms lasting 24 hours or leading to death
Stent thrombosis	ARC[29] criteria
Bleeding event	
Major life-threatening	Fatal, intracranial, intrapericardial with cardiac tamponade, hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the haemoglobin level of 5.0g per decilitre or more, or the need for transfusion of at least 4 units of red cells
Other major bleeding	Bleeding that led to clinically significant disability (e.g. intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the haemoglobin level of at least 3.0g decilitre but less than 5.0g per decilitre or requiring transfusion of 2 to 3 units of red cells
Minor bleeding	Any bleeding requiring medical intervention but not meeting the criteria for major bleeding

ARC= Academic Research Consortium

The manufacturer describes a Health Economics and Quality of Life study (HECON) conducted as part of the PLATO[21] trial. The EQ-5D questionnaire was administered in all participating countries where an official language version was available. It was intended that the questionnaires would be administered at three time points of during the study: at discharge from the index visit, at the 6 month visit and at the end of treatment visit.

Table 6 PLATO trial characteristics

Study	Trial design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes
PLATO[21]	•RCT, Phase III, international, double blind, double dummy •43 countries including UK (18 centres, 281 patients) •18,624 patients admitted to hospital with ACS, with or without ST-segment elevation	• Ticagrelor (180mg loading dose, 90 mg twice daily thereafter) +ASA • Clopidogrel (300mg to 600mg loading dose, 75mg daily thereafter) +ASA ASA dosing Most patients received 75 to 100 mg daily unless they could not tolerate the drug. For those who had not previously been receiving ASA, 325 mg was the preferred loading dose; 325 mg was also permitted as the daily dose for 6 months after stent placement.	• Patients hospitalised for an ACS, with ST-segment elevation or new LBBB during previous 24 hours • Patients hospitalised without ST-segment elevation during the previous 24 hours with at least two of the following: ST-segment changes indicative of ischaemia, a positive test for a biomarker indicative of myocardial necrosis; or one of several risk factors (age >60; previous MI or CABG; coronary artery disease with stenosis ≥50%; previous ischaemic stroke, TIA, carotid stenosis ≥50% or previous cerebral revascularisation; diabetes mellitus; peripheral vascular disease; or renal dysfunction)	•Any contraindication against the use of clopidogrel •Fibrinolytic therapy within 24 hours before randomisation •Need for oral anticoagulation therapy • Increased risk of bradycardia without an implanted pacemaker • Concomitant therapy with a strong cytochrome P450 3A inhibitor or inducer	12 month planned follow-up or until 1780 events had occurred Primary •CE of death from vascular causes, MI or stroke Secondary •Primary endpoint in patients for who early invasive management was planned at randomisation •CE of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischaemic, TIA or other arterial thrombotic events •MI •Death from vascular causes •Stroke •Death from any cause

TIA= transitory ischaemic attack; CE= composite endpoint; LBBB= left bundle branch block

4.3 Description and critique of the manufacturer's approach to validity assessment

A single RCT (PLATO[21]) forms the basis of the clinical and cost-effectiveness evidence in the MS. The results of the PLATO[21] trial have been published previously. This section outlines the strengths and weaknesses of the PLATO[21] trial. Data in this section are taken from the MS as well as from data subsequently provided by the manufacturer as a part of the STA clarification process.

Trial conduct

The PLATO[21] trial was a large, international, multi-centre, double-blind, double dummy RCT. The manufacturer has provided a quality assessment of the trial in the MS; this has been critiqued by the ERG and appears in Appendix 1. The ERG considers the PLATO[21] trial to be well-designed.

The PLATO[21] trial recruited 18,624 patients from 862 centres in 43 countries. Randomisation was applied centrally via an interactive voice response system and the randomisation schedule (computer generated and blocked by site) was created and kept in the possession of a separate group that had no involvement in the study. The ERG considers that these measures demonstrate the robustness of the trial randomisation and blinding processes.

For the results of a trial with so many centres to be meaningfully interpreted, the manner in which the protocol is implemented should be clear and similar across all centres. With so many investigators in different countries, general clinical practice will always be an issue and the results of a trial can only be generalisable if it is executed efficiently. The manufacturer states in the Clinical Study Report[30] (CSR) (CSR, p65) that [redacted] An independent central adjudication committee (ICAC) adjudicated all reported pre-specified suspected endpoint events.

The PLATO[21] trial was a double-blind study in which patients and investigators were all unaware of treatment assignments; blinding was achieved by the use of a matched placebo. The ERG notes that the Food and Drug Administration (FDA[31]) review of the trial was critical of the ease with which it may have been possible to break the blind: the clopidogrel formulation used was a clopidogrel tablet cut in half and placed in two capsules (to match twice daily ticagrelor).

There were differences in the frequencies of some adverse effects (e.g. dyspnoea, ventricular pauses and syncope were more frequent in the ticagrelor arm of the trial); however the event rates were low and the ERG considers it unlikely that these would have led to the unmasking of the treatment regimen.

According to the manufacturer's clarification response, adherence to study medication was assessed by the investigator at each visit and a patient was regarded as being adherent if they reported taking more than 80% of the expected doses. The ERG notes that by this measure compliance was well balanced across the two treatment arms (82.9% in the ticagrelor arm vs 83.0% in the clopidogrel arm). The ERG also notes that in 'routine clinical practice' adherence to twice daily medicines is always less than adherence to once daily medicine.[32]

The manufacturer stated, in the clarification response, that there were a total of 589 protocol deviations (two of these were failure to provide consent, 447 were failure to comply with any other inclusion criteria and 140 were failure to comply with any of the exclusion criteria) throughout the course of the trial. The ERG notes that there is unlikely to be any impact of such protocol deviations as they were balanced across the two treatment groups (3.1% in the ticagrelor group vs 3.2% in the clopidogrel group) and only a small proportion of patients were affected (3.2% in total).

Applicability to the UK and UK clinical practice

Of the 18,624 patients recruited to the PLATO[21] trial, only 281 were from UK centres. However, the ERG is satisfied that enough of the patients in the trial were derived from other EU countries with similar care pathways to the UK.

The treatment arms in the PLATO[21] trial were similar at baseline. However, the manufacturer notes that whilst the percentage of males amongst ACS patients in England and Wales is broadly similar to that within the PLATO[21] trial, there is a considerable difference in both the mean age and the proportion of older patients. (The ERG notes that in the manufacturer's economic evaluation, the event rates of the PLATO[21] trial are age adjusted to more accurately reflect the cost effectiveness of ticagrelor for the ACS population in England and Wales).

It was noted in Section 3 of this report that all patients in the PLATO[21] trial received treatment for at least 6 months. There will be patients in UK clinical practice suffering a STEMI who will be treated with dual antiplatelet therapy for at least 4 weeks in accordance with NICE clinical guideline CG48[10] or for 3 months according to NICE guidance TA152.[8] This means that direct evidence from the trial cannot support a recommendation for the group of patients who are currently treated with dual antiplatelet treatment for 4 weeks or 3 months.

The manufacturer acknowledges the CG48[10] recommendations, but adds that the European guidelines[14] recommend dual antiplatelet therapy for 12 months for all ACS patients including those with STEMI (MS, p12). Whether or not the results of the trial are fully generalisable to the UK population is uncertain primarily because there are no patients in the trial who received clopidogrel for less than 12 months as recommended by NICE.[7-8, 10]

The ERG notes that the loading dose of clopidogrel was different among patients in the PLATO[21] trial depending on whether or not they had already received open-label clopidogrel. The ERG considers that the trial reflects current clinical practice and all patients had received antiplatelet treatment at a clinically meaningful dose.

4.3.1 Description and critique of manufacturers outcome selection

The primary outcome of the PLATO[21] trial was the time to the first occurrence of a composite of death from vascular causes, MI (excluding silent MI–defined as development of a new or presumed pathological Q waves in the absence of cardiac ischaemic symptoms) and stroke. The ERG acknowledges that the manufacturer has excluded 'silent' MIs from the MI count in the primary outcome.

Additional secondary endpoints included:

- time to first occurrence of any of death from any cause, MI and stroke;

- time to first occurrence of any of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack or other arterial thrombotic events;

- time to first occurrence of MI;

- time to death from vascular causes;

- time to first occurrence of stroke; and

- time to death from any cause.

These endpoints and their components are standard endpoints used in the field of cardiology and the manufacturer has applied standard definitions to these.

In the PLATO[21] trial, bleeding events were categorised using 'novel categories' devised by the manufacturer. According to the MS (MS, p69) 'the categories were chosen as an inclusive and clinically-relevant measure suitable for assessing all kinds of bleeding events whether or not associated with surgery or other medical procedure. Definitions used in PLATO[21] were specifically designed to characterise bleeding in both the acute and chronic settings, with

invasive and medical management, and provide improved medical relevance for safety comparison to the primary endpoint events being prevented.'

The ERG is confident that the bleeding categorisation method employed by the manufacturer is relevant and robust. The manufacturer has mapped the PLATO[21] bleeding events onto the TIMI scale by applying an algorithm to the bleeding events. A comparison of PLATO[21] and TIMI bleeding events is presented on page 60 of the MS.

4.4 Describe and critique the statistical approach used

Composite endpoints are commonly used in clinical trials, particularly in the field of cardiology, as they enable investigators to reduce the sample size required and the length of follow-up needed to show a statistical effect.[33] However, their use has been criticised in the published literature.[34] The ERG notes that there are caveats around the use of composite endpoints which must be considered. Recommendations, by Montori and colleagues[35] (which are consistent with EMA[36] guidelines), for the use of composite endpoints state that:

i) the individual components should be of similar importance to patients;

ii) the more or less important endpoints occur with similar frequency;

iii) the component endpoints are those that are likely to have similar relative risk reductions with narrow confidence intervals.

The ERG is concerned that the components of the primary efficacy composite endpoint do not meet these criteria. Firstly, in PLATO[21], the requirement that all components of the endpoint should be of similar importance to patients is not satisfied. This is evident from the value of the mean utility scores during the first 12 months used in the manufacturer's economic evaluation (i.e. vascular death = 0.246; MI = 0.812 and stroke = 0.736), and of course any death cannot be considered equivalent to either a non-fatal MI or a non-fatal stroke. Secondly, there are differences in the frequencies of component endpoints observed in the trial (vascular death = 795/18,624; MI = 1097/18,624; stroke = 231/18,624). Thirdly, the hazard ratio (measure of the relative risk over time) of the component endpoint of stroke differs in direction to that of the other two components (vascular death: HR=0.79, 95% CI 0.69 to 0.91; MI: HR=0.84, 95% CI 0.75 to 0.95; stroke: HR=1.17, 95% CI 0.91 to 1.52). Taken together these problems suggest that the results of the overall composite endpoint should be interpreted cautiously, with the potential for increased risk of stroke discussed further. Nevertheless, the beneficial effects of ticagrelor on the vascular death and MI are consistent. Finally, cardiac and non-cardiac causes of death are competing risks; this does not appear to have been addressed by the manufacturer. In the MS, Kaplan-Meier survival curves

relating to the primary efficacy endpoint were presented, but cumulative incidence survival curves would have been more appropriate.

The sample size calculation for the trial was based on an expected primary composite endpoint (death from vascular causes, MI or stroke) with an event rate of 11% in the clopidogrel group and a relative risk reduction of 13.5% for ticagrelor. The ERG considers this to be inappropriate as the definition of the primary endpoint was time to first occurrence of the composite of death from vascular causes, MI or stroke and it would therefore have been more appropriate to use a survival measure such as a hazard ratio rather than a measure of simply whether patients experienced an event or not.

Randomisation was not stratified by any important prognostic factors measured at baseline. The ERG considers this to be appropriate as in such a large trial prognostic factors would have been balanced across the two treatment groups. However, with so many participating centres it is advisable to have a separate randomisation scheme for each centre;[37] the ERG is confident that this was the case in the PLATO[21] trial as the randomisation schedule was blocked by site.

Primary and secondary efficacy endpoints were analysed using the Cox proportional hazards model with a factor for treatment group. According to the CSR[30] (CSR, p66), [redacted] there is no discussion of the validity of this assumption so it is not possible for the ERG to comment on this.

Randomised treatment was scheduled to continue for 12 months but it was planned that patients would leave the study at their 6 or 9 month follow-up visit if the targeted number of 1780 primary endpoint events had occurred by that time (type II censoring). The ERG is not concerned about this as the numbers of patients in each arm that left the study at each visit were comparable and it was specified in advance that this method would be used. The ERG considers that all patients should have been followed up to at least 12 months as mortality at 12 months is a key outcome in trials of cardiovascular drugs.

Hypothesis testing was conducted at the nominal significance level of 4.97% (two-tailed) in order to account for a planned interim analysis after 1200 events. To address the issue of multiple testing with the secondary endpoints, a closed hierarchical test sequence was planned. The secondary endpoints were tested individually in a pre-specified order until the first non-significant difference was found between the two groups. The first test that was

found not to be statistically significant and all subsequent tests were formally classified as not being 'statistically significant'. The pre-specified order was:

i. the time to first occurrence of any event of the composite of death from vascular causes, MI, or stroke for the subgroup of patients with intent for invasive management at randomisation;

ii. the time to first occurrence of any event of the composite of death from any cause, MI or stroke;

iii. the time to first occurrence of any event of the composite of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack or other arterial thrombotic events;

iv. first occurrence of MI;

v. the time to occurrence of stroke;

vi. occurrence of all-cause mortality.

Treatment comparisons, starting with the first non-statistically significant comparison in the hierarchy, were examined in an exploratory manner and therefore any results from such comparisons should be treated with caution.

To test the relative consistency of treatment effects over time, relative risk ratios were calculated for the periods from randomisation until 30 days and from 31 to 360 days. This is reasonable as most events are likely to occur within the first 30 days of treatment. However it would have been informative to use additional periods also e.g. 31 – 180 days, 181-270 days, and 217-360 days to take account of the follow up protocol. The consistency of effects on efficacy and safety endpoints was explored in 25 pre-specified subgroups and eight *post-hoc* subgroups. The ERG is concerned by the large number of subgroups and possible overemphasis of any significant results from these analyses.

4.5 Results

4.5.1 Overall cohort

Primary endpoint

The results of the primary outcome of the PLATO[21] trial are depicted in Figure 1 whilst the results of the primary outcome (death from vascular causes, MI or stroke) along with the secondary outcomes are described in Table 7. A statistically significant benefit of ticagrelor

was found for the primary composite endpoint (9.8% compared to 11.67% [HR= 0.84; 95% CI 0.77 to 0.92; p<0.001]).

The ERG notes from Figure 1 that after 180 days, the number of patients at risk is markedly reduced (in both arms); as noted in Section 4.3.1, the trial protocol stipulated that once the requisite number of events had accrued, patients were required to leave the trial after their 6 month or 9 month visit. The ERG considers that all patients should have been followed up for 12 months.

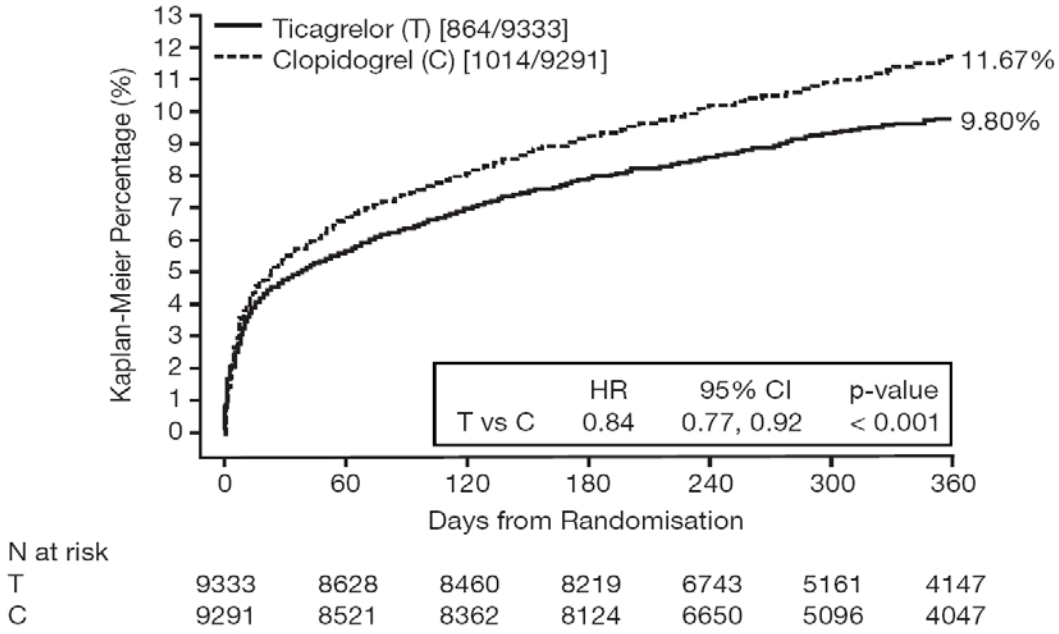


Figure 1 PLATO trial: Kaplan Meier plot for the primary endpoint

Table 7 PLATO trial key outcomes

	Ticagrelor N=9333 No. patients with events (KM%/12 months)	Clopidogrel N=9291 No. patients with events (KM%/12 months))	HR for ticagrelor (95% CI)	p value
Primary				
Death from vascular causes, MI, stroke	864(9.8)	1014(11.7)	0.84(0.77 to 0.92)	<0.001*
Secondary				
Death from any cause, MI or stroke	901(10.2)	1065(12.3)	0.84(0.77 to 0.92)	<0.001*
Death from vascular causes, MI, stroke, severe recurrent ischaemia, recurrent ischaemia, TIA or other arterial thrombotic event	1290(14.6)	1456(16.7)	0.88(0.81 to 0.95)	<0.001*
MI	504(5.8)	593(6.9)	0.84(0.75 to 0.95)	0.005*
Death from vascular causes	353(4.0)	442(5.1)	0.79(0.69 to 0.91)	0.001*
Stroke:	125(1.5)**	106(1.3)	1.17(0.91 to 1.52)	0.22
ischaemic	96(1.1)	91(1.1)		0.74
haemorrhagic	23(0.2)	13(0.1)		0.10
unknown	10(0.1)	2(0.02)		0.04
Death from any cause (exploratory)	399(4.5)	506(5.9)	0.78(0.69 to 0.89)	<0.001
Death from causes other than vascular causes (exploratory)	46(0.5)	64(0.8)	0.71(0.49 to 1.04)	0.08
Severe recurrent ischaemia**	302(3.5)	345(4.0)	0.87(0.74 to 1.01)	0.08
Recurrent ischaemia**	500(5.8)	536(6.2)	0.93(0.82 to 1.05)	0.22

KM= Kaplan-Meier. The percentages are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have had more than one type of endpoint. Death from vascular causes included fatal bleeding. Only traumatic fatal bleeding was excluded from the category of death from vascular causes.
* Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy end points
** data taken from published paper
TIA=transitory ischaemic attack

Secondary endpoints

When the individual components of the composite endpoint are disaggregated, the reduction in the primary endpoint is driven by statistically significant reductions in death from vascular causes (HR= 0.79; 95% CI 0.69 to 0.91; p=0.001) and MI (HR= 0.84; 95% CI 0.75 to 0.95; p=0.005).

There was no statistically significant difference in the overall rate of stroke between the two arms although the number of strokes was higher in the ticagrelor arm. The ERG notes that the rates of ischaemic strokes across the two arms were similar (RR=1.05). However, the rates of

haemorrhagic strokes plus unknown strokes were very different (RR=2.19, p=0.01), with more of the latter strokes occurring in the ticagrelor arm.

For the secondary composite endpoint of death from any cause, MI or stroke a statistically significant benefit of ticagrelor is reported (HR= 0.84; 95% CI 0.77 to 0.92; p<0.001).

An exploratory analysis of total mortality (death from any cause and death from causes other than vascular causes) identified an apparent statistically significant difference in favour of ticagrelor for the outcome of death from any cause (HR= 0.78; 95%CI 0.69 to 0.89; nominal p<0.001).

The rates of recurrent ischaemia were also reported in the published paper. No significant difference is noted between the two arms of the trial for either severe recurrent ischaemia or recurrent ischaemia.

The results of an exploratory analysis on the rate of stent thrombosis in the patients who received a stent during the trial (n=11,289) are also reported in the MS. The results showed the rate of definite stent thrombosis[29] at one year to be lower in the ticagrelor arm (1.3%) than in the clopidogrel arm (1.9%), a statistically significant outcome (HR= 0.67; 95% CI 0.50 to 0.91; nominal p = 0.009).

Primary endpoint over time

The manufacturer provides an analysis of the incidence of the primary composite endpoint for increasing timepoints across the PLATO[21] trial. This is depicted in Figure 2. It is noted in the MS that the early benefits of ticagrelor compared to clopidogrel are seen within the first 30 days of treatment and that these benefits are maintained across the course of the study.

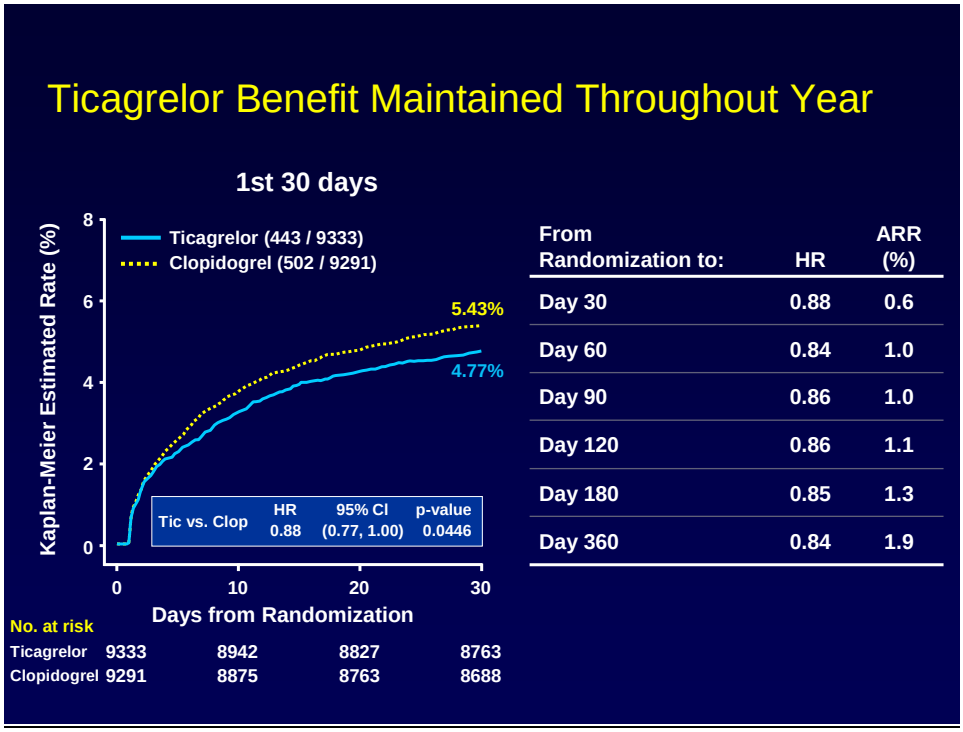


Figure 2 PLATO trial: incidence of primary endpoint over time

4.5.2 Subgroup analyses

Pre-defined analysis of the primary endpoint

The manufacturer reports the results of an analysis of the primary endpoint for specific patient subgroups. The subgroups were identified according to a number of coronary criteria and other variables such as weight, gender and geographic region; these are described in full in Figure 5.5 of the MS (MS, p48) and reproduced in this report in Appendix 2. The ERG considers that the results of these analyses should be interpreted with caution as the large number of comparisons increases the risk of chance findings.

It is reported in the MS (MS, p48) that treatment interaction significance levels of less than 0.05 occurred in three subgroups: geographic region, body weight above or below gender-specific median, and use of lipid-lowering drugs at randomisation. No other treatment interaction was found. The ERG notes that the regional analysis suggests that in the US, patients randomised to clopidogrel did better than those randomised to ticagrelor. The ERG is

aware that this finding is currently the focus of deliberation by the FDA.[31] As part of the clarification process, the ERG requested that the manufacturer provide the outcomes for the cohort of patients from Europe. The manufacturer's complete response is presented in Appendix 3 of this report. In summary, the primary and secondary efficacy endpoint results for the European Union region are consistent with the results observed for the primary and secondary efficacy endpoints results of the full analysis set, i.e. a statistically significant benefit of ticagrelor compared to clopidogrel.

The MS presents a number of subgroup analyses derived from the PLATO[21] study, including an assessment of the effect of ticagrelor on the incidence of primary and secondary endpoint events in:

i) patients identified at randomisation with investigator intent for early invasive strategy (early angiography);

ii) patients identified at randomisation with investigator intent for an early conservative strategy;

iii) patients who presented with STEMI or left bundle branch block (LBBB) and had planned primary PCI;

iv) patients who underwent CABG;

v) patients with and without diabetes mellitus;

vi) the presence or absence of a number of polymorphisms of the gene encoding CYP2C19.

Of these analyses, i) to iv) are reported as pre-specified and v) is reported to be *post-hoc*. It is unclear whether vi) is pre-specified or *post-hoc* as it is described as the former on page 54 of the MS and the latter on page 42.

The ERG notes that the trial was not powered to show differences between subgroups. The ERG also advises caution in the interpretation of the subgroup analyses presented due to their number and exploratory nature.

Patients identified for early angiography (PLATO-INVASIVE)

Patients in this subgroup were those identified at randomisation for early angiography and comprised 72% (n=13,408) of patients randomised to the PLATO[21] trial. The subgroup included patients with STEMI (49%), NSTEMI (38%), UA or other (13%). As the manufacturer has highlighted in the decision problem only 77% of this cohort actually had a PCI; therefore this subgroup is not representative of a PCI-only cohort.

The subgroup analysis results for the primary and secondary outcomes are described in Table 8. These results are also reported in a published paper.[22] For the primary composite endpoint, patients in the ticagrelor arm experienced a statistically significantly reduction in event rate at 12 months compared to the patients in the clopidogrel arm (HR=0.84; 95%CI 0.75 to 0.94; p=0.0025).

When the individual components of the composite endpoint are disaggregated, the reduction in the primary endpoint is driven by statistically significant reductions in death from vascular causes (HR=0.82; 95%CI 0.68 to 0.98; p=0.0250) and MI (HR=0.80; 95%CI 0.69 to 0.92; p=0.023). There was no statistically significant difference in the rate of strokes between the two arms; however there are more strokes in the ticagrelor arm (1.2% vs 1.1%).

For the secondary composite endpoint of death from any cause, MI or stroke a statistically significant benefit of ticagrelor is reported (HR=0.84; 95% CI 0.75 to 0.94; p=0.0016).

Death from any cause appears to be statistically significantly lower in the ticagrelor arm compared with the clopidogrel arm (HR=0.81; 95% CI 0.68 to 0.95; nominal p=0.0103).

Table 8 PLATO trial: key outcomes for patients identified for early invasive strategy

	Ticagrelor N=6732 No. events (KM%/ 12 months)	Clopidogrel N=6676 No. events (KM%/ 12 months)	HR for ticagrelor (95% CI)	p value
Primary				
Death from vascular causes, MI, stroke	569(9.0)	668(10.7)	0.84(0.75 to 0.94)	0.0025
Secondary				
Death from any cause, MI or stroke	595(9.4)	701(11.2)	0.84(0.75 to 0.94)	0.0016
Death from vascular causes, MI*, stroke, severe recurrent ischaemia, recurrent ischaemia, TIA or other arterial thrombotic event	830(13.1)	964(15.3)	0.85(0.77 to 0.93)	0.0005
MI	328(5.3)	406(6.6)	0.80(0.69 to 0.92)	0.0023
Death from vascular causes	221(3.4)	269(4.3)	0.82(0.68 to 0.98)	0.0250
Stroke:	75(1.2)	69(1.1)	1.08(0.78 to 1.50)	0.6460
Ischaemic**	59(0.9)	59(0.9)		1.0000
Haemorrhagic**	12(0.2)	9(0.1)		0.6634
Unknown**	5(0.07)	1(0.01)		0.2187
Death from any cause (exploratory)	252(3.9)	311(5.0)	0.81(0.68 to 0.95)	0.0103

KM= Kaplan-Meier. Data are number (Kaplan-Meier estimated % at 360 days), unless otherwise indicated; p values calculated by use of univariate Cox model, unless otherwise indicated. *Includes silent myocardial infarction. **Data are number (%), and p values calculated with Fisher's exact test.

Patients identified for early conservative strategy (PLATO-MEDICAL)

This subgroup comprised 28% (n=5216) of the patients randomised in the PLATO[21] trial who were not planned to receive early angiography unless they experienced recurrent symptoms or ischaemia. The primary and secondary outcome results for this group are described in Table 9 and indicate that for the primary endpoint, there is a statistically significant benefit of ticagrelor compared to clopidogrel (HR=0.85; 95% CI 0.73 to1.00; nominal p=0.045). The benefit was driven by a statistically significant reduction in death from vascular causes (HR=0.76; 95% CI 0.61 to 0.96; nominal p=0.019). No benefit for stroke or MI is recorded.

Table 9 PLATO trial: key outcomes for patients identified for early conservative strategy

	Ticagrelor N=2601 No. events (KM%/ 12 months)	Clopidogrel N=2615 No. events (KM%/ 12 months)	HR (95% CI)	p value
Primary				
Composite of CV* Death / MI / Stroke	295(12%)	346(14.3%)	0.85(0.73 to 1.00)	0.04
MI	176(7.2%)	187(7.8%)	0.94(0.77 to 1.15)	0.555
CV* death	132(5.5%)	173(7.2%)	0.76(0.61 to 0.96)	0.019
Stroke	50(2.1%)**	37(1.7%)	1.35(0.89 to 2.07)	0.1616
Death from any cause (exploratory)	6.1%	8.2%	0.75(0.61 to 0.93)	0.010

KM=Kaplan Meier; *The ERG notes that the MS uses the term CV here, rather than vascular
**For ticagrelor patients, 50 strokes in the non-invasive group added to 75 strokes in the invasive group = 125. However it was noted by the ERG (see Table 7) that the sum of strokes in the ticagrelor arm adds to 129.

The manufacturer cautions (MS, p53) that patients in this subgroup were initially assigned to a non-invasive medical treatment strategy at randomisation, but may have subsequently required angiography and revascularisation because of recurrent symptoms or ischaemia. In the subgroup of patients intended for an initial non-invasive management strategy, 3948 (76%) were not revascularised with PCI or CABG. In these conservatively managed patients the incidence of primary composite outcomes (vascular death/MI/stroke) was 12.2% in the ticagrelor group and 15.2% in the clopidogrel group at 12 months (HR=0.81; 95% CI 0.68 to 0.97).[24]

Patients with STEMI who received primary PCI (PLATO-STEMI)

The results for patients presenting with STEMI or LBBB (n=7544) are presented in the MS and are also available in a published paper.[26] The primary event rate was recorded as 9.4% per year in the ticagrelor treatment arm compared to 10.8% per year in the clopidogrel treatment arm. This difference was not statistically significant (HR=0.87; 95% CI 0.75 to 1.01; p=0.07).

The MS further reports on the outcomes for patients that had either LBBB or STEMI at presentation or a discharge diagnosis of STEMI (n=8430 patients). The primary endpoint, occurred with an event rate of in 9.3% per year in the ticagrelor treatment group compared to 11% per year in the clopidogrel treatment group (HR=0.85; 95% CI 0.74 to 0.97; nominal p=0.02).

Patients undergoing CABG (PLATO-CABG)

Of the 1261 patients who underwent CABG during the 12 month trial period and who stopped medication ≤7 days prior to surgery, the primary event rate in the ticagrelor arm was 10.6% compared with 13.1% in the clopidogrel arm. This difference was not statistically significant (HR=0.84; 95% CI 0.60 to 1.16; p=0.29). The ERG considers that these data do not differentiate between patients who received primary CABG and those who received post-discharge CABG.

4.5.3 Summary of primary composite endpoint evidence

The MS (MS, p57) provides a summary of the incidence of the primary composite endpoint in the main PLATO[21] trial and the related subgroup analyses. This is replicated in Table 10. Full details of the PLATO-DIABETES and PLATO-GENETICS results are provided in the MS (pg 54-56).

Table 10 Summary of presented evidence

	Patient group (N)	**Ticagrelor (KM %/12 months)**	**Clopidogrel (KM %/12 months)**	**HR (95% CI)**
PLATO	All ACS (18,624)	9.8	11.7	0.84(0.77 to 0.92)
PLATO-INVASIVE	Intended for early angiography (13,408)	9.0	10.7	0.84(0.75 to 0.97)
PLATO-MEDICAL	Conservative management (5216)	12.0	14.3	0.85(0.73 to 1.00)
PLATO-STEMI	STEMI with PCI STEMI or LBBB at presentation (7544)	9.4	10.8	0.87(0.75 to 1.01)
	LBBB/STEMI at presentation or STEMI at discharge (8430)	9.3	11.0	0.85(0.74 to 0.97)
PLATO-CABG	CABG (1261)	10.6	13.1	0.84(0.60 to 1.16)
PLATO-DIABETES	With DM (4,622)	14.1	16.2	0.88(0.76 to 1.03)
	(without DM (13,951)	8.4	10.2	0.83(0.74 to 0.93)
PLATO-GENETICS	No loss of function YP2C19 allelle	8.8	10.0	0.86(0.74 to 1.01)
	Loss of CYP2C19 function allele (consenting patients =10,285)	8.6	11.2	0.77(0.60 to 0.99)

DM= diabetes mellitus

4.6 Heath related quality of life

The PLATO trial[21] included a Health Economics and Quality of Life sub-study. This sub-study employed the paper version of the EQ-5D questionnaire and the manufacturer converted the EQ-5D scores to utility values to inform the cost-effectiveness analyses presented in the MS (MS, p148), using the UK tariff weightings.

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

The results of the EQ-5D questionnaire are summarised in the CSR[30] (CSR, p157); no differences were found between ticagrelor and clopidogrel arms for any of the items on the EQ-5D. The manufacturer stresses (MS, p150) that the HECON sub-study includes the largest collection of EQ-5D questionnaire responses of any ACS study. The EQ-5D is a generic measure of health related QoL.

4.7 Safety/adverse events

The MS (MS, p69) states that all safety data are derived from the safety analysis population, and analysed according to treatment received (all patients randomised to one of the two treatment arms, and receiving at least one dose of that study medication); (total population=18,421; n=9235 for ticagrelor, n=9186 for clopidogrel).

Bleeding events

As noted previously, a novel system for categorising bleeding events was utilised in the PLATO[21] trial. The categories are defined in Section 4.2 of this report.

The incidence of the primary and main secondary bleeding events is described in Table 5.19 of the MS (MS, p72). This is replicated in Table 11 of this report with the HRs and CIs taken from the published paper[21] and added by the ERG. It is evident that there are no statistically significant differences between the two arms of the trial for the endpoints of PLATO major bleed (primary safety) and PLATO major fatal/life-threatening bleed; however, statistically significant differences in favour of clopidogrel are in evidence for the endpoints of PLATO total major + minor bleed, (HR=1.11; 95% CI 1.03 to 1.20; p=0.008) and PLATO non-CABG major bleed (HR= 1.19; 95% CI 1.02 to 1.38; p=0.03).

The MS reports (MS, p70) that no statistically significant differences in PLATO major bleeding between the ticagrelor and clopidogrel arms of the trial were identified. The ERG notes that the published paper reports more fatal intracranial bleeds in the ticagrelor arm (n=11) than in the clopidogrel arm (n=1).

Table 11 PLATO: primary and secondary bleeding events

Endpoint	Ticagrelor N=9235 No. events (KM%/ 12 months)	Clopidogrel N=9186 No. events (KM%/ 12 months)	HR Ticagrelor (95% CI)	p value
PLATO total major bleed (Primary)	11.6	11.2	1.04 (0.95 to1.13)	0.43
TIMI major + minor bleed	11.4	10.9	1.05 (0.96 to1.15)	0.33
PLATO major fatal/life-threatening bleed	5.8	5.8	1.03 (0.90 to1.16)	0.70
TIMI major bleed	7.9	7.7	1.03 (0.93 to1.15)	0.57
PLATO total major + minor bleed	16.1	14.6	1.11 (1.03 to1.20)	0.008
PLATO non-CABG major bleed	4.5	3.8	1.19 (1.02 to1.38)	0.03
PLATO fatal bleed	0.3	0.3	0.87 (0.48 to1.59)	0.66

Other safety events

The MS (MS, p73) reports the incidences of other safety events recorded in the PLATO[21] trial. These are replicated in Table 12. Statistically significantly increased rates are noted in the ticagrelor arm for dyspnoea and ventricular pauses (during the first week) and increases in serum uric acid and serum creatinine from baseline values from the beginning to the end of the trial.

The manufacturer addresses the increased incidences of dyspnoea and ventricular pauses (MS, p73). Relating to the former, it is stated that most reported cases of dyspnoea were mild to moderate in intensity and occurred as a single episode early after starting treatment. Approximately 30% of episodes resolved within 7 days, and the rate of discontinuation due to dyspnoea was 0.9% with ticagrelor versus 0.1% with clopidogrel ($p<0.001$). In 2.2% of affected patients the investigator considered treatment to be causally related to ticagrelor. Ticagrelor does not affect pulmonary function. The higher incidence of dyspnoea with ticagrelor was not associated with new or worsening heart or lung disease.

In relation to ventricular pauses, the manufacturer states that Holter monitoring detected more ventricular pauses during the first week in the ticagrelor group than in the clopidogrel group, but such episodes were infrequent at 30 days and rarely associated with symptoms. There were no significant differences in the rates of clinical manifestations of bradycardia between the two treatment groups at one year. In addition there was no difference in the requirement for a pacemaker between the two treatment groups.

The manufacturer does not discuss the increased incidences of serum uric acid or serum creatinine in ticagrelor patients.

Table 12 PLATO: recorded safety events

	Ticagrelor	**Clopidogrel**	**p value**
	Number of patients with events / number of patients (%)	**Number of patients with events / number of patients (%)**	
Dyspnoea			
Any	1270/9235 (13.8)	721/9186 (7.8)	<0.001
Leading to discontinuation	79/9235 (0.9)	13/9186 (0.1)	<0.001
Bradycardia			
Pacemaker Insertion	82/9235 (0.9)	79/9186 (0.9)	0.87
Syncope	100/9235 (1.1)	76/9186 (0.8)	0.08
Bradycardia	409/9235 (4.4)	372/9186 (4.0)	0.21
Heart Block	67/9235 (0.7)	66/9186 (0.7)	1.00
Holter Monitoring			
First Week			
Ventricular pause ≥3 sec	84/1451 (5.8)	51/1415 (3.6)	0.01
Ventricular pause ≥5 sec	29/1451 (2.0)	17/1415 (1.2)	0.10
At 30 Days			
Ventricular pause ≥3 sec	21/985 (2.1)	17/1006 (1.7)	0.52
Ventricular pause ≥5 sec	8/985 (0.8)	6/1006 (0.6)	0.60
Neoplasm arising during treatment			
Any	132/9235 (1.4)	155/9186 (1.7)	0.17
Malignant	115/9235 (1.2)	121/9186 (1.3)	0.69
Benign	18/9235 (0.2)	35/9186 (0.4)	0.02
Increase in serum uric acid from baseline value - %			
At 1 month	14±46	7±44	<0.001
At 12 month	15±52	7±31	<0.001
1 Month after end of treatment	7±43	8±48	0.56
Increase in serum creatinine from baseline value - %			
At 1 month	10±22	8±21	<0.001
At 12 month	11±22	9±22	<0.001
1 Month after end of treatment	10±22	10±22	0.59

4.8 Indirect comparison: ticagrelor vs prasugrel

The manufacturer carried out a systematic review of the literature to identify trials that might be used to provide data for an indirect comparison of ticagrelor vs prasugrel (MS, p60). The search strategy identified two relevant trials for use in an indirect comparison.[16] The manufacturer presents an appropriate PRISMA[27] flow diagram of the study selection process. The ERG is confident that no relevant studies have been missed.

Two trials,[38-39] of the four potentially relevant studies[16, 21, 38-39] identified by the manufacturer, were excluded by the manufacturer in the final stages of selection. The manufacturer excluded the DISPERSE-2[38] and JUMBO TIMI 26[39] trials on the grounds of inappropriate dosing and short duration. The ERG considers these exclusions to be appropriate.

In the DISPERSE-2[38] trial patients were randomised to receive ticagrelor 90mg twice per day, ticagrelor 180mg twice per day or clopidogrel 300mg followed by 75mg daily. According to the published paper, patients in the ticagrelor group were sub-randomised to receive or not receive an initial loading dose of 270mg. Patients were scheduled to receive 1, 2, or 3 months of study drug, depending on when they were enrolled. Patients treated with PCI within 24 hours of randomisation could, at the investigator's discretion, be given an additional 300mg of clopidogrel (or placebo if in the ticagrelor arm). The primary endpoint of DISPERSE-2[38] was major or minor bleeding at 30 days. Clinical endpoints included death, MI and stroke at 30 days.

The manufacturer also excluded the JUMBO TIMI 26[39] trial. In this phase II dose-ranging RCT, 904 patients undergoing elective or urgent PCI were randomised to either 300mg clopidogrel or one of three doses of prasugrel. The primary endpoint of the trial was non-CABG-related significant haemorrhage at 30 days. The efficacy measure was a composite endpoint of major adverse cardiac events at 30 days.

The only other potentially relevant study in addition to PLATO[21] identified for use in an indirect comparison was the TRITON-TIMI 38[16] trial; this trial compared prasugrel with clopidogrel in patients (n=13,608) with ACS who were to be treated with primary or planned PCI.

However, the manufacturer points to a number of differences between the PLATO[21] and TRITON-TIMI 38[16] trials that make an indirect comparison problematic and inappropriate. A comparison of the two trials is tabulated in the MS (MS, p64) and replicated here in Table 13.

The major concerns regarding the appropriateness of comparing the PLATO[21] and TRITON-TIMI 38[16] trials are discussed in the MS; these refer to differences in the target populations of the two trials, differences in the usage of clopidogrel (dosing and timing) and differences in the assessment of MI.

Differences in target population

The manufacturer states (MS, p61) that TRITON-TIMI 38[16] was a PCI study which enrolled only invasively managed ACS patients. Recruitment was restricted to patients whose anatomy was viewed as amenable to PCI. There was no initial medical management cohort and no patients for whom CABG was the primary means of revascularisation. Patients were randomised on the catheterisation table, immediately prior to planned PCI. In contrast, the PLATO[21] trial included a broad range of ACS patients identified early after presentation. A high proportion (72%) of the study population were intended for initial invasive management; this means that, unlike in the TRITON-TIMI 38[16] trial, a substantial number of patients were intended for medical management.

The TRITON-TIMI 38[16] trial publication reports the results of a subgroup of patients with STEMI; this group included patients who were treated with planned or primary PCI. In contrast, in the PLATO[21] trial, all of the patients with STEMI were intended for primary PCI.

Differences in clopidogrel use

The manufacturer makes the case (MS, p61) that the two trials did not employ the same dosing and timing of administration of clopidogrel (the common comparator). In TRITON-TIMI 38[16] prior clopidogrel use was not allowed resulting in 25% of the patients in the trial receiving their loading dose on the catheterisation table before the first coronary guidewire was introduced and 74% of patients received their loading dose between guidewire introduction and up to an hour after the procedure. The remaining 1% of patients received their loading dose more than an hour after PCI. The manufacturer contends that in the PLATO[21] trial clopidogrel was administered earlier in the treatment pathway; 46% of patients received open-label clopidogrel (including a loading dose) prior to randomisation; patients in the clopidogrel control arm received the study dose of clopidogrel a median of 11.3 hours after the onset of symptoms, and a median of 5.3 hours after being admitted to the hospital.

The loading dose of clopidogrel administered in the TRITON-TIMI 38[16] trial was 300mg. In the control arm of the PLATO[21] trial loading doses of 600 mg were allowed; 19.6% of clopidogrel-treated patients in the overall PLATO[21] cohort, 26.8% in the cohort intended for invasive management and 38.6% in the STEMI cohort received a load of 600 mg or greater of clopidogrel.

The manufacturer argues that low platelet inhibition (resulting from no pre-loading of clopidogrel) would impact on rates of stent thrombosis; and that clinical subgroups in each of the trials would be affected to different extents (STEMI patients made up 26% of the TRITON-TIMI[16] population and 40% of the PLATO[21] population).

Differences in MI assessment

The manufacturer notes (MS, p62) the differences between the two trials in the assessment of peri-procedural MIs. The manufacturer argues that assessing whether a patient has a peri-procedural MI when the angioplasty itself is being carried out is difficult, as any enzyme changes observed may be due to the original MI that triggered the procedure. Assessment is easier if multiple measurements of cardiac enzymes are taken between the initial event and the PCI procedure as it will be possible to differentiate a gradually falling pattern of biomarkers and a subsequent rise after the PCI (consistent with a further MI having occurred at the time of the procedure). This issue is important when examining outcomes in TRITON TIMI 38[16] and PLATO,[21] because of the difference in timing of PCI between the two trials. A single pre-procedure enzyme measurement was available for patients in PLATO.[21] In TRITON-TIMI 38[16] (with the exception of the STEMI primary PCI cohort) there was generally time for at least two pre-procedure enzyme measurements, and peri-procedural MI adjudication was much less confounded by the index event. The high percentage of PCI in TRITON-TIMI 38[16] means that there were a greater number of enzymatic MIs in both the clopidogrel and prasugrel arms of TRITON TIMI 38[16] and in which prasugrel was demonstrated to be superior to clopidogrel. In TRITON-TIMI 38[16] almost half of the "MIs" were purely enzymatic events (triggered for adjudication by laboratory values only) and were included in the primary composite endpoint, while in PLATO[21] mainly clinical MIs were included in the primary composite endpoint. The clinical significance of MI events diagnosed solely on biochemical abnormalities observed after a PCI is of debatable prognostic import.

Manufacturer's conclusions

In summary, for these reasons, the manufacturer chose not to carry out an indirect comparison of ticagrelor vs prasugrel.

Table 13 Comparison of PLATO and TRITON-TIMI 38 RCTs

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

4.8.1 Published indirect comparison of ticagrelor vs prasugrel

The manufacturer identified a recently published indirect comparison of ticagrelor and prasugrel by Biondi-Zoccai et al.[19] The ERG notes that this comparison is based on PLATO,[21] TRITON-TIMI 38[16] and DISPERSE-2[38] trials; the ERG notes that the DISPERSE-2[38] trial had been excluded from the systematic review by the manufacturer.

The published indirect comparison[19] incorporates the data from the 90 mg ticagrelor (n=334) and the clopidogrel arms (n=327) of the DISPERSE-2[38] trial. The ERG considers that results from the DISPERSE-2[38] trial make a negligible contribution to the results of any of the analyses presented in the paper.[19]

Results and conclusions from the published indirect comparison paper

The results of the indirect analysis reported in the published paper[19] (not discussed in the MS) were that the indirect comparison of prasugrel vs ticagrelor showed no significant differences in overall death, MI, stroke, or their composite. Prasugrel was associated with a significantly lower risk of stent thrombosis. Ticagrelor was associated with a significantly lower risk of any major bleeding and major bleeding associated with bypass grafting. However, the risk of major bleeding not related to bypass surgery was similar with either prasugrel or ticagrelor. The report concluded that prasugrel and ticagrelor are superior to clopidogrel for ACS. The indirect comparison suggests similar efficacy and safety of prasugrel and ticagrelor, but prasugrel appears more protective from stent thrombosis, while causing more bleeding.

4.8.2 ERG commentary on the indirect comparison of PLATO and TRITON-TIMI 38

The ERG is of the opinion that the manufacturer makes a convincing case that any comparison between the PLATO[21] and TRITON-TIMI 38[16] trials is problematic. The ERG was involved in a recent appraisal of prasugrel[40] and, in particular, is aware of difficulties in generalising the findings of the TRITON-TIMI 38[16] trial to UK general practice with regard to the loading dose given and the timing of its administration. It was the opinion of the ERG that the under-dosing and late administration of clopidogrel may have biased the outcomes of the TRITON-TIMI 38[16] trial in favour of prasugrel. In the appraisal of the TRITON-TIMI 38[16] trial, the ERG noted that the reported clinical superiority of prasugrel over clopidogrel on the primary efficacy endpoint was driven largely by a reduction in nonfatal MI which comprised clinical (symptomatic) and non-clinical (by biomarkers/ECG readings) MIs. If the non-clinical MIs were excluded, the resultant difference in nonfatal MIs may not be statistically significant. This means that it is inappropriate to compare the rate of MIs across the trials.

The ERG notes that the published indirect comparison paper[19] considered overall death (not cardiovascular death) as part of the primary composite endpoint in the indirect comparison exercise.[20]

In summary, the ERG, in accord with the manufacturer and independent commentary, considers that use of the results from the published indirect analysis is inappropriate.

4.9 Summary of clinical evidence

Direct comparison: ticagrelor vs clopidogrel

- The main source of clinical evidence described in the MS is from the PLATO[21] trial
- Compared with clopidogrel, ticagrelor was superior in preventing thrombotic events as measured by the primary composite endpoint of vascular death, MI, and stroke (9.8% vs 11.7%)
- The reduction in primary events was driven primarily by significant reductions in the rates of MI (5.8% vs 6.9%), and vascular death (4.0% vs 5.1%)
- The number of strokes was greater in the ticagrelor arm compared to the clopidogrel arm, but this did not reach statistical significance
- Similar results are reported across a number of patient subgroups
- Trial-defined major bleeding events were similar in both arms of the trial, but there were statistically significantly more trial-defined major and minor bleeding events in the ticagrelor arm compared with the clopidogrel arm (16.1% vs 14.6%) and more non-CABG related major bleeding (4.5% vs 3.8%)
- Statistically significantly increased rates of dyspnoea were noted in the ticagrelor arm, as were increased numbers of patients with ventricular pauses of length≥3 seconds as identified by Holter monitoring (in the first week of treatment). Increases in serum uric acid and serum creatinine from baseline values from the beginning to the end of the trial were also reported.

Indirect comparison: ticagrelor vs prasugrel

- The manufacturer and the ERG are of the opinion that any indirect analysis comparing ticagrelor and prasugrel is inappropriate as the only relevant clinical data available are derived from two trials with very different patient populations and treatment protocols.

4.9.1 Clinical issues

- Clinical effectiveness analyses of the PLATO[21] data were restricted to patients with 12 months dual antiplatelet treatment. NICE guidelines and guidance for patients in the UK allow for treatment periods of less than 12 months e.g. patients with STEMI and STEMI patients treated with BMS
- There are limited data from PLATO[21] on types and severity of strokes
- There are no data on patients who required revascularisation following treatment. This was stipulated as a requirement in the decision problem issued by NICE.

5 ECONOMIC EVALUATION

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the manufacturer of ticagrelor. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature and (ii) a report of the manufacturer's *de novo* economic evaluation. See Table 14 for a summary of the key information points. The manufacturer also provided an electronic version of the EXCEL based economic model.

Table 14 Key information in the MS

Key information	Section (MS)
Details of the systematic review of the economic literature	6.0
Model structure	6.2.2 to 6.2.5
Technology	6.2.7
Clinical parameters and variables	6.3.1 to 6.3.8
Measurement and valuation of health effects and adverse events	6.4.1 to 6.4.15
Resource identification, valuation and measurement	6.5.1 to 6.5.8
Sensitivity analysis	6.6.1 to 6.6.3
Results	6.7.6 to 6.7.11
Validation	6.8.1
Subgroup analysis	6.9.1 to 6.9.5
Strengths and weaknesses of economic evaluation	6.10.1 to 6.10.4
Assessment of factors relevant to other parties	7.0

5.2 Overview of manufacturer's cost-effectiveness review

The MS provides a brief description of the review of published cost-effectiveness evidence undertaken by the manufacturer. The databases searched and the search terms used appear to be reasonable and both inclusion and exclusion criteria are explicitly stated. The search by the manufacturer did not identify any relevant studies for inclusion in the review. Although there is no mention of searching within in-house databases for relevant studies, the ERG is confident that no relevant published studies are available for inclusion in the review.

The manufacturer did not identify any papers that had evaluated the cost effectiveness of ticagrelor in the treatment of ACS; however the MS included detailed data extraction tables and quality assessment reviews of nine economic evaluations that were considered relevant to inform the structure, assumptions and model inputs for the cost-effectiveness analysis of ticagrelor for the treatment of ACS in the UK.

5.3 Overview of manufacturer's economic evaluation

The manufacturer undertook a *de novo* economic evaluation of ticagrelor plus aspirin (ticagrelor) compared with clopidogrel plus aspirin (clopidogrel) in patients with ACS (UA, NSTEMI, STEMI) including patients managed medically, and those who are managed with PCI or CABG as per the licensed indication. This economic evaluation provides the basis for the manufacturer's claim that ticagrelor is cost effective compared with clopidogrel.

The MS also reports the results of the manufacturer's economic evaluation comparing ticagrelor vs prasugrel (for the invasive subgroup only) based on the results of a published indirect comparison. The manufacturer explicitly states (MS, pg 14) "...that the results of the indirect comparison should be viewed with extreme caution." As the manufacturer has not provided the ERG with the electronic model from which these results are derived, the ERG does not offer a critique of this comparison.

5.3.1 Description of manufacturer's economic model

The manufacturer constructed an EXCEL-based cost-utility model in the form of a two-part construct with a one-year decision tree, based on data from the PLATO[21] study, and a Markov model for long term extrapolation. The model was intended to ensure capture of all major clinical and resource generating events that a patient may experience throughout the course of their remaining life. The structure of the model is presented in Figure 3.

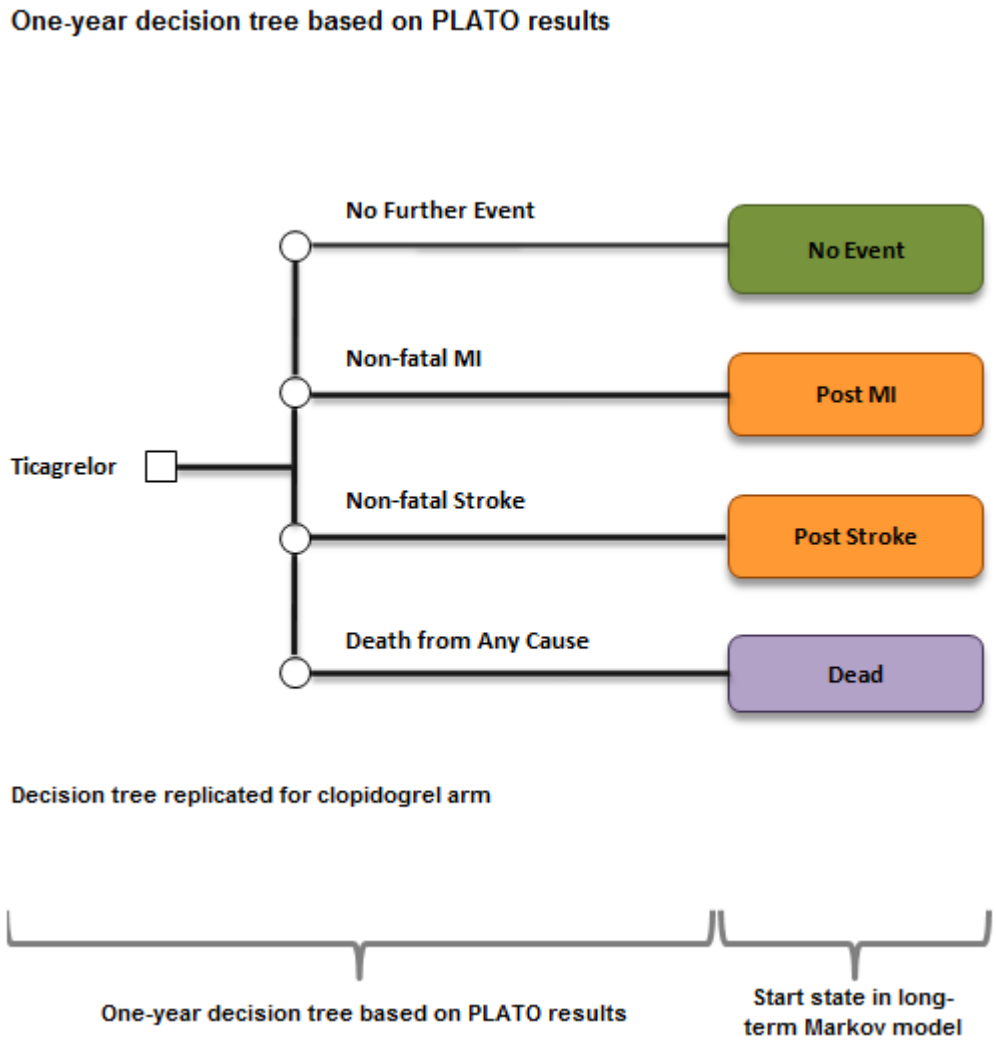


Figure 3 Diagrammatical representation of the health states and patient pathways in both the decision tree and Markov model

There are four mutually exclusive health states in the one-year decision tree: no further event, non-fatal MI, non-fatal stroke and death from any cause. The ERG notes that the health states categorise patients according to first event unless they died. To illustrate, the non-fatal MI health state also captures patients who had an MI and then a stroke. At the end of the one-year period represented by the decision tree, patients are allocated to one of four of the six mutually exclusive health states in the Markov model: no further event, non-fatal MI, post MI, non-fatal stroke, post stroke and dead. The ERG notes that the non-fatal MI and non-fatal stroke health states are tunnel states; use of tunnel states allows for a worse prognosis for patients in the year in which a non-fatal event occurs compared to subsequent years.

5.3.2 Parameters and values

Table 15 presents a summary of the parameters and values used in the manufacturer's economic model.

Table 15 Parameters and values used in the economic model

Variable	Value (95% CI)	Distribution	Source
General			
Mean age	70		MINAP/GPRD* study (MS, Table 6.9)
% Male	64.6%		
% of patients ≥ 75	42.7%		
Event rates for clopidogrel (one-year decision tree)			
Dead any cause	0.0789 (0.0518-0.1202)	Weibull	Weibull regression equations based on PLATO study (MS, Section 6.3.1)
Non-fatal MI	0.0628 (0.0426-0.0935)	Weibull	
Non-fatal stroke	0.0112 (0.0039-0.0347)	Weibull	
Dead vascular	0.0672 (0.0436-0.1038)	Weibull	
Hazard ratios for ticagrelor versus clopidogrel (one-year decision tree)			
Dead any cause	0.7845 (0.6880-0.8945)	LogNormal	Weibull regression equations based on PLATO study (MS, Section 6.3.1)
Non-fatal MI	0.8598 (0.7546-0.9797)	LogNormal	
Non-fatal stroke	1.0894 (0.7949-1.4930)	LogNormal	
Dead vascular	0.7946 (0.6908-0.9139)	LogNormal	
Event rates for ticagrelor (one-year decision tree)			
Death any cause	0.0619 (0.0543-0.0706)	N/A	Combination of clopidogrel event rates and ticagrelor hazard ratios (MS, Section 6.3.1)
Non-fatal MI	0.0540 (0.0474-0.0615)	N/A	
Non-fatal stroke	0.0122 (0.0089-0.0167)	N/A	
Dead vascular	0.0534 (0.0464-0.0614)	N/A	
Event rates (Markov model)			
Non-fatal MI	0.0315 (0.0257-0.0385)	Beta	MINAP/GPRD* study (MS, Section 6.3.2)
Non-fatal Stroke	0.0102 (0.0072-0.0145)	Beta	
Hazard ratios relative to standard life tables (Markov model)			
No event	2.2121 (0.1817-4.2425)	LogNormal	CG48 and Allen et al[41] (MS, Section 6.3.2)
Non-fatal MI	5.8446 (3.7176-7.9717)	LogNormal	
Post MI	2.2121 (01817-4.2425)	LogNormal	
Non-fatal Stroke	7.4286 (6.50-8.50)	LogNormal	Dennis et al[42] (MS, Section 6.3.2)
Post Stroke	2.0715 (1.30-3.32)	LogNormal	

*Information supplied by the manufacturer following ERG request to NICE

5.3.3 Treatment effectiveness within the MS

For the one-year decision tree, a parametric time-to-event survival model with a Weibull distribution was employed in order to determine the baseline risk (risk of events in the clopidogrel arm) and a HR (the treatment effect of ticagrelor) to be applied to the baseline risk. The manufacturer states that transition probabilities were easily derived employing the estimated scale and shape parameters of the Weibull distribution. Data used in the one-year decision tree are derived exclusively from the PLATO[21] study. However, as the mean age as well as the proportion of older patients in England and Wales differ from the mean age and proportion of older patients in the PLATO[21] study, the manufacturer estimated an age-adjusted event rate for the clopidogrel arm in a UK setting in order to ensure that the cost-effectiveness analysis would be generalisable to the UK ACS population.

At the end of the one-year trial period modelled via the decision tree, patients are located in one of four health states: event-free, post MI event, post stroke event or dead. The manufacturer assumes that there is no treatment or rebound effect beyond one year therefore all the transition probabilities in the Markov model are the same irrespective of treatment arm. With the exception of the probabilities for transitioning from the no event health state to the non-fatal MI or non-fatal stroke health state, the probabilities of transitioning between all other health states are based on relative risks applied to the probability of death which is taken from standard UK life tables.[43] The transition from no event to non-fatal MI or non-fatal stroke health state represents the probability of a patient having another event during the year following the initial ACS event and data to inform the transition probability are taken from a study commissioned by the manufacturer which analysed data combining the Myocardial Ischaemia National Audit Project and General Practice Research Database (data supplied by manufacturer following ERG request to NICE) patient records.

5.3.4 Population

The economic evaluation was conducted using the patient population described in the PLATO[21] trial i.e. patients with ACS (NSTEMI, STEMI, UA). The manufacturer presented cost-effectiveness results (ticagrelor vs clopidogrel) for the overall population and also for the following subgroups: STEMI, NSTEMI and UA. The manufacturer also presented cost effectiveness results (ticagrelor vs prasugrel) for the invasive subgroup.

5.3.5 Comparator technology

The comparator technology described in the economic evaluation is clopidogrel plus aspirin (clopidogrel) for a 12 month period. Clopidogrel is the current standard of care for ACS patients in the NHS in England and Wales. However, duration of recommended usage depends on the indication for which it is approved. In the MS, only 12 months use of clopidogrel is considered.

The manufacturer also compares ticagrelor with prasugrel using the results of a published indirect comparison paper for the invasive subgroup only. However, the manufacturer states that the evidence base required to perform such an analysis is inappropriate for this comparison. The ERG discusses the merits of indirectly comparing ticagrelor vs prasugrel in Section 4.

5.3.6 Health related quality of life

The PLATO[21] study included a pre-specified Health Economics (HECON) and Quality of Life sub-study. The EQ-5D was administered to patients in 52 countries (where an official language EQ-5D version was available) and the conversion of the EQ-5D questionnaire scores to utility values was performed as per the UK time-trade-off value set as recommended in the NICE methods guide.[44] For the purposes of the cost-effectiveness analysis, the 12-month cohort was used to calculate the utility accrued in the study.

In addition, a review of utility scores obtained via a literature search was performed by the manufacturer to ensure a level of consistency and these utility values have been used within the sensitivity analysis. The MS presents summary data from 25 studies that contain health state utilities for ACS, acute MI, stoke or major bleed that most closely match the NICE reference case (MS, Section 6.4.6).

The utility values reported in the PLATO HECON sub-study are higher than those reported in the literature; however the manufacturer explains that the relative difference between the two alternative values is fairly consistent across the different health states. A summary of the quality of life values used to inform the cost-effectiveness analysis is presented in Table 16 . It is noted that all of the utility scores from both the PLATO HECON sub-study and the published literature have been adjusted downwards by 0.0328 to reflect characteristics of the UK population.

Table 16 Summary of quality of life values for cost effectiveness analysis (base case)

State	Utility value	Standard error	Reference in submission	Justification
One-year decision tree				
No event (ticagrelor)	0.840	0.003	PLATO HECON sub-study (MS, Section 6.4.3) (AstraZeneca data on file)	Largest collection of EQ-5D questionnaires in any ACS study. Utility scores meet the criteria set out for the reference case
Non-fatal MI (ticagrelor)	0.786	0.014		
Non-fatal stroke (ticagrelor)	0.709	0.062		
Vascular death (ticagrelor)	0.218	0.023		
Non-vascular death (ticagrelor)	0.171	0.042		
Death any cause (ticagrelor)	0.211	0.021		
No event (clopidogrel)	0.844	0.003		
Non-fatal MI (clopidogrel)	0.774	0.014		
Non-fatal stroke (clopidogrel)	0.695	0.032		
Vascular death (clopidogrel)	0.210	0.020		
Non-vascular death (clopidogrel)	0.270	0.057		
Death any cause (clopidogrel)	0.220	0.019		
Markov model				
No event	0.842	0.002	As above	As above
Non-fatal MI	0.779	0.010	As above	As above
Post MI*	0.821	0.038	As above + Lacey et al [45]	Evidence HRQL improved over time
Non-fatal stroke	0.703	0.010	As above	
Post stroke**	0.703	0.038	As above +assumption	No evidence HRQL improves over time
Dead	0.000	N/A	N/A	Convention

5.3.7 Resources and costs

The manufacturer presents extensive resource use and cost information including sources and price years. The manufacturer also reports summary costing information from a literature search which identified 18 relevant published cost papers for use in this STA.

NHS costs

The manufacturer presents full details of the NHS non-elective and NHS elective admissions costs used in the economic evaluation (NHS Reference Costs 2008/09) in the MS (Section 6.5.1).

Intervention and comparator costs

Intervention and comparator costs are taken from Drug Tariff (November 2010)[46] and MIMS (October 2010).[47] The price of ticagrelor was provided by the manufacturer and is considered as commercially-in-confidence data. The key drug costs used in the economic evaluation are as follows: aspirin (28 pack) £0.82; clopidogrel (30 pack) £3.40; ticagrelor (28 pack) £54.60; prasugrel (28 pack) £47.56.

Health-state costs

A detailed within-trial costing analysis was carried out as part of the HECON sub-study and this was used to inform the costs in the submitted economic model (ticagrelor vs clopidogrel). Hospitalisations, interventions (e.g. study drug or concomitant drug), investigations (e.g. PCI with or without stenting, CABG with or without valve replacement) and bleeding-related health care consumption (e.g. re-operations) were recorded for all patients in order to estimate total healthcare costs associated with ticagrelor and clopidogrel within the PLATO[21] study. Resource use was categorised into two time-periods: index hospital (randomisation to time of discharge) and post-index hospitalisation (day after discharge from index hospitalisation to end of study). All costs associated with AEs in the PLATO[21] study were captured as part of the within-trial costing analysis. A list of health states and associated costs used in the economic model are shown in Table 17.

For the comparison of ticagrelor vs prasugrel, where HECON costs were not available, updated NHS Reference costs were used. In the ticagrelor vs prasugrel analysis, it was assumed that the health state costs for the one-year decision tree for prasugrel were the same as those for ticagrelor. With regard to the Markov model, costs from the published literature were used to inform the no event, non-fatal MI, post MI, non-fatal stroke and post stroke health states. Adverse events (e.g. stent thrombosis, major and minor bleeding) were costed separately.

Table 17 List of health states and associated costs in the economic model

Health states	Items	Value
No event (Ticagrelor)	Hospitalisations	£3955
	Investigations	£1082
	Interventions	£3435
	Bleeding related	£72
	Total	£8544
Non-fatal MI (Ticagrelor)	Hospitalisations	£8257
	Investigations	£1593
	Interventions	£6291
	Bleeding related	£502
	Total	£16643
Non-fatal stroke (Ticagrelor)	Hospitalisations	£10050
	Investigations	£1242
	Interventions	£3678
	Bleeding related	£424
	Total	£15394
Death any cause (Ticagrelor)	Hospitalisations	£7034
	Investigations	£900
	Interventions	£3351
	Bleeding related	£468
	Total	£11753
No event (Clopidogrel)	Hospitalisations	£3921
	Investigations	£1079
	Interventions	£3557
	Bleeding related	£76
	Total	£8633
Non-fatal MI (Clopidogrel)	Hospitalisations	£8549
	Investigations	£1626
	Interventions	£6073
	Bleeding related	£114
	Total	£16362
Non-fatal stroke (Clopidogrel)	Hospitalisations	£11934
	Investigations	£1182
	Interventions	£4142
	Bleeding related	£224
	Total	£17483
Death any cause (Clopidogrel)	Hospitalisations	£9105
	Investigations	£867
	Interventions	£3316
	Bleeding related	£627
	Total	£13915

5.3.8 Perspective, time horizon and discounting

The economic evaluation was undertaken from the perspective of the NHS and Personal Social Services (PSS). The time horizon set was 40 years (lifetime) and this was considered by the manufacturer to be adequate to capture complete differences between comparators (as per the NICE reference case); time horizon was varied between 1 year and 40 years in the deterministic sensitivity analysis. Both costs and benefits were discounted at 3.5% per annum.

5.3.9 Model validation

The manufacturer states that the following measures were taken to check and validate the integrity of the model:

1. A health economist, employed by AstraZeneca UK, independently reviewed the model to conducted internal validity checks on the data inputs and calculations;

2. During model development, clinicians were consulted to provide feedback on the clinical relevance of the modelling approach;

3. An advisory board consisting of clinicians and an independent health economist from academia was held to critique the structure of the model, the key assumptions and data inputs;

4. The results of the analysis were compared to results reported in other published results in ACS.

5.4 Results included in manufacturer's submission

The manufacturer presents base-case ICERs for ticagrelor vs clopidogrel in terms of (i) incremental cost per life year gained (Table 18) and (ii) incremental cost per QALY gained (Table 19). The base-case ICERs estimated by the manufacturer fall far below NICE's perceived cost-effectiveness threshold.

The manufacturer also presents a table showing the impact of using different time horizons on the estimated cost per QALY gained (Table 20). Only when using the 1-year time horizon does the ICER differ substantially from the estimated base-case ICER.

Table 18 Base case results – cost per life year gained (deterministic)

Technologies	Total costs (£)	Total LYG	Incremental costs (£)	Incremental LYG	ICER (£) incremental (LYGs)
Clopidogrel	£13,737	7.602			
Ticagrelor	£14,135	7.736	£398	0.129	£3,075

Table 19 Base case results – cost per QALY (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Clopidogrel	£13,737	6.275			
Ticagrelor	£14,135	6.382	£398	0.108	£3,696

Table 20 Cost per QALY using different time horizons

Time horizon	Ticagrelor	Clopidogrel	Incremental	ICER Cost per QALY
40 years				
Costs	£14,135	£13,737	£398	
Life-years	7.736	7.606	0.129	£3,075
QALYs	6.382	6.275	0.108	£3,696
20 years				
Costs	£14,110	£13,713	£397	
Life-years	7.701	7.572	0.129	£3,083
QALYs	6.354	6.247	0.107	£3,705
10 years				
Costs	£13,213	£12,841	£372	
Life-years	6.412	6.306	0.106	£3,499
QALYs	5.302	5.213	0.089	£4,182
5 years				
Costs	£11,722	£11,390	£331	
Life-years	4.068	4.004	0.065	£5,137
QALYs	3.371	3.317	0.055	£6,075
1 year				
Costs	£9,974	£9,690	£284	
Life-years	0.969	0.961	0.008	£33,405
QALYs	0.797	0.789	0.008	£36,177

The manufacturer also presented ICERs for a range of subgroup populations: STEMI, NSTEMI and UA (Table 21). Again, all of the ICERs were estimated by the manufacturer to be well below NICE's cost-effectiveness threshold range.

The manufacturer also showed results for ticagrelor vs prasugrel for the invasive subgroup based on the results of a published indirect comparison. The manufacturer's electronic version of the model does not include the costs and benefits used to generate the ICER for the invasive population and this comparison is therefore not considered further in the ERG report.

Table 21 Results of subgroup analyses

Subgroup	Time horizon	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
STEMI (Ticagrelor vs clopidogrel)	40 years	339	0.120	2825
	20 years	336	0.118	2847
	10 years	299	0.090	3334
	5 years	257	0.052	4946
	1 year	214	0.007	31,933
NSTEMI (Ticagrelor vs clopidogrel	40 years	512	0.098	5230
	20 years	512	0.098	5233
	10 years	497	0.087	5727
	5 years	461	0.056	8162
	1 year	413	0.009	45,810
UA (Ticagrelor vs clopidogrel)	40 years	488	0.091	5374
	20 years	487	0.090	5410
	10 years	460	0.071	6484
	5 years	424	0.042	10,172
	1 year	384	0.005	78,288
Invasive(Ticagrelor vs prasugrel)	40 years	227	0.065	3482
	20 years	222	0.062	3598
	10 years	193	0.042	4562
	5 years	165	0.023	7047
	1 year	NA	NA	NA

NA Results not provided in MS, and no model provided for this comparison

5.4.1 Sensitivity analyses carried out by the manufacturer

Scenario sensitivity analysis

In order to assess the impact of separating out vascular and non-vascular death, the manufacturer used a model structure with five nodes (instead of four): no further event, non-fatal MI, non-fatal stroke, vascular death and non-vascular death. In addition, scenarios were run using 0% and 6% discount rates, using published utility values, removing baseline utility adjustment and removing utility decrement per cycle. The results of the scenario analyses show that ticagrelor vs clopidogrel yields a stable, low ICER despite substantial variation in structure and methodological input.

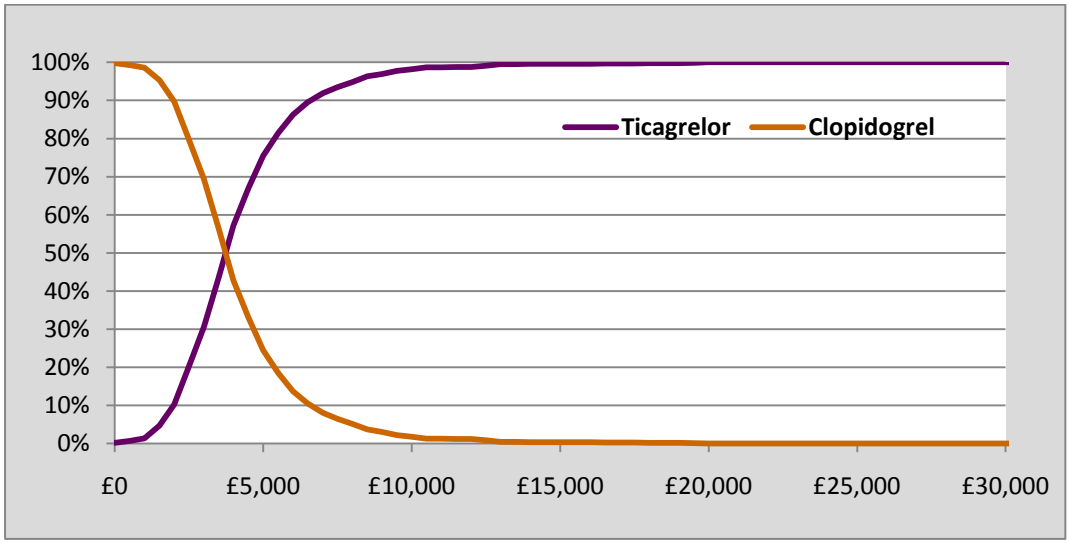
Deterministic sensitivity analysis

The manufacturer carried out extensive deterministic analyses and shows the effects of changing 43 model parameters. Only the change to the costs of the no event health state impacts substantially on the results. When the cost of the ticagrelor no event health state is set to its lowest, ticagrelor dominates clopidogrel. When the cost of the clopidogrel no event health state is set to its lowest, ticagrelor becomes border-line cost effective with an ICER of £21,000 per QALY gained. Changes in all other parameters do not increase the ICER beyond £7,620. Full details of the deterministic analyses are presented in Section 6.7.7 of the MS.

Probabilistic sensitivity analysis

The cost effectiveness acceptability curve (Figure 4) generated by the manufacturer shows that at a willingness to pay of £5,000 per QALY gained, the probability of ticagrelor being cost effective compared to clopidogrel is 76.6%. At a willingness to pay threshold of £20,000 per QALY gained, the probability of ticagrelor being cost effective compared to clopidogrel is 99.9%.

Figure 4 Cost effectiveness acceptability curve for ticagrelor vs clopidogrel



5.5 Critique of the manufacturer's model

This section summarises the ERG's assessment of the manufacturer's economic model against (i) NICE reference case checklist[44] and (ii) Drummond 10-point checklist.[48]

Table 22 shows how closely the manufacturer's submitted economic evaluation accords with the requirements for a base-case analysis set out in the NICE reference case checklist.[44] The main difference between the manufacturer's approach and the NICE reference case checklist[44] is focussed on the choice of comparator. The ERG is concerned about the comparator used in the economic model for patients with STEMI who received BMS. In the economic model, these patients are given clopidogrel for 12 months, whereas NICE guidance[8] recommends 3 months of clopidogrel for these patients. In addition, in the model STEMI patients without stenting are assumed to receive 12 months clopidogrel treatment, whereas NICE guidance[10] recommends at least 4 weeks of clopidogrel treatment.

Table 23 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond 10-point checklist.[48] The ERG has several important criticisms of the submitted economic evaluation in addition to concerns about the comparator. Firstly, the limited proportion of patients followed-up for 12 months in the trial increases the uncertainty in the estimates of the final disposition of patients at the conclusion of the trial which is the prime driver of long-term patient benefits in the Markov model. Secondly, the structure of the model is such that it does not represent real world patient experience as it does not allow patients to suffer multiple cardiovascular events in their lifetime. The consequence of this is that future costs and benefits, in both groups, could be inaccurately estimated. The model also assumes that all patients receive ASA as a long-term preventative treatment; in England and Wales cardiovascular patients with multivascular disease go on to receive long-term clopidogrel treatment. Thirdly, the model applies an average utility score when experience shows that ACS patients suffer from an initial utility decrement which steadily diminishes, the ERG is of the opinion that the effect of applying an average score is to underestimate the size of the ICER at 12 months. Finally, the ERG notes that the subgroups of interest in the economic evaluation do not reflect the subgroups of interest in the clinical section of the MS. The ERG is therefore unable to verify the clinical effectiveness data related to NSTEMI and UA subgroups used in the model. The ERG notes that the UA subgroup is treated as a homogeneous group. However, in clinical practice, patients are typically categorised into low, medium and high risk groups using the GRACE classification. It would have been informative if the manufacturer had presented ICERs for UA patients according to their level of risk. [redacted]

[redacted]which suggests that looking more closely at the clinical effectiveness data for this group of patients is merited.

Section 5.6 offers a detailed critique of the submitted manufacturer's economic model by the ERG.

Table 22 NICE reference case

Attribute	Reference case[44]	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Yes However, the ERG notes that no separate economic data were provided showing ticagrelor vs clopidogrel for the invasive group (presumably subsumed within the STEMI, NSTEMI and UA subgroups)
Comparator(s)	Alternative therapies routinely used in the NHS	Partially. The comparator is appropriate for the UA and NSTEMI subgroups but there is uncertainty regarding the validity of the comparator used in the model for STEMI pts with BMS and STEMI patients without stenting
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	Both costs and benefits are primarily derived from the key trial (PLATO) for the direct comparison of ticagrelor vs clopidogrel. Systematic reviews of the literature have been conducted where appropriate: e.g. utility values, indirect comparison. Clinical subgroups of interest in the economic evaluation are different to clinical subgroups of interest in the clinical section of the MS. The ERG is unable to check clinical effectiveness data used in the model related to NSTEMI and UA subgroups from the MS
Outcome measure	Quality adjusted life years	Yes QALYs are used but application of average year 1 utility score instead of a utility decrement that slowly diminishes over time means that the ICER is underestimated
Health states for QALY	Described using a standardised and validated instrument	Yes (EQ-5D)
Benefit valuation	Time-trade off or standard gamble	Yes (time-trade off)
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes, both sensitivity analysis and probabilistic sensitivity analysis were performed

PSS= Personal Social Services; MS= manufacturer submission; RCT= randomised controlled trial; QALYs= quality adjusted life years; PSA= probabilistic sensitivity analysis; ERG= Evidence Review Group; HRQoL= health related quality of life

Table 23 Critical appraisal checklist

Item	Critical appraisal[48]	ERG comment
Was a well-defined question posed in answerable form?	Partially	Question was posed correctly, but the ERG notes that it was difficult to answer for patients in England and Wales where the ACS population is governed by several different NICE guidelines
Was a comprehensive description of the competing alternatives given?	Yes	Unfortunately the comparator used throughout (12 months clopidogrel+ASA) was inappropriate for some subgroups of patients (e.g. STEMI with BMS, STEMI without stenting). No separate economic analysis was included in the model for ticagrelor vs clopidogrel for the invasive group (presumably subsumed within the STEMI, NSTEMI and UA subgroups)
Was the effectiveness of the programme or services established?	Yes	Clinical effectiveness evidence from the key trial (PLATO) was used to inform the cost effectiveness analysis. The ERG notes that there are limited long-term effectiveness data. Clinical subgroups of interest in the economic evaluation are different to clinical subgroups of interest in the clinical section of the MS. The ERG is unable to check clinical effectiveness data used in the model related to NSTEMI and UA subgroups from the MS
Were all the important and relevant costs and consequences for each alternative identified?	No	Future costs may not have been accurately estimated due to the use of health state average costs instead of future projected non-fatal events in the model
Were costs and consequences measured accurately in appropriate physical units?	Not always	Model assumed that all patients would go on to ASA as a long-term therapy. However, in England and Wales patients with multivascular disease go on to long-term treatment with clopidogrel plus ASA. Future events not explicitly modelled.
Were the cost and consequences valued credibly?	Yes	Difficult to determine of long-term costs remain at a steady level.
Were costs and consequences adjusted for differential timing?	Yes	A discount rate of 3.5% for costs and benefits was applied appropriately
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes – although there are no ICERs for the Invasive group for the ticagrelor vs clopidogrel comparison in the MS (presumably subsumed within the STEMI, NSTEMI and UA subgroups)
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Considerable univariate and scenario sensitivity analyses were undertaken. Probabilistic sensitivity analysis was also performed
Did the presentation and discussion of study results include all issues of concern to users?	No	The manufacturer failed to address the fact that the economic model does not reflect the experience of all ACS patients in England and Wales (e.g. patients with multivascular disease, STEMI patients with BMS)

ERG= Evidence Review Group; SA= sensitivity analysis; PSA= probabilistic sensitivity analysis; BSA= body surface area; ASA=aspirin

5.6 Defining the correct decision problem and appropriate comparator

The submitted model is based on the results of the PLATO[21] trial following 12 months dual antiplatelet treatment initiated as a result of an ACS event. Treatment with ticagrelor is compared to clopidogrel, both prescribed for a period of 12 months from the latest ACS event. The trial population includes patients classified by the type of index ACS event as UA, NSTEMI or STEMI, and in addition to an overall combined model, the model is also applied to each of these subgroups.

In all cases the comparator is defined as 12 months of dual antiplatelet therapy using clopidogrel as used in the PLATO[21] trial. The comparator in a NICE evaluation should correspond to the current recommended regimen in England and Wales as provided in relevant NICE Clinical Guidelines and Technology Appraisal documents, which in this instance are:

- **Clinical Guideline CG94[11]** Unstable Angina and NSTEMI: the early management of unstable angina and non-ST-segment elevation myocardial infarction

- **Clinical Guideline CG48[10]** Post Myocardial Infarction: secondary prevention in primary and secondary care for patients following a myocardial infarction

- **Technology Appraisal Guidance 152[8]** Drug-eluting stents for the treatment of coronary artery disease

- **Technology Appraisal Guidance 210[7]** Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events.

Recommendation R11 of CG94[11] states that for UA and NSTEMI patients:

"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 non-ST-segment-elevation ACS. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended."

However, CG94[11] makes no new recommendation in relation to STEMI ACS patients, referring back to CG48[10] for this subgroup, which reads:

"After an ST-segment-elevation MI, patients treated with a combination of aspirin and clopidogrel during the first 24 hours after the MI should continue this treatment for at least 4 weeks. Thereafter, standard treatment including low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy."

TA210[7] continues to endorse ASA monotherapy as long-term 'standard care' following early dual antiplatelet therapy in MI patients without a history of occlusive vascular disease in other beds (i.e. TIA/stroke or peripheral vascular disease). However, for patients with evidence of multivascular disease clopidogrel is recommended for long-term preventive care.

TA152[8] makes recommendations only in relation to the use of DES compared to BMS in PCI. However, it is accepted as normative that the use of DES should involve extension of the normal period of dual antiplatelet therapy to 12 months:

"There is a risk of stent thrombosis associated with the use of both types of stent (DESs and BMSs). To prevent thrombosis occurring, patients are required to use an antiplatelet drug, such as clopidogrel, in addition to aspirin during and after the implantation of a stent. Following data published in 2006, the US Food and Drugs Administration (FDA)'s Circulatory Devices Systems Advisory Panel recommended that the duration of clopidogrel use should be extended in patients receiving a DES. The American College of Cardiologists/American Heart Association PCI guidelines (also endorsed by the Society for Cardiovascular Angiography Interventions) and the BCIS have recommended that for patients receiving DESs the duration of clopidogrel use should be increased to at least 12 months, after which time continuation of clopidogrel should be reviewed taking into account the risk for further events on an individual patient basis.

The Committee noted the current UK recommendation that clopidogrel should be given for an additional 9 months in patients receiving a DES [compared with BMS] and it therefore considered it appropriate that this should be taken account of in the cost-effectiveness analysis."

Careful consideration of these recommendations raises three important issues in respect of the model analyses undertaken by the manufacturer:

1) The combined base case analysis uses as comparator 12 months treatment with clopidogrel for all patients. However, 4 weeks of clopidogrel is currently recommended for STEMI patients who constitute more than 40% of the PLATO[21] sample.

2) 'Low-dose' ASA is assumed to be 'standard care' for secondary prevention for all patients, whereas TA210[7] indicates that patients with multivascular disease should instead be treated with clopidogrel (TA210, Summary of Key Conclusions page 31).

3) All patients where the early treatment intention is for PCI or CABG (71% of PLATO[21]) are assumed to receive dual antiplatelet treatment (clopidogrel in combination with ASA) for 12 months in the comparator arm (invasive group). In fact only 77% of these patients received PCI and 6% received CABG with the remaining 17% being medically managed. In addition, 29% of PCI patients received only BMS for whom extended dual antiplatelet therapy beyond 3 months is not explicitly recommended.

There are important consequences for the cost-effectiveness results presented by the manufacturer:

- the combined base case results may be invalid since they involve use of an inappropriate comparator for a substantial proportion of the population (40% of patients suffered a STEMI and 39% were revascularised with BMS);

- the 'invasive' subgroup is similarly compromised by the wrong comparator for a substantial proportion of the population;

- the STEMI subgroup analysis may be invalid since it uses the wrong comparator for all patients who did not receive DES;

- none of the presented analyses recognises that patients with multivascular disease should receive clopidogrel for long-term prevention rather than low-dose ASA, or that patients surviving subsequent stroke/TIA events should be switched from low-dose ASA to clopidogrel for long-term prevention.

Table 24 summarises the conflicts identified in the manufacturer's use of PLATO[21] trial data in modelling the cost-effectiveness of ticagrelor.

Table 24 Factors conflicting with current treatment guidelines in the four cost-effectiveness analyses submitted by the manufacturer

Modelled PLATO population	Comparator conflict: mixed STEMI / NSTEMI	Comparator conflict: mixed BMS / DES PCIs	Long-term prevention conflict: mixed MVD / MI
All trial patients (base case)	Yes	Yes	Yes
UA / NSTEMI	No	Not relevant	Yes
STEMI	No	Yes	Yes
Intended invasive treatment	Yes	Yes	Yes

5.7 Model structure

5.7.1 Two-part model

The manufacturer's model employs a Markov structure with an **annual cycle period**. The first cycle is derived from the PLATO[21] trial data, so that the proportion of patients in each health state at the beginning of the second year corresponds to the number of patients alive in each state at the completion of the trial 12-month period. It should be noted that the PLATO[21] trial design did not involve uniform follow-up for the whole sample; patients were allocated to receive treatment for 6, 9 or 12 months depending on the time of enrolment relative to the start of the study (presumably to limit the overall duration of the trial). This is unusual for trials of cardiovascular intervention where a minimum of 12 months follow-up for all patients is the norm. The proportions of patients in each state at 12 months were estimated using Kaplan-Meier survival analysis, which should be reliable, provided the allocation to the three treatment strata does not lead to any bias in baseline characteristics or interaction between the time of censoring and randomised treatment. (The ERG is not aware of any analyses having been undertaken to test for such potential bias). However, the limited proportion of patients followed-up for 12 months increases the uncertainty in the estimates of the final disposition of patients at the conclusion of the trial which is the prime driver of long-term patient benefits in the Markov model.

5.7.2 Separate patient pathways

The model features **two separate pathways**: patients suffering a non-fatal MI as first event at any time during a model cycle remain in that state to the end of the cycle and then progress to the post-MI state for all succeeding cycles until they suffer death (whether from CV or non-CV causes). In parallel, patients may suffer a non-fatal stroke as first event during a period and then progress to the post-stroke state until they die. This is a very simple formulation of

much more complex pathways in real life, and does not realistically represent patient experience. In particular, it does not allow a patient suffering a non-fatal first event to suffer explicitly another non-fatal vascular event (MI or stroke), and for such additional events to modify future risks and life expectancy, or to impact on subsequent health care costs and patient quality of life. In reality patients frequently suffer multiple serious cardiovascular events of different types during their lifetime, and the additional costs and patient disutility arising from these are an important element of the evaluation of any intervention in a chronic condition.

5.7.3 Frequency of vascular events

A direct consequence of this structure is that it seriously understates the true frequency of vascular events, and presents a skewed impression of the relative contributions of MI and stroke events over a lifetime. Table 6.4 of the MS provides a breakdown of patient clinical pathways into 15 categories defined by first non-fatal event followed by second non-fatal event followed by type of death. These data are then aggregated in Table 6.5 in the MS into four simple groups to match the categories used in the model.

In Table 25 the modelled events are compared with a simple count of all non-fatal events (first and second events), indicating that many more events occurred than the model reflects explicitly. Moreover it can be seen that this undercounting is more pronounced for non-fatal strokes than for non-fatal MIs (65-70% vs 82-84%). If instead we wish to compare the incidence of all vascular events (both fatal and non-fatal), it is necessary to apportion the reported vascular deaths between strokes and MIs. In Table 25 this has been carried out crudely pro-rata to the numbers of non-fatal strokes and MIs to illustrate the approximate magnitude of taking account of fatal events. This greatly increases the number of events, and further extends both the ratio between the model representation of events and a reasonable estimate of trial events, as well as increasing the contrast between strokes and MIs. It is likely that even these estimates are understated, since the figures in Table 6.4 in the MS do not allow for patients experiencing more than one stroke or more than one MI in the trial period, which is a relatively common phenomenon during the first 3-6 months after an index event.

The implications of this issue could be far-reaching, since the calculation in the manufacturer's model of future costs does not rely on simple counting of major events and applying a standard unit cost per event. Instead the average cost of a patient suffering a first event (such as MI) must take account of the event itself and all other events occurring in the same period (of both types), and then any further non-fatal or fatal events of either kind must be reflected in the average cost of subsequent post-event model cycles up to a maximum of 40

years. There must be a serious concern that this approach to costing future events may substantially underestimate the real experience of patients. Similarly the loss of health-related quality of life arising from future vascular events is very likely to be inadequately estimated if the true number of clinical events is not reliable.

Table 25 Comparison of vascular events represented in the manufacturer's model, and events estimated from the PLATO trial data

	Strokes-clopidogrel	**Strokes-ticagrelor**	**MIs-clopidogrel**	**MIs-ticagrelor**
Non-fatal events in model (first event only)	74	81	485	421
Non-fatal events (all recorded events)	106	125	593	504
Model: Data ratio	0.70	0.65	0.82	0.84
Fatal & non-fatal events (recorded+estimated events)[a]	309	364	784	666
Model: Data ratio	0.24	0.22	0.62	0.63

[a] vascular deaths allocated between fatal strokes and MIs pro-rata to numbers of non-fatal strokes and MIs

5.7.4 Long-term event risks

A further simplification employed in the model is the use of **fixed transition probabilities** for the risk of patients, previously event-free, suffering a first non-fatal MI or stroke throughout the long-term Markov model. Since a patient's age, and accumulating experience of previous serious cardiovascular events and their sequelae (such as disability) are known to alter risks significantly over time, this omission is may lead to inaccurate estimation of future events, costs and progressive changes in patient outcomes and quality of life.

5.7.5 Statistical modelling of patient status at 12 months

Three parameters are pivotal to the model and dominate both the short and long-term results produced, concerning the proportions of ACS patients who are estimated as:

- dead from any cause

- alive following a non-fatal MI as first event (regardless of any subsequent non-fatal events)

- alive following a non-fatal stroke as first event (regardless of any subsequent non-fatal events).

Of these the most important is the estimated all-cause mortality rate at 12 months, which should be both straightforward and robust to estimate. However, a complication is introduced by the modellers' desire to reconcile the PLATO[21] data with the characteristics of a standard UK population of ACS patients. In particular, they have attempted to overcome a significant difference in the mean age of PLATO[21] patients (62.2 years) compared to reported UK ACS

patients (69.7 years in 2009/10 [data supplied by manufacturer following ERG request to NICE)]), which could distort the model results. The approach taken is to carry out regression modelling of the PLATO[21] survival assuming a Weibull function, using treatment (ticagrelor or clopidogrel) and age>75 as binary covariates. The estimated model coefficients are then used to estimate deaths for both ticagrelor and clopidogrel substituting MINAP age values in place of the trial values. There are some potential problems with this procedure:

- the assumption of a Weibull common function for both sets of data may not be sufficiently accurate to represent the trial data;

- the use of a binary variable to represent age differences may not be accurate, given that in most cases age influences event rates as an increasing curvilinear function;

- the absence of gender as an adjustment variable is questionable since cardiovascular risks are generally lower for women than men of the same age.

The only opportunity for the ERG to test the impact of using model estimates rather than original trial data concerns the all-cause 12 month mortality for the whole PLATO[21] population, where the manufacturer has provided Kaplan-Meier analysis results. These show a mortality difference of 1.36% (confidence interval 0.68% to 2.04%), compared to 1.26% in the model (with no age adjustment). This apparently small discrepancy nonetheless represents an 8% understatement of likely benefits and overestimate of the estimated ICER. Also of concern is the range of uncertainty inherent in the modelled estimated mortality gain, since it is necessarily greater than that obtained from Kaplan-Meier analysis which itself covers a 3-fold confidence range.

5.8 Analysis of year 1 base case ICER

The manufacturer presents very promising economic results in favour of ticagrelor over a projected 40 year period. It is instructive to analyse these findings into their component parts, and consider the basis and robustness of each element. In particular, the submitted model is constructed in two parts: a simple decision-tree for the in-trial initial 12-month period to which is appended a Markov projection model for years 2 to 40. Since these depend on different assumptions and data, they are reviewed separately in this section and the next. It is important to notice that for this intervention both the incremental costs and incremental outcomes are very small, so that the calculated ratio is potentially very volatile to modest changes in both costs and outcomes.

5.8.1 Outcomes

Trial period (12 months)

The manufacturer bases the analysis of patient outcomes in the first year on the proportion of patients falling into four categories at the end of the trial:

- patients alive who did not suffer MI or stroke during the trial

- patients alive who suffered an MI as first event during the trial (regardless of any subsequent non-fatal MI or stoke events)

- patients alive who suffered a stroke as first event during the trial (regardless of any subsequent non-fatal MI or stoke events)

- patients who died of any cause during the trial.

From these proportions estimates are made separately for the mean time alive per patient during the first year (expressed as life years) and the mean QALYs per patient in the same period.

A simple assumption is made in the life-years calculation, that **on average patients in both trial arms who die during the trial do so half-way through the trial** (i.e. 6 months survival is applied). Simple examination of the Kaplan-Meier survival results shows that in fact more than half of all deaths in the trial occurred within the first 60 days, indicating that the 6 months assumption understates patient days in the first year. Re-estimating the survival time for dying patients increases overall mean survival times by a small amount, and improves the expected gain in life years attributable to ticagrelor by 9-10%, and hence reduces the incremental cost per life year gained after one year by about 10%.

The estimation of mean QALYs per patient depends on **assumptions about the likely pattern of utility scores** experienced by patients who died during the trial as well as the timing of death. The manufacturer has not provided details of the derivation of the figures used in the model, though it is clear that slightly different utility values have been used for each arm of the trial based on the results of the economics sub-study. The ERG has considered the PLATO[21] results for EQ-5D scores shown in Table 6.23 of MS and concludes that there is no justification for using separate estimates for the two treatments. However, it is clear that in general ACS patients suffer from an initial utility decrement, which steadily diminishes throughout the trial period. This pattern has previously been observed in patients suffering from MI, and recovering from PCI and CABG. The ERG used a simple exponential decay model to represent the steady improvement in utility over time, and then applied the

results to the pattern of deaths recorded in the PLATO[21] trial in order to arrive at alternative estimates of mean QALYs applicable to the patients who died during the trial. For all dying patients these figures were higher than those originally used, but the increase was greater for patients receiving clopidogrel. This single change had the effect of increasing the 12 month ICER by 44% to over £52,000 per QALY gained.

Applying common utility estimates to patients in both trial arms produces alterations in the opposite direction, resulting in a 29% reduction in the 12 month ICER. Taken together these ERG changes alter estimated 12 month QALYs per patient by very similar amounts, and improve the relative performance of ticagrelor by a small amount so that the ICER at 12 months increases by just 2%.

5.8.2 Costs

Table 26 shows clearly that the additional cost per patient in the first year, attributable to substituting ticagrelor for clopidogrel is made up of two main components: the additional cost of ticagrelor (£651 per patient) offset by an expected saving in health care costs of £371 per patient. However, closer examination reveals that virtually the whole of this saving (£370) appears to arise specifically among patients who die during the first 12 months.

Table 26 Source of incremental cost difference in year 1 of manufacturer's model base case.

Trial end patient category	No event	Non-fatal MI	Non-fatal stroke	Death	Overall
Ticagrelor					
Study drug cost	£622	£39	£9	£22	£692
Aspirin cost	£9	£1	£0	£0	£19
Adverse event costs	£7	£0	£0	£1	£9
Health care costs	£7,450	£899	£187	£727	£9,263
Total cost per patient	**£8,089**	**£938**	**£196**	**£750**	**£9,974**
Clopidogrel					
Study drug cost	£36	£3	£0	£2	£41
Aspirin cost	£9	£1	£0	£0	£10
Adverse event costs	£4	£0	£0	£0	£5
Health care costs	£7,314	£1,028	£195	£1,098	£9,634
Total cost per patient	**£7,353**	**£1,031**	**£196**	**£1,100**	**£9,690**
Difference					
Study drug cost	+£587	+£36	+£8	+£20	+£651
Aspirin cost	+£0	-£0	+£0	-£0	+£0
Adverse event costs	+£3	£0	+£0	+£0	+£4
Health care costs	+£136	-£129	-£8	-£370	-£371
Total cost per patient	**+£726**	**-£93**	**+£0**	**-£350**	**+£284**

Health care resource use is estimated in the model using data from a parallel health economic study which collected details of hospital care received by patients during the trial across 40 different items. These data were only collected for 57.4% of the trial population, and no information is available concerning how this subset was selected for the sub-study. For each patient category in the model the **resource use rate per patient** was calculated separately for each treatment arm, and these rates are multiplied by a corresponding unit cost and totalled to arrive at an overall estimated hospital care cost per patient for the first 12 month period.

There are some important issues relating to this type of resource analysis, and how it has been implemented in this model:

1) A small (statistically non-significant) difference in resource use can be multiplied by a large unit cost to produce an apparently major cost difference between treatments. With so many individual items contributing to the aggregate totals, it is very likely that anomalies can be generated yielding very influential contributions to incremental costs from data which individually show very similar patterns. In this case when the total **estimated cost for patients dying** within the first 12 months is shown separately for those dying of vascular causes and those dying of non-vascular causes, an unsustainably large difference (£10,740 per patient) for the latter group is obtained compared to only £423 per patient for vascular death patients.

2) This points to a serious problem with the resource use data. The number of patients for whom resource use data were obtained in each model group was very small compared to the size of the whole economic study sample, except for those who did not suffer any event in the first year. Out of a total of 10,686 patients surveyed, 567 were in the non-fatal MI group, 103 in the non-fatal stroke group, 470 in the cardiovascular death group and only 71 suffered a non-cardiovascular death. For some calculations the numbers of individual **resource use events are in single figures**, especially when split still further to model subgroups such as STEMI and non-STEMI patients. Resource data are well-known to be subject to heavily skewed statistical distributions, and hence differences are difficult to estimate reliably.

3) It appears likely that some of the most important resources may have been over-estimated by **double-counting** items which in the UK are normally subsumed within broader hospital episode costs. In particular, hospital bed-days are counted in the model in six separate categories, but in the UK these are generally covered by a single hospital episode cost. In addition, some investigations and blood products will only be separately costed when used outside of a normal inpatient stay or outpatient visit. It is not possible for the ERG to

reclassify each of these cost items to arrive at a more defensible estimate. The most obvious problem areas are:

- coronary artery bypass grafts are counted and costed as two HRGs but the bed days related to CABG are also counted and costed separately;

- PCIs are costed as day cases, although non-elective cases will always be admitted as inpatients. In some international centres it is likely that at least some elective patients will also be treated as inpatients. So there is likely to be some double-costing of bed-day costs for these patients;

- the same issue applies to pacemaker fitting, implantable cardiac defibrillators, and intra-aortic balloon pumps;

- 're-operation due to bleeding' may also feature in the bed-day totals as well as an episode cost.

Using the combined analysis of resource use (taking all patient groups together) and making some notional adjustments for double-counting, the ERG suggests that any difference between clopidogrel and ticagrelor is more likely to be around £100 per patient rather than the £371 per patient shown in the manufacturer's base case results, which would have the effect of doubling the estimated ICER after 12 months.

However, there is another cost issue worthy of note. The manufacturer's base case analysis applies **estimated costs for the study drugs on the basis of 100% of usage** in the trial period, despite clear evidence of early deaths in both of the trial arms as well as recorded treatment withdrawals and some poor compliance. Thus the modellers have been quite conservative. Evidence seen in other cardiovascular appraisals suggests that some reduction in dosing costs can reasonably be assumed, and the ERG takes the view that an optional feature of the manufacturer's model which allows use of trial data on drug usage is probably more appropriate. This has the effect of reducing the average cost of both drugs substantially, and the incremental drug cost of ticagrelor compared to clopidogrel from £651 to £507 per patient.

5.8.3 Summary

Taken together these amendments to the manufacturer's model result in a 42% increase in the submitted base case 12 month ICER from £36,177 to £51,204 per QALY gained. However, it should be emphasised that both the incremental costs and additional benefits from using ticagrelor in place of clopidogrel are very small after a maximum of 12 months treatment, and are subject to considerable uncertainty.

5.9 Consideration of the long-term model projections

The long-term projection model is founded on a simple rationale: after 12 months dual antiplatelet treatment there are more patients alive in the ticagrelor arm who have a slightly different distribution in terms of vascular event history. These additional surviving patients continue in the model until death, incurring additional non-fatal events and associated health care costs whilst receiving 'standard care' (usually including long-term ASA). Although there are some minor effects from differences in previous event history, the great majority of outcome differences can be attributed to the survival gain recorded after 12 months dual antiplatelet therapy with ticagrelor.

Despite the various simplifications and shortcomings of the submitted model discussed above, it is still possible to consider the robustness of the long-term projection results and therefore of the overall cost-effectiveness estimates using a straightforward wide-ranging sensitivity analysis. Table 27 details the specific values used for each of the four patient populations represented in the model, together with the widely spaced sensitivity limits used for each long-term variable.

Table 27 Central values and sensitivity ranges for wide-ranging sensitivity analysis

Population	Year 1 incremental QALYs per patient	Year 1 incremental costs per patient	Survival gain at 12 months	Life expectancy at 12 months	Mean long-term utility value	Mean long-term discounted cost per patient year
All patients	0.0080	£411	1.70%	8.6 years	0.826	£4,144
STEMI	0.0086	£461	1.57%	10.8 years	0.838	£5,166
NSTEMI	0.0085	£394	1.81%	7.1 years	0.819	£3,320
UA	0.0061	£404	1.31%	9.8 years	0.828	£4,847
Lower limit			1.0%	6.0 years	0.70	£2,000
Upper limit			3.0%	12.0 years	0.90	£8,000

Values derived from manufacturer's model with ERG adjustments implemented

Overall deterministic cost-effectiveness estimates have been calculated for all combinations of the four long-term variables; a total of 81 estimates for each of the four populations. Table 28 summarises the range of ICERs obtained in each case.

Table 28 Overall 40 year cost-effectiveness results of wide-ranging sensitivity analysis of long-term model variables

	Best result	Central result	Worst result
All patients			
Incremental cost	£1,131	£1,017	£891
Incremental QALYs	0.332	0.129	0.050
ICER	£3,407	£7,897	£17,820
STEMI			
Incremental cost	£1,181	£1,337	£941
Incremental QALYs	0.333	0.151	0.051
ICER	£3,551	£8,872	£18,597
NSTEMI			
Incremental cost	£1,114	£821	£874
Incremental QALYs	0.333	0.114	0.051
ICER	£3,350	£7,215	£17,307
UA			
Incremental cost	£1,124	£1,026	£884
Incremental QALYs	0.330	0.112	0.048
ICER	£3,405	£9,131	£18,378

It appears that the most extreme combination of assumptions results in an estimated ICER below £20,000 per QALY gained for each of the specified populations, indicating that compared to 12 months treatment with clopidogrel, the use of ticagrelor is a cost-effective alternative regimen.

5.10 Discussion of economic findings

In section 5.6 the issue of defining appropriate comparators in the context of current NICE guidance and guidelines was considered. The ERG pointed out that none of the decision problems addressed by the manufacturer fully reflects current advice, due to one or more deviations of the PLATO[21] trial evidence from that which would be considered fully compatible.

The recent guidance issued relating to long-term antiplatelet therapy for secondary prevention of vascular events[7] depends on distinguishing between patients with multivascular disease and those with a history limited to coronary artery disease. Currently there is no universally accepted definition of multivascular disease, and only a limited minority of PLATO[21] patients appear to qualify initially as patients with multivascular disease (about 10% at baseline, and 11-12% after 12 months). However, over a lifetime of accumulating vascular events individual ACS patients may suffer from stroke/TIA and/or peripheral vascular disease and thereby increase the proportion of patients counted as MVD. If the incidence of MVD in a typical UK ACS population can be shown to be similar, then its importance to the cost effectiveness of ticagrelor would be only become relevant if the modelled ICERs were close to the borderline of acceptability. On the basis of the economic results available this does not appear to be the case as the modelled ICERs are low. Therefore for UA and NSTEMI patients the economic evidence appears to support the view that ticagrelor treatment is cost effective compared with clopidogrel.

Determining the true cost effectiveness of ticagrelor vs clopidogrel for STEMI patients is more problematic. The manufacturer considers the STEMI group to represent a homogenous population and estimates a single ICER. However, within this subgroup there are four distinct populations: STEMI without stenting, STEMI with DES, STEMI with BMS and STEMI with other (e.g. CABG). The PLATO[21] trial's reliance on the use of clopidogrel+ASA for 12 months to treat all patients with STEMI means that only a single ICER could be estimated by the manufacturer. However, as NICE recommends that patients with a STEMI receive clopidogrel+ASA for at least 4 weeks and that STEMI patients with BMS receive clopidogrel+ASA for 3 months, the validity of estimating a single ICER for the whole of the STEMI subgroup needs to be explored carefully.

Finally, the ERG considers that the cost-effectiveness claims for ticagrelor depend crucially upon the absolute reduction in 12 month mortality observed in PLATO[21] for ticagrelor compared to clopidogrel. However, at earlier time points in the trial, the OS difference is much smaller and less significant between the two treatments (0.42% at 30 days (p=0.052) and 0.58% at 90 days (p=0.024)). In the absence of additional evidence allowing indirect

comparison of clopidogrel+ASA to clopidogrel therapy and to ASA therapy at 30 days, 90 days and 12 months, there remains some uncertainty as to whether the PLATO[21] trial provides sufficiently strong evidence to render either or both these existing limitations redundant.

6 DISCUSSION

The manufacturer presents the case for the use of ticagrelor compared to clopidogrel for the treatment of patients presenting with ACS. The PLATO[21] trial is considered by the ERG to be a well-conducted, robust RCT. The trial demonstrates a significant benefit of ticagrelor compared to clopidogrel for the primary endpoint (composite of vascular death, non-fatal MI and non-fatal stroke) and a range of secondary endpoints. Unusually, for cardiovascular drugs, a statistically significant mortality benefit was reported in favour of ticagrelor. The risk of overall major bleeding was not increased with the use of ticagrelor although an increase in non-CABG related bleeding compared to clopidogrel was noted.

There was no demonstrated benefit for patients in the ticagrelor arm on the outcome of overall stroke. However for the overall trial population it was clear that patients with non-ischaemic strokes (haemorrhagic plus unknown) in the ticagrelor arm suffered more strokes than the same patients in the clopidogrel arm. In the non-invasive group only, patients in the ticagrelor arm suffered more than twice as many non-ischaemic strokes than in the clopidogrel arm (p=0.016). The ERG is of the opinion that more detailed description and analyses relating to overall stroke and different categories of stroke would have been useful. For example, the number of seriously disabling strokes, how many were fatal, how non-ischaemic stroke related outcomes compare with ischaemic stroke related outcomes.

The trial recruited a large number of patients representing a broad spectrum of ACS patients including those presenting with UA, STEMI and NSTEMI who were treated by medical management or with revascularisation methods. The ERG's main criticism of the PLATO[21] trial is that randomised treatment was scheduled to continue for 12 months but it was planned that patients would leave the study at their 6 or 9 month follow-up visit if the targeted number of 1780 primary endpoint events had occurred by that time. The numbers of patients in each arm that left the study at the 6 month and 9 month visits were similar and the manufacturer pre-specified the use of this method. However, the ERG considers that all patients should have been followed up to at least 12 months as mortality at 12 months is a key outcome in trials of cardiovascular drugs. As only a proportion of trial patients were followed up to 12 months, it was impossible for the manufacturer to present comprehensive data on the need for [future] revascularisation as specified in the NICE scope.

The manufacturer presents convincing clinical and cost-effectiveness evidence supporting the use of ticagrelor for the overall patient population and three subpopulations (STEMI, NSTEMI and UA). However, the ERG was unable to verify the clinical effectiveness data related to NSTEMI and UA groups from the data reported in the MS. The ERG questions

whether each of the subgroups is truly a homogenous group (STEMI and UA subgroups in particular). The ERG offers a detailed critique of the manufacturer's model and has identified several weaknesses and limitations. In particular, the structure of the model is limited and could be improved to allow patients to experience explicitly more than one non-fatal event, and the manufacturer's use of an average utility score for the first 12 months is inappropriate (and unrealistic) and serves only to reduce the size of the ICER. However, after performing extensive sensitivity analyses to determine the robustness of the model's results and when all factors are considered together, the ERG agrees with the manufacturer that, based on the data presented, ticagrelor is cost-effective compared with ticagrelor for all NSTEMI and UA patients.

However, interpretation of the estimated ICER for the STEMI subgroup is problematic and the ERG is unable to ascertain the true cost effectiveness of ticagrelor vs clopidogrel for the different groups of STEMI patients. The treatment of ACS patients with STEMI is governed by two distinct sets of guidelines (CG48[10])/guidance (TA152[8]). Firstly, CG48[10] recommends that patients with STEMI should receive clopidogrel+ASA for at least 4 weeks; secondly, TA152[8] is interpreted by the ERG as recommending clopidogrel+ASA for 3 months for STEMI patients with BMS and 12 months for STEMI patients with DES. This means that despite the manufacturer's endeavours to include a broad spectrum of ACS patients in the PLATO[21] trial, there are at least two subgroups of patients with STEMI who are not represented and for whom it is impossible to estimate ICERs.[21] The manufacturer acknowledges the CG48[10] recommendations, but adds that the European guidelines[14] for the management of STEMI patients recommend dual antiplatelet therapy for 12 months (MS, p12). To add to the debate, the ERG is aware that recent evidence (in press) from clinical practice shows that one third of STEMI patients and one quarter of NSTEMI/UA patients in the UK discontinue treatment approximately 90 days after initiation of dual antiplatelet therapy.[49] In addition, as the manufacturer only estimated a single all-encompassing ICER for the STEMI population, there is also uncertainty about the size of the ICER for those patients with STEMI and DES as estimates of cost effectiveness were not performed separately for this group of patients.

There are no head-to-head trial data comparing ticagrelor with prasugrel. Both the ERG and the manufacturer agree that sufficient clinical evidence is not yet available for the conduct of a credible indirect comparison of ticagrelor vs prasugrel for patients with ACS; this means that the comparative effectiveness and safety of ticagrelor compared with prasugrel remains unknown.

Finally, the annual cost of ticagrelor per patient is much more expensive than clopidogrel and would apply to a large number of patients. Despite ticagrelor being more cost effective than clopidogrel for NSTEMI, UA and possibly STEMI patients, the use of ticagrelor would incur a substantial additional cost to the NHS in order to achieve a relatively small incremental benefit per patient.

6.1 Implications for research

Due to the paucity of long-term evidence for the continued benefit of ticagrelor and its safety, monitoring and surveillance of patients who have been treated with ticagrelor are therefore necessary.

There are no head-to-head clinical effectiveness data comparing ticagrelor vs prasugrel for patients undergoing PCI. A trial of this nature would be informative.

7 REFERENCES

1. Arslanian-Engoren C, Engoren M. Physiological and anatomical bases for sex differences in pain and nausea as presenting symptoms of acute coronary syndromes. Heart & Lung: The Journal of Acute and Critical Care. 2010; 39(5):386-93.
2. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, *et al.* Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart. 2009; 95(1):20-6.
3. Hasin T, Hochadel M, Gitt AK, Behar S, H B, Hasin Y. Comparison of treatment and outcome of acute coronary syndrome in patients with versus patients without diabetes mellitus. The American Journal of Cardiology. 2009; 103(6):772-8.
4. Taylor MJ, Scuffham PA, McCollam PL, Newby DE. Acute coronary syndromes in Europe: 1-year costs and outcomes. Curr Med Res Opin. 2007; 23(3):495-503.
5. National Institute for Health and Clinical Excellence. Ticagrelor for the treatment of acute coronary syndromes: final scope. 2010: Available from: http://www.nice.org.uk/nicemedia/live/12169/50774/50774.pdf.
6. Scarborough P, Bhatnagar P, Wickramasinghe K, Smolina K, Mitchell C, M. R. Coronary heart disease statistics 2010 edition. 2010: Available from: <http://www.ws3.heartstats.web.baigent.net/datapage.asp?id=9075>. .
7. National Institute for Health and Clinical Excellence. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of TA90): TA210. 2010 Available from: http://www.nice.org.uk/nicemedia/live/13285/52030/52030.pdf.
8. National Institute for Health and Clinical Excellence. Drug eluting stents for the treatment of coronary artery disease: TA152. 2008 [cited 2011 21st January]: Available from: http://guidance.nice.org.uk/TA152/Guidance/pdf/English.
9. National Institute for Health and Clinical Excellence. Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention:TA182. 2009: Available from: http://www.nice.org.uk/nicemedia/live/12324/45849/45849.pdf.
10. National Institute for Health and Clinical Excellence. MI: secondary prevention:NICE Clinical Guideline 48. 2007: Available from: http://www.nice.org.uk/nicemedia/live/11008/30493/30493.pdf.
11. National Institute for Health and Clinical Excellence. The early management of unstable angina and non-ST-segment-elevation myocardial infarction: NICE Clinical Guideline 94. 2010: Available from: http://guidance.nice.org.uk/CG48/Guidance/pdf/English.
12. Bassand J-P, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés, *et al.* Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007; 28(13):1598-660.
13. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, *et al.* Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Eur Heart J. 2008; 29(23):2909-45.

14. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, *et al.* Guidelines on myocardial revascularization. Eur Heart J. 2010; 31(20):2501-55.
15. eMC. Summary of product characteristics: Brilique. 2010 [cited 2011 February]; Available from: http://www.medicines.org.uk/emc/medicine/23935/SPC/brilique%2090%20mg%20film%20coated%20tablets/.
16. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. New Engl J Med. 2007; 357(20):2001-15.
17. Fox KAA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, *et al.* Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J. 2010; 31(22):2755-64.
18. The Health and Social Care Information Centre. Hospital Episode Statistics Online. 2008-2009; 2011. Available from: <http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=214>. .
19. Biondi-Zoccai G, Lotrionte M, Agostoni P, Abbate A, Romagnoli E, Sangiorgi G, *et al.* Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. Int J Cardiol. 2010.
20. Hughes S. First "comparison" of prasugrel and ticagrelor 2010 [cited 2010 September]; Available from: http://www.theheart.org/article/1122713.do.
21. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New Engl J Med. 2009; 361 (11):1045-57.
22. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, *et al.* Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. The Lancet. 2010; 375(9711):283-93.
23. Held C, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO trial. American College of Cardiology Annual Scientific Session & Expo 2010 March 14-16; Atlanta.
24. James S, Roe M, Cannon CP, Raev D, Horrow J, Husted S, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for a non-invasive management in PLATO trial. European Society of Cardiology; 2010; Stockholm Sweden.
25. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, *et al.* Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2010; 31(24):3006-16.
26. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, *et al.* Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a platelet inhibition and patient outcomes (PLATO) trial subgroup analysis. Circulation. 2010; 122(21):2131-41.

27. Moher D, Liberati A, Tetzlaff J, Altman D. *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 2009; 6(6): Available from: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000097
28. Thygesen K, Alpert JS, White HD. Universal Definition of Myocardial Infarction. Circulation. 2007; 116(22):2634-53.
29. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, *et al.* Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007; 115(17):2344-51.
30. Astra Zeneca Ltd. PLATO Clinical Study Report D5130C052622009.
31. Department of Health and Human Services, Public Health Service Food and Drug Administration, Center for Drug Evaluation and Research Division of Cardiovascular and Renal Products. Ticagrelor for acute coronary syndromes, NDA 22-433 Memorandum. 2010 [cited 2010 December]: Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220192.pdf.
32. Osterberg LG, Urquhart J, Blaschke TF. Understanding forgiveness: minding and mining the gaps between pharmacokinetics and therapeutics. Clin Pharmacol Ther. 2010; 88(4):457-9.
33. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA. 2003; 289(19):2554-9.
34. Ferreira-González I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, *et al.* Problems with the use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. Br Med J. 2007; 334(7597):786-92.
35. Montori VM, Permaneyer-Miralda G, Ferreira-González I, Busse JW, Pacheco-Huergo V, Bryant DM, *et al.* Validity of composite endpoints in clinical trials. Br Med J. 2005; 330:594-6.
36. European Medicines Agency. Points to consider on multiplicity issues in clinical trials. 2002: Available from: http://www.tga.gov.au/docs/pdf/euguide/ewp/090899en.pdf.
37. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Statistical principles for clinical trials E9: ICH harmonised tripartite guideline. 1998 7th January 2011]: Available from: http://private.ich.org/LOB/media/MEDIA485.pdf.
38. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, *et al.* Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome. Primary results of the DISPERSE-2 trial. J Am Coll Cardiol. 2007; 50(19):1844-51.
39. Wiviott SD, EM. A, Winters KJ, Weerakkody G, Murphy SA, Behounek BD, *et al.* Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. Circulation. 2005; 111(25):3366-73.

40. Greenhalgh J, Bagust A, Boland A, Saborido CM, Fleeman N, McLeod C, *et al.* Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. Health Technol Assess. 2010; 14(Suppl 1):31-8.
41. Allen LA, O'Donnell CJ, Camargo CA, Giugliano RP, Lloyd Jones DM. Comparison of long-term mortality across the spectrum of acute coronary syndromes Am Heart J. 2006; 151(5):1065-71.
42. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. Stroke. 1993; 24(6):796-800.
43. Office for National Statistics. Interim Life Tables, United Kingdom, 2007-2009. 2011; Available from: http://www.statistics.gov.uk/downloads/theme_population/Interim_Life/iltuk-reg.xls.
44. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. 2008 [cited 2011 January]: Available from: http://www.nice.org.uk/pdf/TAP_Methods.pdf
45. Lacey EA, Walters SJ. Continuing inequality: gender and social class influences on self perceived health after a heart attack. J Epidemiol Community Health. 2003; 57(8):622-27.
46. Prescribing Services Ltd. Drugtariff.co.uk. 2011 [cited 2011 January]; Available from: https://www.drugtariff.co.uk/Default.aspx.
47. MIMS. The prescribing reference for general practice. 2010; Available from: http://www.mims.co.uk/go/mims_monthly/.
48. Drummond M, Stoddart G, Torrance G. Methods for the Economic Evaluation of Health Care Programmes. Oxford: 2nd Edition. Oxford University Press; 1997.
49. Bakhai A, Iñiguez A, Ferrieres J, Schmitt C, Sartral M, Belger M, *et al.* Treatment patterns in acute coronary syndrome patients in the United Kingdom undergoing PCI. EuroIntervention. In Press.
50. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. 2008: Available from: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf.

8 APPENDICES

Appendix 1

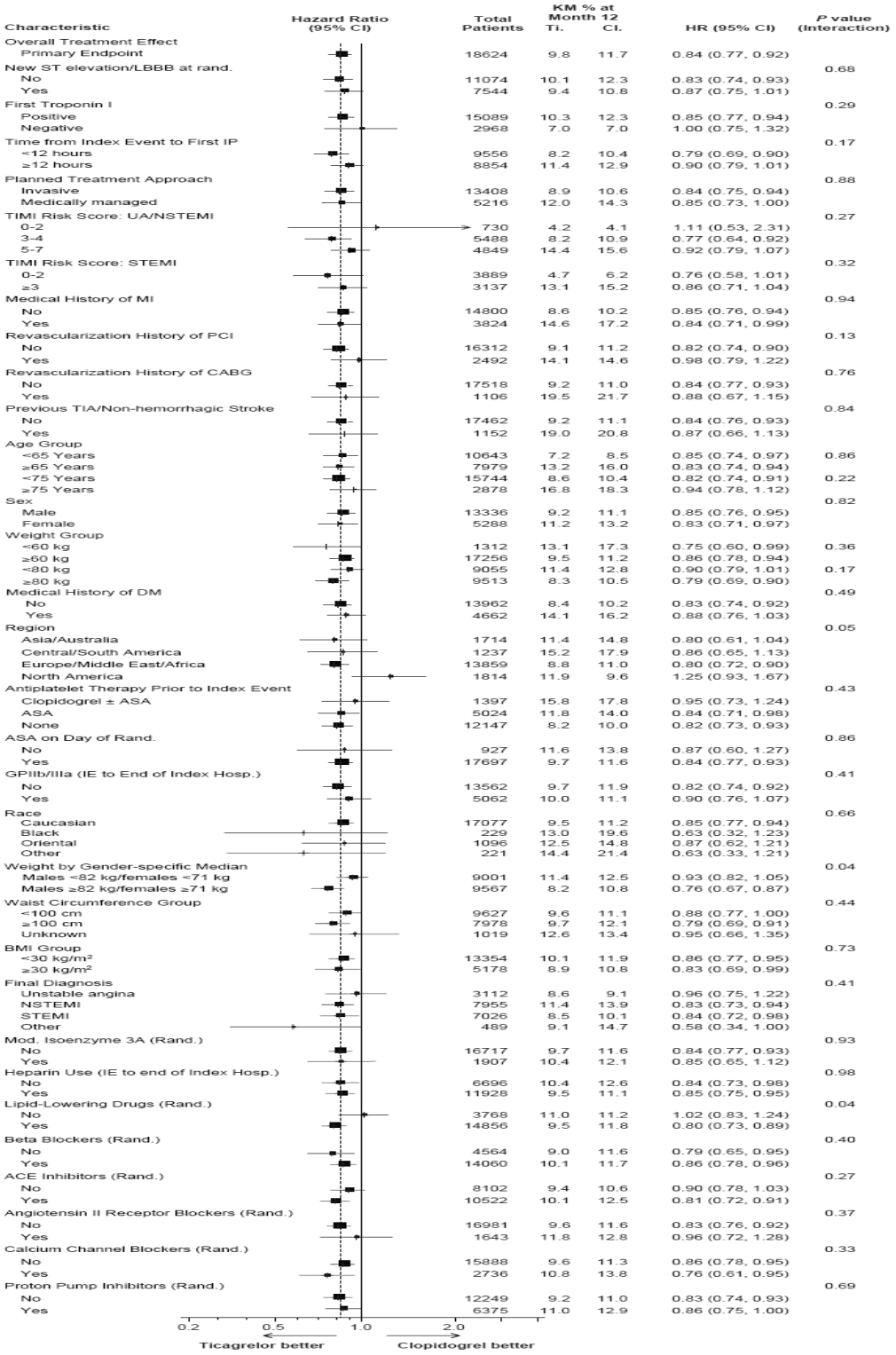
Table 29 Quality assessment of the PLATO trial

Study question	How is the question addressed in the study?	Grade: Yes/no/not clear/NA	ERG comment
Was randomisation carried out appropriately?	Computer generated block of numbers Patients were randomised in a blinded fashion using 1:1 allocation by a third party. The randomisation schedule was created by the AstraZeneca GRAND system. Creation and ownership of the schedule was handled by a separate group that had no direct involvement in the study	Yes	Agree
Was the concealment of treatment allocation adequate?	Double-blind double dummy design Treatment allocation was by interactive voice response system	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Clinical characteristics at baseline were comparable between arms	Yes	Agree Slightly younger and fitter than in UK practice
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Double-blind double dummy design. Independent endpoint adjudication occurred without knowledge of the treatment allocation. Patients, investigators and site personnel were blinded as to treatment allocation	Yes	Agree
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Both arms were well matched in terms of completion rates	Yes	Agree The withdrawals are clearly documented in the MS. The ERG notes that patient follow-up ranged from 6 months up to 12 months as patients were required to leave the trial at 6 months or 12 months once 1780 events had occurred (enough events to show a statistically significant difference between the two treatment arms). The ERG considers that all patients should have been followed up for 12 months
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All study outcomes were pre-specified and reported	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All data was analysed on an intention to treat basis All patients who had been randomly assigned to a treatment group were included in the intent-to-treat analysis	Yes	Agree

Based on checklist produced by the Centre for Reviews and Dissemination[50]

Appendix 2

Hazard ratios and rates of primary endpoint in predefined subgroups of the PLATO study



Appendix 3

PLATO trial key outcomes for European Union patient cohort

Table 3: Primary and secondary efficacy endpoints and primary safety endpoint for the European Union[a] - PLATO full analysis set

Endpoint	Ticagrelor 90 mg bd N=5733 Patients with events	KM%/ year	Clopidogrel 75 mg od N=5713 Patients with events	KM%/ year	HR (95% CI)	p-value
Primary efficacy						
Composite of CV death/ MI (excl. silent MI)/stroke	470 (8.2%)	8.7%	598 (10.5%)	11.2%	0.78 (0.69, 0.88)	<0.0001
Secondary efficacy						
Composite of CV death/ MI (excl. silent MI)/stroke-intent for invasive management	303 (7.4%)	7.9%	338 (9.6%)	10.2%	0.77 (0.66, 0.89)	0.0005
Composite of all-cause mortality, MI (excl. silent MI)/stroke	488 (8.5%)	9.0%	624 (10.9%)	11.7%	0.77 (0.69, 0.87)	<0.0001
Composite of CV death/total MI/Stroke/SRI/RI/TIA/Other ATE	735 (12.8%)	13.6%	873 (15.3%)	16.2%	0.83 (0.75, 0.92)	0.0002
CV death	165 (2.9%)	3.1%	231 (4.0%)	4.4%	0.71 (0.58, 0.87)	0.0008
MI (excl. silent MI)	289 (5.0%)	5.4%	370 (6.5%)	7.0%	0.77 (0.66, 0.90)	0.0010
Stroke	77 (1.3%)	1.5%	70 (1.2%)	1.3%	1.10 (0.79, 1.52)	0.5776
All-cause mortality	190 (3.3%)	3.5%	264 (4.6%)	5.0%	0.72 (0.59, 0.86)	0.0005
Primary safety						
'Total Major' bleeding	600 (10.6%)	11.9%	585 (10.3%)	11.5%	1.03 (0.92, 1.15)	0.6364

[a]European Union includes: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom. Also includes a member of the EEA: Norway.

Hazard ratio and p-value calculated from Cox proportional hazards model with study treatment as only explanatory variable. Kaplan-Meier percentage calculated at 12 months. For patients with multiple events the analysis uses the time to the earliest event: each patient is counted only once in each row. A single event may be counted in more than 1 row.

Note: The number of first events for the components CV death, MI, and stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

ATE Arterial thrombotic events; bd Twice daily dosing; CI Confidence interval; CV Cardiovascular (CV death is death from vascular causes); excl. Excluding; HR Hazard ratio; KM Kaplan Meier; MI Myocardial infarction; od Once daily dosing; RI Recurrent cardiac ischaemia; SRI Severe recurrent cardiac ischaemia; TIA Transient ischaemic attack.