NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

TICAGRELOR FOR THE TREATMENT OF ACUTE CORONARY SYNDROMES

AstraZeneca UK Ltd
600 Capability Green, Luton, LU1 3LU

Date prepared: 12th November 2010

Contents

Section A – Decision Problem	Page
1.Description of technology under assessment	16
2. Context	19
3. Equity and equality	28
4. Statement of the decision problem	29
Section B – Clincal and cost effectiveness	
5. Clinical evidence	32
6. Cost effectiveness	81
Section C - Implementation	
7. Assessment of factors relevant to NHS and other parties	229
8 References	233
9. Appendices	243

List of tables

Table	Page Number
Table 1.1: Unit costs of technology being appraised	17
Table 2.1: NICE Guidance	21
Table 5.1: Eligibility criteria used in search strategy	33
Table 5.2: Phase III RCT included in the document	35
Table 5.3 Summary of methodology for PLATO (Wallentin *et al.* 2009)	37
Table 5.4: Eligibility criteria for PLATO	38
Table 5.5: Baseline characteristics of participants in the PLATO study (Wallentin *et al.* 2009)	39
Table 5.6: PLATO primary and secondary outcomes (Wallentin *et al*. 2009)	40
Table 5.7: Summary of statistical analyses	41
Table 5.8: Subgroup analyses of the PLATO study	42
Table 5.9: PLATO quality assessment results	44
Table 5.10: Efficacy endpoints from the PLATO study (Wallentin *et al.* 2009)	47
Table 5.11: Primary and secondary efficacy endpoints from the PLATO-INVASIVE study (Cannon *et al.* 2010)	51
Table 5.12: Primary and key secondary endpoints from the PLATO – MEDICAL study (James *et al*. 2010)	52
Table 5.13: Incidence of the primary endpoint (time to first MI, CV death, stroke) in the study relative to the sub-group analyses	57
Table 5.14: Key inclusion features in TRITON-TIMI 38 and PLATO	63
Table 5.15 Comparison of TRITON-TIMI 38 and PLATO trials	64
Table 5.16: Summary of the trials used in the published indirect comparison, conducted by an independent group, from which results for health economic modelling were taken (Biondi-Zoccai *et al*. *2010)*	67
Table 5.17: Conversion of results from Biondi-Zoccai *et al.* 2010 into desired format for health economic modelling.	68
Table 5.18: Incidence of the Primary Safety Endpoint (time to first major PLATO defined bleeding event) in the PLATO study relative to the sub-group analyses	72
Table 5.19: Incidence of the primary and main secondary bleeding events (Wallentin *et al.* 2009)	73
Table 5.20: Incidence of additional safety signals (Wallentin *et al.* 2009)	74
Table 6.1: Details of full text cost-effectiveness articles that were excluded from further review	82
Table 6.2: Summary list of other cost-effectiveness evaluations	85
Table 6.3 Key features of analysis	127
Table 6.4 Detailed clinical pathways in the PLATO study	129
Table 6.5 Clinical pathways according to the model structure	130

Table	Page Number
Table 6.6 Results of Weibull regression equations	131
Table 6.7 Comparison of modelled and published data	132
Table 6.8 Comparison of patient characteristics in terms of age and gender	134
Table 6.9 Baseline event rates used in the model to reflect the age of ACS patients in England and Wales	135
Table 6.10 Transition matrix for one year decision tree	135
Table 6.11 Transition matrix for Markov model	136
Table 6.12 Incidence of MI and stroke per 100 patients 12-24 months after index ACS event	137
Table 6.13 Hazard ratios for long-term mortality compared to unstable angina	138
Table 6.14 Rebasing of hazard ratios from Allen *et al*, 2006	138
Table 6.15 SMRs from CG84 revised to include STEMI patients	138
Table 6.16 Studies reporting the relative risk of death post-stroke	139
Table 6.17 Summary of variables applied in the economic model	141
Table 6.18 Total UK Patient Cost (GBP) Across Index and Post-Index Event Summary randomised patients with major bleeding, 12 months cohort	143
Table 6.19 Total UK Patient Cost (GBP) Across Index and Post-index Event Summary Randomised Patients with No Major Bleeding, 12-Month Cohort	143
Table 6.20: Total UK Patient Cost (GBP) Across Index and Post-index Event Summary Randomised Patients with Dyspnoea, 12-Month Cohort	144
Table 6.21: Total UK Patient Cost (GBP) Across Index and Post-index Event Summary Randomised Patients with No Dyspnoea, 12-Month Cohort	144
Table 6.22 Average utility score in the full cohort	149
Table 6.23 Average utility score in the 12-month cohort	149
Table 6.24: Estimated mean utility score by node (including deaths) for the 12-month cohort	150
Table 6.25: Estimated mean utility score by node (including deaths) and treatment for the 12-month cohort	150
Table 6.26 Summary of the HRQL papers	154
Table 6.27 Comparison of utility scores	173
Table 6.28 Comparison of stroke severity	173

Table	Page Number
Table 6.29: Summary of quality-of-life values for cost-effectiveness analysis (base case)	175
Table 6.30 Utilities for no further event/post ACS	177
Table 6.31 Utilities for MI and post MI	177
Table 6.32 Utilities for stroke	177
Table 6.33 Weighted average stroke utility	178
Table 6.34:Summary of quality-of-life values for cost-effectiveness analysis (sensitivity analysis)	178
Table 6.35: National Schedule of Reference Costs Year: '2008-09' - NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data	182
Table 6.36: National Schedule of Reference Costs Year: '2008-09' - NHS Trusts and PCTs combined Elective Inpatient HRG Data	183

Table	Page Number
Table 6.37: 2009/10 Inpatient & Planned Same Day Tariff	184
Table 6.38: Drug costs used in the economic evaluation	192
Table 6.39 Cost of renal monitoring	193
Table 6.40: Mean resource use for No Event health state (all patients)	194
Table 6.41 Resource use and unit costs	196
Table 6.42: Antithrombotic Med. taken Post Randomisation by ATC FULL	197
Table 6.43: Non Antithrombotic Med. taken Post Randomisation by ATC FULL	198
Table 6.44: List of health states and associated costs in the economic model	200
Table 6.45: Cost of acute stroke, Youman et al, 2003	201
Table 6.46 Cost of ongoing care, Youman et al 2003	201
Table 6.47 Costs for stroke in Markov model	202
Table 6.48 Health state costs used in Markov Model	203
Table 6.49 Cost of bleeding from CG94	203
Table 6.50 Cost of stent thrombosis from National Reference Costs 2008/09	204
Table 6.51 Values used in one-way sensitivity analysis	206
Table 6.52 Utility values used in one way sensitivity analysis	207
Table 6.53 Summary of model results compared with clinical data	208
Table 6.54 Model outputs by clinical outcomes	210
Table 6.55 Summary of QALY gain by health state	210
Table 6.56 Summary of costs by health state	211
Table 6.57 Summary of predicted resource use by category of cost	211
Table 6.58 Base-case results – cost per LYG (deterministic)	212
Table: 6.59 Base-case results – cost per QALY (deterministic)	212
Table 6.60 Base case results – cost per QALY probabilistic	212
Table 6.61 Deterministic results with costs and effects discounted	213
Table 6.62 Output of one-way sensitivity analysis	214
Table 6.63 Deterministic results based on dead vascular and dead non-vascular nodes	217
Table 6.64 Results of scenario testing (40-year time horizon)	217
Table 6.65 Results of scenario testing (40-year time horizon)	219
Table 6.66 Characteristics of subgroups	220
Table 6.67 Baseline event rates for clopidogrel for subgroup from PLATO trial	220
Table 6.68 Event rates for ticagrelor from PLATO Invasive study	221
Table 6.69 Event rates for prasugrel based on relative risks from indirect comparison	221

Table	Page Number
Table 6.70: Baseline rate of bleeding and stent thrombosis from PLATO invasive study	221
Table 6.71: Baseline rate of bleeding and stent thrombosis prasugrel from relative risks	222
Table 6.72: Results of STEMI subgroup analysis	222
Table 6.73: Results of Within trials cost analysis for STEMI	223
Table 6.74 Detailed analysis of NSTEMI subgroup	223
Table 6.75: Results of UA subgroup analysis	224
Table 6.76: Results of Within trials cost analysis for UA	225
Table 6.77 Detailed analysis of invasive subgroup	225
Table 7.0 Number of patients eligible for treatment in England and Wales	229
Table 7.1 Volume market shares within ACS market	230
Table 7.2 Volume market shares within the oral antiplatelet market	230
Table 7.3 Results within trial cost analysis	231
Table 7.4 Budget impact of ticagrelor in England and Wales	232

List of figures

Figure	Page Number
Figure 2.1: The spectrum of ACS (Bassand *et al.* 2007)	20
Figure 2.2: Reperfusion strategies – thick arrows represent the preferred strategy (Van der Werf et al. 2008)	23
Figure 5.1 Flow diagram depicting the study selection process	34
Figure 5.2: Flow chart depicting the patient flow within the PLATO study	43
Figure 5.3: Kaplan-Meier plot for the primary endpoint of the PLATO study	46
Figure 5.4: Efficacy of ticagrelor over time	48
Figure 5.5: Hazard ratios and rates of primary endpoint in predefined subgroups of the PLATO study *(Wallentin* et al. *2009)*	49
Figure 5.6: PLATO: Kaplan-Meier plot for the primary endpoint	50
Figure 5.7: Kaplan-Meier plot for the primary endpoint (PLATO-MEDICAL data set compared to the PLATO-INVASIVE analysis) (James *et al.* 2010)	52
Figure 5.8: Kaplan-Meier plot for the primary endpoint: PLATO-DIABETES analysis (James *et al.* 2010)	55
Figure 5.9: Kaplan-Meier plot for the primary endpoint of the PLATO-GENETICS analysis(Wallentin *et al.* 2010)	56
Figure 5.10: Flowchart of trials in the systematic review	60
Figure 5.11: Comparison of the TRITON-TIMI 38 patient population (A) and the PLATO patient population (B) as seen within the overall context of ACS management.	65
Figure 5.12 Contrasting the times of randomisation in PLATO and TRITON-TIMI 38. Randomisation in TRITON occurred much later in the management pathway, after angiography and a decision to proceed with PCI	66
Figure 5.13: Schematic representation of the PLATO bleeding definitions alongside the equivalent TIMI definitions	70
Figure 5.14: Kaplan-Meier plot for the primary safety endpoint of the PLATO study (adapted from Wallentin et al. 2009)	71
Figure 6.1 Flow diagram of literature review of relevant economic evaluations	84
Figure 6.2 Diagrammatical representation of the health states and patient pathways in both the decision tree and Markov model	122
Figure 6.3 Graph showing modelled versus actual survival data for Dead Any Cause node	132
Figure 6.4 Graph showing modelled versus actual survival data for Myocardial Infarction Node	133
Figure 6.5 Graph showing modelled versus actual survival data for Stroke node	133
Figure 6.6 Graph showing modelled versus actual survival data for Dead Vascular node	134
Figure 6.7 Tornado diagram of one way sensitivity analysis	214
Figure 6.8 Scatter plot of incremental costs and QALYs	216
Figure 6.9 Cost effectiveness acceptability curves for ticagrelor vs clopidogrel	216
Figure 6.10 Scatter plot of incremental costs and QALYs	225
Figure 6.11 Cost effectiveness acceptability curves	226

List of abbreviations and terms

ACS	Acute Coronary Syndrome
ADP	Adenosine diphosphate
A&E	Accident and Emergency
AMI	Acute myocardial infarction
ARR	Absolute Risk Reduction
ASA	Acetylsalicylic acid
BD	Twice daily
BMI	Body Mass Index
CABG	Coronary Artery By-Pass Grafting
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPTP	Cyclopentyltriazolopyrimidines
CUA	Cost ultility analysis
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CV	Cardiovascular
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GDG	Guideline Development Group
GRACE	Global Registry of Acute Coronary Events
HR	Hazard ratio
HRQL	Health related quality of life
HTA	Health Technology Assessment
ITT	Intention to treat
IQR	Interquartile range
ISIS	International Study of Infarct Survival
KM	Kaplan Meier
LBBB	Left bundle branch block
MI	Myocardial Infarction
NSTEMI	Non ST elevation Myocardial Infarction
NSTE-ACS	Non ST elevation – Acute Coronary Syndrome
PCI	Percutaneous coronary intervention
SIGN	Scottish Intercollegiate Guideline Network
STEMI	ST elevation Myocardial Infarction
SMC	Scottish Medicines Consortium
TIA	Transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TRITON – TIMI 38	(Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction 38)
OAP	Oral antiplatelet

OD	Once daily
PCI	Percutaneous coronary intervention
PLATO	Study of Platelet Inhibition and Patient Outcomes
PLATO - INVASIVE	PLATO substudy including only those patients identified at randomisation with investigator intent for early invasive management
PLATO - MEDICAL	PLATO substudy including only those patients identified at randomisation with intent for non-invasive medical management
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RRR	Relative risk reduction
TTO	Time Trade Off
SMR	Standardised mortality ratios
SPC	Summary of Product Characteristics
UA	Unstable angina

.

Executive summary

Introduction

Acute coronary syndromes (ACS) are a major cause of morbidity and mortality in the UK. Early diagnosis and prompt, effective therapy are essential to reverse ischaemia, restore normal coronary blood flow, and limit myocardial damage. (see Section 2.1)

In England alone there were approximately 146,000 ACS hospital admissions in 2008-2009. In the UK, approximately 16% of all ACS patients die before admission to a hospital while survivors often have persistent angina symptoms, heart failure and a high risk of further ACS episodes. Effective acute management is essential to reduce the in-hospital risk of morbid and fatal events, while effective longer-term follow-up therapy is also important to reduce the risk of subsequent events that may adversely impact the patients' life expectancy and place additional economic burdens on the health care system. (see Section 2.1)

Initial treatment decisions are primarily guided by the presenting diagnosis – differentiating STEMI (which requires immediate emergency restoration of blood flow in an occluded coronary artery) from UA/NSTEMI (where a partial thrombotic obstruction leads to impaired blood flow that needs to be restored promptly but not urgently). (see Section 2.1)

The aim of the clinical management of acute coronary syndrome is to restore normal coronary blood flow, reverse ischaemia and limit infarction. Regardless of the initial reperfusion strategy chosen to restore coronary blood flow, prevention of further coronary thrombosis with antiplatelet therapy is a key component of acute management. In the long term, antiplatelet therapy is effective in reducing the likelihood of additional, recurrent events. (see Section 2.1)

Ticagrelor is a new class of oral platelet inhibitor which, in comparison to clopidogrel, has demonstrated a significant reduction in the composite of CV death, non-fatal MI, or non-fatal stroke across a broad spectrum of ACS patients, without an increase in overall major bleeding. Ticagrelor has the potential to significantly improve outcomes in ACS patients regardless of management strategy – invasive, conservative, medical, surgical, or percutaneous coronary intervention (PCI). Full adoption of ticagrelor for 12 months use within licensed indications by the NHS could save approximately 160 lives (assuming 12,000 patients taking the drug).

The Technology

The UK approved name: Ticagrelor

UK Brand name: Brilique™

Marketing status: Marketing Authorisation via the European Centralised Procedure is pending. The European Medicines Agency (EMA) Committee for Medicinal Products for Human use (CHMP) adopted a positive opinion on 23rd September 2010. Marketing Authorisation is expected December 2010. (see Section 1.3).

Principal mechanism of action of ticagrelor:

Ticagrelor is a direct-acting $P2Y_{12}$ receptor antagonist that has a different mechanism of action to the thienopyridines. Ticagrelor, one of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines (CPTP), is the first reversibly binding oral adenosine

diphosphate (ADP) receptor antagonist. It is a 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. (see Section 1.2).

The frequency formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated of any repeat courses of treatment and acquisition cost:

Film coated tablets containing 90mg ticagrelor are supplied in packs of 56 tablets (28 days). The acquisition cost has not been finalised although we anticipate that a 28 day pack will cost £54.60. Ticagrelor treatment should be initiated with a single loading dose of 180mg (2 tablets of 90mg) and continued at 90mg twice daily. The licensed duration of treatment will be up to 12 months. Repeated courses are not anticipated. (see Section 1.10)

The indication(s) and any restriction(s): Committee for Medicinal Products (CHMP) positive opinion has been adopted for the following indication:- Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, 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 by-pass grafting (CABG). (see Section1.5).

No significant restrictions are anticipated other than those listed in the SPC and no dose adjustments are required including the elderly population and those with renal impairment or mild hepatic impairment. (see Section 1.10)

The recommended course of treatment: Continuous treatment for up to 12 months is recommended. (see Section 1.10).

The main comparator(s): The comparators identified are clopidogrel (standard of care in UK) and prasugrel (very limited use) (see Section 2.6).

NICE Clinical Guideline 94 recommends dual anti-platelet therapy (clopidogrel and aspirin) for UA or NSTEMI patients with a predicted 6-month mortality of more than 1.5%. Recommended treatment duration is 12 months after the most recent acute episode of non-ST-segment-elevation ACS. Whilst NICE Clinical Guideline 48 advocates the use of clopidogrel for at least 4 weeks post STEMI, European guidelines for management of patients with STEMI recommend dual antiplatelet therapy (clopidogrel with aspirin) for 12 months irrespective of acute treatment. (see Section 2.3).

NICE has also recommended the use of prasugrel (NICE Technology Appraisal 182) in combination with aspirin as an option for preventing atherothrombotic events in people with acute coronary syndromes having PCI only when:

- immediate primary PCI for ST-segment-elevation myocardial infarction is necessary
  or
- stent thrombosis has occurred during clopidogrel treatment
  or
- the patient has diabetes mellitus. (see Section 2.3)

Key Clinical Evidence: The key clinical evidence for ticagrelor comes from a large randomised controlled clinical trial (PLATO/ Wallentin *et al*.2009) that enrolled adult ACS patients (STEMI, NSTEMI and UA, including a UK population) irrespective of planned

intervention (e.g. PCI). PLATO 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 (See Section 5.3). Subgroup analyses of the PLATO study provide supportive evidence for the consistent, broad, efficacy of ticagrelor (see Section 5.5). Safety data are also available for the PLATO study. (see Section 5.9).

The main clinical results of the randomised controlled trials (RCTs) and any relevant non-RCT evidence: In PLATO, treatment with ticagrelor compared to clopidogrel significantly reduced the rate of death from vascular causes, non-fatal myocardial infarction, or non-fatal stroke without an increase in the rate of overall major bleeding. The primary endpoint, time to the first occurrence of the composite of death from vascular causes, non-fatal MI and non-fatal stroke occurred with an event rate of 9.8% per year in the ticagrelor treatment group compared to 11.7% per year in the clopidogrel treatment group (Absolute risk reduction [ARR] 1.9%, relative risk reduction [RRR] 16%, (HR [95%CI]) = 0.84 [0.77-0.92], p<0.001). (see Section 5.5)

Further analysis suggests that the reduction in primary endpoint was driven by approximately equal reductions in the incidence of MI and death from vascular causes. MI occurred with an event rate of 5.8% per year in the ticagrelor treatment group compared to 6.9% per year in the clopidogrel treatment group (ARR 0.9%, RRR 16%, HR [95%CI] = 0.84 [0.75-0.95], p=0.005). Death from vascular causes occurred with an event rate of 4.0% per year in the ticagrelor treatment compared to 5.1% in the clopidogrel treatment group (ARR 1.1%, RRR 21%, HR [95%CI] = 0.79 [0.69-0.91], p=0.001). There was no effect observed on the rate of stroke. (see Section 5.5).

An exploratory analysis of total mortality identified a lower incidence in the ticagrelor arm of the study. Death from any cause occurred with an event rate of 4.5% per year in the ticagrelor treatment group compared to 5.9% per year in the clopidogrel treatment group (ARR 1.4%, RRR 22%, HR [95%CI]) = 0.78 [0.69-0.89], nominal p<0.001). (see Section 5.5).

Sub-group analyses of the PLATO study (see Section 5.5) demonstrated that similar reductions in the primary endpoint were observed in patients:

- identified at randomisation with investigator intent for early invasive strategy (angiography followed by PCI or CABG) or early conservative strategy (angiography only if the patient develops further symptoms or becomes clinically unstable)
- undergoing CABG
- presenting with ST elevation or new left branch bundle block (LBBB) at randomisation or having a final diagnosis of STEMI/LBBB)

Subgroup analyses also demonstrated that the magnitude of the reduction in the primary endpoint with ticagrelor was not affected by diabetes status or by CYP2C19 gene expression. (See Section 5.5)

The PLATO study included specific safety objectives to evaluate the bleeding profile of ticagrelor compared to clopidogrel. Bleeding constitutes the most common, clinically significant safety concern during effective anti-platelet treatment.

There was no overall significant difference in the primary safety endpoint between the ticagrelor and clopidogrel arms of the study. The primary safety endpoint, time to first major PLATO defined bleed had an event rate of 11.6% per year in the ticagrelor treatment group compared to 11.2% per year in the clopidogrel treatment group (absolute risk increase 0.4%; relative risk increase 4%; HR [95%CI] = 1.04 [0.95-1.13], p=0.43). Ticagrelor was, however, associated with a higher incidence of non-CABG-related major bleeding and non-procedural bleeding events compared to clopidogrel. (see Section 5.9).

There are no head to head trials comparing ticagrelor with prasugrel so in order to address the decision problem for this appraisal an indirect comparison was necessary. Following a systematic review, it was found that, other than PLATO, only one study was eligible for inclusion in the indirect comparison: TRITON-TIMI 38 which provides data on prasugrel via the common comparator of clopidogrel (see Section 5.7). We believe that an indirect comparison of these studies is entirely inappropriate because of very important differences in target population, clopidogrel dosing and definition of endpoints. We have explained this in detail in section 5.7. Despite these concerns we have included the results of a published study that attempted to compare ticagrelor with prasugrel in our cost effectiveness analysis to address the decision problem (see Section 5.7).

We emphasise that the results of this indirect comparison should be viewed with extreme caution.

Type of economic evaluation and justification for the approach used: An Excel-based cost-utility model was developed in line with the 'Guide to the methods of technology appraisal', published by NICE in June 2008. The model 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 to ensure that all major clinical and resource generating events that a patient may experience throughout the course of their remaining life are captured. A systematic literature search identified a number of papers that modelled cost-effectiveness in an ACS population (see Section 6.1.2). A review of these papers showed that the approach of using a short-term decision tree followed by a Markov model was common (Karnon *et al*, 2006, Vergel *et al*, 2007, Henriksson *et al,* 2008). In addition, this approach has also been used by independent evidence review groups in the preparation of Health Technology Assessments commissioned by the Institute in the ACS arena (Glycoprotein IIb/IIIa Antagonists, 2002, TA80 Clopidogrel in NSTEMI, 2004). Based on this evidence, the model structure selected was deemed to be valid and appropriate to answer the decision problem.

Pivotal assumptions underlying the model/analysis:

- Adverse events are not modelled explicitly however both costs and health related quality of life decrements associated with all adverse events are still included in the analysis as they are part of the individual patient level data from the PLATO HECON sub-study that are used to estimate costs and QALYs for the different nodes of the short-term decision tree.
- It is assumed that adverse events such as bleeding and dyspnoea have no long-term prognostic impact beyond the duration of the clinical trial.
- No treatment effects were modelled beyond the one-year decision tree.
- The probability of having a non-fatal MI or non-fatal stroke at least one-year post the index ACS event is assumed to be constant at 3.15% and 1.02% respectively.

- The relative risk compared to standard UK life tables of dying at least one-year after having a subsequent MI is assumed to be the same as that of dying at least one year post the index ACS event.
- No discontinuations other than due to death are included in the model.

Cost effectiveness results

The results of the cost-effectiveness analysis are shown in the tables below. It can been seen that ticagrelor is highly cost-effective versus clopidogrel over the 40-year time horizon with a cost per LYG of £3,075 and a cost per QALY gained of £3,696.

Base-case results – cost per LYG (deterministic)

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

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

Estimated budget impact

The estimated annual budget impact for the NHS in England and Wales, in the first five years following the introduction of ticagrelor for the prevention of atherothrombotic events in adult patients with ACS is estimated at £2.9 in 2011 rising to £44.2m in 2015. Taking itnto account the cost of clopidogrel and the resource use saving, the net estimated annual budget impact for the NHS in England & Wales in 2011 is £1.6m in 2011, rising to £24.4m in 2015. Further details of the budget impact analysis can be found in Section C.

Conclusion

Ticagrelor offers potential substantial advances over the current standard of care. Unlike prasugrel it has demonstrated significant clinical advantages over clopidogrel across a broad spectrum of ACS patients, with no increase in major bleeding. Ticagrelor has a substantially favourable efficacy profile over clopidogrel, including a mortality benefit. Importantly, this benefit comes with a cost per QALY of £3,696, and provides the NHS with a new cost effective option for the treatment of ACS.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Generic name: Ticagrelor

Brand name: Brilique™

Approved name: Brilique 90 mg film-coated tablets.

Therapeutic class**:** Platelet aggregation inhibitors excluding heparin. ATC code: B01AC24 ticagrelor.

Ticagrelor was discovered and developed in the UK.

1.2 What is the principal mechanism of action of the technology?

Ticagrelor is a direct-acting $P2Y_{12}$ receptor antagonist that has a different mechanism of action than the thienopyridines. Ticagrelor, one of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines (CPTP), 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.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Marketing Authorisation via the European Centralised Procedure is pending. The European Medicines Agency (EMA) Committee for Medicinal Products for Human use (CHMP) adopted a positive opinion on 23rd September 2010. Marketing Authorisation is expected December 2010.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The European Public Assessment Report (EPAR) is anticipated at the time of Marketing Authorisation. Details on the main issues discussed by the regulatory authorities will be provided when this report is available.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The following is the indication for which the positive opinion has been adopted by the CHMP:

Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, 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 by-pass grafting (CABG).

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

No new studies are due to report within the next 12 months.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is estimated that ticagrelor will be commercially available in the UK end of December 2010 / early January 2011 depending on Marketing Authorisation.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

No

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

AstraZeneca are planning to submit to the Scottish Medicines Consortium (SMC) on 6th December 2010 with advice expected to be published on the SMC website in April 2011.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1.1: Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated tablet
Acquisition cost (excluding VAT)	The acquisition cost has not been finalised. For a 28 day pack an acquisition cost of £54.60 is anticipated.
Pack size	28 day
Method of administration	Oral
Doses	Ticagrelor treatment should be initiated with a single 180mg loading dose (two tablets of 90mg) and then continued at 90mg twice daily
Dosing frequency	Twice daily

Average length of a course of treatment	Up to 12 months
Average cost of a course of treatment	The acquisition cost has not been finalised. For a 28 day pack an acquisition cost of £54.60 is anticipated.
Anticipated average interval between courses of treatments	The anticipated use of ticagrelor is for a single course of treatment up to 12 months. Repeated courses are not anticipated.
Anticipated number of repeat courses of treatments	Not applicable - see above
Dose adjustments	No dose adjustments are required. This includes the elderly population and those with renal impairment or mild hepatic impairment

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Not applicable. There are no additional tests or investigations needed for the selection of patients for treatment.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No monitoring above usual clinical practice is required with ticagrelor.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Patients taking ticagrelor should also take aspirin daily unless specifically contraindicated. Following an initial dose of 300 mg of aspirin, ticagrelor should be used with a maintenance dose of 75-150 mg once a day of aspirin.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

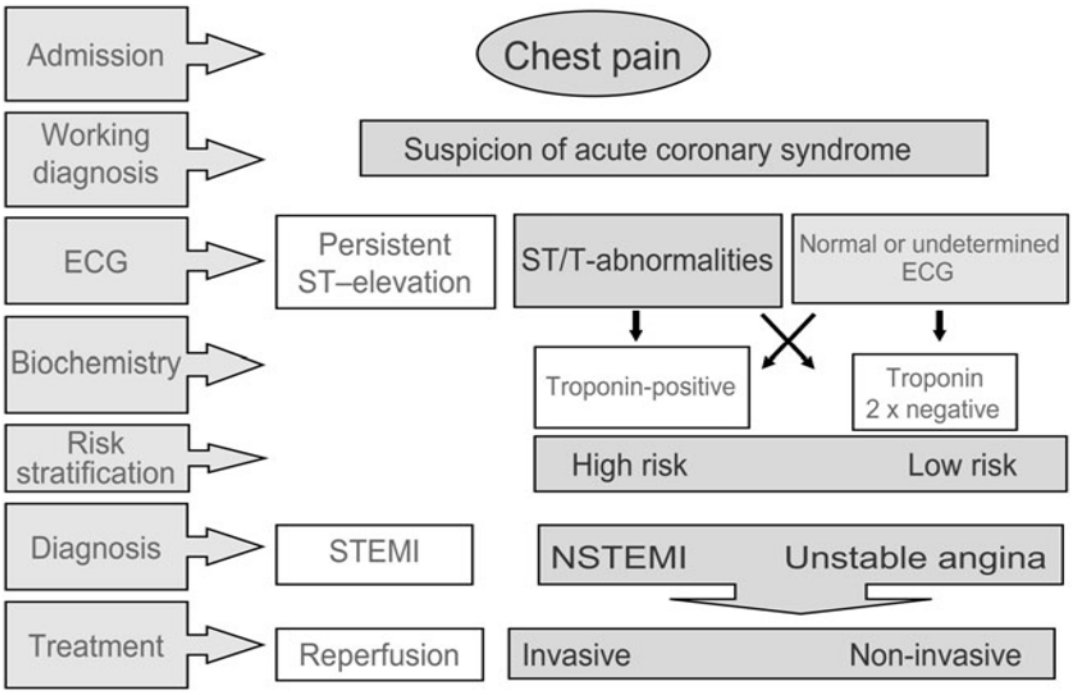
Acute coronary syndromes (ACS) including unstable angina (UA) and acute myocardial infarction (AMI) are a major cause of morbidity and mortality in the developed world (Taylor *et al.* 2007). In 2006/7 there were 70,000 cases of UA, and 113,000 cases of acute myocardial infarction (AMI) with 24,000 subsequent MIs in the UK (NICE scope: Ticagrelor for the treatment of ACS). It is estimated that there were approximately 146,000 hospital admissions with all ACS in England alone for the period 2008 to 2009 (Hospital Episode Statistics Online [HES] 2008-2009). ACS 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 (Scarborough *et al*. 2010).

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 (Arslanian *et al*. 2010, Dey *et al.* 2009, Hasin *et al*. 2009). In the UK, approximately 16% of patients with ACS die before admission to a hospital (Taylor *et al*. 2007). Early diagnosis and classification of the remaining patients determines 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 (Figure 1.1) (Bassand *et al.* 2007).

Figure 2.1: The spectrum of ACS (Bassand *et al.* 2007)



2.2 How many patients are assumed to be eligible? How is this figure derived?

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 (HES online 2009-2010). Up to date hospital episode statistics are not publicly available for Wales however, 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.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Summary details of NICE guidance are provided in Table 2.1.

Table 2.1: NICE Guidance

Title	Guidance Number	Publication Date	Indication	Recommendations
Health Technology Appraisal				
Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention	TA182	Oct-09	ACS	Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in the following patient groups - those with ACS having PCI, only when: • immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary **or** • stent thrombosis has occurred during clopidogrel treatment **or** • the patient has diabetes mellitus.
Clinical Guidelines				
Secondary prevention in primary and secondary care for patients following a myocardial infarction	CG48	May-07	NSTEMI STEMI	The guideline recommends that clopidogrel treatment (in combination with low-dose aspirin) should be continued for 12 months after the most recent acute episode of non-ST-segment-elevation ACS. Combination of aspirin and clopidogrel should be continued for at least 4 weeks after an ST-segment-elevation MI.
The early management of unstable angina and non-ST-segment elevation myocardial infarction	CG94	Mar -10	UA and NSTEMI	**Aspirin** The guidelines recommend than aspirin is offered to all patients unless contraindicated starting with a single 300 mg loading dose with treatment continued indefinitely. For patients with aspirin hypersensitivity clopidogrel monotherapy is suggested. **Clopidogrel** For clopidogrel treatment the guidelines recommend a 300 mg loading dose: • for patients with a predicted 6-month mortality of more than 1.5% and no contraindications (such as excessive bleeding risk) • for all patients with no contraindications who may undergo PCI within 24 hours of admission Continued treatment with the standard

Title	Guidance Number	Publication Date	Indication	Recommendations
				dose for 12 months is recommended. In CABG patients the guidelines recommend considering stopping clopidogrel five days* before CABG in patients with low risk and for patients at intermediate or higher risk, discussing continuation of clopidogrel before CABG with the cardiac surgeon and basing the decision on the balance of ischaemic and bleeding risk. **Glycoprotein IIb / IIIa Inhibitors** Eptifibatide or tirofiban are recommended for patients at intermediate or higher risk if angiography is schedules within 96 hours of admission. In addition the guidelines recommend consideration of abciximab as an adjunct to PCI for patients at intermediate to higher risk who are not already receiving a glycoprotein IIb/IIIa inhibitor.

*Five days is specified in the NICE guideline and varies from the SPC specified duration of seven days.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

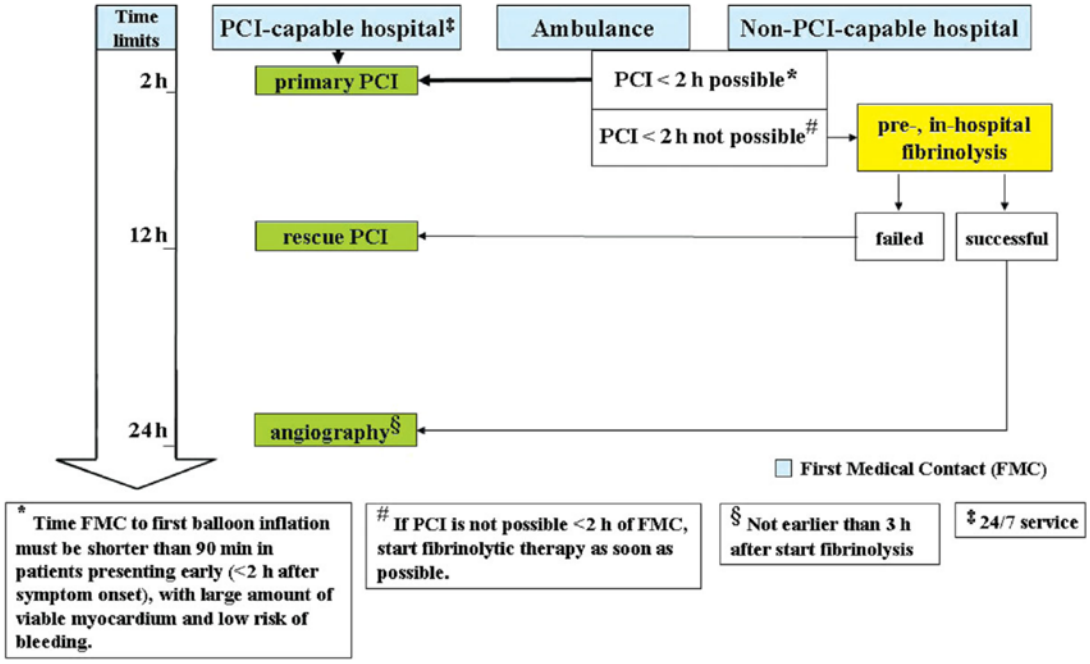
Of patients presenting with chest pain suspected to be ACS, the majority of patients are delivered to hospital from home or General Practice by the ambulance service. A small proportion of patients present directly to Accident and Emergency (A&E) departments.

Clinical pathway for patients with STEMI

Patients that have already been assessed by the paramedical team and found to have ECG changes consistent with STEMI are admitted directly to the cardiac unit/cardiac catheterisation labs. For these patients with confirmed STEMI within 12 hours of onset of symptoms, the recommendation is for immediate primary 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) (Figure 2.2) (Van der Werf *et al*. 2008). 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 therapy (Van der Werf *et al*. 2008).

Figure 2.2: Reperfusion strategies – thick arrows represent the preferred strategy (Van der *Werf et al.* 2008)



In 2008 there were 80,331 PCIs performed in the UK. Of these, 37.95% were in patients with NSTEMI, 16.31% were in patients with STEMI and nearly all of the remaining patients had stable disease (non - ACS) (44.38%) (BCIS Audit Returns 2008).

Clinical pathway for patients with NSTE-ACS (NSTEMI or UA)

For all patients admitted with NSTE–ACS, in line with the NICE guideline on UA and NSTEMI (NICE Clinical Guideline 94. March 2010) first-line treatment should include a single loading dose of aspirin and anticoagulation (e.g. heparin). For patients with hypersensitivity to aspirin, 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 (NICE Clinical Guideline 94. March 2010). Following initial treatment with aspirin antiplatelet therapy should be prescribed as described in Section 2.3.

Background to antiplatelet therapy

Antiplatelet therapy is an integral part of ACS care. Aspirin, a mainstay of current practice, irreversibly blocks platelet activation via inhibition of thromboxane synthesis. The substantial benefits of aspirin over placebo were demonstrated by the ISIS-2 (Second International Study of Infarct Survival 1988) study, which randomised 17,187 STEMI patients to streptokinase alone, aspirin alone, streptokinase plus aspirin, and placebo, with a mean follow-up of 15 months (ISIS-2 1988). Patients treated with aspirin alone had a 2.4% absolute risk reduction in vascular mortality compared to placebo at 5 weeks. The combination of aspirin plus streptokinase resulted in a 5.2% absolute risk reduction in 5-week vascular mortality compared to placebo.

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 (P2Y12), a mechanism distinct from aspirin. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study (Yusuf *et al.* 2001) studied 12,562 UA/NSTEMI patients presenting within 24 hours of symptom onset. All patients received aspirin and were randomised to either clopidogrel or placebo for 3 to 12 months. The primary endpoint, a composite of cardiovascular death, non-fatal myocardial infarction (MI) and stroke was significantly reduced from 11.4% to 9.3%, in patients receiving dual anti-platelet therapy ($p < 0.001$). Death from CV causes did not differ between the treatment groups. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7% vs. 2.7%, p=0.001).

Prasugrel differs from clopidogrel in its metabolism and activation, with greater potency and a faster onset of activity. In the TRITON-TIMI 38 (Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction 38) study (Wivott *et al.* 2007) prasugrel was significantly better than clopidogrel in improving the composite of death, nonfatal MI, and non-fatal stroke in 13,608 invasively managed ACS patients undergoing PCI – but this benefit came at the cost of significantly more major, life-threatening, and fatal bleeding complications, with no overall mortality benefit.

Ticagrelor

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 on the European Society Guidelines for invasively managed patients with NSTE-ACS and STEMI although it is not currently approved in any jurisdiction (Wijns *et al.* 2010).

Ticagrelor has been studied in a large randomised controlled clinical trial (PLATO) that enrolled all adult ACS patient types (STEMI, NSTEMI and UA) including a UK population without restriction on the treatment option (PCI, CABG, medically managed etc.). Consequently, the indication for ticagrelor will reflect clinical practice in the UK (see Section 1.5).

In the PLATO study compared to clopidogrel in combination with aspirin ticagrelor in combination with aspirin demonstrated superior efficacy in reducing the event rate of the primary endpoint cardiovascular death, MI or stroke without increasing the risk of major or fatal bleeding.

The introduction of ticagrelor will not result in any change to the existing pathway for the management of the ACS patient. It does however have the potential to significantly improve outcomes for all patients regardless of management strategy.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

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.

- Clopidogrel is indicated for both NSTEMI and STEMI, but for STEMI it is only indicated for medically treated patients eligible for thrombolytic therapy (Plavix SPC 2010) 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. Consideration of these factors adds an additional level of complexity to the prescribing decision making process.

Even with the current standard of care (i.e. dual antiplatelet therapy with clopidogrel and aspirin) serious CV events recur, most of them within months of the index ACS event (Wiviott *et al.* 2007). Furthermore, the GRACE (Global Registry of Acute Coronary Events) study showed that the five-year morbidity and mortality are just as high in patients with non-STEMI and UA as those with STEMI (Fox *et al*. 2010). To date, the increasing efficacy of anti-platelet therapy has been closely mirrored by an increased risk of bleeding. There remains a need for anti-platelet therapy that provides greater efficacy in terms of improved cardiovascular mortality over current treatments preferably without an increased risk of serious bleeding. Compared with clopidogrel, prasugrel has a more consistent and pronounced inhibitory effect on platelets, resulting in a lower risk of myocardial infarction and stent thrombosis but is associated with a higher risk of major and fatal bleeding in patients with an acute coronary syndrome who are undergoing PCI (Wiviott *et al.* 2007). Clopidogrel has only demonstrated a reduction in all cause mortality in a single 45,000 STEMI patient study performed mostly in China (Chen *et al.* 2005) (see Section 2.4). There are also potential limitations with clopidogrel given its well described inter-individual pharmacodynamic variability with up to 30% of patients having an attenuated anti-platelet response (e.g. non-responders) (Angiolillo *et al.* 2007).

The high risk ACS setting requires rapid intervention with effective antiplatelet therapy as soon as possible after a patient presents with an ACS event. The therapeutic decision needs to be made rapidly and often before final classification of the ACS event. This

classification can be delayed especially when distinguishing between UA and NSTEMI where a blood test for troponin levels is required (NICE Clinical Guideline 94. March 2010).

Unlike clopidogrel and prasugrel, ticagrelor does not require metabolic activation. Ticagrelor has a rapid onset of action compared with clopidogrel (30 minutes vs. approximately 2 hours) (Gurbel *et al*. 2009). In addition ticagrelor is the first reversibly-binding oral ADP receptor antagonist.

2.6 Please identify the main comparator(s) and justify their selection.

The main comparator is clopidogrel with aspirin, the current standard of care in ACS. This is the comparator used in the pivotal ticagrelor trial (PLATO) and represents the majority of antiplatelet therapy use. In addition clopidogrel is use in a similar broad ACS population to that studied in PLATO.

Prasugrel is also used in clinical practice in line with recent NICE guidance (NICE Technology Appraisals Guidance 182. October 2009 see Section 2.3) for a narrow group of patients. [redacted] In response to the NICE scope requirements and decision problem for this appraisal ticagrelor will be compared with both clopidogrel and prasugrel.

Comparison with prasugrel will be via an indirect comparison (Biondi-Zoccai *et al.* 2010). There are, to date, no direct head-to-head outcomes-based comparisons of prasugrel and ticagrelor. There are however a number of issues with the published indirect comparison of ticagrelor plus aspirin with prasugrel plus aspirin and the results cannot be regarded as clinically credible. The indirect comparison is provided solely at the request of NICE and in response to the NICE scope and decision problem. Further details are provided in Section 5.7.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

No specific treatments are required to manage adverse reactions associated with ticagrelor treatment. The nature of an adverse reaction, clinical assessment and physician preference will guide any prescribing decisions.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

It is proposed that ticagrelor and aspirin will be a superior treatment option to clopidogrel and aspirin in an already established ACS treatment pathway.

Ticagrelor, co-administered with aspirin will be initiated in secondary care by cardiologists, interventional cardiologists and physicians in A&E. There is also the possibility that it could be initiated by paramedics in the ambulance setting. After discharge from hospital, subsequent doses of ticagrelor will be prescribed in primary care for a period of up to 12 months unless discontinuation is clinically indicated. Renal function should be checked after

one month and thereafter according to routine medical practice. This monitoring will not however, involve any additional tests or costs and will be entirely consistent with usual clinical practice in ACS patients.

See section 6.5 for further details on costings.

2.9 Does the technology require additional infrastructure to be put in place?

No

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

Not applicable.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

Not applicable.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable.

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Patients presenting with ACS irrespective of whether they have undergone revascularisation	Patients presenting with ACS irrespective of whether they have undergone revascularisation	
Intervention	Ticagrelor plus aspirin	Ticagrelor plus aspirin	
Comparator(s)	For people who are to be managed with PCI: • Clopidogrel plus aspirin • Prasugrel plus aspirin For people who are not to be managed with PCI: • Clopidogrel plus aspirin	For all ACS patients including those medically managed and those to be managed with PCI (as per the full PLATO population). • Clopidogrel plus aspirin Data on the following subgroups: STEMI, NSTEMI and UA will also be presented. For people who are to be managed with PCI: • Prasugrel plus aspirin	The PLATO study included a broad spectrum ACS patient population with no distinction made between those UA and 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 an invasive strategy and 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, myocardial infarction or stroke. Secondary endpoints include: incidences of myocardial infarction alone, vascular death alone, stroke alone, stent

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			thrombosis, and death from any cause. <u>Outcomes which will not be considered</u> 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 whilst for patients with NSTEMI or UA it was left to the investigators discretion 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 quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Cost 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	
Subgroups to be	If the evidence allows the following	Results will be presented for each of the	

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
considered	subgroups will be considered: people with unstable angina, NSTEMI and STEMI	subgroups specified in the scope.	
Special considerations, including issues related to equity or equality	Not applicable	Not applicable	Not applicable

Section B – Clinical and cost effectiveness

5 Clinical evidence

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

Relevant clinical data were identified by means of a Medline search using the keywords 'ticagrelor' and 'AZD6140', with the following limits 'clinical trial' and 'humans'. 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.

5.2 Study selection

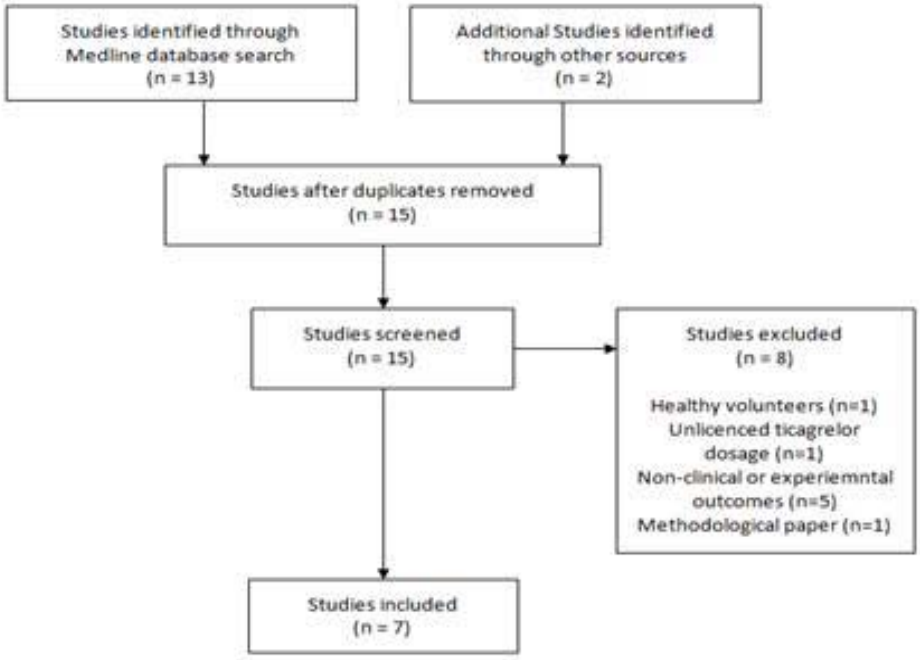
5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table 5.1: Eligibility criteria used in search strategy

	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

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Figure 5.1: Flow diagram depicting the study selection process



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

PLATO is the main phase III study (Wallentin *et al*. 2009). Six of the studies (PLATO-INVASIVE, PLATO-MEDICAL, PLATO-STEMI, PLATO-DIABETES, PLATO-GENETICS and PLATO-CABG) sub-analyses of the main phase are also included (see Section 5.3.7).

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group.

PLATO compares ticagrelor plus aspirin with clopidogrel plus aspirin in patients with ACS (Table 5.2)

Table 5.2: Phase III RCT included in the document

Trial name	Study of Platelet Inhibition and Patient Outcomes (PLATO)
Intervention	Ticagrelor
Comparator	Clopidogrel
Population	Adult patients with acute coronary syndrome
Study reference	Wallentin *et al*. New Eng. J. Med. 2009; 361(11): 1045-1057

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

PLATO compares ticagrelor with the most appropriate comparator, clopidogrel. Clopidogrel is currently the only oral anti-platelet agent with an indication in ACS similar to that submitted for ticagrelor – the treatment of patients with STEMI, NSTEMI and UA, managed via PCI, CABG or through medical intervention only, for 12 months.

The study which is most relevant to the decision problem is the PLATO study. PLATO compared ticagrelor (180 mg loading dose, 90 mg BD thereafter) with clopidogrel (300 or 600 mg loading dose, 75mg thereafter) in 18,624 patients with acute coronary syndromes (STEMI, NSTEMI and UA, managed medically or via PCI/CABG) over a 12 month period.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

The studies identified in the literature but excluded from further discussion are either experimental or Phase I or Phase II studies employing unlicensed doses of ticagrelor and/or unlicensed patient populations and/or report non-clinical endpoints.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

No evidence of this type has been included for consideration

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table 5.3: Summary of methodology for PLATO (Wallentin *et al.* 2009)

Trial	**PLATO**
Location	Worldwide, multi-centre 18 UK centres recruited patients
Design	Randomised, double-blind, double-dummy parallel group, phase III study
Duration of study	12 months
Method of randomisation	Computer generated blocks of numbers, blinded to the investigators (1:1)
Method of blinding (care provider, patient and outcome assessor)	Double-blind (patient and investigator)
Intervention(s) (n=9,333) and comparator(s) (n=9,291)	Ticagrelor (180 mg loading dose, 90 mg twice daily (bid) thereafter, n=9,333) versus clopidogrel (300 or 600 mg loading dose, 75 mg once daily (od) thereafter, n=9,291)
Primary outcomes (including scoring methods and timings of assessments)	Time to first occurrence of composite of death from vascular causes, myocardial infarction or stroke. Endpoint events were independently adjudicated.
Secondary outcomes (including scoring methods and timings of assessments)	The first prespecified secondary endpoint was the primary endpoint in patients for whom early invasive management was planned at randomisation. Additional secondary endpoints (analysed for the entire study population) were; • The composite of death from any cause, myocardial infarction and stroke • The composite of death from vascular causes, myocardial infarction, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischaemic transient ischaemic attack or other arterial thrombotic events • Myocardial infarction alone • Death from vascular causes alone • Stroke alone • Death from any cause
Duration of follow-up	Minimum 6 months Maximum 12 months

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table 5.4: Eligibility criteria for PLATO (Wallentin *et al.* 2009)*

Inclusion criteria	Exclusion criteria
• Patients hospitalised for an acute coronary syndrome, with ST-segment elevation or new LBBB during the previous 24 hours • Patients hospitalised without ST-segment elevation during the previous 24 hours with at least two of the following three criteria; 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)	Main exclusion criteria were; any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 hours before randomisation, a need for oral anticoagulation therapy, an increased risk of bradycardia without an implanted pacemaker, and concomitant therapy with a strong cytochrome P450 3A inhibitor or inducer

*Adapted from the Pharmaceutical Benefits Advisory Committee (PBAC) (2008).Guidelines for preparing submission to the PBAC (Version 4.30. Canberra PBAC)

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 5.5: Baseline characteristics of participants in the PLATO study (Wallentin *et al.* 2009)

Characteristic	Ticagrelor Group (n=9,333)	Clopidogrel Group (n=9,291)
Median age, yr	62.0	62.0
Age ≥75 yr, %	15.0	16.0
Female Sex, %	28.4	28.3
Median Body Weight, kg	80.0	80.0
Body Weight < 60kg, %	7.0	7.1
Median BMI	27	27
Race, %		
White	91.8	91.6
Black	1.2	1.2
Asian	5.8	6.0
Other	1.2	1.2
Cardiovascular Risk Factor, %		
Habitual Smoker	36.0	35.7
Hypertension	65.8	65.1
Dyslipidaemia	46.6	46.7
Diabetes Mellitus	24.9	25.1
Other Medical History, %		
MI	20.4	20.7
PCI	13.6	13.1
CABG	5.7	6.2
Congestive Heart Failure	5.5	5.8
Nonhaemorrhagic Stroke	3.8	4.0
Peripheral Arterial Disease	6.1	6.2
Chronic Renal Disease	4.1	4.4
History of Dyspnoea	15.1	14.6
COPD	5.9	5.7
Asthma	2.9	2.9
Gout	2.9	2.8
Positive Troponin I Test at Study Entry, %	85.3	86.1
Final Diagnosis of ACS, %		
STEMI	37.5	38.0
NSTEMI	42.9	42.5
Unstable Angina	16.6	16.8
Other / Missing Data	3.0	2.7

Outcomes

5.3.5 ***Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).***

Table 5.6: PLATO primary and secondary outcomes (Wallentin *et al*. 2009)

Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Time to first event of composite of death from vascular causes, myocardial infarction or stroke	All clinical endpoints were assessed by an independent adjudicator, blinded to the treatment allocation. This endpoint is directly relevant to clinical practice.	The first prespecified secondary endpoint was the primary endpoint in patients for whom early invasive management was planned at randomisation. Additional secondary endpoints (analysed for the entire study population) were; • The composite of death from any cause, myocardial infarction to stroke • The composite of death from vascular causes, myocardial infarction, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischaemic transient ischaemic attack or other arterial thrombotic events • Myocardial infarction alone • Death from vascular causes alone • Stroke alone • Death from any cause	All clinical endpoints were assessed by an independent adjudication committee blinded to the treatment allocation These endpoints are directly relevant to clinical practice.

Statistical analysis and definition of study groups

5.3.6 ***State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including***

censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table 5.7: Summary of statistical analyses (Wallentin *et al.* 2009)

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PLATO	Ticagrelor is superior to clopidogrel in reducing the primary endpoint	Hypothesis testing was conducted at the nominal significance level of 4.97% (2 tailed) in order to account for a planned interim analysis after 1200 events. To address the issue of multiple testing, a hierarchical test sequence was planned. The secondary efficacy endpoints were tested individually, in the order in which they are listed in the document, until the first non-significant difference was found between the two treatment groups. Thereafter, other treatment comparisons were examined in an exploratory manner and interpreted descriptively, with p values reported as showing nominal significance. The consistency of effects on efficacy and safety end points was explored in 25 pre-specified subgroups and 8 post hoc subgroups, without adjustment for multiple comparisons which adjusts the significance level at the final analysis for one interim analysis. The primary analysis compared the time from randomisation to the first occurrence of any event in the composite endpoint using the Cox proportional hazards model with a factor for treatment group.	1780 events were needed to detect with 90% power a relative risk reduction of 13.5% in favour of ticagrelor. The event rate in the clopidogrel arm was estimated to be 11% at 12 months, giving a sample size of approximately 18,000.	All patients randomised to a treatment group were included in the intention to treat analysis. Patients were to be followed for events through to the end of their planned participation regardless of whether they remained on study medication. Event times on patient who withdrew consent or were lost to follow-up were censored at the time of last contact.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Six subgroup analyses of the PLATO study are included in the discussion of the clinical studies:

- PLATO-INVASIVE analysis (Cannon *et al.* 2010). PLATO INVASIVE was a pre-specified analysis of the main PLATO study and includes only those patients identified at randomisation with investigator intent for early invasive management.

- PLATO-MEDICAL analysis (James *et al* 2010). PLATO MEDICAL was a pre-specified exploratory analysis of the main PLATO study and includes only those patients identified at randomisation with investigator intent for non-invasive medical management

- PLATO-STEMI analysis (Steg *et al*. 2009, Steg *et al.* 2010) a pre-specified exploratory analysis

- PLATO-DIABETES analysis (James *et al.* 2010) a pre-specified subgroup analysis.

- The PLATO-GENETICS (Wallentin *et al*. 2010) and PLATO-CABG (Held *et al.* 2009) analyses both post-hoc analyses.

Details of each study are provided in Table 5.8.

Table 5.8: Subgroup analyses of the PLATO study

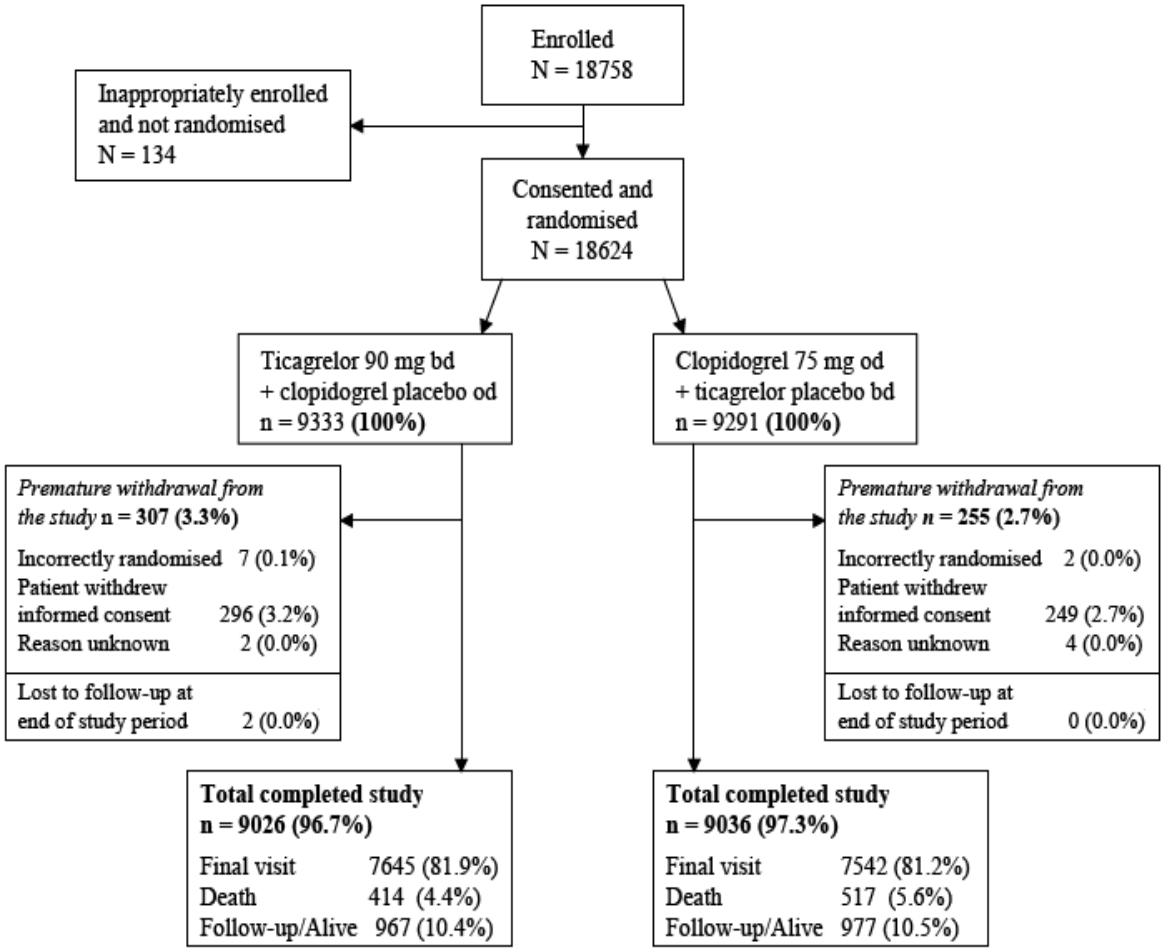
Trial	Intervention	Comparator	Population	Primary study ref.
PLATO-INVASIVE	Ticagrelor	Clopidogrel	Acute coronary syndrome – includes only those patients identified at randomisation with investigator intent for early invasive management	Cannon *et al*. Lancet 2010; 375(9711): 283-293
PLATO-MEDICAL	Ticagrelor	Clopidogrel	Acute coronary syndrome – includes only those patients identified at randomisation with investigator intent for non-invasive medical management	James *et al* 2010. Presentation at European Society of Cardiology Congress 2010 – unpublished at time of submission
PLATO-STEMI	Ticagrelor	Clopidogrel	Patients with a diagnosis of ST-elevation MI (STEMI) within the PLATO study	Steg *at al*. Circulation 2010. DOI: 10.1161/CIRCULATIONAHA.109.927582 Steg *et al.* 2009. Presentation at the American Heart Association Congress 2009 – unpublished at time of submission.
PLATO-DIABETES	Ticagrelor	Clopidogrel	Acute coronary syndrome patients within the PLATO study analysed according to diagnosis of diabetes	James *et al*. European Heart Journal 2010; In Press: doi:10.1093/eurheartj/ehq325
PLATO-GENETICS	Ticagrelor	Clopidogrel	Acute coronary syndrome patients	Wallentin *et al.* Lancet 2010; In Press:

Trial	Intervention	Comparator	Population	Primary study ref.
			within the PLATO study analysed according to presence of genetic polymorphisms hypothesized to influence the efficacy of clopidogrel	DOI:10.1016/S0140-6736(10)61274-3
PLATO-CABG	Ticagrelor	Clopidogrel	Acute coronary syndrome undergoing CABG during the study period and stopping study medication ≤ 7 days before surgery	Held *et al.* 2009. Presentation at American Heart Association Meeting 2009 – unpublished at time of submission

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 5.2: Flow chart depicting the patient flow within the PLATO study
:



5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- ***Was the method used to generate random allocations adequate?***
- ***Was the allocation adequately concealed?***
- ***Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?***
- ***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)?***
- ***Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?***
- ***Is there any evidence to suggest that the authors measured more outcomes than they reported?***
- ***Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?***

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 5.9: PLATO Quality assessment results

Trial	
Was randomisation carried out appropriately?	Yes Subjects 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
Was the concealment of treatment allocation adequate?	Yes

Trial	
	The treatment allocation was by interactive voice response system
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes The baseline characteristics were reported to be similar in both treatment groups (see Section 5.5)
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes Subjects, investigators and site personnel were blinded
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes All patients who had been randomly assigned to a treatment group were included in the intent-to-treat analysis

5.5 Results of the relevant RCTs

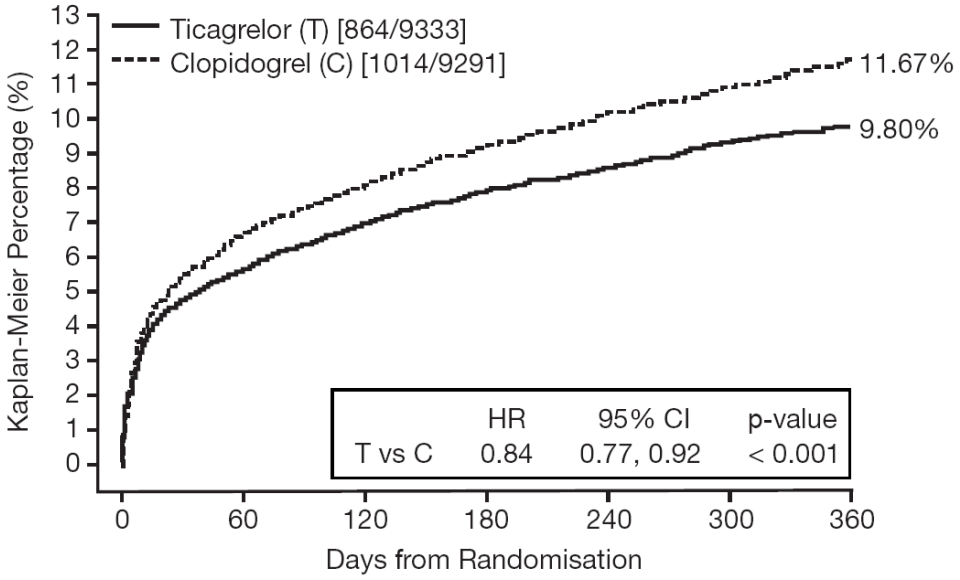
5.5.1 PLATO Study Results

All data are reported on an intention-to-treat (ITT) basis from the full study population (all patients randomised to one of the two treatment arms) (n=18,624; ticagrelor n=9333; clopidogrel, n=9291).

Primary Endpoint

The primary endpoint, time to the first occurrence of the 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 occurred with an event rate of 9.8% per year in the ticagrelor treatment group compared to 11.7% per year in the clopidogrel treatment group. This constitutes an absolute risk reduction (ARR) of 1.9% and a statistically significant relative risk reduction (RRR) of 16%, (HR [95%CI]) =0.84 [0.77-0.92], p<0.001) (Figure 5.3) (Wallentin *et al*. 2009).

Figure 5.3: Kaplan-Meier plot for the primary endpoint of the PLATO study* (adapted from Wallentin *et al*. 2009*)



N at risk							
T	9333	8628	8460	8219	6743	5161	4147
C	9291	8521	8362	8124	6650	5096	4047

Secondary Endpoints

The secondary endpoints of the PLATO study are listed in table 5.10. When the individual components of the primary endpoint (incidence of MI, death from vascular causes and stroke) are considered individually, it can be seen that the reduction in the primary endpoint was driven by approximately equal, statistically significant reductions in the incidence of MI and death from vascular causes. There was no apparent effect observed on the rate of stroke at one year (Table 5.10).

MI occurred with an event rate of 5.8% per year in the ticagrelor treatment group compared to 6.9% per year in the clopidogrel treatment group. This constitutes an absolute risk reduction (ARR) of 0.9% and a relative risk reduction (RRR) of 16%, (HR [95%CI] = 0.84 [0.75-0.95], p=0.005) (Table 5.10).

Death from vascular causes occurred with an event rate of 4.0% per year in the ticagrelor treatment group compared to 5.1% per year in the clopidogrel treatment group (ARR at one year 1.1%, RRR 21%, HR [95%CI] = 0.79 [0.69-0.91], p=0.001) (Table 5.10).

There was no effect observed on the rate of stroke at one year (Table 5.10)

Table 5.10: Efficacy endpoints from the PLATO study (Wallentin *et al.* 2009)

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
Other events — no./total no. (%)				
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Death from causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08

‡‡ Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy end points.

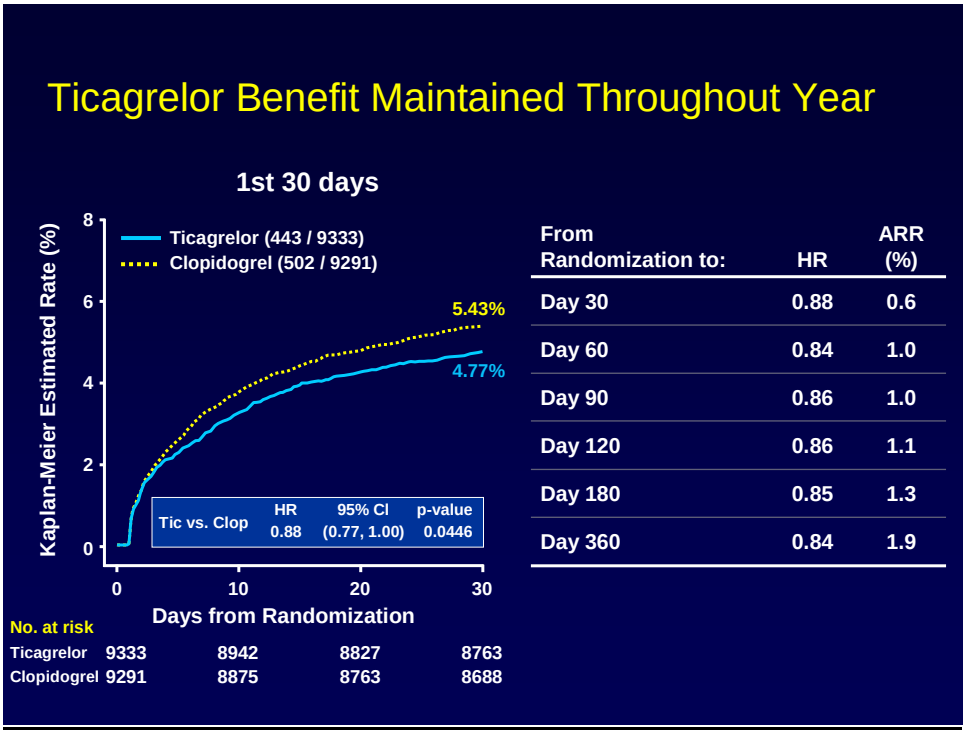
An exploratory analysis of total mortality identified a lower incidence in the ticagrelor arm of the study. Death from any cause occurred with an event rate of 4.5% per year in the ticagrelor treatment group compared to 5.9% in the clopidogrel treatment group (ARR at one year 1.4%, RRR 22%, HR [95%CI]) = 0.78 [0.69-0.89], nominal p <0.001 (Table 5.10).

An exploratory analysis on the rate of definite stent thrombosis was undertaken in the 11,289 patients who received a stent during the study. The rate of definite stent thrombosis at one year (Academic Research Consortium defined) was lower in the ticagrelor group than in the clopidogrel group (1.3% vs. 1.9% respectively, HR [95%CI] = 0.67 (0.50–0.91), nominal p = 0.009)(Wallentin *et al.* 2009).

Additional Endpoint Analyses

An additional analysis of the primary efficacy composite examined the incidence of primary composite events for increasing durations of time in the trial (Figure 5.4). Early benefits are observed within the first 30 days of ticagrelor treatment compared with clopidogrel (ARR at 30 days 0.6%). For patients who have received treatment for 360 days the ARR increases to 1.9%. The benefit is maintained over time with an RRR over the entire duration of the study around 16%.

Figure 5.4: Efficacy of ticagrelor over time (AstraZeneca Core Presentation FDA meeting of the Cardiovascular and Renal Drugs Advisory Committee. 28 July 2010)

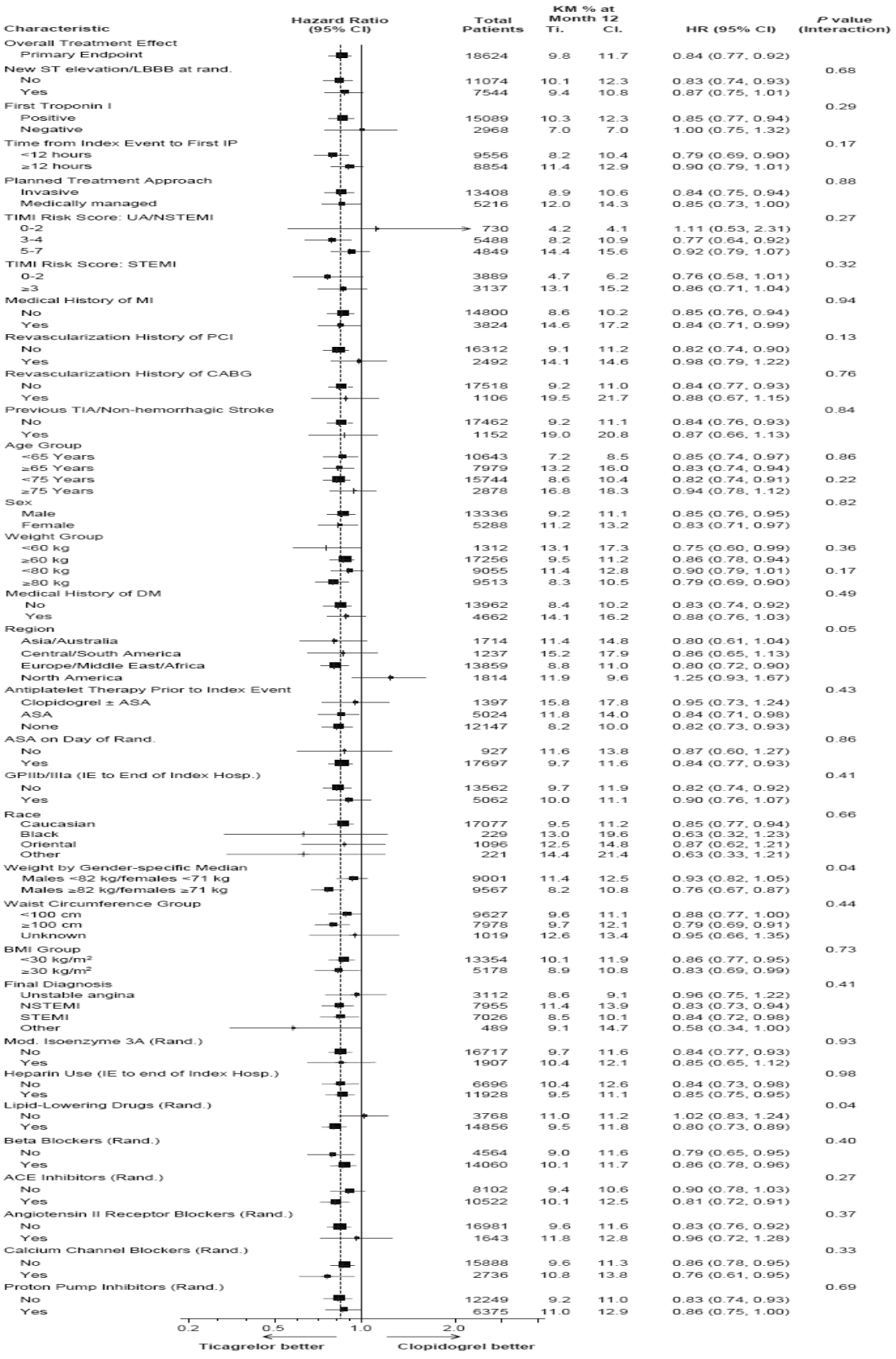


Pre-defined analysis of the primary endpoint

A pre-defined analysis of the primary endpoint was also made in specific subgroups of patients, identified according to a number of coronary criteria (Figure 5.5).

Treatment interaction significance levels of less than 0.05 occurred in three groups, geographic region, body weight above or below gender-specific median, and use of lipid-lowering drugs at randomisation (Figure 5.5). For the primary efficacy outcome treatment did not vary for other tested groups, including by presentation with or without a persistent ST-segment elevation or LBBB (interaction p = 0.68) by positive or negative troponin I (Interaction p = 0.29) or by final diagnosis category (interaction p=0.41) (Figure 5.5).

Figure 5.5: Hazard ratios and rates of primary endpoint in predefined subgroups of the PLATO study *(Wallentin* et al. *2009)*



5.5.2 Subgroup Analyses from the PLATO Study

PLATO-INVASIVE

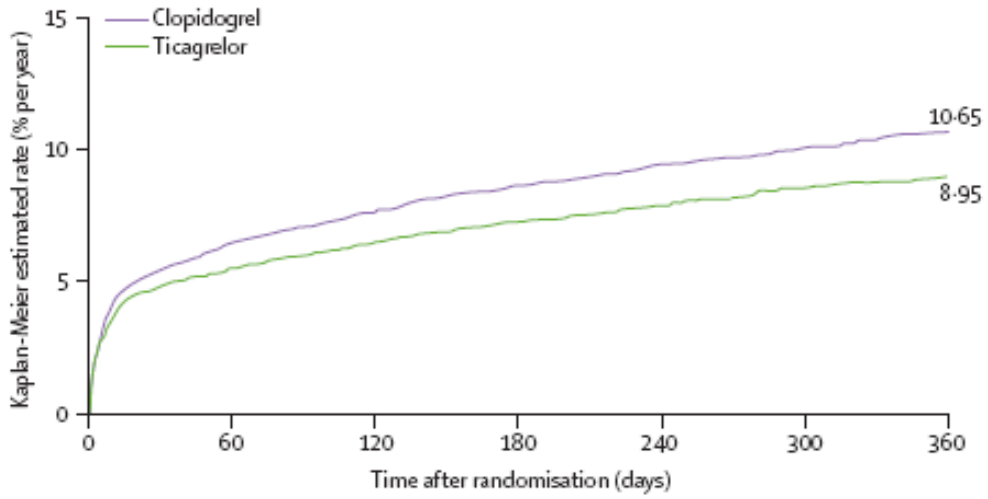
A pre-specified analysis from the PLATO study was an assessment of the effect of ticagrelor on the incidence of primary endpoint events in patients identified at randomisation with investigator intent for early invasive strategy (early angiography) (72% of the study population). This analysis has been published as a separate publication (PLATO-INVASIVE, Cannon *et al*. 2010).

Primary Endpoint

The primary endpoint, the time to the first occurrence of the composite of death from vascular causes, MI and stroke, occurred with an event rate of 9.0% per year in the ticagrelor treatment group compared to 10.7% per year in the clopidogrel treatment group (Figure 5.6) (Table 5.11).

This constitutes an ARR at one year of 1.7% and a statistically significant RRR of 16% (HR [95%CI] = 0.84 [0.75-0.94], p=0.0025) (Figure 5.6).

Figure 5.6: Kaplan-Meier plot for the primary endpoint (Cannon *et al.* 2010)



Number at risk							
Clopidogrel	6676	6129	6034	5881	4815	3680	2965
Ticagrelor	6732	6236	6134	5972	4889	3735	3048

Secondary Endpoints

When these components are considered individually, it can be seen that, as with the full PLATO study results, the reduction in the primary endpoint of the INVASIVE study was driven by approximately equal reductions in the incidence of MI and death from vascular causes (Table 5.11). There was no effect observed on the rate of stroke at one year (Table 5.11).

In addition, in patients with a treatment strategy of planned invasive management ticagrelor treatment results in a RRR of 16% (ARR at one year 1.8%) for the

composite efficacy endpoint of all-cause mortality/MI /stroke and a significant RRR of 15% (ARR at one year 2.2%) for the composite efficacy endpoint CV death/total MI/stroke/severe recurrent ischaemia, recurrent ischaemia/TIA (Table 5.11).

Table 5.11: Primary and secondary efficacy endpoints from the PLATO-INVASIVE study (Cannon *et al.* 2010)

	Ticagrelor (n=6732)	Clopidogrel (n=6676)	Hazard ratio (95% CI)	p value
Primary efficacy endpoint				
Cardiovascular death+myocardial infarction*+stroke	569 (9·0%)	668 (10·7%)	0·84 (0·75–0·94)	0·0025
Secondary efficacy endpoint				
All-cause death+myocardial infarction*+stroke	595 (9·4%)	701 (11·2%)	0·84 (0·75–0·94)	0·0016
Cardiovascular death+myocardial infarction+ stroke+severe recurrent cardiac ischaemia+ recurrent cardiac ischaemia+transient ischaemic attack+other arterial thrombotic event	830 (13·1%)	964 (15·3%)	0·85 (0·77–0·93)	0·0005
Myocardial infarction*	328 (5·3%)	406 (6·6%)	0·80 (0·69–0·92)	0·0023
Cardiovascular death	221 (3·4%)	269 (4·3%)	0·82 (0·68–0·98)	0·0250
Stroke	75 (1·2%)	69 (1·1%)	1·08 (0·78–1·50)	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
All-cause death	252 (3·9%)	311 (5·0%)	0·81 (0·68–0·95)	0·0103

The secondary endpoint of total mortality was also reduced in the ticagrelor arm of the study. Death from any cause occurred with an event rate of 3.9% per year in the ticagrelor treatment group compared to 5.0% per year in the clopidogrel treatment group (ARR at one year 1.1%, RRR 19%, HR [95%CI]) = 0.78 [0.68-0.95], nominal p=0.0103) (Table 5.11).

PLATO-MEDICAL (Non Invasive)

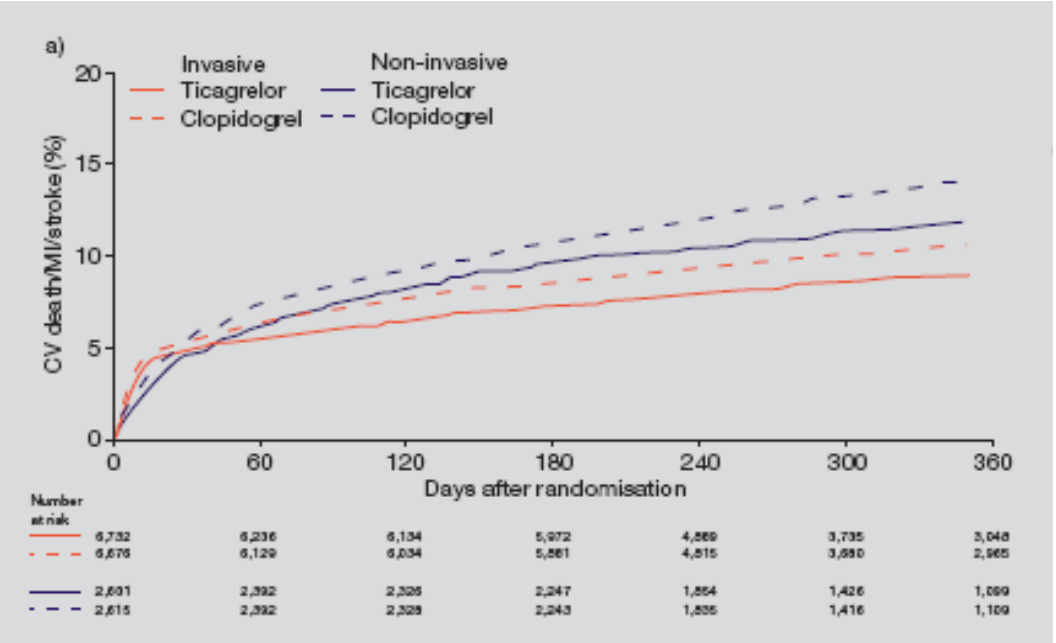
The PLATO-MEDICAL data set is an as yet unpublished sub-analysis (James *et al*. presentation presented at the ESC 2010) from the PLATO study, which comprises the 28% of the PLATO study population which did not fall into the INVASIVE analysis previously presented in this section i.e. those patients identified at randomisation with investigator intent for an early conservative strategy (no early angiography unless recurrent symptoms or ischemia) (n=5216).

Primary Endpoint

The primary endpoint, the time to the first occurrence of the composite of death from vascular causes, MI and stroke, occurred with an event rate of 12.0% per year in the ticagrelor treatment group compared to 14.3% per year in the clopidogrel treatment group.

This constitutes an absolute risk reduction of 2.3% and a relative risk reduction of 15% (HR [95%CI] = 0.85 [0.73-1.00], nominal p=0.045) (Figure 5.7).

Figure 5.7: Kaplan-Meier plot for the primary endpoint (PLATO-MEDICAL data set compared to the PLATO-INVASIVE analysis) (James *et al*. 2010)



Non-invasive = PLATO-MEDICAL

Secondary Endpoints

The individual components of the primary endpoint (incidence of MI, death from vascular causes and stroke) are considered individually. The reduction in the primary endpoint of the PLATO-MEDICAL data set was driven by a reduction in the incidence of death from vascular causes (Table 5.12). These results are in line with those seen for the full PLATO study population.

Table 5.12: Primary and key secondary endpoints from the PLATO - MEDICAL study (James *et al.* 2010)

	Ticagrelor (90 mg bd) (n=2,601)		Clopidogrel (75 mg od) (n=2,615)		Hazard ratio (95% CI)	p-value
	Patients with Events	KM (%/year)	Patients with Events	KM (%/year)		
Composite of CV Death / MI / Stroke	295 (11.3%)	12.0%	346 (13.2%)	14.3%	0.85 (0.73-1.00)	0.04
MI	176 (6.8%)	7.2%	187 (7.2%)	7.8%	0.94 (0.77-1.15)	0.555
CV Death	132 (5.1%)	5.5%	173 (6.6%)	7.2%	0.76 (0.61-0.96)	0.019
Stroke	50 (1.9%)	2.1%	37 (1.4%)	1.7%	1.35 (0.89-2.07)	0.1616

An exploratory analysis of total mortality demonstrated that this was also reduced in the ticagrelor arm of the study. Death from any cause occurred with an event rate of 6.1% per year in the ticagrelor treatment group compared to 8.2% per year in the clopidogrel treatment group. This constitutes an absolute risk reduction of 2.1% and a relative risk reduction of 25% (HR [95%CI]) = 0.75 [0.61-0.93], nominal p=0.010) (James *et al*. 2010).

Although patients in this sub-group were initially assigned to a non-invasive medical treatment strategy at randomisation, these patients may have subsequently required angiography and revascularisation because of recurrent symptoms or ischemia if their treating physician deemed this necessary.

In the subgroup of patients intended for an initial non-invasive management strategy, 3948 (76%) did not actually undergo in-hospital revascularization with PCI or CABG. In these conservatively managed patients who did not undergo in-hospital revascularization, the incidence of primary composite outcomes (CV death/MI/stroke) was 12.2% in the ticagrelor group and 15.2% in the clopidogrel group (HR = 0.81 [95% CI 0.68-0.97]) (James *et al.* 2010).

PLATO-STEMI

The PLATO-STEMI data set is a pre-defined sub-analysis which comprises the 7,544 patients within the PLATO study population who presented with STEMI or LBBB and had planned primary PCI. These patients are in the midst of an acute intracoronary thrombosis and require urgent and effective blockade of the $P2Y_{12}$ platelet receptor.

Results for this study have recently been published (Steg *et al*. 2010) reporting on 7,544 patients with a diagnosis of STEMI at presentation. The primary endpoint, the time to the first occurrence of the composite of death from vascular causes, MI and stroke, occurred with an event rate of 9.4% per year in the ticagrelor treatment group compared to 10.8% per year in the clopidogrel treatment group (ARR at one year 1.4%, RRR 13%, HR [95%CI] = 0.87 [0.75-1.01]) (Steg *et al.* 2010).

In addition to this publication a separate oral presentation was given at the American Heart Association Congress in 2009 (Steg *et al.* 2009) on the outcomes for patients from the PLATO study that had either LBBB or STEMI at presentation or a final diagnosis of STEMI (n=8430 patients). The primary endpoint, the time to the first occurrence of the composite of death from vascular causes, MI and stroke, 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 [95%CI] = 0.85 [0.74-0.97], nominal p=0.02).

PLATO-CABG

The PLATO-CABG data set was a post-hoc analysis undertaken to examine the primary and secondary endpoints of the PLATO study in a subset of patients who underwent CABG during the 12 month study period and who stopped study medication ≤ 7 days prior to surgery (n=1261) (Held *et al.* 2010). Predicting which patients will require CABG in the ACS setting can be difficult. It is however recommended that patients with ACS receive dual antiplatelet therapy at the time of presentation to reduce their risk of fatal ischaemic events.

The primary endpoint, the time to the first occurrence of the composite of death from vascular causes, MI and stroke occurred with an event rate of 10.6% per year in the ticagrelor treatment group compared to 13.1% per year in the clopidogrel treatment group (ARR 2.5%, RRR 16%, HR [95%CI] = 0.84 [0.60-1.16], nominal p=0.29) which was comparable in magnitude to the reduction observed in the full study population (Held *et al.* 2010).

PLATO-DIABETES

The PLATO-DIABETES analysis was a pre-specified sub-group analysis undertaken to examine the primary endpoint of the PLATO study stratified according to presence or absence of a diagnosis of diabetes (James *et al.* 2010). Patients with diabetes mellitus and ACS have a high risk of recurrent CV events and death, and these patients have been known to demonstrate higher platelet reactivity and poorer clinical outcomes compared to non diabetic patients.

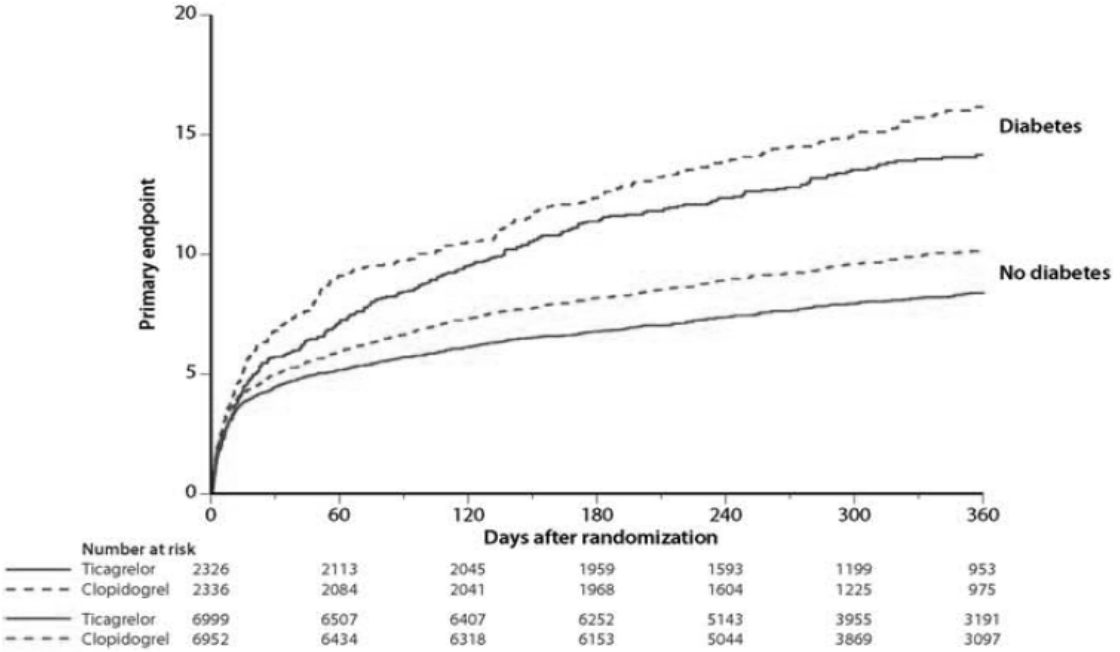
In total 4,662 patients within the PLATO study population had a pre-existing diagnosis of diabetes, (25% of the study population), including 1036 patients on insulin. 13,951 patients did not have a diagnosis of diabetes.

In patients with a diagnosis of diabetes, the primary endpoint, the time to the first occurrence of the composite of death from vascular causes, MI and stroke, occurred with an event rate of 14.1% per year in the ticagrelor treatment group compared to 16.2% per year in the clopidogrel treatment group (ARR at one year 2.1%, RRR 12%, (HR [95%CI] = 0.88 [0.76-1.03]) (Figure 5.8) (James *et al.* 2010).

In patients with no diagnosis of diabetes, the primary endpoint occurred with an event rate of 8.4% per year in the ticagrelor treatment group compared to 10.2% per year in the clopidogrel treatment group. This constitutes an absolute risk reduction of 1.8% and a relative risk reduction of 17% (HR [95%CI] = 0.83 [0.74-0.93]) (Figure 5.8) (James *et al.* 2010).

The magnitude of the reduction in the primary endpoint by ticagrelor for each subgroup was consistent with that of the main study population and was not affected by diabetes status (p for interaction = 0.49).

Figure 5.8: Kaplan-Meier plot for the primary endpoint: PLATO-DIABETES analysis (James *et al.* 2010)



PLATO-GENETICS

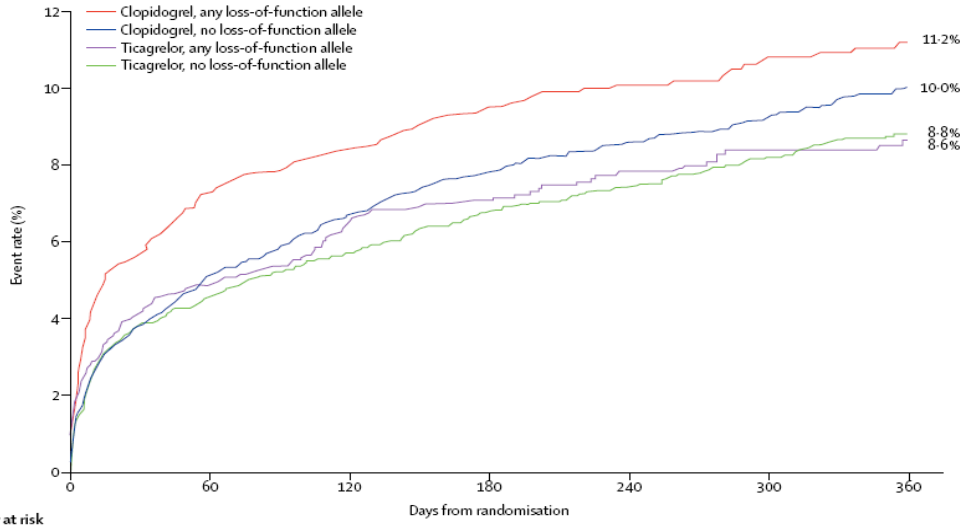
The PLATO-GENETICS analysis was an additional pre-specified analysis undertaken to examine the primary endpoint of the PLATO study stratified according to presence or absence of a number of polymorphisms of the gene encoding CYP2C19, one of the enzymes responsible for the bio-activation of clopidogrel (Wallentin *et al.* 2010). The CYP2C19 genotype is an important determinant of the pharmacokinetic and pharmacodynamic response to clopidogrel. Prior work demonstrates that in patients treated with clopidogrel after an ACS, event or stenting, or both, the presence of any loss-of-function CYP2C19 allele is associated with an increased risk of ischaemic events and stent thrombosis.

In total 10,285 patients consented to give a blood sample for genetic analysis and patient demographics were well balanced between groups. In patients carrying any of the known loss-of-function CYP2C19 alleles, the primary efficacy composite endpoint occurred at a rate of 8.6% per year for patients randomized to ticagrelor compared to 11.2% per year for those randomised to clopidogrel (ARR at one year 2.6%, RRR 23% HR [95% CI] = 0.77 [0·60–0·99], p=0.0380) (Figure 5.9) (Wallentin *et al.* 2010).

In patients not carrying loss-of-function CYP2C19 alleles, the time to the first occurrence of the composite of death from vascular causes, MI and stroke, occurred with an event rate of 8.8% per year in the ticagrelor treatment group compared to 10.0% per year in the clopidogrel treatment group (ARR at one year 1.2%, RRR 14%, HR [95%CI] = 0.86 [0.74-1.01], p= 0.0608) (Figure 5.9) (Wallentin *et al.* 2010).

The magnitude of the reduction in the primary endpoint by ticagrelor was consistent with the main study population and was not affected by CYP2C19 gene expression (p for interaction = 0.46).

Figure 5.9: Kaplan-Meier plot for the primary endpoint of the PLATO-GENETICS analysis (Wallentin *et al.* 2010)



Number at risk							
Clopidogrel							
Any loss-of-function allele	1388	1275	1259	1226	1027	801	658
No loss-of-function allele	3516	3321	3256	3186	2691	2123	1757
Ticagrelor							
Any loss-of-function allele	1384	1305	1274	1250	1053	834	683
No loss-of-function allele	3554	3352	3301	3222	2718	2127	1761

Summary

The incidence of the primary endpoint (time to first MI, CV death stroke) in the full PLATO study and the above sub-groups is displayed in Table 5.13.

Table 5.13: Incidence of the primary endpoint (time to first MI, CV death, stroke) in the PLATO study relative to the sub-group analyses

	Ticagrelor Group (K-M %/year)	**Clopidogrel Group (K-M %/year)**	**Hazard Ratio (95% CI)**
PLATO (Wallentin *et al*. 2009)	9.8	11.7	0.84 (0.77–0.92)
PLATO-INVASIVE (Cannon *et al*. 2010)	9.0	10.7	0.84 (0.75-0.97)
PLATO-MEDICAL (James *et al.* 2010)	12.0	14.3	0.85 (0.73-1.00)
PLATO-STEMI (Steg *et al*. 2010)	9.4	10.8	0.87 (0.75-1.01)
PLATO-CABG (Held *et al.* 2010)	10.6	13.1	0.84 (0.60-1.16)
PLATO-DIABETES (James *et al.* 2010) No diabetes Diabetes	 8.4 14.1	 10.2 16.2	 0.83 (0.74-0.93) 0.88 (0.76-1.03)
PLATO-GENETICS (Wallentin *et al.* 2010) No CYP2C19 loss-of-function CYP2C19 allele Any CYP2C19 loss-of-function CYP2C19 allele	 8.8 8.6	 10.0 11.2	 0.86 (0.74-1.01) 0.77 (0.60-0.99)

5.6 Meta-analysis

There is only one phase III randomised controlled trial available for ticagrelor. The PLATO trial has been previously discussed earlier in Section 5.

5.7 Indirect and mixed treatment comparisons

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

The treatments to be compared with ticagrelor, as described in the decision problem, are clopidogrel and prasugrel. As the PLATO trial only includes ticagrelor and clopidogrel it was necessary to identify trials with prasugrel for the treatment of ACS. The systematic review was conducted in such a manner that the possibility of trials comparing any two of the three treatments would be identified. For the systematic review, the following bibliographic databases were searched for papers and abstracts as of 9th April 2010 with no time restrictions:

- Cochrane Central Register of Controlled Trials (CENTRAL) using the Cochrane Library's online clinical trials search;
- Excerpta Medica Database (EMBASE) using OVID;
- Index Medicus database (MEDLINE) using OVID.

The search strategy was tailored to comply with the searching functionality of each database, but all included terms related to ACS and the treatments under consideration, ticagrelor, clopidogrel and prasugrel. In order to limit the search results to RCTs (studies with a design that minimises bias), a strategy based on the highly sensitive method from the Cochrane Handbook for Systematic Reviews of Interventions was used to identify RCTs in MEDLINE. A similar strategy was employed for EMBASE. No such strategy was necessary for CENTRAL, since it is a database that is restricted to RCTs. In addition, because the CENTRAL database includes the results of hand searches relevant to the subject area, further hand searching was considered unlikely to be of benefit. The systematic review was limited to English-language publications.

The search strategies and results from each database are shown in Appendix 4, Section 9.4.4.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

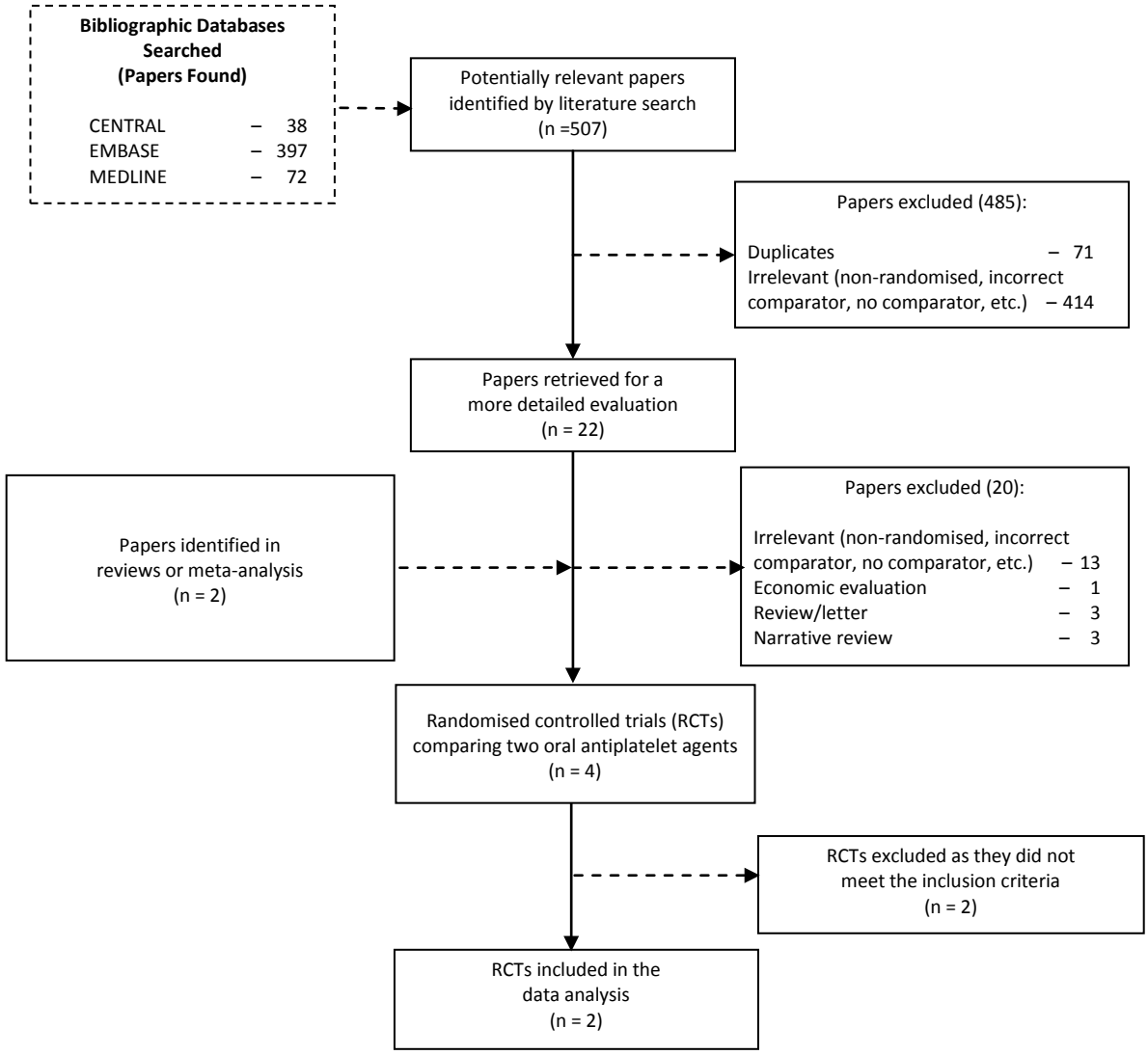
To be eligible for consideration as an input into the analysis, a trial needed to:

- be a randomised controlled trial;
- include a direct comparison of ticagrelor with prasugrel (co-administered with aspirin) *OR* include a comparison of one of the two treatments with clopidogrel co-administered with aspirin (note: the protocol for the systematic review was written with the prior assumption that there is no head-to-head data, but in the event that such data were identified by the literature search, a traditional pairwise meta-analysis could have been conducted in addition to an adjusted indirect comparison);
- involve ACS patients undergoing an invasive procedure during their initial hospital admission;
- report at least one case of an outcome of interest for health economic modelling.

These inclusion and exclusion criteria are also provided in Appendix 4, Section 9.4.6.

Results from the search strategy are presented in Figure 5.10. Of the 507 trials identified, four of them met the inclusion criteria for an adjusted indirect comparison. However, two trials were excluded due to inappropriate dosing (DISPERSE 2 (Cannon *et al.* 2007), where patients received twice daily ticagrelor 90mg or ticagrelor 180mg compared with 300mg loading dose clopidogrel plus 75mg once daily) and/or having a short duration (DISPERSE 2 and JUMBO TIMI-26 [Wiviott *et al.* 2005]) the latter of which compared three doses of prasugrel with clopidogrel for 30 days with TIMI major plus minor bleeds as the primary end point).

Figure 5.10: Flowchart of trials in the systematic review.



The two remaining trials are PLATO (Wallentin *et al.* 2009) and TRITON-TIMI 38 (Wiviott *et al.* 2007). Critical appraisals of PLATO and TRITON TIMI-38 have been provided in Appendix 5, Section 9.5.1.

There are general similarities between TRITON-TIMI 38 and PLATO – both trials were conducted in an ACS population, using a clopidogrel comparator and the same composite primary efficacy endpoint. There are, however, some very important differences between these two studies that make an indirect comparison of the relative benefits of prasugrel over clopidogrel (in TRITON-TIMI 38) and ticagrelor over clopidogrel (in PLATO) – and, inferentially, prasugrel versus ticagrelor – highly problematic and potentially inappropriate. The major differences between the TRITON and PLATO study populations and protocols are summarised in Tables 5.14 and 5.15, and Figures 5.11 and 5.12, and discussed below.

Differences in target population

One of the key differences between TRITON-TIMI 38 and PLATO is the target population. TRITON-TIMI 38 was a PCI study which enrolled invasively managed ACS patients, and required that non-STEMI ACS patients have their anatomy defined prior to randomisation. Recruitment was restricted to patients whose anatomy was viewed as amenable to PCI. It did not include an initial medical management cohort, and did not include patients in whom CABG was the primary means of revascularisation. Randomisation was on the catheterisation table, immediately prior to planned PCI. In contrast, PLATO targeted a broad spectrum of ACS patients (UA, NSTEMI, STEMI) identified early after presentation, and required that the investigators prespecify as to whether they were intended for initial invasive management or initial medical management. It has been estimated that PLATO patients make up about 72% of patients in the ACTION registry (FDA Advisory Committee Briefing Document, 2010). In the Swedish ACS Registry (RIKS-HIA), which includes all patients admitted to Swedish coronary care units, 64% of patients from 1998-2005 (n=205,269) and 79% of patients from 2007 (n=24,695) met PLATO inclusion criteria (Stenestrand *et al.* 2010).

One subgroup that, at first glance, might seem to better lend itself to an indirect comparison are the STEMI cohorts of TRITON-TIMI 38 and PLATO (Montalescot *et al*. 2009; Steg *et al.* 2010). Unfortunately the STEMI subgroup in TRITON-TIMI 38 is a combination of patients undergoing primary PCI (n=2438) and STEMI patients who underwent PCI > 12 hours after the onset of symptoms ("secondary PCI"; n=1094). In contrast, all of the PLATO STEMI cohort were intended for primary PCI. Aside from very top-line results in the primary publication of the TRITON STEMI cohort, few data are available on the TRITON-TIMI 38 STEMI primary PCI subset (Montalescot *et al*. 2009) Moreover, in TRITON-TIMI 38 STEMI patients undergoing primary PCI (in whom prompt platelet inhibition could be very clinically important), clopidogrel was administered on the catheterisation table (with prior clopidogrel use excluded) in approximately two-thirds of the cases.

Differences in clopidogrel loading

Another key difference between TRITON-TIMI 38 and PLATO was the timing of clopidogrel loading and the doses of clopidogrel used. These differences have potential major implications because the dosing and timing of clopidogrel are of paramount importance to the efficacy of the "standard" against which a new form of therapy is judged. In general, results from the two trials that did not employ the same dosing and timing of clopidogrel administration in their 'control' arms should not really be compared. The timing of the 300 mg clopidogrel load in TRITON-TIMI 38 is problematic since prior clopidogrel use was excluded: in the overall TRITON-TIMI 38 study population 25% of patients received their loading dose on the catheterisation table before insertion of the first coronary guidewire; 74% received their loading dose in the time interval from after guidewire insertion up until 1 hour after the PCI procedure; 1% received their loading dose more than 1 hour after PCI (Wiviott *et al.* 2007).

In contrast, in PLATO, patients received clopidogrel much earlier in their hospital course. Additionally, approximately 46% of patients received open-label clopidogrel (including a load) prior to randomisation; patients in the clopidogrel control arm received their study 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 (Wallentin *et al.* 2009). In addition, PLATO allowed for more contemporary clopidogrel loading doses of 600 mg in the control arm – 19.6% of clopidogrel-treated patients in the overall PLATO cohort (Wallentin *et al.* 2009), 26.8% in the cohort intended for invasive management (Cannon *et al* 2010), and 38.6% in the STEMI cohort (Steg *et al.* 2010) received a load of 600 mg or greater of clopidogrel. In contrast, all of the clopidogrel-treated patients in TRITON-TIMI 38 received a 300 mg load (Wiviott *et al.* 2007). A clinical endpoint that would also be potentially differentially affected by low procedural degrees of platelet inhibition (if clopidogrel were given at the time of guidewire placement instead of before the procedure) is stent thrombosis. Consequently, the divergent clopidogrel timing and dosing between TRITON-TIMI 38 and PLATO may have differentially affected clinical subgroups (STEMI – 26% of the TRITON-TIMI 38 population; 40% of the PLATO population) and endpoints (stent thrombosis) that would be most sensitive to the degree of acute procedural platelet inhibition.

Differences in MI assessment

The assessment of peri-procedural MIs is challenging when patients come rapidly to the catheterisation laboratory, especially if they already have positive enzymatic markers at admission. This issue becomes especially important when examining outcomes in TRITON and PLATO, because the timing of PCI was so different in the two studies. The availability of only one pre-procedure enzyme measurement (as was true in PLATO, but not the case in TRITON-TIMI 38), made it much more difficult to detect a subsequent MI in the setting of a pre-existing enzyme elevation from the index event (present in 80% of the PLATO population); MI events that might otherwise have been picked up without pre-existing enzyme elevations would be missed. In TRITON-TIMI 38, by contrast, (excluding the STEMI Primary PCI cohort) there was generally time for at least two pre-procedure enzyme measurements, and MI adjudication was much less confounded by the index event. An additional direct consequence of the high percentage of PCI in TRITON-TIMI 38 is the much greater representation of enzymatic MIs (of much less certain clinical significance) in the TRITON-TIMI 38 adverse outcome events by which prasugrel was judged to be superior to clopidogrel. In TRITON-TIMI 38, almost half of the “MI”s were purely enzymatic events (triggered for adjudication by lab values only), while in PLATO less than 20% of all MIs were purely enzymatic events (FDA Advisory Committee Briefing Document, 2009; FDA Advisory Committee Briefing Document, 2010; Serebruany. 2010).

Table 5.14: Key inclusion features in TRITON-TIMI 38 and PLATO.

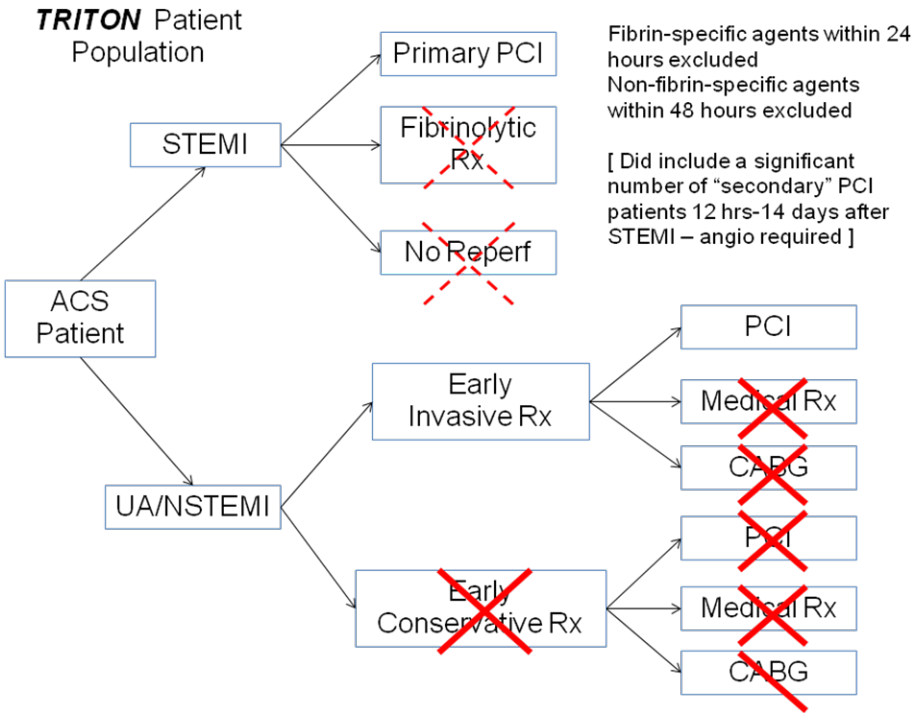
TRITON-TIMI 38 **(n=13,608)**	**PLATO** **(n=18,624)**
ACS patients with scheduled PCI (STEMI and NSTEMI strata)	Patients hospitalised for ACS with or without ST-segment elevation and onset of symptoms within the previous 24 hours
STEMI Within 12 hours if primary PCI planned Within 14 days of medical Rx for STEMI	**STEMI** ST elevation of 0.1 mm in 2 contiguous leads or new LBBB Intention to perform primary PCI
NSTEMI Symptoms lasting 10 minutes occurring within past 72 hours Either ST-segment deviation (1 mm) or elevated cardiac biomarker TIMI Risk Score $\geq$ 3 Age $\geq$ 65 Known CAD (stenosis $\geq$ 50%) Severe angina ($\geq$ 2 episodes in last 24 hrs) ST changes $\geq$ 0.5 mm (+) cardiac markers $\geq$ 3 risk factors (+) family history HTN Elevated cholesterol DM Current smoker	**NSTEMI** Two-thirds of: ischemic ST changes (+) cardiac biomarker Clinical risk factors Age $\geq$ 60 Previous MI or CABG CAD ($\geq$50% stenosis) in 2 vessels Previous cerebrovascular disease Stroke TIA Carotid stenosis $\geq$ 50% Hx cerebral revascularisation DM PAD Chronic renal dysfunction CrCl < 60 ml/min/1.73 m^2 BSA
Patients who had received any thienopyridine within 5 days prior to enrollment were **excluded**	Prior thienopyridine use was **allowed**

Table 5.15: Comparison of the TRITON-TIMI 38 and PLATO trials

	TRITON-TIMI 38	PLATO
N	13,608	18,624
Study population	Early invasively managed ACS scheduled for PCI (Including STEMI and STEMI patients undergoing same admission PCI) Symptom onset within past 72 hours	Broad ACS population (including STEMI) Symptom onset within past 24 hours
Prior clopidogrel	Excluded	Allowed (including in-hospital Rx prior to randomisation)
% STEMI	Capped at 26% (18% undergoing primary PCI)	40.5% (all intended for primary PCI)
Clopidogrel load	Only 300 mg allowed	300 or 600 mg
Timing of randomisation	**Later** After angiography After decision to perform PCI	**Earlier** Usually before angiography (if done)
Randomisation	Prasugrel 60 mg load 10 mg qd Or Clopidogrel 300 mg load 75 mg qd	Ticagrelor 180 mg load 90 mg BID Or Clopidogrel 300 – 600 mg load 75 mg qd
Administration of study drug	Started in the time interval from randomisation up to one hour after PCI	Started immediately after randomisation
Primary efficacy endpoint	CV death/MI/stroke	CV death/MI/stroke
Primary safety endpoint	Non-CABG TIMI major bleeding	PLATO major bleeding
PCI	99% (all at randomisation)	61% (49% within 24 hours of randomisation)
CABG	3.2% (0.35% on primary admission)	10.2% (4.5% on primary admission)
Only medical management (no revascularisation performed)	1.1%	34%
Glycoprotein IIb/IIIa use	54%	27%
Follow up	Up to 15 months	Up to 12 months

Figure 5.11: Comparison of the TRITON-TIMI 38 patient population (A) and the PLATO patient population (B) as seen within the overall context of ACS management.

A



B

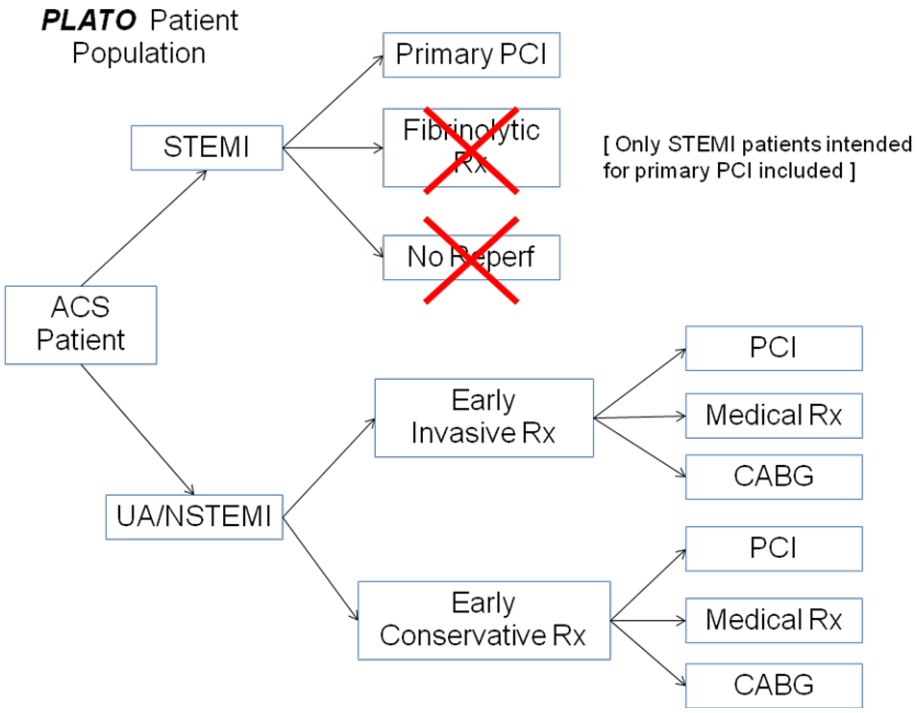
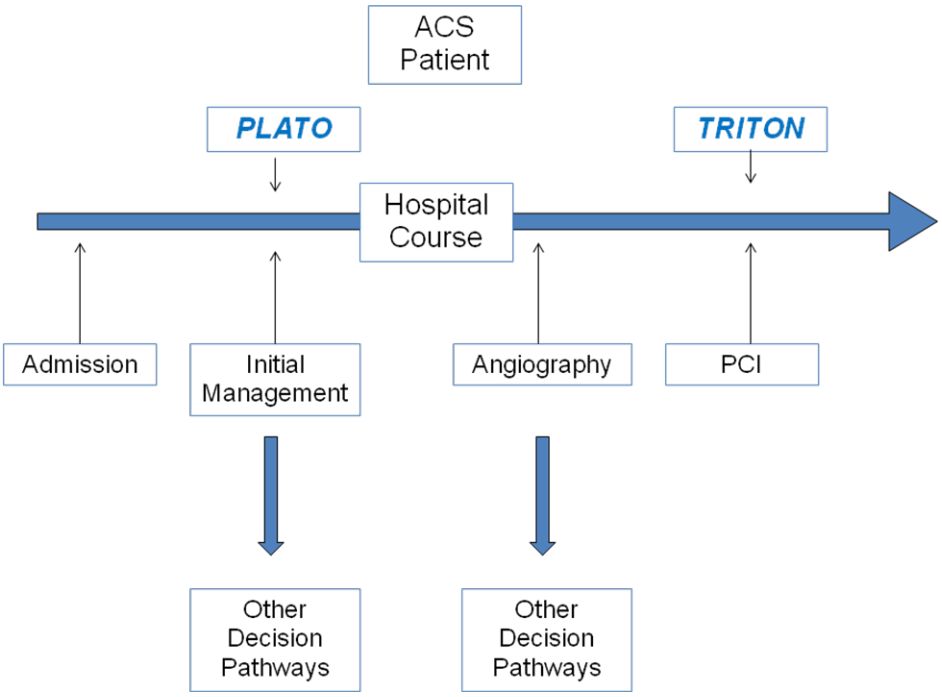


Figure 5.12: Contrasting the times of randomisation in PLATO and TRITON-TIMI 38. Randomisation in TRITON occurred much later in the management pathway, after angiography and a decision to proceed with PCI.



In the previous discussion we have highlighted the inappropriateness of an indirect comparison of relative benefit of prasugrel and ticagrelor. In the absence of any direct head-to-head comparisons, however, a health economic assessment of ticagrelor in relation to prasugrel is necessary to determine where ticagrelor fits in to the existing therapeutic armamentarium. There are two pieces of evidence synthesis currently published, one which looks at the so-called "new" P2Y12 inhibitors (including prasugrel, ticagrelor, cangrelor and elinogrel (Bellemain-Appaix *et al*. 2010), and one which is an indirect comparison of prasugrel and ticagrelor, based on TRITON and PLATO (Biondi-Zoccai *et al.* 2010). Whilst AstraZeneca does not endorse such a comparative clinical approach based on TRITON-TIMI 38 and PLATO (for all the reasons noted above), we have used this one published indirect comparison for health economic modelling purposes.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison.

Table 5.16: Summary of the trials used in the published indirect comparison, conducted by an independent group, from which results for health economic modelling were taken (Biondi-Zoccai *et al*. *2010)*

No. trials	References of trials	Ticagrelor	Clopidogrel	Prasugrel
1	Wallentin 2009	✓	✓	-
1	Wiviott 2007	-	✓	✓
Adapted from Caldwell *et al*. Simultaneous comparison of multiple treatments combining direct and indirect evidence. *BMJ* 2005; 331: 897-900.				

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

Not applicable – the results in Section 5.7.6 are taken from a published indirect comparison conducted by an independent group (Biondi-Zoccai *et al.* 2010).

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable – the results in Section 5.7.6 are taken from a published indirect comparison conducted by an independent group (Biondi-Zoccai *et al.* 2010).

5.7.6 Please present the results of the analysis.

The results – presented in Table 5.17 – are based on a published indirect comparison conducted by an independent group (Biondi-Zoccai *et al.* 2010)The results presented in the paper were odds ratios where values <1 favour prasugrel. However, the health economic model (described in Section 6) was designed to receive as inputs relative risks where values <1 favour ticagrelor. Therefore, the results from the publication were converted in a two-stage process. In the first stage, reciprocals were taken to reverse the direction. In the second stage, the following formula from the *Cochrane Handbook* was used to convert odds ratios into relative risks (control risks were taken to be the absolute event rates in the prasugrel arm of TRITON-TIMI 38):

$$\text{Relative risk} = \frac{\text{Odds ratio}}{1 - (\text{Control risk} * (1 - \text{Odds ratio}))}$$

Table 5.17: Conversion of results from Biondi-Zoccai *et al.* 2010 into desired format for health economic modelling.

Outcome	Values from Biondi-Zoccai et al. 2010			Inversed values (so that <1 favours ticagrelor)			Control risk (prasugrel)	Converted to relative risk (using Cochrane Handbook)		
	Odds ratio	95% lower	95% upper	Odds ratio	95% lower	95% upper		Relative risk	95% lower	95% upper
Primary endpoint	0.987	0.861	1.133	1.01	0.88	1.16	0.099	1.01	0.89	1.14
MI	0.893	0.75	1.062	1.12	0.94	1.33	0.073	1.11	0.95	1.30
Stroke	0.856	0.55	1.331	1.17	0.75	1.82	0.01	1.17	0.75	1.80
All-cause mortality	1.218	0.959	1.546	0.82	0.65	1.04	0.03	0.83	0.65	1.04
Stent thrombosis	0.635	0.433	0.932	1.57	1.07	2.31	0.011	1.56	1.07	2.28
Major bleeding	1.431	1.103	1.858	0.70	0.54	0.91	0.025	0.70	0.54	0.91
Minor bleeding	1.073	0.794	1.451	0.93	0.69	1.26	0.02	0.93	0.69	1.25

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable – the results in Section 5.7.6 are taken from a published indirect comparison conducted by an independent group (Biondi-Zoccai *et al.* 2010).

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable

5.8 Non-RCT evidence

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used

and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendice 6 and 7.

Not applicable

5.9 Adverse events

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in section 9.8 and 9.9, appendices 8 and 9.

Not applicable

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

PLATO Safety Results

Bleeding constitutes the most common, clinically significant safety concern during effective anti-platelet treatment. The PLATO study therefore included specific safety objectives to evaluate the bleeding profile of ticagrelor compared to clopidogrel. PLATO-defined 'Total Major' bleeding was the key safety endpoint; the time to first occurrence of any total 'Major' bleeding event was the key safety variable (Wallentin *et al.* 2009).

All safety data are reported on the safety analysis population, and analysed according to treatment received (all patients randomised to one of the two treatment arms, and receiving at least 1 dose of that study medication) (Total n=18,421, n=9235 for ticagrelor, n=9186 for clopidogrel).

The PLATO study employed a novel method for categorisation of bleeding events. 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 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. Bleeding events reported in PLATO were also mapped onto the TIMI scale by applying an algorithm to the bleeding events. Approximate comparison

between bleeding events assessed by the PLATO and TIMI criteria are displayed in Figure 5.13.

Figure 5.13: Schematic representation of the PLATO bleeding definitions alongside the equivalent TIMI definitions (Rao *et al*. 1988, James *et al*. 2009)

TIMI [Rao 1988:A]	PLATO [James 2009:B]
Major	***Major (fatal/life-threatening)***
Fatal/life-threatening (related to instrumentation, spontaneous, trauma)	Fatal
ICH	ICH
↓ >5 g/dL hemoglobin	↓ ≥5 g/dL hemoglobin
↓ 15% absolute hematocrit	≥4 unit transfusion
	Hypotension requiring pressors or surgery; intrapericardial with tamponade; hypovolemic shock
	Other Major
	Substantially disabling (eg, intraocular with permanent vision loss)
	2-3 unit transfusion
	↓ 3-5 g/dL hemoglobin
Minor	***Minor***
Observed blood loss: clinically overt sign of hemorrhage with ↓hemoglobin 3-5 g/dL or >10% decrease in hematocrit* **No observed blood loss:** ↓hemoglobin ≥4 g/dL or 12% decrease in hematocrit	Requires medical intervention to stop or treat bleeding
Minimal	***Minimal***
Clinically overt sign of hemorrhage with ↓hemoglobin <3 g/dL or <9% decrease in hematocrit	All others not requiring intervention (eg, bruising, bleeding gums, oozing from injection sites, etc)

17

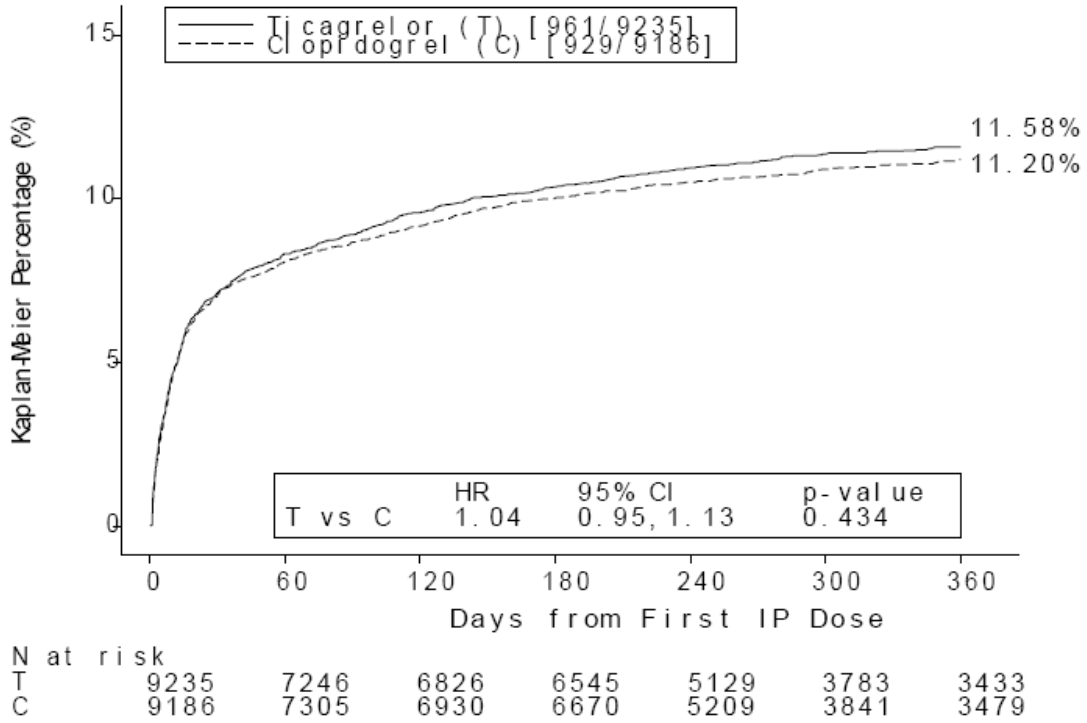
*TIMI minor bleeding resembles PLATO major bleeding by haemoglobin drop

Primary Safety Endpoint

The primary safety endpoint within the PLATO study was the time to first major PLATO bleeding event, which as can be seen from the table above comprises the subsets 'Major Fatal/Life threatening' and 'Major Other' categories.

There was no overall significant difference in the primary safety endpoint between the ticagrelor and clopidogrel arms of the study (Figure 5.14). The primary safety endpoint, time to first major PLATO defined bleed occurred with an event rate of 11.6% per year in the ticagrelor treatment group compared to 11.2% per year in the clopidogrel treatment group (absolute risk increase of 0.4%, relative risk increase of 4%, HR [95%CI]) = 1.04 [0.95-1.13], p=0.43 (Wallentin *et al.* 2009).

Figure 5.14: Kaplan-Meier plot for the primary safety endpoint of the PLATO study (adapted from Wallentin et al. 2009)



No differences in primary safety endpoint were observed between the ticagrelor and clopidogrel arms in any of the sub-group analyses (Table 5.18).

Table 5.18: Incidence of the Primary Safety Endpoint (time to first major PLATO defined bleeding event) in the PLATO study relative to the sub-group analyses

	Ticagrelor Group (K-M %/year)	**Clopidogrel Group (K-M %/year)**	**Hazard Ratio (95% CI)**
PLATO (Wallentin *et al*. 2009)	11.6	11.2	1.04 (0.95–1.13)
PLATO-INVASIVE (Cannon *et al*. 2010)	11.5	11.6	0.99 (0.89-1.10)
PLATO-MEDICAL (James *et al*. 2010)	11.9	10.3	1.17 (0.98-1.39)
PLATO-STEMI (Steg *et al.* 2010)	9.0	9.2	0.98 (0.83 – 1.14)
PLATO-CABG (Held *et al*. 2009)	81.2	80.0	1.07 (0.80-1.43)
PLATO-DIABETES Diabetes No Diabetes (James *et al.* 2010	 14.1 10.8	 14.8 10.0	 0.95 (0.81-1.12) 1.08 (0.97-1.20)
PLATO-GENETICS No CYP2C19 loss-of-function CYP2C19 allele CYP2C19 loss-of-function CYP2C19 allele (Wallentin *et al.* 2010)	 10.3 11.8	 10.6 11.3	 0.96 (0.83-1.12) 1.04 (0.82-1.30)

Secondary Safety Endpoints

A number of additional secondary bleeding endpoints were studied (Table 5.19).

No significant differences in the combined incidence of 'TIMI Major and Minor' bleeding events (similar to those categorised as the primary safety endpoint, PLATO-defined 'Total Major' bleeding events) were observed between the ticagrelor and clopidogrel arms of the study (Table 5.23). Similarly, no significant difference was observed in the incidence of 'PLATO Major Fatal/Life-Threatening', 'TIMI Major' and 'PLATO Major Other' bleeding events, between the ticagrelor and clopidogrel arms of the study (Table 5.19).

The event rate of the composite endpoint 'PLATO Major and PLATO Minor' bleeding events was 16.1% per year in the ticagrelor arm compared with 14.6% per year in the clopidogrel arm (p=0.008) (Table 5.19).

Similarly, analysis of bleeding events relative to CABG or procedures revealed a higher incidence of PLATO defined non-CABG-related major bleeding events in the ticagrelor arm of the study compared to clopidogrel (Table 5.19).

Table 5.19: Incidence of the primary and main secondary bleeding events (Wallentin *et al.* 2009)

	Ticagrelor (K-M %/year) N=9235	**Clopidogrel (K-M %/year) N=9186**	***p***
PLATO Total Major Bleed (Primary Safety Endpoint)	11.6	11.2	0.43
TIMI Major + Minor Bleed	11.4	10.9	0.33
PLATO Major Fatal/Life-Threatening Bleed	5.8	5.8	0.70
TIMI Major Bleed	7.9	7.7	0.57
PLATO Total Major + Minor Bleed	16.1	14.6	0.008
PLATO Non-CABG Major Bleed	4.5	3.8	0.03
PLATO Fatal Bleed	0.3	0.3	0.66

Other Safety Events

Other safety signals observed in the PLATO study are displayed in Table 5.20 below.

Table 5.20: Incidence of additional safety signals (Wallentin *et al.* 2009)

	Ticagrelor Group Number of Patients with Events / Number of Patients (%)	Clopidogrel Group Number of Patients with Events / Number of Patients (%)	p
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 $\geq$3 sec	84/1451 (5.8)	51/1415 (3.6)	0.01
Ventricular pause $\geq$5 sec	29/1451 (2.0)	17/1415 (1.2)	0.10
At 30 Days			
Ventricular pause $\geq$3 sec	21/985 (2.1)	17/1006 (1.7)	0.52
Ventricular pause $\geq$5 sec	8/985 (0.8)	6/1006 (0.6)	0.60
Neoplasm arising during treatment			
Any	132/9235 (1.4)	155/9186 (1.7)	0.17
Malignant	115/9235 (1.2)	121/9186 (1.3)	0.69
Benign	18/9235 (0.2)	35/9186 (0.4)	0.02
Increase in serum uric acid from baseline value - %			
At 1 month	14$\pm$46	7$\pm$44	<0.001
At 12 month	15$\pm$52	7$\pm$31	<0.001
1 Month after end of treatment	7$\pm$43	8$\pm$48	0.56
Increase in serum creatinine from baseline value - %			
At 1 month	10$\pm$22	8$\pm$21	<0.001
At 12 month	11$\pm$22	9$\pm$22	<0.001
1 Month after end of treatment	10$\pm$22	10$\pm$22	0.59

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Ticagrelor was evaluated in a patient population with significant disease burden, interventions and concomitant medications. Considering the totality of safety data, ticagrelor does not substantially add to the background morbidity in the ACS population or pose a safety concern considerably different from that of clopidogrel, the current standard of care for patients with ACS. Bleeding, dyspnoea and ventricular pauses are three noteworthy safety issues from the PLATO study which are further discussed below. Further information on adverse events is provided in the SPC (Appendix 1).

Bleeding

There was no significant difference in the primary safety end point of PLATO 'Major' bleeding between ticagrelor and clopidogrel (11.6% vs. 11.2%, p = 0.43); these findings were consistent across all major subgroups (Wallentin *et al.* 2009). There was an excess of non-procedural bleeding with ticagrelor however, CABG-related bleeding was not different between the treatment groups. Fatal bleeding events were numerically fewer with ticagrelor than clopidogrel (20 vs. 23) (Wallentin *et al.* 2009).

Dyspnoea

Dyspnoea was another observed adverse reaction and was reported more frequently with ticagrelor than clopidogrel (13.8% vs. 7.8%) in the PLATO study (Wallentin *et al.* 2009). Most reported symptoms of dyspnoea were mild to moderate in intensity and 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 (Wallentin *et al.* 2009). In 2.2% of patients the investigator considered treatment to be causally related to ticagrelor (see Appendix 1). Ticagrelor does not affect tests of pulmonary function. The higher incidence of dyspnoea with ticagrelor is not associated with new or worsening heart or lung disease.

Ventricular pauses

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 (Wallentin *et al.* 2009). There were no significant differences in the rates of clinical manifestations of bradyarrhythmia between the two treatment groups at one year (Wallentin *et al.* 2009). In addition there was no difference in the requirement for a pacemaker between the two treatment groups (Wallentin *et al.* 2009).

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The evidence base to support the use of ticagrelor comes mainly from the PLATO study which demonstrated the superiority of a ticagrelor-aspirin strategy compared to the reference standard of clopidogrel-aspirin in a broad spectrum of ACS patients. The protocol specified duration of therapy up to 12 months (n=4147 for ticagrelor, n=4047 for clopidogrel at 12 months) arose from treatment guidelines for dual anti-platelet therapy.

Efficacy

Ticagrelor reduced the rate of the composite efficacy endpoint of CV death, MI, or stroke after ACS events against the active comparator (and current standard of care clopidogrel, with ARR at one year 1.9%, RRR 16% (HR = 0.84 [95% CI 0.77-0.92], p<0.001) (see Table 5.10, Section 5.5.1). This result derives largely from both CV death and MI, with no contribution from stroke. The observed reduction in all-cause mortality at one year with ticagrelor in PLATO (ticagrelor 4.5%; clopidogrel 5.9%; ARR 1.4%; RRR 22%, nominal p<0.001) reinforces the clinical importance of the significant reduction in CV mortality at one year (ticagrelor 4.0%; clopidogrel 5.1%; ARR 1.1%; RRR 21%, p<0.001). (Table 5.10, Section 5.5.1) Clopidogrel has only demonstrated a reduction in all cause mortality in a single 45,000 STEMI patient study performed mostly in China (Chen *et al.* 2005). The survival benefit observed with ticagrelor is the first that has been demonstrated in a much broader ACS population (including STEMI and invasively and conservatively managed UA/STEMI) with a relative risk reduction of over 20% when compared to an active comparator (clopidogrel). The all cause mortality benefit includes the subgroup of patients that were managed both invasively (HR = 0.81 [95% CI 0.68-0.95], nominal p=0.01 (Table 5.11, Section 5.5.1) and medically managed (HR = 0.75 [95% CI 0.61–0.93], p=0.010 (Section 5.5.1).The superiority of ticagrelor over clopidogrel for the primary composite endpoint shows consistency across age, gender, and body weight. The findings are also consistent across all major clinical subgroups of patients, including patients with and without diabetes and patients with and without genetic markers for potentially impaired clopidogrel metabolism. Ticagrelor's advantage over clopidogrel applies to the broad, inclusive population of ACS patients with or without ST-segment elevation on the ECG, whether or not intended for early invasive management. The ARR versus clopidogrel appeared early in the course of treatment and the event curves continue to diverge throughout the 12 month treatment period, strongly supporting a recommendation to treat patients with ticagrelor for 12 months as per the NICE guideline recommendation for clopidogrel (NICE Clinical Guideline 94. March 2010).

Safety

Bleeding is an important safety issue for all antiplatelet medications. Despite greater inhibition of platelet aggregation with ticagrelor, there was no difference in the primary safety endpoint of PLATO major bleeding between the two treatment groups (11.6% vs. 11.2%, p = 0.43) (see Tables 5.18 and 5.19, Section 5.9). Whether

evaluated in the overall population, or restricted to CABG-related bleeds, ticagrelor and clopidogrel did not differ in major fatal/life-threatening bleeding (5.8% vs. 5.8%, p= 0.70), or total fatal bleeding (0.3% vs. 0.3% p=0.66) (see Table 5.19, Section 5.9). While there is an increase in non-CABG related bleeding based on the study criteria (4.5% with ticagrelor vs. 3.8% with clopidogrel, p=0.03 [see Table 5.19, Section 5.9]) this is not unexpected, more potent anti-platelet therapies are almost universally associated with some increases in bleeding indices; what is reassuring for ticagrelor is that the most severe and clinically meaningful bleeding is not significantly increased.

Dyspnoea, a feeling of breathlessness, occurred more frequently with ticagrelor than clopidogrel (13.8% vs. 7.8% p <0.001) (see Table 5.20, Section 5.9). In PLATO, dyspnoea was usually rated mild or moderate in severity, and was not associated with heart failure or lung disease. 0.9% of patients treated with ticagrelor discontinued therapy due to dyspnoea.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

PLATO was a large randomised controlled, double blind; multi-centre trial of oral antiplatelet therapy that reflects UK clinical practice and demonstrates a significant mortality benefit versus the existing standard of care. PLATO recruited a total of 18,642 patients from a broad spectrum of acute coronary syndrome patients (approximately 38% STEMI, 43% NSTEMI, 17% unstable angina, 3% other diagnosis or missing data) in a setting that reflects real world practice, including current practice in the UK (Wallentin *et al.* 2009). Patients were eligible for enrolment if they were hospitalised for ACS with or without ST segment elevation with an onset of symptoms during the previous 24 hours regardless of the subsequent treatment strategy (e.g. immediate PCI, delayed PCI, medical management etc.) and regardless of prior clopidogrel use (Wallentin *et al.* 2009).

Patients identified at randomisation with investigator intent for early invasive strategy via PCI or CABG represented 72% of the study population. A total of 3,948 patients from the full PLATO study population did not have revascularisation during the study period. This distinguishes PLATO from other antiplatelet trials in which enrolment was more restricted and controlled within the ACS management pathway (such as following angiography after a decision for PCI in TRITON-TIMI 38), thus making PLATO reflective of real-world clinical practice.

Importantly patients in PLATO randomised to clopidogrel (the 'control' arm) received a loading dose of clopidogrel (300-600 mg) as soon as possible and within 24 hours of the onset of symptoms, provided they had not received clopidogrel treatment within the previous 5 days in which case a loading dose was not required. Patients were not excluded from the study if they had received a loading dose of clopidogrel during transfer or if they had been on clopidogrel maintenance treatment at the onset of symptoms. This reflects what is commonly seen in clinical practice where the decision to initiate dual antiplatelet therapy is sometimes taken during emergency transfer of the patient to the hospital or at the district general hospital while the patient is being assessed for possible transfer to a unit with PCI facilities. This

approach is consistent with current guidelines (Bassand *et al.* 2007, Van de Werf *et al.* 2008) which recommends the initiation of dual antiplatelet therapy within 24 hours of the initial (index) event, and usually prior to coronary angiography. This also ensured that the comparator was appropriately and optimally dosed according to current guidelines and practice standards.

TRITON-TIMI 38 investigated the role of prasugrel in a very specific subgroup of ACS patients, namely those having undergone angiography in whom a decision had been made to proceed to PCI, in addition to a capped (26%) number of STEMI patients who could be treated either within 12 hours of symptoms ('primary' PCI) or after 12 hours ('secondary' PCI). A major exclusion criterion was the use of any thienopyridine within 5 days of randomization. Furthermore, only 25% of patients received their first dose of oral antiplatelet therapy prior to commencing their PCI procedure; this may have selectively adversely impacted on the efficacy of the comparator clopidogrel, given its slower onset of anti-platelet activity. PLATO permitted open-label clopidogrel in-hospital prior to randomisation and also allowed enrolment of patients taking chronic open-label clopidogrel at the time of the index ACS event.

The superiority of ticagrelor over clopidogrel for the primary composite endpoint was consistently manifested across age, gender, and body weight. The overall clinical outcomes are also consistent across all major subgroups. Furthermore, all the patents included in the PLATO study are in line with the proposed license indication for ticagrelor. Data from the PLATO genetics study also supports the use in patients that may be resistant to clopidogrel thus removing the need for genotyping thereby simplifying the decision making process, while at the same time showing superiority of ticagrelor over clopidogrel even in 'normal' metabolisers of clopidogrel.

Limitations

The PLATO protocol specified a maximum 12 month duration of treatment in line with current guidelines for dual antiplatelet therapy in ACS. In PLATO, the median length of exposure was 9.1months based on a minimum of 6 months treatment for all enrolled patients and trial closure upon achieving the requisite number of events. Whilst most events occur soon after the index event, the consistent benefit demonstrated in PLATO for ticagrelor beyond the 30-day time point means that the absolute risk reduction versus clopidogrel with ticagrelor continues to build up to the 12 month treatment duration allowed in the PLATO trial, and is the basis for the EU licence which recommends treatment for up to 12 months.

The loading dose of clopidogrel was different among patients, depending on whether or not they had already received open-label clopidogrel although this had no significant impact on the benefits patients received as assessed by the primary outcome of the study.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence base to support the use of ticagrelor comes mainly from the PLATO study, a large multicentre, global randomised trial including patients representative of

"real world" practice. PLATO demonstrated the superiority of a ticagrelor-aspirin strategy when compared to routine treatment with clopidogrel-aspirin across a broad spectrum of ACS patients (Wallentin *et al.* 2009). The primary efficacy and safety endpoints measured hard clinical outcomes; ischaemic events and mortality for efficacy and bleeding events for safety, all relevant to the decision problem.

In PLATO, in comparison to clopidogrel, ticagrelor showed a superior reduction in the primary endpoint of death from vascular causes, non-fatal MI, or non-fatal stroke. In addition, there was a benefit for ticagrelor in the secondary endpoint of death from any cause (4.5% vs. 5.9% with clopidogrel, HR = 0.78 [95% CI 0.69-0.89], nominal p<0.001 [See Table 5.10, Section5.5.1]).

Furthermore, the benefit in relation to the primary endpoint was consistent across age, gender and body weight as well as across all major clinical subgroups. With efficacy demonstrated across all major clinical subgroups and no requirement for dosing adjustment ticagrelor provides clinicians a new treatment option which is an advance on current treatments both in terms of efficacy and convenience. In comparison prasugrel is licensed for use in patients with ACS undergoing primary or delayed PCI with dose variations dependant on the patient's age (> 75 years) or on their weight (< 60 kg). The NICE guidance for prasugrel (NICE Technology Appraisals Guidance 182. October 2009) recommends prasugrel as an option only when immediate PCI is necessary, or when stent thrombosis has occurred with clopidogrel, or for patients with diabetes mellitus. The clopidogrel license varies for STEMI and NSTEMI dependant on whether patients will require PCI or whether they will be managed medically.

The improved survival with ticagrelor plus aspirin over the current best standard of care, clopidogrel plus aspirin has been demonstrated across broad ACS population without a concomitant increase in the risk of overall major bleeding.

Therefore ticagrelor is a valid treatment option for patients with ACS.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The PLATO study was designed to reflect the current management strategy across a broad spectrum of ACS patients; current standards of care typically include the initiation of dual oral anti-platelet therapy as quickly as possible after presentation in the treatment centre, prior to any decision being made on the ultimate treatment strategy employed, be that via PCI or CABG, or involving medical management only. The study compared ticagrelor and aspirin to clopidogrel plus aspirin, the current guideline-recommended standard of care (Wallentin *et al.* 2009). Patients were randomised 1:1 to either clopidogrel or ticagrelor as quickly as possible after a confirmatory diagnosis of ACS had been made (Wallentin *et al.* 2009). The patient

characteristics from PLATO are comparable to that seen in the general UK ACS population.

MI adjudication in PLATO was handled using a standardised acute MI definition. This process has the advantage over site-assessed MIs as it is more objective and ensures consistency between clinicians and centres.

The clopidogrel dosage employed within the PLATO study was selected to mirror current practice at time of study design, with the opportunity to use higher loading doses (600 mg) allowed on the basis of the patient's clinical situation, at the clinicians discretion, again mirroring real-world practice.

One hundred percent of the population studied in PLATO are those indicated to receive the dose in the SPC. The indication as stated in the draft SPC reflects the full patient population studied in PLATO.

The clinical evidence base for ticagrelor as presented throughout this submission is relevant to UK clinical practice, and reflects the clinical efficacy benefits of ticagrelor in terms of improving patient outcomes in ACS, with no significant increase in the risk of overall major bleeding.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

Systematic literature searches were conducted to identify cost-utility analyses of oral antiplatelet agents in patients with ACS in the UK.

The following electronic databases were searched (19th January 2010):

- Index Medicus database (MEDLINE), including Medline (R) In-Process using OVID
- Excerpta Medica Database (EMBASE) using OVID
- NHS Economic Evaluation Database (NHS EED) using the Cochrane Library database
- Health Economic Evaluations Database (HEED)

The search strategies were developed in Medline and adapted for use in the other literature databases. A broad search was adopted using a generic stem for ACS that was developed for the SIGN ACS guidelines (2007)[1]. The ACS generic stem was combined with SIGN economic search filters for the searches conducted in Medline and Embase (Appendix 4).

The references retrieved from the initial search were screened in two passes by a single reviewer. The 1st pass involved applying pre-defined inclusion criteria to the bibliographic records to assess their relevance to the NICE decision problem. The board inclusion criteria were articles that reported cost-effectiveness analyses of oral antiplatelet agents for the treatment of ACS.

The 2nd pass of the screening process applied a set of exclusion criteria to the potentially relevant articles identified after the first screening. The exclusion criteria included: health economic perspective outside the United Kingdom, primary prevention, glycoprotein IIb/IIIa inhibitors, low-molecular weight heparins, articles that were not published in English, letter/abstracts and duplicate references.

A detailed review of the full text articles identified in the 2nd pass was undertaken by two reviewers and data extracted that would be used to inform the structure, assumptions and model inputs for the cost-effectiveness analysis of ticagrelor for the treatment of ACS in the UK.

In addition, internet sites of UK Health Technology Assessment (HTA) bodies were also search for economic evaluations reported in relevant HTA appraisals.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

The systematic review identified 28 papers that were of potential value for helping to inform the decision problem (see figure 6.1). Twenty papers were subsequently excluded from further detailed review (see table 6.1).

No papers were identified that had evaluated the cost-effectiveness of ticagrelor in the treatment of ACS.

Table 6.1: Details of full text cost-effectiveness articles that were excluded from further review

Study details	Reason for exclusion
Angiolillo, 2006	Commentary on a long-term cost-effectiveness of clopidogrel
Cannon, 2004	Editorial of the cost-effectiveness of clopidogrel
Cheng, 2007	Review of cost-effectiveness analyses of clopidogrel for the secondary prevention of CAD
Cowper, 2005	Non-UK pharmacoeconomic study. US cost-effectiveness analysis of prolonged clopidogrel after PCI
Durand-Zaleski, 2004	Review of the cost-effectiveness of clopidogrel versus aspirin based on the CAPRIE study
Fox, 2005	Overview and commentary on the cost-effectiveness analysis of clopidogrel in high-risk patients with ACS (Schleinitz MD & Heidenreich, 2005)
Huston & Dawkins, 2008	Review article primarily focusing on the cost-effectiveness of enoxaparin in the treatment of ACS and PCI
Lyseng-Williamson, 2006	Pharmacoeconomic review of clopidogrel in patients with non-ST elevation ACS.
Mahoney, 2006	Non-UK pharmacoeconomic study. US cost-effectiveness analysis of early and sustained clopidogrel in patients with ACS without ST-segment elevation.
Mahoney, 2010	Non-UK pharmacoeconomic study. US cost-effectiveness study of prasugrel versus clopidogrel in patients with ACS and planned PCI.
Malinina, 2007	Review article of the cost-effectiveness of anti-platelet therapy for secondary stroke prevention from a US health care system perspective. Patient population not relevant to the decision problem.
Matchar, 2005	Non-UK pharmacoeconomic study. US cost-effectiveness

Study details	Reason for exclusion
	analysis of antiplatelet therapy in secondary stroke prevention. Patient population not relevant (patients with a history of cerebrovascular disease).
Maxwell, 2009	Non-UK pharmacoeconomic study (US cost-effectiveness analysis).Comparators not relevant to decision problem.
Monaco, 1998	Commentary on the cost-effectiveness of pharmacological preventative strategies for ACS.
Robinson, 2005	Treatment strategies not relevant to the decision problem.
Schleintitz, 2004	Non UK cost-utility analysis (US study) of clopidogrel for the secondary prevention of vascular events.
Schleintitz, 2005	Non UK cost-utility analysis (US study) of clopidogrel plus aspirin versus aspirin alone for patients with high risk ACS.
Weintraub, 2004	Review article of the cost-effectiveness of clopidogrel in the management of ACS.
Weintraub, 2008	Commentary/overview of health economic evaluation using antiplatelet therapy to illustrate fundamental principles.
Weintraub, 2005	Non-UK cost-effectiveness study (US study) of clopidogrel in patients with ACS.

Figure 6.1: Flow diagram of literature review of relevant economic evaluations

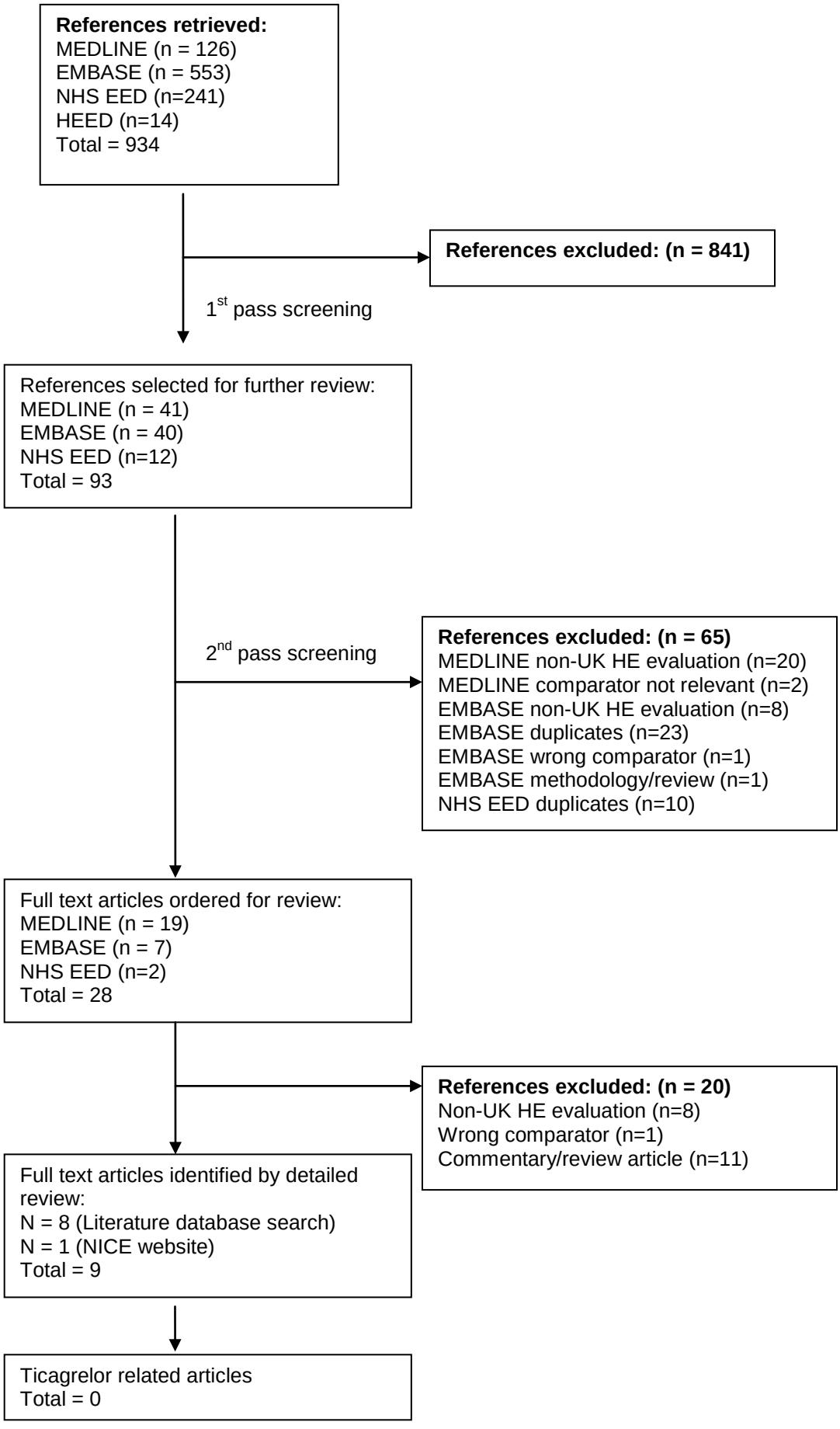


Table 6.2: Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Daiichi-Sankyo/Eli Lilly	2009	UK	Two phase Markov model; a trial based period of 15 months followed by a life time extrapolation (40 years). Base-case treatment duration of 12 months adopted. Clinical events captured by the model include: CV death, MI, stroke to bleeds. It also includes hospitalisation due to major CV and bleed events. TRITON-TIMI 38 was the key source of evidence used to develop the model.	UK patients with NSTEMI, UA and STEMI (aged 61-64 years) with and without diabetes scheduled for PCI.	Base-case estimates Prasugrel 10.15 QALYs Clopidogrel 10.10 QALYs	 Prasugrel £5,334 Clopidogrel £5,163	 £3,220
Heeg *et al.*	2007	Netherlands, UK	Three phase Markov model (first 6 months, second 6 months and subsequent periods of 6 months) with health states for MI, stroke and death. Model used event rate data from CAPRIE, CHARISMA, CURE and PCI-CURE to estimate the cost-effectiveness of clopidogrel versus aspirin. Treatment duration was similar to the treatment duration in the trials. Lifetime horizon was adopted.	Patients (average age 60 years) with recent MI, stroke or symptomatic PAD at high risk of ischaemic events.	Clopidogrel versus ASA CAPRIE ∆LYG 0.02 CHARISMA ∆LYG 0.00 CURE ∆LYG 0.11 PCI-CURE ∆LYG 0.03	 ∆Cost £384 ∆Cost £351 ∆Cost £88 ∆Cost -£268	 £20,243 per LYG £167,486 per LYG £771 per LYG Dominant
Jones *et al.*	2004	UK	Adaptation of a Markov model developed by Sanofi-	UK patients (average age 60	Base-case estimates Scenario 1: lifetime	Base-case estimates	

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			Synthelabo Ltd and Bristol-Myers Squib. Health states for the model of patients with a recent MI were new MI, stroke, Year 1 post-MI, Year 1 post-stroke, vascular death and non-vascular death. A lifetime horizon (40 years) and a cycle length of 1 year were adopted.	years) with recent MI.	treatment duration excluding RR of non-vascular death) Clopidogrel 9.10 QALYs ASA 8.86 QALYs Scenario 2: lifetime treatment duration including RR of non-vascular death) Clopidogrel 8.94 QALYs ASA 8.86 QALYs Scenario 3: 2-year treatment duration excluding RR of non-vascular death) Clopidogrel 8.95 QALYs ASA 8.90 QALYs Scenario 4: 2-year treatment duration including RR of non-vascular death) Clopidogrel 8.91 QALYs ASA 8.87 QALYs	 Clopidogrel £25,585 ASA £18,286 Clopidogrel £25,585 ASA £18,285 Clopidogrel £19,202 ASA £18,285 Clopidogrel £19,078 ASA £18,182	 £31,400 £94,446 £17,081 £21,448
Karnon *et al.*	2010	UK	Markov model with four health states (new MI, post new-MI, stroke and death) patients may stay in or move to following their initial STEMI. The model was used	UK patients (average age 60) recently diagnosed with STEMI.	Base-case (1 month treatment duration) Clopidogrel 7.984 QALYs ASA 7.931 QALYs	 Clopidogrel £18,397 ASA £18,276	 £2,284

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			to estimate the long-term costs and health benefits of clopidogrel utilising data from two clopidogrel trials: COMMIT/CCS-2 (mean follow-up 14.9 days) and CLARITY-TIMI 28 (86-88% patients followed up to 30 days). Transition probabilities for month 1 and months 2-12 were estimated from a German, prospective, multicentre, observational study in patients with STEMI. A life-time horizon and a cycle length of 1 year after an initial 12 month modelled period were adopted.		Base-case (12 month treatment duration) Clopidogrel 8.117 QALYs ASA 7.931 QALYs	 Clopidogrel £18,624 ASA £18,276	 £3,891
Karnon *et al.*	2006	UK	One year decision-tree model followed by a life-time (34 years) Markov model which describes the annual probability of ACS patients experiencing a MI, stroke or death from vascular or non-vascular death in 1 year cycles. The model takes into account age at the time of an event. A 12 month treatment duration was adopted in the base-case analysis.	UK patient diagnosed with non-ST-segment elevation ACS (average age 66 years)	Base-case estimates Clopidogrel 7.3645 QALYs ASA 7.3098 QALYs	 Clopidogrel £11,756 ASA £11,353	 £7,365
Karnon *et al.*	2005	UK	Markov model with discrete health states for new MI, new stroke, post new MI, post	UK patients (average age 60 years) at risk of a	Base-case estimates Clopidogrel 12.00 QALYs	 Clopidogrel £19,200	 £21,489

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			new stroke and death. A treatment duration of 2 years and a lifetime horizon of 40 years were adopted in the base-case.	secondary occlusive vascular event.	ASA 11.96 QALYs	ASA £18,381	
Lamy *et al.*	2004	Canada, Sweden, USA, UK	Trial based economic evaluation was conducted using clinical outcomes data from the CURE trial. No discounting was performed, since the maximum follow-up was 1 year. Average treatment period was 9 months.	Patients that were hospitalised within 24 hour onset of symptoms indicative of ACS that did not have significant ST segment elevation. In the UK, 737 patients participated in this trial. Total trial population was 12,562 patients.	Base-case estimates Clopidogrel versus ASA ∆ Events avoided (composite of CV death, MI or stroke) 2.0%	∆ Cost (UK) £208	£10,366 per event avoided
Main *et al.*	2004	UK	Two part model: (1) an initial 12 month decision-tree model following an episode of ACS during which 3 mutually exclusive events are modelled: MI, death (CV and non-CV) and IHD without non-fatal MI (i.e. event free) (2) a life-time (40 year) Markov model in which patients enter the model from the short-term decision tree model either having experienced a non-fatal MI or	UK patients (average age 60 years) with non-ST-segment elevation ACS	Base-case estimates Clopidogrel 8.2795 QALYs ASA 8.2022 QALYs	Clopidogrel £12,695 ASA £12,225	£6,078

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			being event free (IHD without non-fatal MI). The models consists of 4 discrete health states: well, non-fatal MI (1 cycle only), post-MI and dead (all cause).				
Rogowski *et al.*	2009	UK	Two part model: (1) short-term decision tree characterising a period of 12months following an episode of ACS. Three mutually exclusive outcomes were modelled: IHD without any evidence of MI, non-fatal MI and death. (2) Patients surviving the initial 12 month period enter a long-term Markov model. The model consists of 4 discrete health states: well, MI (one cycle only), post-MI and death. The model was run over a period of 40 cycles (equivalent to 40 years).	UK patients with non-ST-segment elevation ACS (average age was not reported as this was not an explicit parameter in the model).	Base case-estimates Clopidogrel £12, 695 ASA £12,225	Clopidogrel 8.2795 ASA 8.2022	£6,078
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); ASA = aspirin, LYG = life year gained							

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

All items were graded as either √ (item adequately addressed), × (item not adequately addressed), ? (unclear or not enough information), NA (not applicable) or NS (not stated).

Study name: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. Daiichi-Sankyo/Eli Lilly (2009).		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	?	No evidence was presented of the economic burden of ACS in the UK (e.g. NHS resource implications associated with hospital admissions for secondary occlusive vascular events).
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	
5. Were the alternatives being compared clearly described?	√	
6. Was the form of economic evaluation stated?	√	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	√	
Data collection		

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

8. Was/were the source(s) of effectiveness estimates used stated?	√	TRITON-TIMI 38 was the primary source of evidence used to evaluate the cost-effectiveness of prasugrel versus clopidogrel.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	√	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	
12. Were the methods used to value health states and other benefits stated?	√	Background population norms for EQ-5D (Kind 1999) were applied to a hypothetical cohort of UK patients that entered the model following an episode of ACS. Utility decrements for non-fatal MI and stroke were based a US Medical Expenditure Panel Survey (MEPS) that used a US version of the EQ-5D (Sullivan 2006). The utility decrement for patients experiencing a major bleed (25% decrement of the population norm applied for 14 days) was estimated using data from a study reported by Schleinitz 2005.
13. Were the details of the subjects from whom valuations were obtained given?	?	The characteristics of the patients used to elicit a utility decrement for a major bleeding event are not specified in the document.
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	√	

17. Were the methods for the estimation of quantities and unit costs described?	?	Rehospitalisation for endpoint related events and other serious AEs over a 12 month pre-specified period were estimated from a subgroup of 6,705 patients from eight countries (including the UK) that participated in the TRITON TIMI 38 trial. A Poisson regression analysis was performed to predict the occurrence of rehospitalisation. Of the European countries represented in the economic sub-sample the UK, Spain and Italy was grouped together as having relatively low hospitalisation rates compared to France and Germany. This was used in the base case analysis. DRG codes were matched to the corresponding UK 'NHS reference costs' HRG4 code by a consultant cardiology to allocate unit costs to the rehospitalisations. No further details of how DRG codes were matched to HRG codes was provided.
18. Were currency and price data recorded?	√	
19. Were details of price adjustments for inflation or currency conversion given?	×	NHS unit costs for rehospitalisations were not inflated. NHS Reference Costs for 2006/07 were adopted.
20. Were details of any model used given?	√	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	√	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	Lifetime horizon (40 years) was adopted.
23. Was the discount rate stated?	√	A 3.5% discount rate was applied to costs and health benefits incurred after the 1st modelled year.
24. Was the choice of rate justified?	√	Discount rate used was consistent with the NICE reference case.
25. Was an explanation given if cost or benefits were not discounted?	NA	

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	√	
27. Was the approach to sensitivity analysis described?	√	PSA and one way sensitivity analyses were conducted.
28. Was the choice of variables for sensitivity analysis justified?	×	Few details were given of why certain variables were selected for sensitivity analysis. Unit costs for hospitalisation were not included in the one-way sensitivity analysis.
29. Were the ranges over which the parameters were varied stated?	√	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	
31. Was an incremental analysis reported?	√	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	√	
33. Was the answer to the study question given?	√	
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	Sensitivity analysis illustrated that prasugrel would not be cost-effective versus clopidogrel if a 1 year time-horizon were adopted. However, the authors argued that a 1 year time horizon would not adequately capture the full health benefits which would be accrued by the patient over their lifetime.
36. Were generalisability issues addressed?	√	TRITON-TIMI 38 trial was broadly representative of ACS patients treated in the NHS.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Oral antiplatelet therapy in secondary prevention of cardiovascular events – An assessment from the payer's perspective. Heeg *et al* (2007).		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	?	No evidence was presented of the economic burden of ACS in the UK (e.g. NHS resource implications associated with hospital admissions for secondary occlusive vascular events).
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	A UK NHS perspective was adopted.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	
5. Were the alternatives being compared clearly described?	√	
6. Was the form of economic evaluation stated?	√	Cost-effectiveness analysis (incremental cost per LYG)
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	?	It is not clear why a cost-effectiveness analysis was performed in preference to a cost-utility analysis.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	√	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	×	A short description of the RCTs used to provide clinical outcomes for the model was presented as supplementary material (http://pharmacoeconomics.adisonline.com).
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	

12. Were the methods used to value health states and other benefits stated?	NA	
13. Were the details of the subjects from whom valuations were obtained given?	×	Few details were provided on ACS patient characteristics within the paper.
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	√	
17. Were the methods for the estimation of quantities and unit costs described?	?	The authors comment that event costs were obtained from a variety of sources such as previous cost-effectiveness publications and NHS Reference Costs.
18. Were currency and price data recorded?	√	All costs were converted to £ (year 2006 values)
19. Were details of price adjustments for inflation or currency conversion given?	√	A yearly inflation rate of 3.5% was assumed and December 2006 currency exchange rates were applied (£1 = $US 1.978 and £1 = €1.485).
20. Were details of any model used given?	√	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	√	Model had previously been used to estimate the cost-effectiveness of clopidogrel versus aspirin for the secondary prevention of CV events in the high-risk CAPRIE trial population in Denmark. It had also been used in the clopidogrel reimbursement application in the Netherlands.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	
23. Was the discount rate stated?	√	Future costs and health benefits were discounted at a rate of 3.5% per year.
24. Was the choice of rate justified?	?	
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	×	

27. Was the approach to sensitivity analysis described?	√	Multivariate PSA was conducted.
28. Was the choice of variables for sensitivity analysis justified?	?	
29. Were the ranges over which the parameters were varied stated?	√	All costs, age specific risk increases in event rates and relative risks of experiencing subsequent events were varied between 0.75 and 1.25 of their initial value, as this range was expected to be sufficiently wide to capture uncertainty around these parameters. Uniform distributions were applied.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	
31. Was an incremental analysis reported?	√	All results were expressed at Incremental Cost per Life Year Gained.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	×	Only incremental costs per patient and incremental life years gained per patient were presented.
33. Was the answer to the study question given?	√	The pharmacoeconomic analysis confirmed the NICE recommendation to recommend clopidogrel as a treatment option for high risk patients with ACS.
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	
36. Were generalisability issues addressed?	√	The authors commented that the clinical and the epidemiological part of the model were applicable to the UK, as there was no reason to assume that the epidemiology of CV events would differ significantly between the Netherlands and the UK. The only country specific differences that were identified were unit costs, the probability of death for other causes and the rate of discounting.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Clinical effectiveness and cost-effectiveness of clopidogrel and modified release dipyridamole in the secondary prevention of occlusive vascular events. Jones *et al* (2004)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	√	Details of the economic burden of CHD in the UK were reported. Direct and indirect healthcare costs associated with CHD were estimated to be in the order of £7 billion in 1999.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	An extended cost-effectiveness model was developed to provide a consistent model structure with which to assess the cost-effectiveness of a full range of agents licensed for the secondary prevention of occlusive vascular events in four subgroups of patients (MI, stroke, TIA and PAD). The model enabled a lifetime treatment duration to be modelled in the base case.
5. Were the alternatives being compared clearly described?	√	
6. Was the form of economic evaluation stated?	√	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	√	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	√	Effectiveness estimates for patients in the MI subgroup treated with either clopidogrel plus aspirin or aspirin alone were sourced from the CAPRIE trial.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	√	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	
12. Were the methods used to value health states and other benefits stated?	√	Utility estimates for MI and stroke were estimated using UK societal preferences derived from the EQ-5D questionnaire. The authors were unable to find utility estimates for stroke that distinguished between patients in their first or subsequent year following the event, and so the utility associated with stroke was assumed to remain constant with time from the event. The utility estimate for TIA was assumed to be associated with an independent (non-disabled) stroke patient.
13. Were the details of the subjects from whom valuations were obtained given?	×	Details of the subjects from whom utility valuations were obtained were not provided.
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	√	
17. Were the methods for the estimation of quantities and unit costs described?	√	
18. Were currency and price data recorded?	√	
19. Were details of price adjustments for inflation or currency conversion given?	?	.
20. Were details of any model used given?	√	

21. Was there a justification for the choice of model used and the key parameters on which it was based?	√	The extended economic model enabled the investigators to separately address the cost-effectiveness of all licensed agents for the secondary prevention of occlusive vascular events in each relevant subgroup. It enabled an assessment to be made of extending the treatment duration from 2 years to a lifetime. Finally, it allowed an assessment to be made of the impact of including the reported treatment effects on both vascular and non-vascular mortality.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	A lifetime horizon was adopted (equivalent to 40 years).
23. Was the discount rate stated?	√	Costs and QALYs were discounted at a rate of 6% and 1.5% per year, respectively, in the base case
24. Was the choice of rate justified?	×	
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	√	Mean EQ-5D utilities for the health states and their respective standard errors were provided. Mean costs (95% CI) for stroke and MI were also reported.
27. Was the approach to sensitivity analysis described?	√	Extended model was fully probabilistic. Parameters were entered as random variables rather than fixed point estimates. Monte Carlo simulation was used to propagate parameter uncertainty through the model. CEACs were used to present uncertainty in the cost-effectiveness of the competing interventions.
28. Was the choice of variables for sensitivity analysis justified?	√	
29. Were the ranges over which the parameters were varied stated?	√	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	

31. Was an incremental analysis reported?	√	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	×	
33. Was the answer to the study question given?	√	
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	For the MI subgroup, clopidogrel would be considered cost-effective versus aspirin if a treatment duration of 2 years were adopted. If a lifetime treatment duration were used, clopidogrel would be considered more cost-effective than aspirin provided the treatment effects of non-vascular deaths were omitted.
36. Were generalisability issues addressed?	×	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: A cost-utility analysis of clopidogrel in patients with ST elevation acute coronary syndromes in the UK. Karnon *et al* (2010)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	?	Details of the economic burden of ACS in the UK were not reported.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	
5. Were the alternatives being compared clearly described?	√	

6. Was the form of economic evaluation stated?	√	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	√	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	√	The COMMIT/CCS-2 and CLARITY-TIMI 28 trials were the primary sources for the effectiveness estimates.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	√	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	Incremental cost per QALY gained was the primary outcome measured.
12. Were the methods used to value health states and other benefits stated?	√	Utility estimates for stroke were sourced from a meta-analysis of QoL estimates for stroke (Teng 2003). The Harvard utilities database was used to elicit utility estimates for the other health states.
13. Were the details of the subjects from whom valuations were obtained given?	×	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	√	

17. Were the methods for the estimation of quantities and unit costs described?	√	The STEMI event-free health state and non-fatal MI health state costs were estimated from patient level hospital resource use data collected as part of an evaluation of GPA IIb/IIIa inhibitors in ACS (Palmer et al 2002). The costs assigned to the stroke health states were sourced from a UK study that estimated the cost of stroke using data on resource use in primary and secondary care over a period of 1 year (Youman et al 2003). Drug costs were taken from the BNF.
18. Were currency and price data recorded?	√	All costs were reported as 2006 £ values
19. Were details of price adjustments for inflation or currency conversion given?	×	
20. Were details of any model used given?	√	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	√	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	Lifetime horizon was adopted.
23. Was the discount rate stated?	×	The base case discount rate was not reported, however, sensitivity analysis was undertaken that applied a discount rate of 6% for costs and 1.5% for QALYs.
24. Was the choice of rate justified?	NA	
25. Was an explanation given if cost or benefits were not discounted?	?	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	√	
27. Was the approach to sensitivity analysis described?	√	One-way sensitivity analysis was conducted using the lower and upper 95% CIs for key health outcomes and cost parameters. PSA was also performed using Monte Carlo simulation.
28. Was the choice of variables for sensitivity analysis justified?	×	

29. Were the ranges over which the parameters were varied stated?	√	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	
31. Was an incremental analysis reported?	√	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	√	
33. Was the answer to the study question given?	√	
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	Caveats are given relating to the uncertainty around some of the model input parameters that used data from the US and Germany to inform relevant base-case event rates within and beyond the treatment period. The analysis of the 1 year treatment duration is subject to the assumption that clopidogrel continues to be effective in STEMI patients beyond the 4 week trial period of COMMIT/CCS-2 trial. Finally, the investigators did not include the rate of major bleeding in their model as the trial data showed no significant increased risk with clopidogrel plus aspirin versus aspirin alone.
36. Were generalisability issues addressed?	?	The COMMIT/CCS-2 trial was conducted in the People's Republic of China. The authors do not comment on the generalisability of this trial to UK practice.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: A cost utility analysis of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes in the UK. Karnon *et al* (2006)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	√	A poster of the PRAIS-UK study (Bakhai 2001) is used highlight the burden of NSTEMI ACS to the NHS in terms of hospital admissions (114,000 per annum) and despite low dose ASA use, combined rates of death, MI and stroke following NSTEMI ACS are around 14% at 6 months.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	
5. Were the alternatives being compared clearly described?	√	
6. Was the form of economic evaluation stated?	√	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	√	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	√	The CURE trial was the primary source used to inform the model of the clinical effectiveness of clopidogrel versus ASA over a 12 month treatment period.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	√	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	
12. Were the methods used to value health states and other benefits stated?	√	The utility estimates for stroke were obtained from a meta-analysis (Tengs 2003). The authors comment that no data were identified to differentiate utility values for event-free ACS (> 1 year post treatment initiation) and acute MI patients (> 1 year post event) and so a conservation assumption was taken that both have the same utility values (0.93).
13. Were the details of the subjects from whom valuations were obtained given?	×	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	√	
17. Were the methods for the estimation of quantities and unit costs described?	√	
18. Were currency and price data recorded?	√	Costs were reported in £ sterling and updated to the year 2002.
19. Were details of price adjustments for inflation or currency conversion given?	×	
20. Were details of any model used given?	√	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	√	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	Lifetime horizon was adopted. The model runs for 34 years in annual cycles.
23. Was the discount rate stated?	√	An annual discount rate of 6% was adopted for costs and 1.5% for health benefits.
24. Was the choice of rate justified?	√	Based on NICE guidance (2001)

25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	√	
27. Was the approach to sensitivity analysis described?	√	The authors reported that one- and two-way sensitivity analysis was conducted around key variables. PSA was also undertaken.
28. Was the choice of variables for sensitivity analysis justified?	×	
29. Were the ranges over which the parameters were varied stated?	√	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	
31. Was an incremental analysis reported?	√	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	√	
33. Was the answer to the study question given?	√	
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	
36. Were generalisability issues addressed?	√	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Modelling the long term cost effectiveness of clopidogrel for the secondary prevention of occlusive vascular events in the UK. Karnon *et al* (2005)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	√	The authors cited a burden of disease study (Liu 2002) that reported that CHD cost the UK £1.7 billion in direct costs and £5.3 billion in indirect costs. A study by Bosanquet and Franks (1998) was also cited that reported that stroke patients account for £2.3 billion in 1995-1996, the equivalent of 5.8% of the NHS and social services expenditure.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	
5. Were the alternatives being compared clearly described?	√	
6. Was the form of economic evaluation stated?	√	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	√	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	√	Data from the CAPRIE trial was the primary source of evidence used to assess the effectiveness of the competing interventions. Other sources used to elicit estimates of clinical effectiveness included: the Nottingham Heart Attack Registry and the South London Stroke Registry.

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	√	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	
12. Were the methods used to value health states and other benefits stated?	√	Utility estimates for stroke were sourced from a meta-analysis of QoL estimates for stroke (Teng 2003). The Harvard utilities database was used to elicit utility estimates for the other health states.
13. Were the details of the subjects from whom valuations were obtained given?	×	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	√	
17. Were the methods for the estimation of quantities and unit costs described?	√	
18. Were currency and price data recorded?	√	£ Sterling, 2002
19. Were details of price adjustments for inflation or currency conversion given?	×	
20. Were details of any model used given?	√	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	√	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	Life time horizon (40 years)
23. Was the discount rate stated?	√	Costs were discounted at the rate of 6% and QALYs were discounted at the rate of 1.5% per year.

24. Was the choice of rate justified?	×	
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	√	
27. Was the approach to sensitivity analysis described?	√	Univariate, multivariate sensitivity and PSA were conducted.
28. Was the choice of variables for sensitivity analysis justified?	?	
29. Were the ranges over which the parameters were varied stated?	√	Key parameters were varied using the upper and lower 95% CI or by using specific alternative values.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	
31. Was an incremental analysis reported?	√	A two year treatment duration of clopidogrel plus aspirin versus aspirin alone produced an ICER of £21,489/QALY. Drug costs of 2 years treatment with clopidogrel plus aspirin versus aspirin alone were reported as £894.53 and £6.739, respectively.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	√	
33. Was the answer to the study question given?	√	
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	The authors comment that the RR for vascular death greatly affects the ICER and in the extreme worse case, results in ASA dominating clopidogrel. However, the extreme worse case was considered highly unlikely to occur in clinical practice.
36. Were generalisability issues addressed?	√	The authors comment that the CAPRIE trial was not specifically designed with health economic evaluation in mind and as such issues relating to patient disposition and previous disease history could detract from the generalisability of the trial results.

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Study name: The cost-effectiveness of the use of clopidogrel in acute coronary syndromes in five countries based upon the CURE study. Lamy *et al* (2004)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	√	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	
5. Were the alternatives being compared clearly described?	√	
6. Was the form of economic evaluation stated?	√	A trial based cost-effectiveness analysis was undertaken using outcomes data from the CURE trial.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	×	The authors do not disclose why a trial based cost-effectiveness analysis was conducted in preference to a cost utility analysis.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	√	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	√	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	The primary outcome measure was the incremental cost per event (a composite of CV death, MI and stroke) avoided.
12. Were the methods used to value health states and other benefits stated?	NA	
13. Were the details of the subjects from whom valuations were obtained given?	NA	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	×	
17. Were the methods for the estimation of quantities and unit costs described?	√	
18. Were currency and price data recorded?	√	For the UK CEA the currency used was £ sterling for the year 2001.
19. Were details of price adjustments for inflation or currency conversion given?	×	
20. Were details of any model used given?	NA	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	NA	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	The time horizon reflected the maximum follow up of the CURE trial (1 year).
23. Was the discount rate stated?	NA	
24. Was the choice of rate justified?	NA	
25. Was an explanation given if cost or benefits were not discounted?	√	No discounting was performed since the time horizon adopted for the CEA was < 1 year.

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	√	The authors report that boot strapping was used to calculate standard errors and 95% CIs for the difference in average costs. Confidence intervals for average costs and the ICERs were calculated using the bias corrected and accelerated method. These analyses were conducted using SAS 8.0.
27. Was the approach to sensitivity analysis described?	NA	
28. Was the choice of variables for sensitivity analysis justified?	NA	
29. Were the ranges over which the parameters were varied stated?	NA	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	
31. Was an incremental analysis reported?	√	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	√	Hospitalisation costs and drug costs were reported separately.
33. Was the answer to the study question given?	√	
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	The authors commented that non-medical costs such as loss of productivity (i.e. absence from work) and the personal costs associated with family and friends caring for patients that experience an MI or stroke was not included in the cost-effectiveness analyses. Since clopidogrel reduced the risk of major CV events versus aspirin they reasoned that their analysis could be viewed as underestimating the true cost-effectiveness of clopidogrel.

36. Were generalisability issues addressed?	√	The authors approach was to base clinical outcomes and resource use on the whole of the CURE trial population. This was justified by commenting that the clinical benefit would unlikely to vary by country or region, and a retrospective subgroup analysis by individual country would be underpowered and therefore statistically unreliable.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Clopidogrel used in combination with aspirin compared to aspirin alone in the treatment of non-ST-segment elevation acute coronary syndromes: a systematic review and economic evaluation. Main *et al* (2004)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	√	Data from a UK economic burden of CHD study, NHS hospital admission data for angina/AMI and NHS costs for prescribing antiplatelet drugs were used by the authors to illustrate the economic importance of the research question.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	
5. Were the alternatives being compared clearly described?	√	
6. Was the form of economic evaluation stated?	√	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	√	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	√	Clinical effectiveness estimates for the short term model was primarily sourced from the CURE trial, PRAIS-UK, NHAR and a Leeds PCI audit. Data from the NHAR was also used to derive transition probabilities for the long-term model using survival analysis techniques.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	√	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	
12. Were the methods used to value health states and other benefits stated?	×	Little information is given within the HTA report as to how health states were value.
13. Were the details of the subjects from whom valuations were obtained given?	×	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	√	In the short-term model, drug acquisition costs were based on undiscounted prices from the BNF. Other areas of resource use in the included: non-fatal MI, adverse events (stroke and major bleeds) and resource associated with death. Average annual health state costs in the long-term model were calculated by aggregating the resources consumed by each patient in the 1998 NHAR cohort according to whether they would have fallen into one of the three non-dead states in the model (IHD no event, non-fatal MI or post-MI).
17. Were the methods for the estimation of quantities and unit costs described?	√	Resource use and costs were detailed in Appendix 8.
18. Were currency and price data recorded?	√	
19. Were details of price adjustments for inflation or currency conversion given?	√	A 2001-02 price base was used.
20. Were details of any model used given?	√	

21. Was there a justification for the choice of model used and the key parameters on which it was based?	√	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	Life time horizon was adopted (equivalent to 40 years)
23. Was the discount rate stated?	√	A discount rate of 6% was used for costs and 1.5% for health benefits.
24. Was the choice of rate justified?	√	
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	√	
27. Was the approach to sensitivity analysis described?	√	One-way sensitivity analysis and PSA were conducted.
28. Was the choice of variables for sensitivity analysis justified?	√	
29. Were the ranges over which the parameters were varied stated?	√	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	
31. Was an incremental analysis reported?	√	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	√	
33. Was the answer to the study question given?	√	
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	

36. Were generalisability issues addressed?	√	Patients in the CURE were recruited from centres in 28 countries, of which patients from the UK accounted for approximately 6% of study population. The authors commented that in some respects, treatment patterns and resource use in the UK could be expected to differ from those in other centres participating in the CURE trial (e.g. the rate of PCI in UK patients with ACS, and IHD in general, is lower than in other developed countries. An implication of these differences is that baseline event rates in the ASA alone group of the CURE trial were unlikely to provide reliable estimates for UK practice.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis. Rogowski *et al* (2009)		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	√	
2. Was the economic importance of the research question stated?	√	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	√	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	√	
5. Were the alternatives being compared clearly described?	√	
6. Was the form of economic evaluation stated?	√	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	√	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	√	Clinical effectiveness estimates were primarily sourced from the CURE trial, PRAIS-UK - an observational cohort registry of ACS (May 1998 to Feb 1999) and the NHAR.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	√	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	√	
12. Were the methods used to value health states and other benefits stated?	?	Limited information regarding how health states were valued was given. The authors report that a mean utility of 0.8 (SD 0.09) was assigned to all patients who remained alive, irrespective of which health state they were in.
13. Were the details of the subjects from whom valuations were obtained given?	×	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	√	Mean annual costs were assigned to the IHD (event free), non-fatal MI and post-MI health states. In addition, a one off transition cost was also added when a patient died, based on resource data sourced from the NHAR. The state and transition costs related to hospital use only and were based on data collected in 1998 from the NHAR.

17. Were the methods for the estimation of quantities and unit costs described?	√	
18. Were currency and price data recorded?	√	£ sterling, 2001-2
19. Were details of price adjustments for inflation or currency conversion given?	×	
20. Were details of any model used given?	√	A two-phase Markov model was developed. The short-term component relates to the initial 12 month period after a patient presents with NSTE-ACS, and the long-term component extrapolates the patient's life-time costs and health outcomes conditional on surviving the first 12 months after the acute event.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	√	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	√	Life time horizon, equivalent to 40 years.
23. Was the discount rate stated?	√	Costs and health gains were discounted at an annual rate of 6% of 1.5%, respectively.
24. Was the choice of rate justified?	×	
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	×	These were not reported in the paper.
27. Was the approach to sensitivity analysis described?	√	A series of scenario sensitivity analyses were conducted and PSA was undertaken.
28. Was the choice of variables for sensitivity analysis justified?	×	
29. Were the ranges over which the parameters were varied stated?	×	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	√	
31. Was an incremental analysis reported?	√	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	×	
33. Was the answer to the study question given?	√	
34. Did conclusions follow from the data reported?	√	
35. Were conclusions accompanied by the appropriate caveats?	√	The study found that treatment durations in excess of 12 months became increasingly less cost-effective as the underlying event rate reduced over time. In addition, the impact of adverse events (e.g. bleeding) became important in the cost-effectiveness estimates for duration of clopidogrel > 12 months.
36. Were generalisability issues addressed?	√	Results of the cost-effectiveness analysis were consistent with those reported by other researchers in this area (i.e. that clopidogrel plus aspirin compared to aspirin alone provided good value for money in all countries or was cost saving from a societal perspective).
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient group presented in the base case economic evaluation is those patients with acute coronary syndromes (unstable angina, 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 by-pass grafting as per the licensed indication (see section 1.5).

As requested in the scope, results are also presented for the following subgroups: unstable angina, NSTEMI, STEMI and PLATO Invasive.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

An Excel-based cost-utility model was developed in line with the 'Guide to the methods of technology appraisal', published by NICE in June 2008. The model 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 to ensure that all major clinical and resource generating events that a patient may experience throughout the course of their remaining life are captured.

Figure 6.2 provides a diagrammatical representation of the health states and patient pathways in both the decision tree and Markov model.

A systematic literature search identified a number of papers that modelled cost-effectiveness in an ACS population (see Section 6.1.2). A review of these papers showed that the approach of using a short-term decision tree followed by a Markov model was common (Karnon *et al*, 2006, Vergel *et al*, 2007, Henriksson *et al,* 2008). In addition, this approach has also been used by independent evidence review groups in the preparation of Health Technology Assessments commissioned by the Institute in the ACS arena (Glycoprotein IIb/IIIa Antagonists, 2002, TA80 Clopidogrel in NSTEMI, 2004). Based on this evidence, the model structure selected was deemed to be valid and appropriate to answer the decision problem.

Figure 6.2: Diagrammatical representation of the health states and patient pathways in both the decision tree and Markov model.

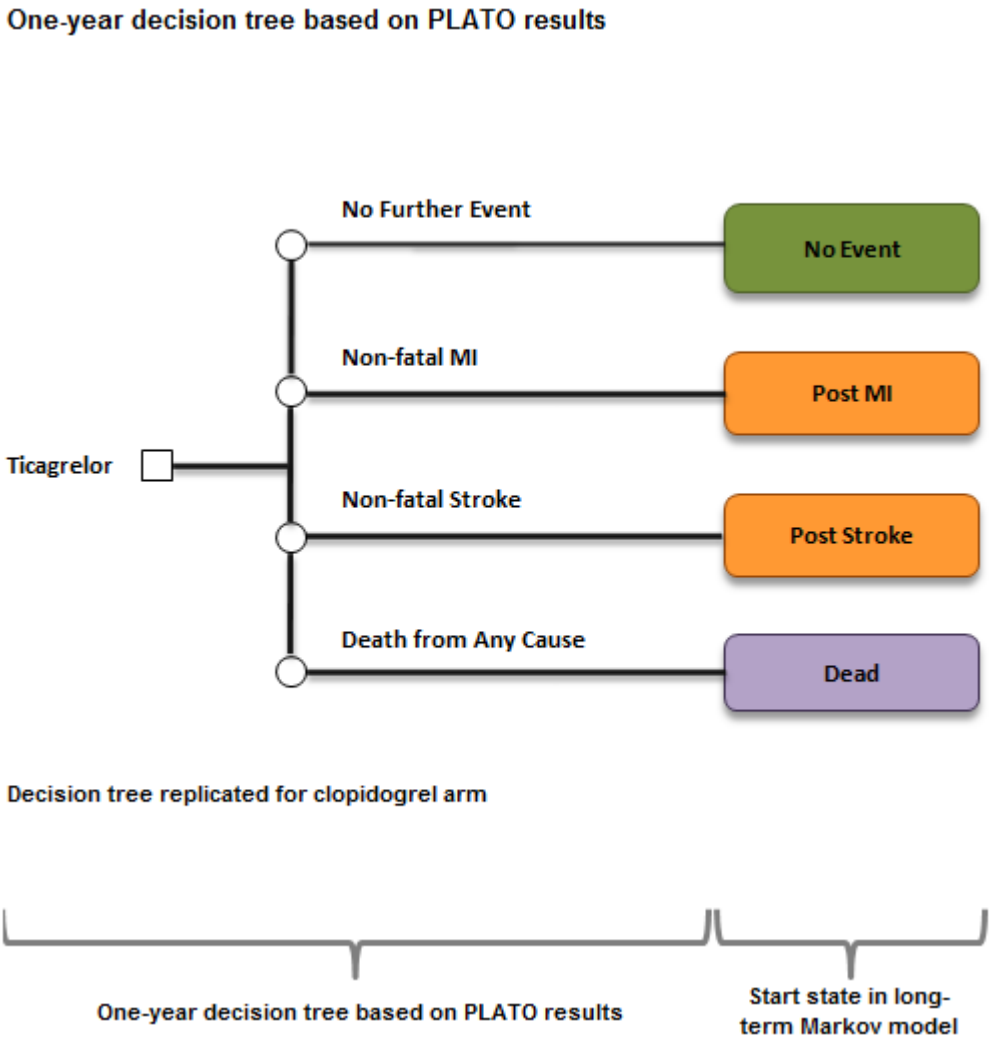
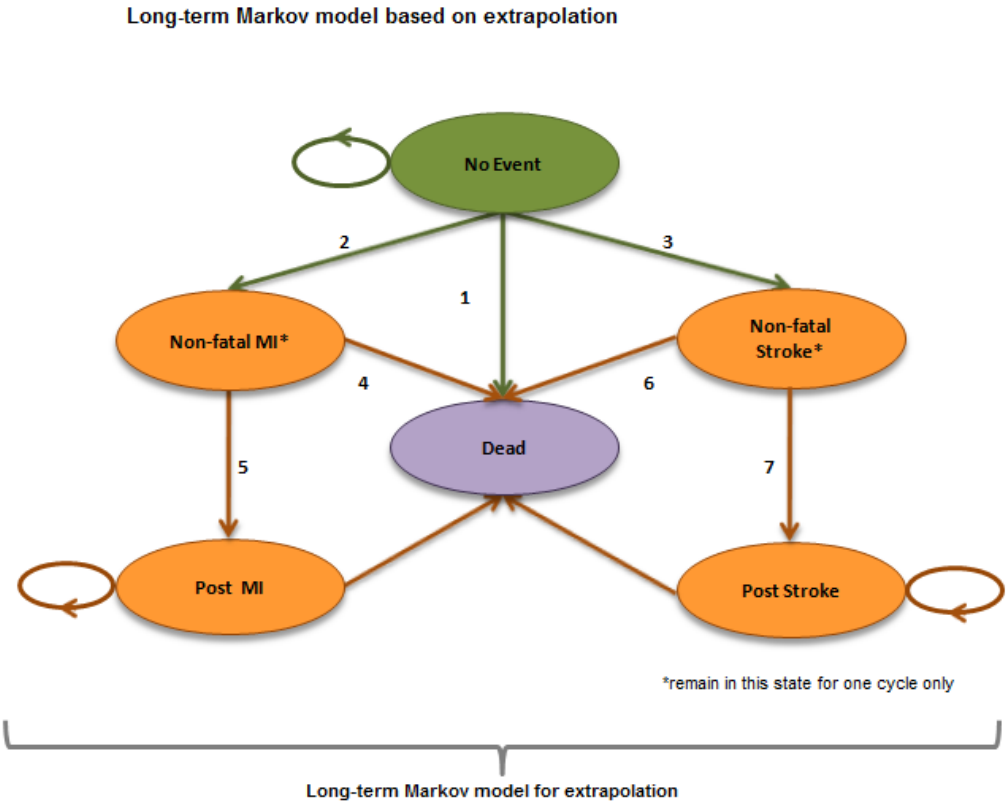


Figure 6.2: Diagrammatical representation of the health states and patient pathways in both the decision tree and Markov model.



1 Mortality risk for patients with no further event in the PLATO study
2 Risk of non-fatal MI for patients with no further event in the PLATO study
3 Risk of non-fatal stroke for patients with no further event in the PLATO study
4 Mortality risk first year after a non-fatal MI
5 Mortality risk second and subsequent years after a non-fatal MI
6 Mortality risk first year after a non-fatal stroke
7 Mortality risk second and subsequent years after a non-fatal stroke

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section2.4.

The PLATO study was designed to reflect the current management strategy across a broad spectrum of ACS patients (STEMI, NSTEMI and UA), which typically features the initiation of dual oral anti-platelet therapy as quickly as possible after presentation, prior to any decision being made on the ultimate treatment strategy employed, be that via PCI or CABG through medical management only. The combination of a one-year decision tree and long-term Markov model was designed to reflect the clinical trial data as closely as possible thus reflecting the current clinical care pathway whilst providing sufficient flexibility to extrapolate the costs and outcomes over the lifetime of the patient.

6.2.4 Please define what the health states in the model are meant to capture.

There are four mutually exclusive health states or nodes in the one-year decision tree:

- No Further Event – this node captures patients who had no further event in the year post their initial ACS event
- Non-fatal MI – this node captures patients who had a non-fatal MI in the year post their initial ACS event (note that this node also captures patients who had an MI followed by a stroke as patients were categorised according to first event unless they died – see Section 6.3.1 for more details)
- Non-fatal Stroke - this node captures patients who had a non-fatal stroke in the year post their initial ACS event (note that this node also captures patients who had a stroke followed by an MI as patients were categorised according to first event unless they died – see Section 6.3.1 for more details)
- Death from Any Cause – this node captures patients who died from either vascular or non-vascular causes in the year post their initial ACS event (note that this node also captures patients who could have had one or more MI, stroke or any combination therefore before they died – see Section 6.3.1 for more details)

The initial decision node reflects the main alternatives being evaluated i.e. whether a patient with ACS receives treatment with either ticagrelor (single 180mg loading dose followed by 90mg twice daily) or clopidogrel (300 or 600mg loading dose followed by 75mg once daily), both administered in combination with aspirin. The possibility of having a non-fatal MI, a non-fatal stroke or dying from either a vascular or non-vascular event, within a year of the initial ACS event, is modelled using chance nodes with the outcomes being conditional upon the initial treatment received by the patient. In addition to outcomes, cost and utility estimates associated with each node are captured as this data was collected as part of the PLATO health economic sub-study.

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. Patients who had an MI or stroke during the trial-based period are allocated to the Post MI and Post Stroke states respectively in the Markov model – the MI and Stroke health states in the Markov model are for patients who experience an event at least one-year post their index ACS event. The one-year decision tree determines the proportion of patients starting the Markov model in each of the six health states:

- No Further Event – this health state captures patients who did not suffer a further event in the decision tree (i.e. within the PLATO study period) and have, therefore, remained event free for at least one year. Each year, patients within this health state are at risk of a non-fatal MI, a non-fatal stroke or a fatal event and if one of these events occurs during a Markov cycle, the patient transitions to the Non-fatal MI, Non-fatal Stroke or absorbing Dead health state respectively. Patients, who do not experience any further event, remain in this health state.

- Non-fatal MI – this health state represents the first-year prognosis in terms of survival for patients suffering a new non-fatal MI after the initial trial period. If a patient dies in the first year after a new non-fatal MI, they transition to the absorbing Dead health state. The Non-fatal MI state is a so-called 'tunnel state' such that patients can only remain in it for one cycle. Patients who are still alive at one-year transition to the Post MI health state.
- Post MI - this health state represents the prognosis in terms of survival for patients in the second and subsequent years after a non-fatal MI. Patients who suffered an MI in the decision tree start the Markov model is this state. Patients who are still alive at the end of the cycle remain in this health state whilst patients who die transition to the absorbing Dead health state.
- Non-fatal Stroke – this health state represents the first-year prognosis in terms of survival for patients suffering a non-fatal stroke after the initial trial period. If a patient dies in the first year after a non-fatal stroke, they transition to the absorbing Dead health state. The Non-fatal Stroke state is a so-called 'tunnel state' such that patients can only remain in it for one cycle. Patients who are still alive at one-year transition to the Post Stroke health state.
- Post Stroke - this health state represents the prognosis in terms of survival for patients in the second and subsequent years after a non-fatal stroke. Patients who suffered a stroke in the decision tree start the Markov model in this state. Patients who are still alive at the end of the cycle remain in this health state whilst patients who die transition to the absorbing Dead health state.
- Dead – this health state represents those patients who have a fatal event (either vascular or non-vascular) during any cycle. This is an 'absorbing' health state in that further transitions are not permitted following entry into this state.

The reasoning behind this construct with regard to the 'tunnel' states is to allow for a worse prognosis the first year after a non-fatal event compared with second and subsequent years. In terms of survival this is consistent with data from the PLATO study whereby patients, conditional on not suffering a further event in the study, faced a lower risk of subsequent events the further away they got from their initial ACS event.

As in any Markov model, each health state is associated with a utility and a healthcare cost. The Markov model is based on a cycle length of one year and is run for a period of 40 years whereby the all of the patients would have died.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model structure selected captures both the acute phase of the disease and the long term outcomes associated with continuing morbidity and mortality by the inclusion of health states for non-fatal myocardial infarction (MI), non-fatal stroke and death. The model can be separated into two distinct phases: the trial based period of 12 months followed by extrapolation to cover the lifetime of the patient.

The one-year decision tree captures patients as they present with acute coronary syndromes (ACS) comprising of unstable angina (UA) or acute myocardial infarction (AMI), which is further separated into ST-elevation MI (STEMI) or non-ST-elevation MI (NSTEMI). With respect to the management of ACS patients, those with STEMI are recommended for early percutaneous coronary intervention (PCI), whilst those with NSTEMI or UA should be assessed using an established scoring system to predict six month mortality and the risk of future adverse cardiovascular events. Patients assessed to be at low risk of early recurrent coronary events should be considered for a conservative non-invasive strategy whilst those of medium to high risk are recommended to have early coronary angiography and revascularisation. All patients undergoing PCI for STEMI should receive aspirin and clopidogrel loading doses followed by maintenance treatment, whilst for those with NSTEMI and UA, antiplatelet therapy should be prescribed as outlined in Section 2.3.

Even with the current standard of care (i.e. dual antiplatelet therapy with clopidogrel and aspirin) serious vascular events recur, most of them within months of the index ACS event (Wivott *et al.* 2007). Within the one-year decision tree, patients are predicted to remain event-free, experience a non-fatal MI, a non-fatal stroke or die due to vascular or non-vascular related causes, with the rate of these events based on data from the PLATO study. At the end of one year, patients will be in one of four of the six health states in the Markov model and their long-term outcomes and life expectancy will be modelled based on the impact of any event they may have experienced in the first year post their index event or in subsequent years. The health states modelled represent the key cardiovascular events for which the ACS population is at risk.

Since antiplatelet treatment is taken for up to 12 months, it is assumed that there is no further treatment effect associated with either antiplatelet after the first year. This conservative approach means that all event rates in the Markov model are the same for patients who had been on either ticagrelor or clopidogrel with the only difference being in the number of patients who start the Markov model in each state.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 6.3: Key features of analysis

Factor	Chosen values	Rationale/Reference
Time horizon	Lifetime (40 years)	NICE Reference Case This is the time period over which all of patients will have died.
Cycle length – decision tree	One year	Clinically relevant given the length of the PLATO study, treatment duration and licence.
Cycle length – Markov model	One year	An annual cycle is sufficient to model disease progression and costs over a lifetime when this is expected to be approximately 40 years.
Half-cycle correction – decision tree	A half-cycle correction has not been applied to the decision tree.	NICE Reference Case
Half-cycle correction – Markov model	Yes, a half-cycle correction has been applied.	NICE Reference Case
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE Reference Case
Discount of 3.5% for utilities and costs	3.5% for costs and utilities	NICE Reference Case
Perspective (NHS/PSS)	NHS	NICE Reference Case
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years		

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The main comparator used in the model is clopidogrel plus aspirin, the current standard of care in ACS and the comparator used in the PLATO study. The patient group presented in the base case economic evaluation is those patients with acute coronary syndromes (STEMI, NSTEMI and unstable angina); including patients

managed medically, and those who are managed with PCI or CABG as per the per the licensed indication (see Section 1.5).

Prasugrel has recently been recommended by NICE as an option for ACS patients undergoing PCI only when immediate PCI for STEMI is recommended, stent thrombosis has occurred during clopidogrel treatment or the patient has diabetes mellitus (TA182 see Section 2.3). Although usage of prasugrel in clinical practice remains low [redacted] ticagrelor will also be compared with prasugrel in line with the NICE scope for this appraisal.

In Section 5.7.2 we have highlighted the inappropriateness of an indirect comparison of relative benefit of prasugrel and ticagrelor. In the absence of any direct head-to-head comparisons, however, a health economic assessment of ticagrelor in relation to prasugrel is necessary to determine where ticagrelor fits in to the existing therapeutic armamentarium. There are two pieces of evidence synthesis currently published, one which looks at the so-called "new" P2Y12 inhibitors (including prasugrel, ticagrelor, cangrelor and elinogrel (Bellemain-Appaix *et al*. 2010), and one which is an indirect comparison of prasugrel and ticagrelor, based on TRITON and PLATO (Biondi-Zoccai *et al.* 2010). Whilst AstraZeneca does not endorse such a comparative clinical approach based on TRITON-TIMI 38 and PLATO (for all the reasons noted in Section 5.7.2), we have used this one published indirect comparison for health economic modelling purposes.

6.2.8 ***Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.***

- ***The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).***
- ***The robustness and plausibility of the endpoint on which the rule is based.***
- ***Whether the 'response' criteria defined in the rule can be reasonably achieved.***
- ***The appropriateness and robustness of the time at which response is measured.***
- ***Whether the rule can be incorporated into routine clinical practice.***
- ***Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.***
- ***Issues with respect to withdrawal of treatment from non-responders and other equity considerations.***

A treatment continuation rule has not been assumed.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

In accordance with the model structure presented in Section 6.2.2, four transition parameters must be obtained to populate the nodes of the one-year decision tree:

- The probability of having a non-fatal MI
- The probability of having a non-fatal stroke
- The probability of dying from any cause
- The probability of not having a further event

It should be noted that the proportion of patients not having a further event is calculated as one minus the combined risk of the other three events.

To understand how the clinical trial data have been implemented into the model, a detailed description of the clinical pathways by treatment group from the PLATO study is shown in Table 6.4.

Table 6.4: Detailed clinical pathways in the PLATO study

Clinical pathway	Clopidogrel n=9291		Ticagrelor n=9333	
	n	Proportion	n	Proportion
1. No event	8226	0.8854	8432	0.9035
2. MI only	476	0.0512	417	0.0447
3. Stroke only	71	0.0076	77	0.0083
4. Dead vascular only	332	0.0357	248	0.0266
5. Dead non vascular only	51	0.0055	37	0.0040
6. MI followed by stroke and no further event	9	0.0010	4	0.0004
7. Stroke followed by MI and no further event	3	0.0003	4	0.0004
8. MI followed by dead vascular	88	0.0095	71	0.0076
9. MI followed by dead non vascular	12	0.0013	3	0.0003
10. Stroke followed by dead vascular	17	0.0018	29	0.0031
11. Stroke followed by dead non vascular	1	0.0001	6	0.0006
12. MI followed by stroke followed by dead vascular	4	0.0004	5	0.0005
13. MI followed by stroke followed by dead non vascular	0	0.0000	0	0.0000
14. Stroke followed by MI followed by dead vascular	1	0.0001	0	0.0000
15. Stroke followed by MI followed by dead non vascular	0	0.0000	0	0.0000

The clinical pathways detailed in Table 6.4 were consolidated into four distinct and mutually exclusive nodes: No Event, Non-fatal MI, Non-fatal Stroke and Dead Any Cause. The result of categorising patients into these four nodes is shown in Table 6.5.

Table 6.5: Clinical pathways according to the model structure

Clinical pathway	Clopidogrel n=9291		Ticagrelor n=9333	
	n	Proportion	n	Proportion
1. No Event	8226	0.8854	8432	0.9035
2. MI	485	0.0522	421	0.0451
3. Stroke	74	0.0080	81	0.0087
4. Dead Any Cause	506	0.0545	399	0.0428

Within this categorisation death takes precedence as it represents a terminal stage in the decision tree. Thus patients dying from either vascular or non-vascular causes are all categorised into the Dead Any Cause node even if an MI or a stroke (or both) occurred before the fatal event. Therefore, patients in rows 4 to 5, and 8 to 15 in Table 6.4 are all categorised as Dead Any Cause. For patients suffering both a non-fatal MI and a non-fatal stroke, the event occurring first takes precedence, therefore patients in row 6 in Table 6.4 are categorised into the MI node and patients in row 7 are categorised into the Stroke node.

The proportions of patients in each group as reported in Table 6.5 are crude proportions based on count data. However, as data in the PLATO study is time-to-event data, these observed proportions cannot be applied directly as probability estimates in the model. Instead, survival analysis is employed to determine the risk of events, and the results of the analysis have to be converted to probabilities in order to be incorporated into the model.

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 (the risk of events in the clopidogrel arm) and a hazard ratio (the treatment effect of ticagrelor) to be applied to the baseline risk. As there was a clear indication that the risk of events declined over time in the PLATO study, the Weibull model was deemed appropriate since it allows the hazard to change as time elapses from randomisation (Collett, 2003). Furthermore, transition probabilities for the relevant time period are easily derived employing the estimated scale and shape parameters of the Weibull distribution. The results of the Weibull regression equations are shown in Table 6.6. The results of the dead vascular analysis have been included as, although not used in the base case, this is used in the sensitivity analysis.

Table 6.6: Results of Weibull regression equations

Variable	Coefficient	Std Error	95% Confidence Intervals	
Dead any cause				
Treatment	-0.243	0.067	-0.374	-0.112
Constant	-5.374	0.093	-5.555	-5.192
ln gamma	-0.830	0.033	-0.894	-0.766
MI				
Treatment	-0.151	0.067	-0.282	-0.020
Constant	-5.202	0.087	-5.373	-5.032
ln gamma	-0.907	0.032	-0.971	-0.843
Stroke				
Treatment	0.086	0.161	-0.230	0.401
Constant	-7.392	0.235	-7.852	-6.931
ln gamma	-0.791	0.079	-0.945	-0.637
Dead vascular				
Treatment	-0.230	0.071	-0.370	-0.090
Constant	-5.359	0.094	-5.544	-5.174
ln gamma	-0.892	0.035	-0.961	-0.824

In order to derive transition probabilities for the one-year decision tree, the results of the statistical equations in Table 6.6 need to be transformed. In the case of a Weibull distribution, the annual transition probability of an event for period (t), denoted TP(t), is given by:

$$TP(t) = 1 - \exp(\lambda(t-1)^{\gamma} - \lambda t^{\gamma}).$$

Applying the above formula yields the transition probabilities or baseline risks for the three nodes in the decision tree as shown in Table 6.7. The results for the Dead Vascular health states have also been provided as this is used in the sensitivity analysis.

It can be seen from the Table 6.7 that the time-to-event analyses for the events of Dead Any Cause and Dead Vascular are identical to that presented in Table 3, Wallentin *et al*, 2009. However, the time-to-event analyses for the events of Non-fatal MI and Non-fatal Stroke differ slightly compared to the results presented in the published paper. The reason for this is that in the published paper, patients with a non-fatal MI or non-fatal stroke followed by death are included in the separate analysis of the endpoints of MI and stroke as well as mortality whereas these patients are only included in the analyses of mortality events in the current analyses. The reason for this is that the different nodes in the decision tree have to be mutually exclusive such that patients can only end up in one of the nodes.

Table 6.7: Comparison of modelled and published data

Node	From regression equations			From published paper		
	Baseline risk	Hazard ratio	95% Conf. Intervals	Baseline risk	Hazard ratio	95% Conf Intervals
Dead Any Cause	5.9%	0.78	(0.69-0.89)	5.9%	0.78	(0.69-0.89)
MI	5.8%	0.86	(0.75-0.98)	6.9%	0.84	(0.75-0.95)
Stroke	0.9%	1.09	(0.79-1.49)	1.3%	1.17	(0.91-1.52)
Dead Vascular	5.1%	0.79	(0.69-0.91)	5.1%	0.79	(0.69-0.91)

Graphs comparing the time-to-event analyses for the three endpoints in the one-year decision tree with the Kaplan Meier curves from the trial itself are shown in Figures 6.3 to 6.6. Note that the analysis for Dead Vascular is also shown as this is used in the sensitivity analysis.

Figure 6.3: Graph showing modelled versus actual survival data for Dead Any Cause node

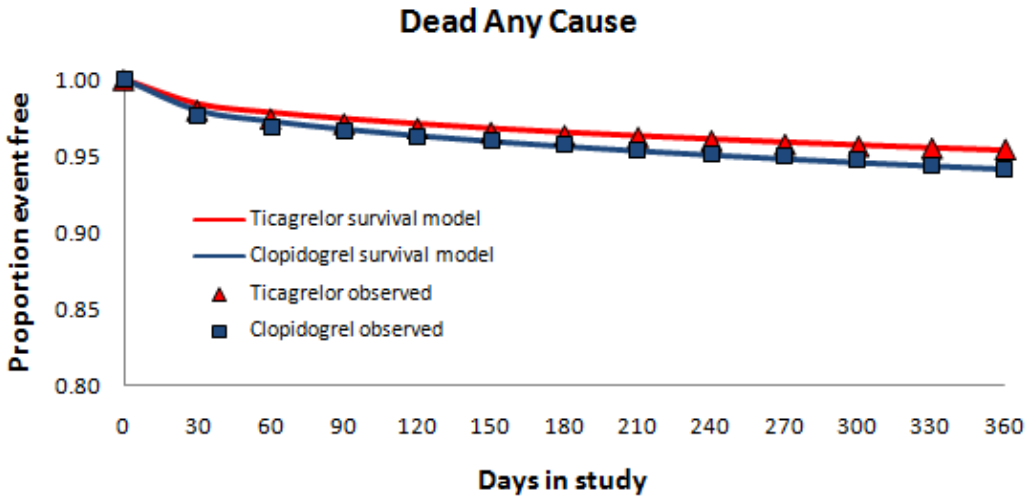


Figure 6.4: Graph showing modelled versus actual survival data for Myocardial Infarction node

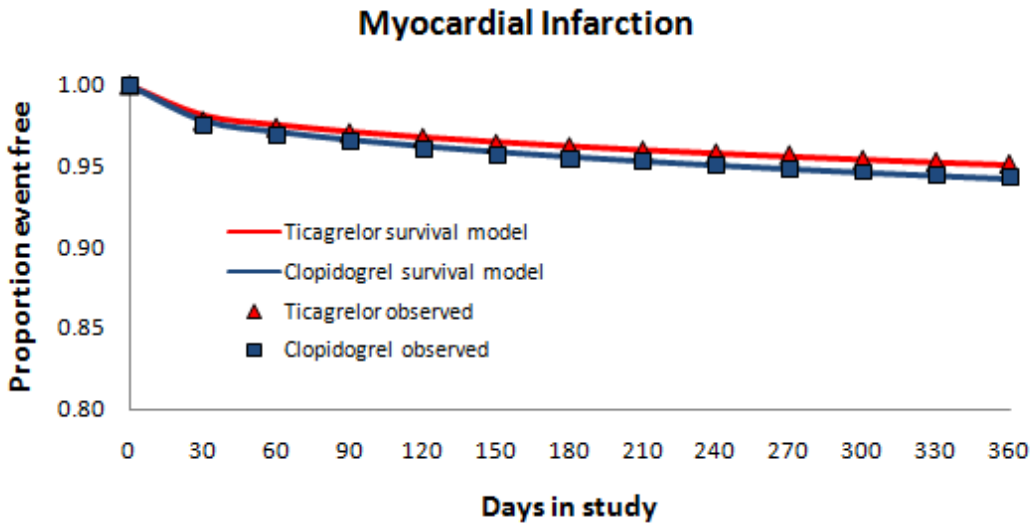


Figure 6.5: Graph showing modelled versus actual survival data for Stroke node

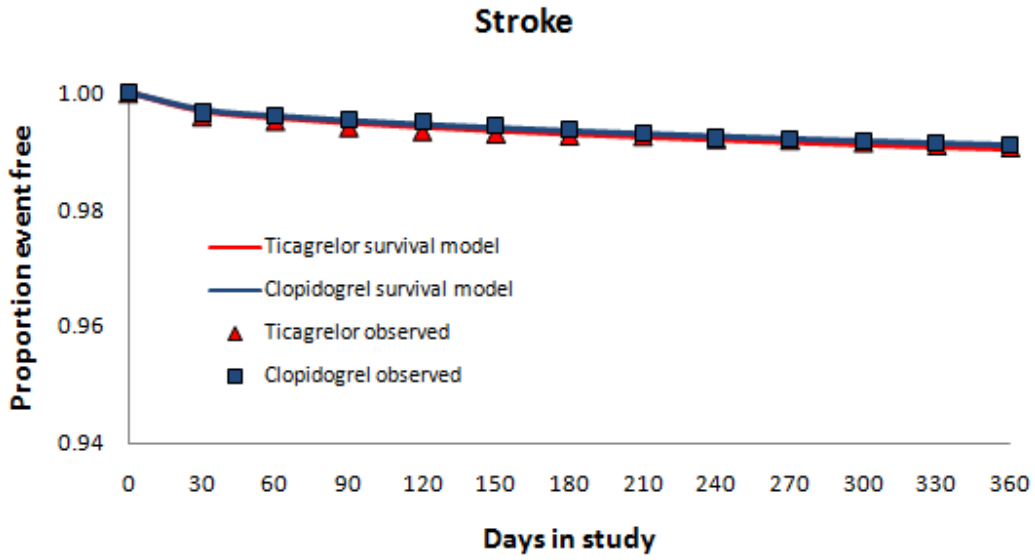
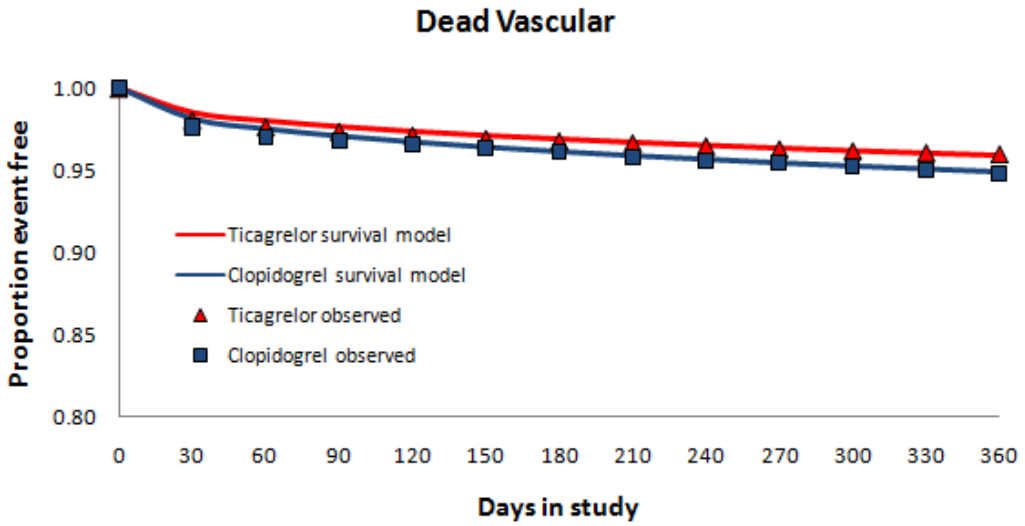


Figure 6.6: Graph showing modelled versus actual survival data for Dead Vascular node



The graphs in Figures 6.3 to 6.6 show that the time-to-event survival model is a very good fit to the actual trial data; therefore the modelled outcomes will provide an accurate reflection of the actual outcomes seen in the trial.

The characteristics of patients in the PLATO study in terms of age and gender have already been shown in Table 5.5. A comparison of these characteristics with those of ACS patients in England and Wales is shown in Table 6.8 (reference: Long-term treatment strategies, outcomes and resource use in patients with acute coronary syndrome – an observational study across secondary and primary care in a UK population. Data on File).

Table 6.8: Comparison of patient characteristics in terms of age and gender

Population	Mean Age	% Male	% Aged ≥75
PLATO study	62	71.6%	15.1%
ACS patients in England and Wales	70	64.6%	42.7%

Whilst the percentage of males amongst ACS patients in England and Wales is broadly similar to that within the PLATO trial, it can be seen that there is a considerable difference in both the mean age as well as the proportion of older patients. In order to accurately reflect the cost-effectiveness of ticagrelor for the ACS population in England and Wales, the Weibull regression equations were run with a dummy covariate taking the value of 1 for patients aged ≥75 years and the value of 0 for patients younger than 75. In order to get an age-adjusted event rate for the clopidogrel arm for a UK setting, the statistical model was run with the age covariate set to both 0 and 1. The baseline event rates used in the model were an average of the event rates for both age groups, weighted by the UK specific percentage of patients in each age group as shown in Table 6.9. It can be seen from Table 6.9 that there is a marked difference in event rates, especially Dead Any Cause and Dead Vascular, in the older age group, therefore adjusting for age is necessary if the cost-effectiveness analysis is to accurately reflect that of the UK ACS population.

Table 6.9: Baseline event rates used in the model to reflect the age of ACS patients in England and Wales

Clinical Endpoint	Age <75 (57.3%)	Aged ≥75 (42.7%)	Weighted average
Dead Any Cause	4.7%	12.2%	7.9%
MI	5.5%	7.4%	6.3%
Stroke	0.8%	1.6%	1.1%
Dead Vascular	4.2%	10.1%	6.7%

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

An explanation of how the transition probabilities for the one-year decision tree were calculated from the clinical data was provided in Section 6.3.1. Note that the clopidogrel probabilities are derived from the rates presented in Table 6.9 and the ticagrelor probabilities are derived by applying the hazard ratios from Table 6.7 to the clopidogrel rates in Table 6.9. The transition matrix for the decision tree is shown in Table 6.10.

Table 6.10: Transition matrix for one-year decision tree

Node	MI	Stroke	Dead Any Cause	No Event*
Clopidogrel	0.0628	0.0112	0.0789	0.8472
Ticagrelor	0.0540	0.0122	0.0619	0.8720

*calculated as 1-sum(pMI+pStroke+pDead) where pMI is the probability of having an MI, pStroke is the probability of having a stroke and pDead is the probability of death due to any cause

At the end of the one-year trial period modelled via a decision tree, patients will find themselves in either the No Event, Post MI, Post Stroke or Dead health state in the Markov model. The Non-fatal MI and Non-fatal Stroke health states in the Markov model are for those patients experiencing a subsequent event after the one-year trial period. It has been assumed 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. The transition matrix for the Markov model is shown in Table 6.11.

Table 6.11: Transition matrix for Markov model

	Transition to:					
Transition from:	**No Event**	**Non-fatal MI**	**Non-fatal Stroke**	**Post MI**	**Post Stroke**	**Dead**
No Event	1-(0.0315+0.0102+[p(d)*2.21])	0.0315	0.0102	0	0	p(d)*2.21
Non-fatal MI	0	0	0	1-[p(d)*5.84]	0	p(d)*5.84
Non-fatal Stroke	0	0	0	0	1-[p(d)*7.43]	p(d)*7.43
Post MI	0	0	0	1-[p(d)*2.21]	0	p(d)*2.21
Post Stroke	0	0	0	0	1-[p(d)*2.07]	p(d)*2.07
Dead	0	0	0	0	0	1

p(d) = probability of death taken from life tables

The transition matrix for the Markov model shows that, with the exception of the probabilities for transitioning from the No Event health state to the MI or Stroke health states, 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 life tables (reference: Interim Life Tables 2007-2009, Office for National Statistics).

The transition from No Event to Non-fatal MI or Non-fatal Stroke represents the probability of having another event for patients during the year following their initial ACS event. This data has been taken from a Myocardial Ischaemia National Audit Project/General Practice Research Database (MINAP/GPRD) study (reference: Long-term treatment strategies, outcomes and resource use in patients with acute coronary syndrome – an observational study across secondary and primary care in a UK population. Data on File). Whilst the MINAP dataset collects information on the acute clinical details of patients who have been admitted to hospital with ACS, and their treatment within hospital, no information on the treatment of these patients once they have been discharged into primary care is collected. The linkage between general practice data in GPRD and the hospital data in MINAP enables patients to be followed throughout their NHS care, allowing an assessment to be made of the impact of prior treatment, severity of ACS, hospital treatment and treatment within general practice following the event, on their eventual outcomes. The outcomes considered include a subsequent ACS event, bleeding, other adverse events and death. The study follows up patients admitted to hospital with ACS for a period of up to 24 months in both secondary and primary care. Based on data from the study, the probability of having a non-fatal MI in the period 12-24 months post initial event was 0.0315 (SE 0.0033) whilst the probability of having a stroke was 0.0102 (SE 0.0019), as shown in Table 6.12. It has been assumed for the purposes of the model that these probabilities remain constant.

Table 6.12: Incidence of MI and stroke per 100 patients 12-24 months after index ACS event

Outcome	Incidence (%)	Std Error	Lower 95% CI	Upper 95% CI
Myocardial infarction	3.15	0.327	2.57	3.85
Stroke	1.02	0.186	0.72	1.45

NICE has recently published clinical guideline CG94 on Unstable Angina and NSTEMI: the early management of unstable angina and non-ST-segment elevation myocardial infarction (March 2010). Within the guideline, the Guideline Development Group (GDG) attempted to extrapolate contemporary mortality rates from the MINAP dataset. Linear extrapolation was deemed to be implausible hence an alternative approach was taken in which standardised mortality ratios (SMRs) for a combined cohort of unstable angina and NSTEMI patients were calculated based on the observed mortality in the MINAP unstable angina and NSTEMI cohort between six months and one year, and mortality rates for the general population. It was assumed that the SMRs past six months are constant over time.

For the purposes of the cost-effectiveness analysis within the Guideline, the GDG needed different estimates of life expectancy for people who were: 1) alive at one year and had had a new MI in the past year; and 2) alive at one year but had not had a new MI in the past year. This was in order to reflect the potential prognostic benefit of avoiding an MI. Additional data was obtained from the MINAP cohort and the SMRs for those patients alive at one year with no new MI and those alive at one year with a new MI were calculated at 1.9720 and 5.2103 respectively.

It is worth noting that in their analysis of the data, the GDG also provided an estimate of the annual probability of having a new MI beyond the first year, based on the rate observed in the MINAP overall cohort between six months and one-year post UA/STEMI event. This annual probability of 4% is very similar to the 3.15% observed in our own study (reference MINAP/GPRD study). The GDG rate is higher than ours because it was estimated assuming that the rate of MI observed between six months and one year in the MINAP analysis overall cohort was constant, whereas our rate is the actual rate of MIs in the period 12-24 months post index event. In their analysis the GDG assumed that the probability of having an MI beyond the first year was constant over time – as assumption that we have also made in our modelling.

The Guideline was based on unstable angina and NSTEMI patients only; however, the population of interest for this cost-utility analysis also includes STEMI patients. A paper by Allen *et al*, 2006, provides hazard ratios for long-term mortality in patients with a spectrum of acute coronary syndromes compared with unstable angina, as shown in Table 6.13.

Table 6.13: Hazard ratios for long-term mortality compared to unstable angina (Allen *et al*, 2006)

Subgroups	Number of patients	Hazard ratio for mortality
Unstable angina	165	1.00
MMD (minor myocardial damage)	263	1.12
NSTEMI	202	1.28
STEMI	130	1.52
All patients	**760**	

By combining the unstable angina, MMD and NSTEMI groups and calculating a weighted average hazard ratio for this new combined group, it is possible to calculate a rebased hazard ratio for the STEMI population compared to the combined group, as shown in Table 6.14.

Table 6.14: Rebasing of hazard ratios from Allen *et al*, 2006

Subgroups combined	Number of patients	Hazard ratio for mortality	Rebased hazard ratio
UA, MMD and NSTEMI	630	1.14	1.00
STEMII	130	1.52	1.33
All patients	**760**		

The rebased hazard ratio of 1.33 for the STEMI population can then be used to calculate SMRs for STEMI patients, both with and without a new MI, using the SMRs calculated by the GDG for the UA/NSTEMI population. Based on the proportion of each subgroup in the ACS population for England and Wales, it is then possible to calculate weighted average SMRs for the total ACS population as shown in Table 6.15.

Table 6.15: SMRs from CG84 revised to include STEMI patients

Subgroups combined	% of ACS Population*	Revised SMRs	
		New MI	***No new MI***
UA and NSTEMI	63.5%	5.2103	1.9720
STEMII	36.5%	6.9478	2.6296
All patients		**5.8446**	**2.2121**

*Source: MINAP/GPRD study

Given that the two SMRs provide the excess mortality risk for an ACS patient over the general population, depending on whether they have had a recurrent MI or not in the last year, these values were used to calculate the transition probabilities to the Dead health state from the No Event and Non-fatal MI states within the Markov model as follows:

No Event to Dead: No new MI in the past year therefore an SMR of 2.21 applied to age and gender specific mortality rates from life tables

Non-fatal MI to Dead: Recurrent MI in the past year therefore an SMR of 5.84 applied to age and gender specific mortality rates from life tables

With regard to the transition from Post MI to Dead, it was assumed that since a patient in the Post MI health state has already had a recurrent MI, he/she would be likely to have a higher mortality risk than a patient in the No Event health state who has had no recurrent event. Conversely, a patient in the Post MI health state has already survived a year beyond their recurrent event and is therefore likely to have a lower mortality risk than patients in the Non-fatal MI health state. It would seem likely therefore that the mortality risk for patients in the Post MI health state would fall somewhere in between the two SMRs, but would be closer to 2.21 as the patient would be at least one year from their last event

A literature search for papers relating to mortality post MI did not reveal any additional data on relative risks that could be used for the Post MI health state. Therefore, in the absence of data, a conservative assumption was made to use the value of 2.21 as per the No Event to Dead transition. An upper 95% confidence interval of 4.2425 was tested in the sensitivity analysis.

Post MI to Dead: No MI in the past year therefore SMR of 2.21 applied to age and gender specific mortality rates from life tables

Transition probabilities were needed for both the Non-fatal Stroke to Dead and Post Stroke to Dead states within the Markov model. A literature search of statistics on stroke survival highlighted several papers reporting the relative risk of death post stroke, as shown in Table 6.16.

Table 6.16: Studies reporting the relative risk of death post stroke

Author	Year of publication	Study locality	Number of patients	Follow-up period	Relative risk of death	
					Year 1	*Year 2 +*
Dennis et al	1993	Oxford, UK	675	6.5 years	7.43	2.07
Hankey et al	2000	Australia	362	5 years	10.00	2.15
Loor et al	1999	Netherlands	221	3 years	NS	2.11

NS = not specified

Only the papers by Dennis *et al*, 1993, and Hankey *et al*, 2000, provide the relative risk of death for the first year post stroke compared with people of a similar age and sex in the general population, in the study locality. A decision was made to use the value of 7.43 from Dennis *et al*, 1993, because, although an older study, it was based on a UK dataset (the Oxfordshire Community Stroke Project), had the longest period of follow-up and the largest number of patients.

All three papers show a high level of consistency in the relative risk of dying in the second and subsequent years after a first stroke, ranging from 2.07 to 2.15. For the same reasons as stated above, the value of 2.07 from Dennis *et al,* 1993, was selected. The relative risk of death for the first year post stroke was taken directly from the paper whilst the relative risk for second and subsequent years was calculated as the average of the remaining years of follow-up which was consistent from year 2 onwards.

The values of 7.43 and 2.07 were used to calculate the transition probabilities to the Dead health state from the Non-fatal Stroke and Post Stroke states within the Markov model as follows:

Non-fatal Stroke to Dead	Year 1 post stroke therefore a relative risk of 7.43 applied to age and gender specific mortality rates from life tables
Post Stroke to Dead	Year 2 onwards post stroke therefore a relative risk of 2.07 applied to age and gender specific mortality rates from life tables

The transition probabilities within the Markov model are not based on any extrapolation of treatment effect but rather on the excess mortality risk of a subsequent MI or stroke and data collected from an observational study of long-term outcomes in ACS. As such it is believed that the extrapolation gives a realistic view of long-term outcomes in terms of life-years and QALYs gained.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Within the Markov model it is assumed that the probability of having a subsequent MI or stroke is constant over time. However, the probability of dying increases with age, therefore by using life tables to model mortality, the impact of increasing age and hence mortality risk with each cycle is accounted for.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No intermediate outcome measures were used.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

No clinical experts were used to estimate any of the parameter values used in the model.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Sections 6.3.1 and 6.3.2 describe how the clinical data were implemented into the model and provide information on the derivation of the transition probabilities respectively. The following table lists all the variables used in the cost-effectiveness analysis. Note that the values for Dead Vascular were not used in the base case analysis but in the sensitivity analysis.

Table 6.17 Summary of variables applied in the economic model

Variable	Value (95% CI)	Distribution	Source
General			
Mean age	70		MINAP/GPRD study see 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 as per 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 as per 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

Variable	Value (95% CI)	Distribution	Source
Non-fatal MI	0.0540 (0.0474-0.0615)	N/A	clopidogrel event rates and ticagrelor hazard ratios as per section 6.3.1
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 as per 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 (01817-4.2425)	LogNormal	CG84 and Allen *et al*, 2006, as per 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 a*l, 1993, as per Section 6.3.2
Post Stroke	2.0715 (1.30-3.32)	LogNormal	

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

Costs and clinical outcomes, in terms of life years and QALYs, continue to accrue beyond the trial follow-up period of one-year; however no treatment effect is assumed beyond one-year. This means that the transition probabilities between states in the Markov model are the same for both treatment arms, the only difference being the number of patients who start the Markov model in each state, which is based on the output of the one-year decision tree.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumption 1:

Adverse events are not explicitly modelled as per the model structure shown in Section 6.2.2.

Adverse events are not modelled as specific health states; however, both costs and health related-quality of life decrements associated with all adverse events are still included in the analysis as they are part of the individual patient level data from the PLATO HECON sub-study that are used to estimate costs and QALYs for the different nodes of the short-term decision tree.

Bleeding constitutes the most common, clinically significant safety concern during effective anti-platelet treatment. PLATO-defined 'Total Major' bleeding was the key safety endpoint in the trial (Wallentin *et al,* 2009) and there was no overall significant

difference in the primary safety endpoint between the ticagrelor and clopidogrel arms of the study.

An analysis of the patient level costs for patients in the 12-month cohort who experienced a major bleed showed that patients with major bleeding in the ticagrelor arm had lower resource use costs than those in the clopidogrel arm, see Table 6.18. Patients who did not suffer a major bleed had substantially lower costs than those patients who did, however, again, these costs were lower in the ticagrelor arm, see Table 6.19.

Table 6.18: Total UK Patient Cost (GBP) Across Index and Post-index Event Summary Randomised Patients with Major Bleeding, 12-Month Cohort

Group	n	Mean	Standard error	Standard Deviation	95% CI on the Mean
Ticagrelor 90 mg bd	570	18888.71	379.614	9063.16	(18143.09, 19634.32)
Clopidogrel 75 mg od	595	19867.05	452.0977	11027.85	(18979.15, 20754.95)
Overall	1165	19388.38	296.5508	10121.9	(18806.54, 19970.21)
Difference	.	-978.34	592.7995	10114.41	(-2141.42,184.73)

Mean, standard deviation, standard error and 95% CI for Differences were obtained from a t-test comparison between treatments; 12 Month Cohort patients have a randomization date before January 18, 2008.

Table 6.19: Total UK Patient Cost (GBP) Across Index and Post-index Event Summary Randomised Patients with No Major Bleeding, 12-Month Cohort

Group	n	Mean	Standard error	Standard Deviation	95% CI on the Mean
Ticagrelor 90 mg bd	4721	8017.47	83.6946	5750.62	(7853.39, 8181.55)
Clopidogrel 75 mg od	4680	8153.77	91.6208	6267.83	(7974.15, 8333.39)
Overall	9401	8085.32	62.0235	6013.72	(7963.74, 8206.90)
Difference	.	-136.31	124.0468	6013.66	(-379.46,106.85)

Mean, standard deviation, standard error and 95% CI for Differences were obtained from a t-test comparison between treatments; 12 Month Cohort patients have a randomization date before January 18, 2008.

Dyspnoea was another observed adverse reaction and was reported more frequently with ticagrelor than clopidogrel (13.8% vs. 7.8%) in the PLATO study (Wallentin *et al.* 2009). Most reported symptoms of dyspnoea were mild to moderate in intensity and 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 (Wallentin *et al,* 2009).

An analysis of the patient level costs for patients in the 12-month cohort who experienced dyspnoea showed that patients experiencing dyspnoea in the ticagrelor arm had lower resource use costs than those in the clopidogrel arm, see Table 6.20. Patients who did not suffer dyspnoea had lower costs than those patients who did, however, again, these costs were lower in the ticagrelor arm, see Table 6.21.

Table 6.20: Total UK Patient Cost (GBP) Across Index and Post-index Event Summary Randomised Patients with Dyspnoea, 12-Month Cohort

Group	n	Mean	Standard error	Standard Deviation	95% CI on the Mean
Ticagrelor 90 mg bd	790	10725.35	291.6812	8198.26	(10152.79, 11297.91)
Clopidogrel 75 mg od	413	11011.60	506.437	10292.02	(10016.08, 12007.13)
Overall	1203	10823.62	258.5911	8969.05	(10316.28, 11330.96)
Difference	.	-286.25	544.7803	8971.75	(-1355.08,782.57)

Mean, standard deviation, standard error and 95% CI for Differences were obtained from a t-test comparison between treatments; 12 Month Cohort patients have a randomization date before January 18, 2008.

Table 6.21: Total UK Patient Cost (GBP) Across Index and Post-index Event Summary Randomised Patients with No Dyspnoea, 12-Month Cohort

Group	n	Mean	Standard error	Standard Deviation	95% CI on the Mean
Ticagrelor 90 mg bd	4501	8918.91	101.2673	6793.97	(8720.37, 9117.44)
Clopidogrel 75 mg od	4862	9344.46	109.5779	7640.65	(9129.64, 9559.28)
Overall	9363	9139.89	74.9125	7248.73	(8993.04, 9286.73)
Difference	.	-425.55	149.88	7246	(-719.35,-131.76)

Mean, standard deviation, standard error and 95% CI for Differences were obtained from a t-test comparison between treatments; 12 Month Cohort patients have a randomization date before January 18, 2008.

Assumption 2:

Adverse events such as bleeding and dyspnoea have no long-term prognostic impact beyond the duration of the clinical trial.

It has been assumed that the trial period of 12 months was a sufficiently long to be able to capture the impact of bleeding and dyspnoea both in terms of cost and impact on HRQL via the PLATO HECON sub-study. Consequently there is no further modelling of these adverse events in the long-term Markov model.

Assumption 3:

There is no explicit modelling of further cardiovascular events when a non–fatal event has occurred in the model (either in the one-year decision tree or in the long-term Markov model).

However, the Non-fatal MI and Non-fatal Stroke states, as well as the Post MI and Post Stroke states, make it possible to model increased costs, decreased utility and reduced life expectancy that on average encompass a worse prognosis due to further cardiovascular events, if deemed appropriate.

Assumption 4:

No treatment effects were modelled beyond the one-year decision tree.

In the absence of any evidence to support the impact of treatment effects beyond the follow-up period of the PLATO trial, it is assumed that in the Markov model, all transition probabilities between states are the same for both treatment arms.

Assumption 5:

The probability of having a non-fatal MI or non-fatal stroke at least one-year post the index ACS event is assumed to be constant at 3.15% and 1.02% respectively.

There is a lack of data showing how the likelihood of a subsequent event changes over time. In the recently published NICE clinical guideline on unstable angina and NSTEMI (CG94, March 2010), a similar assumption was made that the rate of MI remained constant at 4%.

Assumption 6:

The relative risk compared to standard UK life tables of dying at least one-year after having a subsequent MI is assumed to be the same as that of dying at least one year post the index ACS event (see Section 6.3.2 for further details).

Whilst it is acknowledged that patients who have had a subsequent MI may have a higher mortality risk than those have not, given that they have survived a year past this subsequent event, and the lack of data to make any other judgement, a relative risk of 2.21 was assumed.

Assumption 7:

A utility decrement of 0.0328 was applied to the baseline utility values obtained from the PLATO HECON sub-study.

The mean age of patients in the PLATO trial was 62.2 compared to 70.4 for the UK ACS population. Given that utility decreases with age, it was deemed appropriate to reduce the baseline utility to account for the older UK population. A utility decrement of 0.004 per year (Kind *et al,* 1998) was applied.

Assumption 8:

A utility decrement of 0.004 was applied to each cycle beyond the first year.

As already stated, utility decreases with age ((Kind *et al,* 1998). In order to take into account the aging population in the Markov model, a utility decrement of 0.004 was applied to each patient for each cycle that they remained alive.

Assumption 9:

No discontinuations other than due to death are included in the model.

The length of treatment for both ticagrelor and clopidogrel is assumed to be 365 days for those still alive at the end of the one-year trial period. For those patients who died during the year, the length of treatment is assumed to be 183 days assuming that they died on average mid-way through the year. The actual length of treatment from the trial has been used in the sensitivity analysis.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Acute coronary syndrome (ACS) comprises unstable angina and myocardial infarction (MI), both of which have an impact on a patient's quality of life. This impact can be both short-term, with respect to the actual ACS event which will require hospitalisation, and long-term with respect to lifestyle changes that may have to be made post-event to reduce the possibility of recurrence.

Unstable angina is a pain or discomfort felt in the chest, however, in some cases the pain may spread to the arm, neck, stomach or jaw. Some patients describe the feeling as one of severe tightness, while others say that it is more of a dull ache. Symptoms of experiencing shortness of breath have also been reported. The pain may be similar to a bout of stable angina, but it is usually more severe and lasts longer. Indeed, in people who have stable angina, the pain usually goes off after a few minutes, whilst an ACS pain usually lasts more than 15 minutes - sometimes several hours. Unstable angina requires short-term hospitalisation and typical treatment is with a conservative non-invasive strategy.

The symptoms of a myocardial infarction or heart attack vary from one person to another but can range from a severe pain in the centre of the chest, to a mild chest discomfort resulting in a feeling of being generally unwell. The common symptoms of a heart attack include:

- Central chest pain
- A pain which may spread to the arms, neck or jaw
- Feeling sick or sweaty as well as having central chest pain
- Feeling short of breath as well as having central chest pain.

The less common symptoms of a heart attack include:

- A dull pain, ache or 'heavy' feeling in your chest.
- A mild discomfort in the chest that makes you feel generally unwell.
- The pain or discomfort may spread to your back or stomach.
- The pain or discomfort may feel like a bad episode of indigestion.

- Feeling a bit light-headed or dizzy as well as having chest pain.

Patients suffering an ST-elevation MI (STEMI) are recommended to receive either early percutaneous coronary intervention (PCI) or rescue PCI where facilities are not immediately available. Patients suffering a non-ST-segment elevation MI (NSTEMI) are recommended to have early coronary angiography and revascularisation (as per NICE Clinical Guideline 94). These procedures require a longer period of hospitalisation than for unstable angina and may therefore have a greater short-term impact on HRQOL.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

There is likely to be an immediate impact on HRQL with hospitalisation and treatment for the actual ACS event, however this is likely to be a short-term decrement and a patient's HRQL is estimated to improve steadily over the course of the year following the event (Kim *et al,* 2005, Lacey *et al,* 2003).

In Kim *et al*, 2005, patients from 45 centres across England and Scotland, diagnosed with unstable angina or NSTEMI were randomised to an early interventional strategy or to a more conservative strategy. The study investigated the impact of these alternative treatment strategies on HRQL using EQ-5D, which was measured at baseline, four months and one year. Although the results showed that mean changes from baseline were better for the interventional rather than the conservative strategy, both strategies showed a significant improvement in HRQL from baseline to four months. Results for the one-year follow-up showed a further increase in utility scores for both treatment groups.

In Lacey *et al*, 2003, longitudinal HRQL data was collected from patients discharged from two acute hospitals in Sheffield, after recovering from an acute MI. Data was collected at six weeks, six months and one year after discharge from hospital using EQ-5D. The results showed a statistically significant improvement in HRQOL between six weeks and one-year.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- ***Method of elicitation.***
- ***Method of valuation.***
- ***Point when measurements were made.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***

PLATO HECON Sub-study

The PLATO study included a pre-specified Health Economics (HECON) and Quality of Life sub-study. It was pre-specified that the EQ-5D questionnaire would be administered in all countries in the study where an official language version of EQ-5D was available, which, as of March 2006, was: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Guatemala, Hong Kong, Hungary, Indonesia, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, The Netherlands, New Zealand, Norway, Peru, Poland, Portugal, Romania, Russia, South Africa, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom (UK), Uruguay, United States of America (USA) and Venezuela. In addition, it was pre-specified that the UK tariff would be used to convert the EQ-5D results to utility scores. The EQ-5D questionnaires were administered at discharge from the index visit (V1), at the 6 month visit (V4), and at the End of Treatment (V_EOT) which, for patients who completed a full year of study, was Visit 6 (V6).

Data Collection

A paper version of the 5-Dimensional questionnaire part of the EQ-5D instrument was used in the study. The conversion of the EQ-5D questionnaire to utility values was done using the UK Time Trade-Off (TTO) value set (as recommended in the 'Guide to the methods of technology appraisal').

A total of 18,624 patients were enrolled in PLATO (referred to as the full cohort). Of these, 15,212 (82%) had a utility score calculated at discharge from the index hospitalisation (V1). At V4 and V6 the percentage of patients in the full cohort with a utility score was 80% and 79% respectively. Of the 10,686 patients enrolled prior to January 18, 2008, who were eligible for a 12 month follow-up (referred to as the 12-month cohort), 8,840 (83%) had a utility score calculated at V1. The corresponding percentage of patients in the 12-month cohort with utility score at V4 and V6 was 81% and 80% respectively.

Calculations of Utility

For the purpose of the cost-effectiveness analysis, the 12-month cohort was used to calculate the utility accrued in the study. Only the per-protocol EQ-5D questionnaires were considered for this analysis and patients were excluded if they did not have the EQ-5D completed at V1. The utility scores were calculated as follows:

1) The utility was calculated as area under the curve based on the utility estimate at V1, V4 and V6.

2) Patients who had a valid utility estimate at V1 and died prior to V4 and patients with a valid utility estimate at V1 and V4 and who died prior to V6 had their last utility estimate carried forward to the time of death, where it was assumed that the death was instant without any utility decrement from the last observed value to the time of death.

3) The utility accrued during the study, by treatment group, for the initial one-year decision tree was based on the following mutually exclusive groups:

   (a) No Event node: patients who did not experience any primary endpoint event

   (b) Vascular Death node: patients who died from vascular causes

   (c) Non-vascular Death node: patients who died from non-vascular causes

   (d) MI node: patients who were alive at the end of the study and had a non-fatal MI as their first event

   (e) Stroke Node: Patients who were alive at the end of the study and had a non-fatal stroke as their first event

Results

Table 6.22 and Table 6.23 present the average utility score by visit for the full cohort and for the 12-month cohort, respectively. The utility score in the two cohorts are almost identical with the only variation on the third decimal point, indicating that using the 12-month cohort that had a planned 12-month follow-up does not introduce bias. Therefore, the 12-month cohort was used for the additional analyses presented below.

Table 6.22: Average utility score in the full cohort

	Ticagrelor		Clopidogrel	
		Utility score		Utility score
Visit	N	Mean / SE	N	Mean / SE
V1	7631	0.845 / 0.003	7581	0.843 / 0.003
V4	6449	0.865 / 0.002	6464	0.864 / 0.002
V6	3767	0.874 / 0.003	3727	0.876 / 0.003

SE Standard error; V1 Visit 1; V4 Visit 4; V6 Visit 6

Table 6.23: Average utility score in the 12-month cohort

	Ticagrelor		Clopidogrel	
		Utility score		Utility score
Visit	N	Mean / SE	N	Mean / SE
V1	4414	0.843 / 0.004	4426	0.844 / 0.004
V4	3779	0.866 / 0.003	3778	0.866 / 0.003
V6	3597	0.873 / 0.003	3566	0.876 / 0.003

SE Standard error; V1 Visit 1; V4 Visit 4; V6 Visit 6

12-month Cohort patients have a randomisation date before January 18, 2008

Tables 6.24 and 6.25 present the utility estimates for the 12-month cohort by nodes in the one-year decision-tree. In Table 6.24 the results are presented as the average, independent of treatment group, and in Table 6.25 the results are presented by treatment group.

Table 6.24: Estimated mean utility score by node (including deaths) for the 12-month cohort

Node in decision	N	Overall estimated mean utility score		
		Patients with events	Mean utility score	Standard error
No Event	6983	6266	0.875	0.002
MI		361	0.812	0.010
Stroke		49	0.736	0.038
Vascular Death		259	0.246	0.015
Non-vascular death		48	0.264	0.039
All Cause Death		307	0.249	0.014

MI Myocardial infarction; CV Cardiovascular;
A single event may be counted in more than one row.
Only patients with the potential for up to 12 months of exposure are considered.

Table 6.25: Estimated mean utility score by node (including deaths) and treatment for the 12-month cohort

Node in decision	Ticagrelor 90 mg bd				Clopidogrel 75 mg od				
	N	Patients with events	Mean utility score	Std error	N	Patients with events	Mean utility score	Std error	Mean Diff
No Event	3473	3153	0.873	0.003	3510	3113	0.877	0.003	-0.004
MI		164	0.819	0.014		197	0.807	0.014	0.012
Stroke		28	0.742	0.062		21	0.728	0.032	0.014
Vascular Death		109	0.251	0.023		150	0.243	0.020	0.008
Non-vascular death		19	0.204	0.042		29	0.303	0.057	-0.100
All Cause Death		128	0.244	0.021		179	0.253	0.019	-0.009

MI Myocardial infarction; CV Cardiovascular;
A single event may be counted in more than one row.
Only patients with the potential for up to 12 months of exposure are considered

Discussion

The PLATO study obtained the largest collection of EQ-5D questionnaires in any ACS study. In the RITA 3 study, EQ-5D was collected at baseline in 1,798 patients (Kim *et al*, 2005) and in the more recent TRITON-TIMI 38 study, EQ-5D was collected in only 461 patients at baseline (Wiviott *et al*, 2007). Due to the small number of patients who participated in the TRITON quality of life sub-study, the health economic model in the prasugrel NICE submission utilised utility information from the literature rather than empirical data from the trial. One of the strengths of the PLATO study is that sufficient quality of life information was collected to provide trial-based utility estimates for the health economic modelling.

Consistency with Reference Case

The NICE 'Guide to the methods of technology appraisal', states that for the reference case, the measurement of changes in changes in health-related quality of life (HRQL) should be reported directly from patients and the value of these changes should be based on public preferences with the EQ-5D as the preferred measure.

With respect to the HRQL scores obtained from the PLATO HECON sub-study, these were elicited from ACS patients using EQ-5D and converted to utility scores using preference values from a large UK population study. Hence, the utility scores obtained from the trial are consistent with the reference case.

Appropriateness for Cost-effectiveness Analysis

Given that the utility scores collected as part of the HECON sub-study meet the criteria set out for the reference case, these have been used in the base-case cost-effectiveness analysis. However, a review of the utility scores obtained via a literature search was performed to ensure a level of consistency and these utility values have been used within the sensitivity analysis. The utility scores obtained from the literature have also been used in the sub-group analysis versus prasugrel.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- ***Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.***
- ***Details of the methodology used.***
- ***Details of validation of the mapping technique.***

Not applicable

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

Utility weights were elicited from medical journal articles and the Tufts CEA Registry (utility dataset).

A systematic search of the medical literature (EMBASE, MEDLINE and NHS-EED) was conducted for English language articles that could be expected to contain utility weights that would most closely matched the NICE reference case (i.e. health state utilities should be reported directly from patients and based on public preferences using a choice based method [time trade-off]. The EQ-5D is the preferred HRQL measurement instrument).

The search strategy that was used combined a HRQL search filter developed by researchers at ScHARR (www.york.ac.uk/inst/crd/intertasc/qol1.htm) with the generic stem for ACS used to produce the SIGN ACS guidelines (2007). Additional search terms were included to identify utility weights for stroke and major bleed (see section

9.12). The time period of the search was limited to 01/01/2000 to date. Conference abstracts were excluded for further review.

Full text articles were selected for further review by a single assessor according to the following criteria: the title/abstract must contain reference of the effect of ACS, myocardial infarction, stroke or major bleed on HRQL and make reference to the EQ-5D. The study must also have been conducted in a UK patient or general population. Studies conducted in European or US populations were also considered of potential interest.

Sixty three references were identified as being of potential interest and the full text articles were ordered for further review (EMBASE (n=21), MEDLINE (n=25) and NHS-EED (n=17)). Following independent review by two assessors, a total of X studies were identified that contained health states utilities for ACS, acute MI, stroke or major bleed that most closely matched the NICE reference case.

The utility weights reported in the seven cost-utility analyses of oral anti-platelet therapies identified as being of use in helping to inform the ticagrelor CUA (see section 6.1.2) were also extracted.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- ***Population in which health effects were measured.***
- ***Information on recruitment.***
- ***Interventions and comparators.***
- ***Sample size.***
- ***Response rates.***
- ***Description of health states.***
- ***Adverse events.***
- ***Appropriateness of health states given condition and treatment pathway.***
- ***Method of elicitation.***
- ***Method of valuation.***
- ***Mapping.***
- ***Uncertainty around values.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***
- ***Appropriateness of the study for cost-effectiveness analysis.***

The details of the studies in which HRQL was measured (or reported) that may provide utility estimates for the ticagrelor NICE STA submission are presented in table 6.26.

Table 6.26: Summary of the HRQL papers

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
Daiichi-Sankyo/Eli Lilly(2009)	Utility decrements from baseline for the CUA model health states were taken from the US Medical Expenditure Panel Survey (MEPS) [Sullivan 2006]. The survey collected HRQL data from 38,678 US members of the general public. Included in the database were 244 people with a history of MI (mean age 62) and 340 patients with a history of stroke (mean age 68 years). Utility decrements for major bleed were estimated from a paper by Wechowski (2006). The authors assumed a major bleed would result in a 25% decrement in baseline utility for a mean of 14 days.	EQ-5D VAS and EQ-5D HI.	EQ-5D HI utility decrement ACS Stroke/MI	 0.0409 (SE 0.0002) 0.0524 (SE 0.0001)	The utility weights for ACS/stroke and MI were derived from US patients. The scoring algorithm for the EQ-5D index descriptive system was based on US community preferences. These weights are considered inappropriate to use in the ticagrelor CUA.
Dorman *et al.* (2000)	HRQL was assessed in a series of 152 patients identified in a UK (Lothian) hospital	EQ-5D HI score	Dependent stroke	0.38 (0.29 to 0.47)	The utility weights were directly elicited from UK

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	based registry of inpatients and outpatients with first or recurrent stroke. Patients were assessed at a median interval of 72 weeks after the onset of their index stroke (IQR: 43 to 104 weeks). Of the patients that participated in the study, 92 were able to complete the questionnaires by themselves; the remaining 60 could only be assessed by interview.		Independent stroke	0.74 (0.69 to 0.79)	patients (a median of 72 weeks after onset of their index stroke) using the EQ-5D. They were considered of relevance for use in the ticagrelor CUA.
Duncan *et al* (2000)	HRQL data was collected on a sample of 459 US patients that had experienced a stroke to assess post-event recovery. Assessments were made within 14 days post-stroke and re-evaluated at 1, 3 and 6 months. The mean patient age was 70 years (SD 11.4), 46.6% were male, 80% were white, 93.7% had ischaemic strokes and 6.3% were haemorrhagic strokes. Every patient was	TTO	Utility estimate month 6 Mild stroke (Rankin 2-3) Major stroke (Rankin 4-5)	 0.71 (SD 0.31) 0.44 (SD 0.38)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	evaluated within 14 days post-stroke. The mean time to evaluation was 8.5 days (SD 3.6). At month 6, 82 patients had been lost to follow-up (18%) (32 had died, 12 moved away from the region, 37 refused further participation and 1 was unable to be reached. Full recovery rates were estimated to be $\leq$ 25% to 53.8%, depending on the measure of recovery used an cut off scores for the measures.				
Ellis *et al* (2005)	1,217 patients diagnosed with ACS in university hospitals in the US were eligible to participate in the HRQL mailed survey. 490 (40.3%) completed the survey. The mean age of the respondents was 65.2 years (SD 11.3 years), 71% were male and 91.9% were Caucasian. 64.3% of the	EQ-5D VAS and EQ-5D Health Index (HI)	ACS Mean EQ HI score Perceived severity (EQ-5D HI score) ACS Very mild/mild ACS Moderate	0.81 (SD 0.18) 0.86 (SD 0.14) 0.80 (SD 0.18)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	patients were diagnosed with MI and 35.7% with unstable angina. 17.1% had their most recent cardiac event ≤ month 6, 15.9% had their most recent cardiac event 1 year prior to the survey		ACS Severe/very severe	0.72 (SD 0.19)	
Haacke *et al* (2006)	77 patients admitted to the Department of Neurology, Philipps-University Marburg, Germany completed the 4 year follow-up to access the long-term impact of stroke on HRQL. The average patient age was 77 years. 34 patients had experienced an ischaemic infarct, 5 patients had experienced a haemorrhagic stroke and 38 patients were diagnosed with TIA at time of discharge. The proportion of patients completing the HRQL questionnaire was not reported.	EQ-5D VAS and EQ-5D HI	Stroke Mean EQ-5D HI score	0.73 (SD 0.32)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
Jones *et al* (2004)	HRQL data was collected on a sample of 57 US patients with atrial fibrillation considered at high risk of stroke. Mean age 70 years, 86% male, 87% white)	TTO (Gage et al 1995)	Mean stroke utilities Mild (Rankin 1 or 2) Moderate (Rankin 3 or 4) Major (Rankin 4 or 5) Mean utility current health	 0.76 (NR) 0.39 (NR) 0.11 (NR) 0.82 (NR)	This small study was conducted in a predominately white, male population considered at risk of stroke. This may limit the generalisability of these utility weights to the UK patient population that would be treated with ticagrelor.
Karnon *et al* (2010,2006,2005)	NR	Utility values for stroke were elicited from a meta-analysis of HRQoL estimates for stroke (Tengs 2003). The utility values for MI and ACS (event free) were sourced from the Harvard	ACS event-free (≤ year 1) ACS event-free (≥ year 2) MI (≤ year 1) MI (≥ year 2) Stroke	0.80 (0.72 to 0.88) 0.93 (0.89 to 0.97) 0.80 (0.72 to 0.88) 0.93 (0.89 to 0.97) 0.69 (0.60 to 0.78)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
		utilities database. The authors reported that no data was found to differentiate utility values for ACS (event-free) patients and MI patients and so a conservative assumption was made that they would have the same utility values (1 year from initial diagnosis and year 2 onwards).			
Kim *et al* (2005)	Patients from 45 centres across England and Scotland, diagnosed with unstable angina (UA) or NSTEMI were randomised to an early interventional strategy (IS) (n=895) or to a more conservative strategy (CS)	HRQL was assessed at baseline, 4 months and one year follow-up using the EQ-5D VAS and EQ-5D HI. Response rates to individual HRQL questions ranged	EQ-5D HI score UA/NSTEMI baseline (IS) UA/NSTEMI month 4 (IS) UA/NSTEMI year 1 (IS) UA/NSTEMI baseline	 0.671 (SE 0.009) 0.748 (SE 0.009) 0.752 (SE 0.009)	The utility weights are appropriate for use in the ticagrelor CUA. They were elicited from UK patients with UA/NSTEMI

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	(n=915).	from 93% to 99% complete.	(CS) UA/NSTEMI month 4 (CS) UA/NSTEMI year 1 (CS)	0.673 (SE 0.010) 0.714 (SE 0.010) 0.736 (SE 0.010)	using the EQ-5D.
Lacey *et al* (2003)	Longitudinal HRQL data was collected on a consecutive sample patients discharged from two acute hospitals in Sheffield, UK after recovering from an acute MI. The mean aged of the patients was 62.4 years (SD 10 years). Data was collected at six weeks, six months and 1 year after discharge from hospital. Of the 273 patients who agreed to take part in the study, 229 (83.9%) completed all three data collection stages.	EQ-5D HI (n=222)	MI (six week post-event) MI (1 year post event)	0.683 (SD 0.233) 0.718 (SD 0.243)	The utility weights are appropriate for use in the ticagrelor CUA. They were elicited from UK patients with UA/NSTEMI using the EQ-5D.
Lindgren *et al* (2007)	HRQL data was collected from a sample of Swedish patients (n=60) with a history of	EQ-5D VAS and EQ-5D HI score.	EQ-5D HI baseline (n=58)	0.82 (0.80 to 0.86)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	hypertension that had experienced a non-fatal CV event while participating in the ASCOT study. The average age of patients included in the analysis was 69.3 years. 19 patients in this sample experienced ACS and 18 had a stroke.		Utility decrement ACS (1 year post-event) Stroke (1 year post event)	 0.051 (-0.003 to 0.10) 0.145 (0.059 to 0.249)	
Lindgren *et al* (2008)	A HRQL questionnaire was mailed to 393 Swedish patients that were divided into four groups by the time elapsing since their stroke (3, 6, 9 and 12 months). In total, 275 patients (70%) responded and the response was divided evenly between the four groups. The average age of responders was 64.4 years (SD 9.3).	EQ-5D VAS and EQ-5D HI score.	EQ-5D HI score for stroke Three months Six months Nine months Twelve months All patients Recalled utility prior to event General population of	 0.65 (SD 0.31) 0.75 (SD 0.23) 0.62 (SD 0.28) 0.66 (SD 0.66) 0.67 (SD 0.28) 0.84 0.81	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
			similar age		
Main *et al* (2004)	NR	NR	IHD, 1 year post MI IHD, event-free 1 year	0.8 (SD 0.09) 0.8 (SD 0.09)	In the absence of HRQL utility weight to inform the long-term model phase, the authors assumed that all patients who were alive after the first cycle would on average have the same utility irrespective of the health state they were in. This assumption was considered inappropriate to adopt in the ticagrelor CUA.
Nowels *et al* (2005)	HRQL data was collected at cardiology centres in Colorado, US on a sample of English	EQ-5D HI and EQ-5D VAS	EQ-5D HI mean score MI (> 2months < 25		

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	speaking adult patients that had experienced an MI > 2 months but < 25 months previously, and who presented to a cardiologist during the study period (Jan to Sept 1999). 123 patients were identified as having suffered an MI during the specified time frame and were scheduled to see a cardiologist during the study period, 111 patients (90%) attended their appointment. Twenty patients (18%) declined to participate in the study. The average age of the patients that participated in the study was 64 years and 69% were males.		months after the event)	0.73 (NR)	
Pickard *et al* (2004)	HRQL data was collected on a cohort of 124 US patients who were diagnosed with stroke (image verified by CT or MRI, with initial imaging with 24 hours of admission for > 90%	EQ-5D VAS and EQ-5D HI score	EQ-5D HI scores Stroke Baseline Stroke 1 month	 0.31 (SD 0.38) 0.55 (SD 0.36)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	of the patients and proxy pairs (family or friends). The mean age of the patients was 68.3 years (SD 14.6). HRQL measurements were taken at baseline and 1, 3 and 6 months. At baseline most patients experienced severe stroke according to Barthel Index scores, with 60% of patients scoring $\leq$ 60 (dependent) and 5% scoring $\geq$95 (independent). At month 6, 15% of the sample had Barthel Index scores $\leq$ 60% and 50% had scores $\geq$ 95.		Stroke 3 month Stroke 6 month	0.61 (SD 0.30) 0.62 (SD 0.34)	
Ploegmakers *et al* (2010)	HRQL data was collected on patients that underwent a PCI for chronic or stable angina, UA or NSTEMI over two 10 week periods, Jan to March 2007 and April to June 2008, at the McGill University Health Centre in Montreal, Quebec. 141 patients met the inclusion	TTO. The specific TTO question was "If there was a possibility to avoid a return of symptoms and the need for a repeat procedure by giving up some of these make believe	Median TTO associated with restenosis and the need for repeat vascularisation. Median disutility associated with restenosis and the need for repeat	0 wks (IQR 0 to 1.7 wks). 0 years	Methodology used by the investigators to elicit utility weights for restenosis is consistent with the NICE

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	criteria of whom 103 (73%) completed the HRQL interview. The mean patient age was 61.9 years (SD 11.0), 74% of the participants were male. The median time to interview was 14 days post PCI (IQR 14 to 15).	10 years, how many of these make-believe 10 years would you be willing to give up to avoid a return of symptoms and the need for a repeat procedure within 6 months?"	vascularisation.		reference case.
Post *et al* (2001)	Systematic review of the medical database MEDLINE (1966 – 2000), Web of Science (1988 – 2000) and the Cochrane Library (issue 4, 2000) to identify utility values for stroke and explore the impact of the study population and the elicitation method.	EQ-5D, SG, TTO,VAS	EQ-5D (Dorman 2000) Mild stroke (patient elicited) Major stroke (patient elicited) TTO (Duncan 2000) Mild stroke (patient elicited) Major stroke (patient elicited) SG (Thompson 2000[†])	 0.71 (NR) 0.32 (NR) 0.71 (NR) 0.44 (NR) 0.64 (NR)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
			Mild stroke (at risk) Major stroke (at risk) † refer to Robinson (2001)	0.19 (NR)	
Robinson *et al* (2001)	Patients with atrial fibrillation (AF) from three large primary care centres in the North East of England were identified from computerised records and invited by post to participate in the HRQL study. A hundred and eighty invitations were posted and 117 replies were received giving a response rate of 65%. Of these, 69 patients (59%) agreed to participate. Data was complete for 57 patients who had a mean age of 73 years (range 60 to 87 years). Thirty-one were men (545), 28 (49%) were on warfarin and 13 (23%) had had a stroke. It was not possible to arrange interviews for 5	SG	GP managed warfarin Hospital managed warfarin Mild stroke Severe stroke Major bleed	0.948 (SD 0.089) 0.941 (SD 0.101) 0.641 (SD 0.275) 0.189 (SD 0.276) 0.841 (SD 0.172)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	patients and 7 patients could not complete the interview.				
Rogowski *et al* (2009)	See Main et al (2004)	See Main et al (2004)	See Main et al (2004)	See Main et al (2004)	
Rubenstein *et al* (2004)	NR	NR	The authors assumed that a major bleed (oesophageal variceal haemorrhage) would cause a short-term decrement in HRQL equating to a loss of 25% of their health state utility for a 2 week period.	NR	Method for valuing health state is not consistent with the NICE reference case.
Schweikert *et al* (2009)	A follow up study of all MI survivors in the MONICA/KORA registry (Cooperative Health research in the region of Augsburg/Monitoring trends and determinants of cardiovascular disease) was performed to assess the long-term impact of MI on HRQL and compare it with the	German version of the EQ-5D.	EQ-5D HI score (All) MI (median 7.4 years post event).	0.865 (SD 0.153)	Utility value for the post-MI health state elicited from the German patient population is higher than the UK population norm for the corresponding

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	German general population. A postal questionnaire for self completion was sent to all registry patients who had suffered an MI between 1985 and 2004 who had consented to recontact and were known to be alive at the time of the last mortality follow-up (n=4,394). A total of 2,950 patients (mean age 68.0 (SD 9.6), male 79.3%) completed the questionnaire (67.1%).				age group (0.78).
Schwikert *et al* (2006)	114 consecutive patients with ACS (51% MI, 42% CABG, 7% angina) starting inpatient rehabilitation after an acute cardiac event at a rehabilitation hospital in Southern Germany were recruited to this HRQL study at admission. 106 patients completed the questionnaires (93.0%). Mean age of the study population was 55 years (SD 7.6), 85%	EQ-5D	EQ-5D HI score at admission MI CABG	 0.778 (NR) 0.645 (NR)	This study excluded patients > 65 years. The generalisability to the UK ACS patient population is questionable.

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	were male and the mean duration of ACS was 20.6 months (SD 47.7).				
Solli *et al* (2010)	HRQL questionnaires were mailed to a sample of patients that participated in the 2006 Norwegian diabetes survey. A total of 521 patients completed the questionnaire, a response rate of 53% (521/985). The mean age of the 365 patients with type 2 diabetes (T2D) was 64.0 years and 56% were male. In terms of self reported complications, 38 patients (11%) of the patients with T2D had suffered an MI, 27 (8%) had angina and 19 (5%) suffered from stroke.	Norwegian translation of the EQ-5D. EQ-5D responses were translated into EQ-5D index utilities using the UK TTO tariff.	EQ-5D HI scores for 2TD Baseline (All 2TD patients) 1 complication 2 or more complications Any complication Utility decrement stroke	 0.81 (0.79 to 0.83) 0.80 (0.75 to 0.85) 0.64 (0.56 to 0.71) 0.73 (0.69 to 0.78) 0.135 (0.247 to 0.023)	
Sullivan *et al* (2006)	HRQL data on a representative sample of the US general public, aged $\geq$ 18 years, were collected as part of the Medical Expenditure Panel Survey (MEPS). The research	EQ-5D was administered via a paper and pencil self-administered questionnaire. The scoring algorithm for	Mean EQ-5D HI score Angina Pectoris Acute MI	 0.695 (IQR 0.517 to 0.827) 0.704 (IQR 0.575	The utility weights for angina/stroke and MI were derived from US patients. The scoring algorithm

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	reported by Sullivan et al was based on a data set from 2000-2002. HRQL data was reported on a sample of 244 patients (mean age 62 years) that had experienced an acute MI, 340 patients with stroke (mean age 68 years) and 228 patients (mean age 69 years) with angina pectoris.	the EQ-5D index descriptive system was based on US community preferences.	Cerebrovascular accident Utility decrement angina Utility decrement acute MI Utility decrement CVA	to 0.843) 0.650 (IQR 0.463 to 0.816) 0.0412 (SE 0.0002) 0.0409 (SE 0.0002) 0.0524 (SE 0.0001)	for the EQ-5D index descriptive system was based on US community preferences. These weights are considered inappropriate to use in the ticagrelor CUA.
Tengs *et al* (2003)	Systematic review of the medical literature (Medline, NHS Economic Evaluation Database) for articles reporting utility estimates for stroke. Time horizon for the search was 1985 to 2000. Articles had to be written in English and full text. Utility values were elicited from patients, members of the	SG, TTO, VAS or judgement.	Moderate stroke (reference) Utility increment minor stroke Utility decrement major stroke	0.682 (0.533 to 0.830) 0.187 (0.093 to 0.281) 0.165 (0.263 to 0.066)	This study combines 53 utility scores for stroke from 20 articles as such provides robust evidence for stroke utilities. The 'reference group' meets the

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	public or experts. The 'reference group' adopted by the researchers was moderate stroke severity, using TTO, patients as respondents and 'death to perfect health' as the scale bounds.				NICE reference case and it suitable for use in the economic evaluation.
Van Excel *et al* (2004)	As part of the EDISSE study (Evaluation of Dutch Integrated Stroke Services Experiments) HRQL data was collected on consecutive patients with stroke (n=598) that were admitted to eight hospitals in the Netherlands at 2 months and 6 months post-event. The average age of the patient population was 73.5 years (SD 11.7), 46% were male and the mean length of stay in hospital was 26.5 days (SD 33.3). At month 2, 447 were alive after their stroke, of whom 364 (81.4%) completed the HRQL questionnaire. Six months after	EQ-5D	Combined 2 and 6 months Independent stroke Mild stroke Moderate stroke Severe stroke Very severe stroke	 0.78 (0.76 to 0.81) 0.58 (0.55 to 0.62) 0.38 (0.31 to 0.54) 0.08 (0.03 to 0.15) -0.12 (-0.17 to -0.06)	

Study	Population	Assessment method	Health state(s)	QOL weight (95% CI)	Appropriateness for CEA
	the stroke, 421 patients were alive and 411 were interviewed. Response rate to the HRQL questionnaire was 86.9% (n=357).				
IQR = interquartile range, CVA = cerebrovascular accident, NR = not reported., EQ-5D = Euroqol-5 Dimensions, SG = standard gamble, TTO = time trade off, VAS = visual analogue scale					

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The utility values derived from the literature search and those reported in the PLATO HECON sub-study are shown in Table 6.27.

Table 6.27: Comparison of Utility Scores

Health State	Utility Scores		Relative Difference	Sources of literature values
	PLATO	*Literature*		
No Event	0.875	0.744	1.176	Kim *et al*, 2005
MI	0.812	0.683	1.189	Lacey & Walters, 2003
Stroke	0.736	0.628	1.172	Tengs & Lin, 2003 and Youman, 2003

The utility values reported in the PLATO HECON sub-study are higher than those reported in the literature; however the relative difference between the two alternative values is fairly consistent across the different health states. The difference between the two values could be attributed to the following:

- MI: In Lacey *et al*. the utility score of 0.683 was taken at six weeks post MI whilst the PLATO utility score was calculated as the area under the curve for each patient for the whole 12 months, irrespective of when the MI occurred. The one year value for Lacey *et al*. was 0.718 showing that a patient's HRQL improves over the course of the year after a recurrent MI so it is to be expected that the later in the 12 month period the utility value is captured, the higher it is likely to be.
- Stroke: In Youman *et al*. the proportion of strokes that were severe was 54% compared to only 13% in the PLATO study (see Table 6.28), therefore the weighted average utility score for stroke from the literature is likely to be much lower than that seen in PLATO.

Table 6.28: Comparison of Stroke Severity

PLATO Study		Youman et al	
Level of disability	**Percentage**	**Type of stroke**	**Percentage**
No disability	54%	Mild	19%
Slightly to moderately	33%	Moderate	27%
Severely disabling	13%	Severe	54%

- No Event: In the PLATO HECON sub-study, the No Event group were those who remained event free for the remainder of the year post initial ACS event. In Kim *et al*. 3.5% and 4.3% of patients had had a recurrent MI at four months and one-year respectively, and 6.8% and 9.1% of patients had had refractory angina at four months and one-year respectively. This study provides the closest approximation to the PLATO HECON sub-study results; however the fact that a number of patients experienced a further event is likely to result in a lower HRQL score than that seen in PLATO.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Bleeding is an important safety issue for all antiplatelet medications. A major bleeding event will involve hospitalisation and is likely to have a high impact on HRQL though this is likely to be short-term in nature. Indeed, a recently published Health Technology Appraisal (TA90, published October 2010) carried out by Liverpool Reviews and Implementation Group (LRiG), suggested a utility decrement of 0.1426 for a major bleed with the impact lasting for a period of eleven weeks.

Minor bleeds include symptomatic but mild bleeding in areas such as genitourinary, nose, mouth and lung, as well as bruising/haematoma of soft tissues. Typically, minor bleeding is managed in primary care with a much lower impact on HRQL than a major bleeding episode. In TA90, LRiG suggested a utility decrement of 0.0033 for a minor bleeding episode with duration of two days.

Dyspnoea was another observed adverse reaction in the PLATO study. Dyspnoea is a feeling of breathlessness which refers to the sensation of shortness of breath or difficulty breathing. As a symptom it can be both distressing and frightening for patients however, in the PLATO study, dyspnoea was usually rated mild or moderate in severity and was not associated with heart failure or lung disease. The impact of dyspnoea on HRQL is likely to be transient and minor.

Although not expressly modelled, the impact of adverse events on HRQL would have been captured in the HECON sub-study.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

As discussed in section 6.4.3, a health economic sub-study was carried out as part of the PLATO study. Based on the fact that the utility values derived from the HECON sub-study meet the requirements of the reference case, these values have been used in the base case economic analysis. These utility values and standard errors are shown in Table 6.29.

It can be seen that there are three different utility values for the dead health state in the decision tree: Vascular Death, Non-vascular Death and Death Any Cause. Death Any Cause is the value used in the base case as this represents the Dead Any Cause arm in the one-year decision tree. Vascular death and Non-Vascular death have also been provided because a sensitivity analysis was undertaken in which the Death Any Cause arm was split into Vascular Death and Non-Vascular Death to assess the impact on the cost-effectiveness results.

It should also be noted that the usual value for a dead health state is zero. In the case of the PLATO HECON sub-study, however, the utilities are calculated as the area under the curve and patients will accrue a certain amount of utility up until the

point at which they die. Therefore, in the decision tree, the dead utility value is not the utility associated with the Dead health state but rather the accrued utility up to the point at which they enter the Dead health state. The fact that the utility values collected in the HECON sub-study represent accrued utility over a 12 month period could also explain why the values are somewhat higher than those found in the literature, which are based on patients being in a specific health state at a specific time point after an event.

The one-year decision tree utilises treatment specific utility values as per Table 6.25 in section 6.4.3. As no treatment effect was assumed beyond 12 months, the average utility score for No Event, Non-fatal MI and Non-fatal Stroke for all patients has been used in the Markov model, as per Table 6.24 in section 6.4.3. It should be noted, however, that the values shown in Table 6.29 have been adjusted for age as per Assumption 7, in Section 6.3.8 and therefore are lower than those listed in Tables 6.25 and 6.26.

Table 6.29: 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 as per 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

State	Utility value	Standard error	Reference in submission	Justification
Non-fatal MI	0.779	0.010	As above	As above
Post MI	0.821	0.038	As above plus Lacey et al, 2003	Evidence that HRQL improved over time
Non-fatal Stroke	0.703	0.010	As above	
Post Stroke	0.703	0.038	As above plus assumption	No evidence that HRQL improves over time
Dead	0.000	N/A	N/A	Convention

In terms of utility values for the health states Post MI, Post Stroke and Dead in the Markov model, these have been calculated as follows:

- Post MI: Lacey *et al*. 2003, provides utility values for 4 weeks and one-year post MI. The relative difference between these two values has been applied to the MI utility from PLATO to give an estimate of the expected utility one-year post MI.
- Post Stroke: There are a number of papers providing utilities for stroke however none provides any detail of potential improvements in HRQL in the years after a stroke. A review of utilities for the post stroke health state in other Health Technology Appraisals with a similar model structure shows that an assumption has been made that the utility for stroke remains the same irrespective of the number of years after the event. Therefore an assumption has been made that the Stroke and Post Stroke utilities are the same.
- Dead: As per convention, a utility of zero has been applied to the Dead state.

As stated in section 6.4.3, a systematic search was also carried out to identify alternative utility values from the literature. The utility values selected are shown in Table 6.30 whilst the justification for their selection is listed below:

- No Event: There were very few studies identified that provided baseline HRQL values for ACS patients. The only original UK study was Kim *et al*, 2005, and whilst it is the best approximation for the No Event arm of the decision tree a number of patients in the study did experience a recurrent MI or refractory angina hence the utility values are lower than reported in PLATO. An analysis of already published cost-utility studies identified two papers by Karnon *et al.* (2006 and 2010) both of which have utility values for ACS Event- free (Year 1) and ACS Event-free (Post Year 1). However, on further examination, the source for these utilities appears to the Harvard utilities database which was deemed to be less appropriate as based predominantly on US studies.

Table 6.30: Utilities for No Further Event/Post ACS

Author	Year	Region	n =	Event free year 1		Event free > 1 year	
				Mean	*SE*	*Mean*	*SE*
Kim et al.	2005	UK	806 - 820	0.744	0.010		
Karnon et al.	2006, 2010	HUD	NS	0.800	0.041	0.930	0.020

HUD = Harvard Utililties Database; NS = not specified

- MI and Post MI: Two studies were identified with potential utility values for the MI and Post MI health states. Both studies were UK based and used the EQ-5D to elicit utility values from patients. In Lacey et al, the study consisted of patients discharged from hospital after acute MI, however in Goodacre et al, patients were those with acute, undifferentiated chest pain. Based on the fact that 34.5% of patients in Goodacre et al went on to be diagnosed with unstable angina rather than acute MI, Lacey et al was deemed to be the more appropriate study. In addition, Lacey et al provides a utility score for 4 weeks post MI as well as one year post MI.

Table 6.31: Utilities for MI and Post MI

Author	Year	Region	n =	4-6 weeks post MI		6 months post MI		1 year post MI	
				Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*
Lacey et al.	2003	UK	222	0.683	0.016			0.718	0.016
Goodacre et al.	2004	UK	621	0.718		0.763			

- Stroke and Post Stroke: Two studies were identified that provided suitable utilities for stroke. Dorman et al, 2000 uses EQ-5D to measure HRQL in 127 patients from the Lothian Stroke Register in Scotland whilst Tengs et al, 2003 is a meta-analysis combining 53 QoL estimates for stroke from 20 studies. Although Tengs et al, combined data using a range of assessment methods and respondents, the 'reference group' for the regression model was moderate stroke, time trade-off method and patients as respondents as per the reference case. Either study appears to be suitable, however Tengs et al was selected as it has already been used in several Health Technology Assessments (TA90 Clopidogrel and Dipyridamole, 2005, TA132 Ezetimibe, 2007, Lipid Modification Guideline, 2008) as well in published cost utility analyses (Karnon et al. 2006, 2010, Bravo Vergel *et al*, 2007) within ACS.

Table 6.32: Utilities for Stroke

Author	Year	Region	n =	Mild		Moderate		Severe	
				Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*
Tengs & Lin	2003	Various	#	0.869	0.048	0.682	0.076	0.517	0.050
Dorman et al	2000	UK	147	0.880	0.041	0.740	0.026	0.380	0.046

= 53 utility estimates from 20 studies

As Table 6.32 shows, the utilities for stroke are highly dependent on the severity of the event which has an impact on long-term HRQL. To obtain a specific utility for the stroke health state, a weighted average was calculated based on the proportion of strokes that are mild, moderate or severe. As

shown in Section 6.4.7, Table 6.28, there is a considerable difference in the proportion of strokes in each category in the PLATO study and Youman et al, 2003. It was deemed more appropriate to weight the results by Youman et al, as this paper is based on a UK stroke study of 457 patients and has been used in several Health Technology Assessments (list) in addition to a number of published papers in ACS.

Table 6.33: Weighted Average Stroke Utility

Type of Stroke	Percentage	Utility values	
		Mean	***SE***
Mild	19%	0.869	0.048
Moderate	27%	0.682	0.076
Severe	54%	0.517	0.050
Weighted average:		**0.628**	**0.057**

As stated previously, there is very little data on potential improvements in HRQL post stroke therefore, in line with the other Health Technology Appraisals with a similar model structure, it has been assumed that the utility for the Post Stroke health state is the same as that for the Stroke health state.

The list of utility values used in the sensitivity analysis is shown in Table 6.34. It should be noted, however, that the values shown in Table 6.34 have been adjusted for age as per Assumption 7, in Section 6.3.8 and therefore are lower than those listed in Tables 6.30 to 6.33.

Table 6.34: Summary of quality-of-life values for cost-effectiveness analysis (sensitivity analysis)

State	Utility value	Standard error	Reference in submission	Justification
In one-year decision tree:				
No Event	0.711	0.010	Kim et al. 2005	Most appropriate value (see text)
Non-fatal MI	0.650	0.016	Lacey et al 2003	Most appropriate value (see text)
Non-fatal Stroke	0.595	0.057	Tengs et al. 2003 and Youman et al. 2003	Most appropriate value (see text)
Dead	0.000	N/A	N/A	Convention
In Markov model:				
No Event	0.711	0.010	Kim et al. 2005	Most appropriate value (see text)
Non-fatal MI	0.650	0.016	Lacey et al. 2003	Most appropriate value (see text)
Non-fatal Stroke	0.685	0.016	Tengs et al, 2003 and Youman et al. 2003	Most appropriate value (see text)
Post MI	0.595	0.057	Lacey et al. 2003	Evidence that HRQL improves over time

State	Utility value	Standard error	Reference in submission	Justification
Post Stroke	0.595	0.057	Tengs et al. 2003 and Youman et al. 2003	Assumption that HRQL remains the same
Dead	0.000	N/A	N/A	Convention

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were not used to assess the applicability of values available or estimate any values.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The No Event health state represents the HRQL for patients who are at least a year past their index ACS event. Whilst the impact of the ACS event has diminished, HRQL may still be impacted somewhat by potential lifestyle changes that a patient has to make to reduce the possibility of a recurrent event. HRQL in this health state is assumed to be constant over time.

The MI health state represents the HRQL for patients who have a subsequent MI after their initial ACS event. This health state captures the immediate hospitalisation and treatment for an MI and is assumed to be constant over a one-year period. In the model this health state is a 'tunnel state', i.e. a patient will only spend a year in this state and if they survive, will transition to the Post MI health state.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The Post MI health state represents the HRQL for patients who are at least one year past a subsequent MI. As in the No Event health state, the impact of the subsequent MI diminishes over time, however HRQL may still be impacted by potential lifestyle changes aimed at reducing the possibility of further events. HRQL in this health state is lower than that in the No Event health state due to the impact of an additional event and it is assumed to be constant over time.

The Stroke health state represents the HRQL for patients who have a stroke after their initial ACS event. This health state captures the immediate hospitalisation and treatment for a stroke and utilities for this health state are weighted to reflect the impact on HRQOL of the severity of the stroke. HRQL is assumed to be constant over a one-year period. In the model this health state is a 'tunnel state', i.e. a patient will only spend a year in this state and if they survive, will transition to the Post Stroke health state.

The Post Stroke health state represents the HRQL for patients who had a stroke at least one year ago. Whilst there may be an improvement in HRQL for patients who experience a mild stroke, patients suffering a major stroke, especially those requiring discharge to an institution, are unlikely to show any improvement in HRQL. Therefore, based on the weighting of stroke severity, the HRQL is assumed to be the same in this state as in the Stroke state and is assumed to be constant over time.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No relevant health effects were excluded from the analysis.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

In the cost-utility model, the baseline quality of life is assumed to be as per the health state in which the patient finds him/herself at the end of the one-year decision tree.

However, a study by Kind et al, 1998, valued the utility by age in the UK general population using the EQ-5D questionnaire and found significant differences in HRQL between age groups. The mean age of patients in the PLATO study was 62.2, similar to the mean age in Lacey at al. (62.4) and Kim et al. (62) This compares to a mean age of 70.4 for UK ACS patients (reference MINAP/GPRD study). Based on the fact that the utility scores used in the model are derived from a patient population with a mean age of 62, it was deemed appropriate to perform some form of adjustment to take into account the older population in the UK who, based on Kind et al, are likely to have a lower baseline utility. A linear regression analysis (Kind et al, 1998) identified an equation for adjusting for age:

$$\text{Utility} = 1.060 - 0.004 * \text{Age}$$

This means that for every increasing year of age, baseline utility is estimated to reduce by 0.004. Based on the fact that there is 8 years difference between the mean age of the PLATO population and the UK ACS population, all utility scores

from both the PLATO HECON sub-study and the literature were adjusted downwards by 0.0328. The impact of not using an age-based utility decrement is tested in the sensitivity analysis.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The HRQL associated with each health state in the decision tree is assumed to be constant over time. However, as discussed in section 6.4.13, utility decreases with age. In order to account for the increasing age of the population over time, a utility decrement of 0.004 is applied during each cycle of the Markov model as the patient ages by one year. The impact of not adjusting for age with each cycle is tested in the sensitivity analysis.

6.4.15 *Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology*.

Not applicable.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

It is likely that most ACS patients will be admitted to hospital under HRG code EB10Z Acute or Suspected Myocardial Infarction. For patients who then go on to have a PCI there are several HRG codes depending on catheterisation or not and the number of stents. For those patients who suffer a bleeding episode, depending on the site of the bleed, the code could be either a haemorrhagic cerebrovascular disorder or gastrointestinal bleed. The costs for non-elective admissions are shown in Table 6.35, the costs for elective admissions are shown in Table 6.36 and the National Tariff costs are shown in Table 6.37.

Table 6.35: National Schedule of Reference Costs Year: '2008-09' - NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data

HRG Code	Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
EB10Z	Actual or Suspected Myocardial Infarction	73,533	£1,705	£1,278	£1,935
EA31Z	Percutaneous Coronary Intervention (0-2 Stents)	15,735	£3,029	£2,392	£3,779
EA32Z	Percutaneous Coronary Intervention (0-2 stents) and Catheterisation	3,931	£3,245	£2,680	£4,293
EA49Z	Percutaneous Coronary Interventions with 3 or more Stents or rotablation or IVUS or use of pressure wire	1,843	£3,102	£1,898	£4,172
EA50Z	Percutaneous Coronary Interventions with 3 or more Stents or rotablation or IVUS or use of pressure wire and Catheterisation	687	£3,472	£1,645	£5,181
AA23Z	Haemorrhagic Cerebrovascular Disorders	19,140	£2,867	£1,900	£3,397
FZ38D	Gastrointestinal Bleed with length of stay 1 day or more with Major CC	10,906	£1,544	£1,124	£1,728
FZ38E	Gastrointestinal Bleed with length of stay 1 day or more without Major CC	13,465	£1,012	£791	£1,137
FZ38F	Gastrointestinal Bleed with length of stay 0 days	2,078	£1,000	£317	£1,322

HRG Code	Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
FZ16Z	Very Major Procedures for Gastrointestinal Bleed	439	£5,369	£2,316	£6,085

Table 6.36: National Schedule of Reference Costs Year: '2008-09' - NHS Trusts and PCTs combined Elective Inpatient HRG Data

HRG Code	Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
EB10Z	Actual or Suspected Myocardial Infarction	4,719	£1,976	£1,142	£2,669
EA31Z	Percutaneous Coronary Intervention (0-2 Stents)	15,412	£2,610	£1,989	£2,993
EA32Z	Percutaneous Coronary Intervention (0-2 stents) and Catheterisation	1,377	£3,782	£1,733	£3,743
EA49Z	Percutaneous Coronary Interventions with 3 or more Stents or rotablation or IVUS or use of pressure wire	3,012	£2,610	£1,517	£3,532
EA50Z	Percutaneous Coronary Interventions with 3 or more Stents or rotablation or IVUS or use of pressure wire and Catheterisation	375	£3,195	£1,428	£4,218
AA23Z	Haemorrhagic Cerebrovascular Disorders	765	£3,231	£1,308	£4,335
FZ38D	Gastrointestinal Bleed with length of stay 1 day or more with Major CC	222	£1,917	£677	£2,279
FZ38E	Gastrointestinal Bleed with length of stay 1 day or more without Major CC	324	£1,222	£575	£1,489
FZ38F	Gastrointestinal Bleed with length of stay 0 days	116	£617	£256	£727
FZ16Z	Very Major Procedures for Gastrointestinal Bleed	21	£7,226	£3,185	£10,438

Table 6.37: 2009/10 Inpatient & Planned Same Day Tariff

HRG code	HRG name	Planned Same Day tariff (£)	Elective spell tariff (£)	Elective long stay trimpoint (days)	Non-elective spell tariff (£)	Non-elective long stay trimpoint (days)
EB10Z	Actual or Suspected Myocardial Infarction	1,286	2,598	17	3,662	18
EA31Z	Percutaneous Coronary Intervention (0-2 Stents)	2,877	3,180	1	4,706	10
EA32Z	Percutaneous Coronary Intervention (0-2 stents) and Catheterisation	2,894	3,555	4	5,441	16
EA33Z	Percutaneous Coronary Interventions with 3 or more Stents	-	4,220	4	5,281	11

HRG code	HRG name	Planned Same Day tariff (£)	Elective spell tariff (£)	Elective long stay trimpoint (days)	Non-elective spell tariff (£)	Non-elective long stay trimpoint (days)
EA34Z	Percutaneous Coronary Interventions with 3 or more Stents and Catheterisation	-	5,159	4	6,453	17
AA23Z	Haemorrhagic Cerebrovascular Disorders	-	2,604	89	3,635	47
FZ38A	Gastrointestinal Bleed with Major CC	1,014	1,744	28	1,379	24
FZ38B	Gastrointestinal Bleed with Intermediate CC	1,014	1,744	9	1,379	9
FZ38C	Gastrointestinal Bleed without CC	1,014	1,744	9	1,379	8

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs would be appropriate for the costing the intervention however a detailed within-trial costing analysis was performed as part of the PLATO HECON sub-study and this was used to derive the costs in the model. NHS reference costs have been used in the analysis versus prasugrel where costs from the HECON sub-study were not available.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- ***country of study***
- ***date of study***
- ***applicability to UK clinical practice***
- ***cost valuations used in study***
- ***costs for use in economic analysis***
- ***technology costs.***

Reference	Country	Type	Methodology	Technology costs	Source of resource use	Reference year for cost
Bravo Vergel et al, 2007	UK	Cost-effectiveness analysis	Modelled costs	• ACS event free year 1: £431 • MI year 1: £ 1,964 • MI after year 1: £91 • Stroke year 1: £8,786 • Stroke year 2: £2,318	Sculpher et al, 2002 Bagust et al, 2006	2004
De Portu et al, 2006	UK and Italy	Cost-effectiveness analysis	UK costs with Italian resource use	• Non-fatal MI: €4,159 • Non-fatal stroke €3,927 • angioplasty, stenting and arthectomy €6,197		Euros 2003
Heeg et al, 2007	UK	Literature review and cost-effectiveness model	Direct costs associated with the specific health states over a period of 6 months	• MI first 6 months after event £3,300 • MI second 6 months after event £1200 • Stroke first 6 months after event £5,100 • Stroke second 6 months after event £3,500 • MI after first year (per 6 months) £900 • Stroke after the first year (per 6 months) £2,600 • Bleeding £2,600	Karnon et al, 2005 Karnon et al, 2006	2006
Henriksson et al, 2007	UK	Cost-effectiveness analysis	Patient level resource use data collected	• ACS event free year 1: £ 2,735 • MI after year 1: £5,467	Epstein et al, 2007	2003

Reference	Country	Type	Methodology	Technology costs	Source of resource use	Reference year for cost
Hernandez et al, 2007	UK	Cost-effectiveness analysis		• MI £1,122	National Health Service (NHS) reference cost 2001/2002	2001
Jones et al, 2004	UK	Health technology assesment		• acute care recurrent stroke total: £2,933 • rehab disabled total £718 • long term care (3months) disabled total £2,658 • acute MI €6,178 • First 6 months post-MI €2,660 • Second 6 months post-MI €1,197 • Acute stroke €7,366 • First 6 months post-stroke €3,712 • Second 6 months post-stroke €2,591 • Further 6 months post-MI €991 • Further 6 months post-stroke €1,774 • Intracranial haemorrhage €4,522 • GI bleed €1,805	Chambers et al, 1999 Annemans and al, 2003	1996 Euros 2002

Reference	Country	Type	Methodology	Technology costs	Source of resource use	Reference year for cost
				• acute stroke cost per 3 months cycle £3,991.30 • MI year 1: £3,966 • New stroke year 1: £7,465.80 • MI post-year 1: £1,587 • New stroke post-year 1: £ 4,532.80 See the Youman paper	Boerhinger Ingelheim submission Sanofi-synthelabo and BMS submission	2004 2002

Reference	Country	Type	Methodology	Technology costs	Source of resource use	Reference year for cost
					Youman et al, 2003	
Karnon et al, 2008	UK	Cost-utility analysis	Patient level resource use data collected over 21 months	• ACS event free year 1: £1,547 • MI year 1: £4,319 • MI after year 1: £1,728 • Stroke year 1: £8,416	Palmer et al, 2002 Youman et al, 2003	2006
Karnon et al, 2005 a	UK	Cost-utility analysis	Patient level resource use data collected over 21 months	• MI year 1: £ 3,966 • MI after year 1: £1,587 • Stroke year 1: £7,466 • Stroke after year 1: £4,533	Palmer et al, 2002 Chambers et al, 1999	2002
Karnon et al, 2005 b	UK	Cost-utility analysis	Patient level resource use data collected	• ACS event free year 1: £ 1,421 • MI year 1: £ 3,966 • MI after year 1: £1,587 • Stroke year 1: £7,466	Palmer et al, 2002 Tengs et al,	2002

Reference	Country	Type	Methodology	Technology costs	Source of resource use	Reference year for cost
			over 21 months	• Major bleeding event £2,377	2000 NHS ref cost	
Lightowlers et al, 1998	UK	Cost-effectiveness analysis	Cost calculated during a 10-year period. The costs of anticoagulation for 1 year with checks every 3 weeks	• 10 year period treatment of stroke: £17,819.58 • Bleeding 1 year period £610.06	Bamford et al, 1990 Wolfe et al, 1995	1997
Lamotte et al, 2006	UK, Germany, Spain, Italy	Cost-effectiveness analysis	Direct costs from the healthcare payer's perspective	• MI year 1: €1,593 • Fatal MI: €1,824 • Stroke year 1: €3,385 • Fatal Stroke : €5,309 • GI bleed: ₤€,218	HRG NHS reference costs 2003	Euros 2003
Lamotte et al, 2007	UK	Cost-effectiveness analysis	Direct costs from the healthcare payer's perspective	• Acute stroke £3,978 • Stroke follow up per months: £ 455 • Cardiac death £1,227	HRG NHS reference costs 2006 Kavanagh et al, 1999	2006

Reference	Country	Type	Methodology	Technology costs	Source of resource use	Reference year for cost
McKenna et al, 2010	UK	Health technology assessment	HTG AA22Z and EB10Z	• Non-fatal MI: £1,143 • Non-fatal stroke long stay £2,718	HRG NHS reference costs 2007/08	2008
Scuffham et Chaplin, 2004	UK	Cost-effectiveness analysis	HRG E11 and E12	• Acute MI: £1,020	HRG NHS reference costs 2002	2002
Taylor et al, 2009	UK	Cost-effectiveness analysis		• Acute MI: £ 1,176 • Cardiac death: £1,317 • Stroke: £2,275	NHS reference costs 2005 inflated to 2008	2008
Tiemann, 2008	Denmark, England ,France, Germany, Hungary, Italy, Netherlands, Poland, and Spain	Cost comparison	HRG Hospital costs	• Acute MI: €5,013	N/A	Euros 2005
Ward et al, 2007	UK	Health technology assessment	Event costs from patient level resource use data collected	• Fatal MI: £1,152 • Non fatal MI: £4,070 • Non fatal stroke: £2,367 • Fatal stroke: £3,383 • Follow on costs CHD and	Pfizer submission	2004

Reference	Country	Type	Methodology	Technology costs	Source of resource use	Reference year for cost
			(UKPDS) Modelled costs	stroke: £258 • Fatal MI: £2,725 • Non fatal MI: £3,893 • MI after 1 year: £261 • Fatal stroke: £5,552 • Non fatal stroke: £7,661 • Stroke after 1 year: £8,986	BMS submission (Caro et al, 1997)	
Youman et al, 2003	UK	Cost of illness	Cost result per 3 month period from the model	• mild stroke 3-month cost of acute event £ 5,099 • moderate stroke 3-month cost of acute event £ 4,816 • Severe stroke 3-month cost of acute event £ 10,555	Kalra et al, 2000 PSSRU	2001

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

Clinical experts were not used to assess the applicability of values available or estimate any values.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Clopidogrel and aspirin are generic (clopidogrel is now a Category M drug) therefore the costs are taken from the Drug Tariff, November 2010. The cost of prasugrel is taken from MIMS, October 2010. The cost of ticagrelor is as per Section 1.10, Table 1.1.

Table 6.38: Drug costs used in the economic evaluation

Product	Loading dose (mg)	Maintenance dose (mg)	Pack price	Tabs per pack	Cost of LD	Cost of MD	Annual Cost
Aspirin	300	75	£0.82	28	£0.12	£0.03	£10.78
Clopidogrel	600	75	£3.40	30	£0.91	£0.11	£42.16
Ticagrelor	180	90	£54.60	28	£3.90	£1.95	£713.70
Prasugrel	60	10	£47.56	28	£10.19	£1.70	£628.47

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The summary of product characteristics (SPC) recommends that renal function should be checked after one month and thereafter according to routine medical practice. This monitoring will not however, involve any additional tests or costs and will be entirely consistent with usual clinical practice in ACS patients, thus has been excluded from the base case analysis. However, the cost of a surgery visit together with a blood test, as shown in Table 6.39, has been included in the sensitivity analysis.

Table 6.39: Cost of renal monitoring

Cost item	Annual cost
Cost per surgery consultation with GP lasting 11.7 minutes	£31.00
Cost per blood test (DAP841 Biochemistry)	£1.34
Total cost of renal monitoring	**£32.34**

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Within-trial Cost Analysis

A pre-specified sub-study was undertaken in order measure resource use and determine costs in all patients participating in the PLATO study. Hospitalisations, interventions, investigations and bleeding-related health care consumption, were recorded for all patients in order to estimate total healthcare costs associated with ticagrelor and clopidogrel within the PLATO study.

Resource use

The collection of resource use was pre-specified in the case report form (CRF) and included hospitalisations, investigations, interventions, blood product and re-operations due to bleeding and drugs. Resource use was categorised into two time-periods: index hospitalisation (defined as time of randomisation to time of discharge); and post-index hospitalization (defined as the day after discharge from index hospitalisation to the end of the study).

Hospitalisations

The number of bed days in the index hospitalisation was derived from the randomisation and discharge date. The number of bed days post-index hospitalisation was derived from the admission and discharge date. The first two days of the index hospitalisation were categorised as a coronary care unit with the remainder of the index hospitalisation categorised as a cardiology ward. Bed days during the post-index hospitalisation were categorised into general ward, coronary care unit, cardiac intensive care and intensive therapy unit.

Investigations

The investigations included in the study are listed in Table 6.40. The number of different investigations was recorded for each patient.

Interventions

The interventions included in the study are listed in Table 6.40. Percutaneous coronary interventions (PCIs) were categorised into procedures: with or without stenting. If stenting was used, the number of stents and type of stent (bare metal or drug eluting) was recorded. Coronary artery bypass grafting (CABG) was categorised into procedures with or without valve replacement.

Bleeding related

The different types of blood products recorded in the study are listed in Table 6.40. Re-operations due to bleedings were also recorded in the study. It should be noted that hospitalisations or prolonged hospitalisations due to bleeding episodes are accounted for in hospitalisations.

Table 6.40 shows the mean resource use for the No Event health state. Similar tables were generated from the HECON sub-study for the other health states as well as for the total patient population.

Table 6.40: Mean resource use for No Event health state (all patients)

Resource use item	TIC *Mean*	4785 *Std Err*	CLOP Mean	4690 Std Err
Bed day first 2 days index hospitalisation	1.995	0.001	1.996	0.001
Bed days general ward 3rd day to discharge index	5.642	0.086	5.693	0.088
Bed days general ward post index	3.7	0.128	3.488	0.125
Bed day coronary care unit after index hospitalisation	0.119	0.011	0.129	0.013
Bed day intensive care unit after index hospitalisation related to cabg	0.102	0.01	0.105	0.01
Bed day intensive care unit after index hospitalisation not related to cab	0.08	0.012	0.08	0.017
Stress test	0.293	0.009	0.287	0.009
Echocardiography	0.816	0.012	0.805	0.012
Myocardial scintigraphy	0.046	0.003	0.041	0.003
Electrophysiology study	0.003	0.001	0.004	0.001
Holter study	0.044	0.003	0.048	0.003
Ventilation/perfusion scan	0.004	0.001	0.001	0.001
Pulmonary angiography	0.001	0.001	0.001	0.001
Coronary angiography	1.005	0.008	1.002	0.008
Computer tomography Head/brain	0.018	0.002	0.017	0.002
Computer tomography Spinal	0.001	0.001	0.002	0.001
Computer tomography Chest	0.029	0.003	0.023	0.002
Computer tomography Helical	0.001	0	0	0
Computer tomography Abdomen	0.019	0.002	0.017	0.002
Computer tomography Extremity	0.001	0.001	0.001	0.001
Magnetic resonance imaging Head/brain	0.006	0.001	0.005	0.001
Magnetic resonance imaging Spinal	0.002	0.001	0.002	0.001
Magnetic resonance imaging Chest	0.009	0.002	0.01	0.001
Magnetic resonance imaging Abdomen	0.002	0.001	0.001	0
Magnetic resonance imaging Extremity	0.002	0.001	0.002	0.001
Pacemaker	0.014	0.002	0.013	0.002
Implantable cardiac defibrillator	0.005	0.001	0.006	0.001
Intra-aortic balloon pump	0.008	0.001	0.011	0.002

Table 6.40: Mean resource use for No Event health state (all patients)

Resource use item	TIC *Mean*	4785 *Std Err*	CLOP Mean	4690 Std Err
Left ventricular assist device	0	0	0	0
Percutaneous coronary intervention without stent	0.052	0.003	0.052	0.003
Percutaneous coronary intervention with stent (excl. stent cost)	0.708	0.009	0.721	0.01
Bare metal stent	0.668	0.013	0.677	0.013
Drug eluting stent	0.325	0.011	0.358	0.012
Coronary artery bypass grafting without valve replacement	0.092	0.004	0.096	0.004
Coronary artery bypass grafting with valve replacement	0.003	0.001	0.005	0.001
Reoperation due to bleedings	0.002	0.001	0.002	0.001
Units of packed red blood cells	0.221	0.014	0.235	0.017
Units of whole blood	0.024	0.005	0.032	0.006
Units of fresh frozen plasma	0.073	0.009	0.088	0.01
Units of platelets	0.071	0.011	0.073	0.02
Days on study drug	292.178	1.946	298.608	1.91

Drugs

Drugs were categorised as study drug or concomitant drugs. The number of days on study drugs was recorded. For concomitant drugs, drug use was measured at broad ATC-code level (e.g. B01AC). The number of days on a drug within such ATC-code levels was recorded.

Unit costs

In order to value resource use, a unit cost is applied to each resource use. The unit costs applied are for England and Wales and are expressed in 2008/09 GBP. The initial costing analysis was undertaken using 2007/08 costs however these have been inflated using the PSSRU inflation indices (PSSRU Unit Cost of Health and Social Care 2009; Inflation Indices), see Table 6.41.

Hospitalisations

Bed days were not categorised into different ward settings during the index hospitalisation therefore an assumption was made to use a higher cost for the first two days of the index hospitalisation based on the cost of a coronary care unit. From day three and onwards in the index hospitalisation, the cost of a cardiology ward was applied (Table 6.41). For post index hospitalisations, bed days were costed as general ward, coronary care unit, cardiac intensive care and intensive therapy unit as per the information recorded.

Investigations

Investigations were costed per item used.

Interventions

Interventions were costed per item used. Regarding PCI procedures it should be noted that procedures and stents are costed separately.

Bleeding related

Blood products were costed per item used.

Table 6.41: Resource use and units costs

Resource use item	Unit of measure	Unit Cost (£)	Lower quartile	Upper quartile
Hospitalisations				
Index hospitalisation				
Bed day first 2 days (coronary care unit)	per day	486	377	535
Bed day third day to discharge (cardiology ward)	per day	295	192	329
After index hospitalisation				
Bed day general ward	per day	274	195	352
Bed day coronary care unit	per day	486	377	535
Bed day intensive care unit (CABG-related)	per day	1282	995	1516
Bed day intensive care unit (not CABG-related)	per day	1512	1249	1750
Investigations				
Stress test	per procedure	70	44	83
Echocardiography	per procedure	73	39	83
Myocardial scintigraphy	per procedure	313	153	406
Electrophysiology study	per day case	2409	1220	3796
Holter study	per day case	550	362	601
Ventilation/perfusion scan	per procedure	401	301	502
Pulmonary angiography	per procedure	937	587	1161
Coronary angiography	per procedure	937	587	1161
Computer tomography				
Head/brain	per procedure	105	83	123
Spinal	per procedure	105	83	123
Chest	per procedure	105	83	123
Helical	per procedure	105	83	123
Abdomen	per procedure	105	83	123
Extremity	per procedure	105	83	123
Magnetic resonance imaging				
Head/brain	per procedure	212	131	269
Spinal	per procedure	212	131	269
Chest	per procedure	212	131	269
Abdomen	per procedure	212	131	269
Extremity	per procedure	212	131	269
Interventions				
Pacemaker	per day case	2540	1414	3932
Implantable cardiac defibrillator	per day case	9218	5078	16181
Intra-aortic balloon pump	per day case	1018	763	1272
Left ventricular assist device	per procedure	34613	7660	50967
Percutaneous coronary intervention without stent	per day case	2166	1918	2360
Percutaneous coronary intervention with stent (excl. stent cost)	per daycares	2953	2407	3444
Cost of bare metal stent	per unit	131	98	164
Cost of drug eluting stent	per unit	529	397	661
Coronary artery bypass grafting				
Without valve replacement	per HRG	9286	7668	10676
With valve replacement	per HRG	9338	6429	10349

Table 6.41: Resource use and units costs

Resource use item	Unit of measure	Unit Cost (£)	Lower quartile	Upper quartile
Bleeding related				
Reoperation due to bleedings	per procedure	9251	6938	11563
Units of packed red blood cells	per unit	140	105	175
Units of whole blood	per unit	140	105	175
Units of fresh frozen plasma	per unit	36	27	45
Units of platelets	per unit	232	174	290

Drugs

Drug use other than the study drug was excluded from the analyses. Based on the ATC classification system there was a similar use of concomitant drugs in the two treatment arms as shown in Table 6.42 and Table 6.43.

Table 6.42: Antithrombotic Med. taken Post Randomisation by ATC FULL

ATC Class	Randomised Treatment Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291
PROPIONIC ACID DERIVATIVES	618 (6.6%)	640 (6.9%)
OSMOTICALLY ACTING LAXATIVES	585 (6.3%)	580 (6.2%)
AMINOALKYL ETHERS	567 (6.1%)	592 (6.4%)
BENZODIAZEPINE RELATED DRUGS	550 (5.9%)	529 (5.7%)
COMBS OF PENICILLINS INCL BETA LACTAMASE INHIBITOR	528 (5.7%)	540 (5.8%)
SELECTIVE BETA 2 ADRENORECEPTOR AGONISTS	512 (5.5%)	492 (5.3%)
ALPHA ADRENORECEPTOR ANTAGONISTS	502 (5.4%)	513 (5.5%)
BETA BLOCKING AGENTS NON SELECTIVE	490 (5.3%)	476 (5.1%)
OTHER LIPID MODIFYING AGENTS	479 (5.1%)	458 (4.9%)
CONTACT LAXATIVES	468 (5.0%)	444 (4.8%)
OTHER VASODILATORS USED IN CARDIAC DISEASES	457 (4.9%)	481 (5.2%)
ANTICHOLINERGICS	454 (4.9%)	454 (4.9%)
ACE INHIBITORS AND DIURETICS	441 (4.7%)	444 (4.8%)
FIRST GENERATION CEPHALOSPORINS	436 (4.7%)	439 (4.7%)
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	432 (4.6%)	396 (4.3%)
BENZOTHIAZEPINE DERIVATIVES	426 (4.6%)	403 (4.3%)
PREPARATIONS INHIBITING URIC ACID PRODUCTION	419 (4.5%)	361 (3.9%)
THYROID HORMONES	393 (4.2%)	359 (3.9%)
ADRENERGICS/OTHER DRUGS FOR OBSTR AIRWAY DISEASES	392 (4.2%)	353 (3.8%)
THIRD GENERATION CEPHALOSPORINS	386 (4.1%)	415 (4.5%)
DIGITALIS GLYCOSIDES	382 (4.1%)	393 (4.2%)
SECOND GENERATION CEPHALOSPORINS	359 (3.8%)	346 (3.7%)
OTHER GENERAL ANESTHETICS	345 (3.7%)	354 (3.8%)
SOFTENERS EMOLLIENTS	339 (3.6%)	310 (3.3%)
PHENOTHIAZINE DERIVATIVES	329 (3.5%)	333 (3.6%)
SEROTONIN (5HT3) ANTAGONISTS	312 (3.3%)	319 (3.4%)
PENICILLINS WITH EXTENDED SPECTRUM	308 (3.3%)	342 (3.7%)
CARBOHYDRATES	306 (3.3%)	270 (2.9%)
ANGIOTENSIN II ANTAGONISTS AND DIURETICS	305 (3.3%)	308 (3.3%)
IRON BIVALENT ORAL PREPARATIONS	299 (3.2%)	267 (2.9%)
BLOOD SUBSTITUTES AND PLASMA PROTEIN FRACTIONS	296 (3.2%)	295 (3.2%)
XANTHINES	287 (3.1%)	289 (3.1%)
DIPHENYLMETHANE DERIVATIVES	281 (3.0%)	298 (3.2%)
ANTIDOTES	271 (2.9%)	250 (2.7%)

Table 6.42: Antithrombotic Med. taken Post Randomisation by ATC FULL

ATC Class	Randomised Treatment Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291
INSULINS AND ANALOGUES FOR INJ INTERMEDIATE ACTING	271 (2.9%)	296 (3.2%)
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	258 (2.8%)	263 (2.8%)
FIBRATES	253 (2.7%)	240 (2.6%)

Table 6.43: Non Antithrombotic Med. taken Post Randomisation by ATC FULL

ATC Class	Randomised Treatment Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291
BUTYROPHENONE DERIVATIVES	246 (2.6%)	205 (2.2%)
DIPHENYLPROPYLAMINE DERIVATIVES	245 (2.6%)	245 (2.6%)
MACROLIDES	237 (2.5%)	206 (2.2%)
WATERSOL NEPHROTROPIC LOW OSMOL X RAY CONTR MEDIA	237 (2.5%)	225 (2.4%)
INSULINS AND ANALOGUES FOR INJECTION LONG ACTING	234 (2.5%)	210 (2.3%)
AMIDES	233 (2.5%)	247 (2.7%)
SUBSTITUTED ALKYLAMINES	231 (2.5%)	211 (2.3%)
HMG COA REDUCTASE INHIBITORS OTHER COMBINATIONS	227 (2.4%)	225 (2.4%)
ANTACIDS WITH SODIUM BICARBONATE	214 (2.3%)	232 (2.5%)
IMIDAZOLINE RECEPTOR AGONISTS	214 (2.3%)	207 (2.2%)
LOW CEILING DIURETICS AND POTASSIUM SPARING AGENTS	211 (2.3%)	226 (2.4%)
OTHER QUATERNARY AMMONIUM COMPOUNDS	205 (2.2%)	226 (2.4%)
OTHER DRUGS FOR PEPTIC ULCER AND GORD	201 (2.2%)	163 (1.8%)
ANTACIDS	191 (2.0%)	197 (2.1%)
AMINO ACIDS	187 (2.0%)	188 (2.0%)
OTHER ANTIDEPRESSANTS	186 (2.0%)	170 (1.8%)
OTHER PSYCHOSTIMULANTS AND NOOTROPICS	186 (2.0%)	194 (2.1%)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	183 (2.0%)	173 (1.9%)
OPIUM ALKALOIDS AND DERIVATIVES	176 (1.9%)	171 (1.8%)
OPIOID ANESTHETICS	175 (1.9%)	185 (2.0%)
FOLIC ACID AND DERIVATIVES	168 (1.8%)	155 (1.7%)
CALCIUM	167 (1.8%)	194 (2.1%)
GLYCOPEPTIDE ANTIBACTERIALS	152 (1.6%)	151 (1.6%)
PIPERAZINE DERIVATIVES	152 (1.6%)	164 (1.8%)
ANTIPROPULSIVES	147 (1.6%)	114 (1.2%)
COMB/COMPLEXES ALUMINIUM CALCIUM MAGNESIUM COMPS	143 (1.5%)	130 (1.4%)
NON SELECTIVE MONOAMINE REUPTAKE INHIBITORS	142 (1.5%)	175 (1.9%)
DRUGS USED IN NICOTINE DEPENDENCE	141 (1.5%)	134 (1.4%)
OTHER CARDIAC COMBINATION PRODUCTS	138 (1.5%)	111 (1.2%)
PURINE DERIVATIVES	137 (1.5%)	143 (1.5%)
PAPAVERINE AND DERIVATIVES	125 (1.3%)	132 (1.4%)
IMIDAZOLE DERIVATIVES	122 (1.3%)	148 (1.6%)
OTHER AMINOGLYCOSIDES	119 (1.3%)	125 (1.3%)
OTHER LOW CEILING DIURETICS	118 (1.3%)	114 (1.2%)
ASCORBIC ACID (VITAMIN C) PLAIN	112 (1.2%)	91 (1.0%)
VITAMINS WITH MINERALS	111 (1.2%)	89 (1.0%)
NITROFERRICYANIDE DERIVATIVES	109 (1.2%)	104 (1.1%)

Analysis

Health service costs were calculated for each patient over the study period. Patients were followed-up for a minimum of 6 months to a maximum of 12 months, however for the purposes of this analysis, a cohort of patients were used with a full 12-month follow-up. In order to calculate a total cost per patient in the study, resource use was multiplied by the relevant unit costs. Total mean health service cost for each treatment group were estimated and compared.

Results

Mean resource use was calculated for each node in the decision tree by treatment arm and are the results are shown in Table 6.44.

Table 6.44: List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
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	Hospitalisations	£9105	

Health states	Items	Value	Reference in submission
(Clopidogrel)			
	Investigations	£867	
	Interventions	£3316	
	Bleeding related	£627	
	Total	**£13915**	

With regard to the analysis versus prasugrel, in the absence of a head-to-head trial with a within-trial costing analysis, it has been assumed that the health state costs for the one-year decision tree for prasugrel are the same as those for ticagrelor. Costs for significant adverse events have been costed separately and are discussed in Section 6.5.7.

With regard to the Markov model, costs are needed for the No Event, Non-fatal MI, Post MI, Non-fatal Stroke and Post Stroke health states. For the Non-fatal Stroke and Post Stroke health states, a paper by Youman et al, 2003, was used. This paper estimates the cost of treating stroke in the UK and has been referenced in several HTA reports (TA132 Ezetimibe, 2007, TA90 Clopidogrel and Dipyridamole) as well as published papers in the ACS arena (Karnon et al, 2005, 2006, 2010).

Youman et al, provides the cost of acute stroke per 3-month period by stroke classification: mild, moderate and severe (see Table 6.45) as well as the costs for ongoing care whether that is at home or in an institution (see Table 6.46).

Table 6.45: Cost of acute stroke, Youman et al, 2003

Stroke classification	Cost of acute stroke per 3-month period		
	Mean	***L 95% CI***	**U 95% CI**
Mild	£5,099	£4,558	£5,636
Moderate	£4,816	£4,406	£5,225
Severe	£10,555	£9,575	£11,535

Table 6.46: Cost of ongoing care, Youman et al, 2003

Category	Cost of acute stroke per 3-month period		
	Mean	***L 95% CI***	**U 95% CI**
At Home	£326	£195	£457
In Institution	£3,872	£3,669	£4,865

These costs have been used to calculate the annual cost of stroke for the first year and subsequent years dependent on stroke severity and discharge location. A weighted average of these costs based on the proportion of stroke type, inflated to 2008/09 has been used in the model for the Non-fatal Stroke health state (£13,084) and the Post Stroke health state (£3,632) as per Table 6.47.

Table 6.47: Costs for stroke in Markov model

Stroke Type	Prop. of stroke type	Proportion by death and discharge location			3 months acute cost + 9 months ongoing care cost					
					Annual costs		Lower		Upper	
		Home	*Instit.*	*Dead*	*Year 1*	*Post Year 1*	*Year 1*	*Post Year 1*	*Year 1*	*Post Year 1*
Mild	0.19	1.000	0.000	0.000	£6,077	£1,304	£5,143	£780	£7,007	£1,828
Moderate	0.27	0.959	0.008	0.033	£5,882	£1,421	£5,077	£895	£6,705	£1,974
Severe	0.54	0.732	0.172	0.096	£13,557	£4,003	£13,557	£4,003	£13,557	£4,003
Total	**1.00**	**Weighted average cost:**			**£10,059**	**£2,792**	**£9,664**	**£2,550**	**£10,459**	**£3,041**
		Costs inflated to 2008/09:			**£13,084**	**£3,632**	**£12,571**	**£3,317**	**£13,604**	**£3,956**

With regard to the costs for the Non-fatal MI health state, there is a wide range of costs used in both the published literature and previous HTAs. The highest cost quoted is £5762 from UKPDS Study 65 which is used in the recently published update of TA90 Clopidogrel and Dipyridamole (October 2010). The lowest cost quoted is the NHS reference cost for 2006/07 of £1783 which is used in CG94 UA and NSTEMI Guideline published in March 2010. The most commonly referenced cost for MI is that used by Palmer et al, in the review of the glycoprotein IIb/IIIa antagonists (TA47) in 2002. This cost of £3966, which is based on data from the Nottingham Heart Attack Register, has subsequently been used in TA80 Clopidogrel in STEMI (July 2004), the original TA90 (May 2005), TA94 Statins (January 2006) and TA132 Ezetimibe (November 2007). In addition, this reference has also been used in Karnon et al, 2005, 2006 and 2010. In order to remain consistent with other published papers and HTAs already undertaken in the cardiovascular arena, it was decided to use the reference from Palmer et al, inflated to 2008/09 in the base case analysis. For the sensitivity analysis, the 2008/09 NHS reference cost for EB10Z Actual or Suspected Myocardial Infarction, weighted by elective and non-elective activity was used as the lowest cost (£1721) and the figure of £5762 from the update of TA90 was used as the highest cost see Table 6.48.

For the Post MI health state, there was once again a wide range of values in the literature. The highest was Palmer et al, 2002 from TA47, with a value of £1587 based on the Notttingham Heart Attack Register. This value was also used in TA80 Clopidogrel in NSTEMI (July 2004), the original TA90 (May 2005) as well as Karnon et al, 2005, 2006 and 2010. Lower figures have also been reported in the literature e.g. Bravo Vergel et al, 2007 with £91, TA94 Statins (January 2006) with £171, TA132 Ezetimibe with £201 and CG94 UA and NSTEMI (March 2010) with £264. A value of £500 was used in CG34 Hypertension (June 2006), CG48 Secondary Prevention of MI (May 2007) and CG67 Lipid Modification (May 2008), whilst in the updated of TA90 Clopidogrel and Dipyridamole (October 2010) a figures of £578 was used from UKPDS Study 65. Based on the wide range of figures provided, it was decided to use the figure of £264 provided in the CG94 UA and NSTEMI guideline in the base case because it was based on event rates from the MINAP dataset, event costs from NHS reference costs, also included the cost of secondary prevention medication and was in an appropriate population. The value of £1587 from Palmer et al, 2002 inflated to 2008/09 was used as the high value and £201 inflated to 2008/09 from TA132 Ezetimibe was used as the low value (see Table 6.48).

In terms of identifying a cost for the No Event health state there were several costs identified in the literature but again the range was wide. Palmer et al, 2002 reported a figure of £1421 which was much higher than the others which ranged from £171 (CG48 Secondary Prevention of MI, TA94 Statins) to £201 (TA132 Ezetimibe). The figure of £201 seemed reasonable as it was based on 3 times 15 minute GP consultations plus medication costs. Given that patients in the No Event state are likely to be on similar medication as those in the Post MI Health State, these two values seemed reasonable. This figure inflated to 2008/09 was used in the model, as shown in Table 6.48.

Table 6.48: Health state costs used in Markov Model

Health State	Source	Year	Original baseline			Costs inflated to 2008/09		
			Mean	Lower	Upper	*Mean*	*Lower*	*Upper*
No Event	Various	2006	£201	£151	£1,421	£217	£163	£1,793
MI	Palmer et al	2002	£3,966	£1,721	£5,762	£5,003	£1,721	£5,762
Post MI	CG94	2010	£264	£201	£1,587	£285	£217	£2,002

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

All costs associated with adverse events in the PLATO study have been captured as part of the Within-trial Costing Analysis as described in Section 6.5.6. However, for the analysis with prasugrel there are adverse events for which a costs needs to be assigned. In the indirect comparison (Biondi-Zoccai et al, 2010) on which the economic analysis versus prasugrel is based, stent thrombosis, major and minor bleeding were identified as key adverse events.

With regard to costs for bleeding, the clinical guideline for UA and NSTEMI (CG94), published in March 2010, utilises costs based on the additional length of stay, taken from an analysis of the MINAP dataset, together with the cost per day taken from 2006/2007 NHS reference costs. Inflating the daily cost to 2008/09 NHS reference costs whilst using the same additional length of stay gives a cost for major bleeding of £1,260 and a cost for minor bleeding of £420, as shown in Table 6.49.

Table 6.49: Cost of bleeding from CG94

Adverse Event	Additional length of stay (days)	Cost per day			Total cost		
		Mean	*L Qrtl*	*U Qrtl*	*Mean*	*L Qrtl*	*U Qrtl*
Major bleed	6	£210	£160	£240	£1,260	£960	£1,440
Minor bleed	2	£210	£160	£240	£420	£960	£1,440

In addition to bleeding, the other adverse event identified in Biondi-Zoccai et al, 2010, is stent thrombosis. It is assumed that each episode of stent thrombosis will result in another PCI therefore the cost associated with stent thrombosis is assumed to be the weighted average of elective and non-elective HRG code EA31Z for PCI (0-2 stents) as shown in Table 6.50.

Table 6.50: Cost of stent thrombosis from National Reference Costs 2008/09

HRG Code	Description	Activity	National Unit Costs		
			Mean	***Lower Qrtl***	***Upper Qrtl***
EA31Z (Non-elective)	PCI (0-2 Stents)	15,735	£3,029	£2,392	£3,779
EA31Z (Elective)	PCI (0-2 Stents)	15,412	£2,610	£1,989	£2,993
Weighted average		**31,147**	**£2,821**	**£2,192**	**£3,390**

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Not applicable

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The decision tree used in the base case has four nodes: No Further Event, Non-fatal MI, Non-fatal Stroke and Death from Any Cause. This means that data used in the one-year decision tree comes exclusively from the PLATO study. In some cost-effectiveness analyses within the ACS arena, the dead health state is split into two: Vascular Death and Non-vascular Death. In this case, the data for Vascular Death is taken from the clinical trial whilst the data for Non-vascular death is taken from life-tables. The reason for this is that rates of non-vascular death from clinical trials are often thought to be a poor indicator of actual non-vascular mortality as many co-morbidities are screened out during the recruitment phase of the trial. In order to assess the impact of splitting out vascular and non-vascular death, an alternative model structure with five nodes: No Further Event, Non-fatal MI, Non-fatal Stroke, Vascular Death and Non-vascular Death has been tested in the sensitivity analysis.

In addition to altering the structure of the model, scenarios were run with the discount rates set to 0% and 6%, using utility from the literature instead of from the HECON substudy, removing the baseline utility adjustment and removing utility decrement per cycle.

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

A one-way sensitivity analysis was undertaken on all key variables as listed in section 6.3.6. Table 6.51 summarises the low and high values used for the clinical parameters.

Table 6.51: Values used in one-way sensitivity analysis

Variable	Parameter	Range		Source
		Low	High	
Event rates for clopidogrel (one-year decision tree)				
Dead Any Cause	0.0789	0.0518	0.1202	95% confidence intervals based on Weibull regression equations as per section 6.3.1
Non-fatal MI	0.0628	0.0426	0.0935	
Non-fatal Stroke	0.0112	0.0039	0.0347	
Dead Vascular	0.0672	0.0436	0.1038	
Hazard ratios for ticagrelor versus clopidogrel (one-year decision tree)				
Dead Any Cause	0.7845	0.6880	0.8945	95% confidence intervals based on Weibull regression equations as per section 6.3.1
Non-fatal MI	0.8598	0.7546	0.9797	
Non-fatal Stroke	1.0894	0.7949	1.4930	
Dead Vascular	0.7946	0.6908	0.9139	
Event rates for ticagrelor (one-year decision tree)				
Death Any Cause	Since the event rates for ticagrelor are based on a combination of clopidogrel event rates and ticagrelor hazard ratios, sensitivity analysis cannot be undertaken per se, rather it will be done by varying the other parameters as listed above			
Non-fatal MI				
Non-fatal Stroke				
Dead Vascular				
Event rates (Markov model)				
Non-fatal MI	0.0315	0.0257	0.0385	MINAP/GPRD study as per section 6.3.2
Non-fatal Stroke	0.0102	0.0072	0.0145	
Relative mortality risks (Markov model)				
Dead Any Cause	2.21	0.1817	4.2425	CG84 and Allen et al, 2006, as per section 6.3.2
Non-fatal MI	5.84	3.7176	7.9717	
Post MI	2.21	0.1817	4.2425	
Non-fatal Stroke	7.43	6.5000	8.5000	Dennis et al, 1993, as per section 6.3.2
Post Stroke	2.07	1.3000	3.3200	

In addition to the clinical parameters, utilities and resource utilisation were also subjected to one way sensitivity analysis as shown in Table 6.52.

Table 6.52: Utility values used in one-way sensitivity analysis				
Variable	**Parameter**	**Range**		**Source**
		Low	**High**	
Utilities from PLATO HECON substudy				
No Further Event (tica)	0.840	0.834	0.846	95% confidence intervals based on PLATO HECON substudy
Non-fatal MI (tica)	0.786	0.759	0.814	
Non-fatal Stroke (tica)	0.709	0.588	0.831	
Dead Any Cause (tica)	0.211	0.170	0.252	
No Further Event (clop)	0.844	0.838	0.850	
Non-fatal MI (clop)	0.774	0.747	0.802	
Non-fatal Stroke (clop)	0.695	0.632	0.758	
Dead Any Cause (clop)	0.220	0.183	0.257	
No Further Event (mm)	0.842	0.838	0.846	
Non-fatal MI (mm)	0.779	0.760	0.799	
Post MI (mm)	0.821	0.802	0.841	
Non-fatal Stroke (mm)	0.703	0.629	0.778	
Post Stroke (mm)	0.703	0.629	0.778	
Utilities from literature				
No Further Event	0.711	0.693	0.730	95% confidence intervals based on literature
Non-fatal MI	0.650	0.620	0.681	
Post MI	0.685	0.653	0.717	
Non-fatal Stroke	0.595	0.484	0.707	
Post Stroke	0.595	0.484	0.707	
Resource utilisation within trial				
No Further Event (tica)	£8,544	£6,307	£10,053	Unit cost values set to lower and upper quartiles and resource use calculated accordingly
Non-fatal MI (tica)	£16,643	£12,258	£19,871	
Non-fatal Stroke (tica)	£15,394	£11,372	£18,414	
Dead Any Cause (tica)	£11,753	£8,697	£13,847	
No Further Event (clop)	£8,633	£6,378	£10,154	
Non-fatal MI (clop)	£16,362	£12,221	£19,486	
Non-fatal Stroke (clop)	£17,483	£13,000	£20,896	
Dead Any Cause (clop)	£13,915	£10,305	£16,489	

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Yes, probabilistic sensitivity analysis has been undertaken.

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 6.53: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Ticagrelor		
Death any cause	4.5%	6.2%
MI	5.8%	5.4%
Stroke	1.5%	1.2%
Clopidogrel		
Death any cause	5.9%	7.9%
MI	6.9%	6.3%
Stroke	1.3%	1.1%

As explained in Section 6.3.1, due to the classification of patients into mutually exclusive nodes in the decision tree, the modelled events for MI and stroke will be lower than those seen in the clinical paper. As shown in Section 6.3.1, the modelled outcomes for vascular death and death any cause were the same as in the published paper however the results here show a difference. The reason for this is that the PLATO population had a median age of 62 whereas the UK ACS population has a mean age of 70. In addition, the percentage of patients in the UK ACS

population is 42.7% compared to 15.1% in PLATO. The event rate at one-year in patients ≥ 75 was higher than that seen in patients <75 therefore the Weibull regression equations were used to determine a higher baseline risk for the UK population to reflect the difference in age. As expected, the results of the model show that the risk of death is increased in this population due to age.

6.7.2 **Please provide (if appropriate) the proportion of the cohort in the health *state over time (Markov trace) for each state, supplying one for each comparator.***

Markov traces for ticagrelor, clopidogrel and prasugrel have been included in the Appendix 9.13.

6.7.3 ***Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.***

In the decision tree, the QALYs are calculated as the number of patients in each node at the end of the trial period multiplied by the utility accrued for the health state over the one-year period. This is because in the HECON sub-study utility was calculated as the area under the curve for each patient up to the point at which they died.

In the Markov model, the QALYs are calculated as the number of patients in each health state at the end of each cycle (taking into account half-cycle correction) multiplied by the utility value associated with the respective health state. Cumulative QALYs are accrued through each subsequent cycle of the model for each intervention.

6.7.4 ***Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:***

Table 6.54: Model outputs by clinical outcomes (40-year time horizon)

Outcome	LY	QALY	Cost (£)
Ticagrelor			
No event	5.966	5.002	£9,171
Non-fatal MI	0.168	0.130	£858
Post MI	1.185	0.967	£1,271
Non-fatal Stroke	0.054	0.038	£726
Post stroke	0.332	0.232	£1,358
Dead	0.031	0.013	£750
Clopidogrel			
No event	5.002	4.863	£8,414
Non-fatal MI	0.130	0.127	£834
Post MI	0.967	1.009	£1,376
Non-fatal Stroke	0.038	0.037	£705
Post stroke	0.232	0.221	£1,308
Dead	0.013	0.017	£1,100
LY, life years; QALY, quality-adjusted life year			

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 6.55: Summary of QALY gain by health state (40-year time horizon)

Health state	QALY intervention (ticagrelor)	QALY comparator (clopidogrel)	Absolute increment	% absolute increment
No Event	5.002	4.863	0.139	129%
Non-fatal MI	0.130	0.127	0.004	3%
Post MI	0.967	1.009	-0.042	-39%
Non-fatal stroke	0.038	0.037	0.001	1%
Post Stroke	0.232	0.221	0.011	10%
Dead	0.013	0.017	-0.004	-4%
Total	**6.382**	**6.275**	**0.108**	**100%**

Table 6.56: Summary of costs by health state (40-year time horizon)

Health state	Cost intervention (ticagrelor)	Cost comparator (clopidogrel)	Absolute increment	% absolute increment
No Event	£9,171	£8,414	£757	190%
Non-fatal MI	£858	£834	£24	6%
Post MI	£1,271	£1,376	-£105	-26%
Non-fatal stroke	£726	£705	£21	5%
Post Stroke	£1,358	£1,308	£51	13%
Dead	£750	£1,100	-£350	-88%
Total	**£14,135**	**£13,737**	**£398**	**100%**

Tables 6.55 and 6.557 show that over the 40-year time horizon patients who took ticagrelor after their index ACS event accrued 6.382 QALYs and costs of £14,135 versus those patients who took clopidogrel who accrued 6.275 QALYs and costs of £13,737.

Table 6.57: Summary of predicted resource use by category of cost

Item	Cost intervention (ticagrelor)	Cost comparator (clopidogrel)	Increment	% absolute increment
Hospitalisations	£4,373	£4,545	-£172	63%
Investigations	£1,102	£1,099	£3	-1%
Interventions	£3,579	£3,689	-£110	40%
Bleeding related	£114	£110	£4	-1%
Total costs	**£9,168**	**£9,443**	**-£275**	**100%**

Table 6.57 shows the results of the Within-trial Cost Analysis. There is an overall costing saving of £275 with ticagrelor. This cost saving is driven by lower costs in the hospitalisations and interventions categories which is logical given that patients on ticagrelor experience fewer MIs and fewer deaths.

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 6.58: Base-case results – cost per LYG (deterministic)

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

Table: 6.59 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 6.60: Base-case results – cost per QALY (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Clopidogrel	£13,894	6.276			
Ticagrelor	£14,299	6.382	£405	0.106	£3,805

The mean results from the probabilistic sensitivity analysis are shown in Table 6.60. It can be seen from these results that ticagrelor is highly cost-effective when compared to clopidogrel with an incremental cost-effectiveness ratio of £3,805 per QALY gained.

Table 6.61 shows the impact on the cost per QALY over different time horizons. It can be seen that ticagrelor is highly cost effective versus clopidogrel within five years. Indeed the cost per QALY over one year is £36,177 which compares very favourably to that of prasugrel versus clopidogrel which was £159,358 as quoted in the prasugrel STA.

Table 6.61 Deterministic results with costs and effects discounted

Time horizon	*Ticagrelor*	*Clopidogrel*	*Incremental*	*ICER*
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**

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The results of the one-way sensitivity analysis show that the model is very stable to changes in the majority of the parameters. The key parameters that appear to have an influence on the outcome are the costs associated with the No Event health state. This is not surprising as the majority of patients are in this state therefore it will have a large impact on the results. If the cost of the ticagrelor No Event health state is set to its lowest level, ticagrelor becomes dominant over clopidogrel i.e. it is both cheaper and more effective. However if the cost of the clopidogrel No Event health state is set to its lowest level, ticagrelor becomes borderline cost-effective with a cost per QALY of £21k; this is the highest cost per QALY value within the sensitivity analysis. Changes in all the other parameters in the one-way sensitivity analysis do not increase the cost per QALY to beyond £7,620.

Figure 6.7: Tornado diagram of one-way sensitivity analysis

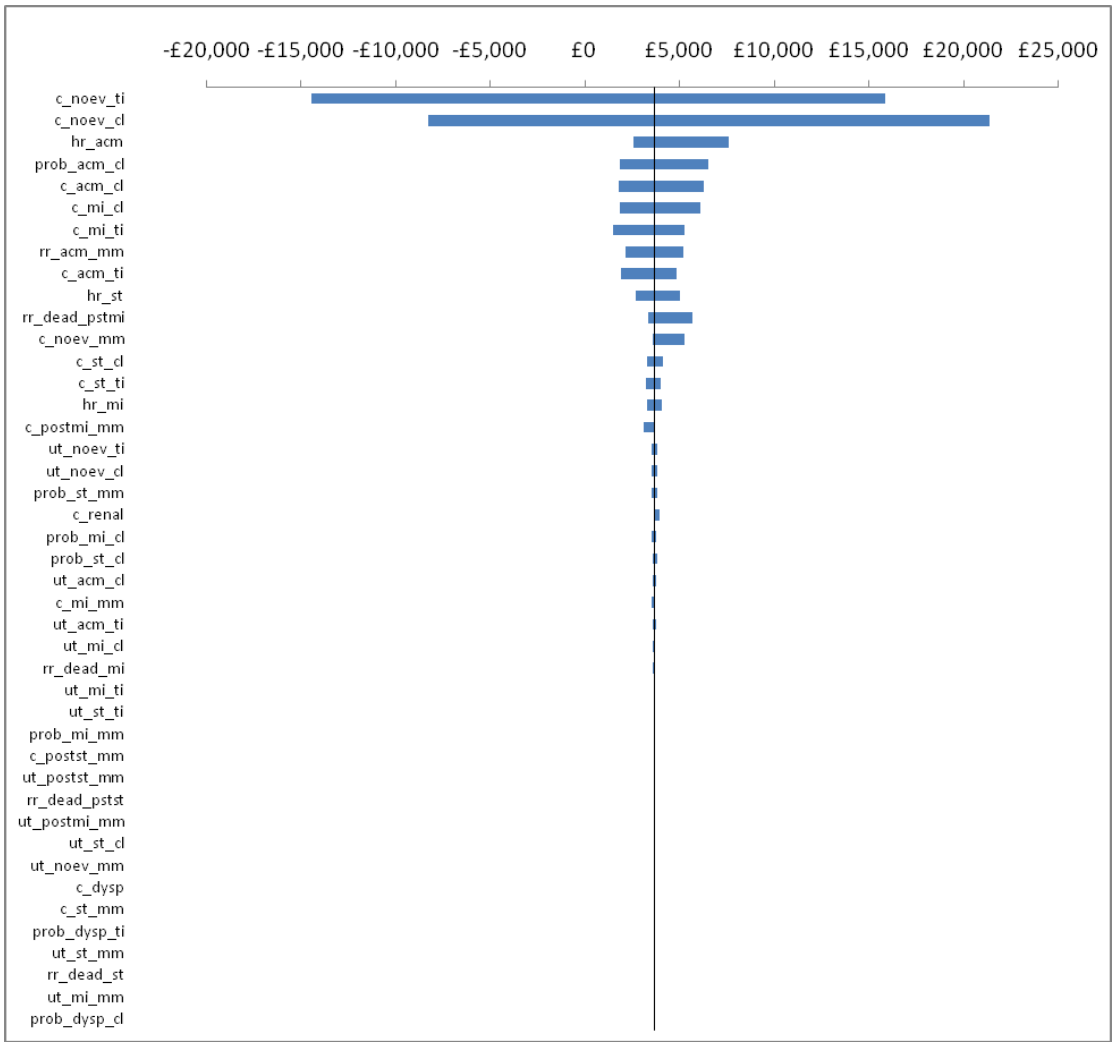


Table 6.62: Output of one-way sensitivity analysis

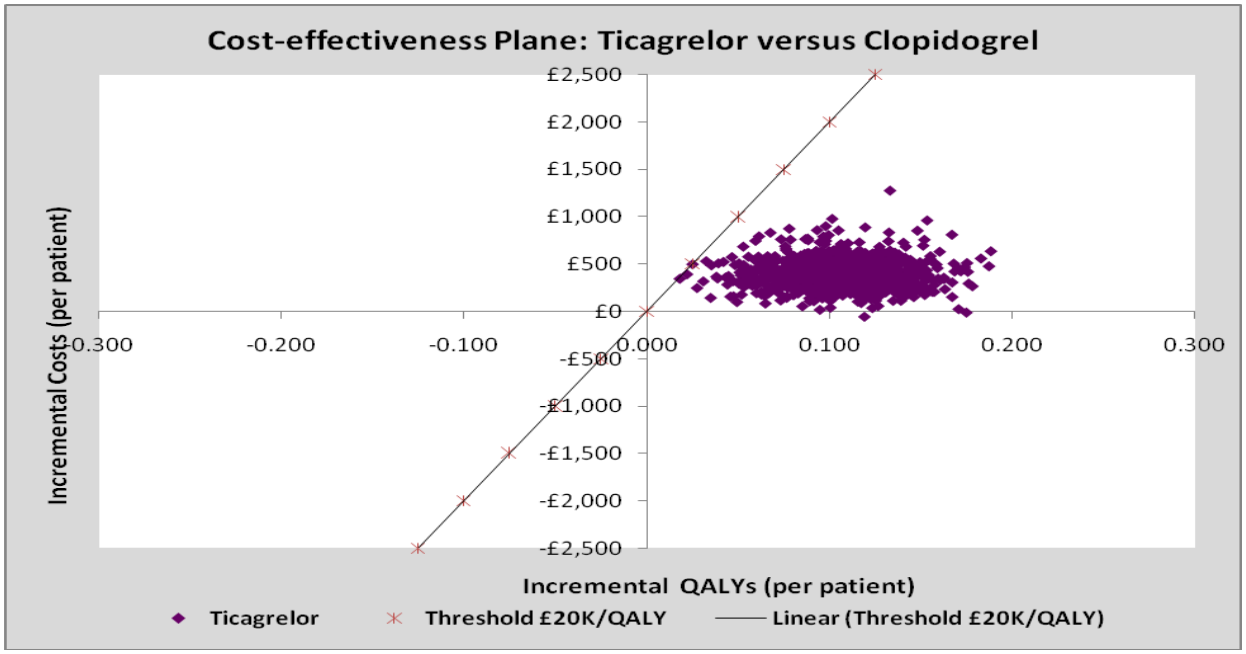
Parameters	Output with low value	Output with high value	Output difference
c_noev_ti	-£14,423.54	£15,903.89	£30,327.43
c_noev_cl	£21,431.53	-£8,274.12	£29,705.65
hr_acm	£2,584.56	£7,619.64	£5,035.08
prob_acm_cl	£6,540.69	£1,866.04	£4,674.65
c_acm_cl	£6,333.47	£1,803.87	£4,529.60
c_mi_cl	£6,103.94	£1,867.26	£4,236.68
c_mi_ti	£1,490.00	£5,307.49	£3,817.49
rr_acm_mm	£2,150.14	£5,231.93	£3,081.79
c_acm_ti	£1,933.30	£4,891.98	£2,958.68
hr_st	£2,736.88	£5,066.28	£2,329.40
rr_dead_pstmi	£5,722.96	£3,393.86	£2,329.10

Table 6.62: Output of one-way sensitivity analysis

Parameters	Output with low value	Output with high value	Output difference
c_noev_mm	£3,622.70	£5,295.58	£1,672.88
c_st_cl	£4,153.72	£3,334.91	£818.81
c_st_ti	£3,234.47	£4,030.13	£795.66
hr_mi	£3,331.87	£4,093.70	£761.83
c_postmi_mm	£3,714.63	£3,148.03	£566.60
ut_noev_ti	£3,873.28	£3,521.22	£352.06
ut_noev_cl	£3,525.78	£3,867.78	£342.00
prob_st_mm	£3,559.87	£3,870.61	£310.74
c_renal	£3,688.87	£3,989.19	£300.32
prob_mi_cl	£3,783.47	£3,545.99	£237.48
prob_st_cl	£3,636.10	£3,862.08	£225.98
ut_acm_cl	£3,590.93	£3,792.31	£201.38
c_mi_mm	£3,540.46	£3,723.17	£182.71
ut_acm_ti	£3,778.22	£3,603.65	£174.57
ut_mi_cl	£3,630.77	£3,748.86	£118.09
rr_dead_mi	£3,636.17	£3,743.30	£107.13
ut_mi_ti	£3,740.34	£3,638.80	£101.54
ut_st_ti	£3,740.22	£3,638.91	£101.31
prob_mi_mm	£3,644.39	£3,739.34	£94.95
c_poststst_mm	£3,648.46	£3,730.47	£82.01
ut_poststst_mm	£3,725.14	£3,653.31	£71.83
rr_dead_pstst	£3,724.21	£3,655.09	£69.12
ut_postmi_mm	£3,659.33	£3,718.89	£59.56
ut_st_cl	£3,665.03	£3,713.02	£47.99
ut_noev_mm	£3,708.43	£3,669.52	£38.91
c_dysp	£3,671.60	£3,706.14	£34.54
c_st_mm	£3,681.35	£3,696.47	£15.12
prob_dysp_ti	£3,684.83	£3,692.92	£8.09
ut_st_mm	£3,692.83	£3,684.92	£7.91
rr_dead_st	£3,692.13	£3,685.10	£7.03
ut_mi_mm	£3,692.09	£3,685.66	£6.43
prob_dysp_cl	£3,692.04	£3,685.71	£6.33

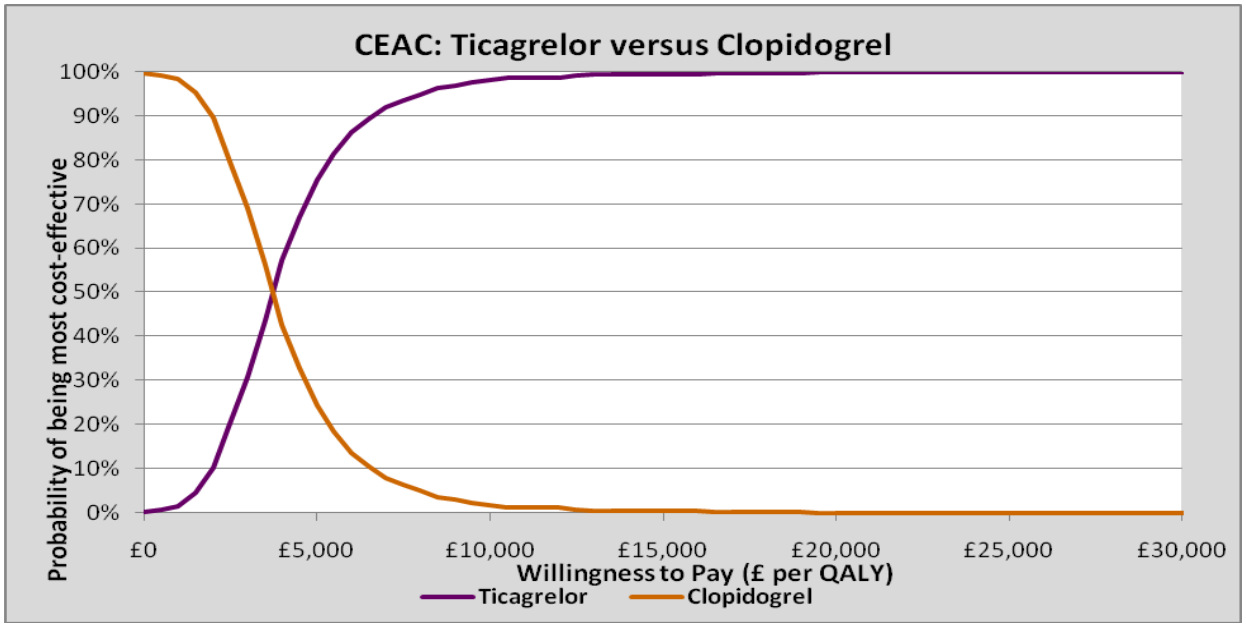
6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 6.8: Scatter plot of incremental costs and QALYs



It can be seen from Figure 6.7 that all the points on the scatter plot lay below the threshold of £20k per QALY. This means that for each point on the graph, ticagrelor offers additional QALYs at a cost that is below a willingness to pay of £20k per QALY.

Figure 6.9: Cost-effectiveness acceptability curves for ticagrelor vs clopidogrel



From the cost-effectiveness acceptability curves it can be seen that at a willingness to pay of £5k per QALY, the probability of ticagrelor being cost-effective is 76.6%. At a willingness to pay of £10k per QALY, the probability of ticagrelor being cost

effective versus clopidogrel is 98.1%. At a willingness to pay of £20k per QALY, the probability that ticagrelor is cost-effective versus clopidogrel is 99.9%.

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

As discussed in Section 6.6.1, the model was also built in an alternative way such the Dead Any Cause node was split into Dead Vascular and Dead Non-vascular. In this alternative model structure the Dead Vascular node was populated using results from the PLATO study whereas the Dead Non-vascular node was populated using cause-eliminated life tables. The structure of the Markov model remained unchanged. The results of this scenario are show in Table 6.63. It can be seen that whilst the cost per QALY has increased to £6,436, ticagrelor is still highly cost-effective versus clopidogrel due to the statistically significant reduction in vascular deaths.

Table 6.63 Deterministic results based on dead vascular and dead non-vascular nodes

Time horizon	*Ticagrelor*	*Clopidogrel*	*Incremental*	*ICER*
40 years				
Costs	£13,742	£13,185	£557	
Life-years	7.698	7.593	0.105	£5,308
QALYs	**6.350**	**6.263**	**0.086**	**£6,436**

Other scenarios that were tested include:

Table 6.64 Results of scenario testing (40-year time horizon)

Time horizon	*Ticagrelor*	*Clopidogrel*	*Incremental*	*ICER*
Discount rate set to 0%				
Costs	£15,201	£14,774	£428	
QALYs	**7.715**	**7.584**	**0.131**	**£3,261**
Discount rate set to 6%				
Costs	£13,573	£13,191	£383	
QALYs	**5.673**	**5.578**	**0.095**	**£4,020**
Utility values from literature				
Costs	£14,135	£13,737	£398	
QALYs	**5.365**	**5.268**	**0.097**	**£4,100**
No baseline utility adjustment				
Costs	£14,135	£13,737	£398	
QALYs	**6.637**	**6.525**	**0.112**	**£3,565**
No utility decrement per cycle				
Costs	£14,135	£13,737	£398	
QALYs	**6.409**	**6.301**	**0.108**	**£3,680**
Treatment duration from trial				
Costs	£13,983	£13,729	£254	
QALYs	**6.382**	**6.275**	**0.108**	**£2,358**
Same costs per health state				
Costs	£13,983	£13,477	£506	
QALYs	**6.382**	**6.275**	**0.108**	**£4,699**

6.7.10 What were the main findings of each of the sensitivity analyses?

In addition to the one-way sensitivity analysis, the results of which are shown in Table 6.62, further sensitivity analysis was undertaken to assess the robustness of the results to other changes in the model parameters. Table 6.64 shows the results of these additional sensitivity analyses. As the table shows, the cost-effectiveness of ticagrelor versus clopidogrel remains consistent with a cost per QALY under £5k in each of the scenarios tested.

6.7.11 What are the key drivers of the cost-effectiveness results?

The key driver of the cost-effectiveness results is the lower probability of death in the one-year decision tree for ticagrelor. This means that at the end of one year, there are more patients in the ticagrelor arm and these additional patients go on to accrue QALYs for the remainder of their lives. No treatment effect is assumed beyond the first year so patients in both arms will have events and die at the same rate, however the fact that there are more patients in the ticagrelor arm to start with means that over a 40-year time horizon they will more costs and more QALYs.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

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 other published results in ACS and in line with other results obtained.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

In line with the scope, ticagrelor has been compared with clopidogrel in the following subgroups based on the PLATO study:

- Unstable angina
- NSTEMI
- STEMI

The scope also requested an analysis in the invasive population comparing ticagrelor with prasugrel. As outlined in Section 5.7, this analysis has been undertaken via the use of a published indirect comparison (Biondi-Zoccai et al, 2010), the issues with which have already been clearly identified in Section 5.7.6.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

The characteristics of the subgroups for unstable angina, NSTEMI and STEMI have been taken from the MINAP/GPRD study to ensure that they are reflective of the subgroups within the ACS population in England and Wales.

With regard to the patient characteristics in the invasive subgroup, this has been taken from the ticagrelor arm of the PLATO invasive paper.

Table 6.65: Characteristics of patients in subgroups

Subgroup	Age Mean	% Male %	% Age ≥75
All patients	70	64.6%	42.7%
UA	69	62.5%	36.1%
NSTEMI	73	60.7%	52.4%
STEMI	67	70.8%	30.6%
PLATO Invasive	61	74.8%	12.5%

6.9.3 Please describe how the statistical analysis was undertaken.

For the subgroups in which ticagrelor is being compared with clopidogrel, Weibull regression equations were run for each of the subgroups to obtain the different baseline event rates associated with each subgroup. Based on the fact that there was no statistically significant interaction between the primary endpoint and final diagnosis (p=0.41) the hazard ratio for the overall population was used to generate the event rate for ticagrelor.

As with the overall population, the regression equations were run once for patients aged ≥75 and then once for patients <75. The resulting event rates were then weighted according to the percentage of patients in each group as per Table 6.65 in section 6.9.2. The baseline event rates are shown in Table 6.66.

Table 6.66: Baseline event rates for clopidogrel for subgroups from PLATO trial

Population	Clinical Endpoint	*Age <75*	*Age ≥75*	*Weighted average*
UA	Dead Any Cause	0.0376	0.1011	0.0647
	MI	0.0405	0.0368	0.0389
	Stroke	0.0079	0.0196	0.0129
	Dead Vascular	0.0334	0.0820	0.0541
NSTEMI	Dead Any Cause	0.0457	0.1190	0.0770
	MI	0.0717	0.0951	0.0817
	Stroke	0.0091	0.0189	0.0132
	Dead Vascular	0.0411	0.0990	0.0658
STEMI	Dead Any Cause	0.0472	0.1309	0.0829
	MI	0.0446	0.0589	0.0507
	Stroke	0.0057	0.0110	0.0080
	Dead Vascular	0.0422	0.1107	0.0715

For the purposes of the analysis versus prasugrel, the baseline event rates were taken from the PLATO Invasive study as shown in Table 6.67.

Table 6.67: Event rates for ticagrelor from PLATO Invasive study

Clinical Endpoint	Event rates
Dead Any Cause	3.9%
MI	5.3%
Stroke	1.2%

Relative risks were converted from the odds ratios taken from the published indirect comparison (Biondi-Zoccai et al, 2010), as per Table 5.1.7 in Section 5.7.6, and applied to the baseline event rates to give the event rate for prasugrel as shown in Table 6.68.

Table 6.68: Event rates for prasugrel based on relative risks from indirect comparison

Clinical Endpoint	Event rates
Dead Any Cause	4.7%
MI	4.8%
Stroke	1.0%

In addition to the odds ratios for death, MI and stroke, the published indirect comparison (Biondi-Zoccai et al, 2010) also provided odds ratios for key adverse events such as bleeding and stent thrombosis. As with the clinical endpoints, these were converted into relative risks as per Table 5.1.7, Section 5.7.6, so that they could be used in the health economic model. The baseline event rates for bleeding and stent thrombosis were taken from the PLATO Invasive study as shown in Table 6.69 and applying the relative risks from published indirect comparison gave event rates for prasugrel as shown in Table 6.70.

Table 6.69: Baseline rate of bleeding and stent thrombosis from PLATO invasive study

Endpoint	Event rates
Major bleeding (TIMI)	7.9%
Minor bleeding (TIMI)	3.8%
Stent thrombosis	2.2%

Table 6.70: Baseline rate of bleeding and stent thrombosis prasugrel from relative risks

Endpoint	Event rates
Major bleeding (TIMI)	11.3%
Minor bleeding (TIMI)	4.1%
Stent thrombosis	1.5%

As discussed in Section 6.5.7, there is a cost associated with bleeding episodes and stent thrombosis. These costs are shown in Tables 6.49 for bleeding (major bleed £1,260 and minor bleed £420) and Table 6.50 for stent thrombosis (£2,821).

In addition to the cost there will also be a utility decrement associated with bleeds and stent thrombosis. As outlined in Section 6.4.8, Liverpool Reviews and Implementation Group (LRiG) have recently published values for bleeding decrements in the update to TA90 for clopidogrel and dipyridamole. These values are a 0.1426 decrement for a major bleed which lasts for 11 weeks and a 0.0033 decrement for a minor bleed which lasts two days. The utility decrement for stent

thrombosis comes from Garg et al, 2008, which suggests there is a net disutility of revascularisation of 0.06 for the year in which the revascularisation takes place.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

STEMI Subgroup

The results of the STEMI subgroup are shown in Table 6.71. The analysis of the STEMI subgroup shows that ticagrelor is highly cost-effective in this subgroup with a cost per QALY gained of £2,825 over 40-year time horizon. Even within a five-year time horizon, ticagrelor has a cost per QALY of £4,946.

Table 6.71: Results of STEMI subgroup analysis

Deterministic results with costs and effects discounted				
Time horizon	***Ticagrelor***	***Clopidogrel***	***Incremental***	***ICER***
40 years				
Costs	£15,822	£15,483	£339	
Life-years	9.159	9.016	0.143	£2,371
QALYs	**7.687**	**7.567**	**0.120**	**£2,825**
20 years				
Costs	£15,706	£15,371	£336	
Life-years	9.008	8.867	0.140	£2,391
QALYs	**7.562**	**7.444**	**0.118**	**£2,847**
10 years				
Costs	£14,198	£13,898	£299	
Life-years	6.915	6.808	0.106	£2,816
QALYs	**5.824**	**5.734**	**0.090**	**£3,334**
5 years				
Costs	£12,448	£12,190	£257	
Life-years	4.187	4.126	0.061	£4,201
QALYs	**3.536**	**3.484**	**0.052**	**£4,946**

The results of the Within-trial costing analysis show that the resource use costs are £331 cheaper for ticagrelor than for clopidogrel in the STEMI subgroup.

Table 6.72: Results of Within trials cost analysis for STEMI

1-year time horizon	***Ticagrelor***	***Clopidogrel***	***Incremental***
Cost type			
Hospitalisations	£4,389	£4,585	-£196
Investigations	£1,262	£1,256	£6
Interventions	£4,125	£4,269	-£144
Bleeding related	£91	£88	£3
Total costs	**£9,868**	**£10,198**	**-£331**

NSTEMI Subgroup

The analysis of the NSTEMI subgroup shows that ticagrelor is cost-effective in this subgroup with a cost per QALY gained of £5,230 over a 40-year time horizon. Again, ticagrelor is cost-effective within a five year time horizon with a cost per QALY of £8,162.

Table 6.73: Results of NSTEMI subgroup analysis

Deterministic results with costs and effects discounted				
Time horizon	***Ticagrelor***	***Clopidogrel***	***Incremental***	***ICER***
40 years				
Costs	£13,653	£13,140	£512	
Life-years	6.685	6.567	0.118	£4,357
QALYs	**5.443**	**5.345**	**0.098**	**£5,230**
20 years				
Costs	£13,649	£13,136	£512	
Life-years	6.678	6.560	0.118	£4,359
QALYs	**5.437**	**5.339**	**0.098**	**£5,233**
10 years				
Costs	£13,145	£12,648	£497	
Life-years	5.905	5.801	0.104	£4,794
QALYs	**4.814**	**4.727**	**0.087**	**£5,727**
5 years				
Costs	£11,945	£11,484	£461	
Life-years	3.938	3.872	0.066	£6,932
QALYs	**3.216**	**3.159**	**0.056**	**£8,162**

The results of the Within-trials costing analysis for the NSTEMI subgroup are shown in Table 6.74. There are cost saving totalling £185 for ticagrelor.

Table 6.74: Results of Within trials cost analysis for NSTEMI

1-year time horizon	***Ticagrelor***	***Clopidogrel***	***Incremental***
Cost type			
Hospitalisations	£4,577	£4,678	-£101
Investigations	£1,083	£1,085	-£2
Interventions	£3,684	£3,767	-£83
Bleeding related	£153	£151	£2
Total costs	**£9,497**	**£9,682**	**-£185**

Unstable Angina Subgroup

Within the unstable angina group, the analysis shows ticagrelor to be cost-effective versus clopidogrel with a cost per QALY of £5,374 over the 40-year time horizon. Over a time horizon of 5 years, ticagrelor is still cost-effective with a cost per QALY of £10,172, see Table 6.75.

Table 6.75: Results of UA subgroup analysis

Deterministic results with costs and effects discounted				
Time horizon	***Ticagrelor***	***Clopidogrel***	***Incremental***	***ICER***
40 years				
Costs	£12,907	£12,419	£488	
Life-years	8.612	8.502	0.110	£4,423
QALYs	**7.170**	**7.079**	**0.091**	**£5,374**
20 years				
Costs	£12,844	£12,357	£487	
Life-years	8.529	8.420	0.109	£4,454
QALYs	**7.102**	**7.012**	**0.090**	**£5,410**
10 years				
Costs	£11,583	£11,123	£460	
Life-years	6.789	6.703	0.086	£5,355
QALYs	**5.669**	**5.598**	**0.071**	**£6,484**
5 years				
Costs	£9,884	£9,461	£424	
Life-years	4.185	4.135	0.050	£8,398
QALYs	**3.505**	**3.463**	**0.042**	**£10,172**

The Within-trial analysis shows a cost saving in the ticagrelor arm of £193 as shown in Table 6.76.

Table 6.76: Results of Within trials cost analysis for UA

1-year time horizon	***Ticagrelor***	***Clopidogrel***	***Incremental***
Cost type			
Hospitalisations	£4,043	£4,183	-£140
Investigations	£833	£821	£11
Interventions	£2,425	£2,478	-£53
Bleeding related	£60	£72	-£11
Total costs	**£7,361**	**£7,554**	**-£193**

Invasive subgroup

Due to the lack of a head-to-head trial and hence any health economic data versus prasugrel, the economic evaluation has been carried out using a published indirect comparision ((Biondi-Zoccai et al, 2010), and utility and cost values from the literature. The costs for the invasive subgroup are much lower than for the other subgroups. The reason for this is that the costs associated with the index event have been excluded as, in the absence of any direct head-to-head trial; they are assumed to be the same.

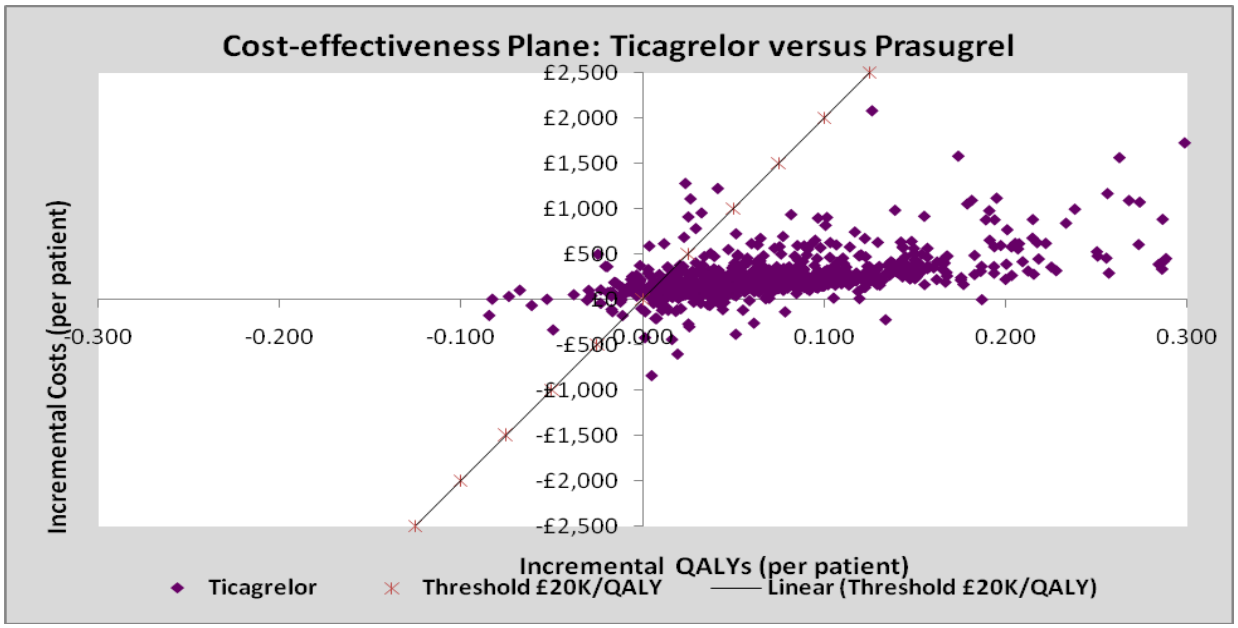
Table 6.77: Results of invasive subgroup analysis

Deterministic results with costs and effects discounted				
Time horizon	***Ticagrelor***	***Clopidogrel***	***Incremental***	***ICER***
40 years				
Costs	£8,072	£7,845	£227	
Life-years	11.177	11.084	0.093	£2,437
QALYs	**8.110**	**8.045**	**0.065**	**£3,482**
20 years				
Costs	£7,620	£7,398	£222	
Life-years	10.620	10.532	0.088	£2,520
QALYs	**7.715**	**7.654**	**0.062**	**£3,598**
10 years				
Costs	£5,272	£5,079	£193	
Life-years	7.469	7.408	0.060	£3,204
QALYs	**5.454**	**5.411**	**0.042**	**£4,562**
5 years				
Costs	£3,240	£3,075	£165	
Life-years	4.350	4.317	0.033	£4,979
QALYs	**3.190**	**3.167**	**0.023**	**£7,047**

The results show that ticagrelor is highly cost-effective versus prasugrel with a cost per QALY of £3,482 at the 40-year time horizon. Even at a 5-year time horizon, ticagrelor is cost-effective with a cost per QALY of £7,047.

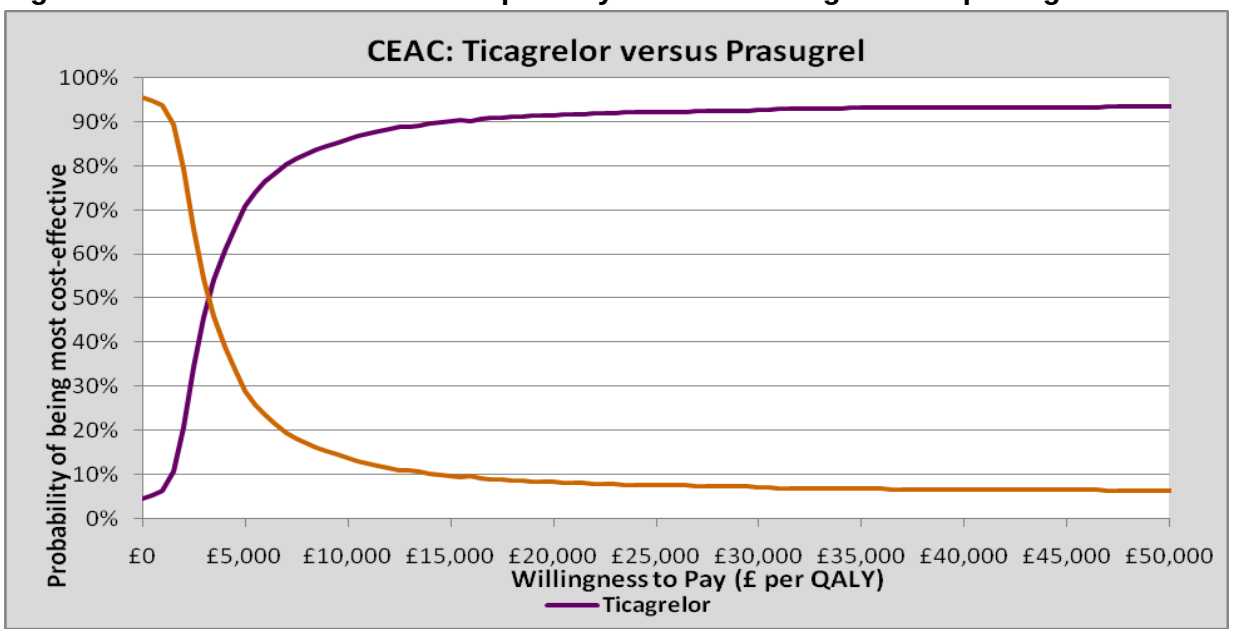
The results of probabilistic sensitivity analysis for the invasive subgroup shown that the majority of the points lie below the £20k threshold.

Figure 6.10: Scatter plot of incremental costs and QALYs



The cost-effectiveness acceptabililty curves show that at a willingness to pay of £10k per QALY, ticagrelor has a 86.2% probability of being cost-effective. At £15k, this probability rises to 90.2% and by £20k, the probability of ticagrelor being cost-effective compared to prasugrel is 91.6%.

Figure 6.11 Cost-effectiveness acceptability curves for ticagrelor vs. prasugrel



6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Analyses of all subgroups identified as relevant in the decision problem have been provided.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results of this economic evaluation as shown in Tables 6.59 and 6.60 are consistent with the published economic literature in the ACS arena, see section 6.2. Published papers comparing clopidogrel with aspirin give cost per QALY results of £3,891 in STEMI patients (Karnon, 2010), and £6,078 to £7,365 in NSTEMI patients (Main et al, 2004, Karnon et al, 2006). The results from this economic evaluation show that ticagrelor is highly cost-effective in all patient groups ranging from £2,825 per QALY in STEMI patients, £5,230 per QALY in NSTEMI patients and £5,374 in patients with UA.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes the economic evaluation is relevant to all groups of patients who could potentially use the technology as per the licensed indication and as outlined in the decision problem.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

The key strengths of this economic evaluation are as follows:

- The economic evaluation was based on results from a very large (>18,000 patients) randomised, controlled, head to head trial which provided a direct comparison between ticagrelor and clopidogrel, the comparators of interest and the current standard of care in England and Wales.
- The model produced outcomes in line with those from the clinical trial and in addition, could be adjusted to provide cost per QALY estimates for a patient population with a higher baseline risk of events as per the ACS population in England and Wales.
- The HECON sub-study obtained the largest number of EQ-5D questionnaires of any study in ACS thereby providing robust utility estimates for use in the model.
- The results in terms of cost per QALY were consistent across all the subgroups thereby suggesting that the model is robust.
- Although extrapolation over the lifetime of the patient is often contentious, the use of relative risks and standardised mortality rates rather than an extension of the treatment effect ensures that the model does not 'over-predict' the efficacy of ticagrelor.
- The model is able to generate similar ICERs to those reported by UK academic researchers (ie ScHARR and/or York University) who were commissioned to conduct HTA of antiplatelet therapies for the treatment of ACS)
- Consistency of modelling approach with UK HTA ACS CUA models: the structure of ticagrelor CUA model and key model inputs are consistent with those used in previous UK HTA of antiplatelet therapies for the treatment of ACS.
- Sensitivity Analysis: extensive sensitivity analysis has demonstrated that the ICER falls well within the CE threshold used to access whether a healthcare technology represents value for money for NHS England and Wales. Probability of ticagrelor being a cost-effective option for the treatment of ACS is 99.9% at a threshold of £20K/QALY.

Weaknesses

There are several limitations in the economic evaluation of ticagrelor versus clopidogrel as follows:

- Randomised treatment was scheduled to continue for one year; however some study subjects left the study at 6-9 months because the targeted number of primary endpoints had occurred. In order to minimise the impact of this on the economic evaluation, costs and utilities were based on the 12-month cohort i.e. a cohort of patients who were followed up for a period of 12 months unless they died in the interim.
- Although the unit costs were based on UK data, the actual resource use was provided for the whole PLATO population which represented a multinational population rather than specifically the UK. However, sensitivity analysis showed that even if the same resource use costs were used for ticagrelor and clopidogrel, ticagrelor remained cost-effective.
- Long-term follow of subjects administered ticagrelor beyond one-year was not available. However, no extension of treatment benefit was assumed in the model therefore it is the efficacy over the one-year period alone that is driving the cost-effectiveness results.
- The model structure only enables patients to have one event (either a one stroke or one MI) post their initial index event. Clinical data from the trial shows that there were a small number of patients who did have multiple events, however due to the small numbers, modelling the additional events would not have had an impact of the overall cost-effectiveness results.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The utility results obtained from the HECON substudy were based on 12-month follow-up. There is little data available on the long-term impact on HRQL post ACS with the much of the data available being for one to two years post event only. Although a study on the long-term impact on HRQL would be useful it is not thought that it would have a huge impact of the cost-effectiveness results as this is driven by the efficacy over the initial one-year period.

The within-trial cost analysis from the HECON substudy provided detailed analysis of the resource use across the PLATO population. It is not clear how representative this is of the UK ACS population therefore further study in this area would potentially be useful.

Taking the above suggestions into account, it should be noted however that the model as it is provides robust and credible results in terms of the cost-effectiveness of ticagrelor versus clopidogrel both in the overall ACS population and in the specified subgroups.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

There are currently approximately 144,000 patients with ACS in England and Wales. The number of patients with unstable angina and STEMI/NSTEMI has been split according to the actual admissions data from HES Online with 48% of patients admitted with unstable angina and 52% admitted with an MI. The proportion of patients with STEMI and NSTEMI has been split according to clinician feedback with one third of patients with STEMI and two thirds of patients with NSTEMI. Therefore the remaining 52% of patients have been split according to the 2:1 ratio such that 35% of patients are in the NSTEMI subgroup and 17% of patients in the STEMI subgroup.

Table 7.0: Number of patients eligible for treatment in England and Wales

		2010	2011	2012	2013	2014	2015
Total ACS Patients		136,010	136,010	136,010	136,010	136,010	136,010
Split between subgroups:							
STEMI	17%	23,122	23,122	23,122	23,122	23,122	23,122
NSTEMI	35%	47,604	47,604	47,604	47,604	47,604	47,604
UA	48%	65,285	65,285	65,285	65,285	65,285	65,285
% of total ACS with PCI		19.3%	19.3%	19.3%	19.3%	19.3%	19.3%
Number of PCI patients		26,223	26,223	26,223	26,223	26,223	26,223

Proportion of UA vs MI from HES data

Proportion of STEMI vs NSTEMI from Myocardial Ischaemia National Audit Project (MINAP) Ninth Public Report 2010 . http://www.rcplondon.ac.uk/clinical-standards/organisation/partnership/Pages/MINAP-.aspx. Accessed 9/11/2010

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

With regard to the current treatment options, the aspirin market is excluded as this is an over-the-counter (OTC) product and many patients do not get this on prescription.

For the uptake of ticagrelor, it is assumed that the duration of therapy in 2011 is 120 days and then 180 days thereafter to reflect the fact that patients will start therapy

throughout the year. However, patients starting treatment in the second half of the year will carry over to the following year such that there are 360 days of treatment in total.

7.3 What assumption(s) were made about market share (when relevant)?

In terms of market share, Table 7.1 shows the estimated market shares for products within the ACS market from 2010 to 2015. It should be noted however that clopidogrel has a wider licence than is expected for ticagrelor and the volume market share of each product within the ACS arena needs to be taken into context with the market share of the overall antiplatelet market which is shown in Table 7.2.

With regard to ticagrelor, the market share is expected to reach 49% of the ACS market by 2015, however this only equates to 30% of the oral antiplatelet market.

Table 7.1 Volume market shares within the ACS market

% MS by volume	2010	2011	2012	2013	2014	2015
Clopidogrel (Plavix)	10%	2%	0%	0%	0%	0%
Generic clopidogrel	89%	88%	74%	59%	47%	36%
Ticagrelor	0%	9%	23%	34%	43%	49%
Others	1%	1%	3%	7%	10%	15%

Table 7.2 Volume market shares within the oral antiplatelet market

% MS by volume	2010	2011	2012	2013	2014	2015
Clopidogrel (Plavix)	10%	2%	0%	0%	0%	0%
Generic clopidogrel	89%	91%	83%	73%	64%	55%
Brilique	0%	6%	14%	20%	26%	30%
Others	1%	1%	3%	7%	10%	15%

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

There are no other significant costs associated with treatment with ticagrelor.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit costs applied in the budget impact analysis are the same as those used in the cost-utility model, regarding drug costs, hospitalisations, investigations, interventions, monitoring and adverse events. Details of these costs can be found in Section 6.5.5 and Section 6.5.6.

7.6 Were there any estimates of resource savings? If so, what were they?

As discussed in Section 6.5.6, a within-trial cost analysis was undertaken as part of the PLATO HECON sub-study. A list of unit costs assigned to each category e.g. hospitalisations, investigations, interventions and bleeding-related are shown in Section 6.5.6, Table 6.32. The results of the within-trial cost analysis shows that there are resource use savings of £275 in the ticagrelor arm of the PLATO HECON sub-study as shown in Table 7.3. It can be seen from Table 7.3 that the majority of the savings are in the form of lower hospitalisation costs, which is to be expected given that ticagrelor had significantly fewer MIs, stent thromboses and deaths (both vascular and non-vascular) in the PLATO study.

Table 7.3: Results of within-trial cost analysis

Resource Use Type	*Ticagrelor*	*Clopidogrel*	*Incremental*
Hospitalisations	£4,373	£4,545	-£172
Investigations	£1,102	£1,099	£3
Interventions	£3,579	£3,689	-£110
Bleeding related	£114	£110	£4
Total resource use	**£9,168**	**£9,443**	**-£275**

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS in England and Wales is shown in Table 7.4. The total cost of ticagrelor is made up of drug costs plus treatment of dyspnoea (over and above that experienced by patients on clopidogrel, as per rates from the PLATO study). These costs are expected to be £2.9m in 2011 rising to £44.2m in 2015.

In terms of cost offsets, the annual cost of clopidogrel plus the resource use savings as shown in Table 7.3, amount to £1.3m in 2011 rising to £19.8m in 2015. Once these cost offsets are taken into consideration, the net budget impact of ticagrelor for the NHS in England and Wales is £1.62m in 2011 rising to £24.4m in 2015.

It should be noted however that the NNT for all cause mortality for ticagrelor is 72. This means that for every 72 patients treated with ticagrelor, one life will be saved. Based on the number of patients expected to be treated with ticagrelor according to Table 7.4, 56 lives will be saved in 2011, rising to 857 in 2015. The cost per life saved is approximately £29,000.

Table 7.4: Budget impact of ticagrelor in England and Wales

Budget Impact (£)	2011	2012	2013	2014	2015
Total number of ACS patients	136,010	136,010	136,010	136,010	136,010
Ticagrelor market share of ACS	9%	23%	34%	43%	49%
Number of ticagrelor patients	12,241	31,282	46,243	58,484	66,645
Ticagrelor drug costs	2,864,371	15,276,643	27,211,521	36,759,423	43,920,349
Adverse events and monitoring	45,536	116,370	172,025	217,562	247,919
Total cost of ticagrelor	**2,909,907**	**15,393,013**	**27,383,546**	**36,976,984**	**44,168,268**
Less:					
Cost of clopidogrel	166,476	887,873	1,581,524	2,136,445	2,552,636
Resource use savings	1,122,083	5,984,440	10,659,784	14,400,059	17,205,265
Total cost offset	**1,288,559**	**6,872,313**	**12,241,308**	**16,536,504**	**19,757,901**
Net cost	**1,621,348**	**8,520,700**	**15,142,238**	**20,440,480**	**24,410,368**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

All the opportunities for resource savings have been identified. However it should be noted that the NNT for all cause mortality is 72, thus for every 72 patients treated with ticagrelor one life will be saved. Based on the number of patients on ticagrelor, it is estimated that by 2015, 857 lives per year could be saved.

8 References

1) National Population Projections 2008. 2010; Available at: http://www.statistics.gov.uk/downloads/theme_population/NPP2008/NatPopProj2008.pdf.

(2) NICE Clinical Guideline 94. The early management of unstable angina and non-ST-segment-elevation myocardial infarction. 2010 March 2010.

(3) AstraZeneca Core Presentation. FDA meeting of the Cardiovascular and Renal Drugs Advisory Committee. 28th July 2010. 2010; .

(4) NICE Technology Appraisal Guidance 182. Prasugrel for the treatment of acute coronary syndromes with percutaneous intervention. 2009 October 2009.

(5) NICE Clinical Guideline 48. Secondary prevention in primary and secondary care for patients following myocardial infarction. 2007 May 2007.

(6) A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996 Nov 16;348(9038):1329-1339.

(7) Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988 Aug 13;2(8607):349-360.

(8) British Cardiovascular Intervention Society Audit Returns. Audit Interventional Procedures January 2009 to December 2009. Presented at Autumn BCIS Conference 2009. Available at: http://www.bcis.org.uk/resources/documents/BCIS%20Audit%202008%20for%20web%2016-10-09%20version%201.pdf.

(9) Hospital Episode Statistics Online 2009-2008. Available at: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=214. Accessed 28th September, 2010.

(10) Report of the Second Phase of the Review of NHS Pathology Services in England, chaired by Lord Carter of Coles, published in December 2008. Available at: http://collections.europarchive.org/tna/20081105144224/http://www.thecarterreview.com/downloads/CarterReviewPathologyReport.pdf. Accessed September 29th, 2010.

(11) Interim Life Tables, United Kingdom, 2007-2009. Available at: http://www.statistics.gov.uk/downloads/theme_population/Interim_Life/iltuk-reg.xls. Accessed 4th November, 2010.

(12) Allen LA, O'Donnell CJ, Camargo CA,Jr, Giugliano RP, Lloyd-Jones DM. Comparison of long-term mortality across the spectrum of acute coronary syndromes. Am.Heart J. 2006 May;151(5):1065-1071.

(13) Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE,Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice

Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J.Am.Coll.Cardiol. 2007 Aug 14;50(7):e1-e157.

(14) Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J.Am.Coll.Cardiol. 2007 Apr 10;49(14):1505-1516.

(15) Angiolillo DJ, Singh D. Clopidogrel for up to one year after PCI is cost-effective for people with acute coronary syndromes. Evid Based.Cardiovasc.Med. 2006 Jun;10(2):116-118.

(16) Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004 Aug 3;110(5):588-636.

(17) Arslanian-Engoren C, Engoren M. Physiological and anatomical bases for sex differences in pain and nausea as presenting symptoms of acute coronary syndromes. Heart Lung 2010 Sep-Oct;39(5):386-393.

(18) AstraZeneca UK Ltd. Ticagrelor briefing document for Cardiovascular and Renal Drugs Advisory Committee meeting. 2010 23rd June 2010;NDA 22-433.

(19) Bellemain-Appaix A, Brieger D, Beygui F, Silvain J, Pena A, Cayla G, et al. New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention: a meta-analysis. J.Am.Coll.Cardiol. 2010 Nov 2;56(19):1542-1551.

(20) Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N.Engl.J.Med. 2006 Apr 20;354(16):1706-1717.

(21) 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 Sep 7.

(22) Bolin K, Mork AC, Willers S, Lindgren B. Varenicline as compared to bupropion in smoking-cessation therapy--cost-utility results for Sweden 2003. Respir.Med. 2008 May;102(5):699-710.

(23) Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005 Oct 15;331(7521):897-900.

(24) Cannon CP. Cost-effectiveness of clopidogrel. Pharmacoeconomics 2004;22 Suppl 4:1-3.

(25) Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010 Jan 23;375(9711):283-293.

(26) 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 Nov 6;50(19):1844-1851.

(27) Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005 Nov 5;366(9497):1622-1632.

(28) Cheng JW. Pharmacoeconomic analysis of clopidogrel in secondary prevention of coronary artery disease. J.Manag.Care.Pharm. 2007 May;13(4):326-336.

(29) Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results form the United Kingdom Prospective Diabetes Study (UKPDS Study No 65). Diabetic Medicine 2003;20:442-450.

(30) Collett D. Modelling survival data in medical research. 2nd ed. London: Chapman and Hall; 2003.

(31) Cowper PA, Udayakumar K, Sketch MH,Jr, Peterson ED. Economic effects of prolonged clopidogrel therapy after percutaneous coronary intervention. J.Am.Coll.Cardiol. 2005 Feb 1;45(3):369-376.

(32) Curtis L. Unit Costs of Health & Social Care 2009. Available at: http://www.pssru.ac.uk/uc/uc2009contents.htm.

(33) 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 Jun;24(6):796-800.

(34) 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 Jan;95(1):20-26.

(35) Dorman P, Dennis M, Sandercock P. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? United Kingdom Collaborators in the International Stroke Trial. J.Neurol.Neurosurg.Psychiatry. 2000 Oct;69(4):487-493.

(36) Duncan PW, Lai SM, Keighley J. Defining post-stroke recovery: implications for design and interpretation of drug trials. Neuropharmacology 2000 Mar 3;39(5):835-841.

(37) Durand-Zaleski I, Bertrand M. The value of clopidogrel versus aspirin in reducing atherothrombotic events: the CAPRIE study. Pharmacoeconomics 2004;22 Suppl 4:19-27.

(38) Eli Lilly and Company. Efient (prasugrel): Cardiovascular and Renal Drugs Advisory Committee Briefing Document. 2009 3rd February 2009.

(39) Eli Lilly and Company, Daiichi Sankyo UK Ltd. Prasugrel - Summary of Product's Characteristics. 2009; Available at: http://www.medicines.org.uk/EMC/medicine/21504/SPC/Efient+5mg+%26+10mg+film-coated+tablets+(Eli+Lilly+and+Company+Ltd+Daiichi+Sankyo+UK+Limited)/. Accessed September 29th, 2010.

(40) Eli Lilly and Company, Daiichi Sankyo UK Ltd. Manufacturer's Submission: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. 2009.

(41) Ellis JJ, Eagle KA, Kline-Rogers EM, Erickson SR. Validation of the EQ-5D in patients with a history of acute coronary syndrome. Curr.Med.Res.Opin. 2005 Aug;21(8):1209-1216.

(42) European Association for Percutaneous Cardiovascular Interventions, Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur.Heart J. 2010 Oct;31(20):2501-2555.

(43) Fox KA. Is clopidogrel plus aspirin more cost-effective than aspirin alone in high-risk patients with acute coronary syndromes? Nat.Clin.Pract.Cardiovasc.Med. 2005 Sep;2(9):444-445.

(44) Fox KA, 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 Aug 30.

(45a) Garg P, Cohen D, Gaziano T, Mauri L. Balancing the risks of restenosis and stent thrombosis in bare-metal versus drug-eluting stents: results of a decision analytic model. J Am. Coll. Cardiol. 2008;51;1844-1853

(45) Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart 2005 Feb;91(2):229-230.

(46) Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009 Dec 22;120(25):2577-2585.

(47) Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R. Long-term outcome after stroke: evaluating health-related quality of life using utility measurements. Stroke 2006 Jan;37(1):193-198.

(48) Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. Stroke 2000 Sep;31(9):2080-2086.

(49) Hasin T, Hochadel M, Gitt AK, Behar S, Bueno H, Hasin Y. Comparison of treatment and outcome of acute coronary syndrome in patients with versus patients without diabetes mellitus. Am.J.Cardiol. 2009 Mar 15;103(6):772-778.

(50) Heeg B, Damen J, Van Hout B. Oral antiplatelet therapy in secondary prevention of cardiovascular events: an assessment from the payer's perspective. Pharmacoeconomics 2007;25(12):1063-1082.

(51) Held C, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO trial. Presented at the American College of Cardiology Annual Scientific Session & Expo 2010, Atlanta, GA. March 14-16 2010. 2010.

(52) Henriksson M, Epstein DM, Palmer SJ, Sculpher MJ, Clayton TC, Pocock SJ, et al. The cost-effectiveness of an early interventional strategy in non-ST-elevation acute coronary syndrome based on the RITA 3 trial. Heart 2008 Jun;94(6):717-723.

(53) Huston SA, Hawkins D. Pharmacoeconomics of anticoagulants in acute coronary syndrome and percutaneous coronary intervention. Curr.Pharm.Des. 2008;14(12):1197-1204.

(54) James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am.Heart J. 2009 Apr;157(4):599-605.

(55) 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 Aug 29.

(56) 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. Presented at European Society of Cardiology, Stockholm, Sweden. 28 August - 1 September. European Society of Cardiology, Stockholm, Sweden 2010.

(57) Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, et al. Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation. Health Technol.Assess. 2004 Oct;8(38):iii-iv, 1-196.

(58) Karnon J, Bakhai A, Brennan A, Pandor A, Flather M, Warren E, et al. A cost-utility analysis of clopidogrel in patients with non-ST-segment-elevation acute coronary syndromes in the UK. Int.J.Cardiol. 2006 May 24;109(3):307-316.

(59) Karnon J, Brennan A, Pandor A, Fowkes G, Lee A, Gray D, et al. Modelling the long term cost effectiveness of clopidogrel for the secondary prevention of occlusive vascular events in the UK. Curr.Med.Res.Opin. 2005 Jan;21(1):101-112.

(60) Karnon J, Holmes MW, Williams R, Bakhai A, Brennan A. A cost-utility analysis of clopidogrel in patients with ST elevation acute coronary syndromes in the UK. Int.J.Cardiol. 2010 Apr 30;140(3):315-322.

(61) Kim J, Henderson RA, Pocock SJ, Clayton T, Sculpher MJ, Fox KA, et al. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). J.Am.Coll.Cardiol. 2005 Jan 18;45(2):221-228.

(62) Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998 Mar 7;316(7133):736-741.

(63) Lacey EA, Walters SJ. Continuing inequality: gender and social class influences on self perceived health after a heart attack. J.Epidemiol.Community Health 2003 Aug;57(8):622-627.

(64) Lamotte M, Annemans L, Bridgewater B, Kendall S, Siebert M. A health economic evaluation of concomitant surgical ablation for atrial fibrillation. Eur.J.Cardiothorac.Surg. 2007 Nov;32(5):702-710.

(65) Lamotte M, Annemans L, Evers T, Kubin M. A multi-country economic evaluation of low-dose aspirin in the primary prevention of cardiovascular disease. Pharmacoeconomics 2006;24(2):155-169.

(66) Lamy A, Jonsson B, Weintraub WS, Zhao F, Chrolavicius S, Bakhai A, et al. The cost-effectiveness of the use of clopidogrel in acute coronary syndromes in five countries based upon the CURE study. Eur.J.Cardiovasc.Prev.Rehabil. 2004 Dec;11(6):460-465.

(67) Lightowlers S, McGuire A. Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. Stroke 1998 Sep;29(9):1827-1832.

(68) Lindgren P, Geborek P, Kobelt G. Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. Int.J.Technol.Assess.Health Care 2009 Apr;25(2):181-189.

(69) Lindgren P, Glader EL, Jonsson B. Utility loss and indirect costs after stroke in Sweden. Eur.J.Cardiovasc.Prev.Rehabil. 2008 Apr;15(2):230-233.

(70) Lindgren P, Kahan T, Poulter N, Buxton M, Svarvar P, Dahlof B, et al. Utility loss and indirect costs following cardiovascular events in hypertensive patients: the ASCOT health economic substudy. Eur.J.Health.Econ. 2007 Mar;8(1):25-30.

(71) Loor HI, Groenier KH, Limburg M, Schuling J, Meyboom-de Jong B. Risks and causes of death in a community-based stroke population: 1 month and 3 years after stroke. Neuroepidemiology 1999;18(2):75-84.

(72) Lyseng-Williamson KA, Plosker GL. Clopidogrel: a pharmacoeconomic review of its use in patients with non-ST elevation acute coronary syndromes. Pharmacoeconomics 2006;24(7):709-726.

(73) Mahoney EM, Wang K, Arnold SV, Proskorovsky I, Wiviott S, Antman E, et al. Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with Prasugrel-Thrombolysis in Myocardial Infarction TRITON-TIMI 38. Circulation 2010 Jan 5;121(1):71-79.

(74) Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, et al. Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation. Health Technol.Assess. 2004 Oct;8(40):iii-iv, xv-xvi, 1-141.

(75) Malinina D, Zema C, Sander S, Serebruany V. Cost-effectiveness of antiplatelet therapy for secondary stroke prevention. Expert Rev.Pharmacoecon Outcomes Res. 2007 Aug;7(4):357-363.

(76) Matchar DB, Jacobson AK, Edson RG, Lavori PW, Ansell JE, Ezekowitz MD, et al. The impact of patient self-testing of prothrombin time for managing anticoagulation: rationale and design of VA Cooperative Study #481--the Home INR Study (THINRS). J.Thromb.Thrombolysis 2005 Jun;19(3):163-172.

(77) Maxwell CB, Holdford DA, Crouch MA, Patel DA. Cost-effectiveness analysis of anticoagulation strategies in non-ST-elevation acute coronary syndromes. Ann.Pharmacother. 2009 Apr;43(4):586-595.

(78) Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. Lancet 2010 Oct 16;376(9749):1312-1319.

(79) Monaco C, Cianflone D, Summaria F, Maseri A, Crea F. Cost-effective pharmacological prevention of acute coronary syndromes. Pharmacol.Res. 1998 Jun;37(6):469-475.

(80) Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009 Feb 28;373(9665):723-731.

(81) Nowels D, McGloin J, Westfall JM, Holcomb S. Validation of the EQ-5D quality of life instrument in patients after myocardial infarction. Qual.Life Res. 2005 Feb;14(1):95-105.

(82) Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. Stroke 2004 Feb;35(2):607-612.

(83) Ploegmakers MM, Viscaal AM, Finch L, Mayo NE, Brophy JM. The disutility of restenosis--the impact of repeat percutaneous coronary intervention on quality of life. Can.J.Cardiol. 2010 Jun;26(6):197-200.

(84) Post PN, Stiggelbout AM, Wakker PP. The utility of health states after stroke: a systematic review of the literature. Stroke 2001 Jun;32(6):1425-1429.

(85) Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial--phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J.Am.Coll.Cardiol. 1988 Jan;11(1):1-11.

(86) Reinhart KM, White CM, Baker WL. Prasugrel: a critical comparison with clopidogrel. Pharmacotherapy 2009 Dec;29(12):1441-1451.

(87) Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. J.Health Serv.Res.Policy 2001 Apr;6(2):92-98.

(88) Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, et al. Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling. Health Technol.Assess. 2005 Jul;9(27):iii-iv, ix-xi, 1-158.

(89) Rogowski W, Burch J, Palmer S, Craigs C, Golder S, Woolacott N. The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis. Health Technol.Assess. 2009 Jun;13(31):iii-iv, ix-xi, 1-77.

(90) Rubenstein JH, Eisen GM, Inadomi JM. A cost-utility analysis of secondary prophylaxis for variceal hemorrhage. Am.J.Gastroenterol. 2004 Jul;99(7):1274-1288.

(91) sanofi-aventis. Plavix. Summary of Product Characteristics. 2010; . Accessed 28th September, 2010.

(92) Scarborough P, Bhatnagar P, Wickramasinghe K, Smolina K, Mitchell C, Rayner M. Coronary heart disease statistics 2010 edition. 2010; Available at: http://www.ws3.heartstats.web.baigent.net/datapage.asp?id=9075. Accessed October 31, 2010.

(93) Schleinitz MD, Weiss JP, Owens DK. Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis. Am.J.Med. 2004 Jun 15;116(12):797-806.

(94) Schweikert B, Hahmann H, Leidl R. Validation of the EuroQol questionnaire in cardiac rehabilitation. Heart 2006 Jan;92(1):62-67.

(95) Schweikert B, Hunger M, Meisinger C, Konig HH, Gapp O, Holle R. Quality of life several years after myocardial infarction: comparing the MONICA/KORA registry to the general population. Eur.Heart J. 2009 Feb;30(4):436-443.

(96) Scuffham PA, Chaplin S. An economic evaluation of fluvastatin used for the prevention of cardiac events following successful first percutaneous coronary intervention in the UK. Pharmacoeconomics 2004;22(8):525-535.

(97) Serebruany VL. The TRITON versus PLATO trials: differences beyond platelet inhibition. Thromb.Haemost. 2010 Feb 1;103(2):259-261.

(98) SIGN. 93 Acute Coronary Syndromes. A national guideline. 2007; Available at: http://www.sign.ac.uk/pdf/sign93strategy.pdf.

(99) Solli O, Stavem K, Kristiansen IS. Health-related quality of life in diabetes: The associations of complications with EQ-5D scores. Health.Qual.Life.Outcomes 2010 Feb 4;8:18.

(100) Steg G, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, et al. Ticagrelor compared with clopidogrel in patients with acute coronary syndromes the PLATelet Inhibition and patient Outcomes trial. Outcomes in patients with STEMI and planned PCI. Presented at American Heart Association Scientific Sessions 2009 in Orlando, Florida, USA 14-18 November 2009. .

(101) Steg G, James S, Harrington RA, et al. Ticagrelor Versus Clopidogrel in Patients With ST-Elevation Acute Coronary Syndromes Intended for Reperfusion With Primary Percutaneous Coronary Intervention. Circulation 2010 epub 8th November 2010.

(102) Stenestrand U, Johansson S, Janzon M. The Platelet Inhibition and Patient Outcomes Trial is Representative of Patients with Acute Coronary Syndromes in a National Heart Registry. J.Am.Coll.Cardiol. 2010;55(Suppl 1):A112.E1046. Abstract 1107-321.

(103) Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med.Decis.Making 2006 Jul-Aug;26(4):410-420.

(104) Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur.Heart J. 2007 Jul;28(13):1598-1660.

(105) Taylor M, Scuffham PA, Chaplin S, Papo NL. An economic evaluation of valsartan for post-MI patients in the UK who are not suitable for treatment with ACE inhibitors. Value Health. 2009 Jun;12(4):459-465.

(106) Taylor MJ, Scuffham PA, McCollam PL, Newby DE. Acute coronary syndromes in Europe: 1-year costs and outcomes. Curr.Med.Res.Opin. 2007 Mar;23(3):495-503.

(107) Teng R, Butler K. Pharmacokinetics, pharmacodynamics, tolerability and safety of single ascending doses of ticagrelor, a reversibly binding oral P2Y(12) receptor antagonist, in healthy subjects. Eur.J.Clin.Pharmacol. 2010 May;66(5):487-496.

(108) Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. Pharmacoeconomics 2003;21(3):191-200.

(109) Tiemann O. Variations in hospitalisation costs for acute myocardial infarction - a comparison across Europe. Health Econ. 2008 Jan;17(1 Suppl):S33-45.

(110) 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: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur.Heart J. 2008 Dec;29(23):2909-2945.

(111) van Exel NJ, Scholte op Reimer WJ, Koopmanschap MA. Assessment of post-stroke quality of life in cost-effectiveness studies: the usefulness of the Barthel Index and the EuroQoL-5D. Qual.Life Res. 2004 Mar;13(2):427-433.

(112) VAN Giezen JJ, Nilsson L, Berntsson P, Wissing BM, Giordanetto F, Tomlinson W, et al. Ticagrelor binds to human P2Y(12) independently from ADP but antagonizes ADP-induced receptor signaling and platelet aggregation. J.Thromb.Haemost. 2009 Sep;7(9):1556-1565.

(113) Vergel YB, Palmer S, Asseburg C, Fenwick E, de Belder M. Is primary angioplasty cost effective in the UK? Results of a comprehensive decision analysis? Heart 2007;93:1238-1243.

(114) Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N.Engl.J.Med. 2009 Sep 10;361(11):1045-1057.

(115) Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010 Oct 16;376(9749):1320-1328.

(116) Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol.Assess. 2007 Apr;11(14):1-160, iii-iv.

(117) Weintraub W, Jonsson B, Bertrand M. The value of clopidogrel in addition to standard therapy in reducing atherothrombotic events. Pharmacoeconomics 2004;22 Suppl 4:29-41.

(118) Weintraub WS. Pharmacoeconomic concepts in antiplatelet therapy: understanding cost-effectiveness analyses using clopidogrel as an example. J.Cardiovasc.Pharmacol.Ther. 2008 Jun;13(2):107-119.

(119) Weintraub WS, Mahoney EM, Lamy A, Culler S, Yuan Y, Caro J, et al. Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation. J.Am.Coll.Cardiol. 2005 Mar 15;45(6):838-845.

(120) Wiviott SD, Antman EM, Winters KJ, Weerakkody G, Murphy SA, Behounek BD, et al. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. Circulation 2005 Jun 28;111(25):3366-3373.

(121) Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N.Engl.J.Med. 2007 Nov 15;357(20):2001-2015.

(122) Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. Pharmacoeconomics 2003;21 Suppl 1:43-50.

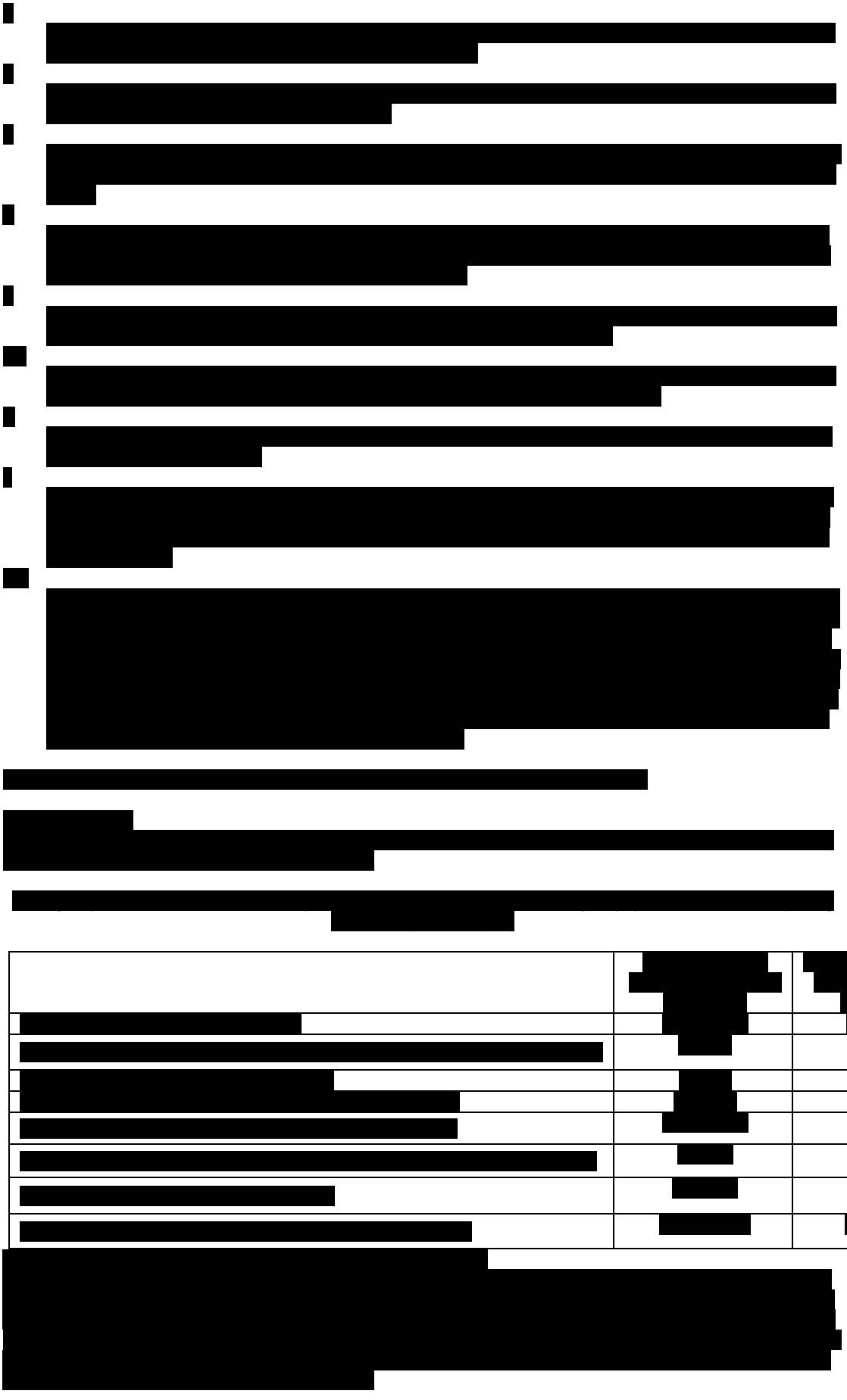
(123) Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N.Engl.J.Med. 2001 Aug 16;345(7):494-502.

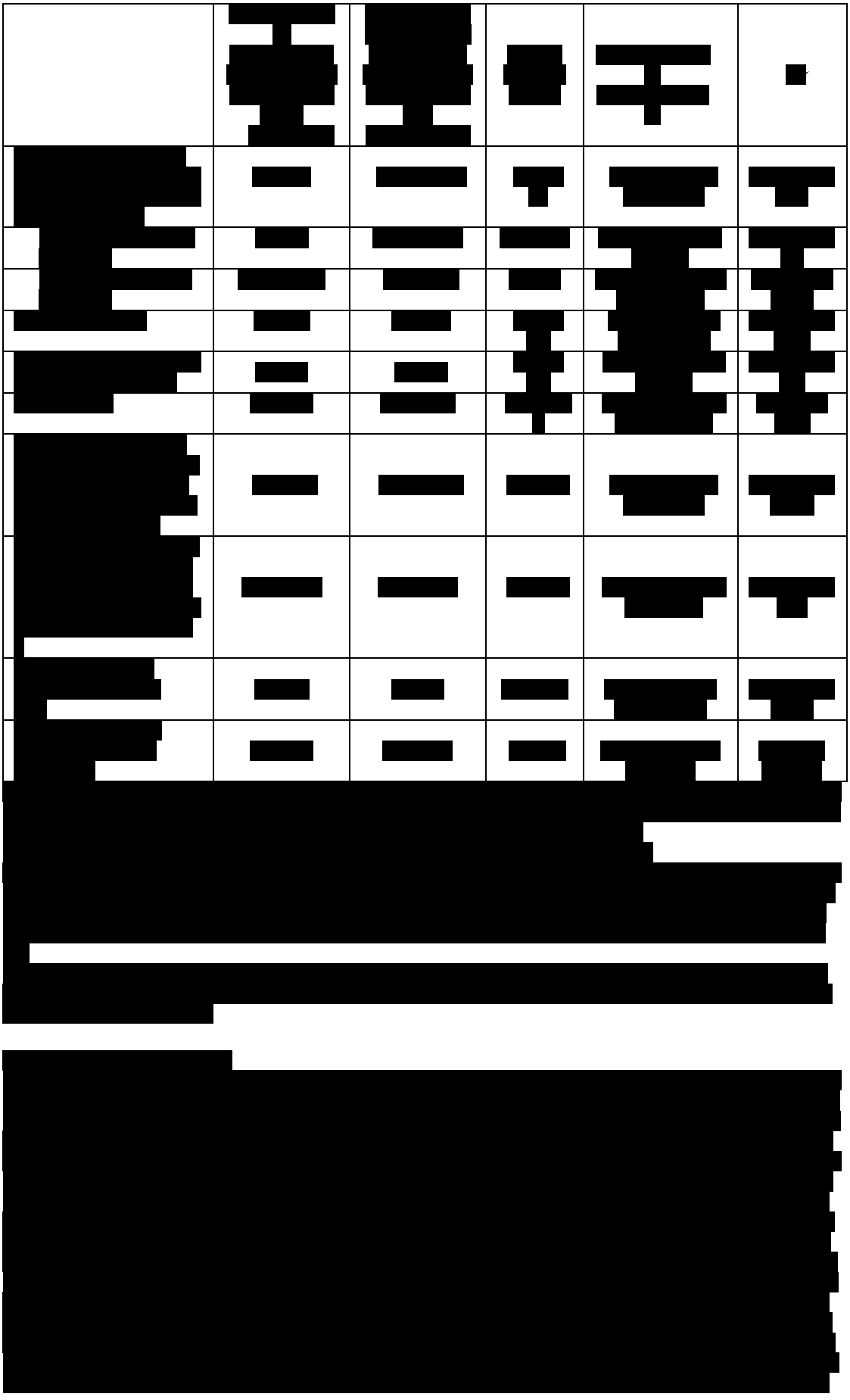
9 Appendices

9.1 Appendix 1 – Draft SPC Commercial in confidence

[redacted]

[redacted]





[redacted]

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Medline (PubMed www.ncbi.nlm.nih.gov/pubmed/)

9.2.2 The date on which the search was conducted.

6/7/10

9.2.3 The date span of the search.

No limits were placed upon the span of the search

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search undertaken using the following keywords ‘ticagrelor’ and ‘AZD6140’ with the following limits ‘clinical trial’ and ‘human’.

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

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.

9.2.6 The inclusion and exclusion criteria.

Inclusion criteria comprised: randomised clinical trials involving the proposed licenced dose of ticagrelor, undertaken in patients with cardiovascular disease. Exclusion criteria comprised: studies undertaken in healthy volunteers, studies which employed unlicenced doses of ticagrelor, studies which described experimental or non-clinical outcomes, and publications which described study design methodologies.

9.2.7 The data abstraction strategy.

Not applicable

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym – PLATO (Wallentin *et al.* 2009)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Computer generated block of numbers	Yes
Was the concealment of treatment allocation adequate?	Double-blind double dummy design	Yes
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
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 dumy deisgn. Independent endpoint adjudication occurred without knowledge of the treatment allocation	Yes
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
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All study outcomes were pre-specified and reported	No
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	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

9.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library.***

The following databases were searched:

- Cochrane Central Register of Controlled Trials (CENTRAL) using the Cochrane Library's online clinical trials search;
- Excerpta Medica Database (EMBASE) using OVID;
- Index Medicus database (MEDLINE), including Medline (R) In-Process, using OVID.

9.4.2 The date on which the search was conducted.

9th April 2010

9.4.3 The date span of the search.

Inception of the relevant database to 9th April 2010.

9.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Embase – 9th April 2010

#	Searches	Results
1	ticagrelor/	236
2	brilinta.mp.	7
3	brilique.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	0
4	1 or 2 or 3	236
5	prasugrel/	737
6	efient.mp.	16
7	effient.mp.	21
8	5 or 6 or 7	738
9	clopidogrel/	17255
10	plavix.mp.	1512
11	9 or 10	17257
12	4 and 8	184
13	4 and 11	224
14	8 and 11	685
15	12 or 13 or 14	733
16	randomized controlled trial/	184888
17	random allocation/	27823
18	double-blind method/	77062
19	Single Blind Procedure/	9242
20	16 or 17 or 18 or 19	229082
21	exp clinical trials/	599519
22	(clin$ adj25 trial$).tw.	163199

23	((singl$ or doubl$ or treb$ or tripl$) adj25 (blind$ or mask$)).tw.	101658
24	placebos/	140338
25	random$.tw.	432949
26	research design/	436963
27	placebo$.tw.	117611
28	21 or 22 or 23 or 24 or 25 or 26 or 27	1379792
29	animal/ not (human/ and animal/)	26839
30	20 or 28	1383107
31	30 not 29	1377115
32	exp Myocardial Infarction/	130700
33	Coronary Thrombosis/	3901
34	acute coronary.tw.	13096
35	exp Angina, Unstable/	9746
36	myocardial infarct$.tw.	91557
37	heart infarct$.tw.	790
38	acs.tw.	5538
39	ami.tw.	9404
40	(coronary adj3 syndrome$).tw.	11765
41	acute angina.tw.	32
42	(unstable adj3 angina).tw.	8771
43	unstable coronary.tw.	626
44	or/32-43	162672
45	15 and 31 and 44	432
46	45	432
47	limit 45 to English language	397

Medline – 9th April 2010

#	Searches	Results
1	RANDOMIZED CONTROLLED TRIAL.pt.	288756
2	CONTROLLED CLINICAL TRIAL.pt.	81093
3	RANDOMIZED CONTROLLED TRIAL.sh.	288756
4	RANDOM ALLOCATION.sh.	67809
5	DOUBLE BLIND METHOD.sh.	105864
6	SINGLE BLIND METHOD.sh.	13815
7	1 or 2 or 3 or 4 or 5 or 6	429617
8	(ANIMALS not HUMANS).sh.	3376400
9	7 not 8	395505
10	CLINICAL TRIAL.pt.	460440
11	exp CLINICAL TRIAL/	605907
12	(clin$ adj25 trial$).ti,ab.	179583
13	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	108545
14	PLACEBOS.sh.	28956
15	placebo$.ti,ab.	125304
16	random$.ti,ab.	502482
17	RESEARCH DESIGN.sh.	58772
18	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	1058545
19	18 not 8	980877
20	19 not 9	599578
21	COMPARATIVE STUDY.sh.	1476401
22	exp EVALUATION STUDIES/	132109

23	FOLLOW UP STUDIES.sh.	401809
24	PROSPECTIVE STUDIES.sh.	277150
25	(control$ or prospectiv$ or volunteer$).ti,ab.	2265692
26	21 or 22 or 23 or 24 or 25	3811153
27	26 not 8	2947455
28	27 not (9 or 20)	2398380
29	9 or 20 or 28	3393463
30	exp Myocardial Infarction/	126978
31	Coronary Thrombosis/	4824
32	acute coronary.tw.	14266
33	exp Angina, Unstable/	9289
34	myocardial infarct$.tw.	118552
35	heart infarct$.tw.	697
36	acs.tw.	6270
37	ami.tw.	10206
38	(coronary adj3 syndrome$).tw.	12418
39	acute angina.tw.	53
40	(unstable adj3 angina).tw.	9742
41	unstable coronary.tw.	653
42	or/30-41	183847
43	brilinta.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	0
44	brilique.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	0
45	ticagrelor.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	56

46	43 or 44 or 45	56
47	prasugrel.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	293
48	efient.mp.	2
49	effient.mp.	4
50	47 or 48 or 49	293
51	clopidogrel.mp.	4947
52	plavix.mp.	124
53	51 or 52	4960
54	46 and 50	27
55	46 and 53	44
56	50 and 53	235
57	54 or 55 or 56	260
58	29 and 42 and 57	76
59	limit 58 to english language	72
60	from 59 keep 1-72	72

Central – 9th April

#	Searches	Results
#1	(brilinta OR brilique OR ticagrelor):ti,ab,kw	3
#2	prasugrel OR efient OR effient	41
#3	clopidogrel OR plavix	880
#4	(#1 AND #2)	0
#5	(#1 AND #3)	3
#6	(#2 AND #3)	35
#7	(#4 OR #5 OR #6)	38

9.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

9.4.6 The inclusion and exclusion criteria.

To be eligible for inclusion in the indirect comparison, a trial needed to:

- be a randomised controlled trial;
- include a direct comparison of ticagrelor with prasugrel (both on a background of aspirin) OR include a comparison of one of the two treatments with clopidogrel on a background of aspirin (note: the protocol for the systematic review was written with the prior assumption that there would be an absence of head-to-head data, but in the event that such data were identified in the literature search a pairwise meta-analysis would have been conducted in addition to the adjusted indirect comparison);
- involve ACS patients undergoing an invasive procedure during their initial hospital admission;
- report at least one case of an outcome of interest (all CV events [a composite of cardiovascular death+MI+stroke]; MI; stroke; CV death; all-cause mortality; stent thrombosis; bleeding (TIMI defined major and minor bleeds); fatal bleeds).

9.4.7 The data abstraction strategy.

- Not applicable – the results in Section 5.7.6 are taken from a published indirect comparison conducted by an independent group (Biondi-Zoccai *et al.* Int J Cardiol 2010)

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

Study ID or acronym – Wallentin et al. 2009		
Study question	How is the question addressed in the study?	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	"Patients were randomly assigned, using […] a blocking size of four. […] The randomisation schedule was created by the AstraZeneca GRAND system. The creation and ownership of the schedule was handled by a separate group that had no direct involvement in the study."	Yes
Was the concealment of treatment allocation adequate?	"Patients were randomly assigned, using an interactive voice response system."	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline characteristics for the two groups are presented in Table 1 in the paper. They are accurately described as being "well balanced" between the groups.	Yes
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)?	The study is described as having a "double-blind, double-dummy design." In the full-population publication (Wallentin 2009), it is noted that: "An independent data and safety monitoring board monitored the trial and had access to the unblinded data."	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There is no evidence of an unexpected imbalance in drop-outs between groups.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest that the authors measured more outcomes than they reported.	Yes
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 analyses were by intention-to-treat." It appears that this was carried out appropriately.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym – Wiviott *et al*. 2007		
Study question	How is the question addressed in the study?	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	"Patients were randomly assigned to the clopidogrel group or the prasugrel group in two strata."	Not clear
Was the concealment of treatment allocation adequate?	No information given	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline characteristics for the two groups are presented in Table 1 in the paper. They are accurately described as being "well matched" between the groups.	Yes
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)?	In the main paper, only the loading-dose phase of treatment is described as being "double-blind," but in the trial design publication it is stated that the maintenance phase was also "double-blind."	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There is no evidence of an unexpected imbalance in drop-outs between groups.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest that the authors measured more outcomes than they reported.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	"Efficacy comparisons were performed on the basis of the time to the first event, according to the intention-to-treat principle. Safety analyses were carried out on data from patients who received at least one dose of the study drug." It appears that this was carried out appropriately.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

Not applicable

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

Not applicable

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

Not applicable.

9.9 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***EconLIT***
- ***NHS EED.***

Databases searched and the service providers used were:

- Ovid MEDLINE(R)
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
- Ovid MEDLINE(R) Daily
- Ovid OLDMEDLINE(R) <1947 to Present>
- Ovid EMBASE <1980 to 2010 Week 28>
- Cochrane Library NHS EED
- Wiley HEED

NB: AstraZeneca does not subscribe to EconLIT

9.9.2 The date on which the search was conducted.

19th July 2010

9.9.3 The date span of the search.

No time restricts were made.

9.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) <1947 to Present>

#	Search terms	Results
1	acute coronary syndrome$.tw.	11,428
2	acs.tw.	6,614

3	exp myocardial infarction/	128,895
4	exp Angina, Unstable/	9,394
5	unstable angina.tw.	9,767
6	(unstable adj2 coronary).tw.	860
7	non-ST-segment elevation.tw.	1,141
8	ST-segment elevation.tw.	6,287
9	(STEMI or non-STEMI or NSTEMI or nonSTEMI).tw.	2,025
10	heart attack.tw.	2,445
11	(heart adj2 infarct$).tw.	2,925
12	ST-elevation.tw.	5,058
13	exp Coronary Thrombosis/	4,922
14	(coronary adj2 thrombos$).tw.	2,333
15	myocardial infarct$.tw.	121,119
16	or/1-15	187,700
17	(ticagrelor or brilinta or brilique).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	72
18	(prasugrel or efient or effient).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	329
19	(clopidogrel or plavix).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	5,256
20	or/17-19	5,337
21	Economics/	25,882
22	"costs and cost analysis"/	38,317
23	cost allocation/	1,883
24	cost control/	18,335
25	Cost savings/	6,692
26	Cost of illness/	13,146
27	Cost sharing/	1,583
28	"deductibles and coinsurance"/	1,245
29	Medical savings accounts/	429
30	Health care costs/	19,834
31	Direct service costs/	911
32	Drug costs/	9,902
33	Employer health costs/	1,014
34	Hospital costs/	6,183
35	Health expenditures/	11,119
36	Capital expenditures/	1,885
37	Value of life/	5,133
38	exp economics, hospital/	16,708
39	Economics, nursing/	3,819
40	Economics, pharmaceutical/	2,115
41	exp "fees and charges"/	24,848
42	exp budgets/	10,581
43	(low adj cost).mp.	15,113
44	(high adj cost).mp.	6,138

45	(health?care adj cost$).mp.	2,474
46	(fiscal or funding or financial or finance).tw.	58,522
47	(cost adj estimate$).mp.	1,079
48	(cost adj variable).mp.	27
49	(unit adj cost$).mp.	1,131
50	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	127,603
51	Cost-benefit analysis/	48,738
52	exp economics, medical/	13,004
53	or/21-52	367,639
54	16 and 20 and 53	126
55	from 54 keep 1-126	126

EMBASE <1980 to 2010 Week 28>

#	**Search Terms**	**Results**
1	acute coronary syndrome$.tw.	11,145
2	acs.tw.	5,886
3	exp myocardial infarction/	134,145
4	Angina, Unstable/	10,004
5	unstable angina.tw.	8,792
6	(unstable adj2 coronary).tw.	803
7	non-ST-segment elevation.tw.	1,151
8	ST-segment elevation.tw.	5,937
9	(STEMI or non-STEMI or NSTEMI or nonSTEMI).tw.	1,967
10	heart attack.tw.	1,768
11	(heart adj2 infarct$).tw.	2,691
12	ST-elevation.tw.	4,731
13	exp Coronary Thrombosis/	3,988
14	(coronary adj2 thrombos$).tw.	1,677
15	myocardial infarct$.tw.	93,717
16	or/1-15	167,037
17	(ticagrelor or brilinta or brilique).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	339
18	(prasugrel or efient or effient).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	923
19	(clopidogrel or plavix).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	18,546
20	or/17-19	18,626
21	Socioeconomics/	37,289
22	Cost benefit analysis/	33,935
23	Cost effectiveness analysis/	64,990
24	Cost of illness/	6,042

25	Cost control/	19,177
26	Economic aspect/	74,345
27	Financial management/	27,900
28	Health care cost/	72,599
29	exp health care financing/	9,961
30	Health economics/	11,650
31	(fiscal or financial or finance or funding).tw.	40,884
32	Cost minimization analysis/	1,663
33	(cost adj estimate$).mp.	995
34	(cost adj variable$).mp.	75
35	(unit adj cost$).mp.	997
36	Hospital cost/	7,307
37	or/21-36	309,460
38	16 and 20 and 37	553
39	39 from 38 keep 1-553	553

NHS Economic Evaluation Database (NHS EED) using Cochrane Library database.

1. (acute coronary syndrome OR acs OR myocardial infarct* OR unstable angina OR non NEXT ST NEXT segment NEXT elevation OR ST NEXT segment NEXT elevation OR STEMI OR non NEXT STEMI or NSTEMI OR nonSTEMI):ti OR (heart attack OR heart NEAR/2 infarct* OR ST NEXT elevation OR coronary NEAR/2 thrombos*):ti and (ticagrelor OR brilinta OR brilique OR prasugrel OR efient OR effient OR clopidogrel OR plavix):ti in Economic Evaluations (241)

Database: Health Economic Evaluation Database (HEED)

1. TI = acute coronary syndrome OR acs OR myocardial infarction OR unstable angina OR STEMI OR NSTEMI OR heart attack OR heart infarction OR coronary thrombosis
2. TI = ticagrelor OR prasugrel OR clopidogrel
3. CS = 1 AND 2 (14)

9.9.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The NICE and SMC websites were searched for HTA appraisals that have evaluated oral antiplatelet agents in the treatment of ACS.

9.10 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

9.11 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.11.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***NHS Economic Evaluation Database (NHS EED)***
- ***EconLIT.***

Databases searched and the service providers used were:

- Ovid MEDLINE(R)
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
- Ovid MEDLINE(R) Daily
- Ovid OLDMEDLINE(R) <1947 to Present>
- Ovid EMBASE <1980 to 2010 Week 28>
- Cochrane Library NHS EED

NB: Astrazeneca UK Ltd does not subscribe to EconLit. It was therefore not possible to search this database.

9.11.2 The date on which the search was conducted.

Ovid MEDLINE databases were searched on 30th September 2010. Ovid EMBASE was searched on 4th October 2010.

9.11.3 The date span of the search.

Ovid MEDLINE 01/01/2000 to date (30/09/2010)

Ovid EMBASE 01/01/2000 to date (04/10/2010)

Cochrane library 01/01/2000 to date (05/10/2010)

9.11.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) <1947 to Present>

#	Search Terms	Results
1	value of life.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	5314
2	quality adjusted life year.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1796
3	quality adjusted life.tw.	3924
4	(qaly$ or qald$ or qale$ or qtime$).tw.	3278
5	disability adjusted life.tw.	731
6	daly$.tw.	771
7	health status indicator.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	30
8	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thiry six or short form thirtysix or short form thiry six).tw.	10943
9	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.	1092
10	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	1548
11	(sf16 or sf 16 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	485
12	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.	308
13	(euroqol or euro qol or eq5d or eq 5d).tw.	2104
14	(hql or hqol or h qol or hrqol or hr qol).tw.	4658
15	(hye or hyes).tw.	50
16	health$ year$ equivalent$.tw.	38
17	health utilit$.tw.	709
18	(hui or hui1 or hui3).tw.	636
19	disutili$.tw.	140
20	rosser.tw.	67
21	quality of wellbeing.tw.	6
22	qwb.tw.	140
23	willingness to pay.tw.	1427
24	standard gamble$.tw.	572
25	time trade off.tw.	541
26	time tradeoff.tw.	183
27	tto.tw.	411
28	or/1-27	30898
29	acute coronary syndrome$.tw.	11788
30	acs.tw.	6833
31	exp myocardial infarction/	130025

32	exp Angina, Unstable/	9442
33	unstable angina.tw.	9853
34	(unstable adj2 coronary).tw.	867
35	non-ST-segment elevation.tw.	1176
36	ST-segment elevation.tw.	6458
37	(STEMI or non-STEMI or NSTEMI ora nonSTEMI).tw.	2165
38	heart attack.tw.	2502
39	(heart adj2 infarct$).tw.	2982
40	ST-elevation.tw.	5215
41	exp Coronary Thrombosis/	4995
42	(coronary adj2 thrombos$).tw.	2349
43	myocardial infarct$.tw.	122600
44	(stroke or cerebrovascular accident or cerebral thrombosis or cerebral embolism).tw.	108688
45	(haemorrhag$3 or hemorrhag$3 or bleed$3).ti.	90559
46	or/29-45	373037
47	28 and 46	1233
48	limit 47 to (abstracts and english language and yr="2000 - Current")	947
49	from 48 keep 31,67,83,104,228,242,313,326,411,419,449,481,527,535,603, 615-616,648,708,748,790,825,874-875,931	25

EMBASE <1980 to 2010 Week 39>

#	Search Terms	Results
1	value of life.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	262
2	quality adjusted life year.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	7365
3	quality adjusted life.tw.	4524
4	(qaly$ or qald$ or qale$ or qtime$).tw.	4074
5	disability adjusted life.tw.	820
6	daly$.tw.	910
7	health status indicator.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	26
8	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thiry six or short form thirtysix or short form thiry six).tw.	12991
9	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.	1166
10	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	1890

11	(sf16 or sf 16 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	551
12	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.	256
13	(euroqol or euro qol or eq5d or eq 5d).tw.	2723
14	(hql or hqol or h qol or hrqol or hr qol).tw.	5606
15	(hye or hyes).tw.	56
16	health$ year$ equivalent$.tw.	41
17	health utilit$.tw.	819
18	(hui or hui1 or hui3).tw.	705
19	disutili$.tw.	172
20	rosser.tw.	78
21	quality of wellbeing.tw.	9
22	qwb.tw.	152
23	willingness to pay.tw.	1726
24	standard gamble$.tw.	600
25	time trade off.tw.	609
26	time tradeoff.tw.	184
27	tto.tw.	503
28	or/1-27	33904
29	acute coronary syndrome$.tw.	14717
30	acs.tw.	8425
31	exp myocardial infarction/	191698
32	exp Angina, Unstable/	12659
33	unstable angina.tw.	11545
34	(unstable adj2 coronary).tw.	1004
35	non-ST-segment elevation.tw.	1405
36	ST-segment elevation.tw.	7315
37	(STEMI or non-STEMI or NSTEMI ora nonSTEMI).tw.	2975
38	heart attack.tw.	2816
39	(heart adj2 infarct$).tw.	3821
40	ST-elevation.tw.	6224
41	exp Coronary Thrombosis/	5097
42	(coronary adj2 thrombos$).tw.	2363
43	myocardial infarct$.tw.	135606
44	(stroke or cerebrovascular accident or cerebral thrombosis or embolism).tw.	162686
45	(haemorrhag$3 or hemorrhag$3 or bleed$3).ti.	91333
46	or/29-45	470082
47	28 and 46	1789
48	limit 47 to (abstracts and english language and yr="2000 - Current")	1371
49	from 48 keep	21

NHS Economic Evaluation Database (NHS EED) using Cochrane Library database.

("acute coronary syndrome" OR acs OR myocardial infarct* OR unstable angina OR non NEXT ST NEXT segment NEXT elevation OR ST NEXT segment NEXT elevation OR STEMI OR non NEXT STEMI OR NSTEMI OR nonSTEMI OR heart attack OR heart NEAR/2 infarct* OR ST NEAR elevation OR coronary NEAR/2 thrombo* OR stroke OR cerebrovascular accident OR cerebral thrombo* OR cerebral emboli*):ti,ab,kw and ("health state preference" OR "health state valuation" OR utilit* OR disutilit* OR euroqol OR ED-5D OR "time trade off" OR TTO OR "standard gamble"):ti,ab,kw in Economic Evaluations (17)

9.11.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

9.11.6 The inclusion and exclusion criteria.

Not applicable

9.11.7 The data abstraction strategy.

Not applicable

9.12 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***NHS EED***
- ***EconLIT.***

Databases searched and the service providers used were:

- Ovid MEDLINE(R)
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
- Ovid MEDLINE(R) Daily

- Ovid OLDMEDLINE(R) <1947 to Present>
- Ovid EMBASE <1980 to 2010 Week 28>
- Cochrane Library NHS EED

9.12.2 The date on which the search was conducted.

Search conducted: 25th October 2010

9.12.3 The date span of the search.

- Ovid MEDLINE 01/01/2000 to date (30/09/2010)
- Ovid EMBASE 01/01/2000 to date (04/10/2010)
- Cochrane library 01/01/2000 to date (05/10/2010)

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search conducted: 25th October 2010

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) <1947 to Present>
Search Strategy:
---
1 acute coronary syndrome$.tw.
2 acs.tw.
3 exp myocardial infarction/
4 exp Angina, Unstable/
5 unstable angina.tw.
6 (unstable adj2 coronary).tw.
7 non-ST-segment elevation.tw.
8 ST-segment elevation.tw.
9 (STEMI or non-STEMI or NSTEMI or nonSTEMI).tw.
10 heart attack.tw.
11 (heart adj2 infarct$).tw.
12 ST-elevation.tw.
13 exp Coronary Thrombosis/
14 (coronary adj2 thrombos$).tw.
15 myocardial infarct$.tw.
16 (stroke or cerebrovascular accident or cerebral thrombosis or cerebral embolism).tw.
17 (haemorrhag$3 or hemorrhage$3 or bleed$3).ti.
18 dyspnoea.tw.
19 or/1-18

20 Economics/
21 "costs and cost analysis"/
22 cost allocation/
23 cost control/
24 Health care costs/
25 Direct service costs/
26 Drug costs/
27 Hospital costs/
28 Health expenditures/
29 Capital expenditures/
30 exp economics, hospital/
31 Economics, pharmaceutical/
32 exp "fees and charges"/
33 exp budgets/
34 (low adj cost).mp.
35 (high adj cost).mp.
36 (health?care adj cost$).mp.
37 (fiscal or funding or financial or finance).tw.
38 (cost adj estimate$).mp.
39 (cost adj variable).mp.
40 (unit adj cost$).mp.
41 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
42 exp economics, medical/
43 or/20-42
44 19 and 43
45 UK.tw
46 United kingdom .tw
47 Great Britain.tw
48 NHS. tw
49 National health service .tw
50 England.tw
51 Scotland.tw
52 Wales.tw
53 Northern Ireland.tw
54 or/45-53
55 44 and 55

Limit(s):

Language: English
Date of publication: 2000 to date

9.12.5 ***Details of any additional searches (for example, searches of company databases [include a description of each database***]).

Not applicable

9.12.6 The inclusion and exclusion criteria.

Not applicable

9.12.7 The data abstraction strategy.

Not applicable

9.13 Appendix 13: Markov Traces

Markov Trace for Ticagrelor (vs clopidogrel)						
No Event	**Non-fatal MI**	**Post MI**	**Non-fatal Stroke**	**Post Stroke**	**Dead**	**Check**
872	0	54	0	12	62	1000
795	27	51	9	12	106	1000
720	25	72	8	18	156	1000
648	23	89	7	24	209	1000
579	20	102	7	28	263	1000
513	18	112	6	31	320	1000
450	16	117	5	33	378	1000
391	14	119	5	34	437	1000
336	12	117	4	34	496	1000
284	11	113	3	33	556	1000
236	9	106	3	31	615	1000
193	7	96	2	28	673	1000
155	6	86	2	25	726	1000
121	5	74	2	22	776	1000
92	4	62	1	19	822	1000
68	3	50	1	15	863	1000
49	2	39	1	12	897	1000
34	2	29	1	9	926	1000
23	1	22	0	7	947	1000
15	1	15	0	5	964	1000
9	0	10	0	3	976	1000
6	0	6	0	2	986	1000
3	0	4	0	1	992	1000
1	0	2	0	1	996	1000
1	0	1	0	0	998	1000
0	0	0	0	0	999	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000

0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000

Markov Trace for clopidogrel						
No Event	**Non-fatal MI**	**Post MI**	**Non-fatal Stroke**	**Post Stroke**	**Dead**	**Check**
847	0	63	0	11	79	1000
772	27	60	9	11	122	1000
699	24	80	8	17	171	1000
629	22	96	7	23	223	1000
563	20	108	6	27	277	1000
499	18	116	6	30	332	1000
437	16	121	5	32	389	1000
380	14	122	4	33	447	1000
326	12	120	4	33	505	1000
276	10	115	3	32	564	1000
230	9	107	3	30	622	1000
188	7	97	2	27	678	1000
150	6	86	2	24	731	1000
118	5	74	2	21	780	1000
90	4	62	1	18	825	1000
66	3	50	1	15	865	1000
48	2	39	1	11	899	1000
33	2	29	0	9	927	1000
22	1	22	0	6	948	1000
15	1	15	0	5	965	1000
9	0	10	0	3	977	1000
5	0	6	0	2	986	1000
3	0	4	0	1	992	1000
1	0	2	0	1	996	1000
1	0	1	0	0	998	1000
0	0	0	0	0	999	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000

0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000

Markov Trace for ticagrelor (vs prasugrel)						
No Event	Non-fatal MI	Post MI	Non-fatal Stroke	Post Stroke	Dead	Check
896	0	53	0	12	39	1000
840	28	52	9	12	59	1000
786	26	77	9	20	82	1000
733	25	100	8	27	107	1000
682	23	120	7	34	134	1000
632	21	138	7	40	162	1000
585	20	153	6	45	192	1000
538	18	165	6	49	224	1000
494	17	174	5	52	258	1000
451	16	182	5	54	292	1000
410	14	186	5	56	329	1000
371	13	188	4	57	367	1000
333	12	188	4	57	407	1000
297	10	185	3	56	448	1000
262	9	179	3	55	491	1000
229	8	171	3	53	536	1000
198	7	162	2	50	580	1000
170	6	150	2	47	625	1000
143	5	137	2	43	670	1000
118	4	123	1	39	715	1000
96	4	107	1	34	758	1000
76	3	92	1	29	798	1000
59	2	77	1	25	835	1000
45	2	63	1	20	870	1000
33	1	49	0	16	899	1000
23	1	38	0	13	925	1000
16	1	28	0	9	946	1000
11	1	20	0	7	962	1000
7	0	14	0	5	974	1000
4	0	9	0	3	983	1000
3	0	6	0	2	989	1000
1	0	3	0	1	994	1000
1	0	2	0	1	997	1000
0	0	1	0	0	998	1000
0	0	0	0	0	999	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000

0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000

Markov Trace for prasugrel						
No Event	**Non-fatal MI**	**Post MI**	**Non-fatal Stroke**	**Post Stroke**	**Dead**	**Check**
895	0	48	0	10	47	1000
839	28	47	9	10	67	1000
784	26	72	9	18	90	1000
732	25	95	8	26	115	1000
681	23	115	7	32	141	1000
632	21	133	7	38	169	1000
584	20	148	6	43	199	1000
538	18	160	6	47	231	1000
493	17	170	5	50	264	1000
451	16	177	5	53	298	1000
410	14	182	5	55	334	1000
370	13	184	4	56	372	1000
332	12	184	4	56	412	1000
296	10	181	3	55	453	1000
262	9	176	3	54	496	1000
229	8	169	3	52	540	1000
198	7	159	2	49	584	1000
169	6	148	2	46	629	1000
142	5	135	2	42	673	1000
118	4	121	1	38	717	1000
96	4	106	1	34	760	1000
76	3	91	1	29	800	1000
59	2	76	1	24	837	1000
45	2	62	1	20	871	1000
33	1	49	0	16	900	1000
23	1	37	0	12	926	1000
16	1	27	0	9	946	1000
11	1	20	0	7	962	1000
7	0	14	0	5	974	1000
4	0	9	0	3	983	1000
3	0	6	0	2	990	1000
1	0	3	0	1	994	1000
1	0	2	0	1	997	1000
0	0	1	0	0	998	1000
0	0	0	0	0	999	1000
0	0	0	0	0	1000	1000

0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000
0	0	0	0	0	1000	1000