NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome

June 2014

Executive summary 3
Section A – Decision problem 6
1 Description of technology under assessment 6
2 Context 13
3 Equality 23
4 Innovation 24
5 Statement of the decision problem 26
6 Clinical evidence 29
6.1 Identification of studies 29
6.2 Study selection 30
6.3 Summary of methodology of relevant RCTs 42
6.4 Critical appraisal of relevant RCTs 71
6.5 Results of the relevant RCTs 72
6.6 Meta-analysis 104
6.7 Indirect and mixed treatment comparisons 104
6.8 Non-RCT evidence 104
6.9 Adverse events 105
6.10 Interpretation of clinical evidence 122
7 Cost effectiveness 137
7.1 Published cost-effectiveness evaluations 137
7.2 De novo analysis 173
7.3 Clinical parameters and variables 183
7.4 Measurement and valuation of health effects 240
7.5 Resource identification, measurement and valuation 278
7.6 Sensitivity analysis 313
7.7 Results 322
7.8 Validation 337
7.9 Subgroup analysis 337
7.10 Interpretation of economic evidence 338
Section C – Implementation 341
8 Assessment of factors relevant to the NHS and other parties 341
9 References 346
10 Appendices

Executive summary

- The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.

Rivaroxaban (Xarelto®) was granted a license in May 2013 through a centralised procedure for the following indication:

> *Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.*

Rivaroxaban will be launched in this indication in the UK in September 2014.

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Anticoagulants are an important component of therapy for ACS in the acute setting. However, excess thrombin generation has been found to persist in stable patients beyond the acute presentation of ACS, providing a rationale for long-term oral anticoagulant therapy for the prevention of recurrent events. The use of anticoagulant therapy in combination with antiplatelet therapy targets complementary mechanisms associated with thrombus formation in patients with ACS.

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

Rivaroxaban will be available for this indication as 2.5 mg film-coated tablets, provided as a pack of 56. The recommended dose is 2.5 mg twice daily which equates to a price of £2.10 per day.

- The indication(s) and any restriction(s).

Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Xarelto 2.5 mg is contraindicated for the treatment of ACS in patients with a prior stroke or TIA.

- The recommended course of treatment.

Treatment with Xarelto should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

Treatment should be evaluated on an ongoing basis in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12

months should be done on an individual patient basis as experience up to 24 months is limited.

- The main comparator(s).

The main comparator is standard of care antiplatelet therapy. In the UK, this is typically aspirin in combination with clopidogrel.

- Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.

The key clinical evidence in the submission comes from ATLAS-ACS 2 TIMI 51 which was an international, multicentre, prospective, randomised, double-blind, placebo-controlled, event-driven phase III study. This is a head to head trial with standard of care.

- The main results of the RCTs and any relevant non-RCT evidence.

The ATLAS ACS 2 TIMI 51 study met its primary objective. In patients with recent acute coronary syndrome, compared with placebo, rivaroxaban (2.5 or 5 mg bd) in addition to standard care (ASA or ASA plus clopidogrel) demonstrated:

- a significant reduction in the first occurrence of the composite endpoint of CV death/MI/Stroke (HR 0.84, 95% CI: 0.74, 0.96, p=0.008)
- When the 2.5mg bd dose is added to standard of care, it also leads to a significant reduction in the primary endpoint (HR 0.84, 95% CI: 0.72, 0.97, p=0.02). This decrease is driven by a 34% reduction in CV death (HR 0.66, 95% CI 0.51, 0.86, p=0.002)

Kaplan-Meier analysis of the ATLAS ACS 2-TIMI 51 trial demonstrated a sustained benefit of rivaroxaban (2.5 mg b.i.d.) in combination with SoC during the second year of treatment.

Regarding the licensed population, the relative risk reduction in the primary endpoint of 20% is higher than the RRR in the overall trial population (16% RRR) and the absolute risk reduction of 1.7% for the primary endpoint of CV death, MI and stroke is clinically meaningful.

Patients with positive biomarkers can expect a 45% RRR in CV death as well as a [redacted] RRR in all-cause death compared to standard of care with anti-platelet therapy.

The only notable safety difference identified in the ATLAS ACS 2 TIMI 51 study was bleeding, as might be expected with the addition of an anticoagulant to standard of care antiplatelet therapy. No other safety events were identified. The overall incidence of treatment-emergent non-CABG TIMI major bleeding events, the principal safety outcome, was low.

On balance, the increase in bleeding risk is outweighed by the substantial reduction in risk of death, particularly CV death, from which patients are at high risk after diagnosis of ACS. The benefit risk was further improved in the licensed population (compared to the overall trial population) because of the increased numbers of ischaemic events prevented.

- In relation to the economic evaluation, details of:
  - the type of economic evaluation and justification for the approach used
  - the pivotal assumptions underlying the model/analysis
  - the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.

A cost-utility analysis has been conducted. The model is a Markov cohort model with a lifetime horizon. A Markov model provides sufficient flexibility to allow for multiple events and varying costs and utilities based on the time since an event, reflecting clinical reality.

Short-term transition probabilities are based on patient level data from ATLAS 2 and sources identified from the systematic review of the literature are used to estimate longer term outcomes, accounting for increased risks due to age and previous events. The model allows for multiple secondary events to occur and costs and utilities are dependent on the time since entering a health state, reflecting clinical reality where risk is highest and prevention measures are most intense immediately following an ACS event. Patients may also experience three non-fatal events in the model. Bleedings and revascularisations are included in the model as transient health states.

- Tabulation of the base-case results as follows:

Base-case cost-effectiveness results

	Rivaroxaban	**CLO+ASA or ASA (ie both strata)**
Total costs	£14,767.63	£14,004.05
Difference in total costs	£763.58	
LYG	11.48	11.34
LYG difference	0.15	
QALYs	9.56	9.44
QALY difference	0.12	
ICER	£6,202.84	

- Subgroup analyses considered and clinical- and cost-effectiveness results.

The licenced population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically

sound as the trial was not powered to draw conclusion about (non-pre-specified) subgroups of subgroups.

Section A – Decision problem

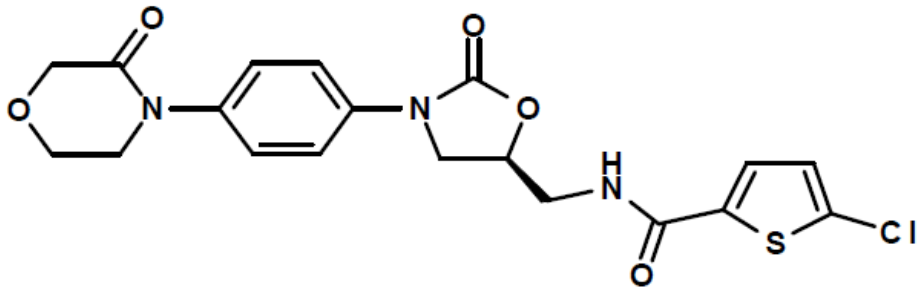
Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

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.

Brand name	Xarelto
Approved name	Rivaroxaban
Therapeutic class	Oral anticoagulant

Rivaroxaban is direct Factor Xa (FXa) inhibitor. The chemical structure is provided below (5-Chloro-*N*-([(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1, 3-oxazolidin-5-ylmethyl)-2-thiophene-carboxamide (C19H18ClN3O5S)).



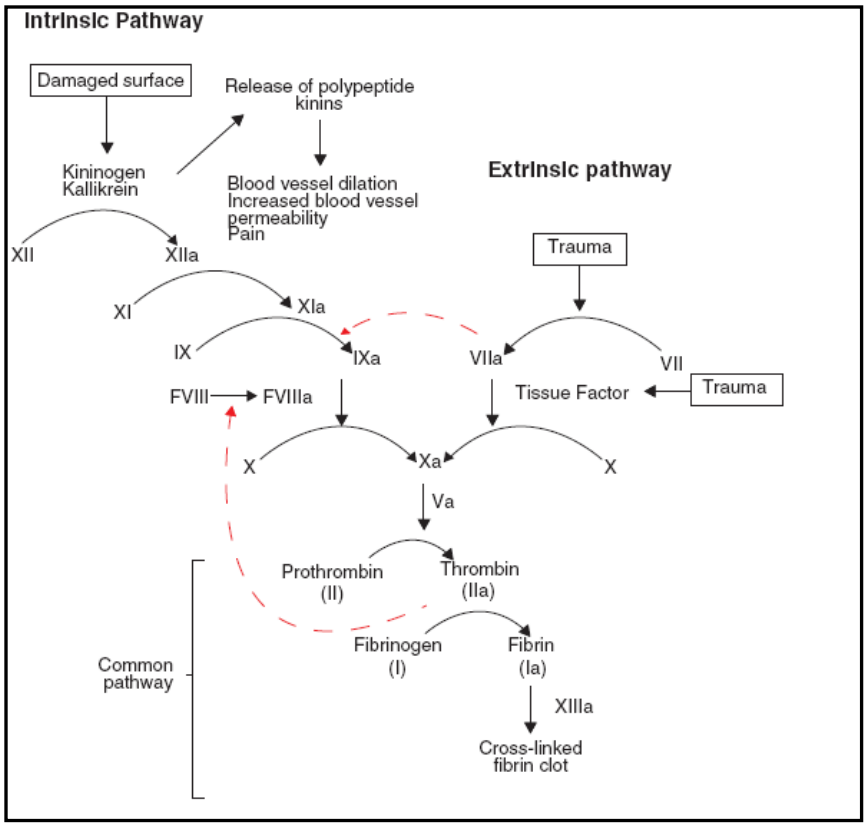
1.2 What is the principal mechanism of action of the technology?

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi (see Figure 1 below).

Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

The prothrombinase complex comprising FXa, FVa, calcium, and a phospholipid surface plays a crucial role in regulating the cleavage of prothrombin to thrombin and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound Xa is increased 300,000-fold compared to that of free FXa and causes a burst of thrombin generation. Inhibition of FXa, because of its pivotal position in the coagulation cascade, has the potential to block the thrombotic process and in so doing, reduce the incidence of subsequent ACS events.

Figure 1. Schematic representation of the clotting cascade



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).

The submission is for the following licensed indication which was received in May 2013 through a centralised procedure.

- Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

Rivaroxaban also holds the following UK marketing authorisations:

- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

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 marketing authorisation).

The potential increase in bleeding when rivaroxaban is added to platelet function inhibitors for secondary cardiovascular prophylaxis in ACS patients was of concern.

A PASS was considered conditional to the MA.

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

The submission is for the following licensed indication which was received in May 2013.

- Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events

in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

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.

NCT00809965 – completed

A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome. Published in full at N Engl J Med. 2012 Jan 5;366(1):9-19.

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

Bayer anticipate that rivaroxaban in this indication will be launched in September 2014.

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

Rivaroxaban for use in the ACS indication is currently approved in ~40 countries, which includes the whole EU.

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?

Rivaroxaban for the ACS indication will be reviewed by the Scottish Medicines Consortium. The timelines are yet to be confirmed.

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 A1 Unit costs of technology being appraised

Pharmaceutical formulation	2.5 mg film-coated tablets
Acquisition cost (excluding VAT)	£2.10 per day
Method of administration	Oral
Doses	2.5mg
Dosing frequency	Twice daily
Average length of a course of treatment	Treatment with rivaroxaban should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued. Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited.
Average cost of a course of treatment	Dependent on duration of therapy – please see above.
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Rivaroxaban is to be used with caution for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min). Use is not recommended in patients with creatinine clearance < 15 ml/min. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) **Elderly population** No dose adjustment **Body weight** No dose adjustment **Gender** No dose adjustment Please refer to SPC for full details of contraindications, precautions and special warnings.

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?

Investigations

It is not anticipated that any additional tests or investigations will be required for selection of patients appropriate for rivaroxaban, over and above those which are part of routine clinical practice.

ACS is an umbrella term that encompasses MI – including STEMI and NSTEMI – and UA. A patient admitted with chest pain and a working diagnosis of ACS will undergo an ECG to initially confirm and classify the type of ACS as well as undergoing cardiac biomarker testing. Elevated levels of cardiac biomarkers are associated with heart injury, and detection of elevated biomarkers, therefore, indicates that a patient with ACS has had an MI (NSTEMI or STEMI), instead of UA.

Administration

There are no particular administration requirements associated with rivaroxaban. Rivaroxaban can be taken with or without food.

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

The consistent pharmacokinetic and pharmacodynamic profiles of rivaroxaban (Xu *et al*. 2012) and limited food/drug interactions mean that no routine coagulation monitoring is required. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

As with other anticoagulants, patients taking rivaroxaban are to be carefully observed for signs of bleeding. Several sub-groups of patients are at increased risk of bleeding. Therefore, the use of rivaroxaban in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

In addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Xu XS, Moore K, Burton P et al. Population pharmacokinetics and pharmacodynamics of rivaroxaban in patients with acute coronary syndromes. Br J Clin Pharmacol 2012;74:86–97.

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 should also take a daily dose of 75 - 100 mg aspirin or a daily dose of 75 - 100 mg aspirin in addition to a daily dose of 75 mg clopidogrel.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

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.

Coronary heart disease (CHD) is a common clinical and pathological condition. The incidence and prevalence rates of CHD remain high throughout the world.

The clinical manifestations of ACS are for the most part the result of atherosclerotic plaque rupture and thrombosis. Hence, atherothrombosis is the major pathophysiological process responsible for the occurrence of severe ischaemic events in patients with CHD. The most common serious clinical manifestation of CHD is Acute Coronary Syndrome, ACS, a term which includes conditions of Unstable Angina (UA), Non-ST-Segment Elevation Myocardial Infarction (NSTEMI) and ST-Segment Elevation Myocardial Infarction (STEMI). Following an ACS event, patients are at high risk of another morbid event of ACS or dying from a CV cause.

The incidence, prevalence and severity of clinical consequences for patients with ACS drove a rapid increase in clinical development activities over the past 3 decades that ultimately resulted in the approval of parenteral, short acting antiplatelet agents for use in the acute setting, oral antiplatelet agents for acute and chronic use, and parenteral anticoagulants also for use in the acute setting. The aim of all of these therapies is preventing thrombus formation at the site of rupture of an atherosclerotic plaque and subsequent adverse cardiovascular events.

An important component of the current standard care for post ACS patients is the long term use of antiplatelet agents, principally aspirin with or without the addition of a thienopyridine, such as clopidogrel.

Despite the widespread use of antiplatelet agents in the acute and chronic setting, the incidence of CV events such as CV death or MI in the post-ACS population remains high.

Patients who receive recommended dual antiplatelet therapies still have a 10% residual risk of experiencing a major CV event during the 12–15 months after ACS has occurred (Yusuf *et al.* 2001; Wiviott *et al.* 2007; Wallentin *et al.* 2009).

The central role of thrombosis in the pathophysiology of ACS, and the platelet-rich composition of arterial thrombi, provide a rationale for the use of antiplatelet agents. After the rupture or erosion of an atherosclerotic plaque, platelets are recruited to the plaque where they adhere to the vessel wall and recruit further platelets, leading to rapid growth of the thrombus.

After atherosclerotic plaque rupture in patients with ACS, the presence of tissue factor in atherosclerotic plaques and in the blood (following endothelial damage), alongside activated platelets, triggers the coagulation cascade, leading to the generation of thrombin and the conversion of fibrinogen to fibrin, which stabilizes the ACS clot (Giesen *et al*. 1999; Monroe

and Hoffmann 2006; Esmon 2008; Mackman 2008; Tamura *et al*. 2009; Angiolillo *et al*. 2010). In parallel, thrombin stimulates platelets by binding to protease-activated receptor 1 (PAR1; also known as the thrombin receptor), inducing release of adenosine diphosphate and thromboxane A2, which further stimulates platelet activation and aggregation (Goto *et al*. 2003; Licari and Kovacic 2009). Most thrombin is produced on the platelet surface, and binding of thrombin to platelets via glycoprotein Ibα is believed to contribute to platelet activation (De Marco *et al*. 1994). Because of these various interactions, mechanisms of platelet activation and coagulation are highly interdependent, with thrombin playing a central role in both.

Anticoagulants are an important component of therapy for ACS in the acute setting. However, excess thrombin generation has been found to persist in stable patients for at least 6–12 months beyond the acute presentation of ACS (Merlini *et al.* 1994; Ardissino *et al.* 2003), providing a rationale for long-term oral anticoagulant therapy for the prevention of recurrent events. The use of anticoagulant therapy in combination with antiplatelet therapy targets complementary mechanisms associated with thrombus formation in patients with ACS.

As proof of principle, a meta-analysis of 10 studies (Rothberg 2005) (n=5,938 subjects), showed that warfarin plus aspirin treated subjects compared with aspirin-treated subjects had lower annual rates of MI (2.2% versus 4.1%, respectively [rate ratio 0.56, CI 0.48-0.69]), ischemic stroke (0.4% versus 0.8%, respectively [rate ratio 0.46, CI 0.2-0.77]), and revascularisation (11.5% versus 13.5%, respectively [Rate ratio 0.8, CI 0.67-0.94]). Subjects receiving warfarin had an increased risk of major bleeding compared with subjects on aspirin alone (1.5% versus 0.6%, respectively (rate ratio 2.48, CI 1.67-3.68]).

Because of difficulties inherent with warfarin monitoring, such as variations in dose response, the need for patient compliance in the monitoring of coagulation parameters and adjustment of dosing, multiple drug and food interactions, and a heightened risk for bleeding, especially when administered in combination with aspirin therapy, there remains an unmet medical need for the development of safer, efficacious, and convenient oral anticoagulants that do not depend on vitamin K antagonism for the treatment of subjects with ACS.

Yusuf S, Zhao F, Mehta SR et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;353:2001–2015.

Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–1057.

Giesen PL, Rauch U, Bohrmann B et al. Blood-borne tissue factor: another view of thrombosis. Proc Natl Acad Sci U S A 1999;96:2311–2315.

Monroe DM, Hoffman M. What does it take to make the perfect clot? Arterioscler Thromb Vasc Biol 2006;26:41–48.

Esmon CT. Crosstalk between inflammation and thrombosis. Maturitas 2008;61:122–131.

Mackman N. Triggers, targets and treatments for thrombosis. Nature 2008;451:914–918.

Tamura N, Kitajima I, Kawamura Y et al. Important regulatory role of activated platelet-derived procoagulant activity in the propagation of thrombi formed under arterial blood flow conditions. Circ J 2009;73:540–548.

Angiolillo DJ, Ueno M, Goto S. Basic principles of platelet biology and clinical implications. Circ J 2010;74:597–607.

Goto S, Tamura N, Li M et al. Different effects of various anti-GPIIb-IIIa agents on shear-induced platelet activation and expression of procoagulant activity. J Thromb Haemost 2003;1:2022–2030.

Licari LG, Kovacic JP. Thrombin physiology and pathophysiology. J Vet Emerg Crit Care (San Antonio) 2009;19:11–22.

De Marco L, Mazzucato M, Masotti A, Ruggeri ZM. Localization and characterization of an alpha-thrombin-binding site on platelet glycoprotein Ib alpha. J Biol Chem 1994;269:6478–6484.

Merlini PA, Bauer KA, Oltrona L et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. Circulation 1994;90:61–68.

Ardissino D, Merlini PA, Bauer KA et al. Coagulation activation and long-term outcome in acute coronary syndromes. Blood 2003;102:2731–2735.

Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. Ann Intern Med. 2005 Aug 16;143(4):241-50.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Further investigation on patient numbers is warranted as there are discrepancies between the figures for 2011/12 and 2012/13.

Using HES Data England & PEDW Tables Wales for 2011/12, there were 53,798 admissions (80,150 for 2012/13) for acute myocardial infarction (*I21.0, I21.1, I21.2, I21.3, I21.4 and I21.9*) and 14,766 (1,502 for 2012/13) for subsequent myocardial infarction (*I22.0, I22.1, I22.8, I22.9*). In total, this is 68,564 admissions using 2011/12 data and 81,652 using 2012/13 data.

Of these patients, a proportion would not be eligible for low dose rivaroxaban. Patients with atrial fibrillation co-existing with ACS are estimated to represent 7.8% of the ACS population (Avezum 2005). This would therefore take the eligible population to between 63,216 and 75,283 annually based on the numbers above.

The following groups of ACS patients listed in the SmPC for this indication would not be suitable for treatment with rivaroxaban:

- Hypersensitivity to the active substance or to any of the excipients
- Active clinically significant bleeding
- Lesion or condition, if considered to be a significant risk for major bleeding
- Concomitant treatment with any other anticoagulants except under the circumstances of switching therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA)
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
- Pregnancy and breast feeding
- Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.
- Use is not recommended in patients with creatinine clearance < 15 ml/min (to be used with caution in patients with creatinine clearance 15 - 29 ml/min)

It is not straightforward to estimate how many patients would have hypersensitivity and clinically significant active bleeding. The numbers of pregnant and breastfeeding women would be expected to be very low. Conservatively, no adjustment is suggested to the eligible patient population for these groups. ACS patients with a history of stroke or TIA represent 8.4% of the ACS population (Avezum 2005). This further reduces the eligible population to between 57,906 and 68,959 annually.

If we further assume that 6.7% would have a creatinine clearance <30ml/min (Santapinto 2003), then this further reduces the eligible population to between 54,026 and 64,339.

Lastly, taking account of the numbers of patients with hepatic disease, if we further assume that this represents approximately 1.4% of an ACS population (Fasa 2010), then the eligible population falls between 53,270 and 63,438 annually. This makes the assumption that there is no overlap in the comorbidities highlighted. If we assume a degree of overlap, the number of patients eligible for rivaroxaban is estimated to be approximately **60,000 to 70,000 annually**.

NHS Information Centre. Hospital Episode Statistics (HES) online. http://www.hesonline.nhs.uk Accessed May 2014

Patient Episode Database for Wales - NHS Wales Informatics Service. Available at http://www.infoandstats.wales.nhs.uk/page.cfm?pid=41010&orgid=869. Accessed May 2014

Avezum A et al. Impact of age on management and outcome of acute coronary syndrome: Observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2005;149:67–73.

Bayer plc. Summary of product characteristics for Xarelto (rivaroxaban) 2.5mg. 2013.

Santapinto et al. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: findings from the global registry of acute coronary events (GRACE). Heart 2003;89:1003–1008.

Fasa et al. Impact of comorbidities on clinical presentation, management and outcome of patients with acute coronary syndrome. Cardiovascular Medicine 2010;13(5):155–161.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Long-term survival after acute myocardial infarction (AMI) has improved over recent decades in developed countries, attributed to improvements in interventional and pharmacological management (Smolina 2012). A recent record linkage study (Smolina 2012) reports on long-term AMI prognosis in England. Residents of England were included in the study if they experienced an AMI event between January 1, 2004 and December 31, 2010, and were still alive after 30 days. Individuals were followed up until March 31, 2011. Of the cohort of patients admitted to hospital for AMI, 86% survived for at least 30 days. Around a quarter of all patients with a first AMI and half of those with a recurrent AMI died during the study period. For men, 69% were still alive 7 years after a first MI and 42% after a recurrent AMI. For women, the corresponding figures were 53% and 26%.

At 7 years, the risk of all-cause mortality in male and female survivors of first AMI was about twice the risk of all-cause mortality in the English general population. By 7 years, the risk of all-cause mortality in both male and female survivors of recurrent AMI was about 3 times higher than the risk of dying in the English general population.

The authors conclude that AMI survivors remain a high-risk group for recurrent events and mortality and reinforce the importance of both acute clinical care and secondary prevention in improving the long-term prognosis of hospitalised AMI patients.

Smolina et al. Long-term Survival and recurrence After caute Myocardial Infarction in England, 2004 to 2010. Circ Cardiovasc Qual outcomes. 2012 Jul 1;5(4):532-40

2.4 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.

NICE guidelines

CG48 MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. May 2007. Replaced by CG172

CG94 Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction. March 2010.

CG95 Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. March 2010.

CG172 MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction**.** November 2013

Technology appraisals

TA80 Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome**.** July 2004. *Updated and replaced by CG94.*

TA182 Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. October 2009. Subgroups specified in the decision problem:

- Patients with a history of stroke or TIA are excluded since they are contraindicated in the SPC. Patients ≥75 years (generally not recommended) or <60kg are only eligible for the 5mg maintenance dose – therefore the 10mg target patient population was analysed separately
- Patients with STEMI and UA/NSTEMI were analysed separately
- Diabetic and non diabetic patients were analysed separately

TA236 Ticagrelor for the treatment of acute coronary syndromes. October 2011. Subgroups specified in the decision problem:

- people with unstable angina, NSTEMI and STEMI

Technology appraisals in development

- Acute coronary syndrome - prasugrel with PCI (review TA182) [ID 648]

Diagnostic guidance in development

- High-sensitivity troponin for the early rule out or diagnosis of acute myocardial infarction in people with acute chest pain

Quality standards in development

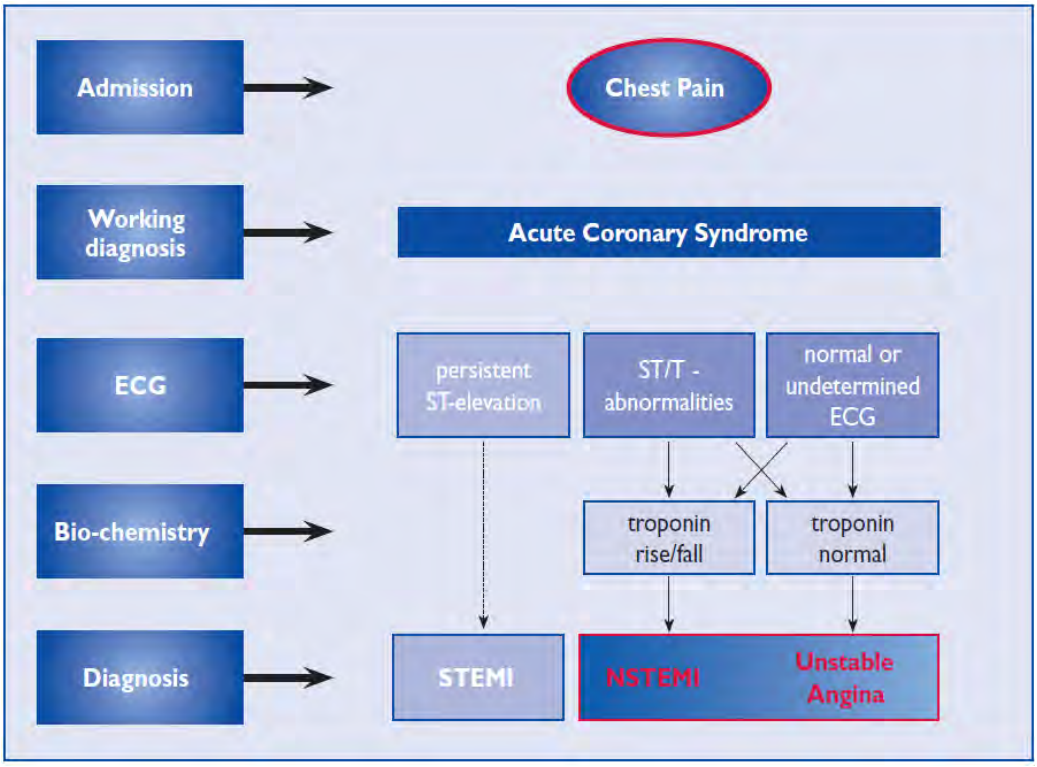
Acute coronary syndromes (including myocardial infarction)

2.5 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.

ACS in the different clinical presentations, shares a widely common pathophysiological substrate. Atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis and distal embolisation resulting in myocardial under-perfusion, form the basic pathophysiological mechanisms in most presentations of ACS.

Figure 2. Spectrum of ACS (Hamm et al. 2011)



The leading symptom of ACS is typically chest pain but the classification of ACS is based on the electrocardiogram (ECG). Patients fall into two broad categories (Hamm et al 2011):

- Patients with acute chest pain and persistent ST-segment elevation (ST-ACS) - Most of these patients will ultimately develop an ST-elevation MI (STEMI).
- Patients with acute chest pain but without persistent ST-segment elevation (NSTE-ACS)

The working diagnosis of NSTE-ACS is a rule-out diagnosis based on the ECG, i.e. lack of persistent ST elevation. Biomarkers (troponins) further distinguish NSTEMI and unstable angina (Hamm et al 2011).

Appropriate triage, risk assessment and timely use of acute pharmacological or invasive interventions are critical for the prevention of future adverse cardiovascular events (myocardial infarction, repeat revascularisation or death) (NICE CG94). Management of the patient is determined by the initial diagnosis.

Dual antiplatelet therapy (aspirin plus a second antiplatelet agent) should be offered to all people who have had an acute MI (CG172). Aspirin should continue indefinitely, unless the patient is aspirin intolerant or they have an indication for anticoagulation (CG172). Clopidogrel should be offered as an antiplatelet treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment and people who have had a STEMI and received a bare-metal or drug-eluting stent. It should also be offered as a treatment option for at least 1 month and consider continuing for up to 12 months to people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent (CG172). NICE TA182 and TA236 make recommendations about the place in therapy of the oral antiplatelets, prasugrel and ticagrelor, respectively.

The second antiplatelet agent should be continued for up to 12 months in people who have had a STEMI and who received coronary artery bypass graft (CABG) surgery (CG172).

Treatment with rivaroxaban should be started as soon as possible after stabilisation of the ACS event.

Rivaroxaban – how may it change the existing pathway?

There remains a residual risk of further ACS events despite treatment with currently available antiplatelet therapy, which may be attributed to higher thrombin levels after an acute coronary event (Merlini *et al.* 1994; Ardissino *et al.* 2003). Platelet aggregation and the coagulation system are the two major mechanisms through which a thrombus is formed. Thrombin generation plays an important role for both mechanisms of clot formation. Low dose rivaroxaban offers a novel mechanism of action by blocking the thrombin generation after ACS (Xa is an essential part of prothrombinase complex). This is complementary to antiplatelets and targets the dual pathway to thrombus formation.

Hamm et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal (2011) 32, 2999–3054

NICE CG94. Unstable angina and NSTEMI. The early management of unstable angina and non-ST-segment-elevation myocardial infarction. March 2010.

CG172 MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. November 2013

NICE TA182 - Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. October 2009.

NICE TA236 - Ticagrelor for the treatment of acute coronary syndromes. October 2011.

Merlini PA, Bauer KA, Oltrona L et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. Circulation 1994;90:61–68.

Ardissino D, Merlini PA, Bauer KA et al. Coagulation activation and long-term outcome in acute coronary syndromes. Blood 2003;102:2731–2735.

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

As highlighted in section 2.1, there remains a residual risk of further ACS events despite treatment with currently available antiplatelet therapy, which may be attributed to higher thrombin levels after an acute coronary event.

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

The main comparator is standard of care antiplatelet therapy. In the UK, this is typically aspirin in combination with clopidogrel.

Rivaroxaban is recommended in combination with antiplatelet therapy – i.e. aspirin alone or aspirin plus a thienopyridine, usually clopidogrel. The decision to use aspirin alone or dual antiplatelet therapy should be determined by the treating physician. Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

The majority of patients randomised to rivaroxaban/ placebo in the pivotal trial (ATLAS ACS 2 TIMI 51), received dual antiplatelet therapy of aspirin with a thienopyridine (93%), with a small number of patients received aspirin alone (7%). As such, for those patients who are not suitable for dual antiplatelet therapy with aspirin and clopidogrel, aspirin alone is a comparator.

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

Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours. Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data.

2.9 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.

Rivaroxaban, co-administered with aspirin ± clopidogrel will most likely be initiated in secondary care by cardiologists. After discharge from hospital, subsequent doses of rivaroxaban could be prescribed in primary care.

Rivaroxaban is administered at a fixed dose and there is no requirement for routine monitoring of coagulation parameters during treatment. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

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

There are no additional infrastructure requirements as a result of the introduction of rivaroxaban in this indication.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Bayer is not aware of any issues relating to inequalities.

3.1.2 How has the analysis addressed these issues?

Bayer is not aware of any issues relating to inequalities.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Bayer considers that rivaroxaban is innovative for the secondary prevention of atherothrombotic events in ACS. Current standard practice focuses on the use of antiplatelets for secondary prevention. However, there remains a residual risk of further ACS events despite treatment with currently available antiplatelet therapy, which may be attributed to higher thrombin levels after an acute coronary event. Platelet aggregation and the coagulation system are the two major mechanisms through which a thrombus is formed. Thrombin generation plays an important role for both mechanisms of clot formation. Low dose rivaroxaban offers a novel mechanism of action by blocking the thrombin generation after ACS (Xa is an essential part of prothrombinase complex). This is complementary to antiplatelets and targets the dual pathway to thrombus formation.

Factor Xa inhibitors are currently used parenterally (e.g. fondaparinux) in the acute management of ACS. It will be the first time that an oral Factor Xa inhibitor will be used in the secondary prevention of ACS through inhibition of thrombin generation and therefore represents a "step-change" in management.

It is hypothesised that addition of rivaroxaban, with a complementary mechanism of action, to standard care will further reduce the risk of subsequent events such as cardiovascular death, MI and stroke.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Not applicable.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with acute coronary syndrome with elevated cardiac biomarkers (STEMI and NSTEMI)	Adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers	Essentially the same but wording as per SPC
Intervention	Rivaroxaban (in combination with aspirin or with aspirin and a thienopyridine [clopidogrel])	Rivaroxaban (in combination with aspirin or with aspirin and a thienopyridine [clopidogrel])	-
Comparator(s)	• clopidogrel with aspirin • aspirin alone for people for whom clopidogrel is considered unsuitable	• clopidogrel with aspirin • aspirin alone for people for whom clopidogrel is considered unsuitable	-
Outcomes	The outcome measures to be considered include: • death from any cause • non-fatal cardiovascular events • incidence of revascularisation procedures • adverse effects of treatment (including bleeding events) • health-related quality of life.	The outcome measures to be considered include: • death from any cause • non-fatal cardiovascular events • incidence of revascularisation procedures • adverse effects of treatment (including bleeding events) • health-related quality of life **In addition, Bayer will present data (subject to availability) on the following outcomes:** • **Cardiovascular mortality** • **Stent thrombosis**	Cardiovascular mortality and stent thrombosis are considered to be important outcomes in ACS
Economic analysis	The reference case stipulates that the cost effectiveness of	The cost effectiveness of rivaroxaban will be presented in terms of the incremental cost	-

	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. Costs will be considered from an NHS and Personal Social Services perspective.	per quality-adjusted life year. The time horizon used in the base case of the model will be lifetime. Costs will be considered from an NHS and Personal Social Services perspective.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: people with NSTEMI, people with STEMI; people with diabetes mellitus; people who received prior primary PCI and people who did not receive prior primary PCI in the acute phase of management. Guidance will only be issued in accordance with the marketing authorisation.	No subgroup data will be considered in the submission	The licenced population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically sound as the trial was not powered to draw conclusion about (non-pre-specified) subgroups of subgroups.
Special considerations, including issues related to equity or equality	N/A	-	-

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 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 10.2, appendix 2.

The following strategies were used to retrieve relevant published and unpublished clinical data concerning rivaroxaban for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.).

Information sources

Databases

MEDLINE® (including Medline In-process), EMBASE® and the Cochrane Library (CENTRAL and CDSR) were searched in March 2014 to identify potentially eligible trials from published sources.

Search strategies included combinations of both subject index headings and free text terms and synonyms for 'rivaroxaban' in combination with 'acute coronary syndrome'.

Study design filters for the identification of randomised controlled trials (RCTs) were applied, and the searches were limited to human and English language publications. Full details of the search strategies are reported in Appendix 2.

Conference proceedings

Conference proceedings were hand searched to retrieve the latest studies, which were not yet been published in journals as full text articles or to supplement results of previously published studies. Abstracts from the following three conference proceedings were searched:

- American Heart Association (AHA) Scientific Sessions (2012-2013)
- European Society of Cardiology (ESC) (2013)
- American College of Cardiology (ACC) (2013)

Full details of the search strategies are reported in Appendix 2.

Records identified through other sources

The bibliographic reference lists of relevant systematic reviews and meta-analyses were also searched for relevant RCTs that were not identified in the literature database searches.

Relevant clinical evidence held by the manufacturer in the form of trial protocols, clinical study reports, and correspondence with regulatory bodies was included where appropriate to supplement the published data.

6.2 Study selection

6.2.1 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.

Publications were to be included if they met the eligibility criteria as outlined in Table 1

Table 1 Eligibility criteria used in clinical review

	Clinical effectiveness	**Rationale/comments**
Inclusion criteria	**Population** • Adults initially hospitalised with ACS (unstable angina, STEMI, or NSTEMI) who are managed for secondary prevention of their ACS event	Consistent with the NICE scope
	Interventions • Rivaroxaban	
	Comparator • Any	All RCTs evaluating rivaroxaban were included irrespective of the comparator
	Outcomes • Clinical (efficacy and safety), patient-reported outcomes	The scope specifies the following outcome measures for consideration: • death from any cause • non-fatal cardiovascular events • incidence of revascularisation procedures • adverse effects of treatment (including bleeding events) • health-related quality of life

	Clinical effectiveness	Rationale/comments
	Study design • Randomised controlled prospective clinical trials • Long-term follow-up studies of RCTs (e.g., open-label follow-up of randomised clinical trials)	RCTs are the gold standard of clinical evidence, minimising the risk of confounding factors and allowing the comparison of the relative efficacy of the interventions.
	Language restrictions • English language	It was expected that the majority of publications of interest to this review were in English language and restricting to such publications is unlikely to exclude useful information
Other considerations	**Sub-groups of interest** • Patients with unstable angina, NSTEMI, and STEMI • Patients with baseline risk of subsequent events • Patients with diabetes mellitus • Patients who received prior primary percutaneous coronary intervention (PCI) • Patients who did not receive prior primary PCI in the acute phase of management	Consistent with the NICE scope
Exclusion criteria	**Population** • Patients with stable angina, or other CV disease that is not ACS • Primary prevention of ACS (mainly relevant for studies with aspirin) • Children • Mixed populations of stable and unstable angina, which do not present data for unstable angina separately	

	Clinical effectiveness	Rationale/comments
	Interventions **Interventions other than rivaroxaban including the following:** • Aspirin • Clopidogrel • Prasugrel • Ticagrelor • Warfarin • Ticlopidine • Vitamin K antagonist • Phenprocoumon • Acute and subacute therapy for ACS (i.e., study intervention period < 30 days after discharge and/or with outcomes measured only at < 30 days after discharge) • Therapies used in the acute phase of ACS management, e.g. (this is not an exhaustive list): • Bivalirudin • Fondaparinux • Enoxaparin • Otamixaban • Streptokinase, alteplase, and other "ase" products that are used for acute management	
	Outcomes • Biochemical or immunological endpoints	
	Study design **Study designs other than RCTs including the following:** • Preclinical studies • Phase 1 studies • Non-comparative phase 2 trials • Prognostic studies • Retrospective studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Single-arm studies • Genetic studies • Non–randomised controlled clinical trials • Prospective observational studies (e.g., phase 4 studies)	Other study designs were not considered as sufficient RCT evidence is available for rivaroxaban in the ACS treatment setting
	Language restrictions • Non-English language	

Validity assessment

The published data identified via the search strategy was screened for inclusion and extraction. Inclusion/exclusion criteria guidelines were developed to ensure that all decisions regarding the inclusion and exclusion of studies were consistent.

Screening of the published data was undertaken in two steps:

- Initial screening (1st pass) - The title and abstracts of all studies was initially screened to identify a list of potentially relevant studies
- Detailed screening (2nd pass) - A detailed screening of the full text versions of the potentially relevant studies was then undertaken to identify the final list of included studies

Two independent reviewers screened all citations and full-text papers and any discrepancies in their decisions were resolved by a third reviewer.

All data collection activities were undertaken within a systematic review database (SRDB), which ensures every study can be easily tracked through the review process, with each decision for inclusion/exclusion recorded.

6.2.2 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.

Databases

As shown in Figure 1, 562 records were identified by the database searches. After the removal of 26 duplicates, the titles and abstracts of 536 records were reviewed, of which 518 were subsequently excluded. A total of 518 citations were excluded based on screening of abstracts and titles as they were reviews/editorials (n=327), animal/in-vitro studies (n=2) involved a non-ACS population (n=99), were not RCTs (n=58), or did not include rivaroxaban (n=32), The full-text of remaining 18 articles were assessed for eligibility from which two articles were excluded as they were review/editorial.

In total, 16 publications relating to 2 relevant RCTs (one Phase II (ATLAS-ACS 2 TIMI 46)(1), one Phase III (ATLAS-ACS 2 TIMI 51)(2;3)) met our inclusion criteria and were accepted for this review, please see section 6.2.4 for the complete list of relevant RCTs.

Conference proceedings

Details of conferences searched along with search terms are provided in Appendix 2. Seven abstracts were included after the screening of the full titles/abstracts. However, these abstracts were

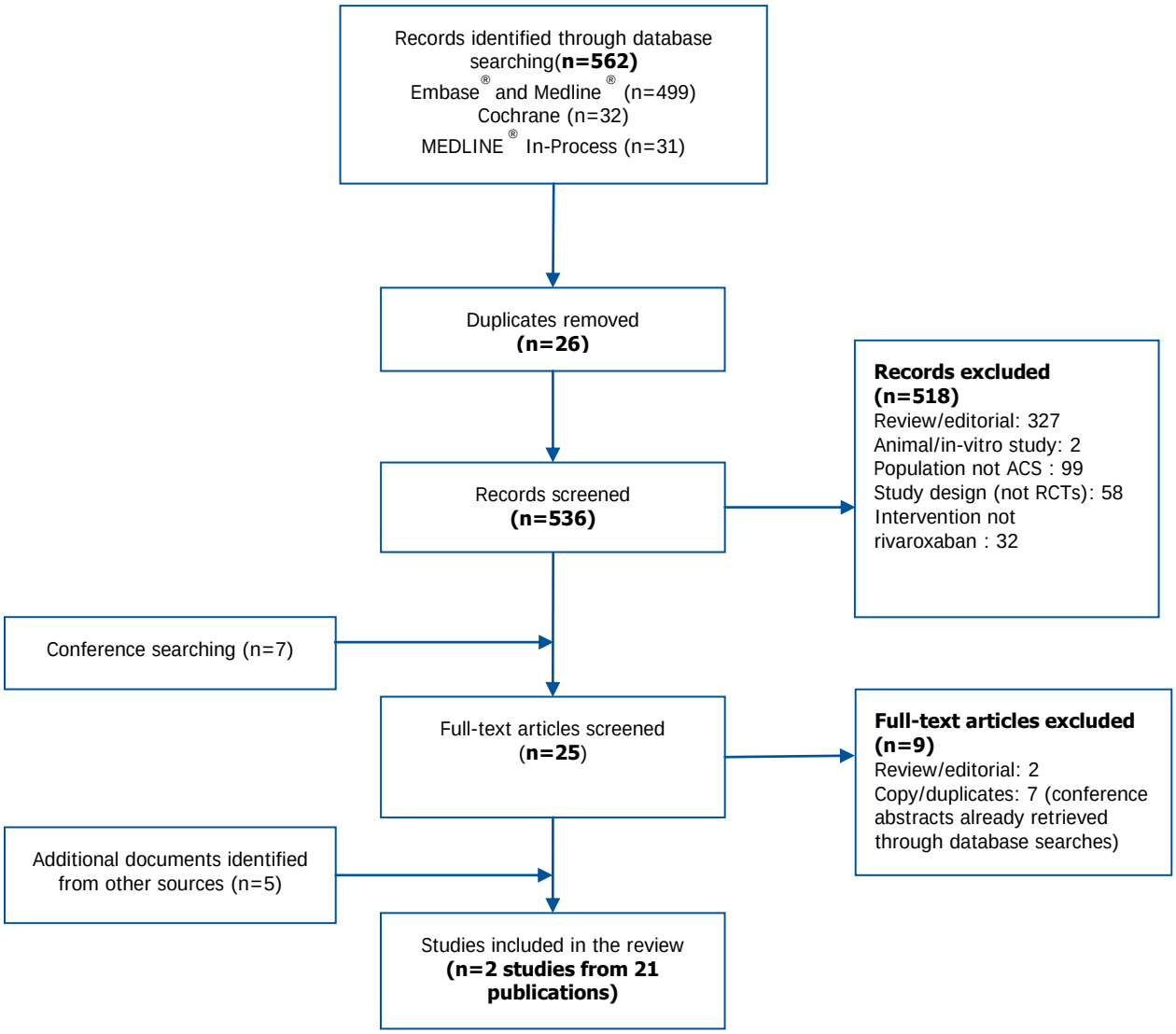
identified as duplicates which were already retrieved in the database searches. Therefore, there were no additional inclusions from conference search.

Records identified through other sources

The manual reference list review of, relevant systematic reviews and meta-analyses did not identify any further articles.

The protocol(4) and clinical study report(5) were included for the Phase III trial, along with pertinent correspondence from discussions with the US Food and Drug Administration (FDA).(6-8)

Figure 1 **PRISMA flow diagram of the numbers of studies included and excluded at each stage**



6.2.3 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.

Presented data from the Phase III (ATLAS-ACS 2 TIMI 51) trial have been drawn from 19 sources including five journal articles and nine conference abstracts. In addition, information from the protocol(4), clinical study report(5), and correspondence with regulatory bodies(6-8) has been included where appropriate to supplement the published data. These inclusions are referenced accordingly.

Table 2 Explanations for studies included in the review

Trial name	Publication	Publication type	Data extracted/other comments
ATLAS ACS TIMI 46	Mega 2009(1)	Full publication	Yes; primary publication
	Geller 2013(9)	Full publication	No; data covered in the primary full publication
ATLAS ACS TIMI 51	Mega 2012(3)	Full publication	Yes; primary publication
	Gibson 2011(2)	Full publication	Yes
	Mega 2013(10)	Full publication	Yes
	Mega 2013(11)	Full publication	Yes
	Cavender 2013(12)	Conference abstract	Yes
	Gibson 2013(13)	Full publication	Yes
	Gibson 2011(14)	Conference abstract	No; data covered in the primary full publication
	Gibson 2012(15)	Conference abstract	
	Mega 2012(16)	Conference abstract	
	Arora 2013(17)	Conference abstract	
	Pride 2012(18)	Conference abstract	No; subgroup data for for rivaroxaban not available
	O'Donoghue 2013(19)	Conference abstract	No; this abstract included data for patients who were/ were not on proton pump inhibitor, this subgroup is not of interest per the NICE scope
	Gibson 2012(20)	Conference abstract	No; AE data reported in NNT format (not relevant for the scope)
	Mega 2013(21)	Conference abstract	Yes

An overview of all Bayer-sponsored phase 2 and 3 rivaroxaban trials relevant to Acute Coronary Syndrome (ACS) is provided in Table 2.

ATLAS ACS TIMI 46 compared rivaroxaban once-daily dosing with twice-daily dosing within the same total daily dose range (5-20mg), and was a safety and efficacy study to determine the most favourable dose and dosing regimen of rivaroxaban for a phase III study.

The phase III ATLAS ACS 2 TIMI 51 study was designed to determine whether rivaroxaban in addition to standard care antiplatelet therapy reduces the risk of composite of CV death, MI or stroke in patients with a recent ACS event compared with placebo.

Table 3 Overview of rivaroxaban trials in ACS

Trial name	Bayer study ID	Phase	Design	Publications	
				Primary reference	Secondary reference
ATLAS ACS TIMI 46	11898	2	Dose escalation Once & twice daily rivaroxaban regimes (range 5-20mg / day) vs. placebo in patients with recent ACS receiving standard of care treatment (aspirin +/- thienopyridine)	Mega 2009(1)	Geller 2013(9)
ATLAS ACS 2 TIMI 51	13194	3	2 x rivaroxaban regimes (2.5mg bd or 5mg bd) vs. placebo in patients with recent ACS receiving standard of care treatment (aspirin +/- thienopyridine)	Gibson 2011(2) [Rationale & design] Mega 2012 (3) [Results] Clinical Study Report (5) Study protocol(4) FDA communications(6-8)	(Gibson 2011(14); Mega 2013(10); Mega 2013(11); Gibson 2013(13); Cavender 2013(12); Pride 2012(18); O'Donoghue 2013(19); Mega 2012(16); Gibson 2012(20); Mega 2013(21); Gibson 2012)(15)

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table 4 List of relevant RCTs

Trial name	Intervention	Comparator	Population	Primary reference
ATLAS ACS TIMI 46	Rivaroxaban 5, 10, or 20mg once daily ***OR*** 5, 10, or 20mg total daily dose given bd, plus standard care antiplatelet therapy* ‡	Placebo plus standard care antiplatelet therapy*	Recent Acute Coronary Syndrome	Mega et al 2009(1)
ATLAS ACS 2 TIMI 51	Rivaroxaban 2.5 or 5mg twice-daily plus standard care antiplatelet therapy*	Placebo plus standard care antiplatelet therapy*	Recent Acute Coronary Syndrome	Mega et al 2012 (3)

*Standard care antiplatelet therapy was aspirin with or without a thienopyridine
‡ In the stratum of patients who were given aspirin plus a thienopyridine (investigator decision), a further dose was tested – 15mg once daily and 15mg total daily dose given bd

6.2.5 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.

ATLAS ACS 2 TIMI 51 compares rivaroxaban added to standard antiplatelet therapy with placebo / standard antiplatelet therapy in a relevant population and dosing regimen, which would be applicable to the UK population and decision problem in this submission. *Note: The study evaluates 2.5mg bd and 5mg bd doses of rivaroxaban. Based on the study results, only the 2.5mg bd dosing (i.e.'low dose rivaroxaban') is being taken forward for licensing in ACS.*

6.2.6 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.

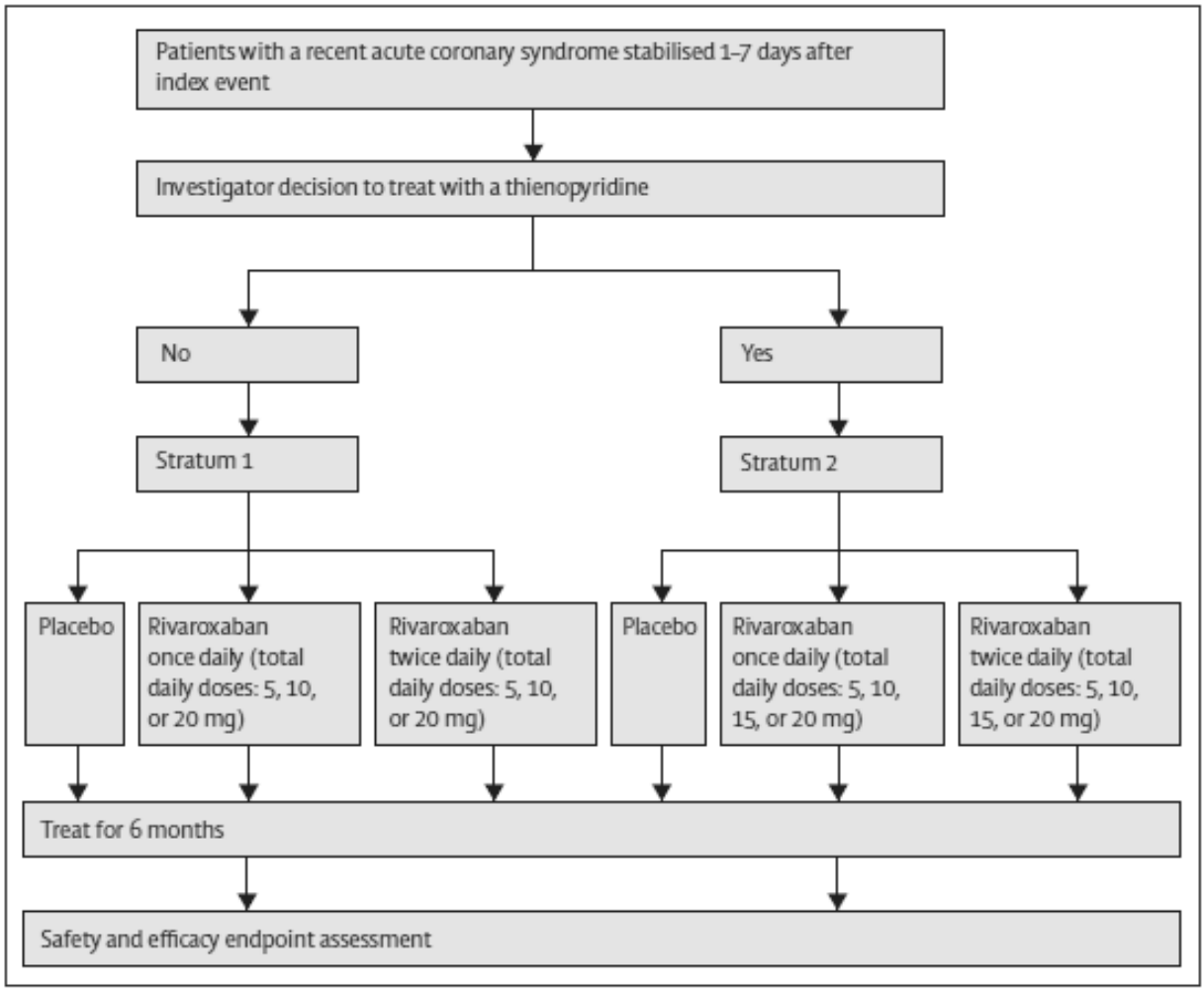
One phase II study identified in the table of relevant RCTs (

Table 4) is excluded from further discussion since it was primarily a dose-escalation study to inform on dose selection for the larger ATLAS ACS 2 TIMI 51 phase III study. However, a brief overview is presented below.

ATLAS ACS TIMI 46(1)

ATLAS ACS TIMI 46 was a phase II dose-finding efficacy and safety study with randomisation stratified by the intention to use thienopyridine as standard care in addition to low dose aspirin (ASA). Patients were randomised to placebo or rivaroxaban, with a range of total daily doses (TDD) and dosing regimens of rivaroxaban being tested (see Figure 2 below).

Figure 2 ATLAS ACS TIMI 46 Study design (adapted from(1))



As can be seen from the study design (Figure 2), the phase II study included a 6-month double-blind treatment period, and as such, will be described briefly here, as it provides some supportive evidence on the efficacy and safety of rivaroxaban in patients with recent ACS.

A total of 3491 patients hospitalised with ACS were randomised to the various rivaroxaban TDD groups of 5mg, 10mg, 15mg, and 20mg, administered as either once-daily or twice-daily regimens.

The primary safety endpoint was clinically significant bleeding (Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding, or bleeding requiring medical attention). The primary efficacy endpoint was the time to first episode of death, MI, stroke or severe recurrent ischaemia requiring revascularisation (SRIR) up to 6 months from enrolment and the main secondary efficacy endpoint was time to death, MI or stroke up to 6 months from enrolment.

Compared with placebo, rivaroxaban was associated with a trend toward a reduction in the incidence of the primary efficacy end point, the composite of death, MI, stroke, or severe recurrent ischemia requiring revascularisation (7.0% [79/1160] with placebo vs 5.6% [126/2331] with rivaroxaban, HR 0·79 [95% CI 0·60–1·05] P=0.10) and a significant reduction in the secondary end point, the composite of death, MI, or stroke (5.5% [62/1160] with placebo vs 3.9% [87/2331] with rivaroxaban, HR=0.69, [95% CI 0.50-0.96] P=0.027). The results by dose are presented in Table 5 and Table 6.

The results also demonstrated a dose-dependent increase in bleeding events, by rivaroxaban when compared with placebo (Table 7).

The 2 lowest doses of rivaroxaban (2.5 and 5.0 mg orally twice a day) were associated with a trend toward improved efficacy. In an exploratory analysis of death, MI, stroke, or TIMI major bleeding, rivaroxaban (2.5 mg twice daily or 5 mg twice daily) as compared with placebo resulted in an HR of 0.72 (0.46-1.12) in the entire cohort, 0.59 (0.30-1.16) in stratum 1, and 0.85 (0.47-1.54) in stratum 2.

Based on the trend for efficacy and the relative safety of these 2 lowest doses in the phase 2 study, the 2.5 and 5.0 mg twice a day dosing were selected for further assessment at phase 3. Twice daily compared with once daily dosing was selected based on lower peaks and higher troughs observed in pharmacokinetic profiling of rivaroxaban.

Table 5

ATLAS ACS TIMI 46 Primary efficacy endpoint (Death, MI, stroke or SRIR) categorised by Total Daily Dose(1)

	Rivaroxaban				Pooled Placebo
	Once-daily dosing		Twice-daily dosing		
	KM rate (n/N)	vs. pooled placebo HR (95% CI)	KM rate (n/N)	vs. pooled placebo HR (95% CI)	KM rate (n/N)
All strata*					
5mg	8.7% (13/155)	1.01 (0.56-1.83)	5.3% (8/153)	0.60 (0.29-1.25)	7.0% (79/1160)
10mg	5.3% (27/529)	0.77 (0.50-1.20)	4.4% (22/527)	0.63 (0.39-1.01)	
20mg	5.2% (15/304)	0.69 (0.40-1.20)	6.5% (19/307)	0.87 (0.53-1.44)	
Stratum 1					
5mg	9.4% (7/77)	0.67 (0.30-1.52)	6.6% (5/77)	0.46 (0.18-1.17)	13.9% (34/253)
10mg	8.3% (8/99)	0.60 (0.28-1.29)	8.7% (8/97)	0.61 (0.28-1.32)	
20mg	4.0% (3/78)	0.27 (0.08-0.88)	8.0% (6/80)	0.54 (0.22-1.28)	
Stratum 2#					
5mg	7.8% (6/78)	1.55 (0.66-3.64)	4.0% (3/76)	0.78 (0.24-2.52)	5.1% (45/907)
10mg	4.6% (19/430)	0.90 (0.53-1.54)	3.4% (14/430)	0.66 (0.36-1.20)	
15mg	6.3% (11/178)	1.24 (0.64-2.40)	6.5% (11/178)	1.28 (0.66-2.48)	
20mg	5.6% (12/226)	1.07 (0.57-2.03)	6.0% (13/227)	1.17 (0.63-2.17)	

Table 6

ATLAS ACS TIMI 46 Secondary efficacy endpoint 1 (Death, MI, stroke) categorised by Total Daily Dose(1)

	Rivaroxaban				Pooled Placebo
	Once-daily dosing		Twice-daily dosing		
	KM rate (n/N)	vs. pooled placebo HR (95% CI)	KM rate (n/N)	vs. pooled placebo HR (95% CI)	KM rate (n/N)
All strata*					
5mg	6.7% (10/155)	0.90 (0.46-1.78)	4.0% (6/153)	0.52 (0.23-1.22)	5.5% (62/1160)
10mg	3.9% (20/529)	0.74 (0.45-1.22)	3.0% (15/527)	0.56 (0.32-0.98)	
20mg	2.8% (8/304)	0.46 (0.22-0.95)	4.1% (12/307)	0.69 (0.37-1.28)	
Stratum 1					
5mg	9.4% (7/77)	0.80 (0.35-1.82)	6.6% (5/77)	0.54 (0.21-1.40)	11.9% (29/253)
10mg	7.3% (7/99)	0.62 (0.27-1.41)	6.7% (6/97)	0.54 (0.22-1.29)	
20mg	2.7% (2/78)	0.21 (0.05-0.88)	6.7% (5/80)	0.52 (0.20-1.36)	
Stratum 2#					
5mg	4.0% (3/78)	1.04 (0.32-3.39)	1.4% (1/76)	0.35 (0.05-2.58)	3.8% (33/907)
10mg	3.2% (13/430)	0.84 (0.44-1.59)	2.2% (9/430)	0.58 (0.28-1.21)	
15mg	4.0% (7/178)	1.07 (0.47-2.42)	5.3% (9/178)	1.42 (0.68-2.97)	
20mg	2.8% (6/226)	0.73 (0.31-1.74)	3.2% (7/227)	0.86 (0.38-1.94)	

Table 7 ATLAS ACS TIMI 46 Primary Safety Endpoint – Clinically significant bleeding (TIMI major, TIMI minor or Bleeding requiring medical attention) categorised by Total Daily Dose(1)

	Rivaroxaban				Pooled Placebo
	Once-daily dosing		Twice-daily dosing		
	KM rate (n/N)	vs. pooled placebo HR (95% CI)	KM rate (n/N)	vs. pooled placebo HR (95% CI)	KM rate (n/N)
All strata*					
5mg	7.4% (11/155)	2.73 (1.38-5.37)	4.8% (7/152)	1.71 (0.76-3.85)	3.3% (37/1153)
10mg	10.8% (55/527)	3.35 (2.21-5.09)	11.0% (55/519)	3.36 (2.21-5.09)	
20mg	16.0% (47/301)	5.32 (3.46-8.18)	14.6% (43/302)	4.8 (3.09-7.45)	
Stratum 1					
5mg	2.9% (2/77)	1.67 (0.31-9.14)	1.4% (1/77)	0.81 (0.09-7.23)	1.7% (4/252)
10mg	7.6% (7/99)	4.74 (1.39-16.19)	5.5% (5/96)	3.40 (0.91-12.65)	
20mg	10.6% (8/78)	6.69 (2.01-22.21)	10.7% (8/79)	6.43 (1.94-21.37)	
Stratum 2#					
5mg	11.7% (9/78)	3.28 (1.57-6.84)	8.2% (6/75)	2.17 (0.91-5.18)	3.8% (33/901)
10mg	11.6% (48/428)	3.21 (2.06-5.00)	12.2% (50/423)	3.34 (2.15-5.19)	
15mg	13.1% (23/178)	3.69 (2.17-6.29)	12.3% (21/175)	3.41 (1.97-5.89)	
20mg	17.8% (39/223)	5.12 (3.22-8.14)	16.0% (35/223)	4.56 (2.83-7.33)	

Notes for Tables: HR=hazard ratio; KM=Kaplan-Meier; *The KM rates in the All category do not take into account stratification; # The 15mg dose tier was tested only in Stratum 2

List of relevant non-RCTs

6.2.7 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 studies of this nature were considered relevant to the decision problem.

6.3 Summary of methodology of relevant RCTs

6.3.1 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. When there is more than one RCT, the information should be tabulated.

ATLAS-ACS 2 TIMI 51: The Second Trial of Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome – *[Also known as study 13194]* **(2;3)**

The **ATLAS-ACS 2 TIMI 51** study was designed to determine whether rivaroxaban, in addition to standard care antiplatelet therapy, reduces the risk of the composite of CV death, MI, or stroke in patients with a recent ACS event compared with placebo. In the phase III study, involving over 15,500 participants worldwide, the efficacy and safety of oral rivaroxaban was compared with placebo in addition to standard care antiplatelet therapy i.e. aspirin (ASA) with or without thienopyridine. All patients enrolled in the study were stratified by the intention to use thienopyridine in addition to ASA (Stratum 1 - ASA only; Stratum 2 - ASA plus a thienopyridine). Enrolment in strata was neither capped nor fixed and was dependent on regional medical practice and investigator choice.

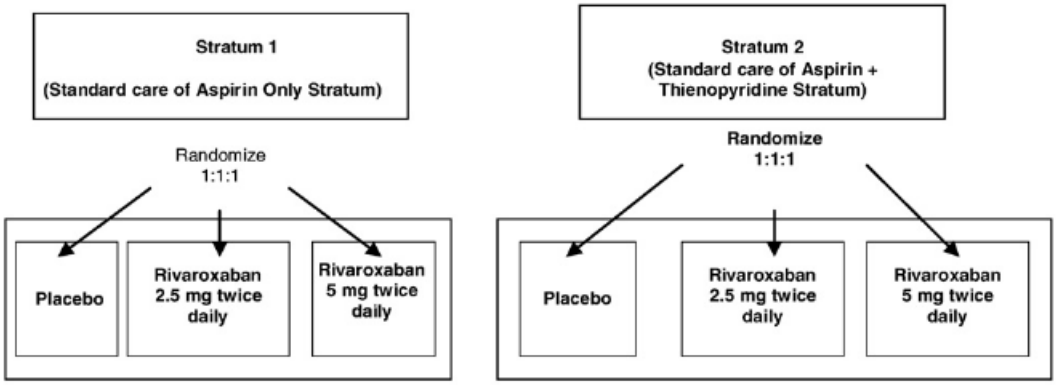
The primary safety objective of ATLAS-ACS 2 TIMI 51 was the occurrence of non-CABG TIMI major bleeding events. Using results of these key outcomes, the 'net clinical benefit' or balance between improved ischaemic risk and bleeding risk could be ascertained.

Key features of the ATLAS-ACS 2 TIMI 51 study are summarised in Table 8 and Figure 3.

Table 8 Key features of ATLAS-ACS 2 TIMI 51 in the reduction of cardiovascular events after recent Acute Coronary Syndrome (ACS)(3;5;22)

	Treatments (number of patients)	Countries	Patient type	Primary endpoints
ATLAS-ACS 2 TIMI 51	**All strata** **Rivaroxaban + standard care (n=10,350)** 2.5mg bd (n=5,174) or 5mg bd (n=5,176) **vs.** **Placebo + standard care (n=5,176)** Stratum 1 (n=1,053) **Rivaroxaban + ASA** 2.5mg bd (n=349) or 5mg bd (n=349) **vs.** **Placebo + ASA** (n=355) Stratum 2 (n=14,473) **Rivaroxaban + ASA + thienopyridine** 2.5mg bd (n=4,825) or 5mg bd (n=4,827) **vs.** **Placebo + ASA + thienopyridine** (n=4,821)	766 sites across 44 countries. ▪ **Asia Pacific:** China, India, Japan, South Korea, Malaysia, Philippines, Thailand ▪ **Eastern Europe:** Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Ukraine ▪ **South America:** Argentina, Brazil, Chile, Colombia, Mexico ▪ **North America:** Canada, United States ▪ **Western Europe:** Belgium, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Greece, United Kingdom. ▪ **Others:** Australia, Egypt, Israel, Morocco, New Zealand, Tunisia, Turkey	Hospitalisation due to symptoms suggestive of an ACS, in whom an ST-segment elevation myocardial infarction (STEMI), a non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina had been diagnosed. If patients were <55 years of age, diabetes mellitus or a prior MI were required in addition to the presenting ACS event.	**Efficacy** Composite of death from cardiovascular causes, myocardial infarction (MI), or stroke (ischaemic, haemorrhagic, or stroke of uncertain cause) **Safety** Thrombolysis in myocardial infarction (TIMI) major bleeding not related to coronary-artery bypass grafting (CABG).

Figure 3 ATLAS-ACS 2 TIMI 51 study design. From reference(2)



Methods

6.3.2 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.

Design

ATLAS-ACS 2 TIMI 51 was an international, multicentre, prospective, randomised, double-blind, placebo-controlled, event-driven phase III study designed to evaluate the efficacy and safety of twice-daily rivaroxaban, at doses of 2.5mg and 5mg, as adjunctive therapy in patients with a recent acute coronary syndrome (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], or unstable angina [UA]). The study design is a scientifically rigorous approach for evaluating efficacy and safety and the design, rationale and results have been fully published(2;3).

The study was conducted between November 2008 and September 2011, during which time 15,526 patients were randomised to treatment (rivaroxaban 2.5mg bd, n=5,174; rivaroxaban 5mg bd, n=5,176; placebo, n=5,176)(3).

The study had three phases, including 1) a 6-day screening phase; 2) a double-blind treatment phase; and 3) a follow-up phase. Patients were not to be randomised in the 24 hours immediately following hospitalisation for the index ACS event(2;3).

Enrolled patients continued treatment (unless prematurely withdrawn) until the pre-specified number of primary efficacy endpoint 'events' had occurred (i.e. ≥ 983 primary efficacy endpoints accrued across both strata, and at least 728 primary efficacy endpoints in Stratum 2). The date accrual of these target 983 primary efficacy endpoint events was reached, is termed the 'global treatment end date'. At this point, patients were to continue taking study drug until they had their End of Treatment (EOT) visit. Approximately 30 days following the EOT visit, a follow-up (End of Study (EOS)) contact (either in person or by telephone) was performed(2;3).

Premature discontinuation of study treatment or withdrawal from the study occurred upon safety concerns, pregnancy, patient request, abnormal liver function (ALT ≥ 5x the upper limit of normal (ULN) with a normal baseline confirmed within 5 days or ALT > 3x the ULN and total bilirubin >2x the ULN), intracranial bleeding, ASA therapy was discontinued permanently or for greater than 28 consecutive days, bleeding into a critical organ including intraocular bleeding, calculated creatinine clearance was <15 mL/min confirmed on retesting within 5 days, the patient had ischemic stroke or TIA and in the opinion of the treating physician needed to receive ASA plus thienopyridine - patients receiving ASA only could continue the study drug, patient had been unblinded to treatment.

Patients who discontinued study drug early completed an end-of-treatment/ early withdrawal visit

[redacted] Thereafter, the patient was encouraged to return for all subsequent site visits until the study ended (except for patients where informed consent was withdrawn).

[redacted]

Where possible, patients who experienced the primary or secondary efficacy endpoint events (except for death) continued to receive blinded study drug and complete all assessments at all scheduled visits(2).

Duration

The duration of the study treatment period depended on the time required to accrue at least 983 primary efficacy endpoint events across both strata and at least 728 primary efficacy events in stratum 2. As a result, the time on study drug varied from patient to patient depending upon when they were enrolled into the study. The anticipated longest duration of study treatment was 33 months, possibly extending to a maximum of 36 months depending on rate of patient recruitment and primary efficacy endpoint rates(3;5). The median time on treatment was 13 months and overall treatment duration was up to almost 3 years(23).

Method of randomisation

Randomisation was stratified by investigator intention to use thienopyridine (clopidogrel or ticlopidine) in addition to ASA (Stratum 1 – ASA only; Stratum 2 – ASA plus a thienopyridine). Enrolment in strata was neither capped nor fixed and was dependent on regional medical practice.

Within each stratum, patients were randomised in a 1:1:1 ratio to receive rivaroxaban 2.5mg twice daily, rivaroxaban 5mg twice daily, or placebo twice daily(3).

Randomisation was performed centrally by Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) using a computer-generated randomisation schedule prepared by the sponsor before the study. The IVRS/IWRS assigned a unique patient number and treatment code and corresponding study drug kits for the duration of study.

Blinding

A double-blind design was chosen to minimise bias during data collection and interpretation of clinical events.

The investigator was not provided with randomised treatment codes and was therefore unaware, as was the patient, as to treatment assigned to each patient. Randomisation codes were maintained within the IVRS / IWRS which, in an emergency, had the functionality to allow the investigator to break the blind for an individual patient(3).

A clinical-events committee (CEC) whose members were unaware of study group/treatment assignments adjudicated all components of the key efficacy and safety end points(3).

Intervention and comparator

Enrolled patients were randomised to one of three treatment groups after being stratified on the basis of whether they were to receive thienopyridine in addition to ASA as standard care (Stratum 1 – ASA only; Stratum 2 – ASA plus a thienopyridine). According to treatment assignment, study drug or placebo tablets were taken orally, twice daily, in the morning and evening (approximately 12 hours apart):

1. '**Rivaroxaban 2.5mg group**' (n=5174) were given 2.5mg rivaroxaban twice daily and standard care treatment consisting of ASA +/- thienopyridine.

2. '**Rivaroxaban 5mg group**' (n=5176) were given 5mg rivaroxaban twice daily and standard care treatment consisting of ASA +/- thienopyridine.

3. '**Placebo group**' (n=5176) were given placebo tablets (identical to the rivaroxaban tablets) twice daily and standard care treatment consisting of ASA +/- thienopyridine.

Since ATLAS ACS 2 TIMI 51 was not intended to evaluate rivaroxaban in the acute care setting, study drug was to be initiated as soon as possible *after* stabilisation of the index ACS event – including completion of revascularisation procedures. The first dose of study drug could be no sooner than 4 hours after the final dose of intravenous unfractionated heparin (UFH), 2 hours after the final dose of bivalirudin, and 12 hours after the final dose of other intravenous or subcutaneous anticoagulants (e.g., enoxaparin or fondaparinux). Enrolment occurred within 7 days after hospital admission for ACS. The median time from the index event to randomisation was 4.7 days(3).

The rivaroxaban dose and dosing regimen selections were based on the results of the phase II study ATLAS ACS TIMI 46. The rationale for studying 2 doses of rivaroxaban at phase III was to further develop understanding of which rivaroxaban dose gives a better balance of efficacy and safety.

The use of clopidogrel plus ASA in patients with ACS is recommended by NICE clinical guidelines [CG94, CG48 and CG172] (24-26) and is considered standard care in the UK following an ACS event. Thienopyridine treatment was clopidogrel or ticlopidine and dosage

followed national or local prescribing information. For clopidogrel, the daily maintenance dose was not to exceed 75 mg/day, and for ticlopidine, the daily maintenance dose was not to exceed 250 mg twice daily.

The ASA dose range (75 to 100 mg/day) is consistent with recommendations from major international cardiovascular organisations and societies(27) and also within the dosing recommended in NICE guidelines(24-26).

Study drug could be interrupted (temporarily discontinued) as necessary for invasive procedures or as medically needed (e.g., in the setting of a bleeding event or a required prohibited therapy), however, these interruptions were to be kept to the minimum period as much as possible, and could not exceed 28 consecutive days. If study drug was discontinued for longer than 28 days, the patient was withdrawn from the study.

Follow up

After screening and randomisation, all patients were seen at 4 weeks, at 12 weeks, and thereafter every 12 weeks(3).

At each visit, a clinical status review was performed. Information on any occurrence of endpoint events, adverse events, and/ or treatment discontinuations was recorded along with concomitant medications, and medical resource utilisation (MRU) data(3).

A quality of life assessment using the EQ-5D questionnaire was also performed in a subset of patients on day 1, at 4 weeks, 24 weeks, 48 weeks, 72 weeks, 96 weeks and at the 'End of Treatment / Early withdrawal visit'(3).

Liver function (ALT and total bilirubin) was assessed at 12 and 24 weeks and at EOT/ early withdrawal visit(3).

Haematology and clinical chemistry assessments were performed during screening, at day 1 and at 4 weeks(3).

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial.

Patients with recent ACS were selected as a population in which to study the effects of rivaroxaban, because 1) despite standard medical therapy (i.e. aspirin plus thienopyridine), patients remain at risk for recurrent cardiovascular events and 2) anticoagulants (warfarin or ximelagatran) combined with aspirin have shown improved CV outcomes after ACS(3;4).

Table 9 Eligibility criteria in the ATLAS-ACS 2 TIMI 51 study (3;4)

Trial no. (acronym): ATLAS-ACS 2 TIMI 51	
Inclusion criteria	**Exclusion criteria**
▪ Age≥ 18 years. Patients aged 18 to 54 years (inclusive) must also have either diabetes mellitus or a prior MI in addition to the presenting ACS event. ▪ Currently receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine (clopidogrel or ticlopidine) ▪ Recently hospitalised for symptoms suggestive of ACS that lasted at least 10 minutes at rest, and occurred 48 hours or less before hospital presentation or who developed ACS while being hospitalized for an indication other than ACS,and have a diagnosis of: -STEMI: elevation of ST-segment more than 0.1 millivolt (mV) in 2 or more continuous ECG leads, or new left bundle branch block, or ST-segment depression 0.1 mV or greater in 2 of the precordial leads V1-V4 with evidence suggestive of true posterior infarction, all with elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin) – NSTEMI: Transient ST-segment elevation, or ST-segment depression, or T-wave changes consistent with myocardial ischemia along with elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin) OR identification of a culprit lesion at coronary angiography demonstrating recent, active intracoronary atherothrombosis (for example, thrombus or an ulcerated plaque) – Unstable Angina with at least 1 of the following: – transient or persistent ST-segment deviation 0.1 mV or greater in 1 or more ECG leads – TIMI risk score of ≥4. ▪ Women must be postmenopausal (for at least 2 years), or surgically sterile, or if sexually active, be practicing an effective method of birth control	▪ Contraindication to anticoagulant therapy ▪ Any condition that would carry increased risk of bleeding e.g. active internal bleeding, clinically significant bleeding, bleeding at a noncompressible site or bleeding diathesis within 30 days of randomisation, platelet count <90,000/µL at screening, history of intracranial haemorrhage, major surgery, biopsy of a parenchymal organ, or serious trauma (including head trauma) within 30 days before randomisation, clinically significant gastrointestinal bleeding within 12 months before randomisation, an International Normalized Ratio (INR) known to be >1.5 at the time of screening, abciximab bolus or infusion within the past 8 hours, or an eptifibatide or tirofiban bolus or infusion within the past 2 hours before randomisation, or any other condition known to increase the risk of bleeding ▪ **Severe concomitant diseases such as:** ▪ Cardiogenic shock at the time of randomisation ▪ Ventricular arrhythmias refractory to treatment at the time of randomisation ▪ Calculated creatinine clearance <30 mL/min at screening ▪ Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis), or liver function test (LFT) abnormalities (confirmed with repeat testing) which would require study drug discontinuation, i.e. ALT >5 times the ULN or ALT >3 times the ULN plus total bilirubin >2 times the ULN ▪ Prior ischaemic stroke or transient ischaemic attack (TIA) (Excluded from Stratum 2) ▪ Prior haemorrhagic stroke ▪ Anaemia (i.e., haemoglobin <10 g/dL) at screening ▪ Known clinical history of HIV infection at screening ▪ Substance abuse (drug or alcohol) problem within the previous 6 months ▪ Any severe condition that would limit life expectancy to less than 6 months

▪ Women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening. ▪ Signed informed consent	▪ **General** ▪ Systemic treatment with strong CYP 3A4 and P-gp inhibitors ▪ Allergy or hypersensitivity to any component of rivaroxaban or placebo excipients ▪ Known aspirin allergy ▪ Atrial fibrillation or other condition requiring anticoagulation ▪ Use of disallowed therapies e.g. ASA doses >100mg/day after randomisation ▪ Received an investigational drug or used an investigational medical device within 30 days before the planned start of treatment, or are currently enrolled in an investigational study ▪ Anticipated need for chronic (more than 4 weeks) therapy with non-steroidal anti-inflammatory drugs (NSAIDs) ▪ Pregnancy or breast-feeding ▪ Previous completion or withdrawal from this study ▪ Any condition that, in the opinion of the investigator, would compromise the well-being of the patient or the study or prevent the patient from meeting or performing study requirements ▪ Employees of the investigator or study centre, with direct involvement in the proposed study or other studies under the direction of that investigator or study centre, as well as family members of the employees or the investigator

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

There were no notable imbalances in baseline demographic, medical history, or index event characteristics between treatment groups (see Table 10).

Of all randomised patients, 74.7% were men, and the mean age was 61.8 years (range 22 to 98 years). The majority of patients were white (73.5%).

Approximately 50% of all randomised patients had STEMI as the index diagnostic event. NSTEMI and unstable angina each comprised about 25% of the ACS index events for the presenting diagnosis.

Patients received standard of care for ACS. For the majority of patients (93%) this consisted of ASA plus a thienopyridine (Stratum 2); however, investigators had discretion to enrol patients who they intended to treat with ASA alone (Stratum 1). Initially it was estimated that approximately 15% of patients were to be enrolled into Stratum 1; during the course of the study, it became apparent that the usage of thienopyridine was more prevalent than expected and ultimately only 7% of all randomised patients were enrolled in Stratum 1.

The demographic and baseline characteristics were representative of a moderate-to-high-risk population of patients with ACS with the majority of all randomised patients having CV risk factors, such as hypertension (67.4%), diabetes mellitus (32.0%), history of MI (26.9%), or hypercholesterolaemia (48.6%). There were 60.5% patients who had a revascularisation procedure for the index event; the vast majority of these being percutaneous coronary intervention (PCI) (99.3%). Overall, 82.1% of patients had elevations in cardiac biomarkers at the index event. There was a low incidence of patients with prior ischaemic stroke (1.8%) and with prior TIA (0.9%) since the protocol excluded patients with a history of haemorrhagic stroke and patients with a history of ischaemic stroke or TIA were eligible only for randomisation in Stratum 1 (ASA only).

The demographic and baseline characteristics in Stratum 2 [redacted]

with those for All Strata.

Table 10 Baseline characteristics of patients participating in ATLAS-ACS 2 TIMI 51 (All randomised patients; ALL STRATA) (3)

Characteristic	Rivaroxaban		Placebo (N=5176)
	2.5mg twice daily (N=5174)	5mg twice daily (N=5176)	
Age			
Mean±S.D. (yr)	61.8±9.2	61.9±9.0	61.5±9.4
≥65yr (n[%])	1905 (36.8)	1921 (37.1)	1835 (35.5)
≥75yr (n[%])	466 (9.0)	441 (8.5)	498 (9.6)
Male sex (n[%])	3875 (74.9)	3843 (74.2)	3882 (75.0)
Race (n[%])[a]			
White	3798 (73.4)	3815 (73.7)	3796 (73.3)
Black	34 (0.7)	34 (0.7)	39 (0.8)
Asian	1099 (21.2)	1055 (20.4)	1075 (20.8)
Other	243 (4.7)	272 (5.3)	266 (5.1)
Weight (kg)			
Median	78.0	78.0	78.0
Interquartile range	68.0-90.0	68.0-88.0	68.0-88.5
Creatinine clearance (ml/min)[b]			
Median	85.1	84.8	85.6
Interquartile range	68.3-105.0	68.5-104.7	68.1-105.1
Medical history (n[%])			
Previous MI	1363 (26.3)	1403 (27.1)	1415 (27.3)
Hypertension	3470 (67.1)	3499 (67.6)	3494 (67.5)
Diabetes	1669 (32.3)	1648 (31.8)	1647 (31.8)
Hypercholesterolaemia	2498 (48.3)	2544 (49.1)	2496 (48.2)
Index diagnosis n[%])			
STEMI	2601 (50.3)	2584 (49.9)	2632 (50.9)
NSTEMI	1321 (25.5)	1335 (25.8)	1323 (25.6)
Unstable angina	1252 (24.2)	1257 (24.3)	1221 (23.6)
PCI or CABG for index event (n[%])	3138 (60.6)	3123 (60.3)	3126 (60.4)
Region (n[%])			
North America	269 (5.2)	293 (5.7)	312 (6.0)
South America	546 (10.6)	583 (11.3)	540 (10.4)
Western Europe	707 (13.7)	775 (15.0)	759 (14.7)
Eastern Europe	2042 (39.5)	2025 (39.1)	2007 (38.8)
Asia	1088 (21.0)	1044 (20.2)	1063 (20.5)
Other	522 (10.1)	456 (8.8)	495 (9.6)
Medications n[%])			
Aspirin	5105 (98.7)	5099 (98.5)	5108 (98.7)
Thienopyridine	4790 (92.6)	4812 (93.0)	4811 (92.9)
Beta-blocker	3426 (66.2)	3394 (65.6)	3444 (66.5)
ACE-inhibitor or ARB	2022 (39.1)	1977 (38.2)	2050 (39.6)
Statin	4304 (83.2)	4342 (83.9)	4321 (83.5)
Calcium-channel blocker	820 (15.8)	742 (14.3)	764 (14.8)

S.D. = Standard deviation; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CABG = coronary-artery bypass grafting; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction

[a] Race was self-reported

[b] Creatinine clearance was calculated with the use of the Cockcroft-Gault equation

In 2013, rivaroxaban received marketing authorisation for the prevention of atherothrombotic events in patients after an acute coronary syndrome (ACS) with elevated biomarkers. One of the listed contraindications excludes patients with a history of stroke or TIA from treatment. Baseline characteristics of patients in ATLAS-ACS 2 TIMI 51, matching these criteria (i.e. elevated cardiac biomarkers without prior stroke/TIA) are presented below in Table 11. When comparing the baseline characteristics of patients with elevated biomarkers without a history of prior stroke/ TIA between treatment groups, baseline characteristics [redacted]

Baseline characteristics were also [redacted]

Differences in baseline characteristics in the pre-specified subgroup with elevated biomarkers compared to the overall study population [redacted]

For patients with elevated biomarkers without a history of prior stroke/ TIA (All Strata and All Randomised Patients), [redacted]

of patients had a STEMI [redacted]

of patients had a NSTEMI [redacted]

had UA as their admitting diagnosis compared to 50.3% with a STEMI, 25.6% with an NSTEMI, and 24.0% with UA in the overall trial population.

Table 11 Baseline characteristics of patients participating in ATLAS-ACS 2 TIMI 51 with elevated biomarkers and without prior stroke/TIA (ALL STRATA)(28)

Characteristic	Rivaroxaban		Placebo (N=4197)
	2.5mg twice daily (N=4142)	5mg twice daily (N=4125)	
Age Mean±S.D. (yr) ≥65yr (n[%]) ≥75yr (n[%])	[redacted]	[redacted]	[redacted]
Male sex (n[%])	[redacted]	[redacted]	[redacted]
Race (n[%])[a] White Black Asian Other	[redacted]	[redacted]	[redacted]
Weight (kg) Median Q1 Q3 Range	[redacted]	[redacted]	[redacted]
Creatinine clearance (ml/min)[b] Median Q1 Q3 Range	[redacted]	[redacted]	[redacted]
Medical history (n[%]) Previous MI Hypertension Diabetes Hypercholesterolaemia	[redacted]	[redacted]	[redacted]
Index diagnosis n[%]) STEMI NSTEMI Unstable angina	[redacted]	[redacted]	[redacted]
Revascularisation procedure for index event (n[%])	[redacted]	[redacted]	[redacted]
Region (n[%]) North America South America	[redacted]	[redacted]	[redacted]

Western Europe	[redacted]	[redacted]	[redacted]
Eastern Europe	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Medications n[%])			
Aspirin	[redacted]	[redacted]	[redacted]
Thienopyridine	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]
ACE-inhibitor or ARB	[redacted]	[redacted]	[redacted]
Statin	[redacted]	[redacted]	[redacted]
Calcium-channel blocker	[redacted]	[redacted]	[redacted]

S.D. = Standard deviation; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CABG = coronary-artery bypass grafting; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction

[a] Race was self-reported

[b] Creatinine clearance was calculated with the use of the Cockcroft-Gault equation

Outcomes (2-4)

6.3.5 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 (HRQL), 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).

The **primary efficacy endpoint** in ATLAS-ACS 2 TIMI 51 was the composite of:

1. Death from cardiovascular causes (CV death)
2. Myocardial infarction (MI), or
3. Stroke (ischaemic, haemorrhagic or stroke of uncertain cause)

Death *was classified in 2 primary categories, cardiovascular or noncardiovascular, and also in 2 secondary categories, coronary heart disease (CHD)-related or non-CHD related. All deaths were assumed cardiovascular in nature unless a noncardiovascular cause could be clearly shown.Myocardial infarctions were counted as events whether they were the reason for the hospitalisation or occurred during a hospitalisation and whether they occurred spontaneously or as the direct consequences of an investigation/procedure or operation. An MI had to be distinct from the qualifying event (i.e., re-infarction for a patient who qualified for the study based on recent MI).*

The definition of ***MI*** *as an endpoint took into account whether a patient had a recent MI or underwent revascularisation with PCI or CABG surgery. In cases where both cardiac troponin and CK-MB are available (collected at similar time points) and were discordant, clinical judgment was used to apply the most relevant biomarker data. The definitions of MI for the 4 clinical settings in which it may occur are presented in Figure 4.*

Figure 4 Definition of MI (2)

A. ***For patients with no recent revascularisation, criteria (1) and (2) or criterion (3) or criterion (4) must be met:***

1. Typical cardiac biomarker rise and fall with the following degrees of elevation accepted as biochemical evidence of myocardial necrosis:

a. Troponin T or I: maximal concentration greater than the MI decision limit;

b. CK-MB: maximal concentration greater than the ULN;

AND

2. At least 1 of the following additional supportive criteria:

a. Ischaemic discomfort at rest lasting ≥10 minutes; or

b. ECG changes indicative of ischemia (ST elevation ≥0.1 mV or ST depression ≥0.05 mV, or new T-wave inversions);

OR

3. Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction;

OR

4. Pathologic findings of an acute MI

B. For patients with no recent revascularisation in who biomarkers from a qualifying (or recent) MI remain elevated, criteria (1) and (2), or criterion (3), or criterion (4), or criterion (5) must be met:

1. Cardiac biomarker re-elevation defined as:

a. Increase by at least 20% of the previous value; and

b. Documentation that the biomarker assayed was decreasing prior to the suspected new MI;

AND

2. At least 1 of the following additional supportive criteria:

a. Ischaemic discomfort at rest lasting ≥10 minutes; or

b. ECG changes indicative of ischaemia (ST elevation ≥0.1 mV or ST depression ≥0.05 mV, or new T-wave inversions);

OR

3. Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction;

OR

4. New elevation of ST-segments ≥0.1 mV in ≥2 contiguous precordial or adjacent limb leads AND

a. Ischaemic discomfort at rest lasting ≥20 minutes; or

b. Ischaemia-mediated new hemodynamic decompensation requiring pharmacologic or mechanical support; or

c. Angiographic evidence of acute coronary occlusion

OR

5. Pathologic findings of an acute MI

C. Within 24 hours after PCI (or felt to be clinically related to a PCI) a patient must have EITHER:

1. CK-MB >3 x ULN and, if the pre-PCI CK-MB was >ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

OR

2. Pathologic finding of an acute MI

Note: symptoms are not required.

D. Within 24 hours after CABG (or felt to be clinically related to CABG) a patient must have had criteria (1) and (2), or criterion (3), or criterion (4):

1. CK-MB >5 x ULN and, if the pre-CABG CK-MB was above ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

AND

2. At least one of the following supportive criteria:

a. Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction, or

b. Angiographically documented new graft or native coronary occlusion, or

c. Imaging evidence of new loss of myocardium

OR

3. CK-MB >10 x ULN and, if the pre-CABG CK-MB was above ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

OR

4. Pathologic findings of an acute MI.

Note: Symptoms are not required.

Note: If cardiac troponin measurements are the only cardiac biomarker data available, they may be used by the CEC, along with the ECG and clinical scenario, in the adjudication of suspected MI after revascularisation (PCI or CABG).

Stroke *was defined as a new, sudden focal neurological deficit resulting from a presumed cerebrovascular cause that was not reversible or resulted in death within 24 hours and was not due to a readily identifiable cause, such as a tumour or seizure. Stroke was subclassified into 1 of the following 4 groups:*

- *Ischaemic infarction*
- *Ischaemic infarction with haemorrhagic conversion*
- *Primary haemorrhagic: an intraparenchymal haemorrhage, subdural or epidural haematoma*
- *Uncertain*

In the rare setting where subdural and epidural bleeding events and ischemic cerebrovascular events lasted less than 24 hours, the convention to be followed was that these events would not be counted as a primary stroke endpoint; these were considered TIAs.

The **secondary efficacy endpoints** were:

1. Composite of all-cause death, MI, or stroke

2. Net Clinical Outcome (i.e., composite of CV death, MI, ischaemic stroke, or TIMI major bleeding event not associated with CABG surgery [non-CABG TIMI major bleeding])

3. Composite of CV death, MI, stroke, or severe recurrent ischaemia requiring revascularisation (SRIR)

4. Composite of CV death, MI, stroke, or severe recurrent ischaemia leading to hospitalisation (SRIH)

Severe recurrent ischemia *was defined as ischaemic discomfort or equivalent meeting the following criteria:*

- *Lasting 10 minutes at rest, or repeated episodes at rest lasting ≤ 5 minutes, or an accelerating pattern of ischaemic discomfort, considered to be myocardial ischaemia upon final diagnosis.*

- *At least one of the following additional criteria for coronary artery disease and/or ischaemia:*
  - *New and/or dynamic ST-depression > 0.05 mV, ST elevation > 0.1 mV, or symmetric T-wave inversion > 0.2 mV on a resting ECG*
  - *Definite evidence of ischaemia on stress echocardiography, myocardial scintigraphy, or ECG-only stress test*
  - *Angiographic evidence of epicardial coronary artery stenosis of > 70% diameter reduction and/or evidence for intraluminal arterial thrombus.*

The **incidence of 'stent thrombosis'** was a pre-specified stand-alone efficacy endpoint. All cases of stent thrombosis were classified by the blinded CEC according to the Academic Research Consortium ARC definitions(2):

Definite,* Probable, and Possible Stent Thrombosis

Definite stent thrombosis

Angiographic confirmation of stent thrombosis†

- The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
  - Acute onset of ischemic symptoms at rest
  - New ischemic ECG changes that suggest acute ischemia
  - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
  - Nonocclusive thrombus
    - Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
  - Occlusive thrombus
    - TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

Pathological confirmation of stent thrombosis

- Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days§
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

**Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.*

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

‡Intracoronary thrombus

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

The **primary safety endpoint** was the incidence of TIMI major bleeding not related to coronary-artery bypass grafting (CABG) surgery [Non-CABG TIMI major bleeding] (see Figure 5). As such, the TIMI scale was the primary bleeding scale for this study.

Figure 5 TIMI Bleeding event classification scale

TIMI major bleeding event*: any symptomatic intracranial bleeding or clinically overt signs of bleeding associated with a decrease in haemoglobin of ≥ 5g/ dL or an absolute drop in haematocrit of ≥ 15%*

TIMI minor bleeding: *any clinically overt bleeding event, including bleeding that is evident on imaging studies, that is associated with a decrease in haemoglobin that is ≥ 3 g/dL but is < 5g/dL from baseline haemoglobin value.*

Bleeding requiring medical attention*: any bleeding event that requires medical treatment, surgical treatment, or laboratory evaluation and does not meet criteria for TIMI major or TIMI minor bleeding event.*

Insignificant bleeding: *a reported blood loss or bleeding event episode not meeting any of the above criteria*

Clinically significant bleeding*: The composite endpoint of TIMI major bleeding, TIMI minor bleeding, or bleeding requiring medical attention*

Two further bleeding scales were used to provide additional information on bleeding.

1. The rivaroxaban program scale using the *International Society on Thrombosis and Haemostasis (ISTH)* major bleeding event classification(2), which has categories of **major bleeding** events, **clinically relevant non-major bleeding** events, and **minimal bleeding** events (see Figure 6). This allowed comparison across studies in the rivaroxaban clinical development program. Bleeding events associated with CABG were evaluated separately for the ISTH scale.

Figure 6 ISTH (and Rivaroxaban program) bleeding event scale

Major bleeding event*: clinically overt bleeding that is associated with a fall in haemoglobin of 2 g/dL or more, or a transfusion of 2 or more units of packed red blood cells or whole blood or a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or a fatal outcome.*

Clinically relevant non-major bleeding event*: an overt bleeding event not meeting the criteria for a major bleeding event but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.*

Minimal Bleeding events*: All other overt bleeding event episodes not meeting the criteria for major or clinically relevant non-major bleeding events.*

2. For comparison with other studies outside the rivaroxaban clinical development program, The Global Strategies for Opening Occluded Coronary Arteries (GUSTO) bleeding scale was also used, capturing **severe**, **moderate** and **mild** bleeding events (see Figure 7).

Figure 7 GUSTO bleeding scale

Severe bleeding: *an intracranial haemorrhage or bleeding that caused haemodynamic compromise and required intervention.*

Moderate bleeding: *bleeding that required blood transfusion but did not result in haemodynamic compromise.*

Mild bleeding: *bleeding that did not meet criteria for either severe or moderate bleeding.*

Other safety evaluations included serious adverse events, adverse events leading to discontinuation of study drug, adverse events of special interest (e.g. any liver-related adverse event, including alanine aminotransferase [ALT] >3 times ULN (with normal baseline) with confirmation by retesting [within 5 days]; any bleeding event that does not meet the criteria for serious adverse event; any event occurring within 30 days before a permanent discontinuation). Analysis of clinical laboratory tests data was also performed.

Other analyses

Additional exploratory efficacy analyses

[redacted]

included **quality of life**, as measured using the EuroQol (EQ-5D) questionnaire, and **medical resource utilisation (MRU)**.

MRU data included hospitalisations, total days or length of stay, emergency room visits, ICU/CCU days, surgeries, and inpatient or outpatient procedures, use of home care, rehabilitation and skilled nursing resource.

Reliability/ validity/ current use in clinical practice

A Clinical Events Committee (CEC), whose members were unaware of treatment group assignments, provided adjudication on all components of the key efficacy and safety end points i.e. death (CV versus non-CV cause), MI, stroke (ischaemic, haemorrhagic, uncertain), severe recurrent ischaemia, and bleeding events. The adjudicated results based on the committee's review were used for all reported analyses. In addition, the CEC also confirmed and classified cases of coronary stent thrombosis according to Academic Research Consortium (ARC) definitions – see page 53.

All assessments, including clinical laboratory tests, and adverse events, were standard validated tests and evaluations were in accordance with GCP to ensure safety of patients participating in research.

All efficacy endpoints were discussed with and agreed by health regulatory authorities worldwide e.g. European Medicines Agency (EMA), US Food and Drug Administration (FDA). The inclusion of CV death was accepted by regulatory authorities providing 'all cause death' was included as a relevant secondary endpoint and that a trend of similar direction of effects is shown. Since a high rate of all-cause deaths are typically adjudicated to have CV causes the inclusion of 'CV death' as opposed to 'all-cause death' in the primary endpoint was not considered to impact study results.

The primary efficacy endpoint components of CV death, MI, and stroke, are accepted, validated, clinical endpoints for the evaluation of treatments for ACS. Following an ACS event, patients are at high risk of another morbid event of ACS (e.g. an MI) or stroke or dying from a CV cause. On that basis, all components of the primary endpoint are relevant clinical outcomes. Other recent landmark clinical trials for ACS such as the CURE trial (clopidogrel plus aspirin / NSTEMI ACS)(29), the TRITON-TIMI 38 study (prasugrel vs. clopidogrel / ACS)(30) and PLATO (ticagrelor vs. clopidogrel)(31) used broadly similar composite efficacy primary endpoints, although actual definitions of endpoint components varied in stringency between studies.

Treatment Compliance

Compliance was tracked via the IVRS / IWRS system which recorded drug dispensed to patients, return of empty drug containers / unused study drug and details of missed doses.

Any unexplained missed doses that resulted in the patient returning more than 15% of the prescribed study drug were recorded as noncompliance. If study drug was missed for more than 28 consecutive days, the patient was to be permanently discontinued from study drug.

Statistical analysis and definition of study groups

6.3.6 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).

- **Primary hypothesis (2)**

The hypothesis of this study is that treatment with rivaroxaban in addition to standard care (whether this is aspirin alone, or aspirin combined with thienopyridine) is superior to treatment with placebo in addition to standard care in reducing the risk of CV death, MI, or stroke in patients with a recent ACS.

- **Definition of study groups/analysis datasets (2;5)**

As prospectively defined in the Statistical Analysis Plan (SAP), the efficacy population included all randomised patients, regardless of treatment exposure and the safety population was defined as all randomised patients who received at least one dose of study drug. Prior to database lock, an amendment to the SAP specified that 184 patients from 3 sites were to be excluded from the efficacy population due to potential trial misconduct[1], but still included in safety analyses. Sensitivity analyses were also performed [redacted].

For the time-to-event analyses of efficacy and safety data, the pre-specified analysis sets defined in the SAP are described in Table 12. These analysis sets were defined both by a patient population and those events considered countable under the censoring rules for that analysis set. The events considered countable under the censoring rules for an analysis set are called 'evaluable events' for that analysis set.

The primary efficacy analysis was based on the modified intention-to-treat (mITT) analysis set, which included all randomised patients and the endpoint events that occurred from

[1] Sites excluded due to potential good clinical practice issues [redacted]

randomisation up to the earlier date of the global treatment end date, or 30 days after last dose of study drug (for patients who discontinued study drug prematurely), or 30 days after randomisation (for patients who were randomised but never treated).

The primary safety analysis set was the Treatment-Emergent Safety analysis set, including all randomised patients who received at least one dose of study drug with all events from first dose up to the date of last dose of study drug plus two days for each patient. This was used for the primary safety analysis on non-CABG TIMI major bleeding, key AE summaries, and the benefit-risk analyses.

Supplementary analysis sets

Prior to database lock, [redacted]

Table 12 Description of Efficacy and Safety analysis sets used in ATLAS-ACS 2 TIMI 51

Analysis set	Population	Event-censoring rule
Primary Efficacy Analysis set		
mITT	All randomised patients excluding 3 sites due to potential GCP issues.	Endpoint events that occurred from randomisation up to the earlier date of the global treatment end date, or 30 days after last dose of study drug (for patients who discontinued study drug prematurely), or 30 days after randomisation (for patients who were randomised but never treated).
Efficacy sensitivity analysis sets		
ITT	All randomised patients excluding 3 sites due to potential GCP issues..	Endpoint events from randomisation up to the global treatment end date.
ITT - Total		Endpoint events from randomisation up to last contact date of each patient.
[redacted]	[redacted]	[redacted]
Per Protocol	[redacted]	[redacted]
Primary Safety Analysis Set		
Treatment-Emergent (TE) Safety	Safety population (i.e., all randomised patients who received at least one dose of study drug)	All events from first dose up to the date of last dose of study drug plus 2 days for each patient
Secondary Safety Analysis Sets		
mITT Approach Safety	Safety population (i.e., all randomised patients who received at least one dose of study drug)	All events that occurred from randomisation up to the earlier date of the global treatment end date, or 30 days after last dose of study drug (for patients who discontinued study drug

Analysis set	Population	Event-censoring rule
		prematurely).
Safety-Observational period		All events from first dose up to the last contact date for each patient
[redacted]	[redacted]	[redacted]

- **Statistical Analysis plan (2;3;5)**

Two simultaneous evaluation strategies were selected on the basis of differing regulatory requirements and were employed for the primary endpoint analyses. The primary evaluation strategy was based on data combined across both strata (i.e., All Strata). A second evaluation strategy was based on the FDA-recommended approach of combined analyses across both dose regimens in patients in Stratum 2 (ASA+Thienopyridine) only.

Primary Efficacy analysis (2;3;5)

The predefined primary efficacy endpoint was the composite of CV death, MI, or stroke. Based on time from randomisation to the first occurrence of the primary efficacy endpoint, the objective of the primary efficacy analysis was to determine whether rivaroxaban is superior to placebo, in addition to standard care, in the reduction of primary efficacy endpoint events in patients with a recent ACS. Time from randomisation to the first occurrence of the primary efficacy endpoint was analysed and tested in the primary mITT analysis set.

The primary efficacy analysis was a stratified (by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) log-rank test between the combined rivaroxaban groups and the placebo group. Due to a small adjustment necessitated by the interim efficacy analysis, a 2-sided α=0.0499982 was used for the primary efficacy analysis. If the combined rivaroxaban groups were found to be superior to placebo, then a similar stratified log-rank test was performed for each rivaroxaban individual dose.

A stratified (by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) Cox proportional regression model was used with treatment group as the covariate to provide a point estimate and 95% confidence interval for the treatment effect of the relative risk reduction (RRR) (RRR=100 X [1 – hazard ratio]%).

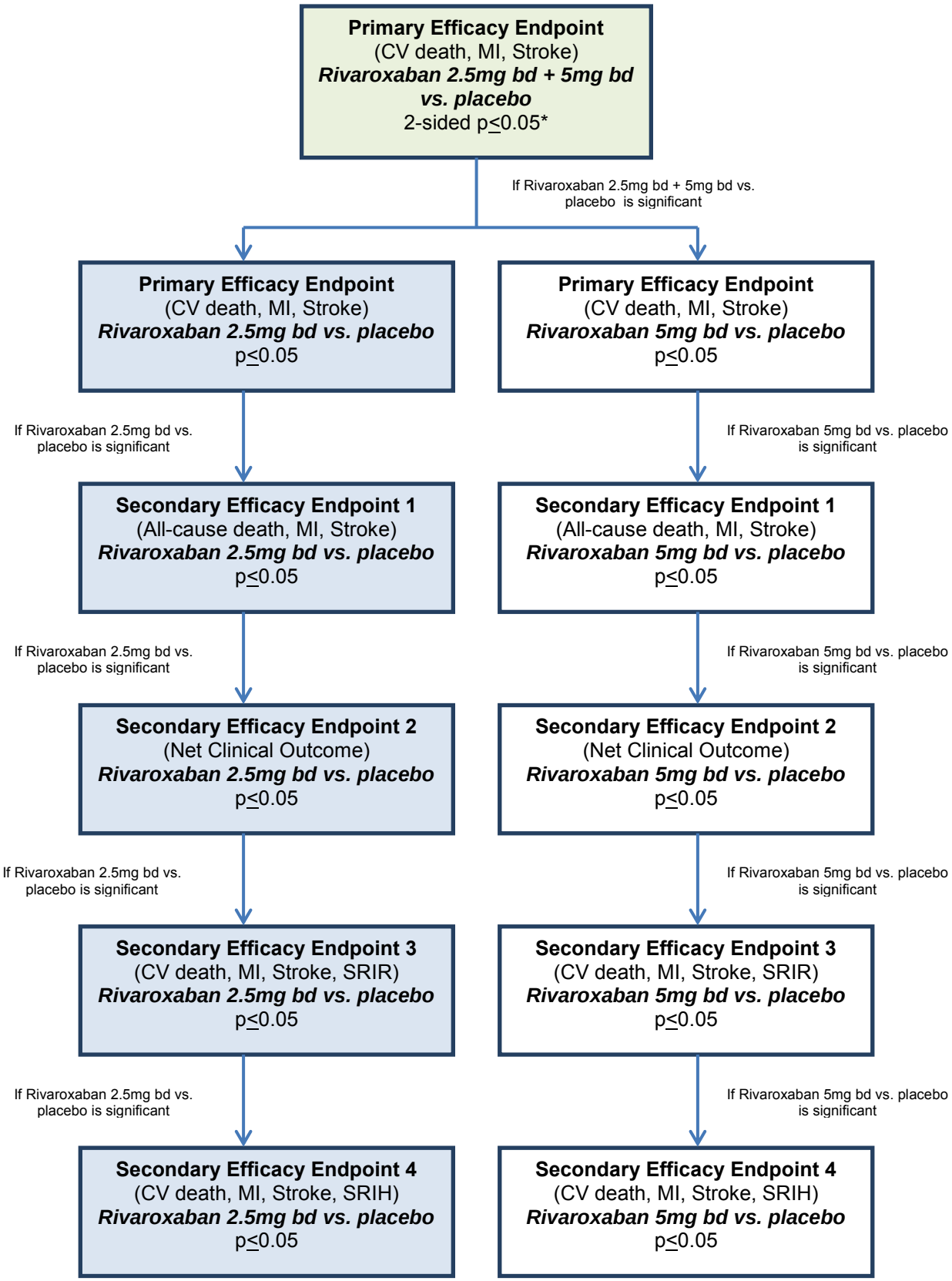
Kaplan-Meier curves were prepared to display the cumulative proportions of events by treatment group.

Time from randomisation to the first occurrence of each of the secondary efficacy endpoints was analysed and tested in the primary mITT analysis set, as well as in the ITT, ITT-Total, [redacted], using the same methods as those used for the primary efficacy endpoint. If superiority of rivaroxaban compared with placebo for the primary efficacy endpoint was declared within a dose group, then the secondary efficacy endpoints were tested sequentially within that dose group.

If the superiority of a dose group was declared for the primary efficacy endpoint, the secondary efficacy endpoints were tested for that dose group, in sequential order (i.e., Secondary Efficacy Endpoint 1, 2, 3, etc.). Each subsequent ordered secondary endpoint could be tested only for the doses that were significant for the previous endpoints. If an individual test during any step was not statistically significant, further testing could continue but significance could not be claimed.

Figure 8 The hierarchical testing strategy for the data combined across both strata

All Strata



* Due to a small adjustment necessitated by the interim efficacy analysis, a 2-sided α=0.0499982 was used for the primary efficacy analysis; SRIR = severe recurrent ischaemia requiring revascularisation; SRIH= severe recurrent ischaemia leading to hospitalisation

Stent thrombosis and its sub-categories were also summarised by treatment group.

Primary Safety Analysis (3;5)

The predefined primary safety endpoint was the occurrence of **non-CABG TIMI major bleeding events**. Time from first dose to the first occurrence of the primary safety endpoint was analysed and tested in the primary Treatment-Emergent Safety analysis set.

Similar to the primary efficacy endpoint analyses, a stratified (by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) log-rank test was the primary analysis for hypothesis testing. A stratified (by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) Cox proportional hazards regression model was also used to provide a point estimate and 95% confidence interval for the treatment effect of the relative risk reduction (RRR) (RRR=100 X [1 – hazard ratio]) with treatment group as a class covariate with placebo as reference. Kaplan-Meier curves were provided for the cumulative proportions of events by treatment group.

The two rivaroxaban doses were compared for the primary safety endpoint.

Similar analyses were performed for all **other bleeding event endpoints**.

Death was summarised by CV, non-CV, and unknown.

Adverse Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0). All reported serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest with onset during the double-blind treatment phase (i.e., treatment-emergent adverse events) were included in the analysis. For each adverse event, the percentage of patients who experienced at least 1 occurrence of the given event was summarised by treatment group. In particular, were identified and summarised using Standardised MedDRA Queries (SMQ).

Clinical Laboratory Tests - The frequency of ALT >3x ULN (during the first 24 weeks of treatment) was summarised and compared across treatment groups. In addition, analyses of the time to first occurrence of an ALT >3x ULN comparing treatment groups were evaluated. Abnormal ALT and total bilirubin was tabulated and summarised by treatment group.

Other analyses - All MRU and EQ-5D analyses were exploratory and descriptively summarised by treatment group.

Interim Analysis

A scheduled interim analysis was performed when approximately 70% (688) of the required total number (983) of primary efficacy events, had occurred, in order to assess whether the study should be stopped for overwhelming superiority. The data cut-off for the interim analysis was November 29, 2010, based on 704 total primary efficacy events. The IDMC met on January 12, 2011 to review the data. The study continued unaltered following that analysis(22).

- **Study power and Sample size (2;3)**

A total of 983 primary efficacy endpoint events provided approximately 96% power to detect a 22.5% relative reduction (i.e. hazard ratio 0.775) between combined doses of rivaroxaban and placebo arms pooled across strata 1 and 2, with a 2-sided type I error rate of 0.05.

The total 983 events was estimated based on the sum of the events required at approximately 90% power in each stratum, to detect a 35% relative reduction in Stratum 1 (255 primary efficacy endpoint events required) and a 22.5% relative reduction in Stratum 2 (728 primary efficacy endpoint events required) comparing combined rivaroxaban doses (2.5 mg twice-daily and 5 mg twice-daily) and placebo arms within each strata. The number of primary efficacy endpoint events required to compare each rivaroxaban dose with the placebo treatment group was estimated to be 2/3 of the total events required for a 3-arm study. Each individual dose arm, pooled across Stratum 1 and 2, was powered at approximately 90% for an overall relative risk reduction of 22.5% (based on 655 primary efficacy endpoint events), within each individual dose arm, and within each individual stratum the study was powered at approximately 80% for the assumed relative risk reduction of 35% in Stratum 1 and 22.5% in Stratum 2.

The double-blind treatment period was to stop on the projected date of accrual of at least 983 primary efficacy endpoint events anticipated to be adjudicated as mITT events (i.e., global treatment end date).

The total sample size was estimated based on the predicted number of adjudicated events and the following assumptions:

- Enrollment projection and placebo event rates (12% at 1 year in Stratum 1; 6% at 1 year in Stratum 2) similar to those for the Phase 2 ATLAS ACS TIMI 46 study
- Total enrollment period of approximately 27 months
- Total treatment duration of approximately 33 months
- Yearly dropout (e.g., withdrawal of consent, lost to follow-up, premature discontinuation of study drug) rate of 10% in each treatment group.

Originally, approximately 13,570 patients, (2,079 in Stratum 1 and 11,491 patients in Stratum 2), were estimated to be needed to reach the expected number of primary efficacy endpoint events to compare the combined rivaroxaban (2.5 mg bd and 5 mg bd) arms with the placebo arm in order to reach the targeted study power.

[redacted]

A total of 15,526 patients (1,053 in Stratum 1 and 14,473 in Stratum 2) were actually randomised in the study.

- **Missing data / Patient discontinuation**

A patient was considered to have completed the study if they completed the EOS visit and did not prematurely discontinue study drug for any reason (Note: temporary discontinuation, defined as ≤28 days in protocol, was allowed). It should be noted that the protocol defined death as one of the reasons for premature discontinuation of study drug, and thus, patients who died prior to the global treatment end date are counted as having prematurely discontinued treatment.

Following the EOT/early withdrawal visit, all patients were to enter the follow-up period. For patients who permanently discontinued study drug before the global treatment end date, the follow-up visit was scheduled approximately 30 days later and then they continued to be followed every 12 weeks for the remainder of the study. Patients who completed the follow-up period were considered to have completed the study.

In cases where a patient was potentially lost to follow-up, every possible effort was made to contact the patient and determine the endpoint status and reason for discontinuation as local law permitted.

Censoring rules for each analysis set are summarised in Table 12.

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

The following pre-specified subgroups determined by baseline characteristics were examined with respect to the efficacy endpoints. Results were examined for general consistency of treatment effect, and interaction testing was performed(3;5):

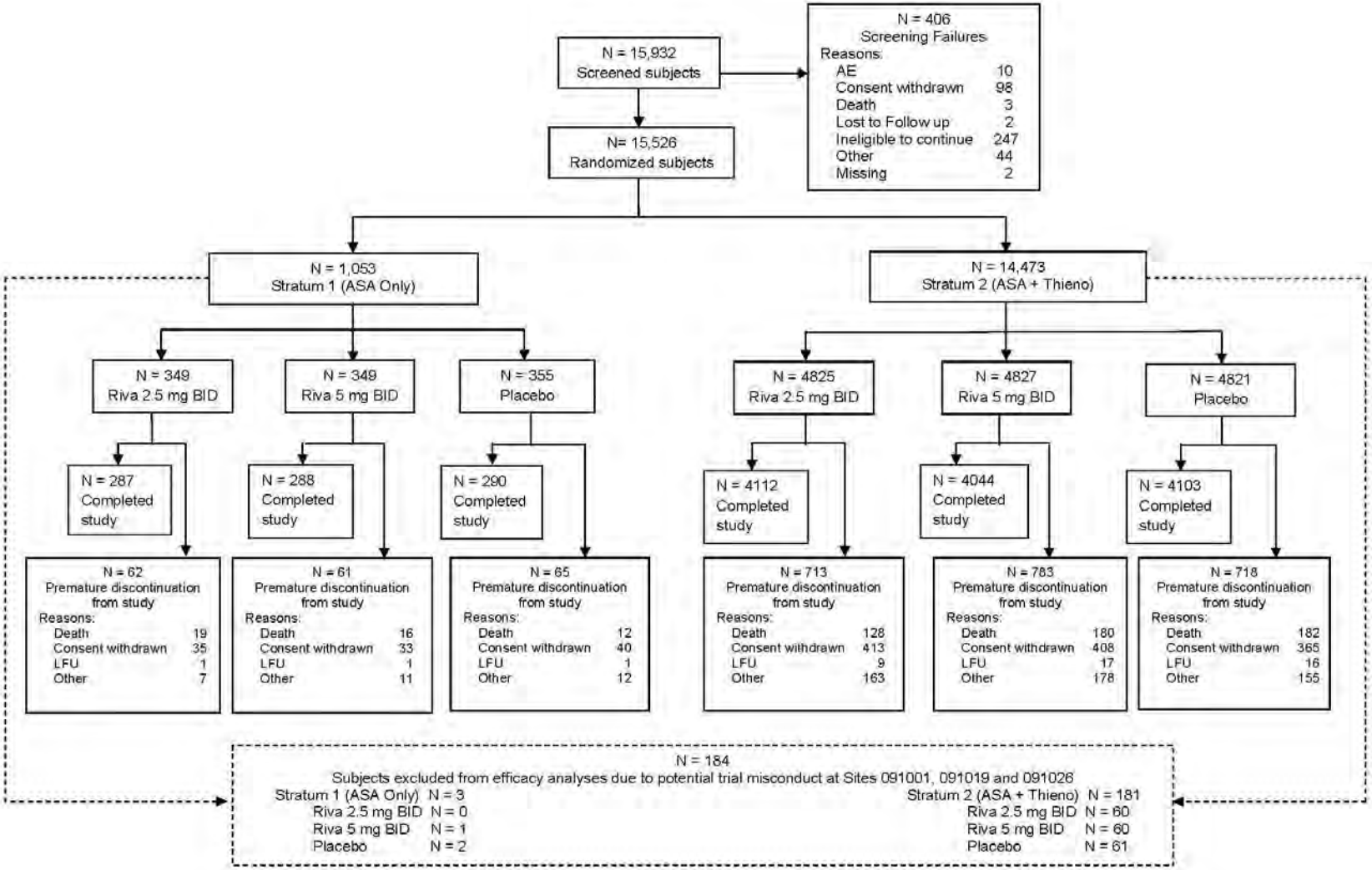
- Intention to use a thienopyridine (yes or no);
- Region (North America, South America, Western Europe, Eastern Europe, and Asia Pacific and Others including Australia, New Zealand, North African countries (including Egypt), Israel, and Turkey.
- Index events (STEMI, non-STEMI, UA, NSTEMI + UA).
- Sex (male, female)
- Age (<55 vs. ≥ 55, <65 vs. ≥ 65, <75 vs. ≥75)
- Race (White or Caucasian, Black or African American, Asian, other)

- Baseline renal function (calculated creatinine clearance < 30, 30-<50, 50-80, >80 mL/min)
- Baseline diabetes (yes or no)
- Prior PCI for index event (yes or no)
- History of congestive heart failure (CHF) (yes or no)
- Prior MI before index event (yes or no)
- Prior ischaemic stroke / prior TIA (yes or no)
- History of hypertension (yes or no)
- Weight (60, ≥70 - 90, ≥90kg)
- Body mass index (BMI) (<25, ≥25-<30, ≥30 kg/m^2)

[redacted]

6.3.8 Participant flow

Figure 9 Patient disposition for ATLAS-ACS 2 TIMI 51(22)



6.4 Critical appraisal of relevant RCTs

6.4.1 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.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

See section 10.3, appendix 3 for further details.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.

Table 13 Quality assessment of RCTs

	ATLAS-ACS 2 TIMI 51(3)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
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

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

ATLAS-ACS 2 TIMI 51

Note: Throughout the results section the term 'ALL STRATA' refers to data from stratum 1 and stratum 2 combined and the term 'COMBINED DOSE' refers to the combining of data from the 2.5mg bd and 5mg bd rivaroxaban arms.

Also, where appropriate, the reporting of results from ATLAS-ACS 2 TIMI 51 will focus on low dose rivaroxaban (i.e.the 2.5mg bd dose), since this is the licensed dose of rivaroxaban in the reduction of thrombotic cardiovascular events in ACS alongside standard care. For

reference, data on the 5mg bd dose is presented in the summary tables, but will generally not be discussed.

ALL STRATA and STRATUM 2 - the primary evaluations will be the main focus of discussion in the presentation of results.

In addition, a post-hoc analysis of primary and secondary endpoints in ATLAS-ACS 2 TIMI 51 was performed for patients with elevated cardiac biomarkers without prior stroke/TIA i.e. the EU licensed population. These results are presented alongside results for the overall study population. This population was identified as the group of patients who derived the most favourable benefit from the addition of rivaroxaban to existing antiplatelet therapy, at the lowest risk.

The efficacy population included 5,114 patients randomised to treatment with 2.5 mg bd, 5,115 patients randomised to 5 mg bd rivaroxaban, and 5,113 patients randomised to placebo. As defined in Table 12, events post-randomisation, irrespective of taking study drug, are included in the efficacy analyses.

The efficacy population matching the licensed population (patients with elevated cardiac biomarkers without prior stroke/TIA) included 4,104 patients randomised to treatment with 2.5 mg bd, 4,089 patients randomised to 5 mg bd, and 4,160 patients randomised to placebo(22).

Results of hierarchical testing

Simultaneous evaluation strategies based on data combined across All Strata and for Stratum 2 only, were used for the efficacy analyses, including a set of log-rank tests (stratified by intention to use a thienopyridine for All Strata) in a pre-specified hierarchical order (see Figure 8).

Results of the hierarchical testing strategy are presented in Figure 10 and Figure 11.

In All Strata, the combined rivaroxaban doses were superior to placebo, in addition to standard care, in reducing the occurrence rate of primary efficacy endpoint events. Further, for All Strata, both the 2.5 mg bd and the 5 mg bd doses of rivaroxaban were individually superior to placebo, in addition to standard care, in reducing the occurrence of primary efficacy endpoint events. Both the 2.5 mg bd and the 5 mg bd doses of rivaroxaban were individually superior to placebo, in addition to standard care, in reducing the occurrence of Secondary Efficacy Endpoint 1 events (i.e., composite of all-cause death, MI or stroke). However, for Secondary Efficacy Endpoint 2 (i.e., composite of CV death, MI, ischaemic stroke, or non-CABG TIMI major bleeding) neither the 2.5 mg bd nor the 5 mg bd dose of rivaroxaban significantly decreased the occurrence of events compared with placebo. As a result, the hierarchical testing for the rest of the secondary endpoints in All Strata was stopped (see Figure 10)(22).

The results in Stratum 2 closely mirrored the results of All Strata. In Stratum 2, the combined rivaroxaban doses were superior to placebo, in addition to standard care, in reducing the occurrence of primary efficacy endpoint events. However, between the 2 dose groups, only the 2.5 mg bd group individually was significantly different compared with placebo. The hierarchical testing for the 5 mg bd group was thus halted. Rivaroxaban 2.5 mg bd was superior to placebo, in addition to standard care, in reducing the occurrence of Secondary Efficacy Endpoint 1 events (i.e., composite of all-cause death, MI or stroke) and, consistent with the results of All Strata, rivaroxaban 2.5 mg bd was not significantly different compared with placebo on Secondary Efficacy Endpoint 2 (i.e., composite of CV death, MI, ischaemic stroke, or non-CABG TIMI major bleeding) in Stratum 2 and the hierarchical testing for the remaining secondary endpoints in Stratum 2 was also stopped (see Figure 11).

Figure 10 Results for hierarchical testing strategy – All Strata, all randomised patients (22)

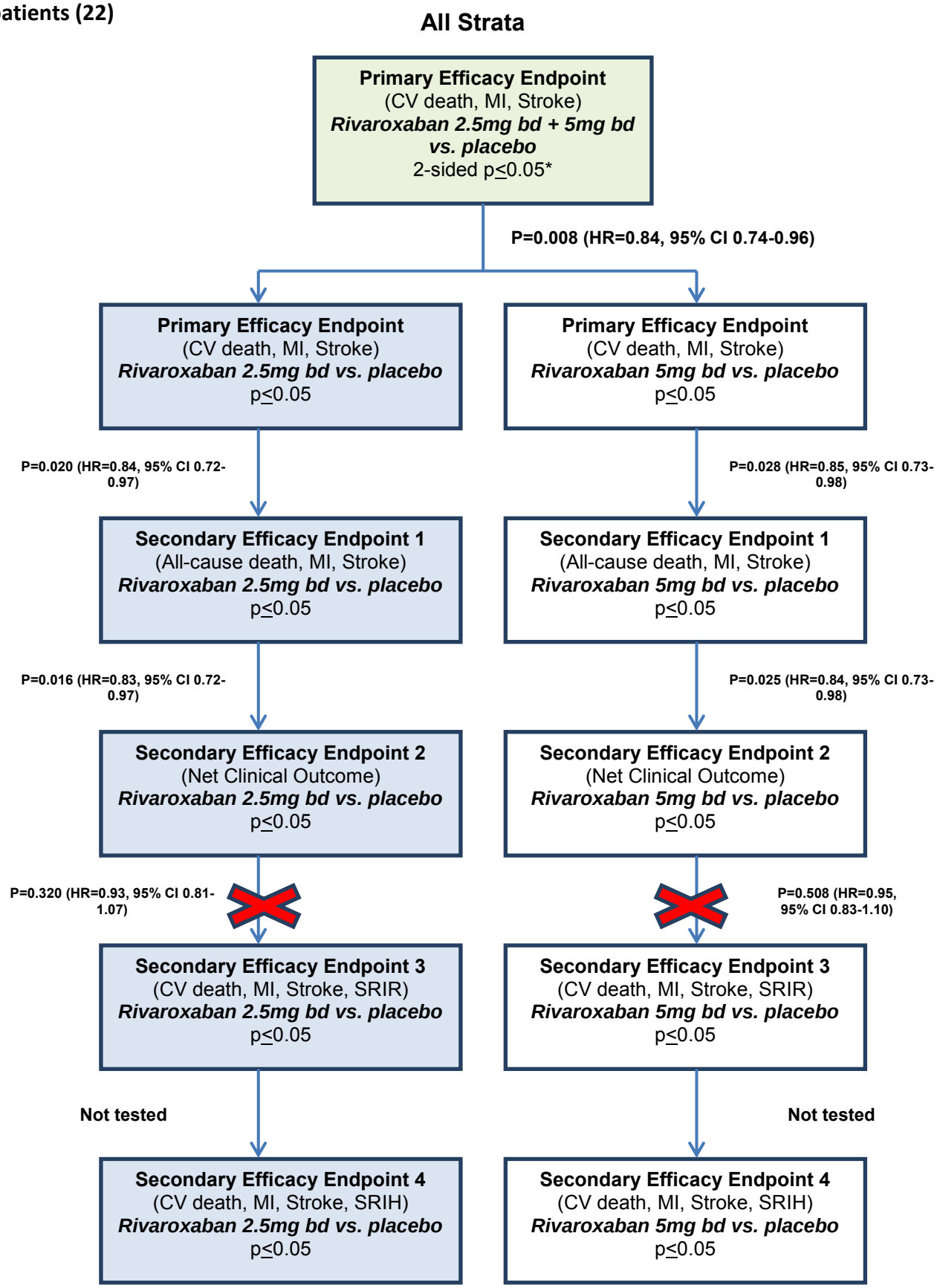
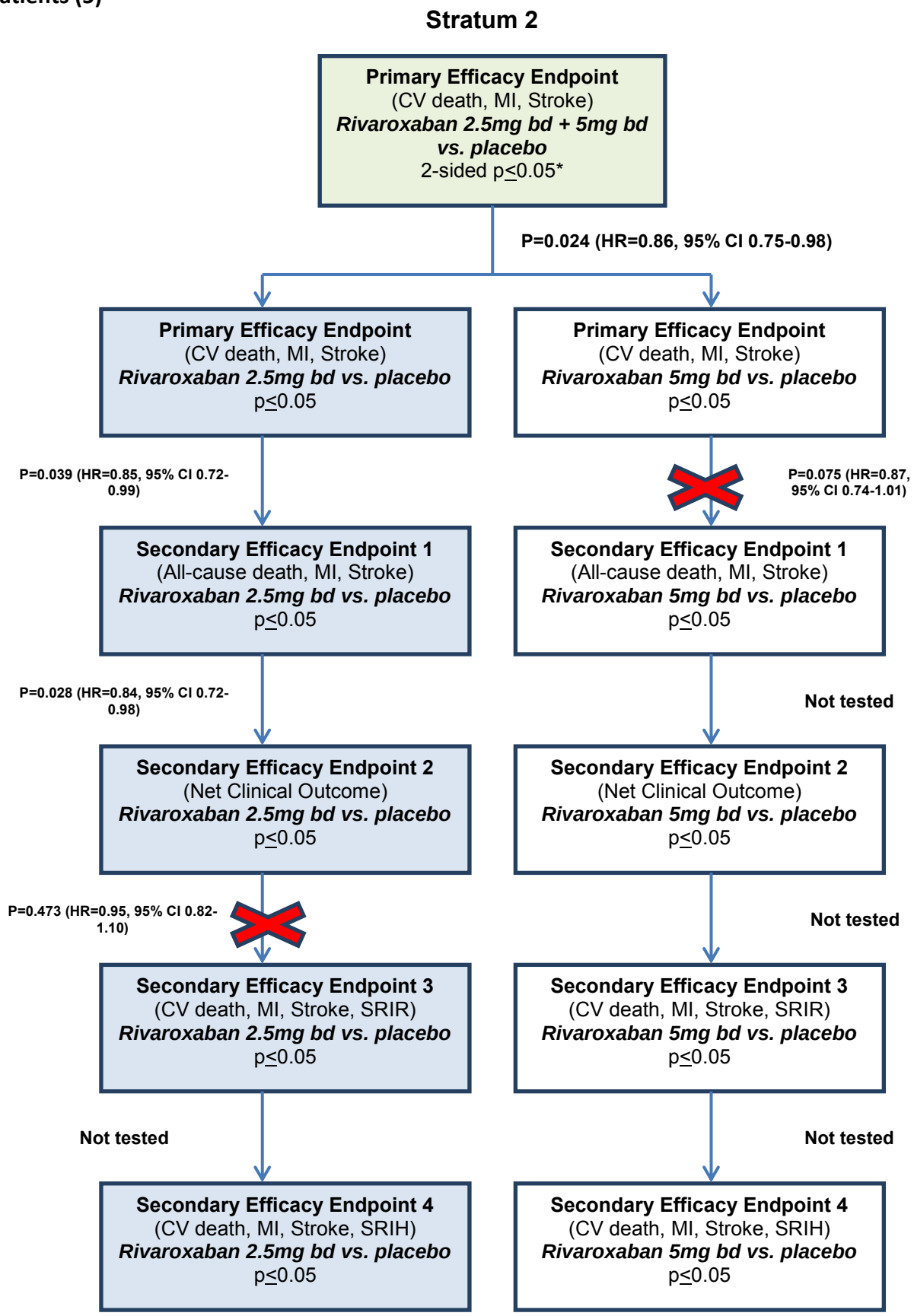


Figure 11 Results for hierarchical testing strategy – Stratum 2, all randomised patients (5)



Primary Efficacy endpoint (3;5)

Please note that the rates presented in the study publication are Kaplan Meier estimates whereas the data presented in this submission are crude rates (using the numbers based on the whole study duration.)

Composite of death from CV causes, myocardial infarction, and stroke

ALL STRATA, COMBINED DOSE - In the primary analysis population (mITT) rivaroxaban significantly reduced the relative risk of CV death, MI or stroke by 16%, as compared with placebo (6.1% vs. 7.4%; Hazard ratio (HR) =0.84; 95% confidence interval (CI) 0.74–0.96; p=0.008) (see Table 14). Thus, ATLAS ACS 2 TIMI 51 was deemed to meet its primary efficacy endpoint. The benefits were established early and continued throughout the 2 years (Figure 12).

ALL STRATA, 2.5mg bd - When evaluated separately, the 2.5mg rivaroxaban dose was also superior to placebo in the primary efficacy analysis: 6.1% vs. 7.4%; HR=0.84; 95% CI 0.72–0.97; p=0.02 (see Table 14 and Figure 13)

STRATUM 2 - Efficacy and safety findings were broadly consistent between Stratum 2 and the overall trial population. This was to be expected since 93% of patients were enrolled into Stratum 2.

STRATUM 2, combined dose - In Stratum 2, the combined rivaroxaban doses were superior to placebo in reducing the occurrence of the primary efficacy endpoint (6.0% vs. 7.1%; HR 0.86; 95% CI 0.75, 0.98; P=0.024).

STRATUM 2, 2.5mg bd - The 2.5 mg bd dose achieved statistical significance for the primary efficacy endpoint in Stratum 2: 6.0% vs. 7.1%; HR 0.85, 95% CI 0.72, 0.99, p=0.039.

STRATUM 1 -Primary efficacy results in Stratum 1 were directionally consistent with those in Stratum 2 and favoured rivaroxaban treatment [**COMBINED DOSE**](7.3% vs. 10.2%; HR=0.69; 95% CI 0.45–1.05; *p*=0.084), with similar trends for **rivaroxaban 2.5 mg bd** (7.7% vs 10.2%; HR=0.74; 95% CI 0.45–1.22; *p*=0.234)(5).

ELEVATED BIOMARKERS WITHOUT PRIOR STROKE/TIA(22;28)

ALL STRATA, COMBINED DOSE – Rivaroxaban significantly reduced the relative risk of CV death, MI or stroke as compared with placebo (6.2% vs. 7.9%; HR=0.79; 95% CI 0.69-0.91; p=0.001).

ALL STRATA, 2.5mg bd – The 2.5mg rivaroxaban dose was also superior to placebo for the primary endpoint: 6.2% vs. 7.9%; HR=0.80; 95% CI 0.68-0.94; p=0.007).

The relative risk reduction of 20% in the mITT for this licensed population is higher than the RRR in the overall trial population (16% RRR) and the absolute risk reduction of 1.7% for the primary endpoint of CV death, MI and stroke is clinically meaningful.

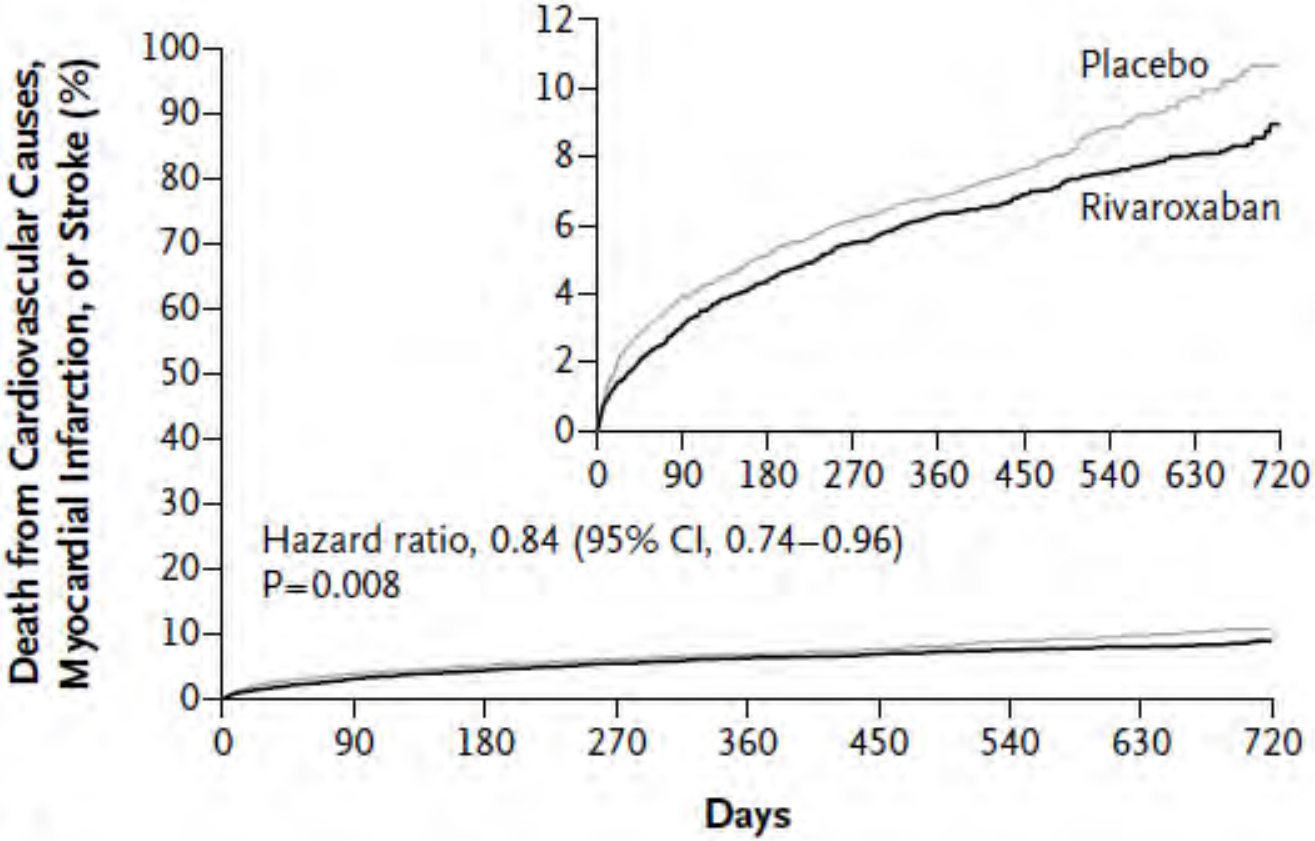
Table 14 Effect of rivaroxaban compared with placebo on the Primary Efficacy End Point and Components(3;5;22;28)

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Parameter	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value mITT	HR (95% CI)	P value mITT	HR (95% CI)	P value mITT
All strata (n)	5114	5115	10229	5113						
Primary Endpoint – Death from CV causes, MI, Stroke	*313 (6.1)*	*313 (6.1)*	*626 (6.1)*	*376 (7.4)*	*0.84 (0.72-0.97)*	*0.02*	*0.85 (0.73-0.98)*	*0.028*	*0.84 (0.74-0.96)*	*0.008*
CV Death	94 (1.8)	132 (2.6)	226 (2.2)	143 (2.8)	0.66 (0.51-0.86)	0.002	0.94 (0.75-1.20)	0.633	0.80 (0.65-0.99)	0.038
MI	205 (4.0)	179 (3.5)	384 (3.8)	229 (4.5)	0.90 (0.75-1.09)	0.270	0.79 (0.65-0.97)	0.020	0.85 (0.72-1.00)	0.047
Stroke	46 (0.9)	54 (1.1)	100 (1.0)	41 (0.8)	1.13 (0.74-1.73)	0.562	1.34 (0.90-2.02)	0.151	1.24 (0.86-1.78)	0.246
Patients with elevated cardiac biomarkers without prior stroke / TIA										
All strata (n)	4104	4089	8193	4160						
Primary Endpoint Death from CV causes, MI, Stroke	[redacted] *(6.2)*	[redacted] *(6.1)*	[redacted] *(6.2)*	[redacted] *(7.9)*	*0.80 (0.68-0.94)*	*0.007*	*0.79 (0.67-0.93)*	*0.004*	*0.79 (0.69-0.91)*	*0.001*
CV Death	[redacted] *(1.7)*	[redacted] *(2.6)*	[redacted] *(2.1)*	[redacted] *(3.1)*	*0.55 (0.41-0.74)*	*<0.001*	*0.89 (0.69-1.15)*	*0.360*	*0.72 (0.57-0.90)*	*0.004*
MI	[redacted] *(4.3)*	[redacted] *(3.6)*	[redacted] *(3.9)*	[redacted] *(4.9)*	*0.88 (0.72-1.08)*	*0.215*	*0.75 (0.61-0.92)*	*0.007*	*0.81 (0.68-0.97)*	*0.021*
Stroke	[redacted] *(0.9)*	[redacted] *(0.9)*	[redacted] *(0.9)*	[redacted] *(0.7)*	*1.23 (0..75-2.02)*	*0.403*	*1.38 (0.85-2.24)*	*0.190*	*1.30 (0.85-2.01)*	*0.225*
Stratum 1 ASA (n)	*349*	*348*	*697*	*353*						
Primary Endpoint	*27 (7.7)*	*24 (6.9)*	*51 (7.3)*	*36 (10.2)*	*0.74 (0.45-1.22)*	*0.234*	*0.64 (0.38-1.07)*	*0.089*	*0.69 (0.45-1.05)*	*0.084*
CV Death	*12 (3.4)*	*9 (2.6)*	*21 (3.0)*	*10 (2.8)*	*1.20 (0.52-2.77)*	*0.673*	*0.89 (0.36-2.20)*	*0.805*	*1.04 (0.49-2.21)*	*0.913*

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Parameter	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value mITT	HR (95% CI)	P value mITT	HR (95% CI)	P value mITT
MI	*16 (4.6)*	*10 (2.9)*	*26 (3.7)*	*22 (6.2)*	*0.72 (0.38-1.37)*	*0.310*	*0.44 (0.21-0.93)*	*0.026*	*0.58 (0.33-1.02)*	*0.053*
Stroke	*2 (0.6)*	*8 (2.3)*	*10 (1.4)*	*7 (2.0)*	*0.28 (0.06-1.37)*	*0.095*	*1.13 (0.41-3.12)*	*0.812*	*0.71 (0.27-1.86)*	*0.483*
Patients with elevated cardiac biomarkers without prior stroke / TIA										
Stratum 1 ASA (n)	[redacted]	[redacted]	[redacted]	[redacted]						
Primary Endpoint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 2 ASA + Thieno (n)	4765	4767	9532	4760						
Primary Endpoint	*286 (6.0)*	*289 (6.1)*	*575 (6.0)*	*340 (7.1)*	*0.85 (0.72-0.99)*	*0.039*	*0.87 (0.74-1.01)*	*0.075*	*0.86 (0.75-0.98)*	*0.024*
CV Death	*82 (1.7)*	*123 (2.6)*	*205 (2.2)*	*133 (2.8)*	0.62 (0.47-0.82)	*<0.001*	0.95 (0.74-1.21)	*0.669*	0.78 (0.63-0.97)	*0.028*
MI	*189 (4.0)*	*169 (3.5)*	*358 (3.8)*	*207 (4.3)*	0.92 (0.75-1.12)	*0.401*	0.83 (0.68-1.02)	*0.077*	0.88 (0.74-1.04)	*0.131*
Stroke	*44 (0.9)*	*46 (1.0)*	*90 (0.9)*	*34 (0.7)*	1.31	*0.238*	1.39	*0.144*	1.35	*0.135*

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Parameter	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value mITT	HR (95% CI)	P value mITT	HR (95% CI)	P value mITT
					(0.84-2.05)		(0.89-2.16)		(0.91-2.00)	
Patients with elevated cardiac biomarkers without prior stroke / TIA										
Stratum 2 ASA + Thieno (n)	[redacted]	[redacted]	[redacted]	[redacted]						
Primary Endpoint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 12 Kaplan-Meier estimates of the primary efficacy endpoint – Rivaroxaban ALL STRATA, COMBINED DOSE vs. placebo (trial population) (3)



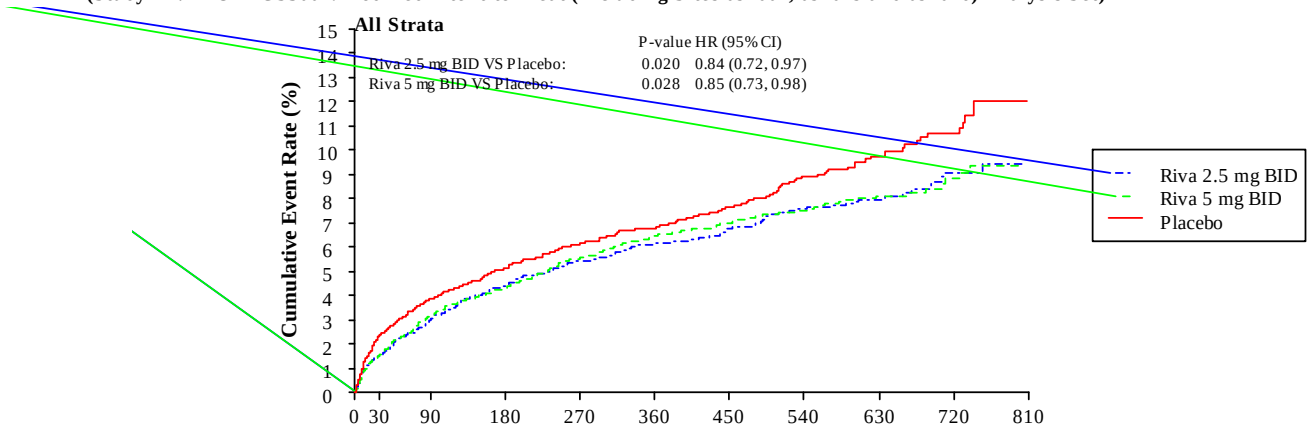
No. at Risk

Rivaroxaban	10,229	8817	7797	6324	5137	3967	2830	1747	831
Placebo	5,113	4437	3974	3253	2664	2059	1460	878	421

Figure 13 Kaplan Meier estimates of the primary efficacy endpoint by stratum / dose (Trial population) (22)

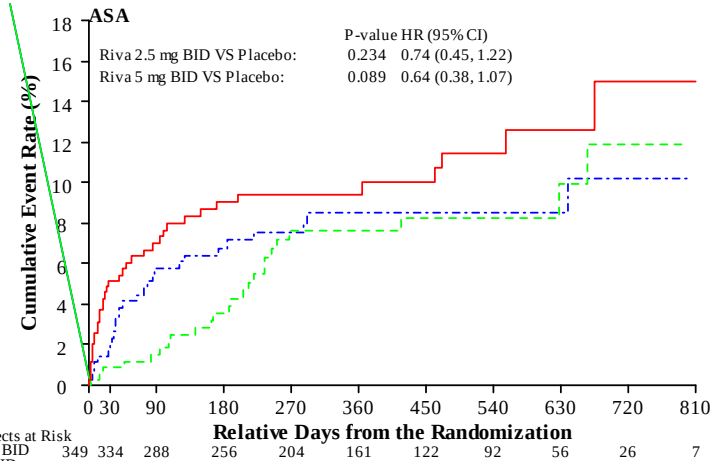
Figure FEFF01A: Kaplan-Meier Estimates of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC

(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)



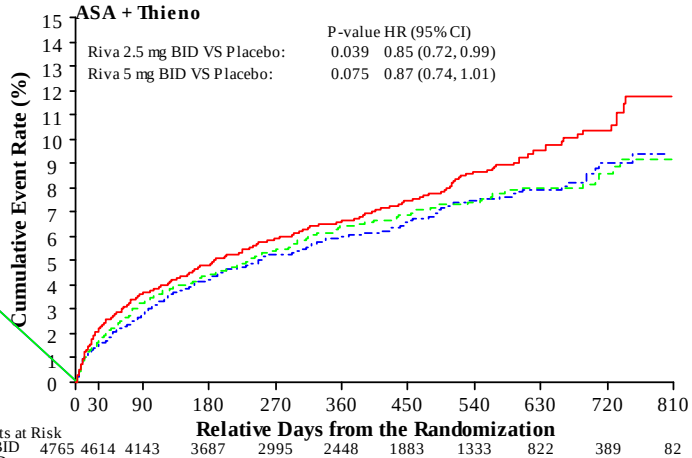
No. of Subjects at Risk

Riva 2.5 mg BID	5114	4948	4431	3943	3199	2609	2005	1425	878	415	89
Riva 5 mg BID	5115	4952	4386	3854	3125	2528	1962	1405	869	416	83
Placebo	5113	4919	4437	3974	3253	2664	2059	1460	878	421	87



No. of Subjects at Risk

Riva 2.5 mg BID	349	334	288	256	204	161	122	92	56	26	7
Riva 5 mg BID	348	338	304	264	205	165	128	97	53	26	6
Placebo	353	328	285	254	197	161	124	91	48	24	5



No. of Subjects at Risk

Riva 2.5 mg BID	4765	4614	4143	3687	2995	2448	1883	1333	822	389	82
Riva 5 mg BID	4767	4614	4082	3590	2920	2363	1834	1308	816	390	77
Placebo	4760	4591	4152	3720	3056	2503	1935	1369	830	397	82

Note: The data shown are for all randomized subjects and the endpoint events occurring at or after randomization and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomization for those subjects who were randomized but not treated.

Note: P-value is based on (stratified, only for all strata) log-rank test and HR (95% CI) is based on (stratified, only for all strata) Cox proportional hazards model.

Note: KM curves for all treatment groups are not displayed when number of subjects at risk in any treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

Figure 14 Kaplan Meier estimates of the primary efficacy endpoint by stratum / dose (Cardiac biomarker positive patients without prior stroke/TIA)(28)

Secondary efficacy endpoints (see Table 15)

As pre-specified in the hierarchical testing strategy (see section 6.3.6, Figure 8), finding significance for the primary efficacy endpoint meant that further analyses for the secondary efficacy endpoints could be performed.

In **ALL STRATA**, both the 2.5mg bd and the 5mg bd doses were superior to placebo in the primary efficacy endpoint analyses, and therefore, both rivaroxaban doses were tested in the secondary efficacy endpoints analyses (see Figure 10).

In **Stratum 2**, only the 2.5mg bd dose met the primary efficacy endpoint, and therefore formal testing of the secondary efficacy endpoints was done on the 2.5mg bd group only (see Figure 11) (22).

Secondary endpoint 1:

Composite of death from any cause, myocardial infarction, or stroke (3;5;22)

The composite Secondary Efficacy Endpoint 1 differs from the primary efficacy endpoint only by replacing the CV death component with all-cause death. Since the majority of all-cause deaths were adjudicated to having CV causes, the results of Secondary Efficacy Endpoint 1 in the mITT analysis set were generally consistent with those of primary efficacy endpoint, for both rivaroxaban doses.

ALL STRATA, COMBINED DOSE - Rivaroxaban reduced the relative risk of the secondary composite efficacy endpoint 1 compared with placebo (6.3% vs. 7.5%; HR=0.84; 95% CI 0.74–0.95; p=0.006).

ALL STRATA, 2.5mg bd - Similar relative risk reductions vs. placebo were observed for rivaroxaban 2.5 mg bd (6.3% vs. 7.5%; HR=0.83; 95% CI 0.72–0.97; p=0.016).

STRATUM 2, COMBINED DOSE – In Stratum 2, rivaroxaban reduced the relative risk of the secondary composite efficacy endpoint 1 compared with placebo (6.2% vs. 7.4%; HR=0.85; 95% CI 0.75–0.97; p=0.019)

STRATUM 2, 2.5mg bd – In Stratum 2, rivaroxaban 2.5 mg bd was superior to placebo, in addition to standard care, in reducing the occurrence of the composite of all-cause death, MI or stroke (HR 0.84; 95% CI: 0.72-0.98). This was driven by a substantial and nominally statistically significant reduction in all-cause mortality (HR 0.64; 95% CI: 0.49-0.83, p<0.001) which was also the case in ALL STRATA (HR 0.68; 95% CI: 0.53-0.87, p=0.002). Numerically lower rates of MIs and numerically higher rates of stroke compared with placebo were also observed in the 2.5 mg bd group.

STRATUM 1, COMBINED DOSE - In Stratum 1, there were numerically less occurrences of secondary endpoint 1 in the rivaroxaban group compared with placebo, however this was not statistically significant (7.5% vs. 10.2%; HR=0.70; 95% CI 0.46–1.07; p=0.101)

STRATUM 1. 2.5mg bd – Similarly to the combined rivaroxaban comparison with placebo in Stratum 1, there were numerically less occurrences of secondary endpoint 1 in the rivaroxaban 2.5mg bd group compared with placebo, however this was not statistically significant (8.0% vs. 10.2%; HR=0.77; 95% CI 0.47–1.26; p=0.291).

Secondary endpoint 2:

Net clinical benefit: composite of CV death, MI, ischaemic stroke and non-CABG TIMI major bleeding events(22)

ALL STRATA, COMBINED DOSE - The difference in this pre-specified composite endpoint did not reach statistical significance when rivaroxaban was compared with placebo (7.1% vs. 7.6%; HR=0.94; 95% CI: 0.83-1.06; *p*=0.337). The benefits of rivaroxaban compared with placebo for reducing the incidence of CV death, MI or stroke were accompanied with an increased risk of non-CABG TIMI major bleeding events (see Table 15).

ALL STRATA, 2.5mg bd - Results directionally favoured rivaroxaban 2.5 mg bd over placebo but were not statistically significant (7.1% vs. 7.6%; HR=0.93; 95% CI 0.81-1.07; p=0.320).

STRATUM 2, COMBINED DOSE – Results directionally favoured rivaroxaban over placebo but were not statistically significant (7.1% vs. 7.5%; HR=0.96; 95% CI 0.85-1.10; p=0.585).

STRATUM 2, 2.5mg bd - Consistent with the results of All Strata, rivaroxaban 2.5 mg bd in Stratum 2 was not significantly different compared with placebo on net clinical outcome (HR: 0.95, 95% CI: 0.82-1.10; p=0.473). As a result, the hierarchical testing for the 2.5 mg bd group in the remaining secondary endpoints in Stratum 2 was also stopped.

STRATUM 1, COMBINED DOSE – rivaroxaban vs, placebo, 7.6% vs. 10.2%. HR=0.72; 95% CI 0.47-1.09; p=0.120.

STRATUM 1. 2.5mg bd – rivaroxaban 2.5mg bd vs, placebo, 8.0% vs. 10.2%. HR=0.77; 95% CI 0.47-1.26; p=0.290.

This type of analysis is considered to be a relatively crude method of assessing benefit-risk as it does not weight the clinical severity of the individual endpoints(6;8). In addition, it is complicated by some events being included in both efficacy and safety endpoints (fatal bleeding events and haemorrhagic stroke were counted both in the primary efficacy endpoint and principal safety outcome), resulting in double counting. Thus, in the pre-specified measure, the benefits of rivaroxaban 2.5 mg bd for significantly reducing CV death (which included no increase in fatal bleeding) are counteracted by increases in non-fatal bleeding. For further discussion of this outcome and details of further post-hoc outcome analyses please see section 6.10.1.

Since the analyses results for All Strata for Secondary Efficacy Endpoint 2 (net clinical outcome) did not meet statistical significance, formal testing of the last 2 additional secondary efficacy endpoints was stopped; however, the results for the analyses of these endpoints are discussed briefly below for completeness:

Secondary endpoint 3:

<u>Composite of CV death, MI, stroke or severe recurrent ischaemia requiring revascularisation</u>

ALL STRATA, COMBINED DOSE - Overall, rivaroxaban did not significantly reduce the occurrence of secondary efficacy endpoint 3 events when compared with placebo (8.4% vs 9.4%) (HR: 0.90, 95% CI: 0.81-1.01; p=0.074).

Similar results were seen for other comparisons, including **ALL STRATA, 2.5mg bd** vs. placebo; **STRATUM 2, COMBINED DOSE** vs. placebo, **STRATUM 2, 2.5mg bd** vs. placebo, **STRATUM 1, COMBINED DOSE** and **STRATUM 1, 2.5mg bd**.

Secondary endpoint 4:

Composite of CV death, MI, stroke or severe recurrent ischaemia leading to hospitalisation (22)

In the **ALL STRATA, COMBINED DOSE** analysis, rivaroxaban significantly reduced the risk of composite secondary endpoint 4 when compared to placebo (see Table 15). Similar results were seen for other comparisons, including **ALL STRATA, 2.5mg bd** vs placebo, **STRATUM 2 COMBINED DOSE** v placebo, **stratum 2 2.5mg bd** vs placebo, but not for **STRATUM 1(COMBINED DOSE or 2.5mg bd)**.

ELEVATED BIOMARKERS WITHOUT PRIOR STROKE/TIA PATIENTS (22;28)

The results in this group of patients show an improved outcome on the secondary composite endpoint and the individual components. Results are directionally consistent with the overall study results, and underline the robustness and validity of the data generated in this pre-specified subgroup.

Secondary endpoint 1:

Composite of death from any cause, myocardial infarction, or stroke

ALL STRATA, COMBINED DOSE – Rivaroxaban significantly reduced the relative risk of all-cause death, MI or stroke as compared with placebo (6.3% vs. 8.1%; HR=0.79; 95% CI 0.69-0.91; p<0.001).

ALL STRATA, 2.5mg bd – The 2.5mg rivaroxaban dose was also superior to placebo for the primary endpoint: 6.4% vs. 8.1%; HR=0.80; 95% CI 0.68-0.94; p= 0.007).

Table 15 Effect of rivaroxaban compared with placebo on Secondary Efficacy End Points and Components as adjudicated by the CEC (mITT) (3;22;28)

Parameter	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
All Strata (n)	**5114**	**5115**	**10229**	**5113**						
Secondary Endpoint 1 *Death/MI/Stroke*	***320 (6.3)***	***321 (6.3)***	***641 (6.3)***	***386 (7.5)***	***0.83 (0.72-0.97)***	***0.016***	***0.84 (0.73-0.98)***	***0.025***	***0.84 (0.74-0.95)***	***0.006***
Secondary Endpoint 2 *(Net Clinical Outcome)*	***361 (7.1)***	***366 (7.2)***	***727 (7.1)***	***391 (7.6)***	***0.93 (0.81-1.07)***	***0.320***	***0.95 (0.83-1.10)***	***0.508***	***0.94 (0.83-1.06)***	***0.337***
Secondary Endpoint 3 *CV Death/MI/Stroke/SRIR*	**437 (8.5)**	**421 (8.2)**	**858 (8.4)**	**481 (9.4)**	**0.92 (0.8-1.04)**	**0.185**	**0.89 (0.78-1.01)**	**0.081**	**0.90 (0.81-1.01)**	**0.074**
Secondary Endpoint 4 *CV Death/MI/Stroke/SRIH*	**372 (7.3)**	**388 (7.6)**	**760 (7.4)**	**447 (8.7)**	**0.84 (0.73-0.96)**	**0.011**	**0.88 (0.77-1.01)**	**0.070**	**0.86 (0.76-0.97)**	**0.011**
Death (all-cause)	103 (2.0)	142 (2.8)	245 (2.4)	153 (3.0)	0.68 (0.53-0.87)	0.002	0.95 (0.76-1.19)	0.662	0.81 (0.66-1.00)	0.044
Ischaemic Stroke	30 (0.6)	35 (0.7)	65 (0.6)	34 (0.7)	0.89 (0.55-1.45)	0.643	1.05 (0.65-1.68)	0.844	0.97 (0.64-1.47)	0.886
Non-CABG TIMI major bleeding	68 (1.3)	85 (1.7)	153 (1.5)	23 (0.4)	2.99 (1.86-4.80)	<0.001	3.81 (2.40-6.04)	<0.001	3.40 (2.19-5.26)	<0.001
SRIR (Severe recurrent ischaemia requiring revascularisation)	132 (2.6)	122 (2.4)	254 (2.5)	121 (2.4)	1.10 (0.86-1.41)	0.445	1.03 (0.80-1.33)	0.798	1.07 (0.86-1.32)	0.557
SRIR (Severe recurrent ischaemia requiring hospitalisation)	74 (1.4)	93 (1.8)	167 (1.6)	99 (1.9)	0.75 (0.56-1.02)	0.063	0.96 (0.73-1.28)	0.798	0.86 (0.67-1.10)	0.223
Patients with elevated cardiac biomarkers without prior stroke / TIA										
All strata (n)	**4104**	**4089**	**8193**	**4160**						
Secondary Endpoint 1 *All cause Death/MI/Stroke*	[redacted] ***(6.4)***	[redacted] ***(6.2)***	[redacted] ***(6.3)***	[redacted] ***(8.1)***	***0.80 (0.68-0.94)***	***0.007***	***0.79 (0.67-0.93)***	***0.004***	***0.79 (0.69-0.91)***	***<0.001***
Secondary Endpoint 2 *(Net Clinical Outcome)*	[redacted] ***(7.2)***	[redacted] ***(7.2)***	[redacted] ***(7.2)***	[redacted] ***(8.1)***	***0.90 (0.77-1.05)***	***0.166***	***0.90 (0.77-1.05)***	***0.184***	***0.90 (0.78-1.03)***	***0.110***
Secondary Endpoint 3	[redacted] ***(8.5)***	[redacted] ***(7.9)***	[redacted] ***(8.2)***	[redacted] ***(9.8)***	***0.87***	***0.059***	***0.81***	***0.006***	***0.84 (0.75-0.95)***	***0.006***

Parameter	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
CV Death/MI/Stroke/SRIR					***(0.76-1.01)***		***(0.70-0.94)***			
Secondary Endpoint 4 *CV Death/MI/Stroke/SRIH*	[redacted] ***(7.1)***	[redacted] ***(7.4)***	[redacted] ***(7.2)***	[redacted] ***(8.9)***	***0.80 (0.68-0.93)***	***0.004***	***0.84 (0.72-0.98)***	***0.026***	***0.82 (0.72-0.93)***	***0.002***
Death (all-cause)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CABG TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIR (Severe recurrent ischaemia requiring revascularisation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIR (Severe recurrent ischaemia requiring hospitalisation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 1 (ASA)	*n=349*	*n=348*	*n=697*	*n=353*						
Secondary Endpoint 1 *Death/MI/Stroke*	***28 (8.0)***	***24 (6.9)***	***52 (7.5)***	***36 (10.2)***	***0.77 (0.47-1.26)***	***0.291***	***0.64 (0.38-1.07)***	***0.089***	***0.70 (0.46-1.07)***	***0.101***
Secondary Endpoint 2 *(Net Clinical Outcome)*	***28 (8.0)***	***25 (7.2)***	***53 (7.6)***	***36 (10.2)***	***0.77 (0.47-1.26)***	***0.290***	***0.67 (0.4-1.11)***	***0.120***	***0.72 (0.47-1.09)***	***0.120***
Secondary Endpoint 3 *CV Death/MI/Stroke/SRIR*	**31 (8.9)**	**28 (8.0)**	**59 (8.5)**	**39 (11.0)**	**0.78 (0.49-1.26)**	**0.313**	**0.69 (0.43-1.13)**	**0.136**	**0.74 (0.49-1.10)**	**0.138**
Secondary Endpoint 4 *CV Death/MI/Stroke/SRIH*	**32 (9.2)**	**30 (8.6)**	**62 (8.9)**	**42 (11.9)**	**0.75 (0.47-1.19)**	**0.219**	**0.69 (0.43-1.09)**	**0.112**	**0.72 (0.48-1.06)**	**0.093**
Death (all-cause)	13 (3.7)	9 (2.6)	22 (3.2)	10 (2.8)	1.30 (0.57-2.96)	0.533	0.89 (0.36-2.20)	0.805	1.09 (0.52-2.31)	0.814
Ischaemic Stroke	1 (0.3)	5 (1.4)	6 (0.9)	6 (1.7)	0.17	0.059	0.82	0.749	0.50	0.216

Parameter	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
					(0.02-1.38)		(0.25-2.70)		(0.16-1.54)	
Non-CABG TIMI major bleeding	2 (0.6)	4 (1.1)	6 (0.9)	0 (0.0)	-	0.160	-	0.046	-	0.085
SRIR (Severe recurrent ischaemia requiring revascularisation)	4 (1.1)	4 (1.1)	8 (1.1)	4 (1.1)	1.00 (0.25-4.01)	0.995	1.00 (0.25-3.99)	0.997	1.00 (0.30-3.32)	0.999
SRIR (Severe recurrent ischaemia requiring hospitalisation)	6 (1.7)	7 (2.0)	13 (1.9)	8 (2.3)	0.74 (0.26-2.13)	0.574	0.87 (0.31-2.39)	0.779	0.80 (0.33-1.94)	0.627
Patients with elevated cardiac biomarkers without prior stroke / TIA										
Stratum 1 (ASA)										
Secondary Endpoint 1 *Death/MI/Stroke*										
Secondary Endpoint 2 *(Net Clinical Outcome)*										
Secondary Endpoint 3 *CV Death/MI/Stroke/SRIR*										
Secondary Endpoint 4 *CV Death/MI/Stroke/SRIH*										
Death (all-cause)										
Ischaemic Stroke					-					
Non-CABG TIMI major bleeding					-	-	-		-	
SRIR (Severe recurrent										

Parameter	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
ischaemia requiring revascularisation)					[redacted]		[redacted]		[redacted]	
SRIR (Severe recurrent ischaemia requiring hospitalisation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 2	***n=4765***	***n=4767***	***n=9532***	***n=4760***						
Secondary Endpoint 1 *Death/MI/Stroke*	***292 (6.1)***	***297 (6.2)***	***589 (6.2)***	***350 (7.4)***	***0.84 (0.72-0.98)***	***0.028***	***0.87 (0.74-1.01)***	***0.068***	***0.85 (0.75-0.97)***	***0.019***
Secondary Endpoint 2 *(Net Clinical Outcome)*	***333 (7.0)***	***341 (7.2)***	***674 (7.1)***	***355 (7.5)***	***0.95 (0.82-1.10)***	***0.473***	***0.98 (0.85-1.14)***	***0.818***	***0.96 (0.85-1.10)***	***0.585***
Secondary Endpoint 3 *CV Death/MI/Stroke/SRIR*	**406 (8.5)**	**393 (8.2)**	**799 (8.4)**	**442 (9.3)**	**0.93 (0.81-1.06)**	**0.276**	**0.91 (0.79-1.04)**	**0.164**	**0.92 (0.82-1.03)**	**0.149**
Secondary Endpoint 4 *CV Death/MI/Stroke/SRIH*	**340 (7.1)**	**358 (7.5)**	**698 (7.3)**	**405 (8.5)**	**0.85 (0.73-0.98)**	**0.022**	**0.90 (0.78-1.04)**	**0.159**	**0.87 (0.77-0.99)**	**0.031**
Death (all-cause)	90 (1.9)	133 (2.8)	223 (2.3)	143 (3.0)	0.64 (0.49-0.83)	<0.001	0.95 (0.75-1.21)	0.698	0.79 (0.64-0.98)	0.030
Ischaemic Stroke	29 (0.6)	30 (0.6)	59 (0.6)	28 (0.6)	1.05 (0.62-1.76)	0.864	1.10 (0.66-1.84)	0.723	1.07 (0.68-1.68)	0.760
Non-CABG TIMI major bleeding	66 (1.4)	81 (1.7)	147 (1.5)	23 (0.5)	2.90 (1.81-4.67)	<0.001	3.64 (2.29-5.78)	<0.001	3.27 (2.10-5.07)	<0.001
SRIR (Severe recurrent ischaemia requiring revascularisation)	128 (2.7)	118 (2.5)	246 (2.6)	117 (2.5)	1.10 (0.86-1.42)	0.438	1.03 (0.80-1.34)	0.794	1.07 (0.86-1.33)	0.551
SRIR (Severe recurrent ischaemia requiring hospitalisation)	68 (1.4)	86 (1.8)	154 (1.6)	91 (1.9)	0.75 (0.55-1.03)	0.077	0.97 (0.72-1.31)	0.853	0.86 (0.66-1.12)	0.259
Patients with elevated cardiac biomarkers without prior stroke / TIA										
Stratum 2 (n)	[redacted]	[redacted]	[redacted]	[redacted]						
Secondary Endpoint 1 *Death/MI/Stroke*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Secondary Endpoint 2 *(Net Clinical Outcome)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary Endpoint 3 *CV Death/MI/Stroke/SRIR*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary Endpoint 4 *CV Death/MI/Stroke/SRIH*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (all-cause)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CABG TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIR (Severe recurrent ischaemia requiring revascularisation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIR (Severe recurrent ischaemia requiring hospitalisation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Components of composite endpoints

CV death (3;22)

For rivaroxaban **ALL STRATA, COMBINED DOSE** compared with placebo, the **relative risk of CV death** was reduced by 20% (2.2% vs. 2.8%; HR=0.80; 95% CI 0.65–0.99; *p*=0.038).

When data for each dose were evaluated separately, rivaroxaban **ALL STRATA, 2.5 mg bd** compared with placebo, significantly reduced the rate of CV death by 34% (1.8% vs. 2.8%; HR=0.66; 95% CI 0.51–0.86; *p*=0.002) (see Table 14).

Of CV deaths, the most common causes (numbers of patients with rivaroxaban 2.5 mg vs. placebo, in the mITT population) were sudden or unwitnessed death, fatal MI and fatal congestive heart failure (CHF)/cardiogenic shock. Studies have shown that sudden or unwitnessed deaths are frequently caused by thrombosis in a coronary artery, although these events are not always recorded as being MIs(32). Results suggest that a reduction in the incidence of fatal heart attacks contributed to the significant reduction in CV mortality achieved by adding rivaroxaban 2.5 mg bd to standard antiplatelet therapy.

CV deaths included all fatal bleeding events. In **ALL STRATA**, for rivaroxaban 2.5 mg vs placebo, rates for fatal non-intracranial bleeding were 0 vs. 1 patients and fatal ICH occurred in 5 (0.1%) vs. 4 patients (0.1%)(22).

STRATUM 2 COMBINED – In line with ALL STRATA, the combined rivaroxaban group demonstrated a significant reduction in CV death compared with the placebo group (2.2% vs. 2.8%; HR=0.78; 95% CI 0.63–0.97; *p*=0.028)(22).

This was also the case when comparing the effects of low dose rivaroxaban with placebo in STRATUM 2:

STRATUM 2, 2.5mg bd - Rivaroxaban 2.5mg bd vs placebo (1.7% vs. 2.8%; HR=0.62; 95% CI 0.47–0.82; *p*=<0.001).

Event occurrences and patient numbers were low in **STRATUM 1**, and confidence intervals large, making any conclusions on the effect of rivaroxaban or placebo unreliable.

STRATUM 1 COMBINED: Rivaroxaban vs placebo (3.0% vs. 2.8%; HR=1.04; 95% CI 0.49–2.21; *p*=0.913).

STRATUM 1, 2.5mg bd- Rivaroxaban 2.5mg bd vs placebo (3.4% vs. 2.8%; HR=1.20; 95% CI 0.52–2.77; p=0.673).

Myocardial infarction (MI) (3;5;22)

The relative risk of MI (fatal and non-fatal, both strata combined) was 15% lower for rivaroxaban **ALL STRATA, COMBINED DOSE** than for placebo (3.8% vs. 4.5%; HR=0.85; 95% CI 0.72–1.00; *p*=0.047).

Rivaroxaban **ALL STRATA, 2.5 mg bd** showed a numerical but not statistically significant reduction in MI events compared with placebo (4.0% vs. 4.5%; HR=0.90; 95% CI 0.75–1.09; *p*=0.270).

Results in Stratum 2 are directionally consistent with All Strata (see Table 14):

STRATUM 2 COMBINED – Rivaroxaban vs placebo (3.8% vs. 4.3%; HR=0.88; 95% CI 0.74–1.04; *p*=0.131).

STRATUM 2, 2.5mg bd - Rivaroxaban 2.5mg bd vs placebo (4.0% vs. 4.3%; HR=0.92; 95% CI 0.75–1.12; *p*=0.401).

STRATUM 1 COMBINED - Rivaroxaban vs placebo (3.7% vs. 6.2%; HR=0.58; 95% CI 0.33–1.02; *p*=0.053).

STRATUM 1, 2.5mg bd - Rivaroxaban 2.5mg bd vs placebo (4.6% vs. 6.2%; HR=0.72; 95% CI 0.38–1.37; *p*=0.310).

Stroke (3;5;22)

Rates of stroke of any type (including ischaemic, haemorrhagic and stroke of uncertain cause) for **ALL STRATA, COMBINED DOSE** were 1.0% for rivaroxaban compared with 0.8% for placebo (HR=1.24; 95% CI 0.86-1.78; *p*=0.246 (see Table 14).

With the exception of **STRATUM 1 COMBINED and STRATUM 1 2.5mg**, where numbers were too small to derive any meaningful conclusion**,** analyses for **ALL STRATA 2.5mg bd, STRATUM 2 COMBINED, STRATUM 2, 2.5mg bd** mirrored the observation for ALL STRATA combined – that rivaroxaban did not reduce the risk of stroke compared with placebo in patients with ACS.

Stent thrombosis[2](3;23) (see Table 16)

ALL STRATA, COMBINED DOSE - Rivaroxaban combined with standard antiplatelet therapy reduced the risk of stent thrombosis (definite, probable or possible), as compared with placebo combined with standard antiplatelet therapy; with rates of [redacted] respectively [redacted]

ALL STRATA, 2.5mg bd - Rivaroxaban 2.5mg bd (all strata) significantly reduced the risk of stent thrombosis by 30% compared with placebo (1.2% vs. 1.7%; HR=0.70; 95% CI 0.51–0.97; p=0.033).

In STRATUM 2, a similar reduction in stent thrombosis was observed in the rivaroxaban treatment groups compared with placebo (**STRATUM 2, COMBINED DOSE**: [redacted] vs. 1.8%; [redacted]

For STRATUM 2, 2.5mg bd, the incidence of stent thrombosis observed in the 2.5mg bd group was also significantly lower than that observed with placebo 1.2% vs. 1.8%; HR=0.68; 95% CI 0.49–0.95; [redacted]

[2] This is reported from the ITT-Total analysis

The reduction in stent thrombosis by rivaroxaban was not observed in Stratum 1, again with low patient numbers and wide confidence intervals.

STRATUM 1 COMBINED - Rivaroxaban vs placebo ([redacted]

STRATUM 1, 2.5mg bd - Rivaroxaban 2.5mg bd vs placebo ([redacted]

Data on stent thrombosis for the licensed population is in Table 16.

Table 16 Effect of rivaroxaban compared with placebo on Stent thrombosis as adjudicated by the CEC (ITT analysis) (3;5;22;23)

Parameter	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd (N=5114) n (%)	5mg bd (N=5115) n (%)	Combined (N=10,229) n (%)	(N=5113) n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
ALL STRATA										
Stent thrombosis	***61 (1.2)***	***61 (1.2)***	[redacted]	***87 (1.7)***	***0.70 (0.51-0.97)***	***0.033***	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 1 (ASA)	[redacted]	[redacted]	[redacted]	[redacted]						
Stent thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 2	[redacted]	[redacted]	[redacted]	[redacted]						
Stent thrombosis	***58 (1.2)***	***60 (1.3)***	[redacted]	***85 (1.8)***	***0.68 (0.49-0.95)***	[redacted]	***0.71 (0.51-0.99)***	[redacted]	[redacted]	[redacted]
Parameter	**Rivaroxaban**			**Placebo**	**2.5mg bd vs. placebo**		**5mg bd vs. placebo**		**Combined vs. placebo**	
	2.5mg bd (N=4104) n (%)	**5mg bd (N=4089) n (%)**	**Combined (N=8,193) n (%)**	**(N=4160) n (%)**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Subjects with Elevated Biomarkers, but without Prior Stroke/ TIA										

Parameter	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd (N=5114) n (%)	5mg bd (N=5115) n (%)	Combined (N=10,229) n (%)	(N=5113) n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
ALL STRATA										
Stent thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 1 (ASA)	[redacted]	[redacted]	[redacted]	[redacted]						
Stent thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 2	[redacted]	[redacted]	[redacted]	[redacted]						
Stent thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All cause-death(3;5) (see Table 15)

ALL STRATA, COMBINED DOSE - The relative risk of all-cause death was reduced by 19% by rivaroxaban when compared with placebo (2.4% vs. 3.0%; HR=0.81; 95% CI 0.66–1.00; *p*=0.044).

ALL STRATA, 2.5mg bd - Rivaroxaban 2.5 mg bd compared with placebo significantly reduced the rate of all-cause death by 32% (2.0% vs. 3.0%; HR=0.68; 95% CI 0.53–0.87; *p*=0.002).

STRATUM 2 COMBINED DOSE - Rivaroxaban vs placebo (2.3% vs. 3.0%; HR=0.79; 95% CI 0.64–0.98; *p*=0.030).

STRATUM 2, 2.5mg bd - Compared with placebo, rivaroxaban 2.5mg bd significantly reduced the rate of all-cause death by 36% (1.9% vs. 3.0%; HR=0.64; 95% CI 0.49–0.83; *p*<0.001),

The reduction in all cause death by rivaroxaban was not observed in Stratum 1. **STRATUM 1 COMBINED** - Rivaroxaban vs placebo (3.2% vs. 2.8%; HR=1.09; 95% CI 0.52–2.31; *p*=0.814). **STRATUM 1, 2.5mg bd** - Rivaroxaban 2.5mg bd vs placebo (3.7% vs. 2.8%; HR=1.30; 95% CI 0.57–2.96; *p*=0.533).

ELEVATED BIOMARKERS WITHOUT PRIOR STROKE/TIA PATIENTS(22;28)

Components of composite endpoints

In patients with elevated biomarkers without prior stroke/TIA, the event rate (ALL STRATA) for the individual component of **CV death** was 1.7% in the rivaroxaban 2.5 mg bd group compared to 3.1% in the placebo group with a HR for CV death of 0.55 (95% CI 0.41-0.74) and a p-value of <0.001. Patients with positive biomarker can expect a 45% RRR in risk for CV death compared to standard of care with dual anti-platelet therapy.

The event rate for **MI** was also reduced in the rivaroxaban 2.5 mg bd group (ALL STRATA) with 4.3% compared to 4.9% in the placebo group. The HR for MI was 0.88 (95% CI: 0.72, 1.08; p= 0.215) and for **stroke** 1.23 (95% CI: 0.75, 2.02; P=0.403). Rivaroxaban did not reduce the risk of stroke compared with placebo in patients with ACS and elevated biomarkers without prior stroke/TIA.

[redacted]

Sensitivity analyses (3;5)

A large number of sensitivity analyses were carried out to test the robustness of the primary analysis.

Table 17 lists all the analyses performed and indicates whether or not each analysis was consistent with the primary mITT analysis.

Table 17 Sensitivity analyses – consistency with mITT

[redacted]

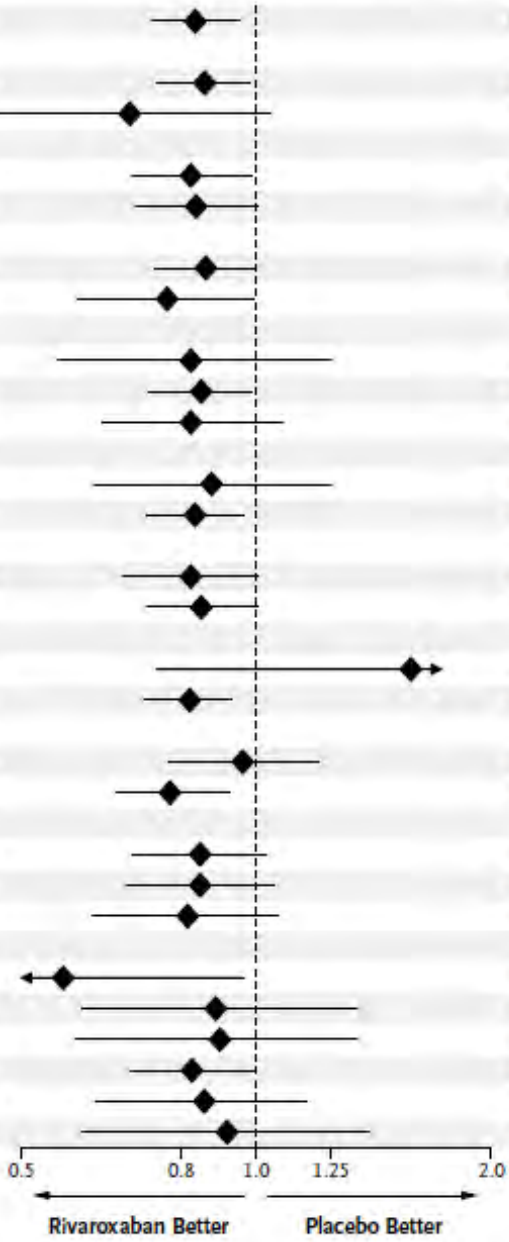
✓= consistent with primary mITT efficacy analysis X = inconsistent with primary efficacy analysis

Subgroup analyses – Efficacy (3;5)

In general, rivaroxaban treatment was consistently associated with improved outcomes on the primary efficacy endpoint across all major subgroups.

Figure 15 **Risks of the Primary Efficacy Endpoint according to major subgroups (ALL STRATA, COMBINED DOSE)(3)**

Subgroup	Combined Rivaroxaban	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no.			
Overall	626/10,229	376/5113	0.84 (0.74–0.96)	
Treatment				0.34
Aspirin plus thienopyridine	575/9532	340/4760	0.86 (0.75–0.98)	
Aspirin alone	51/697	36/353	0.69 (0.45–1.05)	
Age				0.94
<65 yr	326/6440	203/3295	0.83 (0.70–0.99)	
≥65 yr	300/3789	173/1818	0.84 (0.70–1.01)	
Sex				0.40
Male	464/7627	270/3831	0.87 (0.75–1.01)	
Female	162/2602	106/1282	0.77 (0.60–0.99)	
Weight				0.98
<60 kg	61/918	39/462	0.83 (0.56–1.25)	
≥60 to <90 kg	415/6811	248/3432	0.85 (0.72–0.99)	
≥90 kg	150/2494	89/1215	0.83 (0.64–1.08)	
Creatinine clearance				0.82
<50 ml/min	80/686	49/368	0.88 (0.62–1.26)	
≥50 ml/min	541/9411	326/4691	0.84 (0.73–0.96)	
Previous myocardial infarction				0.80
Yes	256/2739	156/1400	0.83 (0.68–1.01)	
No	370/7490	220/3713	0.85 (0.72–1.01)	
Previous stroke or TIA				0.10
Yes	31/284	9/131	1.57 (0.75–3.31)	
No	595/9945	367/4982	0.82 (0.72–0.94)	
Diabetes mellitus				0.14
Yes	232/3268	122/1626	0.96 (0.77–1.20)	
No	394/6961	254/3487	0.78 (0.67–0.92)	
Index event				0.96
STEMI	288/5128	172/2599	0.85 (0.70–1.03)	
NSTEMI	201/2646	121/1321	0.85 (0.68–1.06)	
Unstable angina	137/2455	83/1193	0.82 (0.62–1.07)	
Region				0.80
North America	27/562	27/312	0.57 (0.33–0.97)	
South America	64/1129	35/540	0.89 (0.59–1.34)	
Western Europe	59/1482	34/759	0.90 (0.59–1.37)	
Eastern Europe	306/4067	181/2007	0.83 (0.69–1.00)	
Asia	109/2011	65/1000	0.86 (0.63–1.17)	
Other	61/978	34/495	0.92 (0.60–1.39)	



One exception was the subgroup of patients defined by history of stroke or transient ischaemic attack TIA (eligible for Stratum 1 only). These patients gained no benefit from rivaroxaban treatment. HRs for rivaroxaban versus placebo in the primary efficacy endpoint (analysed across both strata) in patients with (n=415) or without (n=14,927) a history of stroke/TIA were 1.57 and 0.82, respectively. This trend in ATLAS ACS 2 TIMI 51 is consistent with findings from other clinical trials and registries (TRITON, ACTION, GRACE). Consequently, as part of the licensing process, rivaroxaban treatment for ACS is contraindicated in patients with prior stroke or TIA(23).

The trial population reflected patients with ACS who are typically seen in everyday clinical practice (e.g. those with relevant risk factors and underlying co-morbidities). Thus, consistency of the subgroup analyses with the primary efficacy analysis demonstrates that a wide range of patient types benefitted from rivaroxaban added to standard antiplatelet therapy. Nevertheless, a request was made by the EMA, during the marketing authorisation process, for a narrower population of ACS patients to be identified with a more favourable benefit-risk balance derived from treatment with rivaroxaban in addition to dual antiplatelet therapy.

Further exploration of the treatment effect in prespecified subgroups of the ATLAS ACS2 TIMI 51 trial revealed that the population that can be expected to derive the most favourable benefit risk balance from a treatment with rivaroxaban 2.5 mg bd on top of dual antiplatelet therapy after an ACS is patients with elevated cardiac biomarkers. Such patients are at increased cardiovascular risk and additional analysis of this subgroup of patients in the ATLAS ACS2 TIMI 51 study, also excluding patients with prior stroke/TIA, showed an improved outcome on efficacy, both on the primary and secondary composite endpoint and the individual components, when compared to the overall study population (see Table 14 and Table 15).

In the mITT analysis set in All Strata in patients with elevated biomarkers and excluding patients with prior stroke/ TIA, the HR for the primary efficacy endpoint was 0.80 (95% CI: 0.68, 0.94) and a highly nominally significant p-value of 0.007 for rivaroxaban 2.5 mg bd. The absolute risk reduction on the primary composite efficacy endpoint was 1.7%. The event rate for the individual component of CV death was 1.7% in the rivaroxaban 2.5 mg bd group compared to 3.1% in the placebo group with a HR for CV death of 0.55 (95% CI: 0.41, 0.74, p <0.001) and an absolute risk reduction of 1.4%. Whilst outcomes on efficacy were improved in patients with elevated biomarkers at baseline without prior stroke/ TIA, comparable bleeding rates to the overall study population were observed. Consequently, both the Net Clinical Outcome (NCO, Secondary Efficacy Endpoint 2) and the Net Clinical Benefit improved in the subset of patients with elevated biomarkers without a history of prior stroke/ TIA as compared to the overall study population. Compared with placebo, rivaroxaban 2.5 mg bd prevented 159 (95% CI: 50, 269) non-bleeding CV death, MI and ischaemic stroke events per 10,000 patient-years, while causing 3 (95% CI: -20, 26) fatal bleeding or ICH events.

The licenced population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically sound as the trial was not powered to draw conclusion about (non-pre-specified) subgroups of subgroups.

Primary Safety Endpoint – safety endpoint data are reported in Section 6.9.1. and 6.9.2.

Quality of life (using the EuroQol (EQ-5D) questionnaire) (5) Baseline EQ-5D score was[redacted]
among treatment arms (ALL STRATA) with a mean baseline utility of[redacted]

utility score could be seen as the trial progressed i.e. mean utility score at 96 weeks[redacted]

Medical Resource utilisation (MRU) (5)- In line with the results for the Primary Efficacy endpoint, a trend towards improvement
[redacted]

ER visits – For All-cause ER
visits[redacted]

Rehabilitation / Home
Care[redacted]

PCI or CABG Procedures Performed During the Study
- In All Strata, after randomisation, PCI procedures were performed in[redacted]
patients in the combined rivaroxaban groups and [redacted]
patients in the placebo group. Post-randomisation CABG procedures were performed in [redacted]patients in the combined rivaroxaban groups and [redacted]
patients in the placebo group. The percentage of patients who had PCI or CABG procedures performed during the study was[redacted]
in Stratum 2. In Stratum
1,[redacted]

Compliance and Extent of Exposure (5;22) - During treatment, the proportions of patients who were at least 85% compliant with the study drug were 93.9% of patients receiving the 2.5mg dose of rivaroxaban, 94.0% receiving the 5mg dose of rivaroxaban, and 94.6% receiving placebo.

The mean duration of treatment with a study drug was 13.1 months. Maximum follow up was 31 months. In All Strata, the median total duration of treatment (from the first dose of

study drug administration to the last dose of study drug administration including days both on and off study drug) was [redacted] in the rivaroxaban 2.5 mg bd, and [redacted]

days in the placebo group [safety population]. As this was an event-driven study, patients were exposed to study drug for varying lengths of time, depending on when they were randomised. Across all treatment groups, more than 75% of patients were exposed to study drug for ≥6 months, more than half for ≥12 months, and almost one-third were exposed for ≥18 months.
[redacted]

Protocol Deviations (5) – All major protocol deviations were recorded in the eCRF. Of the 15,526 randomised patients in All Strata, [redacted]
had major protocol deviations; the distribution of major protocol deviations [redacted]

Missing data / Patient discontinuation

Premature discontinuation *of treatment*

Among patients who received at least one dose of a study drug (i.e. primary safety analysis population), premature discontinuation of treatment occurred in 26.9% (n=1376) of patients receiving the 2.5mg dose of rivaroxaban, 29.4% (n=1504) receiving the 5-mg dose of rivaroxaban, and 26.4% (n=1351) receiving placebo(3). The most common reasons for discontinuation of study drug were adverse events (see Section 6.9) (8.8% rivaroxaban 2.5 mg bd, 10.9% rivaroxaban 5.0 mg bd and 7.3% placebo arms), consent withdrawal (4.7% rivaroxaban 2.5 mg bd, 4.3% rivaroxaban 5.0 mg bd and 4.3% placebo arms) and 'other'. 'Other' reasons for treatment discontinuation accounted of 11.5%, 11.3% and 11.8% of patients from the rivaroxaban 2.5 mg bd, rivaroxaban 5.0 mg bd and placebo arms, respectively(22). These reasons
included [redacted]

In the event of bleeding, permanent discontinuation from the study was required if the patient experienced intracranial bleeding or bleeding into a critical organ, including intraocular bleeding. Otherwise study drug could be interrupted (temporarily discontinued), as necessary, but could not exceed 28 consecutive days. If study drug was discontinued for longer than 28 days, permanent discontinuation from study drug was requested and such patients entered the follow-up period.

Primary reasons for premature discontinuation of study drug for **all randomised patients** are [redacted]

Premature discontinuation *from study*

Of the 15,526 patients randomised, 13,124 (84.5%) patients completed the study alive

(patients who completed the follow-up period were considered to have completed the study) and 537 patients (3.5%) died.

The remaining 1,865 (12.0%) subjects were categorised as having “incomplete follow-up”. 11,026 (71.0%) randomised patients completed both the double-blind treatment period and the study.

Patients who withdrew consent for study drug administration were encouraged to remain in the study for endpoint event assessment(2).

At study end, of the 1,294 patients who withdrew consent,

177 (13.7%) patients were confirmed to be alive (54, 57, and 66 on rivaroxaban 2.5 mg BID, rivaroxaban 5 mg bd, and placebo, respectively). Vital status therefore remained unknown for 1,117 (86.3%) patients who withdrew consent, of which the sponsor was denied permission to collect vital status information on 1,111 patients, and unable to contact 6 patients after the global treatment end date(5).

The rates of loss to follow-up were 0.2%, 0.3%, and 0.3%, respectively.

During discussions with the FDA, concerns were raised about the level of missing data due to incomplete follow-up of patients who prematurely discontinued from the study for reasons other than death (7).

An extensive plan and effort was put in effect to obtain vital status information on consent withdrawn patients.

With the newly obtained vital status data, the proportion of patients with unknown vital status was reduced to 3.2% (495 patients) in the ITT analysis set and 1.8% (278 patients) in the mITT analysis set(7).

Efficacy Summary

The ATLAS ACS 2 TIMI 51 study met its primary objective. In patients with recent acute coronary syndrome, compared with placebo, rivaroxaban (2.5 or 5 mg bd) in addition to standard care (ASA or ASA plus clopidogrel) demonstrated:

- a significant reduction in the first occurrence of the composite endpoint of CV death/MI/Stroke (HR 0.84, 95% CI: 0.74, 0.96, p=0.008)
- When the 2.5mg bd dose is added to standard of care, it also leads to a significant reduction in the primary endpoint (HR 0.84, 95% CI: 0.72, 0.97, p=0.02). This decrease is driven by a 34% reduction in CV death (HR 0.66, 95% CI 0.51, 0.86, p=0.002)
- Consistent findings across analysis populations, confirming the robustness of the primary efficacy result

Kaplan-Meier analysis of the ATLAS ACS 2-TIMI 51 trial demonstrated a sustained benefit of rivaroxaban (2.5 mg b.i.d.) in combination with SoC during the second year of treatment.

The 2.5mg bd dose also showed a non-significant but directionally consistent benefit for myocardial infarction and a significant reduction in the risk of stent thrombosis, a finding that suggests that enhanced thrombin activity may play a role in these events.

The 2.5mg bd dose in addition to standard care also showed a significant decrease in the risk of all-cause death (HR 0.68, 95% CI 0.53, 0.87, p=0.002)

Results from analysis of Stratum 2 (patients receiving ASA and clopidogrel) demonstrated similar observations to the All Strata analyses for the combined rivaroxaban doses as well as the 2.5 mg bd dose.

In Stratum 1, while the number of events is low, rivaroxaban showed a numerical benefit in the composite primary efficacy endpoint.

Regarding the licensed population, the relative risk reduction in the primary endpoint of 20% is higher than the RRR in the overall trial population (16% RRR) and the absolute risk reduction of 1.7% for the primary endpoint of CV death, MI and stroke is clinically meaningful.

Patients with positive biomarkers can expect a 45% RRR in CV death as well as a [redacted]

RRR in all-cause death compared to standard of care with anti-platelet therapy.

Thus the addition of low dose anticoagulation with rivaroxaban may represent a new treatment strategy in patients with recent acute coronary syndrome.

On the basis of results from ATLAS ACS 2 TIMI 51, the 2.5mg bd rivaroxaban dose has received marketing approval in the EU for the '*prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers*'. An improved outcome on efficacy, both on the primary and secondary composite endpoints and the individual components was demonstrated in this patient population, when compared with the overall trial population.

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

Not applicable.

Data from only one rivaroxaban RCT study (ATLAS-ACS 2 TIMI 51) are relevant to the submission. Therefore, a meta-analysis is not possible.

6.7 Indirect and mixed treatment comparisons

Not undertaken – not applicable.

6.8 Non-RCT evidence

There are no relevant non-RCTs included in this submission.

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 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 sections 9.8 and 9.9, appendices 8 and 9.

Evidence of the safety of rivaroxaban when added to standard care ASA or ASA plus thienopyridine, in patients with recent ACS (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], or unstable angina [UA]), is provided by safety analyses and adverse event reporting from an international, multicentre, prospective, randomised, double-blind, placebo-controlled, event-driven phase III study (ATLAS-ACS 2 TIMI 51)(2;3;5). The design, methodology, all clinical and safety endpoints, statistical plan and efficacy results from ATLAS-ACS 2 TIMI 51 are detailed in sections 6.3 to 6.5.

Since rivaroxaban is an anticoagulant, special attention was paid to bleeding in the study. The **primary safety endpoint** of ATLAS-ACS 2 TIMI 51 was TIMI major bleeding not related to coronary-artery bypass grafting (CABG) [Non-CABG TIMI major bleeding](3). Three bleeding event scales were used to assess bleeding events in the study. The TIMI scale was the primary bleeding scale, with categories of TIMI major, TIMI minor, bleeding requiring medical attention, and insignificant bleeding events. The other two bleeding scales (ISTH and GUSTO) were used to provide additional supportive information on bleeding. Full details of the definitions and bleeding classification scales can be found in section 6.3.5 Outcomes. All bleeding events were adjudicated by the CEC according to all 3 classifications.

The total number of patients valid for the safety analysis from the ATLAS-ACS 2 TIMI 51 study was 15,350 (safety analysis set) (n=5115 rivaroxaban 2.5mg bd; n=5110 rivaroxaban 5mg bd; n=5125 placebo).

Non-CABG TIMI major bleeding(3;5;22)

The overall incidence of treatment-emergent non-CABG TIMI major bleeding events, the **principal safety outcome,** was low. There was a dose-dependent increase in the rate of **non-CABG TIMI major bleeding** events for rivaroxaban added to antiplatelet therapy compared with antiplatelet therapy alone (see Table 18). Note that it is the 2.5mg bd dose that is the licensed dose.

ALL STRATA, COMBINED DOSE - Rates of non-CABG TIMI major bleeding were 1.4% for the combined rivaroxaban group compared with 0.4% for placebo (HR=3.96; 95% CI 2.46–6.38; $p<0.001$).

ALL STRATA, 2.5mg bd - A significant increase compared with placebo was seen with rivaroxaban 2.5 mg bd (1.3% vs. 0.4%; HR=3.46; 95% CI 2.08–5.77; $p<0.001$).

STRATUM 2 – The pattern of increases in non-CABG TIMI major bleeding with rivaroxaban was also seen in Stratum 2 (see **Error! Reference source not found.**).

STRATUM 1 - Treatment-emergent non-CABG TIMI major bleeding was also numerically higher in both the combined and individual rivaroxaban groups compared with placebo in Stratum 1, but none of the differences were statistically significant.

Sensitivity analyses of the primary safety endpoint for the combined and individual doses of rivaroxaban compared with placebo in All Strata and Stratum 2,[redacted]

Table 12[redacted]

ELEVATED BIOMARKERS WITHOUT PRIOR STROKE/TIA PATIENTS (22;28)

As per the efficacy section, results for the now licensed population i.e. patients with elevated cardiac biomarkers without prior stroke/TIA, are presented alongside the results for the overall trial population in the summary tables.

The analyses of bleeding events in patients with elevated biomarkers at baseline without prior stroke/ TIA had comparable bleeding rates as the overall study population. In All Strata in the treatment-emergent safety analysis set, the primary safety endpoint occurred in 1.3% of the rivaroxaban 2.5 mg bd treated patients compared to 0.4% of the placebo patients. The HR for the primary safety endpoint was 3.44 (95% CI: 1.97, 6.01). The individual bleeding categories, such as TIMI major bleeding and clinically significant bleeding,[redacted] and fatal bleedings and ICH events[redacted]

Subgroup analyses of primary safety endpoint

Subgroup analyses showed a consistent pattern of increased non-CABG-related TIMI major bleeding in the rivaroxaban groups compared with placebo across all major subgroups. There were no significant treatment interactions with any of the subgroups; all interaction p values were >0.05.

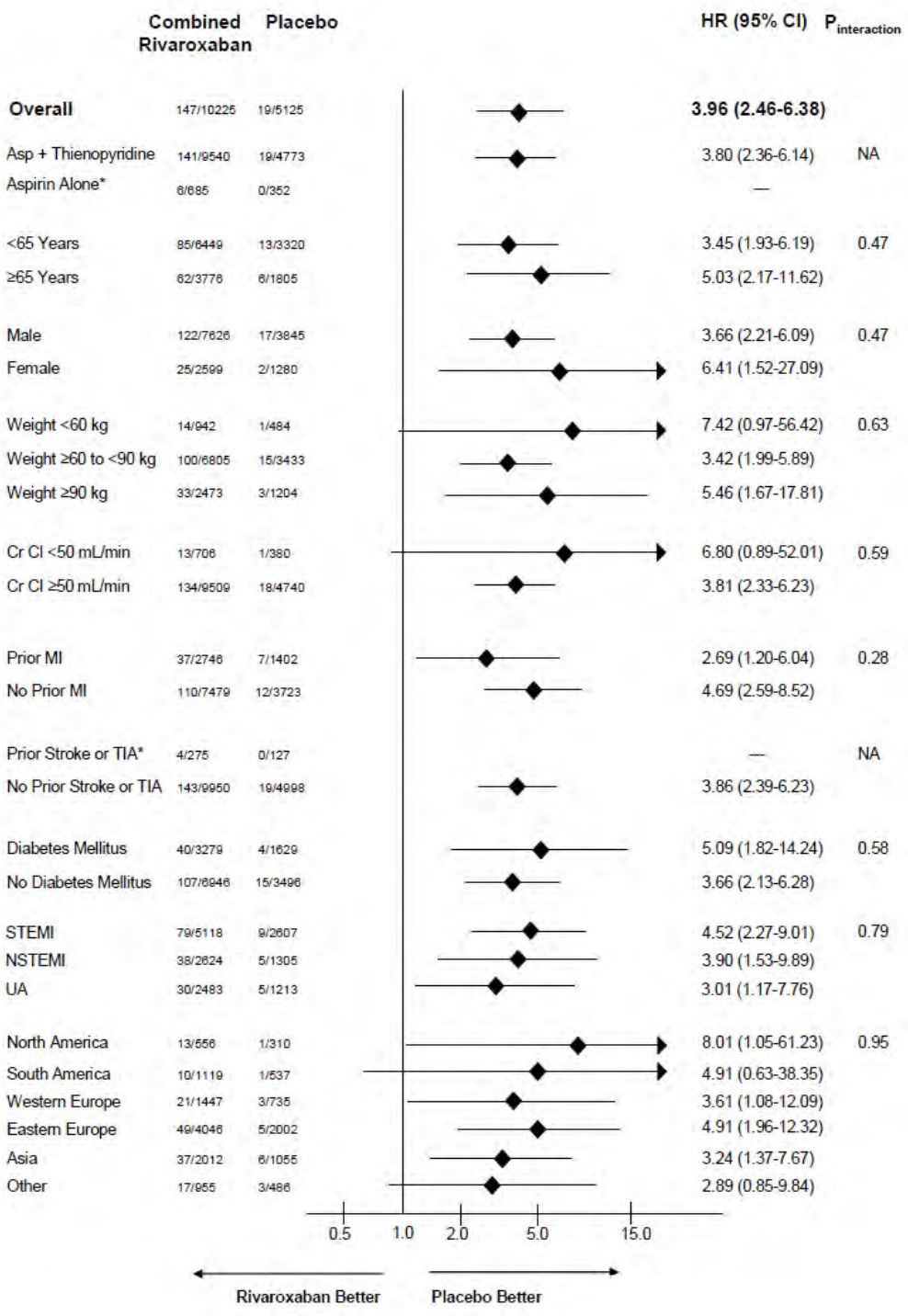
The licenced population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically sound as the trial was not powered to draw conclusion about (non-pre-specified) subgroups of subgroups.

Table 18.Effect of Rivaroxaban compared with Placebo on the Primary Safety Endpoint & other bleeding-related Secondary endpoints (Treatment-emergent safety analysis set)(3;5;22;28;33)

Parameter		Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
		2.5mg bd	5mg bd	Combined							
		n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Primary Safety Endpoint – *Non-CABG TIMI major bleeding*	***All Strata (N)***	**5115**	**5110**	**10,225**	**5125**						
	All Strata	*65 (1.3)*	*82 (1.6)*	*147 (1.4)*	*19 (0.4)*	*3.46 (2.08-5.77)*	*<0.001*	*4.47 (2.71-7.36)*	*<0.001*	*3.96 (2.46-6.38)*	*<0.001*
	Stratum 1 (ASA)	*2 (0.6)*	*4 (1.2)*	*6 (0.9)*	*0 (0.0)*	*-*	*0.154*	*-*	*0.046*	*-*	*0.083*
	Stratum 2	*63 (1.3)*	*78 (1.6)*	*141 (1.5)*	*19 (0.4)*	*3.35 (2.01-5.60)*	*<0.001*	*4.26 (2.58-7.03)*	*<0.001*	*3.80 (2.35-6.14)*	*<0.001*
Patients with elevated cardiac biomarkers without prior stroke / TIA											
Primary Safety Endpoint – *Non-CABG TIMI major bleeding*	***All Strata (N)***	**4096**	**4072**	**8168**	**4157**						
	All Strata	[redacted] *(1.3)*	[redacted] *(1.6)*	[redacted] *(1.5)*	[redacted] *(0.4)*	*3.44 (1.97-6.01)*	*<0.001*	*4.40 (2.55-7.60)*	*<0.001*	*3.91 (2.32-6.59)*	*<0.001*
	Stratum 1 (ASA)	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]		[redacted]
	Stratum 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bleeding-related secondary endpoints & components											
All Strata											
Clinically significant bleeding TIMI major + TIMI minor bleeding + bleeding requiring medical attention		*586 (11.5)*	*748 (14.6)*	*1334 (13.0)*	*327 (6.4)*	1.84 (1.61-2.11)	<0.001	2.43 (2.13-2.76)	<0.001	2.13 (1.89-2.40)	<0.001
Fatal bleeding		6 [redacted]	15 [redacted]	21 [redacted]	9 [redacted]	0.67 (0.24-1.89)	0.45	1.72 (0.75-3.92)	0.195	1.19 (0.54-2.59)	0.664
TIMI major bleeding		*68 (1.3)*	*85 (1.7)*	*153 (1.5)*	*27 (0.5)*	2.55 (1.63-3.98)	<0.001	3.25 (2.11-5.02)	<0.001	2.90 (1.92-4.36)	<0.001
TIMI minor bleeding		32 (0.6)	49 (1.0)	81 (0.8)	20 (0.4)	1.62 (0.92-2.82)	0.09	2.52 (1.50-4.24)	<0.001	2.07 (1.27-3.37)	0.003

Parameter	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
TIMI bleeding requiring medical attention	492 (9.6)	637 (12.5)	1129 (11.0)	282 (5.5)	1.79 (1.55-2.07)	<0.001	2.39 (2.08-2.75)	<0.001	2.09 (1.83-2.38)	<0.001
Intracranial haemorrhage	14[redacted]	18[redacted]	32[redacted]	5[redacted]	2.83 (1.02-7.86)	0.037	3.74 (1.39-10.07)	0.005	3.28 (1.28-8.42)	0.009
Patients with elevated cardiac biomarkers without prior stroke / TIA										
All Strata (n)	**4096**	**4072**	**8168**	**4157**						
Clinically significant bleeding TIMI major + TIMI minor bleeding + bleeding requiring medical attention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI minor bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI bleeding requiring medical attention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intracranial haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 16 Risks of TIMI Major Bleeding not Related to CABG According to Subgroups(Whole trial population, ALL STRATA) (3)



Secondary safety endpoints (bleeding)

Overall population - In All Strata and Stratum 2, the differences between the combined rivaroxaban groups compared with placebo in treatment-emergent clinically significant, TIMI major and minor, and TIMI bleeding requiring medical attention were all statistically significant favouring placebo. This pattern of increased bleeding in the rivaroxaban groups compared with placebo was also true for all TIMI categories of bleeding events in Stratum 1, but none of the differences were statistically significant.

Population with elevated biomarkers without prior stroke/TIA - In the analyses of bleeding events in patients with elevated biomarkers at baseline without prior stroke/ TIA, the individual bleeding categories, such as TIMI major bleeding and clinically significant bleeding [redacted]

Fatal bleeding(3;5) As shown in Table 18, the overall incidence of fatal bleeding events in the study was low.

Overall study population

ALL STRATA, COMBINED DOSE - There was no significant difference in the rates of fatal bleeding associated with rivaroxaban as compared with placebo (0.2% vs. 0.2%, HR=1.19, 95% CI 0.54-2.59; P = 0.664).

In **ALL STRATA** and **STRATUM 2**, the frequency of fatal bleeding events was not increased in the rivaroxaban 2.5 mg b.i.d. group compared with placebo.

ALL STRATA, 2.5mg bd –

Rivaroxaban vs placebo (0.1% vs. 0.2%;

HR=0.67; 95% CI 0.24–1.89; *p*=0.45).

STRATUM 2, 2.5mg bd - Rivaroxaban 2.5mg bd vs placebo (0.1% vs. 0.2%; HR=0.63; 95% CI 0.21-1.93; p=0.416).

The majority of fatal bleeding events were gastrointestinal (GI) or intracranial: 1 (<0.1%) patient in the 2.5 mg bd group and 0 placebo patients had GI bleeding events. Fatal intracranial bleeding events occurred in 5 (0.1%) patients in the 2.5 mg bd group and 4 (0.1%) placebo patients. These results were mirrored in **STRATUM 2**.[redacted]

Fatal bleeding events occurred [redacted] patients in **STRATUM 1**, [redacted]

Population with elevated biomarkers without prior stroke/TIA (ALL STRATA) – Fatal bleeding rates in this population [redacted] to the overall population. The incidence of treatment-emergent fatal bleeding was [redacted] in the rivaroxaban 2.5mg bd group compared with [redacted]

the majority of fatal bleeding events were [redacted]

TIMI Major bleeding (3;5;22)

Overall population

ALL STRATA, COMBINED DOSE – The rate of TIMI major bleeding events in patients treated with rivaroxaban was significantly higher than in patients receiving placebo – 1.5% vs 0.5% (HR 2.90; 95% CI: 1.92-4.36; p<0.001).

ALL STRATA, 2.5mg bd – The rate of TIMI major bleeding events in patients treated with rivaroxaban was significantly higher than in patients receiving placebo - 1.3% vs. 0.5% (HR 2.55; 95% CI: 1.63-3.98; p<0.001).

STRATUM 2 mirrored the results of ALL STRATA**. STRATUM 2 COMBINED DOSE** - Rivaroxaban vs placebo (1.5% vs. 0.5%; HR=3.01; 95% CI 1.97–4.60; *p*<0.001). **STRATUM 2, 2.5mg bd** – rivaroxaban 2.5mg bd vs. placebo (1.4% vs. 0.5%; HR=2.67; 95% CI 1.68–4.23; *p*<0.001).

STRATUM 1 – the incidence of TIMI major bleeding was 0.9% in the combined rivaroxaban dose group, 0.6% in the 2.5mg bd group vs 0.6% in the placebo group (Combined dose vs placebo – HR 1.51; 95% CI: 0.3, 7.47: p=0.612, 2.5mg bd vs placebo – HR 1.02; 95% CI: 0.14, 7.22: p=0.987).

The most frequently reported sites of treatment-emergent TIMI major bleeding were gastrointestinal and intracranial.

In **All Strata**, 88 (0.9%) patients in the **combined** rivaroxaban groups and 13 (0.3%) placebo patients reported gastrointestinal bleeding, and 32 (0.3%) patients in the combined rivaroxaban groups and 5 (0.1%) placebo patients reported intracranial bleeding.

ALL STRATA, 2.5mg bd - 42 (0.8%) patients in the low dose rivaroxaban (**2.5mg bd**) group and 13 (0.3%) placebo patients reported gastrointestinal bleeding, and 14 (0.3%) patients in the low dose rivaroxaban group and 5 (0.1%) placebo patients reported intracranial bleeding.

These event rates were mirrored in **Stratum 2:**

STRATUM 2, COMBINED DOSE – Gastrointestinal TIMI-major bleeding: combined rivaroxaban group 0.9%, placebo 0.3%; Intracranial bleeding: combined rivaroxaban group 0.3%, placebo 0.1%.

STRATUM 2, 2.5mg bd - Gastrointestinal TIMI-major bleeding: Rivaroxaban **2.5mg bd** 0.9%, placebo 0.3%; Intracranial bleeding: Rivaroxaban **2.5mg bd** 0.3%, placebo 0.1%.

In **Stratum 1**, [redacted] patients in the **combined** rivaroxaban groups compared with [redacted]

placebo patients experienced gastrointestinal bleeding, and [redacted] patients in the **combined** rivaroxaban groups and [redacted] patients had intracranial bleeding.

STRATUM 1, 2.5mg bd [redacted] patient in the rivaroxaban 2.5mg group compared with [redacted] placebo patients experienced gastrointestinal bleeding, and [redacted] patient in the rivaroxaban 2.5mg bd group and [redacted] placebo patients had intracranial bleeding.

Population with elevated biomarkers without prior stroke/TIA – TIMI major bleeding events in patients with elevated biomarkers at baseline without prior stroke/ TIA were [redacted]

Clinically significant bleeding - composite of TIMI major, TIMI minor bleeding, TIMI bleeding requiring medical attention (3;5;22)

ALL STRATA, COMBINED DOSE – The incidence of clinically significant bleeding in the ALL STRATA analysis was higher for the combined rivaroxaban groups vs. placebo (13% vs 6.4%, HR 2.13; 95% CI: 1.89-2.40; p<0.001).

ALL STRATA, 2.5mg bd – Rivaroxaban 2.5mg bd also had a higher incidence of clinically significant bleeding compared with placebo (11.5% vs 6.4% HR 1.84; 95% CI: 1.61-2.11; p<0.001).

STRATUM 2, combined dose / STRATUM 2, 2.5mg bd – mirrored the results from the ALL STRATA analyses.

STRATUM 1 –The incidence of clinically significant bleeding in Stratum 1 was higher for the combined rivaroxaban groups vs. placebo (6.1% vs 3.1%, HR 1.93; 95% CI: 0.99, 3.75, p=0.048). This was also reflected with the 2.5mg bd dose (5.5% vs 3.1%, HR 1.77; 95% CI: 0.84, 3.71, p=0.128).

The majority of bleeding events categorised as clinically significant were from the 'bleeding requiring medical attention' category.

Population with elevated biomarkers without prior stroke/TIA – Clinically significant bleeding events in patients with elevated biomarkers at baseline without prior stroke/ TIA were [redacted]

TIMI bleeding requiring medical attention (3;5;22)

Overall population

ALL STRATA, COMBINED DOSE - Rates of TIMI bleeding events requiring medical attention were significantly increased for rivaroxaban compared with placebo (11% vs. 5.5%; HR=2.09; 95% CI 1.83-2.38; p<0.001).

ALL STRATA, 2.5mg bd - rivaroxaban 2.5 mg bd arm vs placebo (9.6% vs. 5.5%; HR=1.79; 95% CI 1.55-2.07; p<0.001).

STRATUM 2, COMBINED DOSE – rivaroxaban vs placebo (11.5% vs 5.7%, HR=2.09; 95% CI 1.83-2.39; p<0.001).

STRATUM 2, 2.5mg bd – rivaroxaban 2.5 mg bd arm vs placebo (10% vs 5.7%, HR=1.79; 95% CI 1.54-2.07; p<0.001).

STRATUM 1 – the rates were higher for the combined dose and rivaroxaban 2.5mg bd vs placebo (5.1%, 4.7% respectively vs 2.6%; HR=1.97; 95% CI 0.95, 4.1, p=0.064 for the combined dose vs placebo and HR=1.82; 95% CI: 0.81, 4.13, p=0.144 for the 2.5mg bd vs placebo comparison).

Table 19 Incidence (by location) of TIMI bleeding requiring medical attention

(All Strata) (5)	**Incidence (%)**			
	Rivaroxaban			**Placebo**
	2.5mg bd	**5mg bd**	**Combined**	
TIMI bleeding requiring attention	[redacted]	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]
Skin	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]
Rectal	[redacted]	[redacted]	[redacted]	[redacted]
Gingival	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

In Stratum 1, epistaxis occurred in [redacted] of patients in the 2.5 mg bd group compared with [redacted] placebo patients, and [redacted] of patients in the 2.5 mg bd group had haematuria compared with [redacted] placebo patients.

Population with elevated biomarkers without prior stroke/TIA – Rates of TIMI bleeding requiring medical attention were [redacted] overall study population [redacted] rates of TIMI bleeding events requiring medical attention were [redacted] for both rivaroxaban doses compared with placebo (rivaroxaban 2.5mg bd = [redacted] rivaroxaban 5mg bd [redacted] placebo= [redacted]

Table 20 Incidence (by location) of TIMI bleeding requiring medical attention in the population with elevated biomarkers without prior stroke/TIA (All Strata)(33)

	Incidence (%)			
	Rivaroxaban			Placebo
	2.5mg bd	5mg bd	Combined	
TIMI bleeding requiring attention	[redacted]	[redacted]	[redacted]	[redacted]

Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]
Skin	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]
Rectal	[redacted]	[redacted]	[redacted]	[redacted]
Gingival	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal	[redacted]	[redacted]	[redacted]	[redacted]

Intracranial haemorrhage (3;5)

Overall population

Patients receiving rivaroxaban had an increased incidence of intracranial bleeding compared with patients receiving placebo.

In **ALL STRATA**, the incidence of intracranial bleeding was 32 (0.3%) in the **combined rivaroxaban group** (HR vs. placebo = 3.28; 95% CI 1.28-8.42; p=0.009) and 14 (0.3%) in the **2.5 mg b.i.d**. group vs 5 (<0.1%) in the placebo group (HR= 2.83; 95% CI 1.02-7.86; p=0.037). However, fatal intracranial bleeding was balanced between the 2.5 mg bd group (5 [0.1%]) and the placebo group (4 [0.1%]).

STRATUM 2, COMBINED RIVAROXABAN vs. placebo: 0.3% vs. 0.1%, HR=2.98; 95% CI 1.15-7.70; p=0.018.

STRATUM 2, 2.5mg bd vs. placebo: the incidence in the 2.5mg bd group was 0.3% vs 0.1% with placebo, HR=2.63; 95% CI 0.94-7.38; p=0.056

Fatal intracranial bleeding events were similarly low in the rivaroxaban 2.5 mg bd (0.1%) and placebo (0.1%) groups.

In **STRATUM 1,** intracranial bleeding events occurred in 1 (0.3%) patient in the 2.5 mg bd group, and 0 patients in the placebo group.

Population with elevated biomarkers without prior stroke/TIA – Intracranial haemorrhage (ICH) rates in this population [redacted] overall population. The incidence of ICH was [redacted] in the rivaroxaban 2.5mg bd group compared with [redacted]) in the placebo group.

Other bleeding scales

The first occurrence of TIMI major and ISTH major treatment emergent bleeding events across rivaroxaban treatment groups was statistically significantly different from placebo (p<0.001) in All Strata and Stratum 2. This pattern was generally true for most bleeding categories within the TIMI, GUSTO, and ISTH scales, with the exception of GUSTO severe bleeding and TIMI minor bleeding in the rivaroxaban 2.5 mg bd group in Stratum 2, which although numerically higher did not reach statistical significance. In Stratum 1, none of the

differences between the combined rivaroxaban groups compared with placebo in treatment-emergent bleeding events within the TIMI, GUSTO, and ISTH scales were statistically significant.

6.9.2 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.

Treatment emergent AEs (3;5)

The overall incidence of treatment-emergent adverse events was 54.1% in the 2.5mg bd rivaroxaban group, 56.7% in the 5mg bd rivaroxaban group, and 52.6% in the placebo group (see Table 21). Treatment-emergent adverse events were defined as those events starting on or after first dose of study drug up to 2 days after the last dose of study medication.

Events in the System Organ Classes of cardiac disorders and gastrointestinal disorders were most common.

Treatment-emergent AEs resulting in permanent discontinuation of study treatment occurred in [redacted] patients receiving rivaroxaban 2.5mg bd, [redacted] of the combined rivaroxaban group, and [redacted] of placebo patients (safety analysis set). [redacted] were the most commonly reported adverse events resulting in discontinuation of study drug in [redacted] of rivaroxaban combined, rivaroxaban 2.5mg bd, and placebo patients, respectively.

A summary of the treatment-emergent adverse events occurring in at least 1% of patients in any treatment group, is provided in Table 21. Overall, the incidence rates of non-bleeding adverse events were similar across treatment groups and strata and the majority of TE-AEs were

[redacted]

Table 21 Treatment-emergent Adverse events in at least 1% patients in any treatment group by System Organ class and preferred term (Safety Analysis Set)(3;5;33)

Body System or Organ Class Preferred term	Rivaroxaban			Placebo	Patients with elevated cardiac biomarkers without prior stroke / TIA	
	2.5mg bd (N=5115) n (%)	**5mg bd (N=5110) n (%)**	**Combined (N=10,225) n (%)**	**(N=5125) n (%)**	**2.5mg bd (N=4096) n (%)**	**Placebo (N=4157) n (%)**
Total number of patients with treatment-emergent adverse events	***2769 (54.1)***	*2898 (56.7)*	*5667 (55.4)*	***2694 (52.6)***	[redacted]	[redacted]
TE AE excluding bleeding AE**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	**905 (17.7)**	934 (18.3)	1839 (18.0)	**973 (19.0)**	[redacted]	[redacted]
Angina Pectoris	**295 (5.8)**	307 (6.0)	602 (5.9)	**340 (6.6)**	[redacted]	[redacted]
Angina Unstable	**246 (4.8)**	269 (5.3)	515 (5.0)	**248 (4.8)**	[redacted]	[redacted]
Acute Myocardial Infarction	**94 (1.8)**	91 (1.8)	185 (1.8)	**114 (2.2)**	[redacted]	[redacted]
Myocardial Infarction	**66 (1.3)**	59 (1.2)	125 (1.2)	**68 (1.3)**	[redacted]	[redacted]
Atrial Fibrillation	**60 (1.2)**	56 (1.1)	116 (1.1)	**68 (1.3)**	[redacted]	[redacted]
Cardiac Failure	**75 (1.5)**	47 (0.9)	122 (1.2)	**56 (1.1)**	[redacted]	[redacted]
Gastrointestinal disorders	**543 (10.6)**	685 (13.4)	1228 (12.0)	**478 (9.3)**	[redacted]	[redacted]
Gingival bleeding	**104 (2.0)**	192 (3.8)	296 (2.9)	**63 (1.2)**	[redacted]	[redacted]
Rectal haemorrhage	**63 (1.2)**	59 (1.2)	122 (1.2)	**41 (0.8)**	[redacted]	[redacted]
Respiratory, Thoracic, Mediastinal Disorders	**496 (9.7)**	582 (11.4)	1078 (10.5)	**387 (7.6)**	[redacted]	[redacted]
Epistaxis	**268 (5.2)**	350 (6.8)	618 (6.0)	**141 (2.8)**	[redacted]	[redacted]
Cough	**63 (1.2)**	58 (1.1)	121 (1.2)	**74 (1.4)**	[redacted]	[redacted]
Dyspnoea	**56 (1.1)**	65 (1.3)	121 (1.2)	**79 (1.5)**	[redacted]	[redacted]
Surgical and Medical Procedures	**497 (9.7)**	448 (8.8)	945 (9.2)	**450 (8.8)**	[redacted]	[redacted]
Percutaneous Coronary Intervention	**249 (4.9)**	247 (4.8)	496 (4.9)	**240 (4.7)**	[redacted]	[redacted]
Coronary Artery Bypass	**82 (1.6)**	76 (1.5)	158 (1.5)	**77 (1.5)**	[redacted]	[redacted]
Coronary Revascularisation	**61 (1.2)**	47 (0.9)	108 (1.1)	**46 (0.9)**	[redacted]	[redacted]
General Disorders & Administration Site Conditions	**374 (7.3)**	410 (8.0)	784 (7.7)	**389 (7.6)**	[redacted]	[redacted]
Chest Pain	**113 (2.2)**	99 (1.9)	212 (2.1)	**90 (1.8)**	[redacted]	[redacted]

Body System or Organ Class Preferred term	Rivaroxaban			Placebo	Patients with elevated cardiac biomarkers without prior stroke / TIA	
	2.5mg bd (N=5115) n (%)	**5mg bd (N=5110) n (%)**	**Combined (N=10,225) n (%)**	**(N=5125) n (%)**	**2.5mg bd (N=4096) n (%)**	**Placebo (N=4157) n (%)**
Total number of patients with treatment-emergent adverse events	***2769 (54.1)***	*2898 (56.7)*	*5667 (55.4)*	***2694 (52.6)***	[redacted]	[redacted]
Non-Cardiac Chest Pain	**86 (1.7)**	98 (1.9)	184 (1.8)	**99 (1.9)**	[redacted]	[redacted]
Injury, poisoning and Procedural Complications	**290 (5.7)**	356 (7.0)	646 (6.3)	**225 (4.4)**	[redacted]	[redacted]
Contusion	**75 (1.5)**	92 (1.8)	167 (1.6)	**53 (1.0)**	[redacted]	[redacted]
Vascular Disorders	**297 (5.8)**	318 (6.2)	615 (6.0)	**291 (5.7)**	[redacted]	[redacted]
Haematoma	**103 (2.0)**	125 (2.4)	228 (2.2)	79 (1.5)	[redacted]	[redacted]
Hypertension	**86 (1.7)**	59 (1.2)	145 (1.4)	75 (1.5)	[redacted]	[redacted]
Infections & Infestations	**291 (5.7)**	323 (6.3)	614 (6.0)	**360 (7.0)**	[redacted]	[redacted]
Nasopharyngitis	**45 (0.9)**	33 (0.6)	78 (0.8)	**52 (1.0)**	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	**262 (5.1)**	275 (5.4)	537 (5.3)	**228 (4.4)**	[redacted]	[redacted]
Ecchymosis	**82 (1.6)**	89 (1.7)	171 (1,7)	**53 (1.0)**	[redacted]	[redacted]
Investigations	**262 (5.1)**	274 (5.4)	536 (5.2)	**251 (4.9)**	[redacted]	[redacted]
Arteriogram Coronary	**59 (1.2)**	72 (1.4)	131 (1.3)	**73 (1.4)**	[redacted]	[redacted]
Alanine Aminotransferase Increased	**44 (0.9)**	41 (0.8)	85 (0.8)	**49 (1.0)**		
Nervous System Disorders	**232 (4.5)**	282 (5.5)	514 (5.0)	**239 (4.7)**	[redacted]	[redacted]
Dizziness	**61 (1.2)**	52 (1.0)	113 (1.1)	**50 (1.0)**	[redacted]	[redacted]
Renal and Urinary disorders	**139 (2.7)**	169 (3.3)	308 (3.0)	**97 (1.9)**	[redacted]	[redacted]
Haematuria	**69 (1.3)**	121 (2.4)	190 (1.9)	**31 (0.6)**	[redacted]	[redacted]

Incidences are based on number of patients, not number of events
Bleeding events and cardiac ischaemic events are not reported here as they were included in Efficacy and Safety endpoints.
Cardiac failure includes the terms cardiac failure, cardiac failure acute, cardiac failure chronic, and cardiac failure congestive

[redacted]

Bleeding-related Treatment-emergent AEs (5)

A total of 2,252 (22%) of rivaroxaban patients [974 (19%) patients in the rivaroxaban 2.5mg bd group] and 643 (12.5%) of placebo patients had treatment-emergent bleeding-related adverse events.

Gastrointestinal bleeding-related AEs and respiratory bleeding-related AEs were the most common in all treatment groups, with gastrointestinal bleeding-related AEs occurring in 7.1%, 5.7, and 3.4% of patients in the combined rivaroxaban, rivaroxaban 2.5mg bd and placebo groups respectively. Gingival bleeding was the most common gastrointestinal bleeding-related AE (2.9% of the combined rivaroxaban groups, 2.0% of the rivaroxaban 2.5mg bd group and 1.2% of the placebo group [see Table 21]). Respiratory bleeding-related events occurred in 6.7% of the combined rivaroxaban groups, 5.8% of the 2.5mg bd rivaroxaban group and 3.0% of the placebo group, with epistaxis the most common respiratory bleeding-related AE (6.0%, 5.2%, and 2.8% of the combined rivaroxaban, rivaroxaban 2.5mg bd and placebo groups respectively [see Table 21]). More treatment-emergent bleeding-related AEs occurred in the 5 mg bd group compared with the 2.5mg bd and placebo dose groups. These results were mirrored in Stratum 2.

Population with elevated biomarkers without prior stroke/TIA

- A total of [redacted] of rivaroxaban patients [redacted] patients in the rivaroxaban 2.5mg bd group] and [redacted] of placebo patients had treatment-emergent bleeding-related adverse events. [redacted] were the most common in all treatment groups. [redacted]

in the combined rivaroxaban, rivaroxaban 2.5mg bd and placebo groups respectively. [redacted] of the combined rivaroxaban groups [redacted] of the rivaroxaban 2.5mg bd group and [redacted] of the placebo group (Table 21). [redacted] of the combined rivaroxaban groups, [redacted] of the 2.5mg bd rivaroxaban group and [redacted] of the placebo group, [redacted]

of the combined rivaroxaban, rivaroxaban 2.5mg bd and placebo groups respectively (Table 21).

Treatment-emergent drug-related AEs (5)

A total of [redacted] rivaroxaban 2.5mg bd patients, [redacted] combined rivaroxaban patients and [redacted] placebo patients had TE AEs that investigators considered to be related to study drug. The most commonly reported drug-related AEs were in the System Organ Classes [redacted] of patients in the

combined rivaroxaban groups [redacted] rivaroxaban 2.5mg bd and [redacted] of patients in the placebo group) and [redacted] of patients in the combined rivaroxaban groups, [redacted] rivaroxaban 2.5mg bd and [redacted] of patients in the placebo group). [redacted] was the most common drug-related [redacted] combined rivaroxaban patients, [redacted] rivaroxaban 2.5mg bd, [redacted] placebo). [redacted] of patients in the combined rivaroxaban groups, [redacted] receiving rivaroxaban 2.5mg bd and [redacted] patients in the placebo group. [redacted] were also recorded across all study arms and all strata.

Population with elevated biomarkers without prior stroke/TIA - A total of [redacted] rivaroxaban 2.5mg bd patients, [redacted] combined rivaroxaban patients and [redacted] placebo patients had TE AEs that investigators considered to be related to study drug. The most commonly reported drug-related AEs were in the System Organ Classes [redacted] of patients in the combined rivaroxaban groups, [redacted] rivaroxaban 2.5mg bd and [redacted] of patients in the placebo group) and [redacted] of patients in the combined rivaroxaban groups [redacted] rivaroxaban 2.5mg bd and [redacted] of patients in the placebo group). [redacted] combined rivaroxaban patients, [redacted] rivaroxaban 2.5mg bd [redacted] placebo [redacted] of patients in the combined rivaroxaban groups, [redacted] receiving rivaroxaban 2.5mg bd and [redacted] patients in the placebo group.

Deaths

In the safety analysis set, there were a total of 532 deaths reported in the study. CV death and all-cause death are discussed further in section 6.5 Clinical Results, as they were components of key efficacy endpoints.

All deaths were adjudicated and, as expected in this population, there were more cardiovascular than non CV deaths. The most common cardiovascular aetiologies were sudden or unwitnessed death, MI, and congestive heart failure/cardiogenic shock. In support of the primary efficacy analyses, fewer all-cause and cardiovascular deaths occurred in patients in the rivaroxaban 2.5 mg bd group than in the placebo group in the safety analysis set. [redacted]

As per the primary efficacy analysis in the mITT data set, the reduction in death observed in the 2.5 mg bd group in the safety analysis set, was due to a reduction in deaths due to congestive heart failure/cardiogenic shock and sudden or unwitnessed death.

The rates of death due to non-cardiovascular causes were similar in all 3 treatment groups. The most common non-cardiovascular aetiologies were malignancy and infection.

Population with elevated biomarkers without prior stroke/TIA – In the safety analysis set, there were a total of [redacted]

reported in the population of patients with elevated biomarkers without prior stroke/TIA. [redacted] the most common cardiovascular aetiologies were [redacted] occurred in patients in the rivaroxaban 2.5 mg bd group than in the placebo group in the safety analysis set. The rates of death due to non-cardiovascular causes [redacted]. The most common non-cardiovascular aetiology was [redacted]

Liver safety

In light of the liver function abnormalities produced by ximelagatran, an oral thrombin inhibitor now withdrawn from research, liver safety was also closely monitored in the ATLAS-ACS 2 TIMI 51 study, involving an external panel of hepatic experts.

Clinical and laboratory liver abnormalities were low and similar among patients treated with rivaroxaban or placebo, with alanine aminotransferase levels of more than three times the upper limit of the normal range and total bilirubin levels of more than two times the upper limit of the normal range occurring in 0.2% of patients in each study group. There were no notable differences between the treatment groups for the outcome of any category of hepatic disorder adverse events. There were no liver-related deaths associated with study drug observed in this study.

These findings were also reflected in the **population with elevated biomarkers without prior stroke/TIA**.

Other safety parameters

Overall there were no noteworthy changes in clinical laboratory test results in the overall study population and also in the population with elevated biomarkers without prior stroke/TIA.

In general, CV events 3 to 30 days after the last dose of rivaroxaban were well-balanced across the rivaroxaban and placebo groups. There was no evidence of increased risk for off-treatment CV ischaemic events up to 30 days following the last dose of rivaroxaban. This was consistent across patients who discontinued at any time of the trial and those who completed the double blind treatment period.

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

The safety of the selected rivaroxaban dose for licensing – 2.5mg bd – was demonstrated by analysis of primary and secondary safety endpoint data, including bleeding, mortality and adverse events from the ATLAS ACS 2 TIMI 51 study.

The only notable safety difference identified in the ATLAS ACS 2 TIMI 51 study was bleeding, as might be expected with the addition of an anticoagulant to standard of care antiplatelet

therapy. No other safety events were identified. These findings are supported by the data from clinical studies in other indications and post-marketing experience with rivaroxaban.

Rates of treatment-emergent non-CABG TIMI major bleeding were low across all treatment groups. The addition of either rivaroxaban 2.5 mg bd or 5 mg bd to standard care antiplatelet therapy increased the risk of the primary safety endpoint (ALL STRATA 2.5mg bd rivaroxaban 1.3% vs. placebo 0.4%; p<0.001), including intracranial haemorrhage (ICH) (ALL STRATA 2.5mg bd rivaroxaban 0.3% vs. 0.1%, P=0.037). This increase in risk of bleeding was not associated with an increase in fatal bleeding (ALL STRATA 2.5mg bd rivaroxaban 0.1% vs. 0.2%, P=0.45) or fatal ICH. Rates of fatal bleeding and fatal ICH were low overall, and balanced between treatment groups.

The majority of bleeding events were events that required medical attention rather than TIMI major or TIMI minor events. The most common bleeding-related adverse events were

associated with gastrointestinal and respiratory disorders, with gingival bleeding the most common gastrointestinal bleeding-related adverse event and epistaxis the most common respiratory bleeding-related adverse event. In all cases, the lower dose of rivaroxaban resulted in less bleeding than the higher dose.

Rivaroxaban 2.5mg bd demonstrated significant reductions (>30%) in all-cause mortality, specifically, the risk of CV death - key components of efficacy endpoints. All findings were consistent across analysis populations and major subgroups.

Rivaroxaban had a non-bleeding safety profile similar to placebo with rates of non-bleeding adverse events balanced between groups and strata, including rates of laboratory and clinical liver abnormalities .

On balance, the increase in bleeding risk is outweighed by the substantial reduction in risk of death, particularly CV death, from which patients are at high risk after diagnosis of ACS. (See section 6.10.1 for further information.) The analyses of bleeding events in patients with elevated biomarkers at baseline without prior stroke/ TIA had comparable bleeding rates as the overall study population and the individual bleeding categories, such as TIMI major bleeding and clinically significant bleeding, were also comparable to the results seen for the overall study population. The benefit risk was further improved in this licensed population (compared to the overall trial population) because of the increased numbers of ischaemic events prevented.

Thus the addition of low-dose anticoagulation with rivaroxaban (2.5mg bd) represents an effective new treatment strategy associated with a predictable safety profile in patients with recent acute coronary syndrome with elevated cardiac biomarkers.

6.10 Interpretation of clinical evidence

Note: This section will focus on the 2.5mg bd dose only since this is the dose for which marketing authorization has been received in Europe in ACS.

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

The ATLAS ACS 2 TIMI 51 study provides the evidence base to support the use of rivaroxaban in addition to standard antiplatelet therapy for the prevention of adverse outcomes in patients with recent ACS.

Compared with placebo, the addition of rivaroxaban 2.5mg bd to antiplatelet therapy (ASA or ASA plus clopidogrel) significantly reduced the risk of the primary efficacy endpoint - composite of CV death / MI / Stroke - in patients with recent ACS (6.1% vs. 7.4%; HR=0.84; 95% CI 0.72-0.97; p=0.02 in the trial population and 6.2% vs 7.9%; HR 0.80; 95% CI 0.68-0.94; p=0.007 in the licensed population). These benefits were established early on in treatment and continued throughout 2 years and were observed in the trial population regardless of whether patients presented with STEMI, NSTEMI or unstable angina as their index event, and across all major subgroups, including those defined by age (<65 or ≥65 years), sex, weight (<60 kg, ≥60 to <90 kg, ≥90 kg), Creatinine clearance (<50 or ≥50 ml/min) and history of prior MI or diabetes. Findings were also consistent across analysis populations, confirming the robustness of the primary efficacy result.

Rivaroxaban's effects on the primary efficacy endpoint were driven largely by more than a 30% reduction in risk of CV death (1.8% vs. 2.8%; HR=0.66; 95% CI 0.51-0.86; p=0.002 in the trial population and 1.7% vs 3.1%; HR 0.55; CI 0.41-0.74; p<0.001 in the licensed population). It also achieved a non-significant but directionally consistent benefit for myocardial infarction risk (4.0% vs. 4.5%; HR=0.90; 95% CI 0.75-1.09; p=0.27 in the trial population and 4.3% vs 4.9%; HR 0.88; CI 0.72-1.08; p=0.215 in the licensed population) but did not modify the risk of stroke (all-cause or ischaemic).

In addition, rivaroxaban 2.5mg bd produced a 32% reduction in risk of death from any cause, when compared with placebo (2.0% vs. 3.0%; HR=0.68; 95% CI 0.53-0.87; p=0.002) in the trial population and [redacted] reduction vs placebo [redacted] vs [redacted] HR [redacted] CI [redacted] in the licensed population.

The positive effect on survival and on the composite primary endpoint was countered by an increase in bleeding in rivaroxaban-treated patients compared with placebo. In all other safety aspects e.g. non-bleeding adverse events, rivaroxaban had a safety profile similar to placebo with rates of non-bleeding adverse events balanced between groups and strata, including rates of laboratory and clinical liver abnormalities and [redacted].

Increased bleeding, could be expected with the addition of an anticoagulant to standard of care antiplatelet therapy and although the incidence of bleeding was higher with rivaroxaban compared with placebo, the overall incidence of major bleeding was low and the majority of bleeding events were categorised as bleeding requiring medical attention or 'insignificant bleeding' on the TIMI scale. The most common bleeding-related adverse events were associated with gastrointestinal (i.e. gingival bleeding) and respiratory disorders (i.e. epistaxis).

Rivaroxaban 2.5 mg bd added to standard care antiplatelet therapy increased the risk of the primary safety endpoint (1.3% vs. 0.4%; p<0.001). This was not associated with an increase in fatal bleeding (0.1% vs. 0.2%, P=0.45).

Secondary efficacy endpoint 2 was intended to assess benefit and risk by combining CV death, MI, ischaemic stroke and non-CABG TIMI major bleeding into a single endpoint of 'Net Clinical Outcome'. The results for this endpoint, while not statistically significant, directionally favoured rivaroxaban 2.5 mg b.d in All Strata and in Stratum 2.

This method of assessing benefit-risk does not weight the clinical severity of the individual endpoints. In addition, it was complicated by some events being included in both efficacy and safety endpoints (fatal bleeding events and haemorrhagic stroke were counted both in the primary efficacy endpoint and principal safety outcome), resulting in double counting.

To provide a more direct comparison of benefits and harms, a post-hoc outcome analysis was performed(8), based on the approach outlined by Unger(34;35), which minimised double-counting of events between endpoints and focused on events that were fatal or led to irreversible harm. Analyses showed a positive benefit-risk outcome for rivaroxaban 2.5 mg bd versus placebo (see Table 22). Compared with placebo, rivaroxaban 2.5 mg bd prevented 125 ischaemic efficacy events per 10,000 patient-years, while causing 10 fatal bleeding or ICH events per 10,000 patient-years (i.e. a 'benefit–risk' ratio of 12–13 to 1). This means that adding rivaroxaban 2.5 mg bd treatment to antiplatelet therapy in patients with ACS would result in one fewer non-bleeding CV death, MI or ischaemic stroke event per 80 patient-years and one additional fatal bleeding or ICH event every 1052 patient-years.

In this context a positive benefit–risk profile is demonstrated.

This benefit risk balance is further strengthened when the results for the narrower, now licensed, population of 'patients after an ACS with elevated cardiac biomarkers' are considered. Compared with placebo in the mITT analysis set in All Strata, rivaroxaban 2.5 mg bd prevented [redacted] non-bleeding CV death, MI and ischaemic stroke events per 10,000 patient-years, while causing [redacted] fatal bleeding or ICH events(28).

Figure 17 Risk differences / 10,000 patient years in the 'with elevated biomarkers and without prior stroke/TIA' population (mITT; All Strata: 2.5 mg bd dose)

Taking all of the efficacy and safety data into account, the CHMP considered by majority that the risk-benefit balance of rivaroxaban co-administrated with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, is favourable and, therefore granted extension of the marketing authorisation for rivaroxaban for this indication.

Table 22 Decomposition of Ischaemic and Haemorrhagic events for Rivaroxaban 2.5mg bd dose (Overall Study Population ALL STRATA mITT) (8)

Time to Event Category	Endpoints	Event rate (a) (/100 Pt/yrs)		Excess Number of Events (Rivaroxaban – Placebo)		
		Rivaroxaban	Placebo	Excess # events for 10,000 pt-yrs	95% CI	NNT/NNH (b)
Efficacy	**Non-bleeding CV death, MI or ischaemic stroke**	**5.62**	**6.87**	**-125***	**(-221, -30)**	**-80**
	Non-bleeding CV death	1.58	2.43	-85*	(-139, -32)	-117
	MI excluding CV death	3.64	3.98	-34	(-108, 41)	-297
	Ischaemic stroke excluding CV death	0.53	0.56	-3	(-31, 25)	-3380
	Non-CV death excluding fatal bleeding	0.17	0.16	0	(-16, 16)	47435
Safety	**TIMI Life-threatening bleeding + TIMI major bleeding**	**1.42**	**0.73**	**69***	**(30, 109)**	**144**
	Fatal Bleeding + symptomatic ICH	0.33	0.24	10	(-11, 30)	1052
	Fatal Bleeding	0.17	0.20	-3	(-20, 13)	-2921
	Intracranial Bleeding (ICH)	0.28	0.11	17	(-1, 34)	599
	Fatal ICH	0.11	0.07	4	(-9, 16)	2649
	Non-Fatal ICH	0.17	0.04	13	(-1,26)	773
	Non-fatal, non-ICH TIMI life threatening bleeding	0.50	0.22	28*	(5, 51)	358
	TIMI Major Bleeding, non-life threatening	0.63	0.27	35*	(10, 61)	282

(a): Event rate (/100 Pt-yrs): Number of events per 100 patient years of follow up.
(b): A negative number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to prevent one additional harmful event (NNT). A positive number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to observe one additional harmful event (NNH).
CI = Confidence Interval; CV =Cardiovascular; MI = Myocardial infarction; ICH =Intracranial Haemorrhage.
* Nominal 2-sided p-value < 0.05 (not adjusted for multiplicity).
The 95% CI is based on constant hazard assumption. Under this assumption the number of events observed has a Poisson distribution. The calculation is carried out using normal approximation to Poisson distribution, conditional on the total duration of treatment exposure.
Non-bleeding CV death excludes deaths adjudicated as due to non-bleeding causes that have fatal bleeding complications (e.g. trauma, malignancy).All haemorrhagic CV deaths and non-haemorrhage CV deaths with fatal bleeding complications are included under fatal bleeding.
CV deaths include deaths adjudicated as Unknown.
No CI provided if the number of events is 0 or 1 in either group; there are no asymptomatic ICHs.

Table 23 Decomposition of Ischaemic and Haemorrhagic events for Rivaroxaban 2.5mg bd dose (Elevated biomarkers without prior stroke or TIA; ALL STRATA mITT) (28)

Time to Event Category	Endpoints	Event rate (a) (/100 Pt/yrs)		Excess Number of Events (Rivaroxaban – Placebo)		
		Rivaroxaban	Placebo	Excess # events for 10,000 pt-yrs	95% CI	NNT/NNH (b)
Efficacy	**Non-bleeding CV death, MI or ischaemic stroke**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-bleeding CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MI excluding CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ischaemic stroke excluding CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-CV death excluding fatal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe recurrent ischaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety	**TIMI Life-threatening bleeding + TIMI major bleeding**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TIMI Life-threatening bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Fatal Bleeding + symptomatic ICH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Fatal Bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Intracranial Bleeding (ICH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Fatal ICH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Non-Fatal ICH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-fatal, non-ICH TIMI life threatening bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-fatal, non-ICH bleeding requiring surgical intervention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-fatal, non-ICH bleeding requiring transfusion ≥ 4 units	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TIMI Major Bleeding, non-life threatening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TIMI Minor bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(a): Event rate (/100 Pt-yrs): Number of events per 100 patient years of follow up.
(b): A negative number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to prevent one additional harmful event (NNT). A positive number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to observe one additional harmful event (NNH).
CI = Confidence Interval; CV =Cardiovascular; MI = Myocardial infarction; ICH =Intracranial Haemorrhage.
* Nominal 2-sided p-value < 0.05 (not adjusted for multiplicity).
The 95% CI is based on constant hazard assumption. Under this assumption the number of events observed has a Poisson distribution. The calculation is carried out using normal approximation to Poisson distribution, conditional on the total duration of treatment exposure.
Non-bleeding CV death excludes deaths adjudicated as due to non-bleeding causes that have fatal bleeding complications (e.g. trauma, malignancy).All haemorrhagic CV deaths and non-haemorrhage CV deaths with fatal bleeding complications are included under fatal bleeding.
CV deaths include deaths adjudicated as Unknown.
No CI provided if the number of events is 0 or 1 in either group; there are no asymptomatic ICHs.

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

Strengths

- Over 12,000 patients have received rivaroxaban in the clinical setting in one Phase II trial (5 mg to 20 mg) and one Phase III trial (2.5 mg to 5.0 mg) assessing the safety and efficacy of rivaroxaban for the secondary prevention of ACS(1;3).

- Rivaroxaban 2.5mg bd was effective in reducing the occurrence of the composite primary endpoint of CV death, myocardial infarction or stroke, compared with placebo. The rigorous design features of ATLAS ACS 2 TIMI 51 - large, prospective, randomised, double-blind, placebo-controlled, event-driven, multicentre, and adequately powered - reinforce the beneficial effects seen with rivaroxaban in the prevention of adverse outcomes in patients with recent ACS.

- Investigators had discretion to enroll patients who they intended to treat with aspirin alone (Stratum 1) or aspirin plus a thienopyridine (Stratum 2). This and the entry criteria allowing inclusion of a broad range of patients with various risk factors and extensive co-morbidities, provided flexibility, enabling patients to receive standard care for ACS according to local guidelines. This ensured recruitment of a broad spectrum of ACS patients to the study and enhanced the applicability of trial results to clinical practice. The trial population reflected moderate-to-high-risk patients with ACS who are typically seen in everyday clinical practice (e.g. those with relevant risk factors and underlying co-morbidities e.g. hypertension, diabetes mellitus, lipid disorders). As expected in a study of this size, there were no important imbalances in baseline demographic or disease characteristics.

- Results of all sensitivity analyses in All Strata, Stratum 2 and Stratum 1 were consistent and confirmed the robustness of the results.

- The benefit of rivaroxaban was consistently demonstrated in the trial population whether patients had STEMI, NSTEMI or unstable angina as their index event. Subgroup analyses of the primary efficacy endpoint in the trial population demonstrate that a wide range of patient types benefitted from rivaroxaban added to standard antiplatelet therapy.

- During treatment, the proportion of patients who were ≥85% adherent to study drug treatment was 93.9% for rivaroxaban 2.5 mg bd and 94.6% for placebo(3). Thus, no issue with adherence to rivaroxaban 2.5 mg bd therapy added to antiplatelet therapy in patients with ACS would be anticipated in clinical practice.

- The addition of an anticoagulant to standard antiplatelet therapy is to further minimise thrombotic risk, thus preventing death or recurrent ACS. In line with the aim of therapy, the primary and secondary efficacy outcomes in ATLAS ACS 2 TIMI 51 included a wide range of outcomes based on the incidence of MI, stroke, bleeding and mortality. Bleeding events were assessed using the TIMI scale and also the GUSTO and ISTH scales, in order to provide a more in-depth understanding of the bleeding profile / risks in patients with ACS treated with standard antiplatelet therapy and rivaroxaban combined with standard antiplatelet therapy.

- The study demonstrates that a long-term anticoagulant can be added to antiplatelet therapies in ACS in order to further improve clinical outcome for these patients.. The identification of a narrower population i.e. patients with positive cardiac biomarkers, results in an even more favourable benefit risk balance when compared to the overall study population.

Limitations

- A relatively high number of patients (n=2402 [15.5%] prematurely discontinued from the study and there were over 1000 patients at the end of the trial with unknown vital status.

  Criticism has been made that the quantity of missing data could affect the overall interpretability of the trial.

  ATLAS ACS 2-TIMI was a long study in which patients were treated for up to 31 months; - high discontinuation rates are not unexpected in studies of longer duration in a population of patients with extensive co-morbidity – for example, in the PLATO study (also in ACS patients), the discontinuation rate for both study arms was >20%(31). Also, it should be noted that in some other contemporary trials in ACS(30;31;36), the definition of patients who completed the study included patients who completed the double-blind treatment period but did not complete the follow-up period, as well as patients who died, and patients who prematurely discontinued from the study but were followed up and for whom vital status information was available at the end of the study. In contrast, in the ATLAS ACS 2 TIMI 51 trial, such patients were counted as having prematurely discontinued from the study. The rates of study discontinuation were similar in both study arms (15.0% rivaroxaban 2.5mg bd patients and 15.1% of placebo patients, see end of section 6.5.3); and overall, post-hoc sensitivity analyses including review of vital status data
  Following discussions with the FDA and extensive efforts to gather missing vital status information (see 'Missing data / Patient discontinuation' at the end of section 6.5.3),

  an array of sensitivity analyses of the primary efficacy endpoint, CV mortality and mortality endpoints were conducted including the newly obtained information(7). Results of the sensitivity analyses were and demonstrate that the findings from ATLAS ACS 2 TIMI 51 (7).

- Placebo-controlled rather than active-controlled. Other than warfarin, which despite beneficial results having been achieved in the ACS setting, has many limitations and is not generally accepted to be a suitable addition to antiplatelet therapy in patients with ACS, there is no other alternative standard oral anticoagulation treatment used in the clinical management of ACS. It could also be argued that the study was 'active-controlled' in the sense that the 'control' was standard care antiplatelet treatment.

6.10.3 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.

Evidence to support the use of rivaroxaban for the prevention of adverse outcomes in patients after the acute management of ACS is provided by results from ATLAS ACS 2 TIMI 51 and subsequent post-hoc analyses to identify a group of patients who would derive the greatest benefit with the lowest risk i.e. patients elevated with cardiac biomarkers without prior stroke / TIA. This was a well designed trial i.e. large, prospective, randomised, double-blind, placebo-controlled, event-driven, multicentre, and adequately powered, demonstrating the superiority of combining rivaroxaban with standard care (aspirin or aspirin-clopidogrel) when compared with patients receiving standard care alone. These study characteristics, in addition to those described below, demonstrate the credibility and relevance of the evidence base to the decision problem.

The most recent 2012 ESC guidelines(37) for patients with STEMI recommend low-dose rivaroxaban (2.5 mg b.d) plus ASA + clopidogrel as a treatment option for patients who are at low risk of bleeding, based on data from the pivotal ATLAS ACS 2-TIMI 51 trial.

Population

ACS represents a spectrum of events ranging from unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI).

A total of 15,526 patients were randomised to treatment in ATLAS ACS 2 TIMI 51 at 766 centres in 44 countries (including 254 patients from the UK). Approximately 50% of all randomised patients had STEMI as the index diagnostic event. NSTEMI and unstable angina each comprised about 25% of the ACS index events for the presenting diagnosis.

The demographic and baseline characteristics were representative of a moderate-to-high-risk population of patients with ACS with the majority of all randomised patients having CV risk factors, such as hypertension (67.4%), diabetes mellitus (32.0%), history of MI (26.9%), or hypercholesterolaemia (48.6%). There were 60.5% patients who had a revascularisation procedure for the index event; the vast majority of these being percutaneous coronary intervention (PCI) (99.3%). Of all randomised patients, 74.7% were men, and the mean age was 61.8 years (range 22 to 98 years). This is comparable to the baseline demographics reported in a publication of the GRACE registry(38), where the mean age was 66, and 70% were male. The proportion with a prior MI (28%) in this publication also closely aligned to the ATLAS ACS 2 TIMI 51 population (26.9%). However, the population in ATLAS ACS 2 TIMI 51 had a higher proportion of hypertension (67.4% vs 46%) and diabetes (32% vs 16%).

The trial population therefore reflected patients with ACS who are typically seen in everyday clinical practice (e.g. those with relevant risk factors and underlying co-morbidities).

The benefits of rivaroxaban, in relation to the primary endpoint, were consistent across all sensitivity analyses and all types of ACS – UA, NSTEMI and STEMI, as well as across all major subgroups and geographical regions. Thus, consistency of the subgroup analyses with the

primary efficacy analysis demonstrates that a wide range of patient types, typical of those presenting in clinical practice in England and Wales, can benefit from rivaroxaban added to standard antiplatelet therapy.

This is with the exception of patients with a history of stroke or TIA. These patients were already excluded from Stratum 2 (aspirin / thienopyridine arm), and findings from analysis of Stratum 1 data demonstrated a lack of benefit in patients with a stroke / TIA history in line with finding from other clinical trials and registries (TRITON, ACTION, GRACE)(30;38;39).

Post-hoc analyses identified a narrower population of patients with recent ACS, in whom rivaroxaban would be most appropriate, providing a more favourable benefit risk profile than in the overall trial population. This led to the EU licensing of rivaroxaban 2.5mg bd for the prevention of atherothrombotic events in adult patients with recent ACS with elevated cardiac biomarkers'. The evidence base remains relevant to the decision problem and licensed population since over 80% of patients in ATLAS ACS 2 TIMI 51 had elevated cardiac biomarkers.

Comparators

ATLAS ACS 2 TIMI 51 employed a design whereby patients hospitalised for acute ACS were only started on study medication once they had been stabilised and after interventional procedures and parenteral anticoagulant therapies had been completed. After acute management of ACS, long-term treatment with antithrombotic agents is recommended to reduce the risk of recurrence of other CV events. In all patients with ACS, aspirin (ASA) therapy should be continued indefinitely. During the first 12 months after ACS, the addition of a thienopyridine or $P2Y_{12}$ inhibitor (i.e. clopidogrel or ticagrelor, with prasugrel also an option in patients who have undergone PCI) is recommended(24;26;37;40-45). At present, clopidogrel is the most widely used thienopyridine / $P2Y_{12}$ inhibitor after ACS. Another thienopyridine, ticlopidine, was also permitted in ATLAS ACS 2 TIMI 51 but its use was extremely low (Clopidogrel >99%). Ticagrelor and prasugrel were not approved or part of standard care protocols at the time ATLAS ACS 2 TIMI 51 was initiated. ASA alone may be used in patients who have a high risk of bleeding or who are unable to tolerate $P2Y_{12}$ inhibitor treatment.

Patients enrolled into ATLAS ACS 2 TIMI 51 were randomised to receive either rivaroxaban or placebo, in addition to aspirin or aspirin / thienopyridine antiplatelet therapy.

In accordance with the decision problem, the comparator in ATLAS ACS 2 TIMI 51 therefore represented standard management of ACS including background antiplatelet therapy.

Intervention

Despite widespread adoption of ASA and clopidogrel as the standard of care, and even with the introduction of novel antiplatelet agents such as prasugrel and ticagrelor, major CV event rates (death, recurrent MI, stroke) after ACS remain at ~10% within 1 year(30;31) and has raised the question of whether or not the addition of long-term anticoagulation would further improve clinical outcome for ACS patients.

Cardiac registry studies have demonstrated that the risk of secondary ACS events remains elevated in patients up to 5 years after an initial ACS event(38).

Since it is believed now that excess thrombin generation occurs in ACS patients, which persists for greater than the period of time just around that index event (46;47), drugs which block thrombin generation are candidates for investigation in the treatment of ACS. In a recent study(48), of coagulation and fibrinolysis in ACS, 87 patients with ACS (and 65 healthy controls) were assessed for thrombin generation, using a calibrated automated thrombogram *in vivo* to measure F1+2 plasma concentrations. At both admission and after 6 months, peak thrombin was higher in patients with ACS compared with controls demonstrating that ACS patients have an increased capacity to generate thrombin, which persists even 6 months after the event. This suggests that acute and long term anticoagulant treatment is required in order to manage elevated thrombin levels. Thereby the rationale for studying rivaroxaban in this setting is soundly based.

Activation of FX to FXa via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation by mediating thrombin formation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. The reaction rate of prothrombinase-bound FXa increases 300,000-fold compared with that of free FXa and causes an explosive burst of thrombin generation. Thrombin has several functions in blood coagulation, including the conversion of fibrinogen to fibrin, the activation of platelets, and the feedback activation of other coagulation factors, resulting in the amplification of its own formation. Essentially, rivaroxaban produces antithrombotic effects by decreasing the amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting the activity of thrombin or platelets.

Based on results of the ATLAS ACS TIMI 46 trial, rivaroxaban 2.5mg bd and 5mg bd, were selected as the most appropriate doses to test in a phase III setting(1). Rivaroxaban TDD of 5 and 10 mg appeared to have an acceptable safety profile, had less bleeding than the higher doses, and the 2.5 mg and 5 mg twice-daily doses were numerically more efficacious than the 5 and 10 mg once-daily doses and offered a more favourable net clinical benefit.

As rivaroxaban was evaluated for long-term reduction of recurrent risk in patients with ACS, it was started after stabilisation of the acute event i.e. after the initial treatments for the index ACS event, including revascularisation procedures.

Outcomes

Following an ACS event, patients are at a high risk of cardiovascular events e.g. MI or stroke which can be fatal. Reduction of the risk of such events is key to clinical management of patients with ACS.

In line with these aims, the primary and secondary efficacy endpoints in ATLAS ACS 2 TIMI 51 included a wide range of outcomes based on the incidence of MI, and stroke and mortality and are therefore relevant clinical outcomes for this decision problem. The primary efficacy endpoint components of CV death, MI, and stroke, are internationally accepted, validated, clinical 'hard' endpoints for the evaluation of treatments for ACS and were broadly similar to those used in other recent landmark clinical trials for ACS such as the CURE trial (clopidogrel plus aspirin / NSTEMI ACS)(29), the TRITON-TIMI 38 study (prasugrel vs. clopidogrel / ACS)(30) and PLATO (ticagrelor vs. clopidogrel)(31).

All efficacy endpoints were discussed with and agreed by health regulatory authorities worldwide e.g. European Medicines Agency (EMA), US Food and Drug Administration (FDA).

All events were objectively verified using validated procedures and classifications and objectively adjudicated by a blinded clinical events committee. All assessments, including clinical laboratory tests, and adverse events, were standard validated tests and evaluations were in accordance with GCP to ensure safety of patients participating in research.

By the very nature of these drugs (i.e. antithrombotic), there is an associated risk of bleeding. Bleeding outcomes were therefore incorporated into the trial to confirm that rivaroxaban can be used safely in clinical practice with a good benefit-risk profile. The primary safety endpoint was non-CABG TIMI major bleeding and the study also assessed a wide range of other bleeding outcomes on the TIMI scale and also on the GUSTO and ISTH scales, in order to gain as much information as possible on the bleeding profile of ACS patients receiving rivaroxaban in addition to standard antiplatelet therapy.

Risk-benefit was proactively studied with the inclusion of the Net Clinical Outcome endpoint (Secondary endpoint 2), however it later became apparent that this was too crude an assessment of the risk-benefit of rivaroxaban in ACS and more sophisticated post-hoc analyses were performed. See Section 6.10.1 for further information.

In the context of the use of these relevant clinical endpoints, the 2.5mg bd dose of rivaroxaban reduced the primary efficacy end point, as compared with placebo, and also reduced the risk of death from cardiovascular causes (relative reduction, 34%; absolute reduction, 1 percentage point for the trial population and relative reduction, 45%; absolute reduction, 1.4 percentage points for the licensed population) and from any cause (relative reduction, 32%; absolute reduction, 1 percentage point for the trial population and relative reductive, 42%; 1.3 percentage points for the licensed population). The 2.5mg bd dose of rivaroxaban showed a non-significant but directionally consistent benefit for myocardial infarction and a significant reduction in the risk of stent thrombosis in the trial population, a finding that suggests that enhanced thrombin activity may play a role in these events. Thus, when viewed as long-term therapy after an acute coronary syndrome, the addition of low-dose rivaroxaban appears to be an attractive option, producing results in line with the scope of the decision problem.

6.10.4 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?

We consider the results of ATLAS ACS 2 TIMI 51, and the subsequent licensing of rivaroxaban for use in patients after an acute ACS with elevated cardiac biomarkers, to be directly applicable to ACS patients routinely treated in England and Wales, receiving standard antiplatelet therapy of aspirin or aspirin combined with thienopyridine.

Trial design

The rigorous design features of ATLAS ACS 2 TIMI 51 - large, prospective, randomised, double-blind, placebo-controlled, event-driven, multicentre, and adequately powered – add robustness to the beneficial effects seen with rivaroxaban 2.5mg bd in the prevention of adverse outcomes in patients with recent ACS.

The discretion to enrol patients to two different antiplatelet regimens i.e. aspirin alone or aspirin plus a thienopyridine, and the inclusion of a broad range of patients with various risk factors and extensive co-morbidities, provided flexibility, and ensured recruitment of a broad spectrum of ACS patients to the study, enhancing the applicability of trial results to clinical practice.

As rivaroxaban was evaluated for long-term reduction of recurrent risk in patients with ACS, it was started after stabilisation of the acute event i.e. after the initial treatments for the index ACS event, including revascularisation procedures. This is how it would be recommended for use in clinical practice.

Demographics of trial population

We have described previously the baseline characteristics of ATLAS ACS 2 TIMI 51 and outcomes relevant to considerations of generalisability of the study to real-life practice (section 6.10.3).

The benefits of rivaroxaban, in relation to the primary endpoint, were consistent in the trial population across all sensitivity analyses and all types of ACS – UA, NSTEMI and STEMI, as well as across all geographical regions and major subgroups - except patients with prior stroke/TIA. The licensed population for rivaroxaban in ACS is represented by over 80% patients in the ATLAS ACS 2 TIMI 51 trial and consistency of this subgroup analysis with the primary efficacy analysis demonstrates applicability to the range of patients presenting in clinical practice in England and Wales.

Comparator

The use of a thienopyridine plus ASA in patients with ACS is recommended by NICE clinical guidelines (25) and is considered standard care in the UK during the first 12 months after the ACS event. Thienopyridine treatment in the pivotal trial was with clopidogrel or ticlopidine and dosage followed national or local prescribing information. The ASA dose range (75 to 100 mg/day) is consistent with recommendations from major international cardiovascular organisations and societies(27) and also within the dosing stated in NICE guidelines.

There is no other alternative standard oral anticoagulation treatment used in the clinical management of ACS, so the most appropriate comparator is, as per the trial, standard of care antiplatelet therapy i.e. aspirin ± clopidogrel.

What proportion of the evidence base is for the dose(s) given in the SPC?

The evidence base included 2.5mg bd and 5mg bd doses and a combined analysis of the 2 doses. The dose now licensed for use in ACS is the 2.5mg bd dose.

Patients with elevated biomarkers (troponin or CK-MB) and without a prior stroke/TIA constituted 80 % of the ATLAS ACS 2 TIMI 51 study population.

Patient selection – use of rivaroxaban in clinical practice

- Rivaroxaban is licensed for use in patients with an acute ACS with elevated cardiac biomarkers(23).

- Patients with active clinically significant bleeding or lesions or conditions, if considered to be a significant risk for major bleeding are contraindicated for rivaroxaban treatment after an acute ACS. This includes current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Patients with prior ICH were excluded from ATLAS ACS 2 TIMI 51(23).

- Patients with prior TIA/stroke did not experience any benefit from addition of rivaroxaban to antiplatelet therapy. Rivaroxaban is contraindicated for the concomitant treatment of ACS with antiplatelet therapy in patients with prior stroke or TIA(23).

- Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C(23)

- Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. CrCl <30 ml/min at screening was an exclusion criterion in ATLAS ACS 2 TIMI 51(3). Therefore, rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min)(23).

Haemorrhagic risk - Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period. As with other anticoagulants, patients taking rivaroxaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. In addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. Rivaroxaban should be discontinued if severe haemorrhage occurs(23).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs),

acetylsalicylic acid (ASA) and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered(23).

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

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 10.10, appendix 10.

A systematic literature review to identify relevant cost-effectiveness studies and studies reporting utility values and estimates of resource use and costs from the published literature was performed to inform sections 7.2, 7.4.9, 7.5.6.

Information sources

Searches encompassed electronic medical databases, conference proceedings and the Internet (specified Web sites). We also asked a topic expert to provide additional references which were not identified by searching the other sources and could inform the economic model.

Databases

The literature review was conducted in March 2014 for which the following electronic databases were searched, with date limits capturing publications since January 2000.

MEDLINE® and EMBASE® (6 March 2014, using the Embase.com interface)

MEDLINE®In-Process (6 March 2014, using the Pubmed.com interface)

EconLit® (6 March 2014, using the American Economic Association interface)

The Cochrane Library (National Health Service's Economic Evaluation Database and Health Technology Assessment Database 6 March 2014)

A date limit of 2000 was chosen as older articles contain older costs, which would need to be inflated to current costs to be useful; however, inflating costs in this way over many years can introduce errors. Further, the standard of care in management of ACS has changed dramatically since 2000, because of the introduction of clopidogrel into clinical practice; therefore, much of the information published before 2000 is not relevant.

The search strategies included combinations of title/abstract free-text terms and Subject Index Headings. Search terms for economic evaluations were adapted from search filters published by SIGN. For full details of the search strategy for each database, please see Appendix 10.

Conference proceedings

Conference abstracts from the following four conference proceedings were searched:

AHA Scientific Sessions: 2012-2013

ESC: 2013

ACC: 2013

International Society for Pharmacoeconomics and Outcomes Research (ISPOR): 2013

For further details, refer to Appendix 10.

UK HTA websites

In addition, the HTA websites of the National Institute for Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC) were searched to identify cost/resource use data, utility data, and cost effectiveness analysis reported in the HTA submissions.

When searching the Websites, specific search terms depended on the nature of the search For full details of the search strategy for each website, please see Appendix 10.

Study selection

Publications were to be included if they met the eligibility criteria as outlined in Table 24. For the eligibility criteria for the utilities review, please see section 7.4.5.

Table 24 Eligibility criteria used in the economic systematic review.

	Economic review	Rationale/comments
Inclusion criteria	**Population** Adults initially hospitalized with ACS (unstable angina, STEMI, or NSTEMI) who are managed for secondary prevention of their ACS event	Consistent with the NICE scope
	Interventions for cost/resource use studies: All studies reporting cost and resource use data will be included in the review regardless of the treatment type **Interventions for economic evaluations:** • Rivaroxaban • Ticagrelor • Prasugrel • Aspirin alone (≤150mg od) • Clopidogrel • Aspirin (≤150mg od) + clopidogrel	Although ticagrelor and prasugrel are not included as comparators in the scope, these interventions were included in the economic review as studies evaluating these interventions would report cost and utility values relevant to the patient population of the current review.
	Outcomes • Direct medical costs of managing secondary prevention in ACS (including management of adverse events), resource utilisation associated with managing secondary prevention in ACS (including management of adverse events), hospitalisations, short-term disability costs of secondary prevention in ACS, indirect costs such as absence from work • Cost-effectiveness and budget-impact analysis results for the relevant therapies in secondary prevention in ACS	

	Economic review	Rationale/comments
	Study design • Any studies (e.g., clinical trials or other prospective or cross-sectional studies) reporting resource utilisation and costs • Economic evaluation studies, e.g., studies based on models, cost analyses performed alongside clinical trials, and budget-impact analyses	• These study designs will provide data on the economic burden of ACS, cost of illness and resource use • These studies report economic evaluations and will provide cost or resource use data adapted from other studies for use as model inputs
	Country United States Canada United Kingdom Germany France Italy Spain	
	Language restrictions English language	

	Economic review	Rationale/comments
	Publication timeframe restrictions 2000-2014	The searches were conducted from 2000 to present in all the literature databases to identify relevant articles with recent cost data. Older articles contain older costs, which would need to be inflated to current costs to be useful; however, inflating costs in this way over many years can introduce errors. Further, the standard of care in management of ACS has changed dramatically since 2000, because of the introduction of clopidogrel into clinical practice; therefore, much of the information published before 2000 is not relevant.
Exclusion criteria	**Population** • Patients with stable angina, or other CV disease that is not ACS • Primary prevention of ACS (mainly relevant for studies with aspirin) • Children • Mixed populations of stable and unstable angina, which do not present data for unstable angina separately	

	Economic review	Rationale/comments

	Interventions
	Following interventions are not of interest for economic evaluations:
	• High-dose aspirin (if dose is > 150 mg/day)
	• Warfarin
	• Ticlopidine
	• Vitamin K antagonist
	• Phenprocoumon
	• Therapies used in the acute phase of ACS management, e.g. (this is not an exhaustive list):
	  ○ Bivalirudin
	  ○ Fondaparinux
	  ○ Enoxaparin
	  ○ Otamixaban
	  ○ Streptokinase, alteplase, and other "ase" products that are used for acute management
	There will be no exclusion on the basis of interventions for cost/resource use studies	

	Outcomes Measures of clinical effectiveness or QoL measures	

	Economic review	Rationale/comments
	Study design **Study designs other than cost/resource use studies and economic evaluations including the following:** • Reviews • Letters • Comment articles • Studies focused on short-term in-hospital treatment of ACS • Models with a time horizon of < 30 days • Any non-primary source of cost or resource use data • Studies not reporting cost/resource use data	
	Country Articles not concerned with any of the countries of interest (the US, Canada, France, Germany, Italy, Spain, the UK)	
	Language restrictions Non-English language	
	Publication timeframe restrictions Studies published prior to 2000	

Validity assessment

The published data identified via the search strategy was screened for inclusion and extraction. Inclusion/exclusion criteria guidelines were developed to ensure that all decisions regarding the inclusion and exclusion of studies were consistent.

Screening of the published data was undertaken in two steps:

- Initial screening (1st pass) - The title and abstracts of all studies was initially screened to identify a list of potentially relevant studies
- Detailed screening (2nd pass) - A detailed screening of the full text versions of the potentially relevant studies was then undertaken to identify the final list of included studies

A single reviewer screened all citations and full-text papers followed by a second check by an independent reviewer.

All data collection activities were undertaken within a systematic review database (SRDB), which ensures every study can be easily tracked through the review process, with each decision for inclusion/exclusion recorded.

Relevant publications included after the second pass screening were advanced to the formal data-extraction and quality-assessment process. Data extraction focused on information that could be used to inform the structure, assumptions and model inputs for the cost-effectiveness analysis of rivaroxaban for the secondary prevention of ACS in the UK.

Identified economic evaluations and cost/resource use studies were also reviewed for any relevant utility data. Similarly, utility studies were also reviewed for any relevant cost/resource use data.

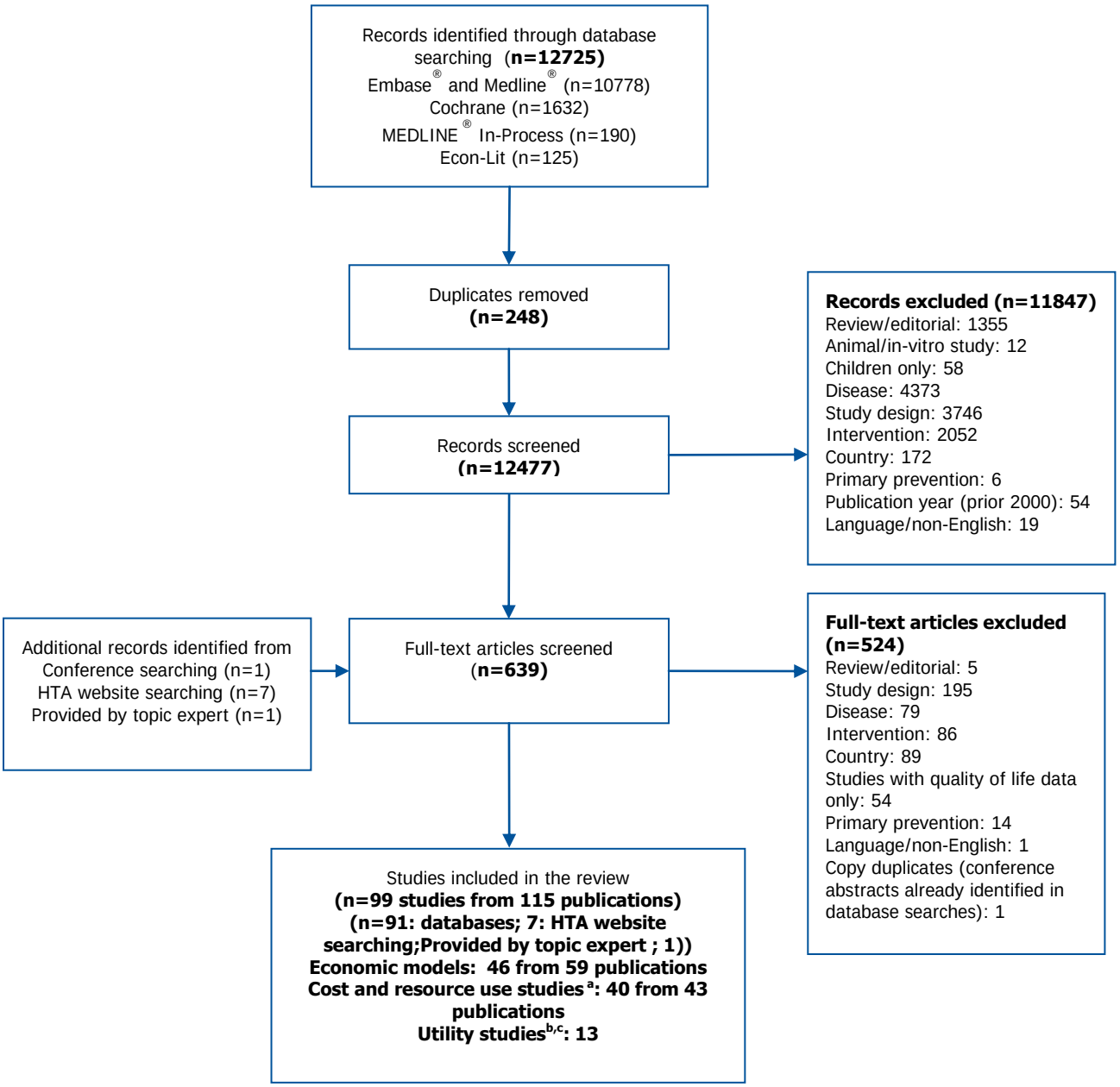
7.1.2 Description of identified studies

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 46 papers that were of potential value for helping to inform the decision problem (see Figure 18).

No papers were identified that had evaluated the cost-effectiveness of rivaroxaban in the secondary prevention of ACS.

Figure 18: PRISMA Flowchart for Economic Literature Review



[a] 30 of the models also provide cost data that have been extracted (Berg et al., 2008; Berg et al., 2007; Bruggenjurgen et al., 2007; Cowper et al., 2005; Heeg et al., 2007; Karnon et al., 2006; Karnon et al., 2010; Kolm et al., 2007; Latour et al., 2008; Latour-Perez et al., 2004; Mahoney et al., 2006; Mahoney et al., 2010; Schleinitz et al., 2005; Schleinitz et al., 2004; Weintraub et al., 2005; Zhang et al., 2009; Greenhalgh al., 2009; NICE, 2011; Bagust et al., 2011; Charland et al., 2011; Coleman et al., 2013; Davies et al. 2013a; Davies et al. 2013b; Grima et al., 2014; Kazi et al. 2014; Lala et al. 2011; Lala et al. 2014; Straub et al. 2014; Theidel et al. 2013; Hillegas 2014).

[b] 21 of the models also provide utility data that have been extracted (Berg et al., 2008; Berg et al., 2007; Karnon et al., 2006; Karnon et al., 2010; Latour et al., 2008; Latour-Perez et al., 2004; Mahoney et al., 2010; Main et al., 2004; Schleinitz et al., 2005; Schleinitz et al., 2004; Zhang et al., 2009; NICE, 2009 (TA182); Greenhalgh al., 2009; Crespin et al., 2011; NICE, 2011; Bagust et al., 2011; Coleman et al., 2013; Theidel et al. 2013; Charland et al., 2010; Lala et al. 2013; Kazi et al. 2014).

3 of the cost studies also includes utility data that have been extracted (NICE, 2007; Bakhai et al., 2012; Zymer et al., 2013).

Table 25 : Summary list of cost-effectiveness evaluations

Study	Year	Secondary publication	Country where study was performed and perspective	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Discount rates applied	Costs (currency) (intervention,comparator)	ICER (per QALY gained)
Bagust A(49)	2011	-	UK NHS and PSS	Combined decision tree and markov model comparing Ticagrelor + ASA with Clopidogrel + ASA for 12 months. A lifetime horizon with annual cycles was used and health states include No event, MI (non-fatal), stroke (non-fatal) and death from any cause in the decision tree and No event, MI (non fatal and post), stroke (non fatal and post) and death in the Markov model. Age adjusted event rates considered in economic model to ensure a representation of the general UK ACS population. Silent MIs excluded from PLATO in primary outcome	70	Ticagrelor: 6.382, Clopidogrel: 6.275	NR	Ticagrelor: £14,135, Clopidogrel: £13,737	£3696 / QALY
Berg et al(50)	2008	-	Europe (Sweden, Germany and France) Sweden-societal (direct and indirect costs). Germany and France-Payer's perspective	Combined decision tree and Markov model comparing clopidogrel + ASA for 12 months with ASA monotherapy. A lifetime horizon was used and health states for MI, stroke, CV death and other death are included. The Swedish Hospital Discharge and Cause of Death Register was the key source of evidence used in the model. Patients without any event during month 1 can suffer same set of events during following year based on Swedish registries and PCI-CLARITY and PCI-CURE. Long term survival based on Swedish registries. Bleeding disutility not applied due to lack of data	63	Sweden: clopidogrel + ASA =10.090, ASA =9.997 Germany: clopidogrel + ASA =9.772, ASA=9.682. France: clopidogrel + ASA =10.246, ASA =10.152.	3% per annum	Sweden: direct + indirect clopidogrel + ASA = €2944, direct + indirect ASA = €2551, direct only clopidogrel + ASA = €2211, direct only ASA = €1626 Germany (direct only): clopidogrel + ASA = €3129, ASA = €2420. France (direct only): clopidogrel + ASA = €2550, ASA = €2056.	Sweden: (direct + indirect) = €4225/QALY, (direct only) = €6282/QALY, Germany: €7871/QALY, France:€5226/QALY
Berg et al(51)	2007	-	Europe (Sweden, Germany and France) Payer perspective	Combined decision tree (1 month) and Markov model comparing clopidogrel + ASA for 12 months with ASA monotherapy. A lifetime horizon was used and health states for MI, stroke, CV death and other death were included. The Clarity and COMMIT trials were the key sources of evidence used in the model, depending on the analysis undertaken. Patients who suffer from a stroke during first month - not at a risk for any events other than death in	57 (Clarity), 61 (COMMIT)	Only incremental QALYs are presented: SWEDEN not presented, GERMANY - Clarity = 0.141, Commit = 0.146. FRANCE - Clarity = 0.142, Commit	3% per annum	Sweden: Clarity - direct + indirect clopidogrel + ASA = €3403, direct + indirect ASA = €4253, direct only clopidogrel + ASA = €1972, direct only ASA = €2083, Commit - direct + indirect clopidogrel + ASA = €2265, direct + indirect ASA = €1858, direct only clopidogrel + ASA = €1542, direct only ASA = €1004.	Cost per QALY: Sweden not presented, Germany (direct only) - Clarity: €94/QALY, Commit: €5452/QALY, France - Clarity: Dominant , Commit: €3674/QALY,

				subsequent years as register does not contain sufficient observations to model the risk by subgroups. Long term survival after all events modelled based on analyses of Swedish registries. No distinction could be made between ICD 10 codes for STEMI and NSTEMI. Major bleeding events included months 2-12 (in accordance to CURE)		= 0.148.		Germany (direct only): Clarity - clopidogrel + ASA = €2607, ASA = €2594, Commit - clopidogrel + ASA = €2004, ASA = €1206. France (direct only): Clarity - clopidogrel + ASA = €2713, ASA = €3080, Commit - clopidogrel + ASA = €1950, ASA = €1405	Cost per LYG: Sweden - Clarity (direct + indirect): dominant, (direct only): dominant ,Commit: (direct + indirect): €2100/LYG, (direct only): €2772/LYG, Germany (direct only) - Clarity: €92/LYG , Commit: €4144/LYG, France (direct)- Clarity: dominant, Commit: €2786/LYG
Bruggenju-rgen et al(52)	2007	-	Germany Payer perspective	Markov model comparing clopidogrel + ASA for 12 months with ASA monotherapy. A lifetime horizon (44 years)was used and health states for MI, ischaemicstroke, CV death and other death were are included. The Swedish Hospital Discharge and Cause of Death Register was the key source of evidence used in the model. Swedish event data was used because corresponding data for MI and IS are lacking for Germany. Risk data for patients with ACS experiencing MI, IS and CV death calculated using Swedish registries. Indirect costs not considered as age of patients is around 66 years.	66	QALYs not reported. LYG Clopidogrel = 9.02, LYG ASA = 8.89	3% per annum	Clopidogrel: €8,953, ASA: €8,548	cost per QALY not reported, cost per LYG: €3,113/LYG
Coleman et al(53)	2014	Coleman 2013(54)	EU5: Italy, Spain, France, Germany, UK Individual countries' health service perspective and included both direct costs and intangible consequences (QALYs)	A hybrid decision tree/Markov model using annual cycles over a lifetime (40 years) period. Health states used were no event, non-fatal MI, non-fatal stroke, post MI, post stroke, and death. It was assumed patients had their index event at 65–70 years of age and had a 42.7% incidence of HPR 24–48 hours post-revascularisation. For universal strategies, it was assumed patients were prescribed the drug without PRA testing. Because the PLATO and TRITON-TIMI 38 trials did not individualize therapy using PRA test results or exclude those with HPR, it was assumed these studies likely underestimated the performance of clopidogrel. The maintenance dosing for the treatment strategies were assumed to be as follows: clopidogrel 75 mg daily, ticagrelor 90 mg twice daily and prasugrel 10 mg daily. For the Markov	65-70 years	Universal ticagrelor: Germany: 3.919, Italy: 3.858, France: 3.764, Spain: 3.822, and UK: 3.413 Platelet reactivity assay (PRA)-driven ticagrelor: Germany: 3.910, Italy: 3.849, France: 3.756, Spain: 3.814, and UK: 3.403Universal	Country specific recommended annual rates	Universal ticagrelor: Germany: €19,611; Italy: €19,806; France: €19,287; Spain: €19,355; and UK: £12,906 PRA-driven ticagrelor: Germany: €19,195; Italy: €19,168; France: €18,965; Spain: €18,851; and UK: £12,540 Universal prasugrel: Germany: €19,636; Italy: €19,373; France: €19,059; Spain: €19,034; and UK: £12,889 PRA-driven prasugrel: Germany: €19,205; Italy: €18,984; France: €18,867; Spain: €18,715; and UK: £12,533	Universal ticagrelor vs. PRA-driven ticagrelor: Germany: 46,222; Italy: 70,889; France: 40,250; Spain: 63,000; and UK: 36,600 Universal prasugrel vs. PRA-driven ticagrelor: Germany: Dominated; Italy: Dominated; France: Dominated; Spain: Dominated; and UK: Dominated

				portion of the model, we assumed patients would discontinue clopidogrel, ticagrelor, and prasugrel, and no additional treatment effect from these drugs would occur. Thus, all event rates in the Markov model were assumed to be the same for patients who had received any of the strategies, with the only difference being the proportion of patients starting in each Markov health state. The costs of recurrent nonfatal MI, nonfatal stroke, and death for the decision tree portion of our model were taken from the clopidogrel arm of the PLATO health economics and quality-of-life substudy and were assumed to be the same for all strategies		prasugrel: Germany: 3.875, Italy: 3.815, France: 3.722, Spain: 3.780, and UK: 3.351 PRA-driven prasugrel: Germany: 3.891, Italy: 3.831, France: 3.738, Spain: 3.796, and UK: 3.377			
Cowper et al(55)	2005	-	USA Societal perspective	A decision analysis comparing treatment with clopidogrel for one year with one month clopidogrel treatment. A lifetime horizon was used and health states for MI, revascularisation, major bleeding and death were included. An unselected, heterogenous population from Duke's Medical Center was the key source of evidence used in the model. Rates of major bleeding were based on CREDO trial data because bleeding complications were not recorded in Duke Information System for Cardiovascular Care (DISCC). Because the SoC at Duke was to treat with clopidogrel for one month, the effect of prolonged therapy was based on CREDO per-protocol data and the relative risk reduction associated with clopidogrel was assumed to be constant across all subgroups. A comparison of CREDO and DISCC patient populations was performed. Costs were based on average DRG categories, average medicare payments, or (for bleeds), the EPILOG economic study. Costs beyond one month were calculated on assumptions but these assumptions are not described in detail. Estimates of life expectancy were based on two previous analyses of longitudinal data, with life expectancy based on Framingham and corrected for post-acute reduction using DISCC data.	62	Not included in model	3% per annum	Between 1 and 12 months post-PCI: Clopidogrel: $3,715 No clopidogrel: $2,819	$15,696 per LYG $34,336 per MI avoided
Charland et al(56)	2011	-	US	Combined literature-based, decision analytic, Markov model to estimate the cost-effectiveness of CYP2C19-guided aspirin plus either clopidogrel or prasugrel therapy vs. no genotyping.Post-initial ACS CVevents were based on the TRITON-TIMI 38 study. Health states used were nonfatal MIand stroke, CV death,	NR	CYP2C19 Genotype-Guided Therapy: 0.7212 No Genotyping:	NR	CYP2C19 Genotype-Guided Therapy: $3,211 (Annual cost) No Genotyping: $3,331 (Annual cost)	CYP2C19 Genotype-Guided Therapy: $4,452/QALY No Genotyping:

				intracranial hemorrhage, other life-threatening bleed, andminor bleed. The model allowed for clopidogrel/prasugrel discontinuation and aspirin monotherapy.		0.6767			$4,921/QALY
Davies et al(57)	2013	Davies 2010(58)	Spain	Markov state transition model was developedusing annual cycles over a lifetime (40 years) period.Patients enter the model and face risks for cardiovascular death, non-fatal MI, or non-fatal stroke, and bleeding (fatal, major or minor), during the 12 months antiplatelet treatment phase.TRITON-TIMI 38 study was the key source of evidence used in the model.	NR	Overall licensed population: Clopidogrel: 14.017 LY, 10.828 QALY Prasugrel: 14.089 LY, 10.883 QALY UA-NSTEMI: Clopidogrel: 14.04 LY, 10.83 QALY Prasugrel: 14.10 LY, 10.87 QALY STEMI: Clopidogrel: 13.95 LY, 10.82 QALY Prasugrel: 14.07 LY, 10.91 QALY ACS diabetes: Clopidogrel: 13.21 LY, 10.16 QALY Prasugrel: 13.39 LY, 10.29 QALY Core Cohort (those aged less than 75 and weighing 60 kg or above): Clopidogrel: 15.10 LY, 11.70 QALY Prasugrel: 15.17 LY, 11.76 QALY	3% per annum	Overall licensed population: Clopidogrel: €213; Total costs: €11,409 Prasugrel: €751; Total costs: €11,923 UA-NSTEMI: Clopidogrel: €214; Total costs: €11,435 Prasugrel: €752; Total costs: €11,936 STEMI:Clopidogrel: €214; Total costs: €11,435 Prasugrel: €752; Total costs: €11,936 ACS diabetes: Clopidogrel: €211; Total costs: €10,898 Prasugrel: €746; Total costs: €11,434 Core Cohort (those aged less than 75 and weighing 60 kg or above): Clopidogrel: €214; Total costs: €12,235 Prasugrel: €755; Total costs: €12,754	Overall licensed population: Prasugrel vs. Clopidogrel: €7198/LYG, 9489/QALY UA-NSTEMI: Prasugrel vs. Clopidogrel: €9367/LYG, 12414/QALY STEMI: Prasugrel vs. Clopidogrel: €4514/LYG, 5913/QALY ACS diabetes: Prasugrel vs. Clopidogrel: €2987/LYG, 3935/QALY Core Cohort (those aged less than 75 and weighing 60 kg or above): Prasugrel vs. Clopidogrel: €7291/LYG, 9582/QALY
Davies et al(59)	2013	-	Germany	A Markov model was developed to facilitate a lifetime horizon for the analysis with a cycle length of 12	≥75 years	Licensed population:	3% per annum	Drug cost: Licensed population:	ICER per QALY vs. Clopidogrel:

				months. The model estimated risks of clinical events (cardiovascular death, non-fatal MI or stroke, and bleeding).Clinicalinputs were based on an analysis of the TRITON-TIMI 38 clinicaltrial. Non-fatal ischemic events that are modelled to have occurred by 12 months are considered prognostic and are assumed to increase long-term all-cause mortality risks in the extrapolation period beyond 12 months.		Clopidogrel: 10.657 Prasugrel: 10.712 UA-NSTEMI: Clopidogrel: 10.661 Prasugrel: 10.702 STEMI: Clopidogrel: 10.647 Prasugrel: 10.740 ACS diabetes: Clopidogrel: 9.972 Prasugrel: 10.109 Core cohort: Clopidogrel: 11.524 Prasugrel: 11.579		Clopidogrel: €226 Prasugrel: €1044 UA-NSTEMI: Clopidogrel: €227 Prasugrel: €1045 STEMI: Clopidogrel: €225 Prasugrel: €1042 ACS diabetes: Clopidogrel: €224 Prasugrel: €1037 Core cohort: Clopidogrel: €227 Prasugrel: €1050	Licensed population: Prasugrel: €14 350 UA-NSTEMI: Prasugrel: €18 530 STEMI: Prasugrel: €9131 ACS diabetes: Prasugrel: €6025 Core cohort: Prasugrel: €14 487

Crespin et al(60)	2011	Crespin 2010(61)	USA Medicare	Combined decision tree and Markov model comparing universal ticagrelor for 12 months with genotype driven treatment. Analyses are conducted on time horizons of 1, 5 and 30years. Two health states were used – post ACS event and death. The US Medicare database was the key source of evidence used in the model. Assumed ticagrelor response to be the same for patients of all genotypes. All events were assumed to be independent of one another. The probability of CYP2C19*2 mutation was obtained by weighting ethnicity-specific estimates by the ethnic composition of the Medicare program; because ethnicity was categorised as white, black, Hispanic, and other, all patients identified as other were assumed to be Asian.	79	After 1 year: Genotype-driven: 56,603, Universal ticagrelor: 58,492. After 5 years: Genotype-driven: 217,711, Universal ticagrelor: 228,049 After 30 years: Universal ticagrelor 0.14 QALYs gained per person relative to genotype driven	3% per annum	After 1 year: Genotype-driven: $713,983,854, Universal ticagrelor: $794,382,109. After 5 years: Genotype-driven: $943,144,383, Universal ticagrelor: $1,047,138,812 After 30 years: Universal ticagrelor 0.14 QALYs gained per person relative to genotype driven	After 1 year: $42,546/QALY. After 5 years: $10,0659/QALY After 30 years: $8827/QALY
Grima et al(62)	2014	Bainey 2013; Grima 2013(63;64)	Canada	A two-part model was developed consisting of a one-year decision tree and a lifetime Markov model. Within the decision tree, patients remained event-free, experienced a non-fatal myocardial infarction (MI), a nonfatal stroke, or death due to vascular or non-vascular related causes based on data from the PLATO trial. The lifetime Markov model followed these patients and allowed subsequent MI, stroke and death. The utility value for post-stroke was assumed to be the same as for new stroke. The following assumptions were made for the base case analysis: no treatment effect after year 1 of the model was assumed, because all transition probabilities were the same for both treatment arms; adverse events such as dyspnea had no long-term prognostic impact beyond the duration of the clinical trial; no discontinuation other than due to death was included in the model; and the length of treatment for both ticagrelor and clopidogrel was assumed to be 365 days for those who survived the 1-year trial period. For those patients who died during the year, the length of treatment was assumed to be 183 days, assuming that they died, on average, mid-way through the year.	62 years	Ticagrelor QALYs: 40 years: 7.016 20 years: 6.801 10 years: 5.386 5 years: 3.442 Clopidogrel QALYs: 40 years: 6.932 20 years: 6.720 10 years: 5.322 5 years: 3.402 Ticagrelor LYs: 40 years: 8.308 20 years: 8.041 10 years: 6.342 5 years: 4.040 Clopidogrel LYs: 40 years: 8.211 20 years: 7.947	5% per annum	Ticagrelor Cost 40 years: $52 490 20 years: $51 393 10 years: $44 801 5 years: $36 195 Clopidogrel Cost 40 years: $51 669 20 years: $50 586 10 years: $44 079 5 years: $35 582 Incremental cost: 40 years: $821 20 years: $807 10 years: $722 5 years: $613	ICER/QALYs (Ticagrelor vs generic clopidogrel): 40 years: $9745 20 years: $9900 10 years: $11 329 5 years: $15 441 ICER/LYs (Ticagrelor vs generic clopidogrel): 40 years: $8438 20 years: $8598 10 years: $9983 5 years: $14046

						10 years: 6.269 5 years: 3.996 Incremental QALY: 40 years: 0.084 20 years: 0.081 10 years: 0.064 5 years: 0.040 Incremental LYs: 40 years: 0.097 20 years: 0.094 10 years: 0.072 5 years: 0.044			

Greenhalgh et al(65)	2009	-	UK NHS and PSS	Decision tree for first 3 days followed by Markov model. Compares Prasugrel + ASA with Clopidogrel + ASA for a 12 month treatment duration. The model horizon was 40 years (lifetime) with monthly cycle lengths. Health states include MI (non-fatal), stroke (non-fatal), CV/bleed death and other death. Model was neither a cohort or discrete simulation type. Instead it can be described as a deterministic patient level simulation which applies baseline characteristics of each patient to estimate expected events over a lifetime based regression risk models derived from analysis on TRITON-TIMI 38 trial.	Not reported	Prasugrel: 1 year = 0.73, 10 years = 5.83, 20 years = 8.69, 40 years = 10.15. Clopidogrel: 1 year = 0.73, 10 years = 5.81, 20 years = 8.65, 40 years = 10.10	NR	Prasugrel: 1 year = £1,036, 10 years = £3,348, 20 years = £4,656, 40 years = £5,334. Clopidogrel: 1 year = £887, 10 years = £3194, 20 years = £4,492, 40 years = £5,163,	1 year: £159,358/QALY, 10 years: £8,477/QALY, 20 years: £4,318/QALY, 40 years: £3,220/QALY
Heeg B et al(66)	2007	-	UK NHS perspective	Markov model with health states of MI, stroke and death. Compares a number of treatment strategies over a lifetime model horizon. Cycles were 6 months in length. The same transition probabilities were applied for the active and comparator treatment arms for the remainder of the patient's lifetime following the discontinuation of active treatment when experiencing an event or after the intended duration of active treatment. The risk of experiencing subsequent events after an MI or stroke was estimated based on the initial transition probabilities.	Not reported	Incremental life-years: Clopidogrel vs ASA: CAPRIE 0.03564, CAPRIE stroke 0.02269, CHARISMA 0.0054, CURE 0.1153, PCI-CURE 0.0293, CLARITY 0.0584, COMMIT 0.0565 Clopidogrel (1 year) vs clopidogrel (28 days): CREDO 0.1068 Dipyridamole + ASA vs ASA: ESPS2 0.07749, ESPRIT 0.2366 Dipyridamole + ASA vs clopidogrel: Indirect comparison of ESPRIT and CAPRIE: -0.1052	NR	Clopidogrel vs ASA: CAPRIE £700, CAPRIE stroke £594, CHARISMA £772, CURE £88, PCI-CURE -£268, CLARITY -£346, COMMIT -£88 Clopidogrel (1 year) vs clopidogrel (28 days): CREDO -£192 Dipyridamole + ASA vs ASA: ESPS2 -£497, ESPRIT -£150 Dipyridamole + ASA vs clopidogrel: Indirect comparison of ESPS2 and ESPRIT -£844 ASA vs placebo: CAPRIE -£508, CAPRIE stroke -£701, CHARISMA -£360, CURE -£494, PCI-CURE -£534, CREDO -£1,036, ESPS2 -£696, ESPRIT -£1,225	Clopidogrel vs ASA: CAPRIE £19,624/LYG, CAPRIE stroke £26,167/LYG, CHARISMA £143,071/LYG, CURE £771/LYG, PCI-CURE dominant, CLARITY dominant, COMMIT dominant Clopidogrel (1 year) vs clopidogrel (28 days): CREDO dominant. Dipyridamole + ASA vs ASA: ESPS2 dominant, ESPRIT dominant Dipyridamole + ASA vs clopidogrel: Indirect comparison of ESPS2 and CAPRIE: dominant ASA vs placebo: CAPRIE dominant, CAPRIE stroke dominant, CHARISMA dominant, CURE dominant, PCI-CURE dominant, CREDO dominant, ESPS2 dominant, ESPRIT dominant

						ASA vs placebo: CAPRIE 0.13, CAPRIE stroke 0.14, CHARISMA 0.09, CURE 0.21, PCI-CURE 0.14, CREDO 0.12, ESPS2 0.04, ESPRIT 0.24			
Hillegas et al(67)	2011	-	US	A Markov-model with baseline acute coronary syndrome (ACS) health state and subsequent death, nonfatal myocardial infarction, stent thrombosis, urgent revascularization, major bleeding, and malignancy was constructed with 15 one month cycles.	NR	NR	NR	NR	Prasugrel was dominant over clopidogrel: In the 1st month after the index event: Prasugrel vs. clopidogrel: $9,988 ± 2,148 saved per QALY 2 months to 15 months: Prasugrel: Incremental estimated cost $5,820 ± 2,136 per QALY saved Prasugrel vs. generic clopidogrel: $42,225 ± 12,499 per QALY saved

Kim et al(68)	2013	-	US health system perspective	A decision model was developed and the probabilities of complications including myocardial infarction (MI), ischemic stroke (IS), vascular death, and major bleeding events were defined based on the Platelet Inhibition and Patient Outcomes (PLATO) trial and sub studies.	NR	Ticagrelor: 10.2579 Clopidogrel: 10.1336	NR	Ticagrelor: $58,922.91 Clopidogrel: $35,366.30	ICER:$189,468.79/QALY
Heller et al(69)	2003	-	UK Payer perspective (Drug costs only)	No model was used, analysis of cost x incidence only. A hypothetical practice size of 10,000 patients is assumed for calculations	50 +	Not included in model	NR	Not reported	Not reported
Karnon et al(70)	2006	-	UK NHS perspective	Combined decision model (1 year) and Markov model comparing clopidogrel + ASA for 12 months with ASA monotherapy. A lifetime horizon (35 years) was used and health states for non-fatal MI, post non-fatal MI, non-fatal stroke, post non-fatal stroke, CV death and other death are included. The model is based on hypothetical patients representing a UK population. No data identified describing subsequent events experiencing stroke, so experience of stroke beyond year 1- not modelled. Conservative assumption- ACS patients experiencing stroke during the 1 year treatment have same event rates as those event free in subsequent years. Estimated costs assume that 35% of secondary strokes result in dependency on care. RRs for the outcome events included in CURE trial are transferable to an alternative population.	66	Clopidogrel = 7.3645, ASA = 7.3098	6% per annum – costs 1.5% per annum - benefits	Clopidogrel: €11,756, ASA: €11,353	€7,365/QALY, €6,991/LYG
Karnon et al(71)	2010	-	UK NHS perspective	Combined decision model (1 year) and Markov model comparing clopidogrel + ASA for 1 or 12 months with ASA monotherapy. A lifetime horizon (35 years) is used and health states for new MI, post MI, stroke, CV death and other death are included. The model is based on hypothetical patients representing a UK population aged 60 years. To accommodate for differences in event rates between Germany and UK- GRACE was used. RR for non-fatal MI and non-fatal stroke was equal to RR for death (months 2-12). UK specific in hospital mortality for month 1 and months 2-12 obtained from GRACE registry. Ratio of mortality in month 1 and months 2-12 is equal to the ratio of non-fatal MI and non-fatal stroke rates in month 1 and months 2012.	60	1 month treatment: Clopidogrel = 8.411, ASA= 8.214, 1 year treatment: Clopidogrel = 8.553, ASA = 8.214	6% per annum – costs 1.5% per annum - benefits	1 month treatment: Clopidogrel = €1571, ASA= €1535, 1 year treatment: Clopidogrel = €1634, ASA = €1535	1 month treatment: €1,857/QALY, €830/LYG. 1 year treatment: €2,925/QALY, €1,461/LYG
Kolm et	2007	-	Canada	Trial-based economic analysis comparing clopidogrel for up to 12 months withplacebo. A lifetime horizon is	64	Not included in	3% per	CURE: Clopidogrel: $12,423	

al(72)			Payer perspective focus on direct medical costs	used. The CURE and PCI-CURE trials were the key sources of evidence used in the model. It was assumed that clopidogrel is stopped at the end of the trial and there would be no further benefits of treatment. Hospitalisation costs were based on the Canadian Case Mix Group (CMG) - collection and reporting of CMG data varies widely across provinces and so the Alberta was chosen to provide sufficient detail to make the most accurate estimation of costs. Life expectancy was estimated from Saskatchewan database		model	annum	Placebo: $12,160 PCI CURE: Clopidogrel: $15,210 Placebo: $14,877	CURE: $3,856 per LYG PCI CURE: $3,763 per LYG
Kazi et al(73)	2014	Kazi 2012(74)	US Societal	Markov model was developed over a lifetime horizon is used with a cycle length of 1 month. Data sources included Published literature, Medicare claims, and life tables. Health states used in te model included stent thrombosis, nonfatal MI,revascularization, intracranial and extracranial bleeding, and death of cardiovascular and noncardiovascular causes, post-MI, and a steady state.	65	QALYs: Drug-only therapy Generic clopidogrel: 9.428 Prasugrel: 9.446 Ticagrelor: 9.533 Low-discrimination scenario Generic clopidogrel: 9.428 Prasugrel: 9.446 Genotyping with prasugrel: 9.461 Genotyping with ticagrelor: 9.486 Ticagrelor: 9.533 High-discrimination scenario Generic clopidogrel: 9.429 Prasugrel: 9.446 Genotyping with prasugrel: 9.488 Genotyping with ticagrelor: 9.513	3%	Drug-only therapy Generic clopidogrel: $366 Prasugrel: $2687 Ticagrelor: $2978 Low-discrimination scenario Generic clopidogrel: $366 Prasugrel: $2687 Genotyping with prasugrel: $1269 Genotyping with ticagrelor: $1352 Ticagrelor: $2978 High-discrimination scenario Generic clopidogrel: $366 Prasugrel: $2687 Genotyping with prasugrel: $1269 Genotyping with ticagrelor: $1353 Ticagrelor: $2978	ICER/QALY vs. generic clopidogrel: Drug-only therapy: Prasugrel: Dominated Ticagrelor: $40 270 Low-discrimination scenario: Prasugrel: Dominated Genotyping with Prasugrel: Dominated Genotyping with ticagrelor: $30 200 Ticagrelor: $52 600 High-discrimination scenario: Prasugrel: Dominated Genotyping with Prasugrel: Dominated Genotyping with ticagrelor: $24 700 Ticagrelor: $104 800 Low-discrimination scenario: Carriers of CYP2C19 Loss-of-Function Polymorphisms Prasugrel: Elimination by extended dominance Ticagrelor:$25,800 Carriers of CYP2C19 Gain-of-Function

						Ticagrelor: 9.533 QALYs: Drug-only therapy Generic clopidogrel: 9.428 Prasugrel: 9.446 Ticagrelor: 9.533 Low-discrimination scenario Generic clopidogrel: 9.428 Prasugrel: 9.446 Genotyping with prasugrel: 9.461 Genotyping with ticagrelor: 9.486 Ticagrelor: 9.533 High-discrimination scenario Generic clopidogrel: 9.429 Prasugrel: 9.446 Genotyping with prasugrel: 9.488 Genotyping with ticagrelor: 9.513 Ticagrelor: 9.533 Life Years: Drug-only therapy Generic clopidogrel: 11.41 Prasugrel: 11.43 Ticagrelor: 11.54			Polymorphisms Prasugrel: Elimination by strict dominance Ticagrelor:$222,600 Noncarriers of CYP2C19 Gain-of-Function or Loss-of-Function Polymorphisms ("Wild Type") Prasugrel: Elimination by extended dominance Ticagrelor: $22,800 High-discrimination scenario: Carriers of CYP2C19 Loss-of-Function Polymorphisms Prasugrel: $21,300 Ticagrelor:$22,800 Carriers of CYP2C19 Gain-of-Function Polymorphisms Prasugrel: Elimination by strict dominance Ticagrelor: Elimination by strict dominance Noncarriers of CYP2C19 Gain-of-Function or Loss-of-Function Polymorphisms ("Wild Type") Prasugrel: Elimination by strict dominance Ticagrelor: $56,600

						Low-discrimination scenario Generic clopidogrel: 11.41 Prasugrel: 11.43 Genotyping with prasugrel: 11.45 Genotyping with ticagrelor: 11.48 Ticagrelor: 11.54 High-discrimination scenario Generic clopidogrel: 11.41 Prasugrel: 11.43 Genotyping with prasugrel: 11.48 Genotyping with ticagrelor: 11.51 Ticagrelor: 11.54 Low-discrimination scenario: Carriers of CYP2C19 Loss-of-Function Polymorphisms Generic clopidogrel: 9.330 Prasugrel: 9.446 Ticagrelor: 9.533 Carriers of CYP2C19 Gain-of-Function Polymorphisms Generic clopidogrel:			

						9.519 Prasugrel: 9.446 Ticagrelor: 9.533 Noncarriers of CYP2C19 Gain-of-Function or Loss-of-Function Polymorphisms (“Wild Type”) Generic clopidogrel: 9.422 Prasugrel: 9.446 Ticagrelor: 9.533 High-discrimination scenario: Carriers of CYP2C19 Loss-of-Function Polymorphisms Generic clopidogrel: 9.234 Prasugrel: 9.446 Ticagrelor: 9.533 Carriers of CYP2C19 Gain-of-Function Polymorphisms Generic clopidogrel: 9.551 Prasugrel: 9.446 Ticagrelor: 9.533 Noncarriers of CYP2C19 Gain-of-Function or Loss-of-Function Polymorphisms (“Wild Type”) Generic clopidogrel: 9.465			

						Prasugrel: 9.446 Ticagrelor: 9.533 Life Years: Drug-only therapy Generic clopidogrel: 11.41 Prasugrel: 11.43 Ticagrelor: 11.54 Low-discrimination scenario Generic clopidogrel: 11.41 Prasugrel: 11.43 Genotyping with prasugrel: 11.45 Genotyping with ticagrelor: 11.48 Ticagrelor: 11.54 High-discrimination scenario Generic clopidogrel: 11.41 Prasugrel: 11.43 Genotyping with prasugrel: 11.48 Genotyping with ticagrelor: 11.51 Ticagrelor: 11.54			
Lala et al(75)	2013	-	US Payer perspective	A Markov model, analyze decision trees was developed.The model tracked QALYs, incidence of adverse events and net cost over 15 months and 10 years time horizon.TRITON TIMI-38 study was the key siure of evidence used in the model. Health states used were: (i) eventfree-survival, (ii) survivalafter one additional event, asymptomatic, (iii) survival after one	60 years	Incremental QALY At 15 months: Genetic testing vs. clopidogrel: 0.004 QALYs Genetic testing	3%	Clopidogrel (monthly): $30.00 ($30.00–$176.10) Prasugrel (monthly): $168.60 ($124.50–$207.30) Genetic testng (monthly): $500 ($60–$750)	Since, genetic testing strategy was dominant (more effective and cheaper) compared with empiric treatment strategies of clopidogrel or

				additional event, symptomatic, (iii) survival after two or moreevents, (iv) cardiovascular death, (v) major bleed-related death, or (vi) other death.		vs. prasugrel: 0.0005 QALYs At 10 years: Genetic testing vs. clopidogrel: 0.117 QALYs (42.7 days) Genetic testing vs. prasugrel: 0.013 QALYs (4.75 days)			prasugrel, ICERs could not be calculated.
Lala et al(76)	2011	-	US	A Markov state transition model was used to conduct a decision analysis and compare strategies. The model tracked QALYs, incidence of adverse events and net cost over 15 months and 10 years time horizon.Probabilities of adverse outcomes were derived from TRITON-TIMI 38 trial.	NR	Incremental QALY At 15 months: Genetic testing vs. clopidogrel: 0.036 QALYs Genetic testing vs. prasugrel: 0.0007 QALYs At 10 years: Genetic testing vs. clopidogrel: 0.112 QALYs Genetic testing vs. prasugrel: 0.0216 QALYs	NR	NR	NR

Lamy et al(77)	2004	-	UK, USA, Sweden, France, Canada Societal	Trial-based economic analysis comparing clopidogrel for 9months with placebo. The model adopts a one year time horizon. Effectiveness was based on CURE and relevant costs were applied for the duration of the trial only. Costs not collected in CURE were not included	Not reported	Not included in model	NR	UK Clopidogrel: £3,312 Placebo: £3,104 US Clopidogrel: $14,100 Placebo: $13,649 Sweden Clopidogrel: 66,635 SKr Placebo: 64,065 SKr France Clopidogrel: €8,207 Placebo: €7,882 Canada Clopidogrel: $12,117 Placebo: $11,956	UK: £10,366 per event avoided US: $22,484 Sweden: 127,951 SKr France: €16,186 Canada: $7,973
Lin et al(78)	2012	-	US healthcare provider's perspective	A decision analytic model was developed to project the lifetime economic and humanistic burden associated with clinical outcomes (including myocardial infarction, stroke and major bleeding) for the three strategies in ACS/PCI patients.Probabilities of outcomes were obtained from the TRITON-TIMI 38 trial.	NR	Clopidogrel: 10.0308 Prasugrel: 10.0353 Genotype-guided therapy: 10.0517	NR	Clopidogrel: $19 763 Prasugrel: $22 886 Genotype-guided therapy: $20 104	Genotype-guided therapy vs. clopidogrel: $16 265
Latour-Perez et al(79)	2008	-	Spain Societal perspective (excluded indirect but included intangible costs)	Combined decision tree and Markov model comparing GPIII/IIIa + ASA+ Clopidogrel with ASA+ Clopidogrel and selective use of abciximab. The treatment duration is 12 months. A lifetime horizon was used and health states for early ACS, late ACS, post MI and death are included. The higher incidence of events during first year in elderly patients was incorporated in the TIMI score. Model analysed separately late mortality attributable to age according to age-specific mortality rates.	65	strategy A: 10.33, strategy B: 10.31, strategy C: 10.29	3% per annum	strategy A (early GPIIb/IIIa): €12,599, strategy B (deferred GPIIb/IIIa): €21,440, strategy C (ASA + clopidogrel with no GPIIb/IIIa inhibitor): €20,993	strategy A v C: €15,150/QALY, B v C: €22,350/QALY
Latour-Perez et al(80)	2004	-	Spain Societal perspective (excluded indirect but	Combined decision tree and Markov model comparing clopidogrel with placebo. The treatment duration is 12 months. A lifetime horizon was used and health states for ACS with MI, ACS with stroke, and death are included. If patients suffer a bleeding event-model	64	Clopidogrel = 8.77, ASA = 8.70	3% per annum	Clopidogrel = €24,806, ASA = €23,962	€12,221 (100% men), €10,299 (women). €7,778 (40 years of age), €23,803 (80 years of

			included intangible costs)	suspends antiplatelet therapy.					age)
Coleman et al(81)	2013	Coleman2013; Coleman 2013; Craig 2013; Limone 2013; Lee 2012(54;82-85)	US Medicare perspective	A hybrid decision tree/Markov model using annual cycles over a lifetime (40 years) period. Health states used were no event, non-fatal MI, non-fatal stroke, post MI, post stroke, and death. CURE study, TRITON-TIMI 38 trial, and PLATO trial were the key sources of evidence used in the model. It was assumed patients had their index event at 65–70 years of age. For universal strategies, it was assumed patients were prescribed the drug without PRA testing. Because the PLATO and TRITON-TIMI 38 trials did not individualize therapy using PRA test results or exclude those with HPR, it was assumed these studies likely underestimated the performance of clopidogrel. For the Markov portion of the model, we assumed patients would discontinue clopidogrel, ticagrelor, and prasugrel, and no additional treatment effect from these drugs would occur. Thus, all event rates in the Markov model were assumed to be the same for patients who had received any of the strategies, with the only difference being the proportion of patients starting in each Markov health state. The costs of recurrent nonfatal MI, nonfatal stroke, and death for the decision tree portion of our model were taken from the clopidogrel arm of the PLATO health economics and quality-of-life substudy and were assumed to be the same for all strategies.	65	All patients: Clopidogrel: 3.487 Ticagrelor: 3.530 Prasugrel: 3.510 Patients with a CYP2C19 reduced function allele: Ticagrelor: 7.945 Prasugrel: 7.925 Patients with high platelet reactivity: Ticagrelor: 3.497 Prasugrel: 3.494		All patients: Clopidogrel: US $30,214 Ticagrelor: US $32,865 Prasugrel: US $32,428 Patients with a CYP2C19 reduced function allele: Ticagrelor: US $49,149 Prasugrel: US $49,214 Patients with high plateletreactivity: Ticagrelor: US $30,615 Prasugrel: US $30,558	All patients: Ticagrelor vs clopidogrel: US $61,651/QALY Prasugrel vs clopidogrel: US $96,261/QALY Ticagrelor vs. PRA-Ticagrelor: US $68,182 Prasugrel vs. PRA-Prasugrel: US $116,875 Patients with a CYP2C19 reduced function allele: Ticagrelor vs clopidogrel: US $5,128/QALY Prasugrel vs clopidogrel: US $13,947/QALY Patients with high platelet reactivity: PRA-Ticagrelor vs. universal clopidogrel : US $40,100 PRA-Prasugrel vs. universal clopidogrel: US $49,143
Mahoney et al(86)	2006	-	USA Societal perspective. Costs associated with outpatient treatment, cardiac rehabilitation or other	Trial-based economic analysis comparing clopidogrel for up to 12 months withplacebo. A lifetime horizon is used. The PCI-CUREtrial was the key source of evidence used in the model. External sources / assumptions used for life expectancy (Saskatchewan). No incremental difference in cost between treatments was assumed beyond one year	Not reported	Not included in model	3% per annum benefits	Medicare: Clopidogrel: $16,508 Placebo: $16,086 MEDSTAT: Clopidogrel: $22,817 Placebo: $22,476 Combined: Clopidogrel: $20,071	Medicare: $4,775 per LYG MEDSTAT: $ 3,856 per LYG Combined: $2,856 per LYG

			institutional care, or indirect costs due to lost productivity were not included.					Placebo: $19,818	
Mahoney et al(87)	2010	-	US Healthcare system	Trial-based economic analysis extrapolated using other sources. Treatment with prasugrel for 6 to 15 months was compared with clopidogrel. A lifetime horizon is used. The model is based on a sub-population of the TRITON-TIMI trial. Longer-term outcomes are based on the Saskatchewan database.	61	Not reported	3% per annum	Prasugrel: $26,067 Clopidogrel: $26,288	Dominant strategy in cost per QALY analysis
Manufacturer submission for clopidogrel (from: Main C, et al.)(88)	2004	-	UK NHS perspective	Short-term decision tree (1 year) and long-term Markov model comparing one year treatment with clopidogrel + ASA with ASA monotherapy. Health states of Event-free ACS, New MI, Post-year 1 MI, Non-vascular death, vascular death are included in the Markov model. The model has a lifetime (40 year) horizon. Short-term model: baseline probabilities were obtained from PRAIS-UK and Leeds audit. Long-term model: probabilities based on analysis of two cohorts from the NHAR.	Not reported	Not reported		Not reported	£5,668/QALY
Mauskopf et al(89)	2012	-	US payer (e.g. Managed care organisation) perspective	Disease progression model comparing prasugrel based therapy for 15months with clopidogrel based therapy. Time horizons of 30 days, 12 months and 15 months are considered. The relative risks of events for the two treatments are the same in the MCO setting as those observed in the clinical trial. Patients who left the plan were assumed to no longer be at risk for further CV or bleeding events that must be treated and paid for by the health plan. The percentage of patients that left the plan that were due to mortality was assumed to be the same for both treatments. Discontinuations of prasugrel-based therapy before 15 months were assumed to be the same as those observed for clopidogrel-based therapy in the i3 In Vision database. After discontinuation of the initial therapy, all patients were assumed to continue taking aspirin only for the remaining 15 months or for as long as they remained enrolled in the MCO. There were assumed to be no crossovers between the arms. The life-expectancy gain from the MCO perspective was assumed to include only the gain from those patients	Not reported	Not reported		Difference in total costs per 100 patients (prasugrel-based therapy - clopidogrel-based therapy): -$97,090	In the lifetime analyses based on clopidogrel prices $3 or $4 per day less than prasugrel, the cost per LYG with prasugrel was $6,643 and $13,906, respectively.

				who stayed enrolled for the full 15-month time period.					
Mittman N et al(90)	2011	-	Canada	Markov model comprising of four health states: "MI", "Stroke", "All cause Mortality" and "Recovered". The model has a lifetime horizon and compares a ticagrelor treatment strategy with a clopidogrel treatment strategy	Not reported	Not reported	5% after 1st year	Not reported	CAN$1,125/LYG
NICE, 2009 (TA182)(42)	2009	-	UK NHS perspective	Model is neither a cohort or discrete simulation type. Instead it can be described as a deterministic patient level simulation which applies baseline characteristics of each patient to estimate expected events over a lifetime based regression risk models derived from analysis on TRITON-TIMI 38 trial. Long term mortality.		0.05 incremental QALYs in target population			£3435/QALY (40 year horizon, licensed population), £3461/QALY target population, £1441/QALY diabetes, £2167/QALY STEMI, £4494 NSTEMI/UA
NICE(43)	2012	-	UK NHS perspective	Two-part model with a 1-year decision tree and a Markov modelcomparing ticagrelor + ASA for 12 months withclopidogrel + ASA. A lifetime horizon is used (40 years) and health states for non-fatal MI, non-fatal stroke, no further event and death are included in the decision tree. The Markov model contains six health states: non-fatal myocardial infarction, post-myocardial infarction, non-fatal stroke, post-stroke, death, and no further event. Non-fatal myocardial infarction and non-fatal stroke are tunnel states, allowing for a worse prognosis the first year after a non-fatal event compared with second and subsequent years. After the first year following a non-fatal event in the Markov model, patients proceed to one of four mutually exclusive health states: post-myocardial infarction, post-stroke, death or no further event. In the model, costs, life years, and quality-adjusted life years (QALYs) accrued beyond the first year of treatment with ticagrelor or clopidogrel; however, the model assumed that the beneficial effect of ticagrelor does not persist beyond 1 year. This means that the transition probabilities between states in the Markov model were the same for both treatment arms; the only difference between treatment arms was the number of patients who started the Markov model in each state, which was based on the output of the 1-year decision tree. Adverse events (notably bleeding) were not included in the structure of the model but the increased costs	70	Not reported	3.5%	Not reported	1-year: ACS population: £33,764/QALY STEMI subgroup: £2,551/QALY NSTEMI subgroup: £5,217/QALY Unstable angina subgroup: £5,310/QALY 40 years: £3,521/QALY

				and decreased health-related quality of life associated with adverse events recorded in PLATO (as part of PLATO-HECON) were included in the first year (decision tree) of the model. The manufacturer assumed that adverse events including bleeding and dyspnoea have no lasting effects beyond the 12-month duration of the trial. To model the incidence of cardiovascular complications beyond 1 year (in the Markov component of the model), the manufacturer assumed a constant probability of 3.15% per year for non-fatal myocardial infarction and 1.02% per year for non-fatal stroke. The risk of death from MI after the index event					
Ojo et al(91)	2012	-	NR	Two separate CE models were constructed for the antiplatelet cost analyses. Health states used were CV death, MI, and stroke. Analysis was based on direct comparisons of relevant ACS clinical trial data.	NR	NR	NR	NR	Prasugrel vs. clopidogrel ICER$28,083 per cardiovascular event avoided ticagrelor versus clopidogrel ICER$58,358 per cardiovascular event avoided
Rao et al(92)	2011	-	US health care provider's perspective	Second-order Monte Carlo simulation model comparing Prasugrel + ASA with Clopidogrel + ASA over a lifetime horizon. Life expectancy estimated using declining exponential approximation of life expectancy (DEALE) method	Not reported	Clopidogrel: 10.4124 QALYs Prasugrel:10.4057 QALYs	NR	Clopidogrel: US $17,208 Prasugrel: US $16,780	For whole population: US $63,840/QALY for clopidogrel For patients with variant CYP2C19: US $2,313,333/QALY
Rogowski et al(93)	2009	-	UK NHS	Short-term decision tree (1 year) and long-term Markov model comparing clopidogrel + ASA versus ASA alone. The model has a lifetime horizon and uses annual cycles. Health states include Well, MI, Post-MI, Dead. The existing decision model (Heeg et al., 2007) was updated and extended, based on clinical and cost-effectiveness reviews, to provide the vehicle for the revised cost-effectiveness estimates and the value of information analysis. The potential impact of rebound was modelled by assuming that patients who withdrew from clopidogrel reverted back instantaneously to the equivalent risk faced by patients on aspirin alone.	Not reported	Clopidogrel: 12 months = 8.1236, 6 months = 8.1094, 3 months = 8.0954, 1 month = 8.0835 Standard therapy: 8.0642		Clopidogrel: 12 months = £19,758, 6 months = £19,493, 3 months = £19,347, 1 month = £19,233 Standard therapy: £19,141	Clopidogrel: 12 months = £18,712/QALY, 6 months = £10,482/QALY, 3 months = £9,489/QALY, 1 month = £4,790/QALY

				Short-term model: baseline probabilities of death, non-fatal MI, and revascularisation were taken from PRAIS-UK and extrapolated to a duration of 12 months. Long-term model: transitional probabilities based on the same analysis of the NHAR as applied in the earlier model.					
Straub et al(94)	2014	-	USA, Germany	A decision tree was developed to calculate the effectiveness and estimated costs of different treatment options for ACS patients undergoing PCI. Oneyear time horizon was used in the model. TRITON-TIMI 38and PLATO studies were the key source of evidence used in the model.	NR	CV Deaths: Prasugrel 275 ticagrelor 253 clopidogrel 311 PFT-guided therapy 269 Stent thrombosis: Prasugrel 120 ticagrelor 182 clopidogrel 250 PFT-guided therapy 182 Major bleeding: Prasugrel 237 ticagrelor 221 clopidogrel 181 PFT-guided therapy 198 Total events: Prasugrel 632 ticagrelor 656 clopidogrel 742 PFT-guided therapy 649	NR	US drug prices: Expected costs: Clopidogrel (generic)$10,586,125 Guided Therapy$14,935,702 Incremental$4,349,577 Expected costs: Clopidogrel (generic)$10,586,125 Prasugrel$31,022,254 Incremental$20,436,129 Expected costs: Clopidogrel (generic)$10,586,125 Ticagrelor$37,707,091 Incremental$27,120,966 German drug prices: Expected costs: Clopidogrel (generic) $11,462,125 Guided Therapy$13,100,277 Incremental$1,638,152 Expected costs: Clopidogrel (generic)$11,462,125 Prasugrel$21,057,754 Incremental $9,595,629 Expected costs: Clopidogrel (generic) $11,462,125 Ticagrelor$23,946,591 Incremental$12,484,466 Expected costs of associated events: Prasugrel (US$ 755) ticagrelor (US$ 825) clopidogrel (US$ 967), PFT-guided therapy (US$ 819)	Prasugrel vs. clopidogrel: $185 784/prevented event Ticagrelor vs. clopidogrel: $314 360/prevented event PFT-guided therapy vs. clopidogrel: $46 770/prevented event Major bleeding: Prasugrel vs. clopidogrel : $87 233/prevented event Ticagrelor vs. clopidogrel: $145 168/prevented event PFT-guided therapy vs. clopidogrel: $17 615/prevented event

								Expected drug costs: Prasugrel (US$ 2348) ticagrelor (US$ 2946) clopidogrel (US$ 91), PFT-guided therapy (US$ 655) Expected costs per patient treated: (US drug prices/German drug prices) Prasugrel (US$ 3102/US$2106) ticagrelor (US$ 3771/US$2395) clopidogrel (US$ 1059/US$1146), PFT-guided therapy (US$ 1494/US$1310)	
Shleinitz et al(95)	2004	-	USA Societal	Markov model comparing clopidogrel + ASA for 12 months with ASA monotherapy. A lifetime horizon is used and health states for MI, stroke, vascular death and other death are included. The CURE and Framingham studies were the key sources of evidence used in the model.	64	Clopidogrel: 9.61, ASA: 9.51		Clopidogrel: $129,300, ASA: $127,700	$15,400/QALY
Shleinitz et al(96)	2005	-	USA Societal	Combined decision tree and Markov model comparing clopidogrel + ASA for 12 months with ASA monotherapy. A lifetime horizon is used and health states for MI, stroke, amputation and CV death are included. CAPRIE study was the key source of evidence used in the model.	63	PAD: Clopidogrel: 9.58, ASA: 9.03, Stroke: Clopidogrel: 8.66, ASA: 8.49, MI: Clopidogrel: 10.83, ASA: 11.09		PAD: Clopidogrel: $123,300, ASA: $109,500, Stroke: Clopidogrel: $201,400, ASA: $196,000, MI: Clopidogrel: $98,500, ASA: $91,700	PAD: $25,100/QALY, Stroke: $31,200/QALY, MI: dominated
SMC(97)	2007	-	Scotland	Markov model comparing Clopdiogrel + ASA with ASA monotherapy. Data to extend the analysis beyond the end of the RCT were taken from a trial of clopidogrel in NSTEMI and registry data from England and Germany.	60	Not reported		Not reported	Chinese protocol: 1 month = £2,284/QALY, 1 year = £3,891/QALY Pivotal study protocol: 1 month = £1,857/QALY, 1 year = £2,925/QALY
SMC(98)	2009	-	Scotland	Markov model comparing 12 months of treatment with Prasugrel + ASA with Clopdiogrel + ASA over a lifetime period. The extrapolation of long-run mortality involved an indirect assessment of the relative risk of mortality associated with non-fatal	Not reported	10 mg maintenance dose = 0.05, STEMI = 0.08, UA/NSTEMI =		10 mg maintenance dose = £186, STEMI = £201, UA/STEMI = £181	10 mg maintenance dose = £3,779/QALY, STEMI = £2,421/QALY, UA/NSTEMI = £4,884/QALY

				MI/stroke events in the phase 3 study.		0.04			
SMC(99)	2011	-	Scotland	Combined decision tree (1 year) and Markov model comparing ticagrelor for 12 months with clopidogrel or prasugrel. A lifetime horizon is used and health states for MI, post-MI, non-fatal stroke, post-stroke, no event and death are included. Clinical data for the comparison with clopidogrel were taken from PLATO for the decision tree phase of the model. Baseline risks from the trial were adjusted to account for the older population of ACS patients in Scotland compared with patients in PLATO. For the Markov phase, the risks of further events were taken from literature sources and published life tables. No treatment effects were assumed for any of the treatments beyond 1 year; therefore, a key driver of the model was the distribution of patients entering the various states of the Markov model. AEs, such as bleeding, were not specifically accounted for in the model structure, but the manufacturer asserted these were incorporated through utility measurement and resource use aspects of the model	Not reported	Incremental QALY gain compared with clopidogrel: 0.095, incremental QALY gain compared with prasugrel: 0.065		Incremental cost compared to clopidogrel: £375, incremental cost compared to prasugrel: £227	Ticagrelor vs. clopidogrel: £3,966/QALY; Ticagrelor vs prasugrel: £3,482/QALY
Thiedel et al(100)	2013	Theidel 2013(101); Theidel 2011(102)	German Statutory Health Insurance perspective	A two-part decision-analytic model, comprising a 1-year decision tree and a long-term Markov model. A lifetime horizon was used with a cycle length of 12 months. The Markov health states corresponded to the clinical endpoints in the PLATO study: overall mortality, myocardial infarction, and stroke. For the long-term model, the German life table from the cause-of-death statistics and selected conservative assumptions were used to extrapolate survival conditional on whether a non-fatal MI, a non-fatal stroke, or no event occurred during the first year. Transition probabilities of clinical events are assumed to be independent of treatment arm in the long term model. Transition probabilities were assumed to be constant beyond year 2 in both arms. Subgroup-specific cost data could be generated for the MI state only. All other MI cost and cost for stroke and death were assumed to be equal	NR	Overall ACS patient population ≤ 150 mg ASA: Ticagrelor: 12.1471 LYs, 10.1349 QALYs Clopidogrel: 11.9674 LYs, 9.9779 QALYs NSTEMI/UA: Ticagrelor: 11.6438 LYs, 9.5356 QALYs Clopidogrel: 11.4853 LYs, 9.3935 QALYs STEMI: Ticagrelor: 12.7890 LYs,	3% per annum	Overall ACS patient population ≤ 150 mg ASA: Ticagrelor: €11,815 Clopidogrel: €11,387 NSTEMI/UA: Ticagrelor: €12,554 Clopidogrel: €112,049 STEMI: Ticagrelor: €10,179 Clopidogrel: 12.5968 LYs, 10.8341 QALYs	Overall ACS patient population ≤ 150 mg ASA: Ticagrelor vs. Clopidogrel: €2385/LYG, €2728/QALY NSTEMI/UA: Ticagrelor vs. Clopidogrel: €3184/LYG, €3552/QALY STEMI: Ticagrelor vs. Clopidogrel: €1426/LYG, €1700/QALY

						10.9953 QALYs Clopidogrel: 12.5968 LYs, 10.8341 QALYs			
Weintraub et al(103)	2005	-	US Societal	Trial-based economic analysis comparing clopidogrel for up to 12 months with placebo. A lifetime horizon is used. The CURE study was the key source of evidence used in the model. Framingham and Saskatchewan used to estimate life expectancy. Assumption that clopidogrel would be stopped at the end of the trial and that there would be no further reduction (or increase) in nonfatal events between the two arms	64	Not included in model		Medicare: Clopidogrel: $13,019 Placebo: $12,578 MEDSTAT: Clopidogrel: $17,924 Placebo: $17,586 Combined: Clopidogrel: $15,357 Placebo: $15,014	No direct costs considered beyond trial period: Framingham: Medicare: $6,318 per LYG MEDSTAT: $4,833 per LYG Combined: $4,910 per LYG Saskatchewan: Medicare: $6,475 per LYG MEDSTAT: $4,953 per LYG Combined: $5,032 per LYG Direct costs considered beyond trial period: Framingham: Medicare: $9,144 per LYG MEDSTAT: $7,654 per LYG Combined: $7,742 per LYG Saskatchewan: Medicare: $9,343 per LYG MEDSTAT: $7,833 per LYG Combined: $7,921 per LYG
Zhang et al(104)	2009	-	USA Societal, although not	Decision model comparing clopidogrel for 12 months with placebo. A lifetime horizon is used and health states are defined based on the first 28 days (death,	61	Not reported		Clopidogrel: $13,897.30 Placebo: $12,628.10	$13,363 per QALY gained (secondary analysis)

			all resource use could be accounted for	MI, stroke, PCI, other complication) and beyond 28 days (death, MI, stroke, refractory ischemia, major bleeding, PCI, CABG). The COMMIT (up to 28 days) and CURE (29 days to 1 year) studies were the key sources of evidence used in the model. Life expectancy based on Framingham. Each patient would only have one event					Primary analysis: $10,691 per LYG

7.1.3 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)[3] or Philips et al. (2004)[4]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Quality assessment was performed for any identified articles reporting economic analyses of the interventions deemed to be relevant —rivaroxaban, clopidogrel, prasugrel, ticagrelor, aspirin (≤150mg od) + clopidogrel and aspirin (if dose was ≤150 mg/day) - using the quality assessment checklist presented in Appendix 11. All items were graded as either 'yes' (item adequately addressed), 'no' (item not adequately addressed), 'unclear' (unclear or not enough information), or NA (not applicable). Identified conference abstracts were not quality assessed. Quality assessments for the full publicationss reporting economic analyses can be found in Appendix 11.

7.2 De novo analysis

Patients

7.2.1 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 1.3 and 6.3.3, 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.

Adult patients with a recent acute coronary syndrome who are biomarker positive and have not suffered a previous stroke / TIA are included in the economic evaluation. The patients reflect those included in the UK marketing authorisation for Rivaroxaban.

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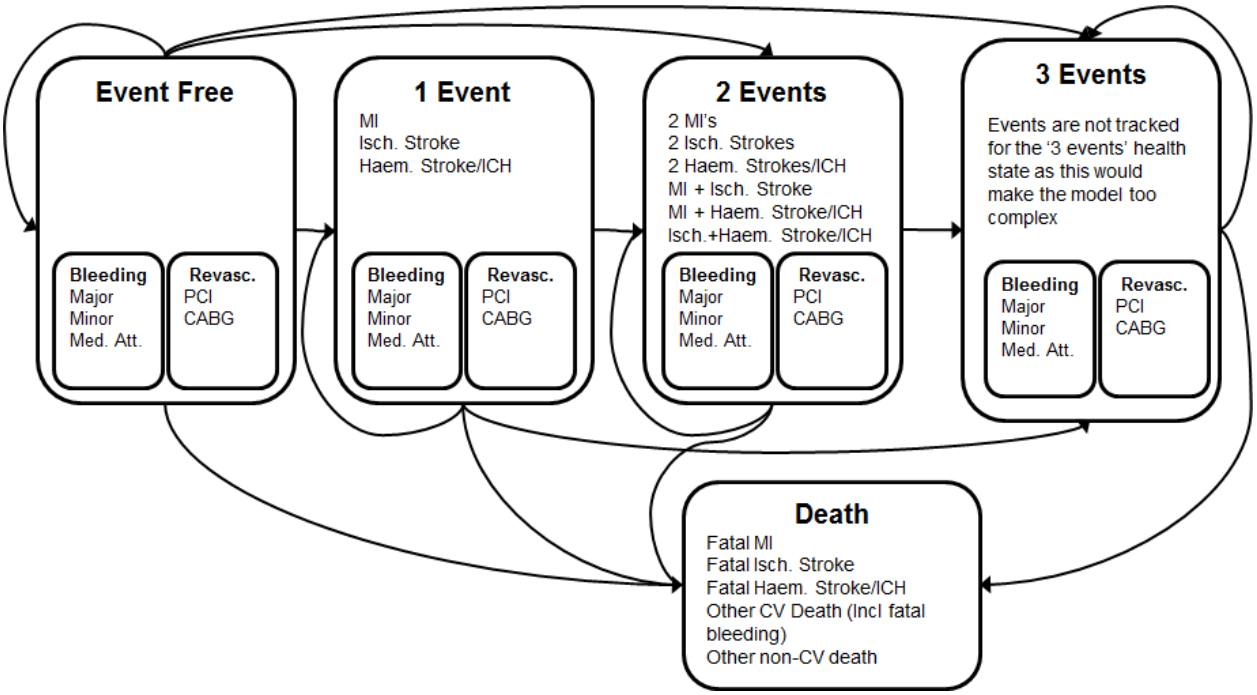
[3] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[4] 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.

Model structure

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

Figure 19 Model structure



MI = Myocardial Infarction, Isch. Stroke = Ischaemic Stroke, Haem. Stroke = Haemorrhagic Stroke, ICH = Intracranial Haemorrhage, Med. Att. = Medical Attention, CV = Cardiovascular

The model is a Markov cohort model with a lifetime horizon. Short-term transition probabilities are based on patient level data from ATLAS 2 and sources identified from the systematic review of the literature are used to estimate longer term outcomes, accounting for increased risks due to age and previous events. The model allows for multiple secondary events to occur and costs and utilities are dependent on the time since entering a health state, reflecting clinical reality where risk is highest and prevention measures are most intense immediately following an ACS event. Patients may also experience three non-fatal events in the model. Bleedings and revascularisations are included in the model as transient health states.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The ATLAS 2 study was designed to reflect the current secondary prevention treatment strategy for stabilised (i.e. after completion of initial management strategies) ACS patients including those with STEMI, NSTEMI or unstable angina. Based on the UK marketing authorisation for rivaroxaban, a subgroup of patients (biomarker positive without prior stroke / TIA) from the ATLAS 2 study are included in the model. The observation period of the model was designed to reflect the clinical trial data and to reflect the fact that patients may suffer

further events of MIs, ISs, HS/ ICHs, fatal MI, fatal IS, fatal HS/ICH, other CV death or other non-CV death throughout their lifetime (modelled during the extrapolation period).

Our chosen health states are generally in line with many of the published ACS economic models identified during our systematic review. However, it should be noted that many previous model publications have less detailed health states and often combine all stroke events (i.e. IS and HS/ICH) into one state (Bagust 2011,Berg 2008, Berg 2007, Coleman 2013a, Coleman 2014, Davies 2013a, Davies 2013b, Greenhalgh 2009, Grima 2014, Heeg 2007, Karnon 2006, Karnon 2010, Lala 2013, Latour-Perez 2004, NICE 2009, NICE 2011, Mittman 2011, Schleinitz 2005, SMC 2011, Theidel 2013, Zhang 2009(42;43;49-51;53;54;57;59;62;65;66;70;71;75;80;90;96;99;100;104)). Some models also combine all fatal events into one 'death' state. (Coleman 2013a, Coleman 2014, Cowper 2005, Greenhalgh 2009, Grima 2014, Heeg 2007, Hillegas 2011, Latour-Perez 2004, Mittman 2011, NICE 2009, NICE 2011, , SMC 2011, Straub 2014, Theidel 2013, Zhang 2009(42;43;53-55;62;65-67;80;90;94;99;100;104)).

A Markov model provides sufficient flexibility to allow for multiple events and varying costs and utilities based on the time since an event, reflecting clinical reality. Such an approach mimics that seen in other models which adopt multiple health states for events representing the time since event occurrence (Coleman 2013a, Coleman 2014, Grima 2014, Karnon 2006, Karnon 2010, Latour-Perez 2008, SMC 2011, Main 2004, Rogowski 2009, NICE 2011, Theidel 2013(43;53;54;62;70;71;79;88;93;99;100)). The use of Markov modelling is common in the economic evaluation literature considering ACS (Bruggenjurgen 2007, Schleinitz 2005, SMC 2009, SMC 2007, Heeg 2007, Kazi 2014, Lala 2013, Davies 2013a, Davies 2013b(52;57;59;66;73;75)).

Other models in this disease area are structured as combined decision trees and Markov models (Berg 2008, Berg 2007, Karnon 2006, Karnon 2010, Latour-Perez 2008, Latour-Perez 2004, Schleinitz 2004, Main 2004, Rogowski 2009, Crespin 2011, NICE 2011, Grima 2014, Coleman 2013a, Coleman 2014, Theidel 2013(43;50;51;53;54;60;62;70;71;79;80;88;93;95;100)). We opted for a Markov model structure to allow for discontinuation of treatment during the observation period, an element which cannot readily be presented as an instantaneous (or fixed time) decision-tree.

We feel our approach has advantages because of the ability to model ACS patients in a way that reflects clinical reality, i.e. with risks of secondary events diminishing over time since the initial event (reflecting the fact that patients are at the highest risk of a subsequent CV event in the period immediately following an event)(3;30;31).

Furthermore, our chosen structure also allows for the costs of follow-up following events to decrease over time, and the patient's quality of life to increase with time following an event. By explicitly modelling IS and HS/ICH health states separately, the impact of HS/ICHs can be realised from a cost perspective. The structure also allows for an increase in event rates due to age and due to the number and type of previous events.

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

Patients may be in one of sixteen health states at any point during the model (No secondary event, non-fatal MI, non-fatal IS, non-fatal HS/ICH, MI + MI, IS + IS, HS/ICH + HS/ICH, MI + IS, MI + HS/ICH, IS + HS/ICH, more than 2 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, non-CV death). Within each of the ten non-fatal event states (non-fatal MI, non-fatal IS, non-fatal HS/ICH, MI + MI, IS + IS, HS/ICH + HS/ICH, MI + IS, MI + HS/ICH, IS + HS/ICH, more than 2 events) there are tunnel states representing the time since the event.

The reasoning behind the tunnel states is to allow for variable transition probabilities, costs and utility decrements following a cardiovascular event. This represents clinical reality, where patients are known to be at a lower risk of subsequent events the longer the time since their last event(3;30;31).

Each health state in the model is associated with a utility and a healthcare cost.

Patients who are alive may experience a bleed or a revascularisation. These events are treated as transient health states and are associated with a one-off cost and short-term utility decrement.

The sixteen main health states in the model, and where relevant for non-fatal events, the three tunnel states within each of the main states, are described further below:

Free of secondary events following index ACS event ('event-free'): patients in this health state have not experienced a secondary cardiovascular event. During each cycle patients in this health state are at a risk of non-fatal MI, non-fatal ischaemic stroke (IS), non-fatal haemorrhagic stroke (HS/ICH), fatal MI, fatal IS, fatal HS/ICH, other cardiovascular (CV) mortality, non-CV mortality, or a combination of events. Patients can remain in the event-free state until they suffer a secondary event.

Non-Fatal MI: patients enter this health state if their first secondary event (i.e. their first event following their index ACS event) is a non-fatal MI. Within this health state are tunnel states depending on the time since the non-fatal MI occurred. In the observation period each tunnel state represents one 12-weekly cycle. In the extrapolation period, each tunnel state represents one cycle of six months in duration and there are three tunnel states: for the first six months, second six months and 'later' periods since the event. When patients enter the non-fatal MI health state they enter the first tunnel state and they remain here until the next cycle. If the patient experiences no further event in the following cycle they are still within the non-fatal MI state, but they move to the second tunnel state, which represents the second cycle since the non-fatal MI event. This pattern continues until the patient reaches the last tunnel state, labelled as 'later' in the model. Patients will remain here until they experience another non-fatal or fatal event which would cause them to move health states. In tunnel states representing times beyond six months from the event, the risk of further events, and the costs and disutility associated with the MI are reduced as these factors have the greatest impact immediately after the event. Patients may transition to any of the following health states from the non-fatal MI state, regardless of the time since the MI: two MIs, MI + IS, MI + HS/ICH, 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

Non-Fatal IS: patients enter this health state if their first secondary event (i.e. their first event following their index ACS event) is a non-fatal IS. As with the non-fatal MI state described in the above paragraph, there are tunnel states depending on the time since the non-fatal IS occurred. Patients may transition to any of the following health states from the non-fatal IS state, regardless of the time since the event: two ISs, MI + IS[5], IS + HS/ICH, 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

Non-Fatal HS/ICH: patients enter this health state if their first secondary event (i.e. their first event following their index ACS event) is a non-fatal HS/ICH. Within this health state are tunnel states depending on the time since the non-fatal HS/ICH occurred. Patients may transition to any of the following health states from the non-fatal HS/ICH state, regardless of the time since the event: two HS/ICHs, MI + HS/ICH, IS + HS/ICH, 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

Non-Fatal MI + Non-Fatal MI: this health state contains patients who have experienced two non-fatal MIs since their index event. Within this health state are tunnel states depending on the time since the second non-fatal MI occurred. In the observation period each tunnel state represents one 12-weekly cycle. In the extrapolation period, each tunnel state represents one cycle of six months in duration and there are three tunnel states: for the first six months, second six months and 'later' periods since the event. When patients enter the MI + MI health state they enter the first tunnel state and they remain here until the next cycle. If the patient experiences no further event in the following cycle they are still within the MI + MI state, but they move to the second tunnel state, which represents the second cycle since the second MI event. This pattern continues until patients reach the last tunnel state, labelled as 'later' in the model. Patients will remain here until they experience another non-fatal or fatal event which would cause them to move health states. In tunnel states representing times beyond six months from the event, the risk of further events, and the costs and disutility associated with the MI + MI state are reduced as these factors have the greatest impact immediately after the event. Patients may transition to any of the following health states from the MI + MI health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

Non-Fatal IS + Non-Fatal IS: this health state contains patients who have experienced two non-fatal ISs since their index event. As with the MI + MI state described in the above paragraph, there are tunnel states depending on the time since the second event causing a patient to be in the IS + IS health state occurred. Patients may transition to any of the following health states from the IS + IS health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

Non-Fatal HS/ICH + Non-Fatal HS/ICH: this health state contains patients who have experienced two non-fatal HS/ICHs since their index event. As with the MI + MI and IS + IS states, within this health state are tunnel states depending on the time since the second non-fatal HS/ICH occurred. Patients may transition to any of the following health states from the non-fatal HS/ICH + non-fatal HS/ICH health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

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[5] MI + IS describes patients that have experienced both an MI and an IS during the model. Which event occurred first does not have an impact on the model. This is also true for the IS + HS/ICH, and MI + HS/ICH health states.

Non-Fatal MI + Non-Fatal IS: this health state contains patients who have experienced the combination of a non-fatal MI and a non-fatal IS since their index event. As with the health states described above where patients have experienced two secondary events, there are tunnel states depending on the time since the second event causing a patient to be in the MI + IS health state occurred. Please note that the second event may be either the non-fatal MI or the non-fatal IS, the sequence of events is not accounted for in this health state. Patients may transition to any of the following health states from the non-fatal MI + non-fatal IS health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

Non-Fatal MI + Non-Fatal HS/ICH: this health state contains patients who have experienced a non-fatal MI and a non-fatal HS/ICH since their index event. As with the health states described above where patients have experienced two secondary events, there are tunnel states depending on the time since the second event causing a patient to be in the MI + HS/ICH health state occurred. Please note that the second event may be either the non-fatal MI or the non-fatal HS/ICH, the sequence of events is not accounted for in this health state. Patients may transition to any of the following health states from the non-fatal MI + non-fatal HS/ICH health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

Non-Fatal IS + Non-Fatal HS/ICH: this health state contains patients who have experienced the combination of a non-fatal IS and a non-fatal HS/ICH since their index event. As with the health states described above where patients have experienced two secondary events, there are tunnel states depending on the time since the second event causing a patient to be in the IS + HS/ICH health state occurred. Please note that the second event may be either the non-fatal IS or the non-fatal HS/ICH, the sequence of events is not accounted for in this health state. Patients may transition to any of the following health states from the non-fatal IS + non-fatal HS/ICH health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death.

Three events: patients in this health state have experienced three non-fatal events since the index ACS event. The three events may be any combination of MIs, ISs and HS/ICHs. Due to the small numbers of patients who experience three separate non-fatal events the distinction between the event types is not made in this health state. However, the distinction of time periods within this health state as described for all other non-fatal event health states above is still considered. Patients may only transition to fatal health states from the three events state: fatal MI, fatal IS, fatal HS/ICH, other CV death or non-CV death.

Fatal events: fatal event health states (fatal MI, fatal IS, fatal HS/ICH, other CV death, non-CV death) are absorbing states. Once a patient enters one of these states they remain there until the end of the model.

7.2.5 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.

Current standard of care for secondary prevention in ACS is treatment with clopidogrel + ASA. For patients unsuitable for clopidogrel, standard of care is ASA monotherapy. Even with these therapies patients often experience further events. By modelling up to three separate cardiovascular events, and by considering that patients are at the highest risk of secondary events in the months immediately following an ACS (or secondary CV) event, and furthermore that the risk of events increases with age and with the occurrence of prior CV events, the model captures this characteristic of the clinical pathway(3;30;31;43;105-110).

The model captures an observation period of two years following an ACS event which is modelled to mimic the trial data for the rivaroxaban label population from ATLAS 2. Outcomes during the extrapolation period (the period from two years since the initial ACS event to end of life) in terms of increased risk of subsequent events and death are also captured. Health states in the model capture key secondary events that ACS patients are at risk of (MI, IS, HS/ICH, death). Bleedings and revascularisations are captured as transient health states and have a cost and short-term QALY implication. The model covers a patient's lifetime in order to capture all consequences of the initial ACS event that a patient may experience in the longer term.

Within the model, it is assumed that there is no treatment effect associated with rivaroxaban or thienopyridine (clopidogrel was the most common thienopyridine used in the ATLAS 2 trial) after the specified treatment length (2 years for rivaroxaban and 1 year for clopidogrel in the base case). All patients are then prescribed ASA monotherapy for the remainder of their lifetime. The event rates from the last observation in the comparator arm are carried forward and transition probabilities for the extrapolation period for both the rivaroxaban and comparator treatment arms are based on these. The trial data does not provide sufficient data on patients ineligible for clopidogrel (i.e. those treated with ASA monotherapy only) to estimate the event rates associated with ASA monotherapy due to the small numbers of patients given ASA monotherapy. To overcome this issue the CURE trial was used to find a relative risk reduction (RRR) associated with ASA monotherapy versus clopidogrel + ASA(29). The CURE trial was chosen as this was the pivotal clinical trial of clopidogrel + ASA versus ASA. It therefore provides a robust source of data for estimating the relative risk ratio (RRR) between these two treatments. A RRR of 0.8 was derived from CURE and applied to the event rate estimates of both the comparator and rivaroxaban arms of the ATLAS 2 trial (after 1 year treatment to reflect the current standard of care in the UK) in the observation period and adjustments are made when carrying these estimates forward into the extrapolation period.

A worked example for the observation period is provided below:

- Assume that the MI event rate in the fifth 12 weekly cycle (to represent the current standard of care – where clopidogrel is given for one year) is 0.47% in the comparator arm.
    - Applying the RRR of 0.8 – this transition probability is adjusted to 0.49/0.8 = 0.59%.

- The RRR of 0.8 is also applied to the transition probabilities in the rivaroxaban arm also from the fifth 12 weekly cycle onwards to adjust for the current standard of care.
- The RRR is applied as a denominator to the fifth, sixth, seventh and eighth 12 weekly cycles to all the events defined (MI, IS, HS/ICH, OCD and NCD) for both the comparator and rivaroxaban arms

Before applying the adjusted event rates in the extrapolation period of the model they are converted into 6 monthly transition probability estimates. A worked example is provided below:

- Assume that the MI event rate in the last cycle of the observation period is 0.35 % in the comparator arm
- A correction is applied for the six month cycle length in the extrapolation period: $(1-(1-0.35\%)^2)=0.58\%$
- Then the RRR is applied to estimate transition probabilities representing patients on ASA monotherapy: 0.58%/0.8 = 0.73%

Because all patients are assumed to switch to ASA monotherapy following active treatment, incremental results are driven by the effectiveness and costs accrued during the active treatment period only.

7.2.6 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 26 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	40 years	Lifetime horizon to follow patients until all die, capturing all implications arising from their ACS events	NICE Guides for the Methods of Technology Appraisal
Cycle length – Observation Period	12 weeks	A 12-week cycle length is used to reflect clinical practice whereby patients are followed up every 3 to 6 months. Data from ATLAS 2 were collected every 12 weeks.	Trial data and communication with KR
Cycle length – Extrapolation period	6 months	The frequency of events diminishes over time. Six months allows for variable transitions, costs and utilities over time following an event. Six month cycles were chosen as a 12-weekly cycle length would not benefit the model any further in the extrapolation period and would instead add complexity to the calculations behind the cost-effectiveness model.	Communication with KR
Half-cycle correction	Yes – this has been applied	NICE reference case	NICE Guides for the Methods of Technology Appraisal
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case	NICE Guides for the Methods of Technology Appraisal
Discount of 3.5% for utilities and costs	3.5% for costs and benefits	NICE reference case	NICE Guides for the Methods of Technology Appraisal
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	NICE Guides for the Methods of Technology Appraisal
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 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 intervention in the model reflects the intervention given to biomarker positive patients without prior TIA / stroke in the ATLAS 2 trial.

The ATLAS 2 trial consists of two strata - patients assigned to intervention treatment were given rivaroxaban in addition to ASA monotherapy or in addition to ASA plus a thienopyridine (e.g. clopidogrel).

- Stratum 1 (ASA + rivaroxaban)
- Stratum 2 (ASA + thienopyridine + rivaroxaban)

The model base case considers both strata hence all rivaroxaban-treated patients fulfilling the rivaroxaban label (stratum 1 and stratum 2). Furthermore, a twice daily dose of 2.5mg of rivaroxaban is assumed in the model, in line with the licence for rivaroxaban in ACS.

The main comparator used in the model is standard of care as used in the ATLAS 2 trial i.e. ASA with or without a thienopyridine. In the study, 93% of patients were given a thienopyridine (such a clopidogrel) plus ASA. The other 7% were prescribed ASA monotherapy at the investigator's discretion. The base case comparator in the model is all strata, i.e. clopidogrel + ASA and ASA. A comparison with thienopyridine + ASA (stratum 2) may also be carried out to reflect the decision problem. The comparators in the trial, and therefore in the model, reflect current standard of care in ACS secondary prevention. Following discussions with KR it is understood that in the UK a lower proportion of ACS patients are likely to receive ASA monotherapy as secondary prevention treatment (an estimate of 1% was provided). Data from ATLAS 2(5) indicates [redacted] of trial patients based in the UK received ASA monotherapy, which is closer to the expectations of KR. The overall trial estimate of 7% is higher due to the multi-national nature of ATLAS 2. A scenario analysis is therefore conducted on the model whereby 100% of patients receive clopidogrel + ASA. The 'real' clinical situation for the UK lies between this analysis and the model base case. No analysis is presented for the "ASA alone" group due to small patient numbers and <2% of patients in the UK are prescribed ASA alone (according to KR) so this comparison has much less relevance than the base case.

7.2.8 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.

No treatment continuation rule has been assumed.

7.3 Clinical parameters and variables

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

The ATLAS 2 trial data, including patients satisfying the criteria of the Uk Marketing Authorisation for rivaroxaban, was reported every 12 weeks from baseline until the end of the trial, with visits registered up to week 132 (from baseline) which is approximately 2.5 years. The number of total events reported in each 12 weekly observation for patients who are biomarker positive and have not experienced a prior stroke or TIA for both the comparator and rivaroxaban arms are presented in Table 27 and Table 28 respectively. A two year treatment duration with rivaroxaban is applied in the model base case, reflecting the treatment duration in the pivotal rivaroxaban clinical trial.

In the model base case the overall trial data for first events of MI, IS, HS/ICH, Other CV death (OCD) and Non-CV death (NCD) are pooled and used to calculate parameter estimates for each 12 weekly cycle of the observation period. Please note that this parametric approach estimates the first eight 12 weekly transition probabilities by applying the overall trial data in its analyses.

For the observation period (2 years), transition probabilities for each of the eight 12-week cycles were derived from data from the biomarker positive, without prior stroke / TIA population from the ATLAS 2 clinical trial. The number of events reported in the intervention

and comparator arms used to model the observation period are presented in the tables below (Table 29 and Table 30). All events were considered and the data is based on the intention to treat (ITT) population.

For the extrapolation period, published literature identified through a stand-alone systematic review, clinical opinion and assumptions were used to model the risk of events beyond the end of the clinical trial, using the transition probabilities from the last 12-weekly cycle (comparator arm) of the observation period as a starting point for extrapolation. The systematic review was designed to identify all clinical studies in ACS patients that report the risk of subsequent events after an initial acute coronary syndrome (ACS) event and after secondary events (myocardial infarction [MI], ischaemic stroke [IS], or haemorrhagic stroke [HS]) and any combination of these, increases in event rates due to age, and life expectancy of patients with ACS events, for estimating transition probabilities for the extrapolation period of the model. The review was conducted in 2012 and updated in January 2014. The review followed NICE single technology appraisal specifications. Literature searches were run in the electronic databases: PubMed (Medline), ProQuest (EMBASE), and internet registry sites (GRACE, MINAP, PRAIS-UK, and APTOR) and the methodology of the systematic literature review is in accordance with a Quality of Reporting of Meta-analyses (QUORUM) statement.

Table 27: 12 weekly data from the ATLAS 2 trial for the comparator arm (biomarker positive, no prior stroke / TIA)

	Comparator: Clopidogrel + ASA + placebo / ASA monotherapy + placebo										
	1st 12 weeks	2nd 12 weeks	3rd 12 weeks	4th 12 weeks	5th 12 weeks	6th 12 weeks	7th 12 weeks	8th 12 weeks	9th 12 weeks	10th 12 weeks	11th 12 weeks
No event	3996	3803	3679	3318	2781	2289	1797	1303	822	417	99
MI	86	32	27	18	13	7	6	7	5	0	0
IS	9	3	1	1	2	1	1	2	0	1	0
HS/ICH	1	0	0	0	0	3	0	0	0	0	0
2 MI	2	0	2	3	0	0	0	0	0	0	0
MI + IS	0	0	0	0	0	0	0	0	0	0	0
MI + HS/ICH	0	0	0	0	0	0	0	0	0	0	0
2 IS	0	0	0	0	0	0	0	0	0	0	0
2 HS/ICH	0	0	1	0	0	0	0	0	0	0	0
3 MI	0	0	0	0	0	0	0	0	0	0	0
3 IS	1	0	0	0	0	0	0	0	0	0	0
4 MI	0	0	0	0	0	0	0	0	0	0	0
MI + 2 HS/ICH	0	0	0	0	0	0	0	0	0	0	0
MI + 2 IS	0	0	0	0	0	0	0	0	0	0	0
Fatal MI	0	0	0	0	0	0	0	0	0	0	0
Fatal bleed	4	0	0	0	0	0	0	0	0	0	0
Other CV death	0	0	0	0	0	0	0	0	1	0	0
Non-CV death	48	15	11	6	4	5	7	3	2	0	0
MI + fatal MI	1	2	5	2	4	1	1	1	0	1	0
MI + fatal bleed	5	1	1	2	1	0	0	0	0	0	0
MI + other CV death	0	0	0	0	0	0	0	0	0	0	0
MI + non-CV death	4	2	0	0	0	0	0	0	0	0	0
IS + fatal IS	0	0	0	0	0	0	0	0	0	0	0
IS + other CV death	2	0	0	0	0	0	0	0	1	0	0
IS + non-CV death	0	0	0	0	0	0	0	0	0	0	0
HS/ICH + fatal HS/ICH	0	0	1	0	0	0	0	0	0	0	0
HS/ICH + other CV death	1	1	0	0	0	0	0	0	0	0	0
HS/ICH + non-CV death	0	0	0	0	0	0	0	0	0	0	0
2 MI + fatal MI	0	0	0	0	0	0	0	0	0	0	0
2 MI + other CV death	0	1	0	0	0	0	0	0	0	0	0

MI + IS + fatal MI	0	0	0	0	0	0	0	0	0	0	0
MI + IS + fatal IS	0	0	0	0	0	0	0	0	0	0	0
MI +HS/ICH + fatal HS/ICH	0	0	0	0	0	0	0	0	0	0	0
IS + HS/ICH + fatal HS/ICH	0	0	0	0	0	0	0	0	0	0	0
2 IS + fatal IS	0	0	0	0	0	0	0	0	0	0	0
2 IS + HS/ICH + fatal HS/ICH	0	0	0	0	0	0	0	0	0	0	0
2 HS/ICH + fatal HS/ICH	0	0	0	0	0	0	0	0	0	0	0
3 MI + other CV death	0	0	0	0	0	0	1	0	0	0	0
3 MI + non-CV death	0	0	0	0	0	0	0	0	0	0	0
3 MI + fatal MI	0	0	0	0	0	0	0	0	0	0	0
3 MI + IS + fatal IS	0	0	0	0	0	0	0	0	0	0	0
3 IS + other CV death	0	0	0	0	0	0	0	0	0	0	0
Sum	4160	3860	3728	3350	2805	2306	1813	1316	831	419	99

Table 28: 12 weekly data from the ATLAS 2 trial for the rivaroxaban arm (biomarker positive, no prior stroke / TIA)

	Intervention: Rivaroxaban 2.5mg + clopidogrel + ASA / Rivaroxaban 2.5mg + ASA monotherapy										
	1st 12 weeks	2nd 12 weeks	3rd 12 weeks	4th 12 weeks	5th 12 weeks	6th 12 weeks	7th 12 weeks	8th 12 weeks	9th 12 weeks	10th 12 weeks	11th 12 weeks
No event	3986	3768	3675	3287	2758	2300	1798	1272	796	393	93
MI	62	42	19	18	6	15	3	7	2	0	0
IS	8	2	5	5	0	2	1	0	1	0	0
HS/ICH	2	1	0	0	2	2	0	1	0	0	0
2 MI	3	0	0	0	0	0	0	0	0	0	0
MI + IS	0	0	0	0	0	0	0	0	0	0	0
MI + HS/ICH	0	0	0	0	0	0	0	0	0	0	0
2 IS	0	0	0	0	0	0	0	0	0	0	0
2 HS/ICH	0	0	0	0	0	0	0	0	0	0	0
3 MI	0	0	0	0	0	0	0	0	0	0	0
3 IS	0	0	0	0	0	0	0	0	0	0	0
4 MI	0	0	0	0	0	0	0	0	0	0	0
MI + 2 HS/ICH	0	0	0	0	0	0	0	0	0	0	0
MI + 2 IS	0	1	0	0	0	0	0	0	0	0	0
Fatal MI	0	0	0	0	0	0	0	0	0	0	0
Fatal bleed	3	0	0	0	0	0	0	0	0	0	0
Other CV death	0	0	0	0	0	0	1	0	0	0	0

Non-CV death	29	11	4	4	1	3	2	2	2	0	0
MI + fatal MI	4	3	1	1	2	1	2	2	0	0	0
MI + fatal bleed	4	2	2	0	0	0	1	0	0	2	0
MI + other CV death	0	0	0	0	0	0	0	0	0	0	0
MI + non-CV death	0	1	0	0	0	1	0	1	0	0	0
IS + fatal IS	0	0	0	0	0	0	0	0	0	0	0
IS + other CV death	0	0	0	0	0	0	0	0	0	0	0
IS + non-CV death	0	0	0	0	0	0	0	0	0	0	0
HS/ICH + fatal HS/ICH	0	0	0	0	0	0	0	0	0	0	0
HS/ICH + other CV death	0	1	0	0	0	0	0	0	0	0	0
HS/ICH + non-CV death	0	0	0	0	0	0	0	0	0	0	0
2 MI + fatal MI	0	0	0	0	0	0	0	0	0	0	0
2 MI + other CV death	1	0	0	0	0	0	0	0	0	0	0
MI + IS + fatal MI	0	1	0	0	0	0	0	0	0	0	0
MI + IS + fatal IS	0	0	0	0	0	0	0	0	0	0	0
MI +HS/ICH + fatal HS/ICH	1	0	0	0	0	0	0	0	0	0	0
IS + HS/ICH + fatal HS/ICH	1	0	0	0	0	0	0	0	0	0	0
2 IS + fatal IS	0	0	0	0	0	0	0	0	0	0	0
2 IS + HS/ICH + fatal HS/ICH	0	0	0	0	0	0	0	0	0	0	0
2 HS/ICH + fatal HS/ICH	0	0	0	0	0	0	0	0	0	0	0
3 MI + other CV death	0	0	0	0	0	0	0	0	0	0	0
3 MI + non-CV death	0	0	0	0	0	0	0	0	0	0	0
3 MI + fatal MI	0	0	0	0	0	0	0	0	0	0	0
3 MI + IS + fatal IS	0	0	0	0	0	0	0	0	0	0	0
3 IS + other CV death	0	0	0	0	0	0	0	0	0	0	0
Sum	4104	3833	3706	3315	2769	2324	1808	1285	801	395	93

These data were redefined based on the sixteen health states included in the economic model. The resulting data (as presented in the tables below) were inputted into the model. All haemorrhagic strokes were classified as ICH in the ATLAS 2 study. To avoid double counting of events, all ICHs were separated from other TIMI major bleeding and grouped with haemorrhagic strokes. If patients experienced a non-fatal event and a fatal event within any 12 week cycle of the observation period (for example, if a patient experienced a non-fatal MI and a fatal MI within one cycle), then the fatal event was assumed for that patient in the model and no consideration was taken of the non-fatal event, only the cost associated with the fatal event is applied (as the model does not capture utility associated with fatal events). It is realised that this approach underestimates costs but this underestimation is expected to be small as the number of patients experiencing a non-fatal and fatal event in the same cycle is minimal (Table 27 and

Table 28). If patients suffered two or more non-fatal events in any one 12 week period then they entered the health state representing the combination of those two non-fatal events and costs and utilities associated with both events are applied.

The data presented in the table below has been adjusted such that the non-fatal and fatal events (Table 27 and Table 28) are combined into the appropriate fatal event state. The model is based on a parametric approach to transition probability estimation. This is described further below.

Table 29: 12 weekly data data used in the economic model for the comparator arm (biomarker positive, no prior stroke / TIA)

	Comparator: Clopidogrel + ASA + placebo / ASA monotherapy + placebo										
	1st 12 weeks	2nd 12 weeks	3rd 12 weeks	4th 12 weeks	5th 12 weeks	6th 12 weeks	7th 12 weeks	8th 12 weeks	9th 12 weeks	10th 12 weeks	11th 12 weeks
No event	3996	3803	3679	3318	2781	2289	1797	1303	822	417	99
Non-fatal MI	86	32	27	18	13	7	6	7	5	0	0
Non- fatal IS	9	3	1	1	2	1	1	2	0	1	0
Non-fatal HS/ICH	1	0	0	0	0	3	0	0	0	0	0
Non-fatal (MI +MI)	2	0	2	3	0	0	0	0	0	0	0
Non-fatal (IS + IS)	0	0	1	0	0	0	0	0	0	0	0
Non-fatal (HS/ICH + HS/ICH)	0	0	0	0	0	0	0	0	0	0	0
Non-fatal (MI + IS)	0	0	0	0	0	0	0	0	0	0	0
Non- fatal (MI+HS/ICH)	0	0	0	0	0	0	0	0	0	0	0
Non-fatal (IS + HS/ICH)	0	0	0	0	0	0	0	0	0	0	0
Non- fatal >=3 events	1	0	0	0	0	0	0	0	0	0	0
Fatal MI	9	2	1	2	1	0	0	0	0	0	0
Fatal IS	2	0	0	0	0	0	0	0	1	0	0
Fatal HS/ICH	1	1	0	0	0	0	1	0	0	0	0
Other CV death	52	17	11	6	4	5	7	3	3	0	0
Non-CV death	1	2	6	2	4	1	1	1	0	1	0
Sum	4160	3860	3728	3350	2805	2306	1813	1316	831	419	99

Table 30: 12 weekly data data used in the economic model for the rivaroxaban arm (biomarker positive, no prior stroke / TIA)

	Intervention: Rivaroxaban 2.5mg + clopidogrel + ASA / Rivaroxaban 2.5mg + ASA monotherapy										
	1st 12 weeks	2nd 12 weeks	3rd 12 weeks	4th 12 weeks	5th 12 weeks	6th 12 weeks	7th 12 weeks	8th 12 weeks	9th 12 weeks	10th 12 weeks	11th 12 weeks
No event	3986	3768.	3675	3287	2758	2300	1798	1272	796	393	93
Non-fatal MI	62	42	19	18	6	15	3	7	2	0	0
Non- fatal IS	8	2	5	5	0	2	1	0	1	0	0
Non-fatal HS/ICH	2	1	0	0	2	2	0	1	0	0	0
Non-fatal (MI +MI)	3	0	0	0	0	0	0	0	0	0	0
Non-fatal (IS + IS)	0	0	0	0	0	0	0	0	0	0	0
Non-fatal (HS/ICH + HS/ICH)	0	0	0	0	0	0	0	0	0	0	0
Non-fatal (MI + IS)	0	0	0	0	0	0	0	0	0	0	0
Non- fatal (MI+HS/ICH)	0	0	0	0	0	0	0	0	0	0	0
Non-fatal (IS + HS/ICH)	0	0	0	0	0	0	0	0	0	0	0
Non- fatal >=3 events	0	1	0	0	0	0	0	0	0	0	0
Fatal MI	8	2	2	0	0	0	1	0	0	2	0
Fatal IS	1	0	0	0	0	0	0	0	0	0	0
Fatal HS/ICH	1	1	0	0	0	0	0	0	0	0	0
Other CV death	29	13	4	4	1	4	3	3	2	0	0
Non-CV death	4	3	1	1	2	1	2	2	0	0	0
Sum	4104	3833	3706	3315	2769	2324	1808	1285	801	395	93

As patient numbers diminish over time particularly visible towards the end of the trial it is difficult to estimate transition probabilities directly from the data for the later cycles within the observation period. Therefore, a parametric approach is applied to estimate transition probabilities for the base case model. This approach uses the data from ATLAS 2 and applies interpolation techniques to remove the data fluctuations caused by a decline in the numbers of observations over the trial.

The parametric approach uses the ATLAS 2 primary event trial data reported for MI, IS, HS/ICH, other CV death and non-CV death for the biomarker positive without prior stroke /TIA population (Table 31) to estimate 12-weekly transition probabilities using a Weibull distribution (Appendix 14 provides the calculations used to estimate the likelihood as well as the first and second order derivatives for the Weibull parameters). Beyond the observation period, it is assumed that all patients are prescribed ASA monotherapy for the remainder of their lifetime. A detailed description of how transition probabilities are estimated beyond the observation period is provided in section 7.2.5.

Table 31: Overall number of events reported in the biomarker positive, no prior stroke / TIA population of the ATLAS 2 trial for the entire trial duration

Event	Rivaroxaban (N=4104)	Comparator (N=4160)
MI	174	201
IS	24	21
HS/ICH	8	4
Other CV Death	63	108
Non-CV Death	16	19

The resulting Weibull parameters implemented in the model are presented in Table 32.

Table 32: Weibull parameters (based on biomarker positive, no prior stroke / TIA ATLAS 2 trial data) applied to the economic model for interpolation in the observation period

		Rivaroxaban	Comparator
MI	mu	12.543180	12.169226
	lambda	-1.017409	-1.017409
IS	mu	16.873670	17.235764
	lambda	-0.931947	-0.931947
HS/ICH	mu	13.139670	14.171658
	lambda	-0.390599	-0.390599
Other CV death	mu	15.383190	14.035403
	lambda	-1.083073	-1.083073
Non-CV death	mu	10.780540	10.580387
	lambda	-0.208511	-0.208511

When choosing a distribution to fit to the trial data it is important to consider one that has a logical interpretation and a distribution that is characterised by a decreasing hazard rate in time to mimic what is seen in the trial data (Figure 20 to Figure 23 to below). Other distributions such as the Gamma and the log normal distribution do provide flexibility and are commonly used, however such distributions often present an initial increase followed by a

decrease in hazard rate, which does not reflect what is seen in the trial data. The Gompertz model is best known for its increase in the probability of events but this is also not suitable for the observation period of the model, where the risk of events decreases over time.

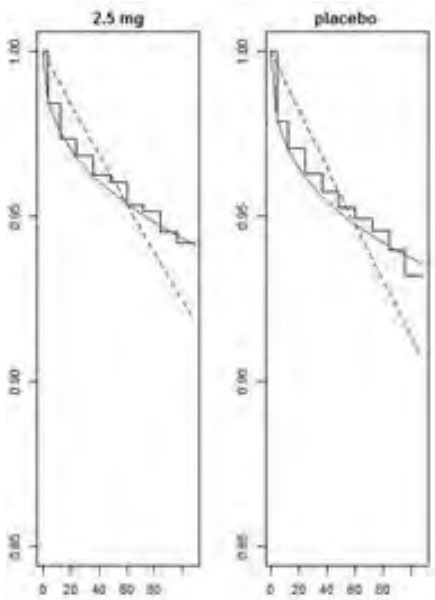
It should be noted that within our estimations we do not follow the guidance as formulated by the NICE DSU concerning fitting parametric survival models (DSU 2011). The reason behind this is that this guidance concerns extrapolation and not interpolation. Contrarily to the case with extrapolation, one already has an estimate that fits the data perfectly (the Kaplan Meier curves). The goal of interpolation is not to obtain the best fit to the data, but to – in those cases where the shape of the Kaplan Meier defies logic - correct the estimate in such a way that it makes sense from a clinical point of view. The need for this interpolation is especially relevant when the data may suggest that the hazard function increases in time. Such increase is rather unlikely and probably a chance finding. In such cases, reporting Aitkin information criteria as well as log log curves as advised in the NICE DSU guidance does not change the choice of the distribution and reporting those statistics has no or very limited value. A summary of the possible distributions and suitability for interpolation of the trial data is presented in Table 33 in line with those recommended by NICE DSU for fitting parametric survival models within the extrapolation periods.

Table 33: Parametric methods for estimating mean survival estimates and applicability to the interpolation of the ATLAS 2 trial data (DSU 2011)

Methods for estimating mean	**General description**	**Applicability to the interpolation of trial data**	**Method included or excluded**
Weibull	Weibull is dependent on the shape and scale parameters – with more flexibility as the hazard function can increase or decrease monotonically but cannot change direction. The Weibull can be parameterised as either a proportional hazards or accelerated failure time model.	Appropriate as hazard function cannot change direction.	Included
Exponential	Simplest parametric model with a constant hazard function over time – is also a proportional hazrds model.	Appropriate as hazard function cannot change direction.	Included
Gompertz	The probability of events increase over time (log-hazard function is linear to time).	Not suitable to interpolate the trial data – where the risk of events decreases over time.	Excluded as this distribution cannot mimic the trend in observations from the trial
Log-logistic	Accelerated failure time model with a hazard function which can be non-monotonic with respect to time.	Not suitable to interpolate – as the hazard rate initially increases then decreases over time. This is not the behaviour observed in the trial.	Excluded
Log normal	Similar to the log-logistic model.	Not suitable to interpolate	Excluded as this

		the trial data – this is not the behaviour observed in the trial (as the hazard rate initially increases then decreases over time).	distribution cannot mimic the trend in observations from the trial
Gamma	Three parameter model – can be generalised as a two parameter model to give the Weibull, exponential and log normal models.	Not suitable to interpolate the trial data – this is not the behaviour observed in the trial (as the hazard rate initially increases then decreases over time).	Excluded as this distribution cannot mimic the trend in observations from the trial.
Piecewise modelling	Exponential models fitted to differing time points	Fixed hazard rates are attached to each time point.	Excluded

Figure 20 Survival Curves for MI comparing the parametric and non-parametric (data) approach: biomarker positive patients without prior stroke / TIA [6]



[6] Black line - actual trial data, dashed line – exponential curve and red line – Weibull curve.

Figure 21: Survival Curves for IS comparing the parametric and non-parametric (data) approach [7]

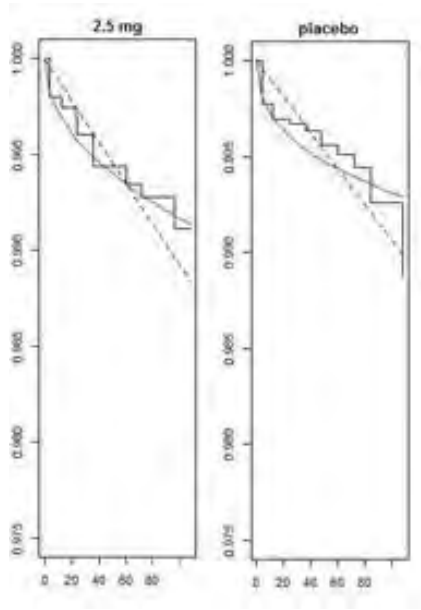


Figure 22: Survival Curves for HS/ICH comparing the parametric and non-parametric (data) approach [8]

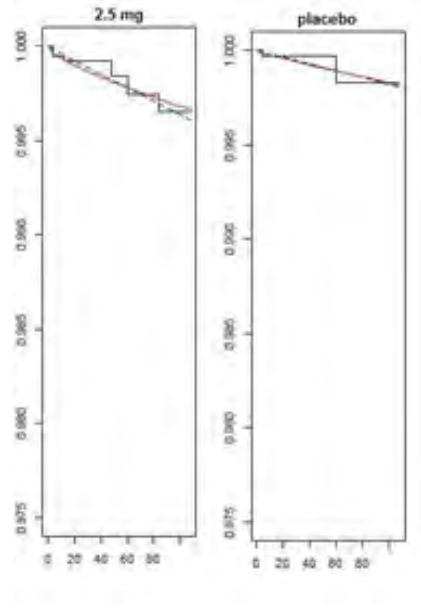


Figure 23: Survival Curves for other cardiovascular death comparing the parametric and non-parametric (data) approach [9]

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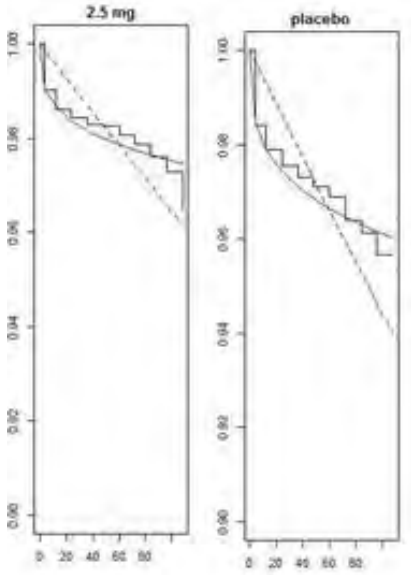
[7] Black line - actual trial data, dashed line – exponential curve and red line – Weibull curve.
[8] Black line - actual trial data, dashed line – exponential curve and red line – Weibull curve.



Graphical comparisons of the parametric (using Weibull distributions – red lines) and a non-parametric approach (plotting the data – black lines) are given in Figure 20 to Figure 23. It can be seen that the Weibull function fits very well to the trial data and helps to smooth out the trial data when compared to the non-parametric approach which shows clear fluctuations in the data that are particularly visible during the latter cycles of the observation period.

Safety endpoints for the intervention and comparator arms are also taken from the biomarker positive, no prior stroke / TIA patients from the ATLAS 2 study and are applied during the observation period of the model (please note that unlike the efficacy data we do not interpolate and as a result only require the first eight 12 weekly observations for the base case). The trial data was reported every 12 weeks from baseline until the end of the trial, with visits registered up to week 132 (from baseline). The model applies a 2 year treatment duration and for this reason we use the first eight 12 weekly cycles in the model for the rivaroxaban arm (first four 12 weekly cycles for the comparator arm are used to represent the current standard of care in the UK in the base case model).

The primary safety endpoint of the trial is defined as non-CABG TIMI major bleeding. Bleeding events are temporary or short term complications that patients may experience from their treatment, and these generally do not have long term consequences. Bleeding events have been considered as transient health states in the cost-effectiveness model. We expect the impact of TIMI major, TIMI minor and TIMI requiring medical attention bleeds in terms of quality of life impact to be less than 1 cycle (12 weeks) and we assume that non-fatal and non-ICH major TIMI bleeds are typically considered to have a 30 day impact on QoL. Minor TIMI bleeds and bleeding requiring medical attention are assumed to have an impact on QoL lasting 2 days. The assumptions around the impact of bleedings have been verified with a clinical expert (KR). Fatal bleeding events in the trial data are included in the other cardiovascular death state.

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[9] Black line - actual trial data, dashed line – exponential curve and red line – Weibull curve.

Percutaneous coronary interventions/percutaneous transluminal coronary angioplasty (PCI/PTCA) and coronary artery bypass graft (CABG) interventions, are also considered as transient health states within the model. PCI / PTCAs are assumed to impact on QoL for 30 days. CABGs are assumed to impact on QoL for 12 weeks (84 days). Both assumptions have been verified with a clinician (KR).

The number of bleeding adverse events and revascularisations for each 12 weekly cycle that occurred during the first two years (first eight cycles) of the ATLAS 2 trial for rivaroxaban and during the first year (first four cycles) of the trial for the comparator (chosen to reflect current standard of care in the UK), for the rivaroxaban label population, are presented in the table below.

Table 34: 12 weekly bleeding and revascularisatrion events reported in the ATLAS 2 trial (biomarker positive, no prior stroke / TIA patients)[10]

	Comparator: Clopidogrel + ASA + placebo / ASA monotherapy + placebo								**Intervention: Rivaroxaban 2.5mg + clopidogrel + ASA / Rivaroxaban 2.5mg + ASA monotherapy**							
	1st 12 weeks	2nd 12 weeks	3rd 12 weeks	4th 12 weeks	5th 12 weeks	6th 12 weeks	7th 12 weeks	8th 12 weeks	1st 12 weeks	2nd 12 weeks	3rd 12 weeks	4th 12 weeks	5th 12 weeks	6th 12 weeks	7th 12 weeks	8th 12 weeks
Bleeding Events																
TIMI major	12	2	4	2	2	0	1	0	21	12	9	5	8	1	2	1
TIMI minor	13	5	3	1	1	0	1	0	9	6	4	3	4	1	1	0
TIMI req med attention	130	54	40	24	24	14	10	6	227	104	65	49	40	18	8	5
Revascularisation Events																
PCI/PTCA	338	99	69	45	39	18	15	9	327	130	80	43	24	22	2	9
CABG	63	20	17	6	6	3	1	0	49	23	11	9	3	3	1	0

[10] Bleeding and revascularisation events are considered as transient health states with short term impact on a patient's quality of life and an assumed one-off cost.

Rates of bleeding and revascularisation events per cycle are estimated directly from the clinical trial data for each bleed (TIMI Major, TIMI Minor, TIMI requiring medical attention) and revascularisation type (PCI / PTCA, CABG) separately (as presented in the table above). Unlike the trial data included in the main modeling framework the bleeding events and revascularisations are considered as transient health states and a parametric approach is not needed here due to the short term nature of these events. Fatal bleeding events are captured in the other cardiovascular death state which is interpolated using the Weibull distribution.

Further to bleeding and revascularisation rates in the observation period being taken directly from the trial data, treatment discontinuation rates as observed in the full ATLAS 2 trial are also taken into consideration.

The permanent continuation rates following an MI, IS or HS/ICH as reported in ATLAS 2 are initially used to model the treatment discontinuation of rivaroxaban and thienopyridine following an event (Table 35 and

Table 36). Data per twelve weeks was not available for treatment discontinuation. Therefore some prediction methods were needed to estimate the discontinuation rates in cycles within both the observation and extrapolation periods of the model. A Weibull distribution is used to provide estimates of patient treatment continuation in a time dependent manner. The probability to discontinue treatment reflects the observations from the trial data where the number of ACS events are greatest at the beginning of the trial and then decline over the 2 year treatment duration. Patients are more likely to discontinue the more events they experience, and the Weibull reflects this within its distribution.The Weibull parameters for the active and comparator treatment arms are estimated separately and the distribution is applied accordingly.

The ATLAS 2 protocol states that the study drug should be discontinued after an intracranial bleed - which is reflected in the model. Cumulative treatment discontinuation rates, recorded over time in the trial from randomisation, are initially used to model the total number of treatment discontinuations for both rivaroxaban and thienopyridine observed in the trial (Table 37).

Please note the continuation rates presented below are based on the full trial population. The decision was taken to use the full population as we wanted to include as many patients as possible. The rationale is that although population will impact on the numbers of events patients may have, the population should not impact on discontinuation due to each individual event.

Table 35: Permanent continuation rates in the rivaroxaban arm – following a MI, IS or HS/ICH event (base case)

	Rivaroxaban
Following a MI	94.69%
Following an IS	54.29%
Following a HS/ICH	0.00%

Table 36: Permanent continuation of thienopyridine in both the rivaroxaban and comparator arms following a MI, IS or HS/ICH event (base case)

	Rivaroxaban	Comparator
Following a MI	69.27%	70.74%
Followin an IS	66.67%	50.00%
Following a HS/ICH	0.00%	0.00%

Table 37: Overall two year treatment discontinuation rates for both rivaroxaban and thienopyridine (base case)

	Rivaroxaban	Comparator
Treatment Discontinuation	31.02%	31.05%
Continuation	68.98%	68.95%

The assumptions behind treatment discontinuations following an event and how this is modelled using the event free health state are as follows:

- Overall treatment discontinuations within the observation period for the event free (no further secondary events) health state is known (refer to Table 37)
    - From this we can estimate the number of patients who continue (1-discontinuation) with treatment
    - Using optimisation tools in Excel we are able to predict the rate of overall continuation per cycle in the event free health state
- Overall discontinuations within the observation period following an ACS event of MI, IS and HS/ICH is known from the clinical trial data (Table 35 and Table 36 for rivaroxaban and thienopyridine, respectively)
    - From this, the number of patients who continue treatment following each event type can be determined
    - A rate per cycle is not predicted as it is assumed that the proportion of patients who discontinue because of an event will not differ regardless of the cycle number.
- For each patient continuation calculation within the model (one per cycle) corrections are made for patients lost following an event with respect to the number of patients within each relevant health state in the model.

In light of the posology description in the rivaroxaban label it is expected that in clinical practice treatment discontinuation in the second year will be higher than observed in the ATLAS 2 study. Hence, treatment discontinuation in the model is further adjusted to reflect the expected rate of discontinuation.

In the model – the base case assumption is that there is a proportional relationship between the change in efficacy and the costs for rivaroxaban. This is deemed a conservative estimate as it is assumed physicians make an informed decision on which patients continue treatment for the second year and hence it can be expected that actually the events prevented may not decrease proportionally to the reduction in treated patients, but that (relatively) more efficacy may be retained. However, in the absence of data to support this, a conservative approach has been chosen.

The change in efficacy and costs considered in the base case are presented in Table 38. The changes themselves are only applied in the second year (from 48-60 weeks onwards). These have been selected to allow an overall treatment discontinuation rate of 81% after one year of treatment - this implies that 19% of patients will continue treatment after 12 months and that this will decline further to 0% at the end of the second year. A linear assumption was applied to the discontinuation calculations as this seemed most plausible and possible in the absence of actual data. Please note that the effective modelled treatment discontinuation is a product of the treatment continuation observed in the ATLAS 2 study and additional assumed treatment discontinuation effect on efficacy and costs as is shown in Table 38.

Table 38: Base case parameters for the change in efficacy and costs to represent patient discontinuation in the second year of treatment.

	ATLAS 2 treatment continuation (2.5 mg BID, combined strata) [1-discontinuation rate]	Change in efficacy*	Change in costs	Effective adjusted model treatment continuation rate
0-4 weeks	1-6.90%=93.10%	100 %	100 %	93.10%x100%=93.10%
4-12 weeks	1-10.46%=89.54%	100 %	100 %	89.54%x100%=89.54%
12-24 weeks	1-13.06%=86.94%	100 %	100 %	86.94%x100%=86.94%
24-36 weeks	1-17.77%= 82.23%	100 %	100 %	82.23%x100%=82.23%
36-48 weeks	1-21.55%=78.45%	100 %	100 %	78.45%x100%=78.45%
48-60 weeks	1-23.94%= 76.06%	25 %	25 %	76.06%x25%=19.02%
60-72 weeks	1-26.51%= 73.49%	18 %	18 %	73.49%x18%=13.23%
72-84 weeks	1-27.94%= 72.06%	12 %	12 %	72.06%x12%=8.65%
84-96 weeks	1-29.73%= 71.27%	6%	6%	71.27%x6%=4.28%

**the numbers in this column were estimated assuming a linear relationship such that the resulting data in the model assumes a 19% continuation rate at 1 year and a 0% continuation rate at 2 years*

The change in efficacy is calculated by taking the relative difference between the event rates with rivaroxaban and the comparator and applying the change in efficacy % as presented in the above table. The transition probabilities for the comparator and rivaroxaban arms without any adjustments imposed on the efficacy is presented in . The change in efficacy takes effect in the model by applying the formula:

Adjusted efficacy for each event = Comparator transition probability ×(1-(1- rivaroxaban event rate/comparator event rate) × change in efficacy).

- *The adjusted efficacy is calculated for each model cycle up to two years and all model events (MI, IS, HS, OCD and NCD).*

- *An example of the adjusted efficacy calculation is provided below for 0-4 weeks and 85-96 weeks for MI:*
    - *0-4 weeks*
        - *The comparator transition probability is 2.01%*
        - *The change in efficacy is 100%*
        - *The relative efficacy between the active and comparator arm is given by 1.76%/2.01% = 0.876%*
        - *The efficacy in the rivaroxaban arm doesn't change and is given by 2.01% × (1-(1-0.876%) × 100%) = 1.76%.*
    - *85-96 weeks*
        - *The comparator transition probability is 0.35%*
        - *The change in efficacy is 6%*
        - *The relative efficacy between the active and comparator arm is given by 0.31%/0.35% = 88.05%*
        - *The adjusted efficacy is given by 0.35% × (1-(1-88.05%) × 6%) = 0.35%.*
- *The adjusted transition probabilities are provided in* Table 40

Table 39 Transition probabilities for the ATLAS 2 trial, label population, without any adjustments.

	Comparator					Rivaroxaban				
	MI	IS	HS	other CV death	non CV death	MI	IS	HS	other CV death	non CV death
After two years										
0-4 weeks	2.01%	0.19%	0.02%	1.37%	0.06%	1.76%	0.22%	0.04%	0.87%	0.05%
5-12 weeks	0.96%	0.11%	0.02%	0.61%	0.08%	0.84%	0.12%	0.04%	0.39%	0.07%
13-24 weeks	0.83%	0.09%	0.02%	0.52%	0.11%	0.73%	0.11%	0.04%	0.33%	0.09%
25-36 weeks	0.59%	0.07%	0.02%	0.36%	0.10%	0.52%	0.08%	0.04%	0.23%	0.08%
37-48 weeks	0.47%	0.06%	0.02%	0.29%	0.09%	0.41%	0.06%	0.03%	0.18%	0.08%
49-60 weeks	0.50%	0.06%	0.02%	0.30%	0.09%	0.44%	0.07%	0.04%	0.19%	0.07%
61-72 weeks	0.43%	0.05%	0.02%	0.27%	0.08%	0.38%	0.06%	0.04%	0.17%	0.07%
73-84 weeks	0.39%	0.05%	0.02%	0.24%	0.08%	0.34%	0.05%	0.03%	0.15%	0.07%
85-96 weeks	0.35%	0.04%	0.02%	0.22%	0.08%	0.31%	0.05%	0.03%	0.14%	0.07%

Table 40 Transition probabilities for the ATLAS 2 trial, label population, with efficacy adjustments

	Comparator					Rivaroxaban				
	MI	IS	HS	other CV death	non CV death	MI	IS	HS	other CV death	non CV death
After two years										
0-4	2.01%	0.19%	0.02%	1.37%	0.06%	1.76%	0.22%	0.04%	0.87%	0.05%

weeks										
5-12 weeks	0.96%	0.11%	0.02%	0.61%	0.08%	0.84%	0.12%	0.04%	0.39%	0.07%
13-24 weeks	0.83%	0.09%	0.02%	0.52%	0.11%	0.73%	0.11%	0.04%	0.33%	0.09%
25-36 weeks	0.59%	0.07%	0.02%	0.36%	0.10%	0.52%	0.08%	0.04%	0.23%	0.08%
37-48 weeks	0.47%	0.06%	0.02%	0.29%	0.09%	0.41%	0.06%	0.03%	0.18%	0.08%
49-60 weeks	0.50%	0.06%	0.02%	0.30%	0.09%	0.48%	0.06%	0.02%	0.28%	0.08%
61-72 weeks	0.43%	0.05%	0.02%	0.27%	0.08%	0.43%	0.05%	0.02%	0.25%	0.08%
73-84 weeks	0.39%	0.05%	0.02%	0.24%	0.08%	0.38%	0.05%	0.02%	0.23%	0.08%
85-96 weeks	0.35%	0.04%	0.02%	0.22%	0.08%	0.35%	0.04%	0.02%	0.21%	0.08%

The corresponding change is costs is calculated by multiplying the % change in costs by the cost of rivaroxaban. An example is given below for the cycle 85-96 weeks.

- The total cost of treatment for each 12 weekly cycle is given as £184.08
- The change in costs is 6%.
- The change in costs is (£184.08 × 0.06) = £11.04.

It is assumed that patients who discontinue the study drug rivaroxaban will remain on either ASA monotherapy or ASA plus a thienopyridine and patients who discontinue thienopyridine will remain on either ASA monotherapy or ASA plus rivaroxaban. It should be noted that discontinuation of concomitant medications is not considered in the model only discontinuation of the antiplatelet therapy is captured. The cost-effectiveness model does not consider the re-initiation of treatment as the difference between the total exposure duration with and without consideration of temporary discontinuation was only 5 days in the trial data. Therefore, only permanent discontinuation of treatment is considered.

Patients are only assumed to discontinue following an event. Based on the trial data, and discussions with a clinical expert (KR), all patients who suffer a HS/ICH are assumed to permanently discontinue treatment. It is also assumed that patients have the same probability to discontinue after a second MI as their probability of discontinuing after a first MI (for example, if there is a 10% probability of discontinuation after a 1st MI, there is also a 10% probability of discontinuation in patients who suffer a second MI). The same assumption is applied to stroke events, (the probability to discontinue is the same regardless of the number of events previously experienced).

Due to the nature of the model structure used for the current analyses, any patients who discontinued treatment were removed from the “event free” health state. This allowed for a simple and transparent method of cost adjustment to be applied due to discontinued treatment.

Efficacy is already correctly adjusted for in the model as transition probabilities already reflect patient discontinuation.

7.3.2 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.

Transition probabilities – observation period

A parametric approach is used to estimate transition probabilities in the base case. As mentioned in section 7.3.1 the parametric approach interpolates the trial data, smoothing out the data and removing the risk of potential problems which can arise due to low patient numbers (a phenomenon which is particularly visible in the later cycles of the observation period). The parametric approach estimates the Weibull parameters based on the overall trial data and considers first events only (transition probabilities for secondary events are subsequently based on these values), these can be used to estimate the transition probabilities (Appendix 14 presents formulae used to calculate the likelihood, first and second derivatives of the Weibull distribtutions) from the 'no event' health state to each individual event state for every 12 week period within the observation period of the model using the following equation:

$$Tp(t|t-1) = \exp\left(-\left(\left(\frac{t-1}{\exp(mu)}\right)^{\exp(lambda)}\right)\right) - \exp\left(-\left(\left(\frac{t}{\exp(mu)}\right)^{\exp(lambda)}\right)\right)$$

- For example, the probability for a patient treated with rivaroxaban to move from the no event state to the MI health state between weeks 0 and 12 is calculated as follows (using the Weibull parameters presented in section 7.3.1):
  - TP(MI: 0-4 weeks) =exp(-((0/exp(12.543180))^exp(-1.017409)))-exp(-((4/exp(12.543180))^exp((-1.017409))) =1.76%.
- The parametric approach is based on first events only and to estimate the probability of a patient on rivaroxaban to move from no event state to the MI + MI health between weeks 0 and 12 is calculated by TP(MI:0-4 weeks) ×TP(MI: 0-4 weeks) = 1.76 % × 1.76 % = 0.03%.

All estimated transition probabilities using this parametric approach during the observation period are presented in the tables below. The example above presents the calculations applied to estimate the transition probability of moving from no event to an event and the examples below the tables show the calculations for movements from one event health state to a health state representing multiple events.

Table 41 Transition probabilities estimated using the parametric approach for the rivaroxaban arm (with the clopidogrel adjustment – RRR =0.8) (licensed population)

	MI	IS	HS/ICH	Other CV Death	Non-CV Death
0-4 weeks	1.76%	0.22%	0.04%	0.87%	0.05%
5-12 weeks	0.84%	0.12%	0.04%	0.39%	0.07%
13-24 weeks	0.73%	0.11%	0.04%	0.33%	0.09%
25-36 weeks	0.52%	0.08%	0.04%	0.23%	0.08%
37-48 weeks	0.41%	0.06%	0.03%	0.18%	0.08%
49-60 weeks	0.35%	0.05%	0.03%	0.16%	0.07%

61-72 weeks	0.31%	0.05%	0.03%	0.14%	0.07%
73-84 weeks	0.27%	0.04%	0.03%	0.12%	0.07%
85-96 weeks	0.25%	0.04%	0.03%	0.11%	0.07%

Table 42: Transition probabilities estimated using the parametric approach for the comparator arm (with the clopidogrel adjustment – RRR =0.8) (licensed population)

	MI	IS	HS/ICH	Other CV Death	Non-CV Death
0-4 weeks	2.01%	0.19%	0.02%	1.37%	0.06%
5-12 weeks	0.96%	0.11%	0.02%	0.61%	0.08%
13-24 weeks	0.83%	0.09%	0.02%	0.52%	0.11%
25-36 weeks	0.59%	0.07%	0.02%	0.36%	0.10%
37-48 weeks	0.47%	0.06%	0.02%	0.29%	0.09%
49-60 weeks	0.50%	0.06%	0.02%	0.30%	0.09%
61-72 weeks	0.43%	0.05%	0.02%	0.27%	0.08%
73-84 weeks	0.39%	0.05%	0.02%	0.24%	0.08%
85-96 weeks	0.35%	0.04%	0.02%	0.22%	0.08%

The estimations from the no event health state to each of the event states provides the basis to calculate the transition probabilities for moving from one event to a multiple event health state during the observation period (for example patients who transition from MI to MI+IS, or from MI to MI+MI - during the first 12 weeks):

- Assume that the transition probability for no event to MI within the first 4 weeks is 2.01% for the comparator arm.
- Assume that the transition probabilities for no event to IS (also in the comparator arm) within the first 4 weeks is 0.19%.
- For patients transitioning from MI to MI+IS we consider the additional event to be the IS in this case. So the transition probability from MI to MI + IS is 0.19%.
- For patients transitioning from MI to 2MIs the additional event of MI is considered when estimating transition probabilities – in this case the transition probability is 2.01%.

Transition probabilities – extrapolation period

The transition probabilities applied during the extrapolation period (beyond 2 years) can be considered in two parts:

1. Transition probabilities of patients moving from the “event free” health state to an event of MI, IS, HS/ICH, other cardiovascular death or non-cardiovascular death.

2. Transition probabilities of patients who have already experienced a non-fatal secondary ACS event during the model and suffer subsequent events

The Weibull distribution is time dependent and provides estimates for each 12 weekly cycle during the observation period as discussed above. Therefore, an average estimate over multiple cycles is not required to base the extrapolation period on. In the extrapolation period as patients move from one health state to another, the last observation from the observation period (85-96 weeks) estimated for the control arm using the parametric approach is applied to both the active and control arm (as rivaroxaban is discontinued after 2 years of treatment in the base case) to estimate transition probabilities beyond the two year observation period. The parametric approach is not sensitive to outliers.Transition probabilities are also corrected for the 6-monthly cycle length used throughout the extrapolation period of the model.

Appendix 14 provides the formula used to calculate the transition probabilities in the extrapolation period -as patients move from the "event free" health state to an event and those who have already had a previous event and go on to suffer subsequent events in the model.

Transition probabilities for subsequent events

As above for patients moving from the 'no event' health state, the last cycle of the observation period estimated using the parametric approach is used to estimate the probabilities during the extrapolation period of subsequent events in those patients who have already suffered a non-fatal secondary CV event in the model. Furthermore, the occurrence of events over time during the ATLAS 2 trial is taken into consideration. That is, it is realised that there are a decreasing number of events over time. The relative risk of suffering subsequent events during the extrapolation period is consequently based on this evidence from the trial.

Table 43 presents the decreasing number of events observed in ATLAS 2 during the first 6 months, second 6 months and post-12 months following an event. The estimates in the table for the second 6 months and post-12 months are relative proportions of events compared to the events observed in the first 6 months. Hemorrhagic strokes are not included in the table due to the low number of occurences. In the extrapolation period, the risk of non-cardiovascular death is based on life tables and is assumed not to be related to previous cardiovascular events. Therefore, non-CV death is not included in the table below.

Table 43 The number of events reported in the ATLAS 2 trial data in comparison to the first 6 months of the trial

Event	1st 6 months	2nd 6 months	Later
MI	100.00%	41.72%	30.45%
Ischaemic Stroke	100.00%	55.87%	47.36%
Other CV Death	100.00%	33.00%	33.00%

The assumption is made that patients have a 1.5 times increased risk of suffering any type of subsequent ACS event in all cycles that occur during the post 12 month period following the previous event (

Table 44). This is based on information presented in Smolina et al 2012(111;112), found through the systematic review described in section 7.3.1 and deemed to be the most appropriate source because it presents data on long-term survival in over 380,000 MI patients from England, where it is estimated that patients who have experienced an MI have a 2 times higher probability of death than the general population. Furthermore, this source states that patients with a second / recurrent MI have a 3 times higher probability of death than the general population. Therefore, the relative risk of death for patients with multiple MIs versus those with only one MI is 3/2, which equals 1.5. As an assumption, this estimate of a 1.5 relative risk is taken as a proxy and applied to increase the risk of secondary events for both fatal and non-fatal events in the later events of the model (Smolina, 2012)(111;112). The relative risk estimates for the first 6 months and second 6 months following a prior event are estimated using this assumption and the decreasing number of events presented in Table 43 above. Please refer to the example calculations below for a worked example of how this is achieved. It should be noted that the relative risks for HS/ICH are assumed to be equal to 1 during the first year following an event due to the small number of HS/ICH events recorded in the trial.

Examples of the calculations used are presented below:

- First 6 months following an event:
    - The relative risk in the post 12 months ('later' period) following an event is given by R(later).
    - The pattern of events occurring in the first 6 months of the ATLAS 2 trial is given by D(first).
    - The pattern of events in the second 6 months, relative to the first 6 months, is given by D(second).
    - The pattern of events in the post 12 months (later), relative to the first 6 months, D(later).
    - The relative risk of suffering a subsequent MI within the first 6 months following a previous MI is given by:
        - R(first) = R(later)×D(first)/D(later).

- Second 6 months following an event:
    - The relative risk of suffering a subsequent MI within the second 6 months following a previous MI is given by:
        - R(second)=R(later)×D(second)/D(later).
    - The relative risk of suffering a subsequent IS within the second 6 months following a previous MI is similar to the calculation for subsequent MI following a previous MI:
        - R(second)=R(later)×D(second)/D(later).
    - The relative risks of suffering a subsequent HS/ICH following a previous MI or previous IS are assumed to be equal to 1 due to the small numbers of all HS/ICH events in the trial.
        - The relative risk of suffering a subsequent HS/ICH following a previous HS/ICH is assumed to be the same that for a subsequent MI following a previous MI.

Table 44: Relative risk of suffering subsequent events

Relative risks for subsequent events	**After MI**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	4.9	2.1	1.5
IS	3.2	1.8	1.5
HS/ICH	1.0	1.0	1.5
Fatal MI	4.9	2.1	1.5
Fatal IS	3.2	1.8	1.5
Fatal HS/ICH	1.0	1.0	1.5
OCD	3.0	1.6	1.5
Relative risks for subsequent events	**After IS**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	4.9	2.1	1.5
IS	3.2	1.8	1.5
HS/ICH	1.0	1.0	1.5
Fatal MI	4.9	2.1	1.5
Fatal IS	3.2	1.8	1.5
Fatal HS/ICH	1.0	1.0	1.5
OCD	3.0	1.6	1.5
Relative risks for subsequent events	**After HS**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	1.0	1.0	1.5
IS	1.0	1.0	1.5
HS/ICH	4.9	2.1	1.5
Fatal MI	1.0	1.0	1.5
Fatal IS	1.0	1.0	1.5
Fatal HS/ICH	4.9	2.1	1.5
OCD	1.0	1.0	1.5
Relative risks for subsequent events	**3 events**		
MI			
IS	1.5		
HS/ICH			
Fatal MI	1.5		
Fatal IS	1.5		
Fatal HS/ICH	1.5		
OCD	1.5		

The information presented in the two tables above combined with the transition probabilities describing the risk of non-fatal MI, non-fatal IS, non-fatal HS/ICH, and health states defined by a combination of two non-fatal events provide the initial estimate for the risk of subsequent events in the extrapolation period for patients who have previously suffered a non-fatal secondary CV event in the model.

An example of the calculations used to estimate the initial values for use in the extrapolation period of the model for patients at risk of subsequent events is presented below.

- The probability for patients to move from the MI to the 2 MIs health state is estimated by multiplying the transition probability of moving to the MI state from the last cycle of

the observation period, estimated using the parametric approach (O(parametric_MI)), and relative risks for subsequent events as described above.

- In the first 6 months the initial value applied to the extrapolation for MI to 2 MIs is given by O(parametric_MI) × RR of MI following MI in first 6 months since first MI
- The initial value applied to the extrapolation illustrating the transition probability for the second 6 months since the first MI is calculated as O(parametric_MI) × RR of MI following MI in second 6 months since first MI
- In the post 12 months period the initial value applied to the extrapolation for movement from the MI state to the 2 MIs state is given by O(parametric_MI) × RR of MI following MI in later periods since first MI

Impact of age on transition probabilities

Transition probabilities also take age into account. That is, a patient's risk of events increases with each year that they get older. This is explained in more detail in section 7.3.3 and during the discussion of transition probabilities in the extrapolation period.

Initial case fatalities

An initial case fatality value for fatal MI was obtained from the trial data. Whilst the review did identify a number of potentially useful sources for this estimate, we felt that the clinical trial data provided the strongest evidence source (our population have already had an ACS event so an MI in the model is in fact a second event of that nature). To estimate the initial case fatality rate of MIs we take a value based on the average number of events in the last cycle of the observation period (fatal MI / (fatal MI + non-fatal MI)), which gives a value of 13.4%.

The initial case fatality value for fatal strokes was estimated from the literature (Hippisley-Cox 2004)(113) because the numbers of first fatal stroke events in the last cycle of the observation period were not large enough to base extrapolation on. As the systematic review did not identify relevant data for stroke in a population with prior ACS, the statistics section of the British Heart Foundation (BHF) website was consulted to identify information from the general population. The Stroke statistics (2009 edition) (BHF 2009)(114) details three potential sources. (Zhang 2012, Hippisley-Cox et al 2004, Rothwell 2005(113;115;116)). Of these, the publication by Hippisley-Cox et al 2004 included information from general practices distributed throughout the UK and was therefore deemed to be the most representative of the population in question (Hippisley-Cox et al 2004)(113).

The incident cases of strokes reported at the end of the observation period of the Hippisley-Cox et al publication was 3,734, of which 855 (22.9 %) were fatal. Hippisley-Cox et al (2004)(113) presents the timing of the death for 0-7 days (33.2 %), 0-30 days (50.9 %) and 31 days and over (49.2 %). Our interest lies with the case fatalities that occurred within the first 30 days. The intial case fatality value for stroke is calculated as the multiplication of the number of fatalities and the number of fatalities within the first 30 days and is estimated to be 11.7 % (22.9 % × 50.9 %).

The background non cardiovascular-related mortality applied in the model has been taken from UK life tables available from the Office of National Statistics (ONS) which differentiates between mortality rates for males and females for death by any cause, CHD death and death from stroke (http://www.statistics.gov.uk/hub/index.html). To estimate the overall mortality

rates a gender weighted average using the proportion of male and female patients who participated in the ATLAS 2 trial was used (the model allows the user to choose the average age of the patient cohort, in the base case this is set to the average age of the label population from ATLAS 2).

Model calibration

Following the before mentioned literature review, Smolina et al (2012b)(111) was deemed the most appropriate source to use during model calibration. We needed a source with long-term follow-up and Smolina was deemed most appropriate because it presented life expectancy over 7 years for a large UK-based patient population. Furthermore, by presenting the relative risk of death after both first and second MIs we could estimate a weighted life expectancy which considers those with multiple events in addition to those who have had one MI. This was a benefit over other sources, especially as our model considers multiple events.

Smolina et al (2012b)(111) provides age standardised mortality rates over seven years. These suggest that for the first two years after a first MI patients are at a risk of mortality which is approximately twice as high as that of the (non-MI suffering) general population (for males the risk of mortality is approximately 2.20 and for females the risk of mortality is approximately 1.88). After a second MI, the risk of mortality is more than 3 times as high as in those who have not experienced an MI (for males the risk of mortality following a recurrent MI is approximately 3.54 and for females the risk of mortality is approximately 3.21). By applying these estimates to the average life expectancy of a 64-year old (the mean age of patients entering the ATLAS 2 trial plus two years – i.e. the age of patients at the start of the extrapolation period), and applying weights based on the gender distribution of the ATLAS 2 trial, an average life expectancy of 13.55 years is expected. The information used to obtain this estimate is provided below:

- When calculating this we obtain the life expectancy following a first MI to be 15.33 for females and 13.71 for males.
- The life expectancy following a recurrent MI are 14.12 for females and 10.82 for males.
- The estimation takes into consideration that 76% of the patients considered in Smolina et al (2012b)(111) were males and 83% had no prior MI.

Therefore, the model is calibrated to predict an overall life expectancy of approximately 13.55 years (refer to Table 45 below).

Table 45: Life expectancy estimated using information presented in Smolina et al (2012) (111)and the life expectancy predicted by the model

Event	Life expectancy from literature	Life expectancy predicted by the model	Literature source
Life expectancy following a MI	13.55	13.40	Smolina et al 2012 (b)

The annual age specific increased risk of non-fatal and fatal events extracted from Smolina et al 2012(111) and Hippisley-Cox et al 2004(113) (detailed 7.3.3) are subsequently predicted by the model using calibration methods. It should be noted that values extracted from literature are used to check the outputs from the life time model. The actual annual age specific increased risk of events (estimated from literature) are presented in Table 46. The estimates obtained

from the calibration are presented in Table 47 - these annual risks are applied to each cycle of the extrapolation period.

Table 46: Annual age specific increased risk estimated for non-fatal events obtained from literature and predicted by the model

Event	% Increase with age from literature	% Increase with age predicted by the model	Literature source
MI	1.075	1.074	Smolina et al 2012 (a)(112)
IS	1.093	1.093	Hippisley-Cox et al 2004(113)
HS/ICH	1.093	1.094	Assumption based on Hippisley-Cox et al 2004(113)
OCD	1.103	1.087	Smolina et al 2012 (a) (112)
NCD	1.097	1.089	ONS 2012
Case fatality MI	1.045	1.046	Smolina et al 2012 (a) (112)
Case fatality IS	1.056	1.048	Factor of 1.67 based on relative difference in fatal and non-fatal MI presented in Smolina et al 2012
Case fatality HS/ICH	1.056	1.048	Assumption based on case fatality IS

Table 47: Annual age specific increased risk estimates derived by means of calibration and applied to each model cycle within the extrapolation period

Event	% Increase with age from literature	Source
MI	8.70%	Calibration
IS	10.65%	Calibration
HS/ICH	10.73%	Calibration
OCD	10.03%	Calibration
NCD	10.28%	Calibration
Case fatality MI	-13.90%	Calibration
Case fatality IS	-9.00%	Calibration
Case fatality HS/ICH	-9.00%	Calibration

* Negative values are caused by the increasing competing risk of OCD and NCD, reducing the risk of fatal MI, IS and HS/ICH

The literature review also identified a paper by Wong et al (117)which provided survival data over 7 years for patients with and without ACS, including a biomarker positive subpopulation. This source was deemed inappropriate due to the following:

- Less than 200 patients were included in the ACS biomarker positive cohort
- The paper suggests a hazard rate of 1.97 for death in ACS patients who are biomarker positive vs those who are not. When disregarding the first 2 years of data (as in the current model this is based on trial data), this hazard rate does not hold true when viewing the survival curves. The change in mortality from year 2 to 7 is smaller in the biomarker positive group that in the biomarker negative group. Whether this is significant is unclear but the proportional hazards assumption does not seem to hold and thus the data are not appropriate for use in our modelling approach.

Markov matrix – Extrapolation period

The table below presents the transition probability matrix used to estimate the probabilities for all possible combinations of the model health states. The transition probability matrix is applied during each cycle of the extrapolation period of the model. As mentioned previously the last cycle of the comparator arm of the observation period provides the intial estimates for patients moving from the "event free" (clean) health state to an event of non fatal MI, non-fatal IS, non-fatal HS/ICH and other cardiovascular death (the Office of National Statistics provides estimates for non cardiovascular death). The OCD estimates are used to calculate the probabilities for fatal MI, fatal IS and fatal HS/ICH - where an average value over the four events is assumed. The transition probability matrix below provide the estimates for patients who have already suffered a non-fatal event and suffer subsequent events. The relative risks of suffering from subsequent events and decreasing number of events (discussed above) observed in the ATLAS 2 trial are used to estimate these transition probabilities. Note that the transition probabilities presented here are prior to any adjustments due increased risk due to age. This matrix is then used to find the dynamic transition probabilities for all the possible model health states and this is done by applying the formulae presented in Appendix 14 where increased risk of event due to age are incorporated into the calculation for each cycle of the extrapolation period of the model.

Table 48: Extrapolation Markov matrix

TO / FROM	C	M1	M2	M3	I1	I2	I3	H1	H2	H3	2M1	2M2	2M3	2I1	2I2	2I3	2H1	2H2	2H3
C	98.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
M1	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
M2	0.0%	94.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
M3	0.0%	0.0%	97.2%	97.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
I1	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
I2	0.0%	0.0%	0.0%	0.0%	94.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
I3	0.0%	0.0%	0.0%	0.0%	0.0%	97.2%	97.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
H1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
H2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	98.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
H3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	98.3%	97.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2M1	0.0%	3.8%	1.6%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2M2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	96.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2M3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	97.6%	97.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2I1	0.0%	0.0%	0.0%	0.0%	0.3%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2I2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	96.8%	0.0%	0.0%	0.0%	0.0%	0.0%
2I3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	97.6%	97.7%	0.0%	0.0%	0.0%
2H1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2H2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	97.9%	0.0%	0.0%
2H3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	97.9%	97.7%
M+I1	0.0%	0.3%	0.2%	0.1%	3.8%	1.6%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
M+I2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
M+I3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
M+H1	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.8%	0.8%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
M+H2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
M+H3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
I+H	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
I+H2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
I+H3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
3E1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%
3E2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
3E3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+MI	0.1%	0.5%	0.2%	0.2%	0.5%	0.2%	0.2%	0.1%	0.1%	0.2%	0.5%	0.2%	0.2%	0.5%	0.2%	0.2%	0.1%	0.1%	0.2%
+IS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+HS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+OV	0.4%	1.1%	0.6%	0.5%	1.1%	0.6%	0.5%	0.4%	0.4%	0.5%	1.1%	0.6%	0.5%	1.1%	0.6%	0.5%	0.4%	0.4%	0.5%
O	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%

TO / FROM	M+I1	M+I2	M+I3	M1+H1	M+H2	M+H3	I+H1	I+H2	I+H3	3E1	3E2	3E3	+MI	+IS	+HS	+OV	O

C																		
M1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
M2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
M3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
I1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
I2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
I3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
H1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
H2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
H3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2M1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2M2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2M3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2I1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2I2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2I3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2H1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2H2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
2H3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
M+I1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
M+I2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
M+I3	96.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
M+H1	0.0%	97.6%	97.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
M+H2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
M+H3	0.0%	0.0%	0.0%	96.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
I+H	0.0%	0.0%	0.0%	0.0%	97.6%	97.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
I+H2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
I+H3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	97.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
3E1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	97.7%	97.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
3E2	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
3E3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	98.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
+MI	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	99.0%	99.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
+IS	0.5%	0.2%	0.2%	0.5%	0.2%	0.2%	0.4%	0.2%	0.2%	0.5%	0.2%	0.2%	100.0%	0.0%	0.0%	0.0%	0.0%	
+HS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	
+OV	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	
O	1.1%	0.6%	0.5%	1.1%	0.6%	0.5%	0.9%	0.5%	0.5%	1.1%	0.6%	0.5%	0.0%	0.0%	0.0%	100.0%	0.0%	

Mx = myocardial infarction in x month period since event, Ix = ischaemic stroke in x month period since event, Hx = haemorrhagic stroke/ICH in x month period since event, +OV = other cardiovascular death, O = non-cardiovascular death, +MI = fatal MI, +IS = fatal ischaemic stroke, +HS = fatal haemorrhagic stroke/ICH, 2Mx / 2Ix / 2Hx = 2 MIs / ISs / HS/ICHs in x month period since event, M+Ix / M+Hx / I+Hx = Combinations of 2 events in x month period since 2nd event, 3Ex = 3 events in x month period since 3rd event.

7.3.3 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 cardiovascular event is highest immediately following a non-fatal CV event(3;30;31).

In a lifetime cost-effectiveness model once the initial estimates for the extrapolation have been defined, the factors that will affect patients over the remaining duration of their lives must be considered. One of the primary concerns when modelling this indication is the ageing population and the growing risks of suffering subsequent ACS events as patients get older. As well as the sources identified to determine the model inputs, it is clear that there is an increase in risk with age based on The Rotterdam Study (identified through previous work undertaken by the model developers) and published papers by Lee et al(118) (identified through expert opinion) and Hippisley-Cox et al(113) (identified through systematic review). (Hollander 2003, Lee 2011, Hippisley-Cox et al 2004(109;113;118))

The age specific increases in the risk of suffering non-fatal and fatal MIs and strokes are estimated using UK age specific incidence rates reported in Smolina et al (2012a)(112) and Hippisley-Cox et al (2004)(113) respectively.

The risk of first MI events due to age is presented in Smolina et al (a)(112) (

Figure 24).

Figure 24: Incidence rates for first MIs in England (Smolina 2012)(112)

Table 2 Population-based incidence rates of first acute myocardial infarction (AMI) by sex and age, England, 2010

Sex	Age (years)	First AMIs, n			Incidence rate per 100 000		
		Hospital admissions	Sudden deaths	Total first AMIs	Hospital admissions	Sudden deaths	Overall
Men	0–29	86	19	105	0.0	0.2	1.0
	30–34	106	17	123	0.5	1.0	7.4
	35–39	409	53	462	1.8	2.9	26
	40–44	1009	136	1145	5.1	6.7	59
	45–49	1917	282	2199	12.2	14.2	116
	50–54	2700	406	3106	22.4	23.5	190
	55–59	3112	535	3647	34.2	33.7	250
	60–64	3961	838	4799	45.3	50.8	313
	65–69	3633	967	4600	64.1	73.9	392
	70–74	3940	1134	5074	111	103	524
	75–79	3939	1387	5326	172	162	711
	80–84	3632	1493	5125	292	245	998
	85–89	2741	1291	4032	442	384	1450
	90+	1305	641	1946	525	457	1692
	All ages	32490	9199	41689	24.2	23.8	130
Women	0–29	37	2	38	0.0	0.0	0.4
	30–34	37	6	43	0.2	0.4	2.6
	35–39	84	13	97	0.3	0.6	5.4
	40–44	264	31	295	0.8	1.5	15
	45–49	498	59	557	3.1	2.8	29
	50–54	679	81	760	4.1	4.4	45
	55–59	889	112	1001	7.6	6.7	66
	60–64	1342	230	1572	12.4	12.6	98
	65–69	1690	355	2045	24.4	24.0	162
	70–74	2237	535	2772	48.4	43.0	256
	75–79	2946	879	3825	83.1	78.8	416
	80–84	3578	1238	4816	145	139	651
	85–89	3531	1514	5045	257	241	982
	90+	2663	1203	3866	341	323	1329
	All ages	20475	6258	26733	10.1	9.6	55.9

Figure 25: Estimated resident population mid 2010 by selected age groups and gender (ONS 2012)(119)

Age group	Men	Women	All
0–29	11,958,700.00	11,384,529.00	23,343,229.00
30–34	1,959,754.00	1,931,632.00	3,891,386.00
35–39	2,084,624.00	2,117,116.00	4,201,740.00
40–44	2,293,419.00	2,338,633.00	4,632,052.00
45–49	2,250,028.00	2,316,072.00	4,566,100.00
50–54	1,964,710.00	2,016,391.00	3,981,101.00
55–59	1,758,587.00	1,819,750.00	3,578,337.00
60–64	1,840,077.00	1,923,522.00	3,763,599.00
65–69	1,412,107.00	1,519,564.00	2,931,671.00
70–74	1,160,309.00	1,307,442.00	2,467,751.00
75–79	893,914.00	1,107,841.00	2,001,755.00
80–84	607,090.00	885,545.00	1,492,635.00
85–89	326,079.00	608,473.00	934,552.00
90+	116,405.04	284,672.26	476,059.00
ages	30,625,803.04	31,561,182.26	62,261,967.00

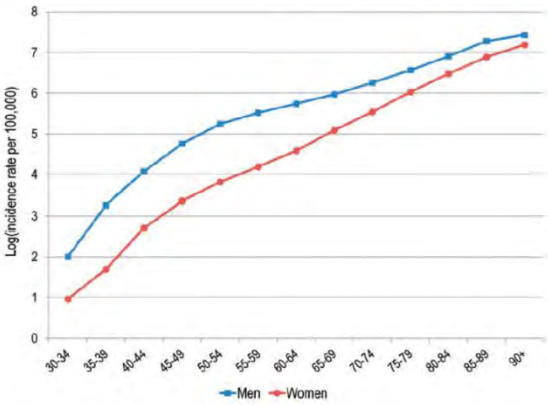
Figure 26: Incidence for the adjusted UK population for first AMI using information from the ONS

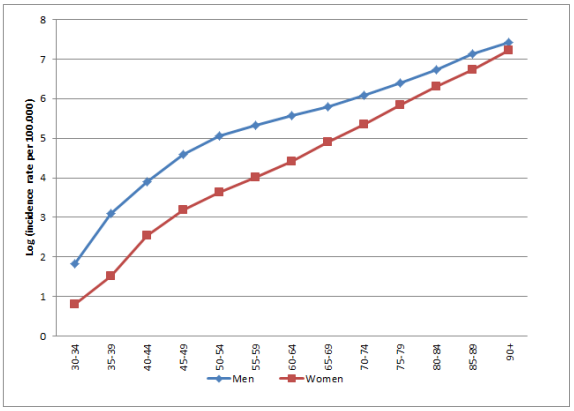
	Men	Women
0-29	-0.13008	-1.09725
30-34	1.83678	0.80025
35-39	3.098391	1.522071
40-44	3.910531	2.534824
45-49	4.58223	3.180107
50-54	5.063161	3.629424
55-59	5.334564	4.007471
60-64	5.56377	4.403361
65-69	5.786144	4.902145
70-74	6.080613	5.356667
75-79	6.389916	5.844316
80-84	6.738379	6.298666
85-89	7.120048	6.720371
90+	7.421626	7.213807

The incidence rate for first MIs for each gender and each age group reported by Smolina et al (112) is first extracted from the table above. The purpose of this is to map the incidence rates reported by Smolina et al to the current UK population and recreate the log incidence and 30 day case fatality graph presented in this study (Figure 27). The incidence rates reported in Smolina et al are applied to the current UK population (available from the Office of National Statistics http://www.statistics.gov.uk/hub/index.html) for the age categories defined in the literature (Figure 25). The log incidence for each gender / age group is then estimated (using the equation below and presented in Figure 26) and plotted to allow comparison against the data provided by Smolina et al as presented in Figure 27.

$$Age\ specific\ incidence\ rates = ln\left(\frac{Incidence\ number\ \times Total\ first\ AMI\ (per\ age\ group)}{Population\ from\ ONS\ (per\ age\ group)}\right)$$

Figure 27 (left) Incidence rates from Smolina et al (112) (right) Incidence rates applied to the current UK population and used to estimate annual increased risk of suffering a non-fatal MI due to age





The relative difference in risk from one age group to another is calculated for males and for females using the information presented in Figure 26. We ignore the following age groups 0-29, 30-34, 35-39 and 40-44 years – keeping in mind the population of interest as represented in the model. An average of these relative differences for each gender is taken (Figure 28 – for males it is approximately 5.5% and for females it is approximately 9.5%) these are then averaged to provide a population estimate of 7.5% increased risk of suffering a non-fatal MI due to age. Please note that these values differ slightly to what is presented in the model due to means of calibration.

Figure 28 Relative difference across the age groups (also refer to **Table 46**)

Relative %	Men	Women
45-49 and 50-54	1.104956	1.14129
50-54 and 55-59	1.053604	1.104162
55-59 and 60-64	1.042966	1.098788
60-64 and 65-69	1.039968	1.113273
65-69 and 70-74	1.050892	1.092719
70-74 and 75-79	1.050867	1.091036
75-79 and 80-84	1.054533	1.077742
80-84 and 85-89	1.056641	1.066951
85-89 and 90+	1.042356	1.073424
age/gender specific incr	1.055198	1.095487
Overall average	1.075343	

The Smolina et al 2012 (112) paper also provides information on the age specific number of all, first and recurrent MIs (Figure 29). From

Figure 30 below we can estimate the average percentage per annum of secondary MIs expected and adjust for fatalities reported. The age specific increased risk of patients with an incident MI suffering from secondary MIs is approximately 10.3%. This age specific estimate is applied as a proxy for other cardiovascular death (OCD) in the extrapolation period of the model.

Figure 29: Number of all, first and recurrent AMI (Smolina 2012) (112)

Table 1 Characteristics of all, first and recurrent AMI events, England, 2010

Characteristics	All AMI	First AMI			Recurrent AMI		
	n	All	Fatal		All	Fatal	
		n	n	All cases (%)	n	n	All cases (%)
Total	82 252	68 422	21 715	31.7	13 830	4334	31.3
Type of event							
Hospital admission	63 864	52 965	6258	11.8	10 899	1403	12.9
Sudden AMI death	18 388	15 457	15 457	100	2931	2931	100
Sex							
Male	50 071	41 689	12 187	29.7	8382	2593	30.9
Female	32 181	26 733	9328	34.9	5448	1741	32.0
Age							
Mean	72.9	72.2	77.4	–	76.6	80.1	–
Median	75	74	80	–	79	82	–
Age group (years)							
0–29	147	144	30	20.8	3	1	33.3
30–54	9678	8787	1251	14.2	891	109	12.2
55–64	12 527	11 019	2109	19.1	1508	271	18.0
65–74	17 154	14 491	3948	27.2	2663	701	26.3
75–84	23 711	19 092	7214	37.8	4619	1557	33.7
≥85	19 035	14 889	7163	48.1	4146	1695	40.9
Deprivation							
Least deprived, 1	17 048	14 522	4594	31.6	2526	822	32.5
2	16 604	13 950	4355	31.2	2654	851	32.1
3	16 265	13 467	4322	32.1	2798	882	31.5
4	16 146	13 291	4279	32.2	2853	877	30.7
Most deprived, 5	16 189	13 190	4165	31.6	2999	902	30.1

Figure 30: Average % of patients with incident MI that suffer secondary MIs per year

		First AMI		*Recurrent AMI*		
Age group	All events	All	Fatal	All	Fatal	All
0–29	147	144	30	3	1	0.020833333
30-54	9678	8787	1251	891	109	0.116470588
55-64	12527	11019	2109	1508	271	0.091062802
65-74	17154	14491	3948	2663	701	0.098254806
75-84	23711	19092	7214	4619	1557	0.118493625
>=85	19035	14889	7163	4146	1695	0.088766138
						0.102609592

The increased risk of a fatal MI due to age is also estimated based on data from Smolina et al (a)(112) for all, first and recurrent MIs (Figure 31).

Figure 31 Overall 30 day case fatality all, first and recurrent AMI events – Smolina et al (2012a) (112)

Factors	Overall case fatality, all AMI (n = 82 252) OR[a] (95% CI)	Overall case fatality, first AMI (n = 68 422) OR[a] (95% CI)	Overall case fatality, recurrent AMI (n = 13 830) OR[a] (95% CI)	Hospitalized case fatality, all AMI (n = 63 864) OR[a] (95% CI)
Age				
30–54	Ref.	Ref.	Ref.	Ref.
55–64	1.47 (1.36–1.58)	1.45 (1.35–1.57)	1.59 (1.25–2.02)	2.04 (1.71–2.43)
65–74	2.38 (2.23–2.55)	2.34 (2.18–2.51)	2.65 (2.13–3.30)	4.34 (3.70–5.09)
75–84	3.87 (3.63–4.12)	3.86 (3.61–4.13)	3.84 (3.11–4.74)	8.48 (7.27–9.89)
≥85	5.91 (5.53–6.32)	6.05 (5.64–6.48)	5.40 (4.36–6.69)	14.56 (12.5–17.0)
Sex				
Women	Ref.	Ref.	Ref.	Ref.
Men	1.12 (1.09–1.16)	1.11 (1.07–1.15)	1.20 (1.11–1.30)	0.97 (0.92–1.02)
Deprivation				
Least deprived, 1	Ref.	Ref.	Ref.	Ref.
2	1.00 (0.95–1.05)	1.00 (0.95–1.05)	0.98 (0.87–1.11)	1.04 (0.96–1.12)
3	1.06 (1.01–1.12)	1.08 (1.02–1.13)	1.00 (0.89–1.12)	1.04 (0.96–1.12)
4	1.12 (1.07–1.18)	1.15 (1.09–1.21)	1.01 (0.89–1.13)	1.08 (1.00–1.16)
Most deprived, 5	1.21 (1.16–1.27)	1.25 (1.18–1.31)	1.06 (0.94–1.20)	1.21 (1.12–1.31)
History				
No history of AMI	Ref.	–	–	Ref.
Previous AMI event	0.82 (0.79–0.85)	–	–	0.87 (0.82–0.93)

a: OR = odds ratio; adjusted for all other factors shown

The relative increase in case fatality risk per age group is estimated separately for first and recurrent MIs by dividing the odds ratio of overall case fatality for a particular age group with the odds ratio of overall case fatality in the previous (younger) age group. Averages are then taken and corrected for the fact that each age group contains 10 years (excluding ≥ 85 year olds). The resulting age-corrected annual risk increase estimates are averaged to get an overall annual increase in risk of approximately 4.5%.

The risk of strokes and TIA due to age is presented in Hippisley-Cox et al (2004)(113) (Figure 32).

	age bands	incidence rate of TIA per 1000 patient years	incidence rate of stroke per 1000 person years	overall incidence of stroke or TIA
Both	<45 years	0.05	0.07	0.11
	45 to 64 years	0.93	0.96	1.77
	65 to 74 years	3.62	3.49	6.73
	75 plus	8.00	9.49	16.70
	Total	**1.23**	**1.36**	**2.46**

Figure 32: Incidence of stroke and TIA over 2 years – Hippisley-Cox et al 2004 (113)

The incidence rate of strokes for each age category reported by Hippisley-Cox et al (2004) (113) is extracted and used to estimate the age specific risk of strokes. Patients under the age of 45 years are excluded in the estimation keeping in mind the trial population. The relative difference in risk from one age group to another is calculated using a reference group of those aged 45-64 years. An average of these relative differences is taken and an assumption is made that all age categories beyond the reference case include 10 years (Figure 33).

Figure 33: Calculation of age-specific increase in risk of non-fatal strokes

	Incidence rate of stroke per 1000 person years	Relative difference across age groups
<45 years	0.07	
45-64 years	0.96	0.9600
65-74 years	3.49	3.6354
75 +	9.49	2.6104
Average		**2.4019**
Annual Increase Due to Age (2.4019^(1/10))		**1.092**

When applying this assumption the resulting age corrected annual risk increase estimates are averaged to get an overall annual increase of approximately 9.3%. In the absence of the differentiation between incident rates for fatal and non-fatal strokes, we assume the same relative difference as for fatal and non-fatal MIs (factor of 1.67– calculated as follows: 7.5% (non-fatal MI) / 4.5% (fatal MI) = 1.67. Using the factor of 1.67 and a value for non-fatal stroke of 9.3% provides an annual increased risk of fatal stroke due to age estimate of approximately 5.6% (9.3% / 1.67).

7.3.4 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?

Intermediate outcome measures were not used in the model.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[11]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated

[11] 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.

- declaration of potential conflict(s) of interest from each expert or medical specialist 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).

Based on his knowledge of ACS in the UK, KR was contacted to verify assumptions and values used in the economic model. KR was independently approached to participate and was sourced independently of Bayer. Prior to meeting, KR was provided with an overview document of key assumptions and values used in the model. No information on the treatments included in the model, the label population, or the ATLAS 2 clinical trial was provided. Evidence was discussed and verified with KR via telephone interview. Below, the assumptions discussed and the feedback given by KR are provided. Where a change to the proposed model was suggested, comments are also provided.

Table 49: Clinical validation with KR

Model Function	Assumption	Feedback	Comment/ Action
Health States	Non fatal and fatal MI, IS, HS/ICH, multiple event states, other CV death, and non-CV death are included in the model	To be most accurate the model should distinguish events in the 3 or more event state	Data does not allow for distinction of individual events within the 3 or more event state. The number of patients experiencing 3 or more events is low.
	Intracranial haemorrhages are included in the HS/ICH health state	KR agreed with assumption	No action required
	Bleeding and revascularisation are considered as transient health states	KR agreed with assumption	No action required
	Patients who suffer a non-fatal and fatal event in any given cycle are considered as a fatality in that cycle	KR thought this assumption was reasonable, but costs will be underestimated	The potential underestimation of costs will be small due to low numbers of patients experiencing non fatal and fatal events within the same cycle. There are approximately 8% of events that are combined fatal and non-fatal events as a percentage of the total number of non-fatal and combined fatal and non-fatal events reported in the ATLAS 2 trial.
Cycle length during observation period	Cycles are assumed to be 12 weeks in length	KR agreed with this assumption – clinical follow-up generally takes place every 3 to 6 months	No action required

Cycle length during extrapolation period	Cycles are assumed to be 6 months in length	KR agreed with this assumption – clinical follow-up generally takes place every 3 to 6 months	No action required
Trial data	In the trial 93% of patients were treated with ASA + clopidogrel (+ rivaroxaban or placebo), and 7% were treated with ASA monotherapy (+ rivaroxaban or placebo)	It is expected that approximately 99% of patients would be treated with clopidogrel + ASA. *Note – this confirmed our decision Not to present data for the aspirin alone arm of the study.*	Trial population provides an estimate of [redacted] of patients treated with clopidogrel + ASA in the UK. However, the UK trial population is too small for analysis. A scenario analysis is conducted on the model where 100% of the modelled patients are given clopidogrel + ASA
Discontinuation rates	Patients who discontinue treatment following a MI, IS and HS/ICH are deducted from the clean health state to allow for adjustment of costs. Efficacy does not need to be adjusted for as this is already included in the trial data.	KR agreed with this assumption	No action required
	Treatment discontinuation rates seen in the clinical trial: Overall discontinuation (active, placebo): 30%, 31% Following an MI (active, placebo): 5%, 30%	KR agreed with rates seen for overall discontinuation, and HS/ICH KR felt that the discontinuation rates following an MI would be around 5 to 10%, and was surprised by the differences between the arms KR felt that the discontinuation rates following an IS would	The clinical trial data from ATLAS 2 is the strongest data for discontinuation in ACS.Scenario analyses are possible within the current modelling framework to examine the impact of different proportions of patients discontinuing active or comparator treatments, both treatments or to examine the impact of no discontinuation

	Following an IS (active, placebo): 45%, 49% Following a HS/ICH (active, placebo): 100%, 100%	be lower (around 25%)	
Impact of adverse events	TIMI Major Bleed = 30 day impact on QoL	KR agreed with this assumption	No action required
	TIMI Minor Bleed = 2 day impact on QoL	KR agreed with this assumption	No action required
	TIMI Bleed requiring medical attention = 2 day impact on QoL	KR agreed with this assumption	No action required
	PCI / PTCA = 30 day impact on QoL	KR agreed with this assumption	No action required
	CABG = 30 day impact on QoL	KR commented that this impact should be much longer – approximately 3 months	The impact on QoL of CABG was subsequently updated to 12 weeks in the model
	Would we expect to see positive health outcomes (in terms of reductions in events) following revascularisation?	Yes, but no need to account further as this is part of patient management and results of trial already reflect this	No action required
	Fatal bleeds are captured in the other cardiovascular death health state	KR agreed with this approach	No action required

Relative risks of events applied in extrapolation period	Assumed risk 1.5 times higher for MI, IS and HS/ICH beyond 12 months	The risk of IS / HS/ICH will be high immediately after event and then decline from approximately 30 days onwards. The risk of stroke is less than MI following an ACS event. Risk of MI remains higher for longer than IS.	No action required – RRs decline over time and RR of stroke is lower than of MI in the model throughout the first year
Increased risk of events due to ageing	The same values are applied for MIs, ISs and HS/ICHs	It is fine to assume that the increased risk is the same for IS and HS/ICH. However, for MIs a different value should be used	Using data from Smolina et al 2012 (111;112) and Hippisley-Cox et al 2004 (113)we were able to estimate different risk increases per event

KR has received honoraria for lectures, advisory boards or for serving as a steering committee member or executive committee member for Pfizer, Novartis, Novo NordDisk, AZ, Abbott, Kowa, Roche, Daiichi Sankyo, Lily, MSD, GSK, BMS, Regeneron, and Sanofi.

Summary of selected values

7.3.6 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 7.3.1 and 7.3.2 describe how transition probabilities in the model are estimated. The transition probabilities for the observation period (using the parametric approach) are presented in the tables below. Please refer to Table 48 (extrapolation Markov matrix) for the starting probabilities for the extrapolation period. The range of transition probabilities is varied in sensitivity analyses based on the difference in event rates between the treatment arms. This is described further in section 7.7. All other input parameters and their distributions are presented in Table 52 and Table 69.

Table 50: Transition probabilities from the observation period of the comparator arm

TO\ FROM	C1	C2	C3	C4	C5	C6	C7	C8	M1	M2	M3	M4	M5
C	98.21%	98.42%	98.86%	99.08%	99.03%	0.43%	99.23%	99.29%					
M1	0.96%	0.83%	0.59%	0.47%	0.50%	0.05%	0.39%	0.35%	98.22%	98.43%	98.87%	99.08%	99.04%
I1	0.11%	0.09%	0.07%	0.06%	0.06%	0.02%	0.05%	0.04%					
H1	0.02%	0.02%	0.02%	0.02%	0.02%	0.00%	0.02%	0.02%					
2M1	0.01%	0.01%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.96%	0.83%	0.59%	0.47%	0.50%
2I1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
2H1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
M+I1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.11%	0.09%	0.07%	0.06%	0.06%
M+H1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.02%	0.02%	0.02%	0.02%	0.02%
I + H1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
3E1	0.00%	0.00%	0.00%	0.00%	0.00%	0.07%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
+ MI	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%
+ IS	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%
+ HS	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%
+OV	0.15%	0.13%	0.09%	0.07%	0.08%	0.08%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%
+O	0.08%	0.11%	0.10%	0.09%	0.09%	0.43%	0.08%	0.08%	0.08%	0.11%	0.10%	0.09%	0.09%
TO\ FROM	M6	M7	M8	I1	I2	I3	I4	I5	I6	I7	I8	H1	H2
C													
M1	99.15%	99.23%	99.29%										
I1				98.22%	98.43%	98.87%	99.08%	99.04%	99.15%	99.23%	99.29%		
H1												98.22%	98.43%
2M1	0.43%	0.39%	0.35%										
2I1				0.11%	0.09%	0.07%	0.06%	0.06%	0.05%	0.05%	0.04%		
2H1												0.02%	0.02%
M+I1	0.05%	0.05%	0.04%	0.96%	0.83%	0.59%	0.47%	0.50%	0.43%	0.39%	0.35%		
M+H1	0.02%	0.02%	0.02%									0.96%	0.83%
I + H1				0.02%	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%	0.11%	0.09%
3E1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
+ MI	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%
+ IS	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%
+ HS	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%
+OV	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%
+O	0.08%	0.08%	0.08%	0.08%	0.11%	0.10%	0.09%	0.09%	0.08%	0.08%	0.08%	0.08%	0.11%
TO\ FROM	H3	H4	H5	H6	H7	H8	2M1	2M2	2M3	2M4	2M5	2M6	2M7
C													

M1													
I1													
H1	98.92%	99.12%	99.08%	99.18%	99.26%	99.32%							
2M1							98.22%	98.43%	98.87%	99.08%	99.04%	99.15%	99.23%
2I1													
2H1	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%							
M+I1													
M+H1	0.59%	0.47%	0.50%	0.43%	0.39%	0.35%							
I + H1	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%							
3E1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1.09%	0.95%	0.67%	0.54%	0.57%	0.50%	0.45%
+ MI	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%
+ IS	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%
+ HS	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%
+OV	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%
+O	0.10%	0.09%	0.09%	0.08%	0.08%	0.08%	0.08%	0.11%	0.10%	0.09%	0.09%	0.08%	0.08%
TO\ FROM	**2M8**	**2I1**	**2I2**	**2I3**	**2I4**	**2I5**	**2I6**	**2I7**	**2I8**	**2H1**	**2H2**	**2H3**	**2H4**
C													
M1													
I1													
H1													
2M1	99.29%												
2I1		98.22%	98.43%	98.87%	99.08%	99.04%	99.15%	99.23%	99.29%				
2H1										98.22%	98.43%	98.87%	99.08%
M+I1													
M+H1													
I + H1													
3E1	0.41%	1.09%	0.95%	0.67%	0.54%	0.57%	0.50%	0.45%	0.41%	1.09%	0.95%	0.67%	0.54%
+ MI	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%
+ IS	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%
+ HS	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%
+OV	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%
+O	0.08%	0.08%	0.11%	0.10%	0.09%	0.09%	0.08%	0.08%	0.08%	0.08%	0.11%	0.10%	0.09%
TO\ FROM	**2H5**	**2H6**	**2H7**	**2H8**	**M+I1**	**M+I2**	**M+I3**	**M+I4**	**M+I5**	**M+I6**	**M+I7**	**M+I8**	**M+H1**
C													
M1													
I1													
H1													
2M1													

2I1													
2H1	99.04%	99.15%	99.23%	99.29%									
M+I1					98.22%	98.43%	98.87%	99.08%	99.04%	99.15%	99.23%	99.29%	
M+H1													98.22%
I + H1													
3E1	0.57%	0.50%	0.45%	0.41%	1.09%	0.95%	0.67%	0.54%	0.57%	0.50%	0.45%	0.41%	1.09%
+ MI	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%
+ IS	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%
+ HS	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%
+OV	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%
+O	0.09%	0.08%	0.08%	0.08%	0.08%	0.11%	0.10%	0.09%	0.09%	0.08%	0.08%	0.08%	0.08%
TO\ FROM	**M+H2**	**M+H3**	**M+H4**	**M+H5**	**M+H6**	**M+H7**	**M+H8**	**I+H1**	**I+H2**	**I+H3**	**I+H4**	**I+H5**	**I+H6**
C													
M1													
I1													
H1													
2M1													
2I1													
2H1													
M+I1													
M+H1	98.43%	98.87%	99.08%	99.04%	99.15%	99.23%	99.29%						
I + H1								98.22%	98.43%	98.87%	99.08%	99.04%	99.15%
3E1	0.95%	0.67%	0.54%	0.57%	0.50%	0.45%	0.41%	1.09%	0.95%	0.67%	0.54%	0.57%	0.50%
+ MI	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%
+ IS	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%
+ HS	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%
+OV	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%
+O	0.11%	0.10%	0.09%	0.09%	0.08%	0.08%	0.08%	0.08%	0.11%	0.10%	0.09%	0.09%	0.08%
TO\ FROM	**I+H7**	**I+H8**	**3E1**	**3E2**	**3E3**	**3E4**	**3E5**	**3E6**	**3E7**	**3E8**			
C													
M1													
I1													
H1													
2M1													
2I1													
2H1													
M+I1													
M+H1													

I + H1	99.23%	99.29%											
3E1	0.45%	0.41%	99.31%	99.38%	99.54%	99.62%	99.61%	99.65%	99.68%	99.71%			
+ MI	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%			
+ IS	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%			
+ HS	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%			
+OV	0.06%	0.05%	0.15%	0.13%	0.09%	0.07%	0.08%	0.07%	0.06%	0.05%			
+O	0.08%	0.08%	0.08%	0.11%	0.10%	0.09%	0.09%	0.08%	0.08%	0.08%			

TO\ FROM	**+MI**	**+IS**	**+HS+ICH**	**+OV**	**O**
C					
M1					
I1					
H1					
2M1					
2I1					
2H1					
M+I1					
M+H1					
I + H1					
3E1					
+ MI	100.00%				
+ IS		100.00%			
+ HS			100.00%		
+OV				100.00%	
+O					100.00%

Cx = cycle x since entering clean state, Mx = cycle x since entering MI state, Ix = cycle x since entering ischaemic stroke (IS) state, Hx = cycle x since entering haemmorhagic stroke/ICH (HS/ICH) state, 2Mx = cycle x since entering the 2 MI health state, 2Ix = cycle x since entering the 2 IS health state, 2Hx = cycle x since entering the 2 HS/ICH health state, M+Ix = cycle x since entering the MI + IS state, M+Hx = cycle x since entering the MI + HS/ICH state, I+Hx = cycle x since entering the HS/ICH + IS state, 3Ex = cycle x since entering the 3 event state, +MI = fatal MI, +IS = fatal IS, +HS = fatal HS/ICH, +OV = other cardiovascular death, +O = other non=cardiovascular death

Table 51: Transition probabilities from the observation period of the rivaroxaban arm

TO\ FROM	C1	C2	C3	C4	C5	C6	C7	C8	M1	M2	M3	M4	M5
C	98.53%	98.69%	99.05%	99.23%	99.07%	99.17%	99.24%	99.30%					
M1	0.84%	0.73%	0.52%	0.41%	0.48%	0.43%	0.38%	0.35%	98.53%	98.70%	99.06%	99.23%	99.07%
I1	0.12%	0.11%	0.08%	0.06%	0.06%	0.05%	0.05%	0.04%					
H1	0.04%	0.04%	0.04%	0.03%	0.02%	0.02%	0.02%	0.02%					
2M1	0.01%	0.01%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.84%	0.73%	0.52%	0.41%	0.48%
2I1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
2H1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
M+I1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.12%	0.11%	0.08%	0.06%	0.06%
M+H1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.04%	0.04%	0.04%	0.03%	0.02%
I + H1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
3E1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
+ MI	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%
+ IS	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%
+ HS	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%
+OV	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%
+O	0.07%	0.09%	0.08%	0.08%	0.08%	0.08%	0.08%	0.08%	0.07%	0.09%	0.08%	0.08%	0.08%
TO\ FROM	M6	M7	M8	I1	I2	I3	I4	I5	I6	I7	I8	H1	H2
C													
M1	99.17%	99.24%	99.30%										
I1				98.53%	98.70%	99.06%	99.23%	99.07%	99.17%	99.24%	99.30%		
H1												98.53%	98.70%
2M1	0.43%	0.38%	0.35%										
2I1				0.12%	0.11%	0.08%	0.06%	0.06%	0.05%	0.05%	0.04%		
2H1												0.04%	0.04%
M+I1	0.05%	0.05%	0.04%	0.84%	0.73%	0.52%	0.41%	0.48%	0.43%	0.38%	0.35%		
M+H1	0.02%	0.02%	0.02%									0.84%	0.73%
I + H1				0.04%	0.04%	0.04%	0.03%	0.02%	0.02%	0.02%	0.02%	0.12%	0.11%
3E1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
+ MI	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%
+ IS	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%
+ HS	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%
+OV	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%
+O	0.08%	0.08%	0.08%	0.07%	0.09%	0.08%	0.08%	0.08%	0.08%	0.08%	0.08%	0.07%	0.09%
TO\ FROM	H3	H4	H5	H6	H7	H8	2M1	2M2	2M3	2M4	2M5	2M6	2M7
C													

M1													
I1													
H1	99.10%	99.26%	99.11%	99.20%	99.27%	99.33%							
2M1							98.54%	98.70%	99.06%	99.23%	99.07%	99.17%	99.24%
2I1													
2H1	0.04%	0.03%	0.02%	0.02%	0.02%	0.02%							
M+I1													
M+H1	0.52%	0.41%	0.48%	0.43%	0.38%	0.35%							
I + H1	0.04%	0.03%	0.02%	0.02%	0.02%	0.02%							
3E1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1.00%	0.88%	0.63%	0.51%	0.57%	0.50%	0.45%
+ MI	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%
+ IS	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%
+ HS	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%
+OV	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%
+O	0.08%	0.08%	0.08%	0.08%	0.08%	0.08%	0.07%	0.09%	0.08%	0.08%	0.08%	0.08%	0.08%
TO\ FROM	**2M8**	**2I1**	**2I2**	**2I3**	**2I4**	**2I5**	**2I6**	**2I7**	**2I8**	**2H1**	**2H2**	**2H3**	**2H4**
C													
M1													
I1													
H1													
2M1	99.30%												
2I1		98.54%	98.70%	99.06%	99.23%	99.07%	99.17%	99.24%	99.30%				
2H1										98.54%	98.70%	99.06%	99.23%
M+I1													
M+H1													
I + H1													
3E1	0.41%	1.00%	0.88%	0.63%	0.51%	0.57%	0.50%	0.45%	0.41%	1.00%	0.88%	0.63%	0.51%
+ MI	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%
+ IS	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%
+ HS	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%
+OV	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%
+O	0.08%	0.07%	0.09%	0.08%	0.08%	0.08%	0.08%	0.08%	0.08%	0.07%	0.09%	0.08%	0.08%
TO\ FROM	**2H5**	**2H6**	**2H7**	**2H8**	**M+I1**	**M+I2**	**M+I3**	**M+I4**	**M+I5**	**M+I6**	**M+I7**	**M+I8**	**M+H1**
C													
M1													
I1													
H1													
2M1													

2I1													
2H1	99.07%	99.17%	99.24%	99.30%									
M+I1					98.54%	98.70%	99.06%	99.23%	99.07%	99.17%	99.24%	99.30%	
M+H1													98.54%
I + H1													
3E1	0.57%	0.50%	0.45%	0.41%	1.00%	0.88%	0.63%	0.51%	0.57%	0.50%	0.45%	0.41%	1.00%
+ MI	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%
+ IS	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%
+ HS	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%
+OV	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%
+O	0.08%	0.08%	0.08%	0.08%	0.07%	0.09%	0.08%	0.08%	0.08%	0.08%	0.08%	0.08%	0.07%
TO\ FROM	**M+H2**	**M+H3**	**M+H4**	**M+H5**	**M+H6**	**M+H7**	**M+H8**	**I+H1**	**I+H2**	**I+H3**	**I+H4**	**I+H5**	**I+H6**
C													
M1													
I1													
H1													
2M1													
2I1													
2H1													
M+I1													
M+H1	98.70%	99.06%	99.23%	99.07%	99.17%	99.24%	99.30%						
I + H1								98.54%	98.70%	99.06%	99.23%	99.07%	99.17%
3E1	0.88%	0.63%	0.51%	0.57%	0.50%	0.45%	0.41%	1.00%	0.88%	0.63%	0.51%	0.57%	0.50%
+ MI	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%
+ IS	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%
+ HS	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%
+OV	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%
+O	0.09%	0.08%	0.08%	0.08%	0.08%	0.08%	0.08%	0.07%	0.09%	0.08%	0.08%	0.08%	0.08%
TO\ FROM	**I+H7**	**I+H8**	**3E1**	**3E2**	**3E3**	**3E4**	**3E5**	**3E6**	**3E7**	**3E8**			
C													
M1													
I1													
H1													
2M1													
2I1													
2H1													
M+I1													
M+H1													

I + H1	99.24%	99.30%											
3E1	0.45%	0.41%	99.54%	99.58%	99.69%	99.74%	99.64%	99.67%	99.70%	99.71%			
+ MI	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%			
+ IS	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%			
+ HS	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%			
+OV	0.06%	0.05%	0.10%	0.08%	0.06%	0.05%	0.07%	0.06%	0.06%	0.05%			
+O	0.08%	0.08%	0.07%	0.09%	0.08%	0.08%	0.08%	0.08%	0.08%	0.08%			

TO\ FROM	**+MI**	**+IS**		**+OV**	**O**
C					
M1					
I1					
H1					
2M1					
2I1					
2H1					
M+I1					
M+H1					
I + H1					
3E1					
+ MI	100.00%				
+ IS		100.00%			
+ HS			100.00%		
+OV				100.00%	
+O					100.00%

Cx = cycle x since entering clean state, Mx = cycle x since entering MI state, Ix = cycle x since entering ischaemic stroke (IS) state, Hx = cycle x since entering haemmorhagic stroke (HS/ICH) state, 2Mx = cycle x since entering the 2 MI health state, 2Ix = cycle x since entering the 2 IS health state, 2Hx = cycle x since entering the 2 HS/ICH health state, M+Ix = cycle x since entering the MI + IS state, M+Hx = cycle x since entering the MI + HS/ICH state, I+Hx = cycle x since entering the HS/ICH + IS state, 3Ex = cycle x since entering the 3 event state, +MI = fatal MI, +IS = fatal IS, +HS = fatal HS/ICH, +OV = other cardiovascular death, +O = other non=cardiovascular death

Table 52 Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Age	62	-	
Continuation rate: after MI, rivaroxaban	94.69%	Beta, min = 71.02%, max = 100%	7.3.1
Continuation rate: after MI, comparator	69.27%	Beta, min = 51.95%, max = 86.59%	7.3.1
Continuation rate: after IS, rivaroxaban	54.29%	Beta, min = 40.72%, max = 67.86%	7.3.1
Continuation rate: after IS, comparator	51.52%	Beta, min = 38.64%, max = 64.40%	7.3.1
Continuation rate: after HS/ICH, rivaroxaban	0.00%	-	7.3.1
Continuation rate: after HS/ICH, comparator	0.00%	-	7.3.1
Increased risk due to age [12]			
MI	8.70%	Beta, min=6.53 %, max = 10.88%	7.3.2
IS	10.65%	Beta, min= 7.98 %, max = 13.31%	7.3.2
HS/ICH	10.73%	Beta, min= 8.05%, max = 13.41%	7.3.2
Other CV death	10.03%	Beta, min =7.52%, max = 12.53%	7.3.2
Non-CV death	10.28%	Beta, min =7.71%, max = 12.85 %	7.3.2
Fatal MI	-13.90%[13]	Beta, min = -10.42%, max = -17.37%	7.3.2
Fatal IS	-9.00%	Beta, min = -6.75%, max = -11.25%	7.3.2
Fatal HS/ICH	-9.00%	Beta, min =-6.75%, max = -11.25%	7.3.2
Increased (relative) risk of subsequent events			
After MI			7.3.2
MI (1st 6 months)	4.9	Beta, min=3.7, max = 6.1	7.3.2
MI (2nd 6 months)	2.1	Beta, min=1.6, max = 2.6	7.3.2
MI (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
IS (1st 6 months)	3.2	Beta, min=2.4, max = 4.0	7.3.2
IS (2nd 6 months)	1.8	Beta, min=1.4, max = 2.3	7.3.2
IS (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
HS/ICH (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
HS/ICH (2nd 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
HS/ICH (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal MI (1st 6 months)	4.9	Beta, min=3.7, max = 6.1	7.3.2
Fatal MI (2nd 6 months)	2.1	Beta, min=1.6, max = 2.6	7.3.2
Fatal MI (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal IS (1st 6 months)	3.2	Beta, min=2.4, max = 4.0	7.3.2
Fatal IS (2nd6 months)	1.8	Beta, min=1.4, max = 2.3	7.3.2
Fatal IS (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2

[12] The increase risks due to age are estimated by means of calibration and these values are implemented into each model cycle within the extrapolation period to account for the increasing risk of suffering fatal and non-fatal events within the ageing population. Using these values the model is able to predict the average annual age specific risk of suffering fatal and non-fatal events extracted from literature (Smolina et al 2012 and Hippisley-Cox et al 2004)

[13] Negative values are caused by the increasing competing risk of OCD and NCD, reducing the risk of fatal MI, IS and HS

Fatal HS/ICH (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Fatal HS/ICH (2nd 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Fatal HS/ICH (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Other CV Death (1st 6 months)	3.0	Beta, min=2.3, max = 3.8	7.3.2
Other CV Death (2nd 6 months)	1.6	Beta, min=1.2, max = 2.0	7.3.2
Other CV Death (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
After IS			7.3.2
MI (1st 6 months)	4.9	Beta, min=3.7, max = 6.1	7.3.2
MI (2nd 6 months)	2.1	Beta, min=1.6, max = 2.6	7.3.2
MI (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
IS (1st 6 months)	3.2	Beta, min=2.4, max = 4.0	7.3.2
IS (2nd 6 months)	1.8	Beta, min=1.4, max = 2.3	7.3.2
IS (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
HS/ICH (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
HS/ICH (2nd 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
HS/ICH (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal MI (1st 6 months)	4.9	Beta, min=3.7, max = 6.1	7.3.2
Fatal MI (2nd 6 months)	2.1	Beta, min=1.6, max = 2.6	7.3.2
Fatal MI (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal IS (1st 6 months)	3.2	Beta, min=2.4, max = 4.0	7.3.2
Fatal IS (2nd6 months)	1.8	Beta, min=1.4, max = 2.3	7.3.2
Fatal IS (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal HS/ICH (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	
Fatal HS/ICH (2nd 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Fatal HS/ICH (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Other CV Death (1st 6 months)	3.0	Beta, min=2.3, max = 3.8	7.3.2
Other CV Death (2nd 6 months)	1.6	Beta, min=1.2, max = 2.0	7.3.2
Other CV Death (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
After HS/ICH			7.3.2
MI (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
MI (2nd 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
MI (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
IS (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
IS (2nd 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
IS (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
HS/ICH (1st 6 months)	4.9	Beta, min=3.7, max = 6.1	7.3.2
HS/ICH (2nd 6 months)	2.1	Beta, min=1.6, max = 2.6	7.3.2
HS/ICH (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal MI (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Fatal MI (2nd 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Fatal MI (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal IS (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Fatal IS (2nd6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Fatal IS (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal HS/ICH (1st 6 months)	4.9	Beta, min=3.7, max = 6.1	7.3.2

Fatal HS/ICH (2nd 6 months)	2.1	Beta, min=1.6, max = 2.6	7.3.2
Fatal HS/ICH (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
Other CV Death (1st 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Other CV Death (2nd 6 months)	1.0	Beta, min=0.8, max = 1.3	7.3.2
Other CV Death (later)	1.5	Beta, min=1.1, max = 1.9	7.3.2
After 3 events			
MI			
IS	1.5	Beta, min=1.1, max = 1.9	7.3.2
HS			
Fatal MI	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal IS	1.5	Beta, min=1.1, max = 1.9	7.3.2
Fatal HS/ICH	1.5	Beta, min=1.1, max = 1.9	7.3.2
Other CV Death	1.5	Beta, min=1.1, max = 1.9	7.3.2
Case Fatality			
MI	13.19%	Beta, min = 9.89%, max =16.49%	7.3.2
HS/ICH	11.65%	Beta, min =8.7%, max = 14.56%	7.3.2
IS	11.65%	Beta, min = 8.7%, max = 14.56%	7.3.2
Decrease in risk of events over time (proportion of events occurring in comparison to first 6 months)			
MI 1st 6 months	100%	-	7.3.2
MI 2nd 6 months	41.72%	Beta, min = 31.29%, max =52.15%	7.3.2
MI later	30.45%	Beta, min = 22.84%, max =38.06%	7.3.2
IS 1st 6 months	100%	-	7.3.2
IS 2nd 6 months	55.87%	Beta, min = 41.90%, max =69.84%	7.3.2
IS later	47.36%	Beta, min = 35.52%, max =59.20%	7.3.2
Other CV death 1st 6 months	100%	-	7.3.2
Other CV death 2nd 6 months	33.00%	Beta, min = 24.75%, max =41.25%	7.3.2
Other CV death later	33.00%	Beta, min = 24.75%, max =41.25%	7.3.2
Efficacy following discontinuation of clopidogrel (to estimate transition probabilities for ASA monotherapy)			
Relative efficacy	80%	Beta, min = 60%, max = 100%	7.2.5
Weibull parameters for the comparator arm (to interpolate ATLAS 2 trial data in the observation period)			
MI (mu)	12.543180	Normal, min =12.263131, max = 12.823229	7.3.1
MI (lambda)	-1.017409	Normal, min = -1.047144, max = -0.987674	7.3.1
IS (mu)	16.873670	Normal, min =16.131453, max = 17.615887	7.3.1
IS (lambda)	-0.931947	Normal, min = -0.980898, max =-0.0882995	7.3.1
HS/ICH (mu)	13.139670	Normal, min = 12.302669, max = 13.976671	7.3.1
HS/ICH (lambda)	-0.390599	Normal, min =-0.472618, max =-0.308580	7.3.1
OCD (mu)	15.383190	Normal, min = 14.983563, max = 15.782817	7.3.1
OCD (lambda)	-1.083073	Normal, min = -1.116170, max = -1.049976	7.3.1
NCD (mu)	10.780540	Normal, min =10.372252, max = 11.188828	7.3.1

NCD (lambda)	-0.208511	Normal, min = -0.264369, max = -0.152654	7.3.1
Weibull parameters for the rivaroxaban arm (to interpolate ATLAS 2 trial data in the observation period)			
MI (mu)	12.169226	Normal, min =11.889176, max = 12.449275	7.3.1
MI (lambda)	-1.017409	Normal, min = -1.047144, max = -0.987674	7.3.1
IS (mu)	17.235764	Normal, min =16.493547, max =17.977981	7.3.1
IS (lambda)	-0.931947	Normal, min = -0.980898, max =-0.0882995	7.3.1
HS/ICH (mu)	14.171658	Normal, min =13.334657, max =15.008659	7.3.1
HS/ICH (lambda)	-0.390599	Normal, min =-0.472618, max =-0.308580	7.3.1
OCD (mu)	14.035403	Normal, min =13.635776, max =14.435029	7.3.1
OCD (lambda)	-1.083073	Normal, min = -1.116170, max = -1.049976	7.3.1
NCD (mu)	10.580387	Normal, min =10.172099, max =10.988675	7.3.1
NCD (lambda)	-0.208511	Normal, min = -0.264369, max = -0.152654	7.3.1
CI, confidence interval; CABG, coronary arterial bypass graft; PCI. Percutaneous coronary intervention; MI, myocardial infarction; CV, cardiovascular; IS, ischaemic stroke; HS/ICH, hemorrhagic stroke/intracranial hemorrhage			

7.3.7 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.

Life years gained, QALYs and costs are extrapolated beyond the trial follow-up period. No treatment effects are assumed beyond the length of the trial. After the treatment length applied in the model (one year for the comparator arm and two years for rivaroxaban) all patients are assumed to take ASA monotherapy. As such, the transition probabilities in the intervention arm are the same as in the comparator arm during the extrapolation period. Differences in costs and effects may however be accrued during the extrapolation period because patients will be distributed across health states differently in the intervention and comparator arms at the end of the observation period (section 7.3.6).

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

Structural Assumptions

1. Tunnel states are used to model the first six months, second six months and later periods after an event. This allows variable transitions, costs and – where relevant – utilities, dependent on the time since the event, allowing more accurate reflection of clinical reality.

2. In the extrapolation period 6 monthly cycles are applied which was supported by the clinical expert (KR).

3. The model does not differentiate event types once patients suffer 3 events or more. The clinical expert (KR) suggested the distinction should be made, however the low number of patients who suffer 3 events or more in the trial does not substantiate disentanglement of the ATLAS 2 trial data.

4. Discontinuation is only applied to the 'free of secondary events' health state, i.e. in any cycle the total number of patients experiencing discontinuation of treatment due to MI, IS or HS/ICH is subtracted from the total number of patients in the free of secondary events health state. This approach was supported by the clinical expert (KR).

5. The interruption bleeding events may have on antithrombotic or antiplatelet therapy is not modelled within the discontinuation as this only has short–term impact of 5-7 days after which the decision to re-initiate treatment is solely based on the physician's decision.

6. Bleeding events and revascularisations are considered transient health states. A cost and utility is applied but no long term impact of these events is considered in the model (benefits in terms of reduced event risks following a revascularisation procedure are already captured in the clinical trial data). This reflects evidence in the literature sourced in the systematic review of economic models, which suggests short-term impacts of bleeding events. (Greenhalgh 2009, (53;54;65;80;96))

7. Intracranial haemorrhages and fatal bleeds are more severe and are expected to have a larger impact than all severities of TIMI bleeds. Therefore these are considered in other model health states. Intracranial haemorrhages are considered in the haemorrhagic stroke state, and fatal bleeds are considered in the other cardiovascular death state and also supported by the clinical trial. The bleeding states considered in the model are TIMI major bleeds (excluding ICH and fatal bleeds), TIMI minor bleeds, and TIMI bleeds requiring medical attention.

8. Patients who suffer a non-fatal and fatal event in any given cycle of the model will be considered as a fatality in that cycle.

9. Transition probabilities for the extrapolation period are based on the last cycle from the observation period of the comparator arm to allow for estimation of transition probabilities when all patients are on ASA monotherapy, corrections for the difference in cycle length (because the cycle length in the observation period is 12 weeks and the cycle length in the extrapolation period is 6 months) and RRR associated with lifetime ASA monotherapy are applied.

10. The extrapolation period factors in increased risks of events due to ageing, the increased risk of case fatalities due to ageing, relative risks of suffering subsequent events and decreasing number of events observed over time in the ATLAS 2 trial.

11. The initial case fatalities estimate for MI is taken from the trial data and we use Hippisley-Cox et al (2004)(113) to derive initial case fatality estimates for stroke.

12. Data from Smolina et al (2012)(111;112) and Hippisley-Cox et al (2004) (113) are used to estimate the increased risk of suffering a non-fatal MI and non-fatal stroke respectively.

13. Data from Smolina et al (2012) (111;112) and Hippisley-Cox et al (2004) (113) are used to estimate the increased risk of suffering a fatal MI and fatal stroke respectively.

14. In the absence of suitable data to differentiate between the increased risk due to age of suffering a non-fatal stroke and the increased risk of suffering a fatal stroke, we apply the relative difference between the increased annual risk of a non-fatal MI and fatal MI to estimate the increased risk of suffering a fatal stroke relative to the risk of suffering a non-fatal stroke.

Health Related Quality of Life Assumptions

1. Estimates of utility at baseline and after cardiovascular events are taken from the literature. The values used are similar to those obtained during the trial. Using values from the literature results in more robust estimates as the trial was not designed nor powered to make conclusions based on quality of life. Therefore, the base case utilises published values collected in large samples of ACS patients. Where possible, UK specific estimates have been used. Utility estimates derived from the ATLAS 2 trial are implemented in a scenario analysis.

2. No utility is assumed following fatal events.

3. Utility values are assumed to be the same in both treatment arms following any particular event. There is no evidence to suggest that treatment choice impacts the utility of a patient following a cardiovascular event.

4. For multiple events a multiplicative approach to estimating utility values is taken. That is, if a patient experiences 2 MIs, the estimated utility value is UMI x UMI. This allows for worsening health related quality of life following multiple events. (Bach 2011(120))

5. Tunnel states are used to allow health related quality of life to improve over time since the event. (Beck 2001(121))

6. The utility value for the "no event" health state remains constant over time in the model.

Cost Assumptions

1. Costs for the three months immediately following an event are based on NHS reference costs. Therefore, costs reflect actual UK practice as accurately as possible as the reference costs are based on actual hospital activity throughout England and Wales.

2. Where multiple HRG definitions exist that could all apply to a particular event in the model, a weighted average of these HRGs has been applied. HRG codes used throughout the model have been validated by a clinician (KR).

3. Follow-up costs are estimated in addition to the costs provided in the reference costs. This is because the NHS reference costs present only the in-hospital costs, yet costs will be incurred beyond this period, especially in the case of strokes. Follow-up costs are estimated based on the published literature.

4. The number of rehabilitation days applied to the MI, IS and HS/ICH event states is 5, 7 and 28, respectively. The number of rehabilitation days attached to each event has been validated by a clinical expert (KR).

5. For multiple events occurring within the same cycle or as separate admissions, the costs of each individual event are summed to provide estimates in the cycles immediately after the event and those representing the period of follow-on care (beyond 3 months since the event).

6. For patients who suffer a non-fatal and fatal event in any given cycle the cost of the fatal event is applied.

Bleeding Assumptions

1. The impact of major bleeding in terms of health related quality of life is assumed to last 30 days. This is in line with the ATLAS 2 trial and the literature identified during the systematic review(80). Furthermore, KR agreed with this assumption.

2. Minor bleeds and bleeds requiring medical attention are less severe than TIMI major bleeds. The impact of these events on health related quality of life is assumed to last for 2 days(73). The assumption of a 2 day impact has been agreed with KR.

Revascularisation Assumptions

1. The impact of PCI / PTCA revascularisation events in terms of health related quality of life is assumed to last 30 days. This is in line with the ATLAS 2 trial and the literature identified during the systematic review(80). Furthermore, KR agreed with this assumption.

2. The impact of CABG on health related quality of life is assumed to last for 12 weeks following discussions with KR.

7.4 Measurement and valuation of health effects

Patient experience

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

Acute coronary syndrome (ACS) is a medical emergency and requires immediate hospital admission. ACS refers to a range of acute myocardial ischaemic states, which include:

- ST-elevation ACS with the majority of patients developing an STEMI (ST-elevation MI)
- Non-ST-elevation ACS, further divided into:
    - Unstable angina
    - NSTEMI (Non-ST-elevation MI)

Symptoms, treatment (e.g. invasive procedures such as PCI/ CABG surgery) and follow-up of ACS can affect patient's quality of life (QoL).

Common symptoms of ACS include:

- chest pain and pain in other parts of the body including the arms, jaw, neck, back and abdomen
- shortness of breath
- nausea and vomiting
- palpitations
- sweating
- dizziness and light-headedness

Accompanying these symptoms, the patient is likely to feel anxious, not only during the acute event, but long term, due to concern about their cardiovascular health.

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

The biggest impact on quality of life is likely to be during the ACS event and the hospitalisation period associated with that. Once at home a patient's quality of life should improve and they will be able to resume most of their usual daily activities over the weeks following hospital discharge.

ACS patients are at a particularly high risk of secondary cardiovascular events, including MIs and strokes. This will invariably give rise to anxiety about cardiovascular health. If such events are experienced patients will suffer further health related quality of life decrements. The severity of events will vary on an individual basis, however it is generally accepted that a stroke has the potential for a greater health related quality of life decrement associated with it than an MI.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (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.

Health related quality of life data was collected in the ATLAS 2 trial. EQ-5D data were collected from sites in eight countries (Australia, Canada, Spain, Netherlands, Korea, the United Kingdom, Sweden, and Japan). The descriptive part of the questionnaire was used to generate utility scores (0 to 1) by applying weights derived from the general UK population. The visual analog scale followed the descriptive questions. Health related quality of life data were collected at baseline, 4 weeks, 24 weeks, 48 weeks, 72 weeks and 96 weeks. Data were also collected in early study withdrawal patients. The table below details the average utility values of patients after each event. Utility data following revascularization was not specifically collected. Further, due to the low numbers of IS and HS/ICH events in the trial, the average utility after a stroke is estimated, which incorporates both IS and HS/ICH. The utility estimates for stroke and TIMI major bleed are based on fewer than 35 observations. The utility values reported in the trial do not differentiate between the tunnel states defined in the model hence the improvement following an event is not captured instead an average before and after the event is taken. The low numbers of observations for some of the estimates from the trial also mean the data are not robust enough for use in the base case analyses.

Table 53 Utility values collected from the ATLAS 2 trial

Event	Value	95% Confidence Interval
No Event	0.88	0.51 to 1.00
MI	0.78	0.25 to 1.00
Stroke	0.67	0.00 to 1.00
TIMI Major Bleed (excluding ICH)	0.77	0.19 to 1.00
TIMI Minor Bleed	0.84	0.31 to 1.00
TIMI Bleed requiring medical attention	0.87	0.47 to 1.00

The NICE 'Guide to the methods of technology appraisal' states that health-related quality of life outcomes 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. The quality of life data collected in ATLAS 2 was elicited from ACS patients using EQ-5D descriptive questionnaire and visual analogue scale. Therefore, the utility values derived from the trial are consistent with the NICE reference case. However, because the ATLAS 2 trial was not designed to collect robust quality of life data, the utility estimates collected from the trial are only used in a model scenario analysis. The base case uses utilities from ACS populations identified during a systematic review and expert discussion.

Mapping

7.4.4 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.

No mapping techniques were used.

HRQL studies

7.4.5 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 10.12, appendix 12.

A systematic literature review to identify relevant cost-effectiveness studies and studies reporting utility values and estimates of resource use and costs from the published literature was performed to to inform sections 7.2, 7.4.9 and 7.5.6. Please see section 0 and Appendix 10 for details of the methodology. Economic evaluations and cost/resource use studies identified in their respective reviews were also screened to identify any relevant utility data.

For the utility review, publications were to be included if they met the eligibility criteria as outlined in Table 54.

Table 54: Eligibility criteria used in the utility systematic review

	Utility review	Rationale/comments
Inclusion criteria	**Population** Adults initially hospitalized with ACS (unstable angina, STEMI, or NSTEMI) who are managed for secondary prevention of their ACS event	Consistent with scope
	Outcomes Utility or preference weights and disutility associated with adverse events	
	Study design • Studies reporting utility estimates (general or disease specific), preference weights (including EQ-5D, SF-36, HUI, time trade-off, etc.) • Utility mapping studies • Cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses	Economic evaluations were included as they can provide utility data, which were adapted from other studies for use as model inputs
	Country United States Canada United Kingdom Germany France Italy Spain	
	Language restrictions English language	
	Publication timeframe restrictions 2000-2014	
Exclusion criteria	**Population** • Patients with stable angina, or other CV disease that is not ACS • Primary prevention of ACS (mainly relevant for studies with aspirin) • Children • Mixed populations of stable and unstable angina, which do not present data for unstable angina separately	
	Outcomes Utility data not presented, QoL measures from which utilities cannot be derived	
	Study design • Any non-primary sources of utility weights • Methodological studies • Studies focused on short-term in-hospital treatment of ACS	

	Utility review	Rationale/comments
	Country Articles not concerned with any of the countries of interest (the US, Canada, France, Germany, Italy, Spain, the UK)	
	Language restrictions Non-English language	
	Publication timeframe restrictions Studies published prior to 2000	

7.4.6 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.

Thirty-seven articles were identified as potential sources of utility data for the model. The search was not limited to UK-based sources although the model will use estimates based on the UK population as far as possible. Thirteen of the articles identified are quality of life studies, twenty-one are economic models and three were identified as cost studies but also included relevant utility data. In the table below key details are presented.

Table 55 :Overview of quality of life studies identified in the literature review

Author	Indication	Country	Population	Recruitment	Sample Size	Response Rate	Health States	Measurement	Appropriate for CE analysis?	Utility values (95% CI)
Bach et al, 2011(120)	MI / Stroke / General Population	Germany	Patient data were collected in the DETECT (Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment) study including 55,000 patients. In this paper, 3,109 patients (33.3% female) with myocardial infarction (MI), stroke or both were compared to patients with a wide range of other diagnoses.	Cross-sectional point prevalence study of unselected consecutive patients with patient sampling performed on a target half day. Patients were informed by posters and leaflets about the possibility of study participation.	59,403	93.50%	No MI or Stroke / MI / Stroke / MI and Stroke (EQ-5D Health States)	EQ-VAS, EQ-5D	No - time since event is not recorded	History of MI: 0.66 History of stroke: 0.62 History of MI& stroke: 0.57 No history of MI or stroke: 0.74
Beck et al, 2001(121)	Acute MI	Canada	The study population included patients enrolled in a prospective cohort study of quality of life after AMI. Patients recruited for this study included all patients with a confirmed diagnosis of AMI (Q or non-Q wave) and treated in an acute care facility (coronary care unit) at 10 Quebec hospitals between December 28, 1996,	All patients with a confirmed diagnosis of AMI (Q or non-Q wave) and treated in an acute care facility (coronary care unit) and 10 Quebec hospitals between Dec 28th 1996 and Nov 1st 1998	587	Baseline Data: 97% PCS and MCS, 94% EQVAS, 6 months: 82%, 1 year: 84%	after MI	SF-36 PCS and MSC, EQ-VAS	Yes – if UK data not available	MI: 0.7 (0.68, 0.72) 6 months post MI: 0.71 (0.69, 0.72) 1 year post MI: 0.73 (0.71, 0.74)

			and November 1, 1998.							
Ellis et al, 2005(122)	ACS	USA	Patients prospectively chronicled in the Acute Coronary Syndrome/Myocardial Infarction Patient Registry maintained at the University of Michigan. Patients eligible for this registry include those admitted to and discharged from the University of Michigan Hospital for treatment related to acute coronary syndrome, who were 18 years of age or older at the time of presentation. Registry patients obtained from July 1999 to November 2002 and alive at the time of this survey (December 2002 to mid-January 2003) constituted the study sample.	Registry patients (Acute Coronary Syndrome / Myocardial Infarction Patient Registry) obtained between July 1999 and November 2002	1,217	40.30%	EQ-5D classified states in patients after ACS	EQ-VAS, EQ-5D index	No – patients most likely CHD patients at time of data collection	ACS EQ5D VAS: 0.726 (sd 0.207) EQ5D Index: 0.81 (sd 0.18)
Kim et al, 2005(123)	ACS	England and Scotland	Patients with ACS. Patients were eligible for the study if they experienced chest pain at rest and had documented electrocardiographic or previous	As in RITA 3 trial - patients from 45 centres in England and Scotland who met inclusion criteria were recruited	1,810	93-99%	IS and CS for all questionnaire states	EQ-5D, EQ-VAS, SF-36, SAQ	Yes	Baseline interventional strategy (IS): 0.671 Baseline conservative strategy (CS): 0.673 4 months IS: 0.748 4 months CS: 0.714 12 months IS: 0.752

			arteriographic evidence of coronary artery disease.							12 months CS: 0.736
Lacey and Walters, 2003(124)	MI	England	A consecutive sample of 273 people who had recently had a diagnosis of AMI. Patients with a first or subsequent AMI were included, with an upper age limit of 80 years.	Consecutive recruitment of 273 people with recent AMI from 2 hospitals in a Northern English city	273	84%	EQ-5D single index and SF36 domains (physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social functioning, emotional role functioning, mental health)	SF-36 / EQ-5D single index	Yes	6 weeks after MI: 0.683 (sd 0.233) 1 year after MI: 0.718 (sd 0.243)
NICE, 2012(43)	ACS	UK	PLATO - patients in the model had ACS (STEMI, NSTEMI or unstable angina) and included patients whose condition was managed medically or with PCI or CABG	Patients from the PLATO study enrolled prior to January 18, 2008, who were eligible for a 12 month follow-up (referred to as the 12-month cohort)	6,983	Not reported	The 1-year decision tree contained four mutually exclusive health states: non-fatal myocardial infarction, non-fatal stroke, death from any cause, and no further event. The Markov model included six states: non-fatal myocardial infarction, post-myocardial infarction, non-fatal stroke, post-stroke, death, and no further event. Non-fatal myocardial infarction and non-fatal stroke were tunnel states, which allowed for a worse prognosis the first year after a non-fatal event compared with second and subsequent years. After the first year following a non-fatal event, patients proceeded to one of four mutually exclusive	EQ-5D	Yes	MI: 0.76 (0.7, 0.9) Subsequent MI: 0.88 (0.7, 0.9) No event: 1.00 Revascularisation: 0.8 Post-revascularisation: 0.88 2nd revascularisation: 0.8 Post-2nd revascularisation: 0.88 Death: 0.00 Utility weights by age: 45-54: 0.85 55-64: 0.79 65-74: 0.78 75+: 0.73

							health states: post-myocardial infarction, post-stroke, death or no further event			
Pilote et al, 2002(125)	MI	Canada	The study population consisted of patients who were treated in an acute care facility (coronary care unit) for AMI diagnosed according to the World Health Organization criteria. Patients had to be admitted through the emergency department. Patients were excluded if they had been transferred from another hospital for treatment of their index AMI or from another floor in the hospital. Any patient able to read and understand French or English was eligible for the study if he or she had sustained a Q- or non–Q-wave AMI and had survived up to 24 hours after hospital admission. A patient was excluded if he or she was physically incapable of responding to a	Patients treated in an acute care facility for AMI were recruited	587	Not reported	scores after angiography or no angiography	EQ-VAS, SF-36, Torrance feeling thermometer, beck depression inventory questionnaire	Yes – if UK data not available	Baseline MI: With angiography: 0.71 Without angiography: 0.69 6 months after MI: With angiography: 0.72 Without angiography: 0.70 1 year after MI: With angiography: 0.74 Without angiography: 0.72

			questionnaire or if unable to give informed consent.							
Schweikert et al, 2006(126)	MI	Germany	For the study, 114 consecutive patients with ACS starting inpatient rehabilitation after an acute cardiac event were recruited at admission to the Schwabenlandklinik, a rehabilitation hospital in Southern Germany. Exclusion criteria were age above 65 years, insufficient command of the German language, and an acute cardiac event occurring more than three months before admission to the rehabilitation hospital. 106 patients completed the questionnaire (51% myocardial infarction, 42% coronary artery bypass grafting, 7% angina)	consecutive patients starting inpatient rehabilitation after an acute cardiac event	114	93%	EQ-5D findings presented for MI and CABG patients	EQ-VAS, EQ-5D index, SF-36, MacNew questionnaire	Yes – if UK data not available	MI baseline: EQVAS: 0.703 EQ5D index: 0.778 CABG at admission: EQVAS: 0.571 EQ5D index: 0.645
Schweikert et al, 2009(127)	MI	Germany	Patients for this study were drawn from the MONICA/KORA (Cooperative Health research in the region of Augsburg/Monitorin	All patients from MONICA/KORA registries who suffered an MI between 1985 and 2004	4,394	67%	MI	EQ-VAS, EQ-5D index	No - measurements were taken on average more than 7 years after MI event and are based on a German population	MI (median 7.4 years since event): EQ-VAS: 0.657 EQ5D index: 0.865

			g trends and determinants of cardiovascular disease) Myocardial Infarction Registry. This is a population-based registry that comprises all hospitalised cases of acute non-fatal MI at least surviving 24 h and coronary deaths occurring in inhabitants of a defined study region—the city of Augsburg and the two surrounding counties—who are aged between 25 and 74 years.							
Shah et al, 2009(128)	STEMI	USA	Consecutive patients aged 85 years presenting with STEMI and admitted to the coronary care unit of the Washington Hospital Center from October 2002 to September 2007 were included.	Consecutive patients aged >84 years presenting with STEMI and admitted to the coronary care unit of the Washington Hospital Centre from October 2002 to September 2007	1,847	1.70%	STEMI	EQ-5D, VAS	No - STEMIs are not individually defined	STEMI: EQVAS: 0.705 (+/- 0.045) EQ5D index: 0.78 (+/- 0.04)
Stafford et al, 2012(129)	MI	England	English population with cardiovascular disease and predisposing conditions based on the Health Survey for England (HSE). The HSE is an annual cross-sectional	Health Survey for England 2003 and 2006	26,104	Not reported	BMI status, hypertension, diabetes, angina, heart attack, stroke (all vs no predisposing condition)	EQ-5D	Yes	Disutility MI: -0.139 Disutility stroke: -0.160

			survey of a new random sample, representative of the non-institutionalised population in England. The HSE focuses on different conditions and/or population subgroups each year, in addition to including a core set of questions. In HSE 2003 and 2006, the EQ-5D was included along with measures of cardiovascular disease and cardiovascular risk factors. The HSE uses a multi-stage sampling procedure, stratified by proportion of households headed by someone in a non-manual occupation, and each address has an equal chance of selection. All adults within each household (to a maximum of 10, randomly selected if more) are eligible.							
Bagust A, 2011(49)	ACS (STEMI, NSTEMI and UA)	52 countries (not presented)	HECON Substudy (ACS Patients): Of the total number of 18,624 patients, 15,212 (82%) had a	Not reported	Not reported	Not reported	No Event Non-fatal MI, Post MI Non-fatal stroke Post stroke	EQ-5D questionnaire	Each health state has an associated cost, and an average utility to enable an estimate of costs	ACS (SE): 0.842 (0.002) Non-Fatal MI: 0.779 (0.010) Post MI: 0.821

			utility score calculated at discharge from the index hospitalisation (visit 1). At visit 4 (6 months) and visit 6 (12 months) the percentage of patients in the full cohort with a utility score was 80% and 79% respectively. Of the 10,686 patients who were eligible for a 12 month follow-up referred to as the 12-month cohort), 8840 (83%) had a utility score calculated at visit 1. The corresponding percentage of patients in the 12-month cohort with utility score at visit 4 and visit 6 was 81% and 80% respectively				Dead		and QALYs associated with each treatment option	(0.038) Non-fatal Stroke: 0.703 (0.010) Post Stroke: 0.703 (0.038) One year decision tree Utility (SE) No event (ticagrelor): 0.840 (0.003) 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)
Berg J et al, 2008(50)	PCI	Sweden, France, and Germany	PCI-CURE: 2658 (NSTEMI ACS undergoing PCI) CREDO: 2116 (symptomatic CAD with evidence of ischaemia undergoing elective PCI or deemed to be of high likelihood of undergoing PCI) PCI-CLARITY: 1863 (STEMI ACS undergoing PCI) Swedish Register: 47404 (data collected from patients with inpatient admissions of PCI, and subsequent admissions of MI and stroke between 1995 and 2003, cause of death register used to collect CV and other deaths)	Age adjusted utilities were taken from a cross-sectional Swedish Study (Burstroom et al, 2001, Health Policy). Event based disutilities were taken from a cross-sectional survey of hospitalised patients at coronary-care units in Sweden.	Not reported	Not reported	Death Myocardial Infarction Stroke Alive Health States divided by time.	Not reported	Yes – if UK data are not available	Disutility MI: 0.1156 Disutility IS: 0.2743 Disutility revascularisation: 0.03 Age specific utilities: 50-59: 0.82 60-69: 0.76 70-79: 0.71 80-84: 0.61
Berg J et al, 2007(51)	STEMI	Sweden, France, and Germany	CLARITY: 3491 (STEMI or left-bundle branch block scheduled to undergo angiography - short term RR data) COMMIT: 45852 (STEMI, left-bundle branch block, or MI with ST depression-short term RR data) CURE: 12562	Age adjusted utilities were taken from a cross-sectional Swedish Study (Burstroom et al, 2001, Health Policy). Event based disutilities were taken from a cross-sectional survey of	Not reported	Not reported	Death Myocardial Infarction Stroke Alive Health States divided by time.	Not reported	Yes – if UK data are not available	Disutility MI: 0.1157 Disutility IS: 0.2744 Disutility revascularisation: 0.03 Age specific utilities: 50-59: 0.82 60-69: 0.76 70-79: 0.71 80-84: 0.61

			(NSTEMI - longer term RR data) Swedish Register: 184995(MI as main diagnosis and MI or stroke subsequentsubmissions - baseline risks of events)	hospitalised patients at coronary-care units in Sweden.						
Coleman 2013(81)	ACS	US	Cohort of ACS patients, aged 65 years: patients with ACS (e.g., unstable angina, noneST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction) managed medically, with percutaneous coronary intervention or coronary artery bypass grafting	Model assumed a cohort of 65-year-old patients with acute coronary syndrome	NR	Poor response on clopidogrel	Patients not experiencing recurrent MI, stroke, or death were placed in the "no event" health state. Those patients experiencing recurrent MI or a stroke during the decision tree were entered in the Markov model in the "post-MI" and "poststroke" health state, respectively. The "nonfatal MI" and "nonfatal stroke" states were reserved for patients who had experienced an event 1 year after the index ACS event. These served as "tunnel states	Utility values were derived from the PLATO health economics and quality-of-life substudy	Yes	Decision tree utilities: Nonfatal MI 0.77 Nonfatal stroke 0.70 No event 0.84 Bleeding -0.02 Death 0.22 Markov model utilities: Nonfatal MI 0.78 Nonfatal stroke 0.7 No event 0.84 After MI 0.82 After stroke 0.70 Death 0
Charland 2011(56)	ACS	US	NR	TRITON-TIMI 38 study	NR	NR	Post ACS utility reported	NR	No	Baseline post-ACS utility: 0.83
Greenhalgh et al(65)	2009	UK / US	UK population norm utility data was corrected for ACS and subsequent events based on a paper reporting utility values for a US population with chronic medical	Not reported	Not reported	Not reported	Entry Cardiovascular/bleed death Bleed endpoint event non-fatal MI Non-fatal stroke Death	SAQ-AF SAQ-PL EQ-5D Utility EQ-5D VAS Dyspnea	The analysis described in the MS uses a Markov model structure with cohorts of patients modelled to experience events over the course of the	Utility decrements compared to the general population: ACS: 0.0409 (+/- 0.0002) Stroke: 0.0524 (+/- 0.0001) Major bleed: 25% decrement to

			conditions						TRITON-TIMI 38 study period with long-term mortality based on adjustment of population life tables to reflect prognostic implications of the events modelled over the short-term. The model also permits in-hospital costs to accumulate after the end of the trial follow-up period. The model can be separated into two distinct phases: (i) the trial based period of 15 months and (ii) extrapolation beyond the trial to a lifetime horizon (40 years).	population norm for 14 days
Karnon J et al, 2006(70)	NSTEMI ACS patients	UK	Utility values were based on a number of published sources. A meta analysis was used to estimate utility associated with stroke.	Not reported	Not reported	Not reported	ACS event-free MI year 1 MI post-year 1 Stroke year 1 Stroke post-year 1 Death	Not reported	Yes	ACS (year 1): 0.80 (0.72, 0.88) ACS (post year 1): 0.93 (0.89, 0.97) MI (year 1): 0.80 (0.72, 0.88) MI (post year 1): 0.93 (0.89, 0.97) Stroke (year 1): 0.69 (0.60, 0.78)
Karnon J et al, 2010(71)	STEMI ACS	UK	A meta analysis is used for stroke utilities. The Harvard utilities database was used for other health states. No	Not reported	Not reported	Not reported	STEMI event New MI Post-New MI Stroke Death	Not reported	Yes	ACS (year 1): 0.80 (0.72, 0.88) ACS (post year 1): 0.93 (0.89, 0.97) MI (year 1): 0.80 (0.72, 0.88)

			further information is provided							MI (post year 1): 0.93 (0.89, 0.97) Independent stroke: 0.78(0.68, 0.87) Dependent stroke: 0.52 (0.44, 0.60) Combined stroke: 0.69 (0.60, 0.77)
Kazi 2014(73)	ACS	US	Cohort of 100 000 patients aged 65 years with ACS who had PCI with 1 or more drug-eluting stents	TRITON-TIMI 38 study and PLATO trial	100,000	NR	MI, cardiovascular death, and intracranial bleed	NR	Yes	Bleeding Intracranial: 0.61 (0.4–0.8) Extracranial: 0.2 for 14 d (7–21 d) Minor: 0.2 for 2 d (0–7 d) CABG-related bleed: 0.5 for 7 d (3–14 d) Revascularization CABG: 0.5 for 14 d (7–21 d) PCI: 0.5 for 7 d (3–14 d) Ticagrelor-related dyspnea Mild: 0.071 (0.018–0.124) Moderate: 0.102 (0.043–0.161) Severe: 0.338 (0.150–0.526) Syncope or bradyarrhythmia: 0.24 for 3 d (1–7 d) Nonfatal MI: 0.13 (0.05-0.25) for 1 month then 0.12 (0.07-0.16)
Levin 2013(130)	ACS	862 centers in 43 countries	Patients hospitalized with an ACS, with or without ST-segment elevation	Patients enrolled in PLATO trial from October 2006 through July	Ticagrelor: 7631 Clopidogrel: 7581	NR	NR	EQ-5D	Yes	EQ-5D at discharge (All patients) Ticagrelor: 0.847 Clopidogrel: 0.846

				2008						EQ-5D at 12 months (All patients) Ticagrelor: 0.840 Clopidogrel: 0.832 EQ-5D (excluding patients who died) Ticagrelor: 0.864 Clopidogrel: 0.863
Lala 2013(75)	ACS	US	Hypothetical cohort of patients aged 60 years (mean age in TRITON TIMI-38) with ACS undergoing PCI	TRITON-TIMI 38 study	NR	NR	ACS, MI, cerebral event, major bleed, CV death or major bleed-related death, other death	EQ-5D and other published literature	Yes	Event-free survival: 0.83 (0.80–0.85) Survival after 1 additional event: 0.72 (0.65–0.80) Survival after 1 additional event (symptomatic): 0.55 (0.47–0.64) Survival after 2 or more events: 0.50 (0.35–0.60) Non-fatal MI: 0.70 (0.56–0.84) Non-fatal cerebral event: 0.65 (0.52–0.78) Major bleed: 0.80 (0.64–0.96)
Latour-Perez PJ et al, 2008(79)	NTEMI ACS	Spain	Utilities were derived from a nonsystematic review of the literature. Therefore it is unclear which populations these are based on	Not reported	Not reported	Not reported	Early ACS Late ACS Post acute MI Dead	Not reported	Yes – if UK data are not available	Old MI: 0.80 (0.6, 0.94) Disutility PCI: 0.05 (0, 0.1) Disutility CABG: 0.1 (0, 0.2) Disutility major bleed: 0.05 (0, 0.1) Disutility adverse event: 0.1 (0, 0.1)
Latour-Perez J et al, 2004(80)	NSTEMI ACS patients	Spain	Utilities are taken from various published sources. Therefore it is	Not reported	Not reported	Not reported	The Markov tree used considered two periods (an early period and a late period) and four	Not reported	Yes – if UK data are not available	ACS complicated with non-lethal infarction: 0.80 (0.5, 0.85)

			unclear which populations these are based on				basic states: uncomplicated acute coronary syndrome (UACS), acute coronary syndrome complicated with myocardial infarction (MI), acute coronary syndrome complicated with stroke (ACSS) and death.			ACS complicated with non-lethal stroke: 0.79 (0.5, 0.9) Disutility revascularisation: 0.04 (0, 0.15) Disutility serious haemorrhage: 0.13 (0.0001, 0.5) (one month)
Mahoney EM et al, 2010(87)	ACS and planned PCI	USA	Utilities based on Beaver Dam Health Outcomes study with adjustments for MI, stroke and major bleeding	Not reported	Not reported	Not reported	MI Stroke (Major Bleed) Death	Not reported	Yes – if UK data are not available	MI 1st year: 0.88 Stroke lifetime adjustment: 0.52 Disutility major bleed: 0.15
Manson 2010(131)	ACS	US and Canada	The population samples were a reasonable match to the population of Canada and the US in terms of demographics	Brief Literature review and exploratory and validation interviews	176	NR	MI/Stroke/angina	EQ-5D	No	Unstable angina: 0.66
Main et al, 2004(88)	NSTEMI ACS patients	Not reported	Not reported	Not reported	Not reported	Not reported	ACS event-free, year 1. ACS event-free, post-year 1. Independent stroke. Dependent stroke. New MI, year 1. New MI, post-year 1.	Not reported	No – cannot be sure of measurement technique or appropriateness of population	ACS event free, year 1: 0.80 (0.70-0.90 range). ACS event-free, post-year 1: 0.93 (0.88-0.98 range). New MI, year 1: 0.80 (0.70-0.90 range). New MI, post-year 1: 0.93 (0.88-0.98 range). Independent stroke: 0.74 (0.69-0.79 range). Dependent stroke: 0.38 (0.29-0.47 range).
NICE	ACS with PCI	Based on	Not reported	Not reported	Not	Not	Not reported	Not reported	No – cannot be sure	ACS Disutility:

TA182, 2009(42)		US study with background UK population norms			reported	reported			of measurement techniques or sample population	0.0409 Stroke/MI Disutility: 0.0524 Utility major bleed: 25% reduction
Theidel 2013(100)	ACS	Germany	PLATO trial population- patients hospitalized for NSTEMI that was managed invasively or medically, or STEMI scheduled for primary PCI strategy	Patients enrolled in PLATO trial	NR	NR	Overall mortality, myocardial infarction, stroke, no event, non-fatal MI, non-fatal stroke	EQ-5D	Yes	Overall ACS patient population ≤150 mg ASA: No event: Ticagrelor- 0.875, Clopidogrel- 0.878 Non-fatal myocardial infarction: Ticagrelor- 0.817, Clopidogrel- 0.801 Non-fatal stroke: Ticagrelor- 0.748, Clopidogrel- 0.720 Death: Ticagrelor- 0.259, Clopidogrel- 0.249 No event (age 60–69): 0.877 No event (age 70–79): 0.838 No event (age 80+): 0.773 NSTEMI/UA ≤150 mg ASA: No event: Ticagrelor- 0.864, Clopidogrel- 0.863 Non-fatal myocardial infarction: Ticagrelor- 0.794, Clopidogrel- 0.777 Non-fatal stroke: Ticagrelor- 0.736, Clopidogrel- 0.677

										Death: Ticagrelor- 0.275, Clopidogrel- 0.235 No event (age 60–69): 0.864 No event (age 70–79): 0.826 No event (age 80+): 0.762 STEMI ≤150 mg ASA: No event: Ticagrelor- 0.891, Clopidogrel- 0.899 Non-fatal myocardial infarction: Ticagrelor- 0.879, Clopidogrel- 0.855 Non-fatal stroke: Ticagrelor- 0.763, Clopidogrel- 0.833 Death: Ticagrelor- 0.228, Clopidogrel- 0.281 No event (age 60–69): 0.895 No event (age 70–79): 0.856 No event (age 80+): 0.789
Schleinitz MD and Heidenreich PA, 2005(96)	High Risk ACS	USA	utility values based on published population-based studies including the following populations: stroke, cerebrovascular stroke, major stroke, mild stroke, myocardial infarction,	Not reported	Not reported	Not reported	Well Alive after single event Alive after multiple events Dead	Not reported	Yes – if UK data is not available	Severe stroke: 0.11 (0, 0.35) Moderate stroke: 0.39 (0.25, 0.55) Mild stroke: 0.76 (0.55, 0.95) Intracerebral Haemorrhage: 0.30 (0, 0.60) Disutility GI bleed: 0.005 (0, 0.01) CAD: 0.87 (0.80,

			nonvalvular AF							0.95)
Schleinitz MD et al, 2004(95)	ACS/PAD	USA	Published, population based values were used for utilities. Populations considered in the publications were femoropopliteal disease, peripheral vascular disease, intermittent claudication, vascular disease, stroke, cerebrovascular stroke, major stroke, mild stroke, MI, nonvalvular AF	Not reported	Not reported	Not reported	Well Alive after single event Alive after multiple events Dead	Not reported	Yes – if UK data is not available	MI: 0.87 (0.80, 0.95) Severe stroke: 0.11 (0, 0.35) Moderate stroke: 0.39 (0.25, 0.55) Mild stroke: 0.76 (0.55, 0.95) Intracerebral Haemorrhage: 0.30 (0, 0.60) Disutility GI bleed: 0.005 (0, 0.01) PAD: 0.80 (0.60, 1.00)
Zhang Z et al, 2009(104)	STEMI	USA	Utilities considered in secondary analysis only and were based on assumption	Not reported	Not reported	Not reported	Utility applied to STEMI patients	Not reported	No - exploratory secondary analysis	STEMI: 0.8
Ara et al, 2010(132)	Heart attack, angina or stroke	England	Health Survey for England - The 2003 and 2006 surveys a random sample of participants (aged 16 to 98 years) who reported a history of CV condition(s).	Health Survey for England - The 2003 and 2006 surveys a random sample of participants (aged 16 to 98 years) who reported a history ofCV condition(s) and were asked to complete the EQ-5D questionnaire. Preference-based HSUVs were estimated using the weights obtained using time trade off	26,679 of which 25,080 were event free, remainder dvidided over 11 health states	100%	Event-free Angina <12 months, history of just angina No event <12 months, history of just angina Angina <12 months, history of angina + other CV condition No event <12 months, history of angina + other CV condition Heart attack <12 months, history of just heart attack No event <12 months, history of just heart attack Heart attack <12 months, history of heart attack + other CV	EQ-5D (UK TTO value set)	Yes - presents utility data for MI and stroke over time and is based on UK cohort using validated instrument	Angina <12 months, history of just angina 0.615 (SE 0.019) No event <12 months, history of just angina 0.775 (SE 0.015) Angina <12 months, history of angina + other CV condition 0.541 (SE 0.022) No event <12 months, history of angina + other CV condition 0.715 (SE 0.022) No event <12 months, history of just heart attack 0.742 (SE 0.020)

				valuations from the UK general public			condition No event <12 months, history of heart attack + other CV condition Stroke <12 months, history of just stroke No event <12 months, history of just stroke Stroke <12 months, history of stroke + other CV condition No event <12 months, history of stroke + other CV condition			Heart attack <12 months, history of just heart attack 0.721 (SE 0.045) No event <12 months, history of heart attack + other CV condition 0.685 (SE 0.024) Heart attack <12 months, history of heart attack + other CV condition 0.431 (SE 0.066)No event <12 months, history of stroke + other CV condition 0.641 (SE 0.037) Stroke <12 months, history of stroke + other CV condition 0.479 (SE 0.087)
Bakhai et al, 2012(133)	ACS with PCI and antiplatelet therapy	France, Spain, and UK	APTOR, a noninterventional, prospective observational cohort study enrolling patients presenting with ACS and undergoing PCI with either initiation or continuation of any antiplatelet therapy between January 2007 and August 2007	Patients from APTOR study cohort presenting with ACS and undergoing PCI with either initiation or continuation of any antiplatelet therapy between January 2007 and August 2007 from 122 sites from France, Spain, and the United Kingdom.	1,335	94%	Not reported	EQ-VAS, EQ-5D	Yes – for ACS event free health state	ACS index hospitalisation discharge: 0.79 ACS 1 year: 0.80 Composite outcome death / MI / stroke / UA / urgent target vessel revascularisation / acute heart failure With composite outcome hospitalisation discharge: 0.74 With composite outcome 1 year: 0.73 Without composite outcome hospitalisation

										discharge: 0.80 Without composite outcome 1 year: 0.81
Crespin et al, 2011(60)	ACS	USA	The cohort's baseline utility values were obtained from a nationally representative survey of non-institutionalised Americans utilising the EuroQol five-dimensional (EQ-5D) questionnaire. The CEA Registry was searched to locate utility weightings for each outcome state within the model, limiting results to reports on American patient populations published since 1998.	Not reported	Not reported	Not reported	Health States: post-ACS event, deceased. Outcome States: MI, Bleeding, Dyspnoea	EQ-5D	Yes – if UK data not available	Average ACS 66-74 years: 0.86 Average ACS 75-95 years: 0.84 Average ACS: 0.85 MI 1st year: 0.87 MI post 1st year: 0.91 GI bleed: 0.75 (1 month) Death: 0.91
NICE, 2012(43) (manufacturer submission)	Post MI	UK	Model considered a cohort of patients who had had a recent MI. The trial evidence that the model was based on included relatively few older (>65) or black patients, so the results may not be reliable for these groups.	Not reported	Not reported	Not reported	No event Revascularisation Post Revascularisation MI MI (subsequent) Revascualrisation 2 Post revascualrisation 2 Post OPD Death	Not reported	Yes	MI: 0.812 Stroke: 0.736 Vascular death: 0.246 Non-vascular death: 0.264 All cause death: 0.249 ACS: 0.875
Zeymer 2013(134)	ACS	France, Spain, the UK, Czech	APTOR a non-interventional, prospective observational cohort	Data were from the prospective, observational APTOR study of	4184	NR	STEMI patients and UA/NSTEMI patients	EQ-VAS, EQ-5D	Yes - Quality of life was assessed at hospital discharge and 1 year using the	Optimal therapy; EQ-5D health index: Hospital discharge: 0.82±0.22

		Republic, Germany, Greece, Austria, Hungary, Belgium, the Netherlands, Sweden, Norway, Denmark and Finland	study enrolling patients presenting with ACS and undergoing PCI. The initial cohortwas enrolled between January 2007 and August 2007 from 122 sites from France, Spain and the UK. The second cohort was enrolled with consistent methodology between April 2008 and May 2009 from 113 sites from the Czech Republic, Germany, Greece, Austria, Hungary, Belgium, the Netherlands, Sweden, Norway, Denmark and Finland.	14 European countries from 2007 to 2009					EQ-5D standardized five-item instrument questionnaire for health outcomes	1 year: 0.83±0.23 Change from discharge to 1 year: 0.01±0.24 Optimal therapy; EQ-5D visual analog scale (VAS): Hospital discharge:68.2±22.3 1 year: 75.6±17.4 Change from discharge to 1 year: 7.5±22.7 Non-Optimal therapy; EQ-5D health index: Hospital discharge:0.81±0.24 1 year: 0.82±0.23 Change from discharge to 1 year: 0.01±0.26 Non-Optimal therapy; EQ-5D visual analog scale (VAS): Hospital discharge: 66.4±23.9 1 year: 74.4±17.7 Change from discharge to 1 year: 7.7±24.1

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

The primary source for most utility estimates in the model is a UK based report by Bagust et al(49). The same utility values as presented in this report are also applied in Coleman 2013(81). Justification for the sources selected is presented in Table 56.

No quality of life values were derived from the clinical trial for revascularisation procedures. For all other events, a comparison between the quality of life values from the trial and those chosen from the literature are provided below.

Table 56 Comparison of the utility values taken from literature and those collected in the ATLAS 2 trial

Health State / Event	Value from trial	Value from literature	Difference	Literature reference
No Event (ACS)	0.88	0.842	+0.038	Bagust 2011(49)
MI 1st 6 months	0.78	0.779	+0.001	Bagust 2011(49)
MI 2nd 6 months	0.78[14]	0.821	- 0.041	Bagust 2011(49)
MI later	0.78	0.821	- 0.041	Bagust 2011(49)
IS 1st 6 months	0.67	0.703	-0.033	Bagust 2011(49)
IS 2nd 6 months	0.67	0.748	-0.078	Bagust 2011 + adjustment based on Ara 2010(132). The stroke utility from Bagust 2011 is 0.703 (no variation of utility over time is given).The stroke utility from Ara 2010 for stroke <12 months (history of stroke + other CV condition) is 0.479 and for "no event" <12 months (history of stroke + other CV condition) is 0.641. Taking the increase in utility over time between patients who experience no event and those who suffer from a stroke - (0.641-0.479)/0.479 = 0.33 (33%). If this factor is applied to the utility estimate obtained from Bagust 2011 then later utility is given by 1.33 ×0.703 = 0.941. Since this exceeds the utility for "no event" – further adjustments are made 0.941 × 0.842 (no event utility) = 0.792. To separate the 12 month utility into the tunnel states defined in the model we take (0.792 -0.703)/2(+0.703) = 0.748 to define the utility of IS for the second 6 months
IS later	0.67	0.792	-0.122	Bagust 2011 + adjustment based on Ara 2010(132) We take the corrected value of 0.792 (see description above)
HS/ICH 1st 6 months	0.67	0.703	-0.033	In the absence of utility values identified in the systematic review for HS – we assume the same utility values for IS apply here. Bagust 2011
HS/ICH 2nd 6 months	0.67	0.748	-0.078	In the absence of utility values identified in the systematic review for HS – we assume the same utility values for IS applies here. Bagust 2011 + adjustment based on Ara 2010(132) (see description for IS 2nd 6 months)
HS/ICH later	0.67	0.792	-0.122	In the absence of utility values for HS found in the systematic review – we assume the same utility values

[14] Note that utility values over time following an event are not available from the clinical trial. For the purpose of presenting information in this table an assumption that utility values are constant over time has been applied. This is also the case for MIs after the first 6 months in the literature.

				for stroke applies here. Bagust 2011 + adjustment based on Ara 2010(132) (see description for IS 2nd 6 months and IS later)
Major Bleed	0.77	0.75	+0.02	Crespin et al 2011(60)
Minor Bleed	0.84	0.80	+0.04	Kazi et al 2014(73)
Bleed requiring medical attention	0.87	0.80	+0.07	Kazi et al 2014(73)

The ATLAS 2 trial is closest in value to the literature for the MI first six months health state. The values from the trial are lower than those from the literature for later periods in the MI health state. The 'no event' health state utility value is slightly higher in the clinical trial. The trial reports lower utility values following a stroke than those reported in the literature source used in the model. The largest difference in values are seen post 12 months after a stroke. These estimates are based on a combination of literature sources. In the literature, utility values for bleeding events are not widely reported. Therefore, one source has been used for TIMI major bleeds and one source (and therefore the same utility) has been used for TIMI minor bleeds and TIMI bleeds requiring medical attention. The differences in quality of life estimates for bleeding events between the ATLAS 2 trial and the clinical literature become more apparent as the severity of the bleed declines.

Revascularisations are also considered in the model. CABGs are invasive procedures involving an average of 5 to 7 days hospitalisation plus recovery time. Latour-Perez (2008)(79) suggests that CABG procedures are associated with a disutility of 0.1. PCIs are percutaneous surgical procedures and are less invasive than CABGs. Furthermore, the recovery time is less after a PCI procedure. However, patients undergoing a PCI are still expected to experience a short-term decrement in their utility (0.04 to 0.05 – Latour-Perez, 2008; Latour-Perez, 2004(79;80)).

Adverse events

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

The risk of bleeding is a well-known potential adverse event associated with antithrombotic treatments. Major bleeds will lead to hospitalisation and will likely result a large, short-term decrement in utility (60;73;79;87). Minor bleedings are less severe in nature and therefore have a lower impact on utility. Again, any decrement is likely to be short-term. Bleeds requiring medical attention are even less severe than minor bleeds and are expected to be associated with minimal utility decrements(73).

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

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 57: Summary of quality of life values for the cost-effectiveness analysis

State	Utility value	Confidence interval	Reference	Justification
No event	0.842	Beta, min=0.632, max= 1.000	Bagust et al 2011(49)	Large UK based source of utility estimates in ACS patients. Source identified in systematic review and has been applied in NICE submission for ticagrelor.
MI 1st 6 months	0.779	Beta, min=0.584, max= 0.974	Bagust et al 2011(49)	Large UK based source of utility estimates in ACS patients. Source identified in systematic review and has been applied in NICE submission for ticagrelor
MI 2nd 6 months	0.821	Beta, min=0.616, max= 1.000	Bagust et al 2011(49)	Evidence that QoL improves over time after an MI (Lacey & Walters 2003(124)). UK based utility estimates in ACS patients. Source identified in systematic review and has been applied in NICE submission for ticagrelor
MI later (post 12 months)	0.821	Beta, min=0.616, max= 1.000	Bagust et al 2011(49)	Evidence that QoL improves over time after an MI (Lacey & Walters 2003(124)). UK based utility estimates in ACS patients. Source identified in systematic review and has been applied in NICE submission for ticagrelor
IS 1st 6 months	0.703	Beta, min=0.527, max= 0.879	Bagust et al 2011(49)	UK based utility estimates in ACS patients. Source identified in systematic review and has been applied in NICE submission for ticagrelor
IS 2nd 6 months	0.748	Beta, min=0.561, max= 0.935	Bagust et al 2011 (49)plus adjustment based on Ara et al 2010(132)	UK based utility estimates available in Bagust et al, these can be adjusted based on Ara et al - allowing for increase in stroke utility over time (as recommended by KR).
IS later (post 12 months)	0.792	Beta, min=0.594, max= 0.990	Bagust et al 2011 (49)plus adjustment based on Ara et al 2010(132)	UK based utility estimates available in Bagust et al, these can be adjusted based on Ara et al - allowing for increase in stroke utility over time (as recommended by KR).
HS/ICH 1st 6 months	0.703	Beta, min=0.527, max= 0.879	Bagust et al 2011 (49) plus assumption that utility after a HS/ICH is the	UK based utility estimates in ACS patients. Source identified in systematic review and has been applied in NICE submission for ticagrelor

			same as utility after an IS	
HS/ICH 2nd 6 months	0.748	Beta, min=0.561, max= 0.935	Bagust et al 2011(49) plus adjustment based on Ara et al 2010 (132) (plus assumption that utility after an HS/ICH is the same as after an IS)	UK based utility estimates available in Bagust et al, these can be adjusted based on Ara et al - allowing for increase in stroke utility over time (as recommended by KR).
HS/ICH later (post 12 months)	0.792	Beta, min=0.594, max= 0.990	Bagust et al 2011 (49)plus adjustment based on Ara et al 2010 (132) (plus assumption that utility after an HS/ICH is the same as after an IS)	UK based utility estimates available in Bagust et al; these can be adjusted based on Ara et al - allowing for increase in stroke utility over time (as recommended by KR).
MI + MI 1st 6 months	0.607	Beta, min=0.455, max= 0.759	Bagust et al 2011 (49) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011(120))
MI + MI 2nd 6 months	0.674	Beta, min=0.506, max= 0.843	Bagust et al 2011 (49) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011)(120)
MI + MI later (post 12 months)	0.674	Beta, min=0.506, max= 0.843	Bagust et al 2011 (49) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011)(120)
IS+ IS 1st 6 months	0.494	Beta, min=0.371, max= 0.618	Bagust et al 2011 (49) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
IS +IS 2nd 6 months	0.559	Beta, min=0.419, max= 0.0.699	Bagust et al 2011(49) and adjustment based on Ara et al 2010(132) plus assumption that utility values should be	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 – which captures the increase in stroke utility over time. Evidence to suggest further utility

			multiplied in the case of multiple events	decrement after subsequent events (Bach et al, 2011) (120)
IS + IS later (post 12 months)	0.627	Beta, min=0.471, max= 0.784	Bagust et al 2011 (49) and adjustment based on Ara et al 2010 (132) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
HS/ICH + HS/ICH 1st 6 months	0.494	Beta, min=0.371, max= 0.618	Bagust et al 2011(49) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
HS/ICH + HS/ICH 2nd 6 months	0.559	Beta, min=0.419, max= 0.699	Bagust et al 2011 (49) and adjustment based on Ara et al 2010 (132) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
HS/ICH +HS/ICH later (post 12 months)	0.627	Beta, min=0.471, max= 0.784	Bagust et al 2011(49) and adjustment based on Ara et al 2010 (132) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
MI + IS 1st 6 months	0.548	Beta, min=0.411, max=0.685	Bagust et al 2011 (49) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
MI + IS 2nd 6 months	0.614	Beta, min=0.460, max= 0.767	Bagust et al 2011 (49)and Ara et al 2010(132) adjustment for IS plus assumption that utility values should be multiplied in the	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility

			case of multiple events	decrement after subsequent events (Bach et al, 2011) (120)
MI + IS later (post 12 months)	0.650	Beta, min=0.488, max= 0.813	Bagust et al 2011 (49) and Ara et al 2010 (132)adjustment for IS plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
MI + HS/ICH 1st 6 months	0.548	Beta, min=0.411, max=0.685	Bagust et al 2011 (49) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
MI +HS/ICH 2nd 6 months	0.614	Beta, min=0.460, max= 0.767	Bagust et al 2011 (49) and Ara et al 2010 (132)adjustment for HS/ICH plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
MI + HS/ICH later (post 12 months)	0.650	Beta, min=0.488, max= 0.813	Bagust et al 2011 (49)and Ara et al 2010 (132)adjustment for HS/ICH plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
IS + HS/ICH 1st 6 months	0.494	Beta, min= 0.371, max=0.618	Bagust et al 2011 (49)plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
IS + HS/ICH 2nd 6 months	0.559	Beta, min=0.419, max= 0.699	Bagust et al 2011 (49)and Ara et al 2010 (132)adjustment plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
IS +HS/ICH later	0.627	Beta, min=0.471,	Bagust et al	UK based utility estimates in ACS

(post 12 months)		max= 0.784	2011(49) and Ara et al 2010 (132)adjustment plus assumption that utility values should be multiplied in the case of multiple events	patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
3 events 1st 6 months	0.385	Beta, min=0.289, max= 0.481	Bagust et al 2011 (49)plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
3 events 2nd 6 months	0.459	Beta, min=0.344, max= 0.574	Bagust et al 2011 (49)and adjustment based on Ara et al 2010 (132)plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
3 events later (post 12 months)	0.515	Beta, min=0.386, max= 0.644	Bagust et al 2011(49) and adjustment based on Ara et al 2010(132) plus assumption that utility values should be multiplied in the case of multiple events	UK based utility estimates in ACS patients are taken from Bagust et al 2011. Adjustments are made using UK based utility values from Ara et al 2010 - captures the increase in stroke utility over time. Evidence to suggest further utility decrement after subsequent events (Bach et al, 2011) (120)
PCI/PTCA	0.792	Beta, min=0.594, max= 0.990	Latour-Perez 2008	Only source identified by systematic review that provides QoL estimates following both PCI/PTCA and CABG. KR in agreement with values.
CABG	0.742	Beta, min=0.557, max= 0.928	Latour-Perez 2008	Only source identified by systematic review that provides QoL estimates following both PCI/PTCA and CABG. KR in agreement with values.
TIMI Major bleeding	0.750	Beta, min=0.563, max= 0.938	Crespin et al, 2011	UK based utility estimate identified in systematic review. Utilities are from an ACS population
TIMI Minor bleeding	0.800	Beta, min=0.600, max= 1.000	Kazi et al, 2014	UK based utility estimate. No study identified by the literature review reported a value for minor bleed. Sullivan et al was identified via the TUFTS website
TIMI requiring medical attention	0.800	Beta, min=0.600, max= 1.000	Sullivan et al, 2006	UK based utility estimate. No study identified by the literature

				review reported a value for bleed requiring medical attention. Sullivan et al was identified via the TUFTS website

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[15]:

- 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 specialist 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).

Based on his knowledge of ACS in the UK, KR was contacted to verify assumptions and values used in the economic model. KR was the only expert who was approached to participate and was sourced independently of Bayer. Prior to meeting, KR was provided with an overview document of key assumptions and values used in the model. No information on the treatments included in the model, the label population of rivaroxaban, or the ATLAS 2 clinical trial was provided. Evidence was discussed and verified with KR via telephone interview. Below, the assumptions discussed and the feedback given by KR are provided with associated actions where appropriate.

[15] 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.

Table 58: Quality of life validation with KR

Model Function	Assumption	Feedback	Comment / Action
Multiple Events	Utilities for multiple events are estimated using a multiplicative approach	KR agreed with this approach	No action required
Health state utilities	The utility value for patients with no secondary events remains constant over time	Utilities would be expected to improve over time – use improvement in MI as a proxy	Investigated in scenario analysis
	Utility following a stroke remains constant over time	A constant utility is not unreasonable. An improvement in utility of approximately 10% could be expected	An improvement in stroke utility based on Ara has been estimated
Duration of impact of adverse events	TIMI Major Bleed = 30 day impact on QoL	KR agreed with this assumption	No action required
	TIMI Minor Bleed = 2 day impact on QoL	KR agreed with this assumption	No action required
	TIMI Bleed requiring medical attention = 2 day impact on QoL	KR agreed with this assumption	No action required
	PCI / PTCA = 30 day impact on QoL	KR agreed with this assumption	No action required
	CABG = 30 day impact on QoL	KR commented that this impact should be much longer – approximately 3 months	The impact on QoL of CABG was subsequently updated to 12 weeks in the model
Disutility of bleeding /	The same utility value is assumed for all bleeding	The utility values should not be the same	Different sources are now used, utility values differ per bleed

revascularisation	severities	for all bleeds.	type
	TIMI Major utility = 0.712	KR agreed with this value	Different values are now applied in the model to allow distinction of major bleed (0.75 – Crespin et al 2011(60))
	TIMI Minor utility = 0.712	Should be higher than Major bleed	Different values are now applied in the model (0.80 – Sullivan et al 2006)(135)
	TIMI requiring medical attention utility = 0.712	Should be higher than Major bleed	Different values are now applied in the model (0.80 – Sullivan et al 2006) (135)
	PCI / PTCA utility = 0.792	Bleeds are more debilitating than revascularisations so it makes sense that the revascularisation utilities are higher	Suitable disutilities for bleeding and revascularisation was not available from one literature source and the values selected in the model do show major bleeds to be more debilitating than revascularisations. Utility values for minor bleeds and those requiring medical attention are higher based on recommendations from KR during this validation step. Sensitivity analyses have been conducted to test the impact on the model outcomes.
	CABG utility = 0.742		
	Adverse event disutilities are one-off short-term decrements	KR agreed with this assumption	No action required
Fatal Events	Utility values of zero are applied to patients who	KR agreed with this assumption	No action required

	have died		

KR has received honoraria for lectures, advisory boards or for serving as a steering committee member or executive committee member for Pfizer, Novartis, Novo NordDisk, AZ, Abbott, Kowa, Roche, Daiichi Sankyo, Lily, MSD, GSK, BMS, Regeneron, and Sanofi.

7.4.11 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 patients who have recently suffered an ACS event but have not experienced a secondary cardiovascular event. The health related quality of life of patients in this health state is assumed constant over time as little data is available showing how ACS patient's utility changes over time. This is a conservative approach as the rivaroxaban arm has more patients in the health state where patients have not experienced a secondary event. A sensitivity analysis is conducted testing the impact of the constant utility assumption.

The non-fatal MI health state contains patients who have had a subsequent MI. This health state is split into three tunnel states, representing the first 6 months, second 6 months and later time since the MI. The first 6 month period is assumed to be a period of intense treatment and risk management, including the patient's hospitalisation. Utility during this time is expected to be lower than in the second six month or later periods in the MI health state. After the second 6 months the health related quality of life of patients in the MI health state is assumed to be constant over time.

The non-fatal IS health state contains patients who have had a subsequent ischaemic stroke. This health state is split into three tunnel states, representing the first 6 months, second 6 months and later time since the IS. Following discussions with a clinical expert, utility estimates from Bagust 2011(49) are adjusted using information from Ara et al(132), which demonstrate that utility improves over time since the event, are used in the model.

The non-fatal HS/ICH health state contains patients who have had a subsequent haemorrhagic stroke. This health state is split into three tunnel states, representing the first 6 months, second 6 months and later time since the HS/ICH. Utility data on HS/ICH was not available. Therefore, the same source as is used for IS is applied in the model.

Health related quality of life for patients in one of the combined event health states (MI + MI, IS + IS, HS/ICH + HS/ICH, MI + IS, MI + HS/ICH, IS + HS/ICH, 3 events) is assumed to equal the utility of the first event multiplied by the utility of the second event. Multiple events health states are split into three tunnel states, representing the first 6 months, second 6 months, and later time since the most recent event. Because the utility following an MI or stroke is assumed to increase from the second six months onwards, the health related quality of life in combined health also increase from the second six months onwards.

Dis-utilities due to adverse events (i.e. bleeds) and disutilities associated with revascularisations are considered one-off short-term decrements and do not vary over time.

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

No important health effects identified in the literature or clinical trials were excluded from the analysis.

7.4.13 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 model, the baseline utility value (i.e. the health related quality of life in the no event health state) is higher than the utility applied to subsequent event health states to account for the fact that subsequent events will have a decremental effect on patient quality of life. Utilities immediately following an MI are taken from the same literature source as the baseline utility value(49). Utilities following an IS or HS/ICH are taken from Bagust 2011(49) and adjusted based on another published literature source (Ara 2010)(132). This allowed for variable utilities to be applied in the model representing the time since a stroke event. No single literature source provides utility estimates for acute coronary syndrome patients, secondary MIs and secondary stroke events. Therefore, two separate sources were used. (Bagust 2011(49), Ara 2010) (132). Furthermore, the utility values from Bagust 2011(49) are also used in recent economic models in ACS (Greenhalgh 2011(136), Coleman 2013a)(81)

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

Health related quality of life is assumed to be constant over time if a patient does not experience any subsequent events. Following an MI, IS or HS/ICH patients will experience a drop in utility. Their utilities are expected to increase over time, but will not return to their pre-event level.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values in sections 7.4.3 to 7.4.8 have not been amended.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 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.

Multiple HRG codes are applicable for costing the health states and events in the model (Table 59).

The table below provides the data used in the model from the NHS reference costs 2012/2013. Long-stay, short-stay, day case and accident & emergency admission data from NHS trusts and primary care trusts were consulted for these costs.

For the events 'MI', 'IS', 'HS-ICH' and 'CABG', costs are based on long-stay admission data. The costs for the events 'TIMI Minor Bleed' and 'Bleed requiring medical attention' are based on accident & emergency admissions. 'PCI' costs are based on short stay admission data and 'TIMI Major Bleed' costs are based on a combination of long-stay, short-stay and day case admissions.

As most of the events are composed of multiple HRG-codes (health care services), a weighted average cost (with its lower- and upper quartile) is calculated for every event. The average cost for each HRG-code is a weighted average of the costs made in different health care departments which provide the service.

All costs presented in the table are weighted average costs, based on the events registered in the NHS reference costs 2012/13.

Table 59 NHS reference costs 2012/13 considered in the model. Unit costs are provided for MI, IS and HS/ICH are applicable to the first 12 weeks of the model and unit costs for bleeding and revascularisation events are one-off cost estimates (see section 7.5.6 for costs of rehabilitation)

Event	HRG code and Description	Activity*	Average cost	Lower quartile costs	Upper quartile costs
MI	Weighted average of EB10A: Actual or Suspected Myocardial Infarction with CC Score 13+, EB10B: Actual or Suspected Myocardial Infarction with CC Score 10-12, EB10C: Actual or Suspected Myocardial Infarction with CC Score 7-9, EB10D: Actual or Suspected Myocardial Infarction with CC Score 4-6 and EB10E: Actual or Suspected Myocardial Infarction with CC Score 0-3		£2,154.95	£1,665.97	£2,489.16
	EB10A: Actual or Suspected Myocardial Infarction with CC Score 13+	Long-Stay: 2,771	£3,810.27	£2,613.99	£4,551.47
	EB10B: Actual or Suspected Myocardial Infarction with CC Score 10-12	Long-Stay: 7,482	£2,974.30	£2,221.03	£3,533.19
	EB10C: Actual or Suspected Myocardial Infarction with CC Score 7-9	Long-Stay: 12,749	£2,294.84	£1,764.25	£2,596.96
	EB10D: Actual or Suspected Myocardial Infarction with CC Score 4-6	Long-Stay: 17,761	£1,886.80	£1,499.05	£2,205.61
	EB10E: Actual or Suspected Myocardial Infarction with CC Score 0-3	Long-Stay: 12,902	£1,555.21	£1,273.16	£1,724.60
IS	Weighted average of AA22C: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 14+, AA22D: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 11-13, AA22E: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 8-10, AA22F: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 5-7 and AA22G: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 0-4		£3,063.95	£2,056.78	£3,738.08
	AA22C: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 14+	Long-Stay: 431	£7,390.09	£3,515.04	£9,244.09
	AA22D: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 11-13	Long-Stay: 950	£4,932.54	£2,706.57	£6,454.43
	AA22E: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 8-10	Long-Stay: 1,882	£4,022.77	£2,448.88	£5,147.14

	AA22F: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 5-7	Long-Stay: 3,119	£3,012.98	£2,106.56	£3,652.06
	AA22G: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 0-4	Long-Stay: 6,938	£2,302.17	£1,748.48	£2,680.54
HS/ICH	Weighted average of AA23C: Haemorrhagic Cerebrovascular Disorders with CC Score 14+, AA23D: Haemorrhagic Cerebrovascular Disorders with CC Score 10-13, AA23E: Haemorrhagic Cerebrovascular Disorders with CC Score 6-9, AA23F: Haemorrhagic Cerebrovascular Disorders with CC Score 3-5 and AA23G: Haemorrhagic Cerebrovascular Disorders with CC Score 0-2		£3,394.02	£2,241.30	£4,162.84
	AA23C: Haemorrhagic Cerebrovascular Disorders with CC Score 14+	Long-Stay: 296	£7,908.48	£3,944.38	£10,690.15
	AA23D: Haemorrhagic Cerebrovascular Disorders with CC Score 10-13	Long-Stay: 1,012	£5,085.44	£2,873.94	£6,270.76
	AA23E: Haemorrhagic Cerebrovascular Disorders with CC Score 6-9	Long-Stay: 2,170	£3,374.86	£2,323.10	£4,137.02
	AA23F: Haemorrhagic Cerebrovascular Disorders with CC Score 3-5	Long-Stay: 2,221	£2,715.55	£1,917.42	£3,333.04
	AA23G: Haemorrhagic Cerebrovascular Disorders with CC Score 0-2	Long-Stay: 1,294	£2,235.17	£1,775.71	£2,488.76
TIMI Major Bleed	Weighted average of FZ24G: Major Therapeutic Endoscopic Upper or Lower Gastrointestinal Tract Procedures, 19 years and over with CC Score 3+, FZ24H: Major Therapeutic Endoscopic Upper or Lower Gastrointestinal Tract Procedures, 19 years and over with CC Score 1-2, FZ24J: Major Therapeutic Endoscopic Upper or Lower Gastrointestinal Tract Procedures, 19 years and over with CC Score 0, FZ27E: Intermediate Therapeutic General Abdominal Procedures, 19 years and over with CC Score 3+, FZ27F: Intermediate Therapeutic General Abdominal Procedures, 19 years and over with CC Score 1-2, FZ27G: Intermediate Therapeutic General Abdominal Procedures, 19 years and over with CC Score 0, FZ38G: Gastrointestinal Bleed, with Multiple Interventions, with CC Score 5+, FZ38H: Gastrointestinal Bleed, with Multiple Interventions, with CC Score 0-4, FZ38J: Gastrointestinal Bleed, with Single Intervention, with CC Score 8+, FZ28K: Gastrointestinal Bleed, with Single Intervention, with CC Score 5-7, FZ38M: Gastrointestinal Bleed, without Interventions, with CC Score 9+, FZ38N: Gastrointestinal Bleed, without Interventions, with CC Score 5-8, FZ38L: Gastrointestinal Bleed, with Single Intervention, with CC Score 0-4, FZ38P: Gastrointestinal Bleed, without Interventions, with CC Score 0-4, FZ59Z: Intermediate upper GI tract procedures, 19 years and over, FZ60Z: Diagnostic endoscopic upper GI tract procedures, 19 years and over, FZ70Z: Therapeutic endoscopic upper GI tract procedures, 19 years and over, FZ83G: Major Oesophageal, Stomach or Duodenum Procedures, 19 years and over with CC Score 7+, FZ83H: Major Oesophageal, Stomach or Duodenum Procedures, 19 years and over with CC Score 4-6, FZ83J: Major Oesophageal, Stomach or		£669.83	£492.98	£782.64

	Duodenum Procedures, 19 years and over with CC Score 2-3 and FZ83K: Major Oesophageal, Stomach or Duodenum Procedures, 19 years and over with CC Score 0-1				
	FZ24G: Major Therapeutic Endoscopic Upper or Lower Gastrointestinal Tract Procedures, 19 years and over with CC Score 3+	Long-Stay: 220	£3,395.07	£1,868.83	£4,603.09
		Short-stay: 233	£720.06	£399.49	£881.77
		Day Cases: 441	£622.64	£442.47	£772.96
	FZ24H: Major Therapeutic Endoscopic Upper or Lower Gastrointestinal Tract Procedures, 19 years and over with CC Score 1-2	Long-Stay: 271	£2,257.66	£1,455.06	£2,822.36
		Short-stay: 529	£758.74	£466.55	£959.99
		Day Cases: 2,861	£659.45	£485.71	£788.75
	FZ24J: Major Therapeutic Endoscopic Upper or Lower Gastrointestinal Tract Procedures, 19 years and over with CC Score 0	Long-Stay: 287	£1,953.63	£1,412.11	£2,424.63
		Short-stay: 886	£960.56	£593.56	£1,225.96
		Day Cases: 7,263	£614.50	£453.82	£711.93
	FZ27E: Intermediate Therapeutic General Abdominal Procedures, 19 years and over with CC Score 3+	Long-Stay: 257	£5,649.44	£3,417.23	£6,756.57
		Short-stay: 77	£1,552.43	£731.90	£2,485.61
		Day Cases: 129	£567.15	£480.66	£581.53
	FZ27F: Intermediate Therapeutic General Abdominal Procedures, 19 years and over with CC Score 1-2	Long-Stay: 440	£3,727.83	£2,693.90	£4,459.69

		Short-stay: 192	£1,150.29	£803.78	£1,340.23
		Day Cases: 305	£1,065.05	£775.51	£1,186.74
	FZ27G: Intermediate Therapeutic General Abdominal Procedures, 19 years and over with CC Score 0	Long-Stay: 692	£2,978.02	£2,240.55	£3,465.78
		Short-stay: 203	£1,299.61	£795.50	£1,614.96
		Day Cases: 1,295	£1,222.11	£891.94	£1,379.20
	FZ38G: Gastrointestinal Bleed, with Multiple Interventions, with CC Score 5+	Long-Stay: 736	£4,785.82	£2,820.02	£6,294.25
		Short-stay: 18	£2,307.19	£1,715.22	£3,387.41
	FZ38H: Gastrointestinal Bleed, with Multiple Interventions, with CC Score 0-4	Long-Stay: 1,131	£2,929.46	£1,909.43	£3,803.50
		Short-stay: 13	£1,312.92	£393.82	£2,534.32
	FZ38J: Gastrointestinal Bleed, with Single Intervention, with CC Score 8+	Long-Stay: 635	£3,518.38	£2,241.46	£4,298.43
		Short-stay: 18	£1,278.17	£940.78	£1,121.23
	FZ38K: Gastrointestinal Bleed, with Single Intervention, with CC Score 5-7	Long-Stay: 1,663	£3,518.38	£2,241.46	£4,298.43
		Short-stay: 22	£1,278.17	£940.78	£1,121.23
	FZ38M: Gastrointestinal Bleed, without Interventions, with CC Score 9+	Long-Stay: 1,033	£2,680.46	£1,607.97	£3,551.08
		Short-stay: 556	£558.47	£348.34	£637.44

	FZ38N: Gastrointestinal Bleed, without Interventions, with CC Score 5-8,	Long-Stay: 5,389	£1,848.81	£1,401.68	£2,118.29
		Short-stay: 4,763	£503.89	£357.91	£579.40
		Day Cases: 21	£1,057.64	£869.61	£1,233.80
	FZ38L: Gastrointestinal Bleed, with Single Intervention, with CC Score 0-4	Long-Stay: 6,912	£1,801.76	£1,446.39	£2,020.29
		Short-stay: 65	£849.15	£521.29	£1,038.30
		Day Cases: 17	£925.45	£814.96	£1,051.82
	FZ38P: Gastrointestinal Bleed, without Interventions, with CC Score 0-4	Long-Stay: 21,395	£1,282.09	£1,063.21	£1,422.41
		Short-stay: 43,787	£448.22	£339.19	£509.77
		Day Cases: 537	£401.12	£268.49	£526.39
	FZ59Z: Intermediate upper GI tract procedures, 19 years and over	Long-Stay: 21	£2,944.29	£1,835.97	£3,824.85
		Short-stay: 1,291	£556.98	£333.42	£709.04
		Day Cases: 7,175	£345.86	£205.22	£500.05
	FZ60Z: Diagnostic endoscopic upper GI tract procedures, 19 years and over	Long-Stay: 388	£2,115.76	£1,310.63	£2,287.27
		Short-stay: 20,025	£515.50	£330.96	£649.86

		Day Cases: 140,004	£396.91	£299.48	£451.05
	FZ70Z: Therapeutic endoscopic upper GI tract procedures, 19 years and over	Long-Stay: 146	£2,635.91	£1,099.42	£3,401.48
		Short-stay: 4,977	£646.57	£402.95	£787.16
		Day Cases: 14,668	£520.41	£391.05	£595.84
	FZ83G: Major Oesophageal, Stomach or Duodenum Procedures, 19 years and over with CC Score 7+	Long-Stay: 286	£7,934.23	£5,118.83	£10,341.16
		Short-stay: 106	£2,908.20	£1,360.79	£3,512.68
	FZ83H: Major Oesophageal, Stomach or Duodenum Procedures, 19 years and over with CC Score 4-6	Long-Stay: 440	£5,276.54	£3,760.14	£6,524.24
		Short-stay: 130	£2,682.26	£1,059.87	£3,174.42
		Day Cases: 4	£839.68	£569.93	£977.67
	FZ83J: Major Oesophageal, Stomach or Duodenum Procedures, 19 years and over with CC Score 2-3	Long-Stay: 836	£4,204.90	£3,238.92	£4,942.38
		Short-stay: 195	£2,113.95	£743.91	£2,724.77
		Day Cases: 50	£1,144.93	£350.12	£1,617.90
	FZ83K: Major Oesophageal, Stomach or Duodenum Procedures, 19 years and over with CC Score 0-1	Long-Stay: 406	£3,559.31	£2,743.68	£4,277.10
		Short-stay: 258	£966.39	£442.10	£1,174.45
		Day Cases: 588	£1,140.16	£450.98	£1,657.58

TIMI Minor Bleed	VB11Z: Emergency Medicine, No Investigation with No Significant Treatment	A&E: 455,7222	£67.79	£48.97	£80.37
Bleed requiring medical attention	Weighted average of VB01Z: Emergency Medicine, Any Investigation with Category 5 Treatment, VB02Z: Emergency Medicine, Category 3 Investigation with Category 4, VB03Z: Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment, VB04Z: Emergency Medicine, Category 2 Investigation with Category 4 Treatment, VB05Z: Emergency Medicine, Category 2 Investigation with Category 3 Treatment, VB06Z: Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment, VB07Z: Emergency Medicine, Category 2 Investigation with Category 2 Treatment, VB08Z: Emergency Medicine, Category 2 Investigation with Category 1 Treatment and VB09Z: Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment		£130.26	£109.12	£148.81
	VB01Z: Emergency Medicine, Any Investigation with Category 5 Treatment	A&E: 35,264	£318.75	£173.02	£467.11
	VB02Z: Emergency Medicine, Category 3 Investigation with Category 4	A&E 108,387	£304.50	£249.77	£364.57
	VB03Z: Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	A&E 544,047	£213.30	£163.86	£248.94
	VB04Z: Emergency Medicine, Category 2 Investigation with Category 4 Treatment	A&E 836,967	£205.04	£170.29	£232.05
	VB05Z: Emergency Medicine, Category 2 Investigation with Category 3 Treatment	A&E 462,642	£159.26	£133.07	£179.90
	VB06Z: Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	A&E 746,828	£93.89	£79.40	£107.14
	VB07Z: Emergency Medicine, Category 2 Investigation with Category 2 Treatment	A&E 1,966,223	£137.81	£119.17	£152.66
	VB08Z: Emergency Medicine, Category 2 Investigation with Category 1 Treatment	A&E 4,413,580	£140.83	£119.92	£159.75
	VB09Z: Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	A&E 4,692,465	£91.67	£76.15	£106.65
PCI	Weighted average of EA31A: Percutaneous Coronary Intervention, 0 to 2 Stents, with CC Score 11+, EA31B: Percutaneous Coronary Intervention, 0 to 2 Stents, with CC Score 7-10, EA31C: Percutaneous Coronary Intervention, 0 to 2 Stents, with CC Score 3-6, EA31D: Percutaneous Coronary Intervention, 0 to 2 Stents, with CC Score 0-2, EA49A: Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire, with CC Score 9+, EA49B: Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire, with CC Score 6-8, EA49C: Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire, with CC Score 3-5 and EA49D: Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire, with CC Score 0-2		£2,081.77	£1,352.64	£2,637.64

	EA31A: Percutaneous Coronary Intervention, 0 to 2 Stents, with CC Score 11+	Short stay: 171	£2,556.98	£1,265.28	£3,413.21
	EA31B: Percutaneous Coronary Intervention, 0 to 2 Stents, with CC Score 7-10	Short stay: 682	£2,192.49	£1,399.88	£2,643.93
	EA31C: Percutaneous Coronary Intervention, 0 to 2 Stents, with CC Score 3-6	Short stay: 5,003	£2,044.11	£1,367.95	£2,627.41
	EA31D: Percutaneous Coronary Intervention, 0 to 2 Stents, with CC Score 0-2	Short stay: 7,789	£1,960.35	£1,297.03	£2,466.03
	EA49A: Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire, with CC Score 9+	Short stay: 119	£3,301.68	£1,391.21	£4,111.30
	EA49B: Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire, with CC Score 6-8	Short stay: 175	£2,554.20	£1,244.54	£3,199.93
	EA49C: Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire, with CC Score 3-5	Short stay: 861	£2,434.73	£1,765.90	£2,799.10
	EA49D: Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire, with CC Score 0-2	Short stay: 1,259	£2,435.71	£1,350.82	£3,303.43
CABG	Weighted average of EA14A: Coronary Artery Bypass Graft (First Time), with CC Score 12+, EA14B: Coronary Artery Bypass Graft (First Time), with CC Score 7-11, EA14C: Coronary Artery Bypass Graft (First Time), with CC Score 3-6, EA14D: Coronary Artery Bypass Graft (First Time), with CC Score 0-2, EA16A: Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA, with CC Score 9+, EA16B: Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA, with CC Score 6-8, EA16C: Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA, with CC Score 3-5 and EA16D: Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA, with CC Score 0-2		£9,618.84	£7,445.76	£11,282.71
	EA14A: Coronary Artery Bypass Graft (First Time), with CC Score 12+	Long-Stay: 213	£13,320.80	£9,002.50	£14,920.26
	EA14B: Coronary Artery Bypass Graft (First Time), with CC Score 7-11	Long-Stay: 688	£9,860.40	£8,182.07	£11,041.41
	EA14C: Coronary Artery Bypass Graft (First Time), with CC Score 3-6	Long-Stay: 1,562	£8,746.09	£6,530.36	£10,901.62
	EA14D: Coronary Artery Bypass Graft (First Time), with CC Score 0-2	Long-Stay: 897	£8,473.40	£5,846.92	£11,021.26
	EA16A: Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention,	Long-Stay: 355	£12,873.45	£11,399.66	£13,551.83

	Pacing, EP or RFA, with CC Score 9+				
	EA16B: Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA, with CC Score 6-8	Long-Stay: 410	£10,521.39	£9,160.62	£10,711.89
	EA16C: Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA, with CC Score 3-5	Long-Stay: 730	£9,764.76	£7,630.77	£10,383.61
	EA16D: Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA, with CC Score 0-2	Long-Stay: 452	£9,185.25	£6,968.05	£11,959.34

* Note that the activity presented is the sum of the activity in the different department for the related HRG-code.

There are no HRGs that describe fatal cardiovascular events. Therefore, costs from the literature are applied to the fatal event states. Heeg et al 2007(66) provides unit costs which were inflated to 2013 prices (to be in line with costs sourced from NHS reference costs 2012/2013) with an inflation factor of 1.20 and included in the model(137). The Heeg et al paper was chosen as the source for fatal event costs because the health states in this paper are similar to those applied in the current model. The Heeg et al paper was identified through systematic review. The resulting costs are provided in the table below.

Table 60: Costs for fatal events (Heeg et al 2007(66), inflated to 2013 values(137))

Event	Cost	Cost Year	Inflated costs (2012/2013)
Fatal MI	£1,250.00	2006	£1,500.10
Fatal stroke	£3,750.00	2006	£4,500.31
Other cardiovascular death	£2,500.00	2006	£3,000.21
Other non-cardiovascular death	£250.00	2006	£300.02

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

NHS reference costs are used in the model, as these provide relevant costs and volume estimates that enable the calculation of a weighted average that reflects the pattern of care delivered in the NHS. Furthermore, Reference Costs represent the cost burden to the NHS rather than a reflection of internal reimbursement between NHS organisations. Also, when compared to values from the NHS National Tariff, the Reference costs allow for a greater level of granularity to be assessed and are typically more conservative.

Resource identification, measurement and valuation studies

7.5.3 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 10.13, 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.

A systematic literature review to identify relevant cost effectiveness studies and studies reporting utility values and estimates of resource use and costs from the published literature was performed to to inform sections 7.2, 7.4.9 and 7.5.6. Please see section 0 and Appendix 10 for details of the methodology. Economic evaluations and utility studies identified in their respective reviews were also screened to identify any relevant cost/resource use data.

For the resource use review, publications were to be included if they met the eligibility criteria as outlined in Table 24, please see section 0.

The systematic reviews were designed to identify international evidence focussing on EU-5, US and Canada. Because for the current model UK-based evidence is of interest, not all identified literature from the review is presented in this submission, and only those papers reporting values in GBP are included in the table below. Hence, out of a total of 70 (40 studies reporting cost and resource use data and 30 economic modelling studies reporting cost data)

cost and resource use studies included in the review, only eight studies reporting values in GBP are presented in the submission.

The table below presents an overview of costs identified in the literature review that are both relevant to the UK and to the current model.

Table 61:Cost sources identified in the literature review based on UK data

Reference	Currency	Cost Year	Costing Methods	Costs
Bakhai A et al, 2012(133)	GBP	2008/09	Total direct costs during the study were estimated for each patient by applying specific unit costs of services and products to the patient's recorded health care resource use. Unit costs were obtained from the United Kingdom. Total costs were the sum of in-hospital and post-discharge costs related to medication use and resource use, which included CV-related procedures, hospital stays, and visits to health care professionals.	In-hospital costs: £4,810 to £5,292 In-hospital medication costs: £159 to £160 In-hospital resource use costs: £4,650 to £5,133 Post-discharge costs: £999 to £3,695 Post-discharge medication costs: £420 to £423 Post-discharge resource use costs: £5,809 to £8,988
Heeg B et al, 2007(66)	GBP	2006	Event costs were derived from a variety of sources, such as previous cost-effectiveness publications and the NHS Reference costs published by the UK Department of Health.	MI first 6 months after event: £3,300, MI second 6 months after event: £1,200. MI after first year (per 6 months): £900, second MI assumed to cost the same as first MI, Stroke first 6 months after event: £5,100, Stroke second 6 months after event: £3,500. Stroke after the first year (per 6 months): £2,600, Costs after a second stroke and after multiple events were assumed to be equal to those after the first stroke, Haemorrhage: £2,600, Fatal MI: £1,250, Fatal

				stroke: £3,750, Other CV death: £2,500, Other non-CV death: £250
Karnon J et al, 2006(70)	GBP	2002	The costs of PCI and CABG revascularisation interventions are based on the NHS reference costs for all hospital trusts in England and Wales, for the HRG codes E04 and E15. To treat major bleeding, expert panel opinion suggested that the average bleed would require two blood count test, a gastroscopy (with or without injection) and a transfusion of two units of blood. Mean estimates of the health state costs for ACS patients remaining event-free, and ACS patients experiencing a MI, are taken from the literature. First year stroke costs are based on published estimates derived from expert opinion.	MI Follow-Up: £3,966 (1 year), £1,587 (post-MI) Stroke: £7,466 (1 year) PCI: £2,455 CABG: £6,275 Major bleed: £2,377 ACS (event-free): £1,421 (year 1), £1,421 (post-year 1)
Karnon J et al, 2010(71)	GBP	2006	Health state costs for patients with STEMI who remained event-free were based on published estimates of patient level resource use describing patients with ACS who remain event-free. Health state costs associated with patients with MI were obtained from the same primary costing study.	MI Follow-Up: £4,319 (1 year), £1,728 (year 2+) Stroke: £8,416 (1 year) ACS (event-free): £1,547 (after year 1)

			The cost of stroke was taken from a UK study that estimated the cost of stroke using detailed data on resource use in primary and secondary care over a period of 1 year.	
Main C et al, 2004(88)	GBP	2002	The costs associated with stroke are taken from the study by Chambers and colleagues and inflated to the current price year. The costs in the Chambers study were largely derived from expert clinical opinion. The costs include long-term care but not informal, personal or indirect costs. The costs associated with MI and ACS are taken from Palmer et al, which calculated them from the subgroup of ACS patients in NHAR. The costs of revascularisation procedures are taken from NHS references costs and the costs of bleeding events are taken from Lightowlers et al. The costs of revascularisation differed from the estimates reported by Palmer and colleagues, which were based on fully-allocated costs according to the observed length of hospitalisation and interventions reported in PRAIS-UK. The costs of ACS and MI were modelled as normal distributions	MI year 1: £3,966.00 (£3,209 - 4,723), MI post-year 1: £1,587.00 (£840 - 2,334), Stroke year 1: £7,465.80 (£5,599 - 11,199), Stroke post-year 1: £4,532.80 (£3,400 - 6,799), PCI intervention: £2,445.00 (£1,504 - 2,520), CABG intervention: £6,275.00 (£5,144 - 7,034), Bleed intervention: £2,377.24 (£1,781 - 3,566), ACS event-free: £1,421.00 (£1,316 - £1,526)

			truncated at a minimum of £500. The cost of stroke, PCI, CABG and bleeding events were modelled as triangular distributions.	
NICE, 2007(138)	GBP	2005	Costs were calculated using cost weights for each of the states of the model, multiplied by the time spent in each state. Costs for revascularization which includes hospitalisation were taken from the NHS reference cost 2005. It was assumed that 67% of patients will have PCI and 33% will have CABG and the costs were weighted to reflect this (expert opinion). The cost of the well states was assumed to be the outpatient cost. The cost of cardiac rehabilitation was taken from a published review. Costs of acute MI (non-fatal reinfaction) were assumed to be the same as those of patients treated with thrombolysis, which includes the cost of hospitalisation.	MI: £4,448 Second MI: £500 No event: £171 Revascularisation: £8,676 Post-revascularisation: £500
NICE, 2012(43)	GBP	2008/09	The PLATO-HECON substudy measured resource use and determined costs for all patients participating in the PLATO study by recording admissions to hospital, interventions, investigations, blood	MI: £16,643 (ticagrelor), £16,362 (clopidogrel) Stroke: £15,394 (ticagrelor), £17,483 (clopidogrel) Death any cause: £11,753 (ticagrelor), £13,915 (clopidogrel)

			products, re-operations due to bleeding, and use of concomitant or study drugs to estimate total healthcare costs associated with ticagrelor and clopidogrel. Resource use included costs from randomisation to the time of discharge from hospital, as well as after discharge from hospital to the end of the PLATO study.	No event: £8,544 (ticagrelor), £8,633 (clopidogrel)
Zeymer et al. 2013(134)	GBP	2008/09	Total direct costs during the study were estimated for each patient by applying specific unit costs of services and products to the patient's recorded healthcare resource use.Unit costs were obtained from the UK: NICE guidance CG94; 2010; British National Formulary: BNF 59 British National Formulary: BNF 592010; Curtis L. Unit costs of health and social care 2009; Department of Health. NHS reference costs 2008–2009; 2010. Patients with ACS requiring PCI were categorised into optimal and non-optimal therapy cohorts based on prior medications and procedural characteristics by use of optimal therapy. Optimal therapy was defined as use of aspirin and clopidogrel along with ≥3 of the	Optimal therapy (cohort); In-hospital cost: £4295 (£4105-£4500) Medication cost: £130 (£125-£137) Resource use cost: £4165 (£3980-£4363) Post-discharge costs:£1760 (£1682-£1844) Post-discharge medication cost: £552 (£528-£579) Post-discharge resource use cost£1208 (£1154-£1266) Total costs by 1 year: £6056 (£5787-£6344) Non-optimal therapy: N=2364; In-hospital costs:£4351(£4181-£4532) Medication cost (£): £125 (£120-

			following 4 therapies at both hospital discharge and at one-year post-PCI: statins, beta-blockers, ARB/ACEinhibitors,	£130) Resource use cost: £4226 (£4061-£4402) Post-discharge costs: £1492 (£1434-£1554) Post-discharge medication cost: £383 (£368-£399) Post-discharge resource use cost: £1109 (£1066-£1156) Total costs by 1 year (£5843 (£5615-£6086)

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[16]:

- 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 specialist 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).

Based on his knowledge of ACS in the UK, KR was contacted to verify assumptions and values concerning resource use. KR was the only expert who was approached to participate. Prior to meeting, KR was provided with an overview document of key assumptions and values used in the model. Evidence was discussed and verified with KR via telephone interview. Below, the assumptions discussed and the feedback given by KR are provided.

[16] 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.

Table 62: Resouce use validation with KR

Model Function	Assumption	Feedback	Comment / Action
Costs of multiple events	Costs for multiple event states in the observation period are assumed to be equal to the sum of the costs of the individual events	KR agreed with this assumption	No action required
	Costs of multiple events in the extrapolation period are assumed to equal the cost of the highest costing event both for the acute care cost and the follow-up care cost	These should also be summed	This was updated in the model and the summed costs are now applied. Follow-up care costs are taken from the literature (66) and Curtis 2013(137) and individual event costs are summed for multiple event health states.
HRG codes applied for cost estimation	MI – EB10A, EB10B, EB10C, EB10D, EB10E	KR agrees with this approach	No action required
	IS – AA22C, AA22D, AA22E, AA22F. AA22G	KR agrees with this approach	No action required
	HS/ICH – AA23C, AA23D, AA23E, AA23F, AA23G	KR agrees with this approach	No action required
	PCI / PTCA – EA31A, EA31B, EA31C, EA31D, EA49A, EA49B, EA49C, EA49D	KR agrees with this approach	No action required
	CABG – EA14A, EA14B, EA14C, EA14D, EA16A, EA16B, EA16C, EA16D	KR suggested that codes EA16A and EA16D could be removed as these HRGs are generally related to non-ACS treatments	As it is not certain exactly how clinicians code CABG procedures, and there is likely some heterogeneity in their coding, we have comprised a comprehensive list to cover possible CABG-related HRGs. Analysis of the model indicates that reducing the cost of CABG has negligible impact on the

			ICER (a reduction in cost of 50% reduces the ICER by <1%). No action taken
	TIMI Major Bleeding – FZ24G, FZ24H, FZ24J, FZ27E, FZ27F, FZ27G, FZ38G, FZ38H, FZ38J, FZ38K, FZ38M, FZ38N, FZ38L, FZ38P, FZ59Z, FZ60Z, FZ70Z, FZ83G, FZ83H, FZ83J, FZ83K	More diagnoses fall under the umbrella term of major bleed, including life-threatening situations. Haemorrhagic strokes should be included in TIMI major bleed	Not including life threatening situations will have a negligible impact on results are these events are rare. Further, it is not clear which additional HRGs would be included. It is not relevant for the current model to include haemorrhagic strokes in the major bleed cost as these are included in the HS/ICH health state. No action taken.
	TIMI Minor Bleeding – VB11Z	On the one hand, using only the code VB11Z may underestimate the cost of all minor bleeds. On the other hand, not all bleeds will need treating so we could be overestimating the cost.	Any under/over estimation of the cost will have a negligible impact on the ICER as bleeds are not a key model driver. Further, it is not clear whether the cost estimate may be under or over estimated. No action taken
	TIMI Bleed requiring medical attention – VB01Z, VB02Z, VB03Z, VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z	This could be included as part of the TIMI minor bleeding	In the model TIMI minor bleeds and bleeds requiring medical attention are considered separate events. Therefore, they are also considered separately for costing. No action taken
Cost of non-fatal events	Costs are considered for the first 12 weeks and follow-	KR agrees with this approach	No action required

	up periods (subsequent 12 week periods)		
	Compounded costs are used in the model (HRG cost + (rehabilitation resource use days * rehabilitation cost)	KR agrees with this approach	No action required
	7 days rehabilitation is assumed following an MI	KR expects 3-5 days in hospital rehabilitation and 12 weeks of rehabilitation post hospitalisation following an MI	5 days rehabilitation is assumed following an MI
	14 days rehabilitation is assumed following a stroke	KR expects 14-28 days in hospital rehabilitation. and 2 to 3 months of rehabilitation (post-hospitalisation) following an IS and 6 months rehabilitation (post-hospitalisation) following a HS/ICH	14 days rehabilitation is assumed following an IS, 28 days rehabilitation is assumed following a HS/ICH
Cost of fatal events	Values from Heeg et al are applied to fatal event health states	KR agreed with this approach	No action required
Cost of bleeding	Costs are taken from NHS reference costs	Preferably use National Tariff for adverse event costs	NHS reference costs are used as they reflect a weighted average reflecting NHS patterns of care and they represent the cost burden to the NHS rather than a reflection of internal reimbursement between NHS organisations. Because reference costs are used for event health states (agreed upon with KR), we use the same source for adverse event costs to ensure consistency in the model.

KR has received honoraria for lectures, advisory boards or for serving as a steering committee member or executive committee member for Pfizer, Novartis, Novo NordDisk, AZ, Abbott, Kowa, Roche, Daiichi Sankyo, Lily, MSD, GSK, BMS, Regeneron, and Sanofi.

Intervention and comparators' costs

7.5.5 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 7.2.2.

Clopidogrel and aspirin are available as generic medicines. The cost of these drugs is taken from the UK Drug Tariff (May 2014). The indicative cost of rivaroxaban is £2.10 per day.

Table 63: Unit costs associated with the technology in the economic model

Drug	Loading Dose	Daily Dose (Maintenance)	Pack Size	Pack Price	Cost of loading dose	Cost per day
Rivaroxaban		2 x 2,5mg	28-tabs	£58.80		£2.10
Clopidogrel	300mg	75mg	28-tabs	£1.74	£0.25	£0.06
Aspirin	300mg	75mg	28-tabs	£0.82	£0.12	£0.03

Health-state costs

7.5.6 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 7.2.4.

As the model is primarily a secondary prevention model predicting the cost-effectiveness of a therapy that is not anticipated to change the acute care of events once they happen, a macro-costing approach is taken for the model, i.e. all treatment costs associated with the treatment of an individual event (excluding the costs of long-term antithrombotic therapy) are compounded into a single cost before being included in the model. The costs of long-term antithrombotic therapy are calculated separately.

The National Reference Costs 2012-2013 is used to provide units costs for MI, IS, HS/ICH, bleeding events (TIMI major excl. ICH, TIMI minor and TIMI requiring medical attention) and revascularisations (PTCA/PCI and CABG). The systematic review is used to provide costs for all types of death considered in the model. The follow up costs for MI and stroke are also taken from the systematic review(66)and Curtis 2013(137). The same unit costs apply to both the comparator and rivaroxaban treatment arms.

Unit costs available in the National Reference Costs 2012-2013 define the initial hospitalisation following an event, however the events simulated in the model result in long term costs and these should be captured throughout the relevant model cycles. Costs implemented in the model consider acute and follow up phases for MI, IS and HS/ICH. The model considers the first

12 weeks to define the acute phase and later 12 weekly cycles refer to the follow on care phase. The costs applied to the acute phase for MI, IS and HS/ICH not only include the unit cost per event but also the costs associated with rehabilitation.

The rehabilitation costs as presented in the table below are based on the NHS reference costs 2012/2013.

There is a unique HRG-code for rehabilitation for myocardial infarction and other cardiac disorders (VC38Z), which is used to describe the rehabilitation of an MI event. The events IS and HS/ICH are described by the same HRG-code - that for rehabilitation for stroke (VC04Z).

The presented costs in Table 64 are weighted average costs, composed of rehabilitation costs made at different rehabilitation service levels and include admitted patient care and other patient care. The costs are weighted for the number of bed days of provided care.

The cost estimates taken from Heeg et al (2007)(66) are inflated and applied to fatal event health states. Follow up costs for MI, IS and HS/ICH are also taken from the Heeg et al (2007) (66) publication (we assume in the absence of costs for HS that the costs for stroke can be used for both IS and HS).

For a number of events (including IS, HS/ICH and TIMI major bleeding) - a weighted average of HRGs in the National Reference Costs 2012-2013 which describe such events are used to provide suitable estimates. The upper and lower quartile costs are also provided in the National Reference Costs 2012-2013 for all costs sourced. Rehabilitation costs associated with MI, IS or HS/ICH are included in the compounded acute phase cost estimates only (described further below).

To estimate the cost of an MI, IS and HS/ICH in the acute phase (which defines the first 12 weeks of the model) the following assumptions are made:

- Unit costs of the event - U(c)
- The number of days for rehabilitation R(d) following an MI, IS and HS/ICH are 5, 14 and 28 days respectively
- The costs of rehabilitation per day is given by R(c)
- The total cost in the acute phase is given by T(acute)= U(c) +R(d)×R(c)
    - For MI the total cost in the acute phase = £2,154.95 + 5×£286.12 = £3,585.55

Table 64 Rehabiliation costs taken from the NHS reference costs 2012/2013

Event	HRG code	Description	Source	Number of days for rehabilitation	Average cost (per day)	Lower quartile costs	Upper quartile costs
MI	VC38Z	Rehabilitation for myocardial infarction and other cardiac disorders	REHAB	5	£286.12	£250.05	£314.76
IS	VC04Z	Rehabilitation for stroke	REHAB	14	£335.15	£279.59	£397.53
HS/ICH	VC04Z	Rehabilitation for stroke	REHAB	28	£335.15	£279.59	£397.53

The costs of follow up care after an MI or stroke event are taken from Heeg et al (2007)(66) and are presented in the table below. The costs provided in Heeg et al have been inflated to 2013 prices by a factor of 1.20. (Curtis, 2013)(137). In the absence of costs for haemorrhagic stroke follow-up the same costs as for ischaemic stroke are assumed.

Table 65: Follow on costs considered in the economic model

Model Description	Heeg et al Description	Cost (from Heeg 2007)	Cost Year	Adjustment for model cycle length	Inflated costs per cycle (2012/2013)
MI second 12 weeks	MI first 6 months	£3300.00	2006	£1650.00 (=£3300.00/2)	£1980.14
MI third and fourth 12 weeks	MI second 6 months	£1200.00	2006	£1200.00	£1440.10
MI follow up (post 1 year)	MI after first year (per 6 months)	£900.00	2006	£900	£1080.07
IS second 12 weeks	Stroke first 6 months/2	£5100.00	2006	£2550.00 (=£5100.00/2)	£3060.21
IS third and fourth 12 weeks	Stroke second 6 months	£3500.00	2006	£3500.00	£4200.29
IS follow up	Stroke after first year (per 6 months)	£2600.00	2006	£2600.00	£3120.22
HS/ICH second 12 weeks	Stroke first 6 months/2	£5100.00	2006	£2550.00 (=£5100.00/2)	£3060.21
HS/ICH third and fourth 12 weeks	Stroke second 6 months	£3500.00	2006	£3500.00	£4200.29
HS/ICH follow up	Stroke after first year (per 6 months)	£2600.00	2006	£2600.00	£3120.22

The model is devised into two parts: observation and extrapolation periods with differing cycle lengths. This impacts how cost estimates are presented and calculated. The following assumptions apply when estimating costs for the remaining 12 weekly cycles (follow-up costs) in the observation period. In the extrapolation period, a cycle is 6 months in length (twice the length of observation period cycles).

- To estimate costs in the second 12 weeks following an event - the costs presented in Heeg et al (2007)(66) for the first 6 months following an event are divided by 2 to obtain a 12-weekly cost estimate
    - The costs of the second 12 weeks following a MI is £3,300/2 = £1,650 the inflated cost is £1,650 × 1.20 (inflation factor) = £1,980.14
- To estimate the costs for the third 12 weeks + the fourth 12 weeks combined - the costs for the second 6 months in the Heeg et al (2007) (66) model is applied.
    - The costs of the 3rd and 4th 12 weeks following an MI is £1,200 and the inflated cost is £1,440.10
        - Cost for the 3rd 12 weeks only following a MI is £1,440.10/2 = £720.05
        - Cost for the 4th 12 weeks only following a MI is £1,440.10/2 = £720.05
- The remaining cycles of 5th 12 weeks + 6th 12 weeks and 7th 12 weeks + 8th 12 weeks are estimated by applying the inflated costs from Heeg et al (2007) (66) after the first year (per 6 months).
    - Cost for 5th and 6th 12 weeks is £900 (Heeg et al 2007) (66) and the inflated cost is £1080.07
        - Cost for the 5th 12 weeks is given by £1080.07/2 = £540.04
        - Cost for the 6th 12 weeks is given by £1080.07/2 = £540.04

    - Cost for 7th and 8th 12 weeks is by £900 (Heeg et al 2007) (66) and inflated cost is £1080.07
        - Cost for the 7th 12 weeks is given by £540.04
        - Cost for the 8th 12 weeks is given by £540.07
- All other 6 monthly cycles in the extrapolation period apply the cost from Heeg et al (2007) (66) after the first year (as seen above for the 5th 12 weekly cycle onwards)
- Heeg et al (2007) (66) defines the upper and lower quartiles by +/- 25% (for follow up costs) of the base value. These margins are implemented in sensitivity analyses conducted on the current model (refer to Table 69 for all costs and their corresponding upper and lower quartiles).

The model considers that patients may experience multiple ACS events. In the absence of specific cost estimates for multiple ACS events such as MI+MI or MI+IS from the systematic review and the National Reference Cost 2012-2013 the sum of individual costs for the acute phases is applied in the model. For the follow-up phases, the sum of the follow-up costs for the individual events is applied if two different events have been experienced. If two events of the same type (e.g. MI + MI) are experienced, then only one set of follow-up costs is applied. This assumption has been verified with a clinical expert (KR) and the following steps are taken for cost estimation:

- Hospitalisations for multiple events were few, even in the overall ATLAS 2 trial (18/1578 hospitalisation were for multiple events) and were balanced between arms. Separate costs are attached to individual events in the acute phase:
    - For a MI + MI the cost is given by £3,585.55 + £3,585.55 = £7,171.10
    - For a MI +IS the cost is given by £3,585.55 + £7,756.05= £11,341.60
- Individual follow on care costs apply to multiple events of unlike events:
    - Separate costs are attached to follow on costs for the second 12 weeks and later periods.
        - For MI + IS in the second 12 weeks is given by £1,980.14 + £3,060.21 = £5,040.35
        - This applies to all other cycles in the model and for all combinations of (unlike) multiple events

Table 66: List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission	Justification
MI	Acute Care (3 months)	£3,585.55	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E) + VC38Z	NHS reference case
	Follow-on care (second 3 months)	£1,980.14	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth 3 months)	£1,440.10	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (later per 3 months)	£540.04	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
IS	Acute Care (3 months)	£7,756.05	NHS reference costs 2012/2013 (Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G) + VC04Z	NHS reference case
	Follow-on care (second 3 months)	£3,060.21	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth 3 months)	£4,200.29	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care	£1,560.11	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS

	(later 3 months)			reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
HS/ICH	Acute Care (3 months)	£12,778.22	NHS reference costs 2012/2013 (Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) +VC04Z	NHS reference case
	Follow-on care (second 3 months)	£3,060.21	Heeg et al (2007)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth 3 months)	£4,200.29		Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (later 3 months)	£1,560.11		Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
Fatal MI		£1,500.10	Heeg et al (2007) (66)	Fatal event costs not provided by NHS reference costs. Heeg et al paper identified via systematic review and health states defined in that paper closely match those in the current model
Fatal IS		£4,500.31	Heeg et al (2007) (66)	Fatal event costs not provided by NHS reference costs. Heeg et al paper identified via systematic review and health states defined in that paper closely match those in the current model
Fatal HS/ICH		£4,500.31	Heeg et al (2007) (66)	Fatal event costs not provided by NHS reference costs. Heeg et al paper identified via systematic review and health states defined in that paper closely match those in the current model
Other CV death		£3,000.21	Heeg et al (2007) (66)	Fatal event costs not provided by NHS reference costs. Heeg et al paper identified via systematic review and health states defined in

				that paper closely match those in the current model
Non-CV death		£300.02	Heeg et al (2007) (66)	Fatal event costs not provided by NHS reference costs. Heeg et al paper identified via systematic review and health states defined in that paper closely match those in the current model
MI + MI	Acute Care (3 months)	£7,171.10	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E) + VC38Z	NHS reference case. Clinical expert opinion (KR) supports the summation of costs of the individual events experienced in the multiple event states
	Follow-on care (second 3 months)	£1,980.14	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth 3 months)	£1,440.10	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (later 3 months)	£540.04	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
IS + IS	Acute Care (3 months)	£15,512.10	NHS reference costs 2012/2013 (Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G) + VC04Z	NHS reference case. Clinical expert opinion (KR) supports the summation of costs of the individual events experienced in the multiple event states
	Follow-on care (second 3 months)	£3,060.21	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth	£4,200.29	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a

	3 months)			systematic review and includes health states which closely match those in the current model
	Follow-on care (later 3 months)	£1,560.11	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
HS/ICH + HS/ICH	Acute Care (3 months)	£25,556.44	NHS reference costs 2012/2013 (Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) + VC04Z	NHS reference case. Clinical expert opinion (KR) supports the summation of costs of the individual events experienced in the multiple event states
	Follow-on care (second 3 months)	£3,060.21	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth 3 months)	£4,200.29	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (later 3 months)	£1,560.11	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
MI + IS	Acute Care (3 months)	£11,341.60	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E plus Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G) + VC04Z + VC38Z	NHS reference case. Clinical expert opinion (KR) supports the summation of costs of the individual events experienced in the multiple event states
	Follow-on care (second 3 months)	£5,040.35	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match

				those in the current model
	Follow-on care (third and fourth 3 months)	£5,640.39	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (later 3 months)	£2,100.15	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
MI + HS/ICH	Acute Care (3 months)	£16,363.77	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E plus Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) + VC04Z + VC38Z	NHS reference case. Clinical expert opinion (KR) supports the summation of costs of the individual events experienced in the multiple event states
	Follow-on care (second 3 months)	£5,040.35	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth 3 months)	£5,640.39	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (later 3 months)	£2,100.15	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
IS + HS/ICH	Acute Care (3 months)	£20,534.27	NHS reference costs 2012/2013 (Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G plus Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) + (2× VC04Z)	NHS reference case. Clinical expert opinion (KR) supports the summation of costs of the individual events experienced in the multiple event states
	Follow-on care	£6,120.42	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS

	(second 3 months)			reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth 3 months)	£8,400.58	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (later 3 months)	£3,120.22	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
3 Events	Acute Care (3 months)	£24,119.82	NHS reference costs 2012/2013 (Weighted average of EB10A, EB10B, EB10C, EB10D, EB10E plus Weighted average of AA22C, AA22D, AA22E, AA22F, AA22G plus Weighted average of AA23C, AA23D, AA23E, AA23F, AA23G) + VC38Z + (2×VC04Z)	NHS reference case. Clinical expert opinion (KR) supports the summation of costs of the individual events experienced in the multiple event states
	Follow-on care (second 3 months)	£8,100.56	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (third and fourth 3 months)	£9,840.68	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model
	Follow-on care (later 3 months)	£3,660.25	Heeg et al (2007) (66)	Follow-up costs beyond hospitalisation are not provided by NHS reference costs. The Heeg et al paper was identified via a systematic review and includes health states which closely match those in the current model

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. 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 7.2.2.

The National Reference Costs 2012-2013 is used to provide unit costs for bleeding events (TIMI major excl. ICH, TIMI minor and TIMI requiring medical attention). The costs for bleeding events are one off costs based on the related HRG-code costs as found in the National Reference Costs 2012-2013. For major bleeds and TIMI requiring medical attention weighted average costs of HRGs that represent very similar events that fall under wider umbrella terms in the National Reference Costs 2012-2013 are used. Moreover, the related HRG-code costs are weighted average costs for the HRGs treated in different health care services. For TIMI minor bleeds, only one HRG is used (VB11Z).

Table 67 List of adverse events and summary of costs included in the economic model

Adverse events	Value	Reference in submission
TIMI Major Bleed	£669.83	NHS reference costs 2012/2013 (Weighted average of FZ24G, FZ24H, FZ24J, FZ27E, FZ27F, FZ27G, FZ38G, FZ38H, FZ38J, FZ28K, FZ38M, FZ38N, FZ38L, FZ38P, FZ59Z, FZ60Z, FZ70Z, FZ83G, FZ83H, FZ83J, FZ83K)
TIMI Minor Bleed	£67.79	NHS reference costs 2012/2013 (VB11Z)
Bleed requiring medical attention	£130.26	NHS reference costs 2012/2013 (Weighted average of VB01Z, VB02Z, VB03Z, VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z)

Miscellaneous costs

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

The National Reference Costs 2012-2013 is used to provide units costs for revascularisation procedures. The costs for revascularisations are one off costs available as unit costs found in the National Reference Costs 2012-2013. For revascularisation events weighted average costs of HRGs that represent very similar events that fall under the wider umbrella terms (e.g. PCI/PTCA) in the National Reference Costs 2012-2013 are used. As the revascularisation procedures can be performed in different health care departments, the HRG reference costs used to calculate the revascularisation event costs are average costs weighted for the number of procedures in the different departments.

Table 68: Revasculation costs included in the economic model

Revascularisation	Value	Reference in submission
PTCA / PCI	£2,081.77	NHS reference costs 2012/2013 (Weighted average of EA31A, EA31B, EA31C, EA31D, EA49A, EA49B, EA49C, EA49D)
CABG	£9,618.84	NHS reference costs 2012/2013

		(Weighted average of EA14A, EA14B, EA14C, EA14D, EA16A, EA16B, EA16C, EA16D)

7.6 Sensitivity analysis

7.6.1 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.

A number of the structural assumptions applied in the model are varied in scenario analyses.

An analysis is considered in which patients are assumed not to be at risk of subsequent events if they have already experienced an MI, IS or HS/ICH. This analysis models only single events. Modelling only the first secondary CV event is something applied by many economic models exploring secondary prevention in ACS patients. (Berg 2008, Berg 2007, Bruggenjurgen 2007, Cowper 2005, Karnon 2006, Karnon 2010, Latour-Perez 2008, Latour-Perez 2004, Schleinitz 2005, Schleinitz 2004, Zhang 2009, Bagust 2011, SMC 2011, Main 2004, Rogowski 2009, Crespin 2011, NICE 2012, Coleman 2013a, Coleman 2014, Straub 2014, Grima 2014, Theidel 2013(43;49-53;55;60;62;70;71;79-81;88;93-96;99;100;104))

The impact of not assuming an increased risk of events due to ageing is also considered. Again, the assumption that event risk increases with age is not often considered in ACS models. (Berg 2008, Berg 2007, Bruggenjurgen 2007, Cowper 2005, Karnon 2006, Karnon 2010, Latour-Perez 2008, Latour-Perez 2004, Schleinitz 2005, Schleinitz 2004, Zhang 2009, Bagust 2011, SMC 2011, Main 2004, Rogowski 2009,NICE 2012(43;49-52;55;70;71;79;80;88;93;95;96;99;104))

A further analysis removes the assumptions that event risk is influenced by age and prior events. Here, transition probabilities are assumed constant throughout the extrapolation period. This approach is in line with a number of previously published ACS models. (Berg 2008, Berg 2007, Bruggenjurgen 2007, Cowper 2005, Karnon 2006, Karnon 2010, Latour-Perez 2008, Latour-Perez 2004, Schleinitz 2005, Schleinitz 2004, Zhang 2009, Bagust 2011, SMC 2011, Main 2004, Rogowski 2009, NICE 2012(43;49-52;55;70;71;79;80;88;93;95;96;99;104)).

7.6.2 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 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

In the cost-effectiveness model non-efficacy and efficacy related parameters are considered in different ways for the purpose of the sensitivity analyses. The safety events are included as non-efficacy related parameters, and uncertainty is applied to the duration and costs associated with bleeding events and revascularisations in the deterministic sensitivity analysis. The primary endpoints in the ATLAS 2 trial include the composite of cardiovascular

death, MI or stroke. The deterministic analysis reflects the primary endpoints by investigating the difference in transition probabilities for MI, IS, HS/ICH and OCD within the observation period. Non- cardiovascular death is not included in the analysis as this was not considered independently in the primary or secondary endpoints.

Efficacy related inputs considered in the sensitivity analyses are:

- The difference in event rates for non-fatal MI between the comparator and rivaroxaban arms
- The difference in event rates for non-fatal IS between the comparator and rivaroxaban arms
- The difference in event rates for non-fatal HS/ICH between the comparator and rivaroxaban arms
- The difference in event rates for other cardiovascular (OCD) death between the comparator and rivaroxaban arms. The OCD death state includes fatal MI, fatal IS, fatal HS/ICH and fatal bleeds. Due to the small numbers for each fatal event these events are grouped together for the purposes of the sensitivity analyses. The transition probabilities in the model are estimated separately for fatal MI, fatal IS and fatal HS/ICH using the combined OCD to calculate these.

Please note that unlike the differences for efficacy data for MI, IS, HS/ICH and OCD, the safety trial data for bleeding events and revascularisations are not considered using this approach. Bleeding events and revascularisations have short-term complications and impact on the quality of life of a patient. In the model they are considered as transient health states and essentially the differences between the events are captured by taking the one off costs and disutilities attached to these events. An approach that looks at differences (in a similar way to the differences for efficacy related data) in the safety data will have have minimal impact on the overall model outcomes.

Uncertainty margins cannot be directly applied to efficacy data as it is currently presented in the cost-effectiveness model. The model presents individual transition probabilities that are time dependent with many zero values present in each transition probability matrix. It is always difficult to consider suitable (if any) uncertainty that surrounds the probability of 0. Therefore, an alternative approach is taken which looks at the difference in the risk of events for non-fatal MI, non-fatal IS, non-fatal HS/ICH and OCD (these are the primary efficacy endpoints considered in the ATLAS 2 trial) across the comparator and rivaroxaban treatment arms.

The uncertainty surrounding the efficacy data is addressed using the following steps:

- A probabilistic sensitivity analysis using a normal distribution (taking the Weibull parameter estimates for MI, IS, HS/ICH and OCD) to provide the uncertainty in the model is run
- Using the values obtained from the PSA the mean and standard deviation for the relevant difference in event rates is estimated
- This is then used to find the 95% confidence interval range (x +/- 1.96 × standard error)
- A regression analysis is then applied to determine the corresponding upper and lower ICER values for the univariate sensitivity analysis

    - This method is very different from how the other input parameters are considered in the model as we are taking the upper and lower ICER based on the PSA and regression analyses, instead of applying factors to the input parameters

Non-efficacy related input parameters considered in the sensitivity analyses are:

- Cost of rivaroxaban
- Discount rates
- Utility per event (including the bleeding and revascularisation events)
- Cost per non-fatal event (including the bleeding and revascularisation events)
    - Event acute care costs
    - Event follow up costs
- Cost for all fatal events
- Annual age specific % increase per event
- Age specific initial case fatalities
- Initial case fatalities
- Duration of disutility for each bleeding and revascularisation event
- Continuation rates in both treatment arms
- Relative risk of later events

The uncertainty margins for the univariate sensitivity analyses for costs taken from the National Reference Costs 2012-2013 are based on the upper and lower quartile average costs provided in the same source.

Discount rates are varied using the NICE recommendations of applying a factor of 0 and 2 for the lower and upper limits.

For all other remaining non-efficacy input parameters large uncertainty margins based on uniform distributions are assumed. The non-efficacy parameters varied in this way are:

- Cost of rivaroxaban
- Utilities (please note that utility values are capped to a maximum value of 1 in the model sensitivity analyses as utilities, by definition, cannot take a value greater than 1)
- Costs of fatal events
- Event follow-up costs
- Annual age specific % increase per non-fatal event
- Age specific % increase of case fatalities
- Initial case fatalities
- Duration of disutility
- Continuation rates in both treatment arms
- Relative risks of later events

To examine which parameters have significant impact on the model outcomes it is important to chose uncertainty margins which are sufficiently wide enough to account for the large uncertainty surrounding some of the model parameters for which limited data is available. A 25% margin either side of the input value is considered (this is supported by Heeg et al 2006) for all inputs with the exception of the cost of rivaroxaban, relative risk of later events, increased risks of events due to age, and the initial case fatalities. In these cases greater uncertainty margins are considered to reflect the greater uncertainty around these inputs,

particularly as these inputs are not often included in other ACS models. In these cases, a 50% increase and decrease of the mean value is applied in univariate analyses.

7.6.3 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 7.3.6, 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).

A probabilistic analysis was undertaken. The uncertainty surrounding the efficacy data in the PSA is the same as is applied in the deterministic analyses and is described in section 7.5.10. For the remaining (non-efficacy related including the safety trial data where uncertainty surrounding the proportion of bleeds and revascularisations are applied) input parameters beta distributions are applied to provide uncertainty for each iteration of the PSA. The beta distribution is defined as β(x, α, γ) where α and γ are both positive scale parameters. Analyses of the cost-effectiveness model found that a beta distribution with a scale of 0.5 for both α and γ provided a good fit to the trial data. The beta distribution has an interval of [0,1] and to implement greater uncertainty we apply minimum (min) and maximum (max) values of 0.75 and 1.25 respectively (hence providing 25 % variability). All inputs varied in the PSA, along with their distributions and uncertainty margins are provided in the table below.

Table 69: PSA distributions

Input	Mean Value	Distribution	Minimum	Maximum
EVENT RATES				
Difference in MI between comparator and rivaroxaban arms	0.04 %	Beta	0.0317%	0.0529%
Difference is IS between comparator and rivaroxaban arms	-0.01%	Beta	-0.0082 %	-0.0049 %
Difference is HS/ICH between comparator and rivaroxaban arms	-0.02 %	Beta	-0.0204 %	-0.0122 %
Difference is OCD between comparator and rivaroxaban arms	0.08 %	Beta	0.0576 %	0.0960 %
Safety data				
TIMI major bleeding: rivaroxaban	1.44%	Beta	1.08%	1.80%
TIMI minor bleeding: rivaroxaban	0.68%	Beta	0.51%	0.85%
TIMI requiring medical attention: rivaroxaban	12.57%	Beta	9.43%	15.72%
PCI/PTCA: rivaroxaban	15.52%	Beta	11.64%	19.40%
CABG: rivaroxaban	2.41%	Beta	1.81%	3.02%
TIMI major	0.48%	Beta	0.36%	0.60%

bleeding: comparator				
TIMI minor bleeding: comparator	0.53%	Beta	0.40%	0.66%
TIMI requiring medical attention: comparator	5.96%	Beta	4.47%	7.45%
PCI/PTCA: comparator	13.25%	Beta	9.93%	16.56%
CABG: comparator	2.55%	Beta	1.91%	3.19%
UTILITY VALUES				
No event	0.842	Beta	0.633	1.000
MI 1st 6 months	0.779	Beta	0.586	0.974
MI 2nd 6 months	0.821	Beta	0.617	1.000
MI later (post 12 months)	0.821	Beta	0.617	1.000
IS 1st 6 months	0.703	Beta	0.529	0.879
IS 2nd 6 months	0.748	Beta	0.562	0.935
IS later (post 12 months)	0.792	Beta	0.594	0.990
HS/ICH 1st 6 months	0.703	Beta	0.529	0.879
HS/ICH 2nd 6 months	0.748	Beta	0.562	0.935
HS/ICH later (post 12 months)	0.792	Beta	0.5946	0.990
MI + MI 1st 6 months	0.607	Beta	0.456	0.759
MI + MI 2nd 6 months	0.674	Beta	0.507	0.843
MI + MI later (post 12 months)	0.674	Beta	0.507	0.843
IS+ IS 1st 6 months	0.494	Beta	0.371	0.618
IS +IS 2nd 6 months	0.559	Beta	0.419	0.698
IS + IS later (post 12 months)	0.627	Beta	0.472	0.784
HS/ICH + HS/ICH 1st 6 months	0.494	Beta	0.371	0.618
HS/ICH + HS/ICH 2nd 6 months	0.559	Beta	0.419	0.699
HS/ICH + HS/ICH later (post 12 months)	0.627	Beta	0.472	0.784
MI + IS 1st 6 months	0.548	Beta	0.412	0.685
MI + IS 2nd 6 months	0.614	Beta	0.462	0.767
MI + IS later (post 12 months)	0.650	Beta	0.489	0.813
MI + HS/ICH 1st 6 months	0.548	Beta	0.412	0.685
MI +HS/ICH 2nd 6 months	0.614	Beta	0.462	0.767
MI + HS/ICH later (post 12 months)	0.650	Beta	0.489	0.813
IS + HS/ICH 1st 6 months	0.494	Beta	0.372	0.618
IS + HS/ICH 2nd 6 months	0.559	Beta	0.419	0.699
IS + HS/ICH later	0.627	Beta	0.472	0.784

(post 12 months)				
3 events 1st 6 months	0.385	Beta	0.289	0.481
3 events 2nd 6 months	0.459	Beta	0.345	0.574
3 events later (post 12 months)	0.515	Beta	0.387	0.644
PCI/PTCA	0.792	Beta	0.596	0.990
CABG	0.742	Beta	0.558	0.928
TIMI Major bleeding	0.750	Beta	0.564	0.938
TIMI Minor bleeding	0.800	Beta	0.600	1.000
TIMI requiring medical attention	0.800	Beta	0.600	1.000
DIRECT COSTS				
no event comparator per 12 weeks	£7.68	Beta	£5.76	£9.60
No event rivaroxaban per 12 weeks	£184.08	Beta	£138.06	£230.10
MI - first three months (acute phase)	£3,585.55	Beta	£2,915.05	£4,062.43
MI- second three months	£1,980.14	Beta	£1,485.11	£2,475.18
MI second 6 months	£1,440.10	Beta	£1,080.08	£1,800.13
MI post 12 months (per 6 months)	£1,080.08	Beta	£810.06	£1,350.10
IS- first three months (acute phase)	£7,756.05	Beta	£5,972.16	£9,307.26
IS -second three months	£3,060.21	Beta	£2,295.16	£3,825.26
IS second 6 months	£4,200.29	Beta	£3,150.22	£5,250.36
IS post 12 months (per 6 months)	£3,120.22	Beta	£2,340.17	£3,900.28
HS/ICH- first three months (acute phase)	£12,778.22	Beta	£10,069.24	£15,295.53
HS/ICH -second three months	£3,060.21	Beta	£2,295.16	£3,825.26
HS/ICH second 6 months	£4,200.29	Beta	£3,150.22	£5,250.36
HS/ICH post 12 months (per 6 months)	£3,120.22	Beta	£2,340.17	£3,900.28
PCI/PTCA	£2,081.77	Beta	£1,353.15	£2,637.60
CABG	£9,618.84	Beta	£7,444.98	£11,282.90
TIMI Major bleeding	£669.83	Beta	£493.00	£782.36
TIMI Minor bleeding	£67.79	Beta	£48.94	£80.40
TIMI requiring medical attention	£130.26	Beta	£109.16	£148.76
other cardiovascular death	£3,000.21	Beta	£2,250.16	£3,750.26
non cardiovascular death	£300.02	Beta	£225.02	£375.03

death MI	£1,500.10	Beta	£1,125.08	£1,875.13
death IS	£4,500.31	Beta	£3,375.23	£5,625.39
death HS/ICH	£4,500.31	Beta	£3,375.23	£5,625.39
INCREASE IN EVENTS DUE TO AGE [17]				
MI	8.70%	Beta	6.53%	10.88%
IS	10.65%	Beta	7.98%	13.31%
HS/ICH	10.73%	Beta	8.05%	13.41%
Other CV death	10.03%	Beta	7.52%	12.53%
Non-CV death	10.28%	Beta	7.71%	12.85%
Case fatality MI	-13.90% [18]	Beta	-10.42%	-17.37%
Case fatality IS	-9.00%	Beta	-6.75%	-11.25%
Case fatality HS/ICH	-9.00%	Beta	-6.75%	-11.25%
RELATIVE RISK LATER EVENTS				
After MI				
MI (1st 6 months)	4.9	Beta	3.7	6.1
MI (2nd 6 months)	2.1	Beta	1.6	2.6
MI (later)	1.5	Beta	1.1	1.9
IS (1st 6 months)	3.2	Beta	2.4	4.0
IS (2nd 6 months)	1.8	Beta	1.4	2.3
IS (later)	1.5	Beta	1.1	1.9
HS/ICH (1st 6 months)	1.0	Beta	0.8	1.3
HS/ICH (2nd 6 months)	1.0	Beta	0.8	1.3
HS/ICH (later)	1.5	Beta	1.1	1.9
Fatal MI (1st 6 months)	4.9	Beta	3.7	6.1
Fatal MI (2nd 6 months)	2.1	Beta	1.6	2.6
Fatal MI (later)	1.5	Beta	1.1	1.9
Fatal IS (1st 6 months)	3.2	Beta	2.4	4.0
Fatal IS (2nd6 months)	1.8	Beta	1.4	2.3
Fatal IS (later)	1.5	Beta	1.1	1.9
Fatal HS/ICH (1st 6 months)	1.0	Beta	0.8	1.3
Fatal HS/ICH (2nd 6 months)	1.0	Beta	0.8	1.3
Fatal HS/ICH (later)	1.5	Beta	1.1	1.9
Other CV Death (1st 6 months)	3.0	Beta	2.3	3.8
Other CV Death (2nd 6 months)	1.6	Beta	1.2	2.0
Other CV Death (later)	1.5	Beta	1.1	1.9
After IS				
MI (1st 6 months)	4.9	Beta	3.7	6.1
MI (2nd 6 months)	2.1	Beta	1.6	2.6
MI (later)	1.5	Beta	1.1	1.9
IS (1st 6 months)	3.2	Beta	2.4	4.0

[17] The increase risks due to age are estimated by means of calibration and these values are implemented into each model cycle within the extrapolation period to account for the increasing risk of suffering fatal and non-fatal events within the ageing population. Using these values the model is able to predict the average annual age specific risk of suffering fatal and non-fatal events extracted from literature (Smolina et al 2012 and Hippisley-Cox et al 2004)

[18] Negative values are caused by the increasing competing risk of OCD and NCD, reducing the risk of fatal MI, IS and HS

IS (2nd 6 months)	1.8	Beta	1.4	2.3
IS (later)	1.5	Beta	1.1	1.9
HS/ICH (1st 6 months)	1.0	Beta	0.8	1.3
HS/ICH (2nd 6 months)	1.0	Beta	0.8	1.3
HS/ICH (later)	1.5	Beta	1.1	1.9
Fatal MI (1st 6 months)	4.9	Beta	3.7	6.1
Fatal MI (2nd 6 months)	2.1	Beta	1.6	2.6
Fatal MI (later)	1.5	Beta	1.1	1.9
Fatal IS (1st 6 months)	3.2	Beta	2.4	4.0
Fatal IS (2nd6 months)	1.8	Beta	1.4	2.3
Fatal IS (later)	1.5	Beta	1.1	1.9
Fatal HS/ICH (1st 6 months)	1.0	Beta	0.8	1.3
Fatal HS/ICH (2nd 6 months)	1.0	Beta	0.8	1.3
Fatal HS/ICH (later)	1.5	Beta	1.1	1.9
Other CV Death (1st 6 months)	3.0	Beta	2.3	3.8
Other CV Death (2nd 6 months)	1.6	Beta	1.2	2.0
Other CV Death (later)	1.5	Beta	1.1	1.9
After HS/ICH				
MI (1st 6 months)	1.0	Beta	0.8	1.3
MI (2nd 6 months)	1.0	Beta	0.8	1.3
MI (later)	1.5	Beta	1.1	1.9
IS (1st 6 months)	1.0	Beta	0.8	1.3
IS (2nd 6 months)	1.0	Beta	0.8	1.3
IS (later)	1.5	Beta	1.1	1.9
HS/ICH (1st 6 months)	4.9	Beta	3.7	6.1
HS/ICH (2nd 6 months)	2.1	Beta	1.6	2.6
HS/ICH (later)	1.5	Beta	1.1	1.9
Fatal MI (1st 6 months)	1.0	Beta	0.8	1.3
Fatal MI (2nd 6 months)	1.0	Beta	0.8	1.3
Fatal MI (later)	1.5	Beta	1.1	1.9
Fatal IS (1st 6 months)	1.0	Beta	0.8	1.3
Fatal IS (2nd6 months)	1.0	Beta	0.8	1.3
Fatal IS (later)	1.5	Beta	1.1	1.9
Fatal HS/ICH (1st 6 months)	4.9	Beta	3.7	6.1
Fatal HS/ICH (2nd 6 months)	2.1	Beta	1.6	2.6
Fatal HS/ICH (later)	1.5	Beta	1.1	1.9
Other CV Death (1st 6 months)	1.0	Beta	0.8	1.3
Other CV Death (2nd 6 months)	1.0	Beta	0.8	1.3
Other CV Death (later)	1.5	Beta	1.1	1.9

CASE FATALITY				
MI	13.37%	Beta	10.63%	16.71%
IS	11.65%	Beta	8.74%	14.56%
HS/ICH	11.65%	Beta	8.74%	14.56%
DECREASE IN EVENTS OVER TIME (proportion of events occurring in comparison to first 6 months)				
MI 2nd 6 months	41.72%	Beta	31.29%	52.15%
MI later	30.45%	Beta	22.84%	38.06%
IS 2nd 6 months	55.87%	Beta	41.90%	69.84%
IS later	47.36%	Beta	35.52%	59.20%
Other CV death 2nd 6 months	33.00%	Beta	24.75%	41.25%
Other CV death later	33.00%	Beta	24.75%	41.25%
EFFICACY IN COMPARATOR ARM FOLLOWING DISCONTINUATION OF CLOPIDOGREL				
Relative efficacy	80%	Beta	60%	100%
CONTINUATION RATES [19]				
Rivaroxaban continuation rate: after MI, rivaroxaban	94.69%	Beta	71.02%	100%
Rivaroxaban continuation rate: after IS, rivaroxaban	54.29%	Beta	40.72%	67.86%
Thienopyridine continuation rate: after MI, rivaroxaban	69.27%	Beta	51.95%	86.59%
Thienopyridine continuation rate: after MI, comparator	70.74%	Beta	53.06%	88.43%
Thienopyridine continuation rate: after IS, rivaroxaban	66.67%	Beta	50.00%	83.34%
Thienopyridine continuation rate: after IS, comparator	50.00%	Beta	37.50%	62.50%
Overall continuation on the treatment: rivaroxaban	68.98%	Beta	51.74%	86.23%
Overall continuation on the treatment: comparator	59.05%	Beta	44.29%	73.81%
DURATION OF DISUTILITIES (proportion of a year)				
Duration of TIMI major	0.0822	Beta	0.0617	0.1028
Duration of TIMI minor	0.0055	Beta	0.0041	0.0069
Duration of TIMI req med attention	0.0055	Beta	0.0041	0.0069
Duration of PCI/PTCA	0.0822	Beta	0.0617	0.1028

[19] A proportion of patients discontinue the study (rivaroxaban) treatment following an event. A proportion of patients also discontinue thienopyridine in both the rivaroxaban and comparator arm.

Duration of CABG	0.2301	Beta	0.1726	0.2876
WEIBULL PARAMETER FOR THE COMPARATOR ARM (interpolation of the ATLAS 2 trial data)				
MI (mu)	12.543180	Normal	12.263131	12.823229
MI (lambda)	-1.017409	Normal	-1.047144	0.987674
IS (mu)	16.873670	Normal	16.131453	17.615887
IS (lambda)	-0.931947	Normal	-0.980898	-0.0882995
HS/ICH (mu)	13.139670	Normal	12.302669	13.976671
HS/ICH (lambda)	-0.390599	Normal	-0.472618	0.308580
OCD (mu)	15.383190	Normal	14.983563	15.782817
OCD (lambda)	-1.083073	Normal	-1.116170	1.049976
NCD (mu)	10.780540	Normal	10.372252	11.188828
NCD (lambda)	-0.208511	Normal	-0.264369	0.152654
WEIBULL PARAMETER FOR THE RIVAROXABAN ARM (interpolation of the ATLAS 2 trial data)				
MI (mu)	12.169226	Normal	11.889176	12.449275
MI (lambda)	-1.017409	Normal	-1.047144	-0.987674
IS (mu)	17.235764	Normal	16.493547	17.977981
IS (lambda)	-0.931947	Normal	-0.980898	-0.0882995
HS/ICH (mu)	14.171658	Normal	13.334657	15.008659
HS/ICH (lambda)	-0.390599	Normal	-0.472618	-0.308580
OCD (mu)	14.035403	Normal	13.635776	14.435029
OCD (lambda)	-1.083073	Normal	-1.116170	-1.049976
NCD (mu)	10.580387	Normal	10.172099	10.988675
NCD (lambda)	-0.208511	Normal	-0.264369	-0.152654

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), 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 70: Summary of model results compared with clinical data for the observation period

	Clinical trial result (licensed population)	Model result (from interpolation)
Rivaroxaban		
MI	4.24%	5.92%
IS	0.58%	0.80%
HS/ICH	0.19%	0.27%
OCD	1.54%	3.41%
NCD	0.39%	0.90%
Comparator	**Clinical trial result**	**Model result (from interpolation)**
MI	4.83%	6.42%
IS	0.50%	0.72%
HS/ICH	0.10%	0.17%
OCD	2.60%	4.57%
NCD	0.46%	0.96%

If we compare the actual trial data for the label population and the interpolated data obtained by applying parametric techniques to estimate the transition probabilities as presented in Table 70 – it is immediately interpretable that the efficacy data is much lower than that predicted by the base case parametric approach. As discussed in 7.3.1 due to few observations towards the end of the trial, it is difficult to estimate the transition probabilities directly from the ATLAS 2 trial data, particularly for the later cycles within the observation period. The ATLAS 2 trial data is interpolated using a Weibull parametric approach to help "smooth" the data by removing fluctuations caused by fewer observations. The Weibull parameter estimates are based on the licensed population data from the ATLAS 2 trial for non-fatal MI, non-fatal IS, non-fatal HS/ICH and NCD. The parameters are then used to estimate the transition probabilities for each 12 weekly cycle of the observation period for all the health states considered in the model.

7.7.2 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.

The Markov traces for the comparator and rivaroxaban are presented in Appendix 15 and these summarise all the health states considered in the model. The markov traces presented in Appendix 15 do not differentiate between the tunnel states considered in the model (first six months, second six months, and later). The observation period is 12 weeks to mimic the ATLAS 2 trial and the cycle length in the extrapolation period is 6 months.

7.7.3 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.

The model applies QALYs to each cycle by applying a half cycle correction to each non-fatal health state. The QALYs are calculated as the number of patients (N_e) present in each health state at the end of each cycle multiplied by the corresponding utility value (U_e).

- QALYs is given by $N_e \times U_e$

The model does not apply utility values to the fatal events in the base case. Utility values are applied to the fatal death states as a scenario analysis and the results are presented in 7.7.9.

7.7.4 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.

The model outcomes are presented in Table 71 and Table 72. Table 71 presents outcomes for no event, non-fatal MI, non-fatal IS, non-fatal HS/ICH, later events and death (only applicable to costs). Model outcomes for the non-fatal events for MI, IS and HS/ICH include both first and secondary events. For example non-fatal MI include patients who suffer a MI and MI+MI. The later event category presented in Table 71 captures all other combination of non-fatal secondary and tertiary events (MI+IS, MI+HS/ICH, IS+HS/ICH and 3 events or more). Table 72 presents model outcomes for the transient health states for TIMI major, TIMI minor, TIMI requiring medical attention, PCI/PTCA and CABG. Please note that bleeding events and revascularisations are transient health states and therefore captured only as a cost and disutility in the model.

Table 71 Model outputs by clinical outcomes

Outcome	**LY**	**QALY**
Rivaroxaban		
No event	9.75	8.21
Non-fatal MI	1.36	1.09
Non-fatal IS	0.19	0.15
Non-fatal HS	0.07	0.06
Later events	0.11	0.07
Death	-	-
	LY	**QALY**
Comparator		
No event	9.58	8.07
Non-fatal MI	1.40	1.12
Non-fatal IS	0.18	0.14
Non-fatal HS	0.06	0.05
Later events	0.11	0.07
Death		
LY, life years; QALY, quality-adjusted life year		

The life years and QALYs are greatest in the no event health states for both the comparator and rivaroxaban arms. The decrements in QALYs resulting from bleeding events and revascularisations suggests that revascularisations (PCI/PTCA and CABG) provide the greatest decrement in both the rivaroxaban and comparator arms resulting from a greater frequency of such events reported in the trial data.

Table 72 Model outputs by clinical outcomes: decrements of bleeds and revascularisations

Outcome	LY	QALY
Rivaroxaban		
TIMI major bleeding	-	0.0001
TIMI minor bleeding	-	0.0000
TIMI requiring medical attention	-	0.0000
PCI/PTCA	-	0.0006
CABG	-	0.0006
	LY	**QALY**
Comparator		
TIMI major bleeding	-	0.0000
TIMI minor bleeding	-	0.0000
TIMI requiring medical attention	-	0.0000
PCI/PTCA	-	0.0005
CABG	-	0.0006
LY, life years; QALY, quality-adjusted life year		

7.7.5 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 73 and Table 74 present the QALYs gained and the costs per health state over the 40 year time horizon (rivaroban treatment duration of 2 years and comparator duration of 1 year) following their index ACS event when we apply an indicative rivaroxaban price of £2.10 per day (current price of rivaroxaban). The patients treated with rivaroxaban in addition to standard of care (ASA + thienopyridine) accrued 9.56 QALYs and costs of £14,767.63. Patients treated with standard of care only (comparator arm) accrued 9.44 QALYs and costs of £14,004.05. This suggests there is a difference in QALYs of 0.12 and costs of £763.58 between rivaroxaban and the comparator arm. The breakdown of costs by event suggest that patients treated with rivaroxaban experience fewer non-fatal MIs and fatal events. The number of later events which accounts for all types of multiple events (MI + IS, M+HS/ICH, IS+HS/ICH and 3 events or more) is greater - as patients live longer when compared to the standard of care where patients have a greater risk of experiencing fatalities overall. The number of IS and HS events is also higher with rivaroxaban.

Table 73: Summary of QALY gain by health state

Health state	**QALY intervention (Rivaroxaban)**	**QALY comparator CLO+ASA or ASA (ie both strata)**	**Increment**	**Absolute increment**	**% absolute increment**
No event	8.21	8.07	0.14	0.13	73.63%
Non-fatal MI	1.09	1.12	-0.03	0.03	17.45%
Non-fatal IS	0.15	0.14	0.01	0.01	4.18%
Non-fatal HS	0.06	0.05	0.01	0.01	4.08%
Later events	0.07	0.07	0.00	0.00	0.54%
Death					
Sub-total (1)	*9.56*	*9.44*	*0.12*	*0.18*	*99.89%*
Transient health states	**QALY intervention (Rivaroxaban)**	**QALY comparator CLO+ASA or ASA (ie both strata)**	**Increment**	**Absolute increment**	**% absolute increment**
TIMI major bleeding	0.0001	0.0000	0.0001	0.0001	0.04%
TIMI minor bleeding	0.0000	0.0000	0.0000	0.0000	0.00%
TIMI requiring medical attention	0.0000	0.0000	0.0000	0.0000	0.01%
PCI/PTCA	0.0006	0.0005	0.0001	0.0001	0.05%
CABG	0.0006	0.0006	0.0000	0.0000	0.02%
Sub-total (2)	*0.0013*	*0.0012*	*0.0002*	*0.0002*	*0.11%*
Total (sub-total (1) – sub-total (2))	**9.56**	**9.44**	**0.12**	**0.19**	**100%**

QALY, quality-adjusted life year

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

Table 74 Summary of costs by health state

Health state	**Cost intervention (Rivaroxaban)**	**Cost comparator CLO+ASA or ASA (ie both strata)**	**Increment**	**Absolute increment**	**% absolute increment**
No event (treatment only)	£716.04	£46.90	£669.14	£669.14	56.00%
Non-fatal MI	£6,270.83	£6,422.27	-£151.44	£151.44	12.67%
Non-fatal IS	£2,381.05	£2,263.80	£117.25	£117.25	9.81%
Non-fatal HS	£960.26	£846.08	£114.18	£114.18	9.56%
Later events	£2,612.28	£2,596.15	£16.13	£16.13	1.35%
Death	£1,245.55	£1,296.67	-£51.12	£51.12	4.28%
Sub- total (1)	*£14,186.01*	*£13,471.88*	*£714.13*	*£1,119.26*	*93.67%*
Transient health state	**Cost intervention (Rivaroxaban)**	**Cost comparator CLO+ASA or ASA (ie both strata)**	**Increment**	**Absolute increment**	**% absolute increment**
TIMI major bleeding	£9.63	£3.22	£6.41	£6.41	0.54%
TIMI minor bleeding	£0.46	£0.36	£0.10	£0.10	0.01%
TIMI requiring medical attention	£16.38	£7.77	£8.61	£8.61	0.72%
PCI/PTCA	£323.12	£275.73	£47.39	£47.39	3.97%
CABG	£232.03	£245.10	-£13.06	£13.06	1.09%
Sub –total (2)	*£581.62*	*£532.17*	*£49.45*	*£75.57*	*6.33%*
Total (sub-total (1) + sub-total (2))	**£14,767.63**	**£14,004.05**	**£763.58**	**£1,194.84**	**100%**

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

Base-case analysis

7.7.6 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 75: Base-case results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) incremental (LYG)	ICER (£) incremental (QALYs)
Rivaroxaban	£14,767.63	11.48	9.56	£763.58	0.15	0.12	£5,244.00	£6,202.84
CLO+ASA or ASA (ie both strata)	£14,004.05	11.34	9.44					
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 76 : Base-case results- (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Rivaroxaban	£14,802.17	9.53	£702.98	0.13	£6,297.56
CLO+ASA or ASA (ie both strata)	£14,099.20	9.40			
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Table 75 and Table 76 present the deterministic results for the base case scenario and the probabilistic results where an average is taken over the 1000 iterations from the PSA results also for the base case scenario. It can be interpreted from the deterministic results that rivaroxaban may be considered cost-effective when compared to the standard of care (ASA + clopidogrel) with an ICER of £6,202.84 per QALY estimated from the model. The probabilistic results also present a cost-effectiveness ratio of £6,297.56 per QALY, which is well within the accepted threshold for cost-effectiveness.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Figure 34 and Figure 35 present the tornado plots derived from the deterministic sensitivity analysis for the non-efficacy and efficacy related input parameters. Table 77 and Table 78 provide the outputs from both sensitivity analyses. The tornado plot and corresponding outputs for the non-efficacy related inputs presented in the tables show that the model is robust to changes in these parameters, with a large proportion of the parameters tested having minimal impact on the overall ICER. The key parameters (the top 5 most influential) that affect the overall ICER when conducting the sensitivity analysis are as follows:

1. Cost of rivaroxaban: the cost of rivaroxaban is considerably higher than clopidogrel, ASA or combined clopidogrel + ASA. In the model the cost of events are considered to be the same for both treatment arms which suggests that the cost of the intervention will impact greatly on the model. Please note that we do not test the sensitivity around the cost of comparator treatment of either ASA, clopidogrel or combined as

they are not under investigation here and also the current standard of care is given to patients in both treatment arms.

2. Utility no event: the baseline utility will have significant impact on the overall ICER as the number of patients who remain in the event free health state is considerably greater than the number of patients experiencing fatal or non-fatal ACS events.

3. Discount rates: the discount rates impact on the overall ICER as this is applied to all non-fatal and fatal events. Discount rates apply to the QALYs and costs for each cycle in the model and will influence the overall ICER. Increase in the discount rates will reduce the incremental QALYs and incremental costs between the treatment arms – which in turn will increase the ICER.

4. Increase in age – MI: MI is the most commonly occurring ACS event in the model so uncertainty applied to the age specific increased risk of non-fatal MI as expected will have an impact on the ICER.

5. Direct costs of MI: MI is the most commonly occurring ACS event in the model so uncertainty applied to the cost of non-fatal MI as expected will have an impact on the ICER.

The sensitivity analysis for the efficacy related inputs suggest that the difference in event rates has a similar impact on the ICER regardless of the event. Overall, MI impacts greatest on the overall ICER as this is the most common event in patients at risk of secondary ACS events. This is not surprising considering the way in which the sensitivity analysis is conducted where we estimate the ICER using regression analysis from the results from the PSA.

Figure 34: Tornado plot of the one-way sensitivity analysis for the non-efficacy input parameters

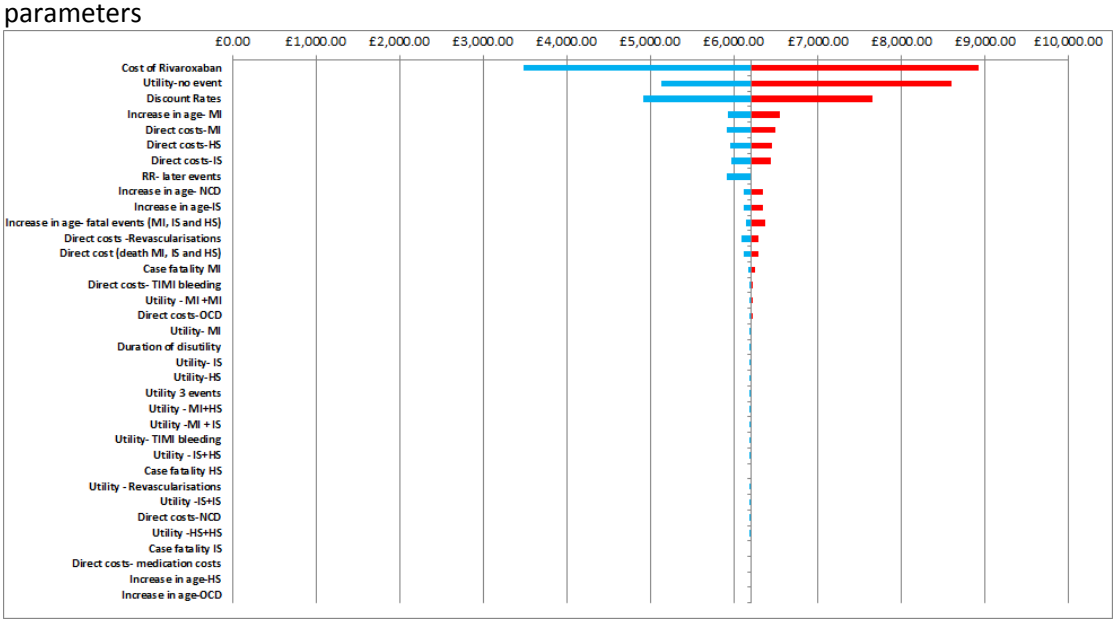


Figure 35: Tornado plot of the one-way sensitivity analysis for the efficacy related parameters

Table 77 : One-way sensitivity ICER outputs for the non-efficacy parameters

Input parameters	Lower value	Upper value	Difference
Cost of Rivaroxaban	£3,485.47	£8,920.22	£5,434.75
Utility-no event	£5,128.93	£8,602.61	£3,473.68
Discount Rates	£4,911.59	£7,658.89	£2,747.30
Increase in age- MI	£5,924.82	£6,543.47	£618.65
Direct costs-MI	£5,906.43	£6,499.66	£593.24
Direct costs-HS	£5,953.52	£6,451.31	£497.80
Direct costs-IS	£5,962.83	£6,441.44	£478.61
RR- later events	£5,918.59	£6,202.84	£284.26
Increase in age- NCD	£6,111.46	£6,342.30	£230.84
Increase in age-IS	£6,115.35	£6,345.28	£229.93
Increase in age- fatal events (MI, IS and HS)	£6,148.24	£6,369.76	£221.53
Direct costs -Revascularisations	£6,092.10	£6,287.27	£195.17
Direct cost (death MI, IS and HS)	£6,113.95	£6,291.74	£177.80
Case fatality MI	£6,162.98	£6,249.08	£86.10
Direct costs- TIMI bleeding	£6,177.53	£6,221.68	£44.15
Utility - MI +MI	£6,187.16	£6,218.61	£31.45
Direct costs-OCD	£6,187.57	£6,218.12	£30.55
Utility- MI	£6,192.38	£6,213.35	£20.97
Duration of disutility	£6,198.82	£6,216.50	£17.68
Utility- IS	£6,195.40	£6,210.30	£14.90
Utility-HS	£6,195.49	£6,210.22	£14.73
Utility 3 events	£6,198.87	£6,206.83	£7.96
Utility - MI+HS	£6,199.46	£6,206.23	£6.77
Utility -MI + IS	£6,201.07	£6,204.62	£3.56
Utility- TIMI bleeding	£6,201.74	£6,203.95	£2.22
Utility - IS+HS	£6,201.86	£6,203.83	£1.97
Case fatality HS	£6,202.94	£6,204.54	£1.60
Utility - Revascularisations	£6,202.06	£6,203.63	£1.57
Utility -IS+IS	£6,202.07	£6,203.62	£1.56
Direct costs-NCD	£6,202.49	£6,203.20	£0.71
Utility -HS+HS	£6,202.55	£6,203.14	£0.58
Case fatality IS	£6,204.52	£6,205.01	£0.49
Direct costs- medication costs	£6,202.84	£6,202.84	£0.00
Increase in age-HS	£6,202.84	£6,202.84	£0.00
Increase in age-OCD	£6,202.84	£6,202.84	£0.00
% continuations	£6,202.84	£6,202.84	£0.00

Table 78: Sensitivity analysis ICER outputs for the efficacy parameters

Input parameters	Lower value	Upper value	Difference
Difference in MI	£5879.78	£6604.65	£724.86
Difference in OCD	£5971.67	£6665.87	£694.20
Difference in HS	£5899.34	£6573.99	£674.64
Difference in IS	£5908.31	£6573.99	£665.68

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The scatter plot and CEAC are presented in Figure 36 and Figure 37. The scatter plot suggests that almost all the points lay within the first top right hand quadrant of the scatter plot plane suggesting QALY benefits with rivaroxaban, but for additional cost. Further, almost all points are within the £20,000 per QALY threshold (points are below the diagonal line running through the x-axis).

The CEAC suggest that the probability of rivaroxaban being cost effective at a willingness to pay threshold of £20,000 is >99.9% (cost of rivaroxaban = £2.10 per day).

Figure 36: Scatterplot from the PSA

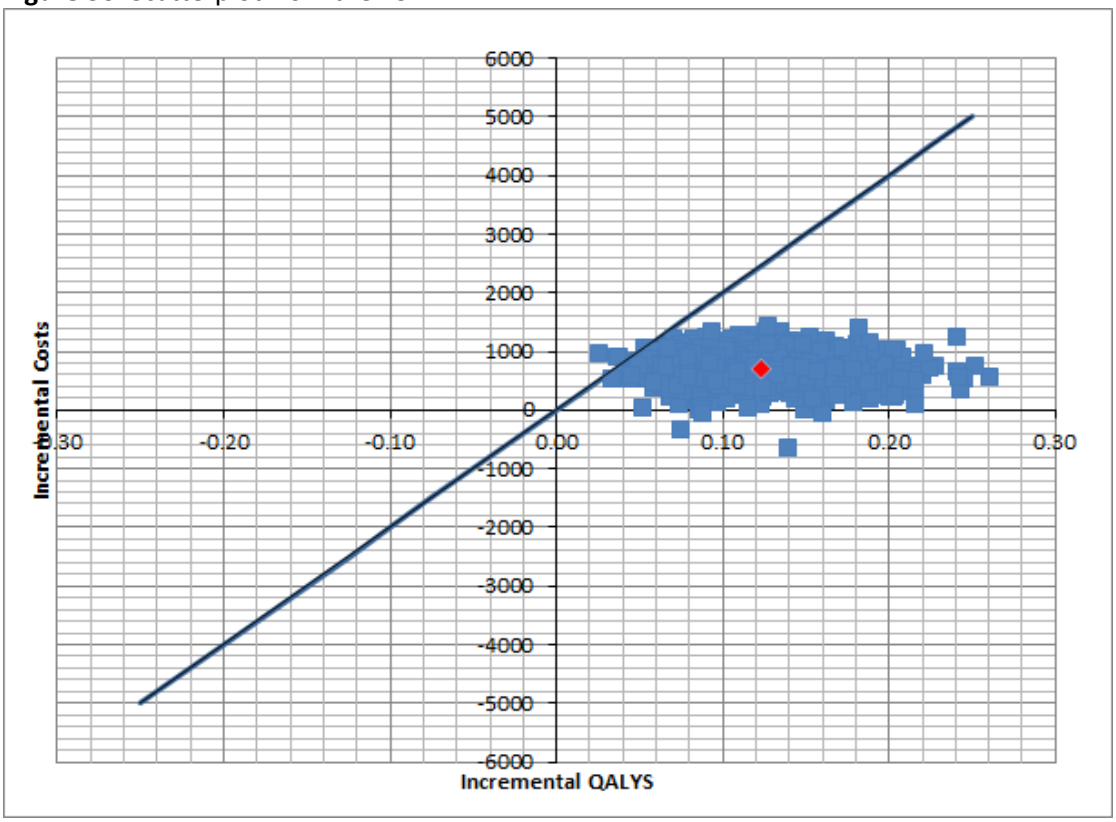
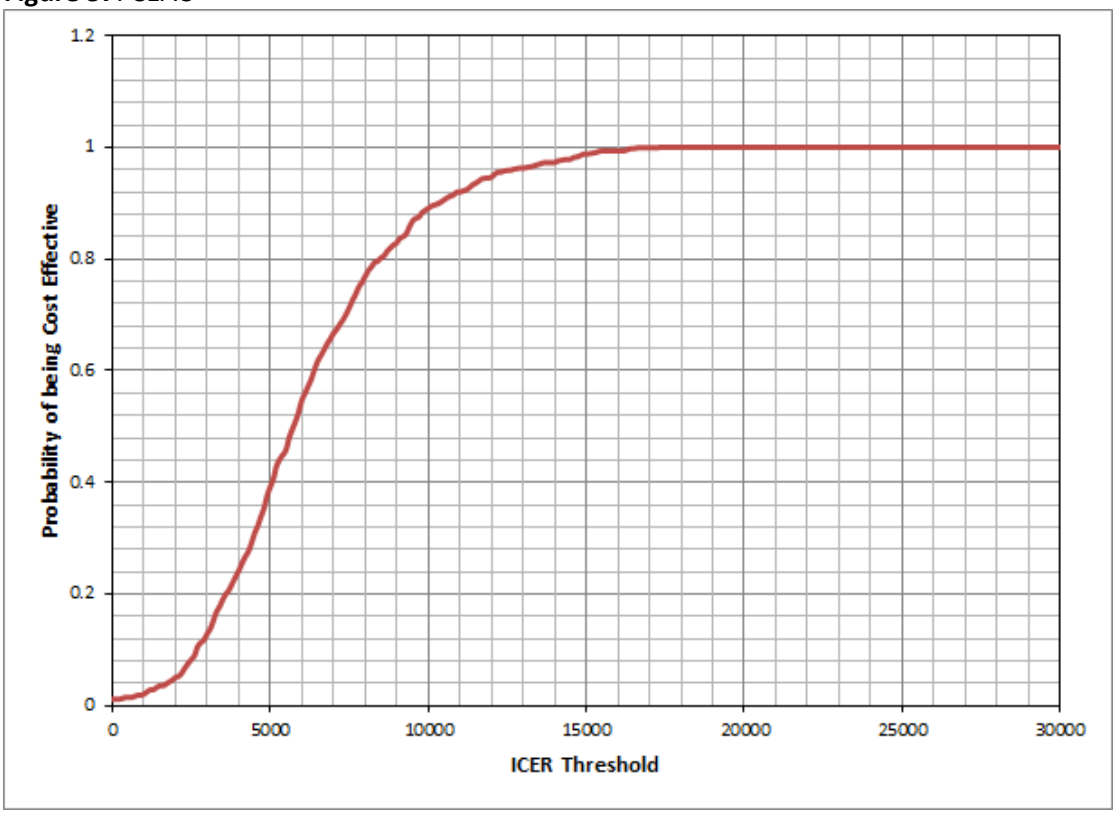


Figure 37: CEAC



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Scenario analyses were undertaken to further test the robustness of the model by manipulating and stress testing the input parameters and structural assumptions deemed to be important to the model outcomes. The following parameter groups were considered:

- Strata and transition probabilities
- Utilities
- Cost of events
- Increased risk of events due to age and relative risks of suffering subsequent events following an event

Details of the scenario analyses considered here are presented inTable 79, where a description and summary of the outcomes are also provided. The actual results from the model for each scenario is presented in Table 80.

Table 79 Scenarios considered in the model and the anticipated impact on the input parameters.

Parameters tested	Scenarios
Strata and transition probabilities (proportional hazards)	
Stratum 2 (ASA + thienopyridine + rivaroxaban vs. ASA + thienopyridine)	Stratum 2 from the trial to test the impact on the ICER of adding rivaroxaban to ASA+clopidogrel vs. ASA+clopidogrel
Transition probabilities	
Non-parametric	Using the ATLAS 2 trial data as it was reported without any adjustments (hence no interpolation)
Clopidogrel efficacy	
Clopidogrel RRR = 1	Adjustments are no longer made for the standard of care treatment duration of 1 year. The scenario will present the efficacy data as it was reported in the ATLAS 2 trial data and comparing rivaroxaban in addition to the standard of care (ASA + clopidogrel) versus clopidogrel for the observation period.
Utilities	
Utility values from trial	Utilities obtained from the trial where there is no distinction between the tunnel states considered in the model.
Utility values return to the baseline utility value in the post event cycles	Utilities for MI, IS, HS are applied to the first 6 months only. After this, utility values are assumed to revert back to the baseline “no event” utility.
Utility applied to fatal events	A utility of 0.22 (Bagust et al 2011) is applied to all the fatal events in the model in both the observation period and the full 40 year time horizon.
Cost of events	
Cost of death = £0.00	Costs of mortality is not captured by the ICER.
Increased risk of events due to age and subsequent events	
RR = 1 for all subsequent events following a MI, IS or HS	Patients are not at an increased risk of suffering a subsequent event following a MI, IS or HS/ICH. Patients suffering from non-fatal and fatal events will be driven by the efficacy data and increased risk of ageing in the extrapolation period.
Increased risk due to age = 0	The dynamic transition probabilities will remain unchanged over time as patient will not be at an increased risk of suffering an event in the extrapolation period.
RR = 1 and increased risk due to age = 0	Patients have no increased risk of suffering an event due to ageing or from having a prior event.

Table 80: Results from the scenario analysis applied to the 40 year time horizon

Parameters tested	Rivaroxaban		"standard of care"		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
Strata and transition probabilities (proportional hazards)							
Stratum 2	£15,362.74	9.52	£14,479.67	9.40	£883.07	0.12	£7,404.53
Transition probabilities							
Non-parametric	£16,290.40	9.75	£15,431.41	9.62	£858.99	0.13	£6,468.00
Clopidogrel efficacy							
Clopidogrel RRR=1	£13,794.17	10.09	£13,044.73	9.96	£749.44	0.13	£5,824.01
Utilities							
Utility values from trial	£14,767.63	9.83	£14,004.06	9.71	£763.58	0.13	£5,935.11
Utility values return to the baseline utility value in the post event cycles	£14,767.63	9.61	£14,004.05	9.49	£763.58	0.12	£6,195.36
Utility values applied to fatal events	£14,767.63	13.39	£14,004.05	13.28	£763.58	0.10	£7,147.39
Cost of events							
Cost of death = £0.00	£13,522.08	9.56	£12,707.38	9.44	£814.70	0.12	£6,618.13
Increased risk of events due to age and subsequent events							
RR = 1 for all subsequent events following a MI, IS or HS	£15,960.00	9.81	£15,169.14	9.68	£790.86	0.12	£6,439.04
Increased risk due to age = 0	£31,093.77	14.09	£30,194.98	13.91	£898.79	0.18	£4,927.81
RR = 1 and increased risk due to age = 0	£29,633.17	14.34	£28,704.75	14.16	£928.42	0.18	£6,745.04

A clopidogrel RRR of 1 presents a scenario to mimic the ATLAS 2 trial data -where standard of care is given beyond the 1 year approved label duration (for clopidogrel at the physicians discretion). The results show an improved ICER when compared to the base case. The difference in the parametric and non-parametric approach for the base case population does not differ significantly (a difference of approximately £465). The increased risk of suffering an event due to ageing also seems to be an important factor on the ICER. When assuming there are no increased risk associated with ageing then the ICER improves – the RR associated with subsequent events does not impact greatly on the ICER. Most models within this indication do not consider the increased risks of ageing and the risks associated with subsequent events and this scenario suggests that the increased risk of suffering due to ageing can impact the model outcomes – with its exclusion improving model results. Changes to utility values has little impact, using utilities from the trial and resetting utilities to baseline values beyond 6 months after an event improve the ICER slightly. Including a utility value associated with death increases the ICER as this benefits the comparator arm more than the rivaroxaban arm because more people die in the comparator arm. Similarly, setting the cost of death to zero favours the comparator arm.

Table 81: Summary of the scenarios and the model outcomes.

Parameters tested	Impact on structural sensitivity
Strata and transition probabilities (proportional hazards)	
Stratum 2 (ASA+rivaroxaban vs. ASA)	The ICER increased slightly but is still within acceptable boundaries of cost-effectiveness
Transition probabilities	
Non-parametric	The ICER is greater than that estimated for the base case –the fluctuations in the last few observations may be responsible for the discrepancy.
Clopidogrel efficacy	
Clopidogrel RRR=1	The ICER improves from the base case - as adjustments to the transition probabilities after 1 year treatment are not made.
Utilities	
Utility values from trial	The ICER improves from the base case by a small amount
Utility values return to the baseline utility value in the post event cycles	The impact of this scenario is miminal
Utility applied to fatal events	The ICER increases but remains within acceptable cost-effectiveness range
Cost of events	
Cost of death = £0.00	ICER increases as this scenario favours the comparator arm where more deaths occur earlier on
Increased risk of events due to age and subsequent events	
RR = 1 for all subsequent events following a MI, IS or HS	ICER increases but not substantially because only a few patients have subsequent events
Increased risk due to age = 0	ICER improves. Removing the increased risk will lower the number of patients suffering further events, which favours the rivaroxaban arm.
RR = 1 and increased risk due to age = 0	ICER increases but remains within acceptable cost-effectiveness range

7.7.10 What were the main findings of each of the sensitivity analyses?

The main findings from the deterministic sensitivity analysis suggest that the cost of rivaroxaban, baseline utility, discount rates, age specific increased risk of non-fatal MI, and acute cost of non-fatal MI are the 5 most influential parameters in the the model. Some of these are further supported by the scenario analyses, with the age specific increased risk of events scenario having a relatively large impact on the model outcomes.

7.7.11 What are the key drivers of the cost-effectiveness results?

The key driver of the cost-effectiveness results is the cost of rivaroxaban.

7.8 Validation

7.8.1 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 steps were taken during model validation:

1. A health economist employed by the agency that developed the model, but not involved in the model development, independently reviewed the model and checked structure and calculations.

2. Clinicians were consulted to provide feedback on the clinical relevance of the modelling approach and the inputs used

3. An independent health economist checked and validated the model structure

4. No cost-effectiveness analyses of rivaroxaban for the secondary prevention of ACS exist. Therefore, it was not possible to compare our results with others in the public domain.

7.9 Subgroup analysis

7.9.1 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 because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroup analyses have been undertaken. The licenced population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup. Such analyses are not statistically sound as the trial was not powered to draw conclusion about (non-pre-specified) subgroups of subgroups.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable as no subgroups analysed.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable as no subgroup analyses were undertaken.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable.

7.9.5 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 5.

The base case population contains all patients meeting the label population criteria from the ATLAS 2 trial. No subgroups of this population have been identified in the decision problem.

7.10 Interpretation of economic evidence

7.10.1 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 7.7.6 demonstrate cost-effectiveness of rivaroxaban when compared with standard of care. The results shown here are slightly higher than the ICERs of approximately £3,500 to £4,000 per QALY reported in most publications and reports from Bagust (2011)(49), SMC (2011)(99) and NICE (2012)(43). A key reason for this is our inclusion of an increase in event risk due to age. Differences in event unit costs, and separate consideration of ischemic and haemorrhagic strokes also go some way in explaining the differences. Inclusion of increased risks due to age and prior events, as well as distinction between stroke types and fatal event types represent a model structure which more closely mimics clinical practice than is seen in previously published model structures. The ICER estimated by Coleman and Limone (Coleman 2014)(53), was almost double the ICER presented here. Coleman and Limone only modelled a 5 year time horizon, which explains why their ICER was higher. A lifetime model horizon is a commonly applied and accepted modelling methodology in cardiovascular disease as it is important to capture future costs and benefits relating to such a disease.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The economic evaluation considers patients with acute coronary syndromes who have elevated biomarkers and have not suffered a previous stroke / TIA. No additional groups are identified in the decision problem as potentially benefiting from rivaroxaban.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The key strengths and weaknesses of the economic evaluation are provided below:

Strengths

- The economic evaluation was based on results from a large randomised, controlled global study that provides direct comparison between rivaroxaban and its comparator of standard of care.

- The economic model is consistent to those already used in previous UK HTA submissions – however the economic evaluation provided is more detailed.

    - The model distinguishes between stroke types (ischaemic and haemorrhagic), fatal events and multiple events (non-fatal, fatal and combined fatal and non-fatal) with the Markov model structure.

- The economic model also captured the RR of experiencing a subsequent event and increased risk of suffering an event in response to the ageing population.

- The economic model was able to generate outcomes similar to what had been observed in the clinical trial data to provide cost per QALY estimates for patients with elevated biomarkers without prior stroke or TIA.

- The ATLAS 2 trial provides data for standard of care beyond the 1 year label treatment duration, and the model can be used to provide comparisons between rivaroxaban +ASA + thienopyridine vs. ASA + thienopyridine, applying the assumption that thienopyridine is given for two years in both arms(rather than for 1 year as is applied in the model base case).

- Sensitivity analyses demonstrate the model is robust to changes in parameter values with the ICER still falling within the willingness to pay threshold (with minimal impact on the overall ICER). The probability of rivaroxaban being cost effective in the secondary prevention of ACS is estimated to be >99% at a threshold of £20,000 per QALY.

Weaknesses

- The patient level data used in the model were not from a UK specific population and the UK specific population group was far too small to base the economic evaluation on.

- The ATLAS 2 trial was not specifically designed to collect EQ5D data. The economic model applied utility values from literature in the base case model.

- The model does not differentiate multiple events once a patient has experienced more than two events per model cycle. Due to small numbers this was not possible however the model already captures a great level of detail for multiple events and

further additional separation of the events would not impact on the overall cost-effectiveness results.

- The combined fatal and non-fatal events could not be captured within the Markov model framework – however due to the small number of occurrences these would not have impacted on the overall cost-effectiveness results.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The ATLAS 2 trial was not designed to collect EQ5D data specifically and patient observations diminished greatly over time in the trial. The trial EQ5D was not very reliable due to a low number of observations and as a result alternative literature sources were used. The use of the trial specific EQ5D may be preferred as quality of life data would then be obtained directly from the same population as the efficacy data on which the cost-effectiveness analysis is based. However, it is not believed this would have impacted greatly on the overall cost-effectiveness results (see scenario analysis).

Resource use data from ATLAS 2 was available but was not used in the model due to a number of reasons. Firstly, the unit costs included in the model already include multiple resource elements (procedures, staff-time, rehabilitation, hospital stay etc). Any further dissection of these cost elements is not expected to impact on the overall cost-effectiveness results. Secondly, the unit costs applied in the model are heavily based on UK-specific HRGs which are considered to more accurately reflect pathways of clinical care in the UK than the ATLAS 2 data might. This is because ATLAS 2 was conducted in multiple countries and it is likely that care pathways and resource use differs across countries. Furthermore, the unit costs and resource use assumed in the model have been verified by a UK-based clinical expert (KR).

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 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.

The estimated population with ACS who are eligible for treatment with rivaroxaban in England and Wales for 2015 is 65,000.

This population has been estimated from HES Data England and PEDM Tables Wales for 2012/2013 (see section 2.2 for further explanation).

The model takes into account the expected growth rate of the total population of England and Wales over the five year time horizon. This has been estimated using population growth forecasts from the Office of National Statistics. The population of ACS patients eligible for treatment is assumed to grow over time in line with the growth rate of the general population of England and Wales (Table 82).

Section 8.2 highlights the breakdown of the estimation method and relevant assumptions concerning the eligible patient population.

Table 82: Number of Patients eligible for treatment in England and Wales

	2015	**2016**	**2017**	**2018**	**2019**
Population Growth Rate	NA	0.79%	0.72%	0.70%	0.64%
Total ACS Patients	65,000	65,511	65,984	66,448	66,872

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Rivaroxaban is on average administered 5 days after an ACS event occurs(3). Therefore, in year 1, rivaroxaban is given for 360 days.

In the second year of treatment, the average number of days of treatment with rivaroxaban increases to 365 days.

Rivaroxaban patients are also given clopidogrel and/or ASA.

Clopidogrel patients are given a loading dose on day 1 and a regular dose for the remaining 364 days of the year.

ASA may be given as monotherapy or in combination with the other treatments considered in the BIM. There is no loading dose with ASA. Therefore 365 days of treatment are assumed for each year of the BIM.

Treatment switching and discontinuation has been taken into account in the BIM. It is assumed that rivaroxaban patients discontinue treatment and switch to ASA monotherapy after 2 years. Clopidogrel patients are assumed to switch to ASA monotherapy after 1 year of treatment, reflecting current standard of care.

8.3 What assumption(s) were made about market share (when relevant)?

It has been assumed that 99% of the patient population are prescribed clopidogrel plus ASA and 1% are prescribed ASA monotherapy (validated with KR).

Table 83 shows the assumed market uptakes for rivaroxaban and resulting market shares of clopidogrel and ASA from 2015 to 2019. It is assumed that all of rivaroxaban's market share comes from clopidogrel (I.e. the ASA market share remains constant at 1% over the time horizon of the BIM).

Table 83: Market share within the ACS market

	2015	**2016**	**2017**	**2018**	**2019**
Clopidogrel	94%	87%	85%	85%	85%
ASA	1%	1%	1%	1%	1%
Rivaroxaban	5%	12%	14%	14%	14%

8.4 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).

No other significant costs are associated with treatment of Rivaroxaban.

8.5 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?

Unit costs used in the budget impact model are the same as those used in the cost-effectiveness model.

Unit costs include drug costs, the total cost associated with secondary events; as well as costs associated with bleeds, revascularisations and mortality. For each non-fatal cardiovascular event, two year follow-up costs are considered. From year 2 onwards, inflation rates are applied to event and mortality costs. Section 7.5.3 (Resource identification, measurement and validation) describes the cost calculations in further detail.

Table 84: Unit costs applied in BIM

Rivaroxaban (per day)	£2.10
Generic clopidogrel (per day)	£0.06
Aspirin (per day)	£0.03
CV-related mortality	£3,000.21
Non-CV related mortality	£300.02
MI	£9,165.95
Ischemic stroke	£21,256.99
Haemorrhagic stroke	£26,279.16
TIMI major bleed	£669.83
TIMI minor bleed	£67.79
TIMI bleed requiring medical attention	£130.26
CABG	£9,618.84
PTCA / PCI	£2,081.77

8.6 Were there any estimates of resource savings? If so, what were they?

Most of the resource savings are from savings due to reduced numbers of secondary events. The introduction of Rivaroxaban results in estimated cost savings of approximately £1m over five years due to lower incidence rates of secondary events (Table 85).

Table 85: Resource savings

Type of Resource utilised	Without rivaroxaban	With rivaroxaban	Incremental
Secondary Event	**£351,722,393**	**£350,694,328**	**-£1,028,065**

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The total cost of rivaroxaban introduction takes into consideration drug costs, adverse event costs and secondary event costs. The costs will be expected to rise from £79m in 2015 to £172m 2019 with uptake of rivaroxaban.

The overall budget impact for the NHS due to the introduction of rivaroxaban in England and Wales is £2.4m in 2015 rising to £8.3m in 2019.

The total budget impact over the 5 years from 2015 to 2019 is estimated to be £33m which is a 5.52% increase due to the introduction of rivaroxaban.

Table 86: Budget impact of rivaroxaban in England and Wales

Budget Impact (£)	**2015**	**2016**	**2017**	**2018**	**2019**
Number ACS patients eligible for secondary prevention treatment	65,000	65,511	65,984	66,448	66,872
Rivaroxaban Market share of ACS	5%	12%	14%	14%	14%
Rivaroxaban drug costs	**£4,565,184**	**£9,205,140**	**£11,593,146**	**£12,531,394**	**£13,273,925**
Secondary Events	**£40,633,094**	**£54,636,198**	**£69,400,543**	**£84,909,845**	**£101,114,649**
Bleedings and Revascularisations	**£34,008,312**	**£39,780,676**	**£45,757,048**	**£51,993,240**	**£58,486,092**
Total Cost with Rivaroxaban	**£79,206,589**	**£103,622,015**	**£126,750,738**	**£149,434,478**	**£172,874,666**
Less:					
Cost of Clopidogrel & ASA	**£76,793,316**	**£97,348,672**	**£118,827,102**	**£141,256,362**	**£164,618,140**

Net Cost	£2,413,273	£6,273,343	£7,923,635	£8,178,116	£8,256,525
% increase in cost due to Rivaroxaban	3.14%	6.44%	6.67%	5.79%	5.02%

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The various opportunities for resource savings or redirection have been quantified in the analysis.

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 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.

The following databases were searched to identify potentially eligible trials from published sources:
MEDLINE® and EMBASE® databases were searched using the Embase.com interface. Cochrane Central Trials Register and the Cochrane Database of Systematic Reviews were searched using the Cochrane library interface. MEDLINE® In-Process was searched using the Pubmed.com interface.

10.2.2 The date on which the search was conducted.

All database searches were conducted on 6 March 2014

10.2.3 The date span of the search.

- MEDLINE® In-Process (6/03/2014)
- EMBASE® and MEDLINE® (1947 to 6/03/2014)
- Cochrane Library (CENTRAL and CDSR) (from inception to 6/03/2014)

10.2.4 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).

Database search strategies were developed in March 2014, and included combinations of both subject index headings and free text terms and synonyms for 'rivaroxaban' in combination with 'acute coronary syndrome'.
Study design filters for the identification of randomised controlled trials (RCTs) were applied. Study design filters were adapted from the Scottish Intercollegiate Guidelines Network (SIGN) search filters. The searches were limited to human and English language publications.
Please see the full search strategies with ensuing numbers of hits below.

MEDLINE® In-Process. Pubmed.com

Date searched 6/03/2014

S. No.	Search Terms	Hits	Term Group
#1	myocardial infarct*[Title/Abstract] OR "unstable angina"[Title/Abstract] OR "heart attack"[Title/Abstract] OR "ACS"[Title/Abstract] OR heart event*[Title/Abstract] OR heart arrest*[Title/Abstract] OR cardiac arrest*[Title/Abstract] OR acute coronary syndrome*[Title/Abstract] OR "heart infarction"[Title/Abstract] OR STEMI[Title/Abstract] OR NSTEMI[Title/Abstract] OR “NON-STEMI”[Title/Abstract] OR NONSTEMI[Title/Abstract] OR “NON STEMI”[Title/Abstract] OR (acute[Title/Abstract] AND coronary[Title/Abstract]) OR (coronary[Title/Abstract] AND syndrome*[Title/Abstract]) OR "non ST segment elevation myocardial infarction"[Title/Abstract] OR "ST segment elevation myocardial infarction"[Title/Abstract]	208 836	Population
#2	Rivaroxaban OR “bay 59-7939” OR “bay 59 7939” OR “bay 597939” OR “bay59-7939” OR “bay59 7939” OR “bay597939” OR xarelto	1328	Intervention
#3	#1 AND #2 AND (inprocess[sb] OR pubstatusaheadofprint)	31	Trials in progress

EMBASE and MEDLINE (since 1947). Embase.com platform

Date Searched 6/03/2014

S. No.	Search Terms	Hits	Term Group
#1	'acute coronary syndrome'/syn OR 'heart infarction'/exp OR 'unstable angina pectoris'/exp OR (myocardial NEXT/1 infarct*):ab,ti OR 'unstable angina':ab,ti OR 'heart attack':ab,ti OR acs:ab,ti OR ('acute coronary' NEXT/1 syndrome*):ab,ti OR 'heart infarction':ab,ti OR stemi:ab,ti OR nstemi:ab,ti OR 'non stemi':ab,ti OR nonstemi:ab,ti OR (acute:ab,ti AND coronary:ab,ti) OR (coronary:ab,ti AND syndrome*:ab,ti) OR 'non st segment elevation myocardial infarction':ab,ti OR 'st segment elevation myocardial infarction':ab,ti OR (heart NEXT/1 (event* OR arrest*)):ab,ti OR (cardiac NEXT/1 arrest*):ab,ti	380 060	Population
#2	Rivaroxaban/syn OR Rivaroxaban/de OR ('bay 59-7939' OR 'bay 59 7939' OR 'bay 597939' OR 'bay59-7939' OR 'bay59 7939' OR 'bay597939' OR xarelto):ab,ti	4227	Intervention
#3	'randomized controlled trial'/de OR 'controlled clinical trial'/exp OR randomized:ab,ti OR placebo*:ab,ti OR 'clinical trial'/de OR randomly:ab,ti OR trial*:ab,ti OR ('randomized controlled' NEXT/1 trial*):ab,ti OR ('randomised controlled' NEXT/1 trial*):ab,ti OR ('randomized clinical' NEXT/1 trial*):ab,ti OR ('randomised clinical' NEXT/1 trial*):ab,ti OR (randomized NEXT/1 trial*):ab,ti OR (randomised NEXT/1 trial*):ab,ti OR 'random allocation':ab,ti OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'double blind method':ab,ti OR 'single blind method':ab,ti OR ((singl*:ab,ti OR doubl*:ab,ti OR treb*:ab,ti OR tripl*:ab,ti) AND (blind*:ab,ti OR mask*:ab,ti)) OR (random NEXT/1 assignment*):ab,ti OR ('open label' NEXT/1 trial*):ab,ti OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR randomization:ab,ti OR randomisation:ab,ti OR 'double blind procedure':ab,ti OR 'single blind procedure':ab,ti OR 'crossover procedure'/de	1 715 203	Clinical Trials

S. No.	Search Terms	Hits	Term Group
#4	#1 AND #2 AND #3	544	All clinical studies
#5	#4 NOT [animals]/lim	545	Exclusion terms – exclude animals
#6	(Comment*):ti OR 'Case Report'/de OR 'Case Study'/de OR 'Phase 1 Clinical Trial'/de OR (case NEXT/1 stud*):ti,ab OR (case NEXT/1 report*):ti,ab OR 'case series':ti,ab OR 'Retrospective Study'/de OR retrospective:ti,ab	2 655 765	Exclusion terms – study type
#7	#5 NOT #6	531	All relevant studies
#8	#7 AND [english]/lim	499	Limit by language

Cochrane Library. Wiley InterScience.

Date searched 6/03/2014

S. No.	Search Terms	Hits	Term Group
#1	MeSH descriptor: [Acute Coronary Syndrome] explode all trees OR MeSH descriptor: [Angina, Unstable] explode all trees OR MeSH descriptor: [Myocardial Infarction] explode all trees OR (myocardial:ab,ti,kw and infarct*:ab,ti,kw) or "unstable angina":ab,ti,kw or "heart attack":ab,ti,kw or acs:ab,ti,kw or ("acute coronary" next/1 syndrome*):ab,ti,kw or "heart infarction":ab,ti,kw or stemi:ab,ti,kw or nstemi:ab,ti,kw or "non stemi":ab,ti,kw or nonstemi:ab,ti,kw or (acute:ab,ti,kw and coronary:ab,ti,kw) or (coronary:ab,ti,kw and syndrome*:ab,ti,kw) or "non st segment elevation myocardial infarction":ab,ti,kw or "st segment elevation myocardial infarction":ab,ti,kw or (heart:ab,ti,kw and (event*:ab,ti,kw or arrest*:ab,ti,kw)) or (cardiac:ab,ti,kw and arrest*:ab,ti,kw)	25 216	Population
#2	Rivaroxaban OR "bay 59-7939" OR "bay 59 7939" OR "bay 597939" OR "bay59-7939" OR "bay59 7939" OR "bay597939" OR xarelto	222	Intervention
#3	#1 AND #2, in Cochrane Reviews (Reviews and Protocols), Trials and Methods Studies	32	Clinical trials

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Conference proceedings were hand searched to retrieve the latest studies, which were not yet been published in journals as full text articles or to supplement results of previously published studies. Abstracts from the following three conference proceedings were searched:

- American Heart Association (AHA) Scientific Sessions (2012-2013)
- European Society of Cardiology (ESC) (2013)
- American College of Cardiology (ACC) (2013)

Details of conference searching

Web Site/ Database/ Register Searched	Date of Search	URL	Search Terms Used /Limits	Studies Identified (n)	Studies included
American Heart Association (AHA) 2012	18 March 2014	http://my.americanheart.org/professional/Sessions/ScientificSessions/Archive/Archive-Scientific-Sessions_UCM_316935_SubHomePage.jsp	Rivaroxaban, xarelto, BAY59-7939, ACS, Acute coronary syndrome, angina, myocardial infarction	3639	3
American Heart Association (AHA) 2013	18 March 2014	http://circ.ahajournals.org/content/vol128/22_MeetingAbstracts		3360	1
European Society of Cardiology (ESC) 2013	18 March 2014	http://congress365.escardio.org/Acute-Coronary-Syndrome		643	0
American College of Cardiology (ACC) 2013	18 March 2014	http://www.sciencedirect.com/science/journal/07351097/61/10/supp/S	Full supplement was searched	2126 (E1-E2126)	3

The bibliographic reference lists of relevant systematic reviews and meta-analyses were also searched for relevant RCTs that were not identified in the literature database searches.
Relevant clinical evidence held by the manufacturer in the form of trial protocols, clinical study reports, and correspondence with regulatory bodies was included where appropriate to supplement the published data.

10.2.6 The inclusion and exclusion criteria.

Please see **Error! Reference source not found.** in section 6.2.1 for inclusion and exclusion criteria.

Table 1

10.2.7 Table 1 Eligibility criteria used in The data abstraction strategy.

Data were extracted as required for completion of sections 6.3 - 6.5 by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved by consensus and by consulting a third reviewer where necessary.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

ATLAS-ACS 2 TIMI 51(3)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Computer-generated randomisation schedule prepared by the sponsor before the study., with stratification by investigator intention to use thienopyridine (clopidogrel or ticlopidine) in addition to ASA (Stratum 1 – ASA only; Stratum 2 – ASA plus a thienopyridine). Within each stratum, patients were randomised in a 1:1:1 ratio to receive rivaroxaban 2.5mg twice daily, rivaroxaban 5mg twice daily, or placebo twice daily(3). The IVRS/IWRS assigned a unique patient number and treatment code and corresponding study drug kits for the duration of study.	Yes
Was the concealment of treatment allocation adequate?	Computer-generated randomisation schedule prepared by the sponsor before the study. Randomisation via central 24-hour IVRS or IWRS. Unique randomisation number of patient used on all medication labels. Placebo and active treatments were identical in appearance. Investigators were not provided with randomisation codes. All suspected events were adjudicated by independent, blinded, Clinical Events Committee (CEC) and adjudicated decisions were the basis of final decisions.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no notable imbalances in baseline demographic, medical history, or index event characteristics between treatment groups. See section 6.3.4 Baseline characteristics.	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 was a double-blind design. Investigators were not provided with randomisation codes. Placebo tablets matched exactly the appearance of active tablets. All suspected events were adjudicated by independent, blinded, Clinical Events Committee (CEC) and adjudicated decisions were the basis of final decisions.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Although discontinuation rates were slightly higher than some similarly designed studies, they were similar in both study arms and were not thought to have an adverse effect on the final study outcomes.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results of all pre-specified outcomes have been reported in full, see section 6.5 Results.	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?	ATLAS-ACS 2 TIMI 51 included an ITT analysis as a supporting analysis. The primary analysis was a modified ITT analysis which included all randomised patients, except those from the three excluded sites, and endpoint events that occurred from randomisation up to the earlier date of the global treatment end date, or 30 days after last dose of study drug (for patients who discontinued study drug prematurely), or 30 days after randomisation (for patients who were randomised but never treated).	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 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.

N/A

10.4.2 The date on which the search was conducted.

N/A

10.4.3 The date span of the search.

N/A

10.4.4 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).

N/A

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A

10.4.6 The inclusion and exclusion criteria.

N/A

10.4.7 The data abstraction strategy.

N/A

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

N/A

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

No studies of this nature were considered relevant to the decision problem.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

N/A

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The adverse events and safety data included in this submission are reported from the ATLAS-ACS 2 TIMI 51 trial which was identified during the search for rivaroxaban clinical studies in Acute Coronary Syndromes. See Sections 6.1 and 6.2 for the study identification and selection, and also Section 10.2, Appendix 2 for search strategy.

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

See section 6.4 and Section 10.3, Appendix 3.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

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 for the reviews were:

MEDLINE® and EMBASE®using the Embase.com interface

MEDLINE® In-Processusing the Pubmed.com interface

EconLit using the American Economic Association interface

The Cochrane Library (National Health Service's Economic Evaluation Database and Health Technology Assessment Database)

2. The date on which the search was conducted.

The searches were conducted on 6 March 2014 in all the literature databases to identify relevant articles with recent cost data.

3. The date span of the search.

From January 2000 to March 2014.

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).

Table 87: Search strategy for both MEDLINE and EMBASE databases, using the Embase.com interface (search conducted on 6 March 2014; date limits: January 2000 to 6 March 2014)

Term Group		Search Terms	No. of articles
Population	#1	'acute coronary syndrome'/syn OR 'heart infarction'/exp OR 'unstable angina pectoris'/exp OR (myocardial NEXT/1 infarct*):ab,ti OR 'unstable angina':ab,ti OR 'heart attack':ab,ti OR acs:ab,ti OR ('acute coronary' NEXT/1 syndrome*):ab,ti OR 'heart infarction':ab,ti OR stemi:ab,ti OR nstemi:ab,ti OR 'non stemi':ab,ti OR nonstemi:ab,ti OR (acute:ab,ti AND coronary:ab,ti) OR (coronary:ab,ti AND syndrome*:ab,ti) OR 'non st segment elevation myocardial infarction':ab,ti OR 'st segment elevation myocardial infarction':ab,ti OR (heart NEXT/1 (event* OR arrest*)):ab,ti OR (cardiac NEXT/1 arrest*):ab,ti	380 060
Economic models	#2	Cost/exp OR 'Cost Benefit Analysis'/de OR 'Health Economics'/exp OR Pharmacoeconomics/exp OR 'cost analysis':ti,ab OR (cost NEXT/1 effective*) OR 'cost utility':ti,ab OR (economic NEXT/1 model*):ti,ab OR costminimization:ti,ab OR costminimisation:ti,ab OR 'cost minimisation':ti,ab OR 'cost minimization':ti,ab OR 'Cost effectiveness analysis'/de OR 'economic aspect'/exp OR (model*:ti,ab AND (cost*:ti,ab OR economic* OR pharmacoeconomic*:ti,ab))	1 277 910
Interventions	#3	Aspirin/syn OR rivaroxaban/syn OR clopidogrel/syn OR Prasugrel/syn OR ticagrelor/syn OR Aspirin/de OR rivaroxaban/de OR clopidogrel/de OR Prasugrel/de OR ticagrelor/de OR 'acetylsalicylic acid'/de OR ('bay 59-7939' OR 'bay 59 7939' OR 'bay 597939' OR 'bay59-7939' OR 'bay59 7939' OR 'bay597939' OR xarelto):ab,ti OR (zorpin OR 'acetyl salicylic acid' OR acesal OR acetan OR acetard OR aceticil OR aceticyl OR acetosal OR alkaspirin OR anasprin OR andol OR anopyrin OR ansin OR anthrom OR aptor OR asaflow OR asaphen OR asatard OR asawin OR aspec OR aspent OR aspergum OR aspex OR aspilets OR aspirem OR aspirgran OR aspirina OR aspirine OR aspirinine OR caprin OR easprin OR ecasil OR ecosprin OR ecotrin OR entrophen OR eskotrin OR euthermine OR proprin OR pyronoval OR reumyl OR rhodine OR rhonal OR ronal OR salacetin OR salacetogen OR saletin OR soldral OR solpyron):ab,ti OR (clopilet OR grepid OR iscover OR 'pcr 4099' OR pcr4099 OR plavix OR 'sr 25989' OR 'sr 25990c' OR sr25989 OR sr25990c OR zopya OR zylagren OR zyllt):ab,ti OR ('cs 747' OR cs747 OR effient OR efient OR 'ly 640315' OR ly640315):ab,ti OR ('azd 6140' OR azd6140 OR brilinta OR brilique OR possia):ab,ti	217 218
Economic models of specific interventions	#4	#2 AND #3	13405
Economic and resource-use studies	#5	('Cost of Illness':ti,ab OR 'Cost of Illness'/de OR 'burden of illness':ti,ab OR 'Health Care Cost'/exp OR 'Health Economics'/exp OR Pharmacoeconomics/exp OR 'Health Care Utilization'/de OR Fee/exp OR 'Health Care Cost'/exp OR (healthcare NEXT/1 cost*):ti,ab OR ('health care' NEXT/1 cost*):ti,ab OR economic*:ti OR pharmacoeconomic*:ti,ab OR 'resource use':ti,ab OR 'resource utilization':ti,ab OR 'resource utilisation':ti,ab OR (direct NEXT/1 cost*):ti,ab OR (indirect NEXT/1 cost*):ti,ab OR (medication NEXT/1 cost*):ti,ab OR (physician NEXT/1 cost*):ti,ab OR (hospitalisation NEXT/1 cost*):ti,ab OR (hospitalization NEXT/1 cost*):ti,ab OR (hospital NEXT/1 cost*):ti,ab OR 'hospital cost'/exp) NOT (model*:ti OR (cost NEXT/1 effective*):ti OR (cost-effective*):ti OR 'cost utility':ti)	625 350

Term Group		Search Terms	No. of articles
Studies on utility and impact on patient life	#6	'Quality of Life'/exp OR 'quality of life':ti,ab OR QoL:ti,ab OR hrqol:ti,ab OR hqol:ti,ab OR (patient NEXT/1 report*):ti,ab OR 'health utility':ti,ab OR 'health utilities':ti,ab OR 'standard gamble':ti,ab OR 'time trade off':ti,ab OR TTO:ti,ab OR EuroQol:ti,ab OR EQ5D:ti,ab OR 'EQ 5D':ti,ab OR 'quality of well being':ti,ab OR HUI:ti,ab OR 'SF 6D':ti,ab OR QALY:ti,ab OR ('quality adjusted life' NEXT/1 year*):ti,ab OR 'SF 36':ti,ab OR SF36:ti,ab OR 'sickness impact profile':ti,ab OR sf6*:ti,ab OR (sf NEXT/1 6)':ti,ab OR ('short form' NEXT/1 6):ti,ab OR (shortform NEXT/1 6):ti,ab OR 'sf six':ti,ab OR sfsix:ti,ab OR 'shortform six':ti,ab OR 'short form six':ti,ab OR 'sf 36':ti,ab OR 'short form 36':ti,ab OR 'shortform 36':ti,ab OR 'sf thirtysix':ti,ab OR 'sf thirty six':ti,ab OR 'shortform thirtysix':ti,ab OR 'shortform thirty six':ti,ab OR 'short form thirty six':ti,ab OR 'short form thirtysix':ti,ab OR 'short form thirty six':ti,ab OR 'Short Form Health Survey':ti,ab OR 'willingness to pay':ti,ab OR (utilit*AND score*):ti,ab OR (utilit* AND weight*):ti,ab OR Rosser:ti,ab OR (health AND utilit*):ti,ab OR (utilit* AND value):ti,ab OR disutility:ti,ab OR (health* AND year NEXT/1 equivalent*):ti,ab OR 'Health Survey'/de	488 233
All studies	#8	#1 AND (#4 OR #5 OR #6)	22 655
Exclusion terms – exclude animals	#9	#8 NOT [animals]/lim	22 395
Exclusion terms – study type	#10	(Comment*):ti OR 'CaseReport'/de OR 'CaseStudy'/de OR 'Phase1ClinicalTrial'/de OR (case NEXT/1 stud*):ti,ab OR (case NEXT/1 report*):ti,ab OR 'caseseries':ti,ab OR 'RetrospectiveStudy'/de OR retrospective:ti,ab OR 'primary prevention':ti	2 660 507
All relevant studies	#11	#9 NOT #10	20 469
Limit by language, and by date	#12	#11 AND [english]/lim AND [2000-2014]/py	16 344
Restrict by publication type	#13	#12 NOT ([editorial]/lim OR [letter]/lim OR [review]/lim)	10 778

Table 88: Search strategy for MEDLINE In-Process, using the PubMed.com interface (search conducted on 6 March 2014; date limits: January 2000 to March 2014)

Term Group		Search Terms	No. of articles
Population	#1	myocardial infarct*[Title/Abstract] OR "unstable angina"[Title/Abstract] OR "heart attack"[Title/Abstract] OR "ACS"[Title/Abstract] OR heart event*[Title/Abstract] OR heart arrest*[Title/Abstract] OR cardiac arrest*[Title/Abstract] OR acute coronary syndrome*[Title/Abstract] OR "heart infarction"[Title/Abstract] OR STEMI[Title/Abstract] OR NSTEMI[Title/Abstract] OR "NON-STEMI"[Title/Abstract] OR NONSTEMI[Title/Abstract] OR "NON STEMI"[Title/Abstract] OR (acute[Title/Abstract] AND coronary[Title/Abstract]) OR (coronary[Title/Abstract] AND syndrome*[Title/Abstract]) OR "non ST segment elevation myocardial infarction"[Title/Abstract] OR "ST segment elevation myocardial infarction"[Title/Abstract]	208 836

Term Group		Search Terms	No. of articles
Quality of life	#2	"quality of life"[Title/Abstract] OR "QoL"[Title/Abstract] OR "hrqol"[Title/Abstract] OR "hqol"[Title/Abstract] OR patient report*[Title/Abstract] OR "health utility"[Title/Abstract] OR "health utilities"[Title/Abstract] OR "standard gamble"[Title/Abstract] OR "time trade off"[Title/Abstract] OR “time trade-off” OR "TTO"[Title/Abstract] OR "EuroQol"[Title/Abstract] OR "EQ5D"[Title/Abstract] OR "EQ 5D"[Title/Abstract] OR "EQ-5D"[Title/Abstract] OR "quality of well being"[Title/Abstract] OR "quality of well-being"[Title/Abstract] OR "HUI"[Title/Abstract] OR "SF-6D"[Title/Abstract] OR "QALY"[Title/Abstract] OR quality adjusted life year*[Title/Abstract] OR quality-adjusted life year*[Title/Abstract] OR quality adjusted life-year*[Title/Abstract] OR quality-adjusted life-year*[Title/Abstract] OR "SF-36"[Title/Abstract] OR "SF36"[Title/Abstract] OR "sickness impact profile"[Title/Abstract] OR sf6*[Title/Abstract] OR sf 6*[Title/Abstract] OR short form 6*[Title/Abstract] OR shortform 6*[Title/Abstract] OR “sf six” [Title/Abstract] OR “sfsix”[Title/Abstract] OR “shortform six” [Title/Abstract] OR “short form six”[Title/Abstract] OR “sf 36”[Title/Abstract] OR “short form 36”[Title/Abstract] OR “shortform 36”[Title/Abstract] OR “sf thirtysix”[Title/Abstract] OR “sf thirty six”[Title/Abstract] OR “shortform thirtysix”[Title/Abstract] OR “shortform thirty six”[Title/Abstract] OR “short form thirty six”[Title/Abstract] OR “short form thirtysix”[Title/Abstract] OR “short form thirty six”[Title/Abstract] OR “Short Form Health Survey”[Title/Abstract] OR “willingness to pay”[Title/Abstract] OR (utilit*[Title/Abstract] AND score*[Title/Abstract]) OR (utilit*[Title/Abstract] AND weight*[Title/Abstract]) OR “Rosser”[Title/Abstract] OR (health[Title/Abstract] AND utilit*[Title/Abstract]) OR (utilit*[Title/Abstract] AND value[Title/Abstract]) OR disutility[Title/Abstract] OR health* year equivalent*[Title/Abstract]	165317
Cost studies	#3	healthcare cost*[Title/Abstract] OR health care cost*[Title/Abstract] OR health-care cost*[Title/Abstract] OR economic*[Title] OR pharmacoeconomic*[Title/Abstract] OR "resource use"[Title/Abstract] OR "resource utilization"[Title/Abstract] OR "resource utilisation"[Title/Abstract] OR direct cost*[Title/Abstract] OR indirect cost*[Title/Abstract] OR medication cost*[Title/Abstract] OR physician cost*[Title/Abstract] OR hospitalisation cost*[Title/Abstract] OR hospitalization cost*[Title/Abstract] OR hospital cost*[Title/Abstract] OR "cost of illness"[Title/Abstract] OR "burden of illness"[Title/Abstract]) NOT (model*[Title] OR cost-effective*[Title] OR cost effective*[Title] OR “cost-utility”[Title] OR “cost utility”[Title])	60 984
Interventions	#4	aspirin[MeSH Terms] OR ("Aspirin" OR "rivaroxaban" OR "clopidogrel" OR "Prasugrel" OR "ticagrelor" OR "acetlysalicylic acid" OR "xarelto" OR “bay 59 7939” OR “bay 597939” OR “bay59-7939” OR “bay59 7939” OR “bay597939” OR xarelto OR zorpin OR “acetyl salicylic acid” OR acesal OR acetan OR acetard OR aceticil OR aceticyl OR acetosal OR alkaspirin OR anasprin OR andol OR anopyrin OR ansin OR anthrom OR aptor OR asaflow OR asaphen OR asatard OR asawin OR aspec OR aspent OR aspergum OR aspex OR aspilets OR aspirem OR aspirgran OR aspirina OR aspirine OR aspirinine OR caprin OR easprin OR ecasil OR ecosprin OR ecotrin OR entrophen OR eskotrin OR euthermine OR proprin OR pyronoval OR reumyl OR rhodine OR rhonal OR ronal OR salacetin OR salacetogen OR saletin OR soldral OR solpyron OR clopilet OR grepid OR iscover OR “pcr 4099” OR pcr4099 OR plavix OR “sr 25989” OR “sr 25990c” OR sr25989 OR sr25990c OR zopya OR zylagren OR zyllt OR “cs 747” OR cs747 OR effient OR efient OR “ly 640315” OR ly640315 OR “azd 6140” OR azd6140 OR brilinta OR brilique OR possia[Title/Abstract])	59 316
Economic evaluations	#5	“cost analysis”[Title/Abstract] OR “cost-analysis”[Title/Abstract] OR cost effective*[Title/Abstract] OR cost-effective*[Title/Abstract] OR “cost utility”[Title/Abstract] OR “cost-utility”[Title/Abstract] OR economic model*[Title/Abstract] OR “costminimization”[Title/Abstract] OR “costminimisation”[Title/Abstract] OR “cost-minimisation”[Title/Abstract] OR “cost-minimization”[Title/Abstract] OR (model*[Title/Abstract] AND (cost*[Title/Abstract] OR economic*[Title/Abstract] OR pharmacoeconomic*[Title/Abstract]))	132 260
Trials in progress	#6	#1 AND (#2 OR #3 OR [#4 AND #5]) AND (inprocess[sb] OR pubstatusaheadofprint)	190

Search strategy for NHS EED and HTAD, using the Cochrane library interface (search conducted on 6 March 2014; date limits: January 2000 to 6 March 2014)

Term Group		Search Terms	No. of articles
Population	#1	MeSH descriptor: [Acute Coronary Syndrome] explode all trees OR MeSH descriptor: [Angina, Unstable] explode all trees OR MeSH descriptor: [Myocardial Infarction] explode all trees OR (myocardial:ab,ti,kw and infarct*:ab,ti,kw) or "unstable angina":ab,ti,kw or "heart attack":ab,ti,kw or acs:ab,ti,kw or ("acute coronary" next/1 syndrome*):ab,ti,kw or "heart infarction":ab,ti,kw or stemi:ab,ti,kw or nstemi:ab,ti,kw or "non stemi":ab,ti,kw or nonstemi:ab,ti,kw or (acute:ab,ti,kw and coronary:ab,ti,kw) or (coronary:ab,ti,kw and syndrome*:ab,ti,kw) or "non st segment elevation myocardial infarction":ab,ti,kw or "st segment elevation myocardial infarction":ab,ti,kw or (heart:ab,ti,kw and (event*:ab,ti,kw or arrest*:ab,ti,kw)) or (cardiac:ab,ti,kw and arrest*:ab,ti,kw)	25 216
Intervention	#2	"Aspirin" OR "rivaroxaban" OR "clopidogrel" OR "Prasugrel" OR "ticagrelor" OR MeSH descriptor: [Aspirin] explode all trees OR “bay 59 7939” OR “bay 597939” OR “bay59-7939” OR “bay59 7939” OR “bay597939” OR xarelto OR zorpin OR “acetyl salicylic acid” OR acesal OR acetan OR acetard OR aceticil OR aceticyl OR acetosal OR alkaspirin OR anasprin OR andol OR anopyrin OR ansin OR anthrom OR aptor OR asaflow OR asaphen OR asatard OR asawin OR aspec OR aspent OR aspergum OR aspex OR aspilets OR aspirem OR aspirgran OR aspirina OR aspirine OR aspirinine OR caprin OR easprin OR ecasil OR ecosprin OR ecotrin OR entrophen OR eskotrin OR euthermine OR proprin OR pyronoval OR reumyl OR rhodine OR rhonal OR ronal OR salacetin OR salacetogen OR saletin OR soldral OR solpyron OR clopilet OR grepid OR iscover OR “pcr 4099” OR pcr4099 OR plavix OR “sr 25989” OR “sr 25990c” OR sr25989 OR sr25990c OR zopya OR zylagren OR zyllt OR “cs 747” OR cs747 OR effient OR efient OR “ly 640315” OR ly640315 OR “azd 6140” OR azd6140 OR brilinta OR brilique OR possia	10 761
Economic evaluations and technology assessments	#3	#1 AND #2 AND in Technology Assessments and Economic Evaluations	102
Quality of life	#4	MeSH descriptor: [Quality of Life] this term only OR MeSH descriptor: [Health Status Indicators] this term only OR "Quality of life":ab,ti,kw or "QoL":ab,ti,kw or "hrqol":ab,ti,kw or "hqol":ab,ti,kw or "health utility":ab,ti,kw or "health utilities":ab,ti,kw or "standard gamble":ab,ti,kw or “patient report*”:ab,ti,kw or "time trade off":ab,ti,kw or "time trade-off":ab,ti,kw or "TTO":ab,ti,kw or "EuroQol":ab,ti,kw or "EQ5D":ab,ti,kw or "EQ 5D":ab,ti,kw or "EQ-5D":ab,ti,kw or "quality of wellbeing":ab,ti,kw or "quality of well-being":ab,ti,kw or "HUI":ab,ti,kw or "SF-6D":ab,ti,kw or "QALY":ab,ti,kw or "quality adjusted life year*”:ab,ti,kw or "quality-adjusted life year*”:ab,ti,kw or “quality adjusted life-year*”:ab,ti,kw or "quality-adjusted life-year*”:ab,ti,kw or "SF-36":ab,ti,kw or "SF36":ab,ti,kw or "sickness impact profile":ab,ti,kw or sf6*:ab,ti,kw or "sf 6*":ab,ti,kw or "short form 6*":ab,ti,kw or "shortform 6*":ab,ti,kw or "sf six":ab,ti,kw or "sfsix":ab,ti,kw or "shortform six":ab,ti,kw or "short form six":ab,ti,kw or "sf 36":ab,ti,kw or "short form 36":ab,ti,kw or "shortform 36":ab,ti,kw or "sf thirtysix":ab,ti,kw or "sf thirty six":ab,ti,kw or "shortform thirtysix":ab,ti,kw or "shortform thirty six":ab,ti,kw or "short form thirty six":ab,ti,kw or "short form thirtysix":ab,ti,kw or "short form thirty six":ab,ti,kw or "Short Form Health Survey":ab,ti,kw or "willingness to pay":ab,ti,kw or (utilit*:ab,ti,kw and score*:ab,ti,kw) or (utilit*:ab,ti,kw and weight*:ab,ti,kw) or "Rosser":ab,ti,kw or (health:ab,ti,kw and utilit*:ab,ti,kw) or (utilit*:ab,ti,kw and value:ab,ti,kw) or disutility:ab,ti,kw or "health year equivalent*":ab,ti,kw	48 341
Quality of life	#5	#1 AND #4	1530
Combined facet	#6	#3 OR #5	1632

Search strategy for EconLit, using the American Economic Association interface (search conducted on6 March 2014; date limits: January 2000 to February 2014)

Term Group	Search Terms	Hits
Combined facet	"acute coronary syndrome" OR "acute coronary syndrome*" OR "myocardial infarct*" OR "myocardial infarction" OR "unstable angina" OR "heart attack" OR "heart event" OR "heart events" OR "heart event*" OR "heart arrest*" OR "cardiac arrest*" OR "heart infarction" OR STEMI OR NSTEMI OR "non stemi" OR nonstemi OR "non st segment elevation myocardial infarction" OR "st segment elevation myocardial infarction" OR "acute coronary" OR "coronary syndrome*" OR "heart infarct*" yearmin:2000 yearmax:2014 (Language: English)	125

5. Details of any additional searches (for example, searches of company databases [include a description of each database]).

Conference proceedings

Conference abstracts from the following four conference proceedings were searched:

AHA Scientific Sessions: 2012-2013

ESC: 2013

ACC: 2013

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)_2013

Web Site/Database/Register Searched (Name, Address)	Date of Search	Search Terms Used/Limits	URL	Studies Retrieved (n)	Studies included
American Heart Association 2012	18-Mar-14	ACS, “acute coronary syndrome," “acute coronary syndromes” “myocardial infarction," “unstable angina," “heart attack," “cardiac arrest”	http://my.americanheart.org/professional/Sessions/ScientificSessions/Archive/Archive-Scientific-Sessions_UCM_316935_SubHomePage.jsp	3622	0
American Heart Association 2013	18-Mar-14		http://circ.ahajournals.org/content/vol128/22_MeetingAbstracts	3343	0
American College of Cardiology 2013	18-Mar-14	Full supplement was searched	http://www.sciencedirect.com/science/journal/07351097/61/10/supp/S	2126	1
European Society of Cardiology 2013	18-Mar-14	ACS, “acute coronary syndrome," “acute coronary syndromes” “myocardial infarction," “unstable angina," “heart attack," “cardiac arrest”	http://congress365.escardio.org/Acute-Coronary-Syndrome	642	0
International Society for Pharmacoeconomic and Outcomes Research 2013	18-Mar-14	ACS, “acute coronary syndrome," “acute coronary syndromes” “myocardial infarction," “unstable angina," “heart attack," “cardiac arrest”	http://www.ispor.org/research_study_digest/research_index.asp	37	0

UK HTA websites

In addition, the HTA websites of the National Institute for Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC) were searched to identify cost/resource use data, utility data, and cost effectiveness analysis reported in the HTA submissions.

Searches results by HTA searching

Web Site/Database/Register Searched (Name, Address)	Date of search	Search Terms Used/Limits	Selection Criteria	Studies Retrieved (n)	Studies Included (n)
National Institute for Health and Clinical Excellence (TA and ERG report)	18-Mar-14	rivaroxaban	ACS, unstable angina, STEMI, NSTEMI	0	0
		clopidogrel		1	0
		prasugrel		2	2
		ticagrelor		2	2
		aspirin		0	0
Scottish Medicines Consortium	18-Mar-14	rivaroxaban		0	0
		clopidogrel		2	1
		prasugrel		1	1
		ticagrelor		1	1
		aspirin		0	0

We also asked a topic expert to provide additional references which were not identified by searching the other sources and could inform the economic model. One publication was identified in this way.

6. The inclusion and exclusion criteria.

Please refer to section 0 for the inclusion and exclusion criteria.

7. The data abstraction strategy.

Data were extracted by one reviewer and independently checked for accuracy by a second reviewer.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

Identified conference abstracts were not quality assessed.

Bagust et al, 2011		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		

1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
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)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	NA	Productivity not included
15. Was the relevance of productivity changes to the study question discussed?	NA	Productivity not included
16. Were quantities of resources reported separately from their unit cost?	No	Quantities of resources not reported
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
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?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
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?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	No justification but sensible choice
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	

36. Were generalisability issues addressed?	Yes	

Berg et al, 2008		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	CEA of pre treatment and long term treatment with clopidogrel in PCI
2. Was the economic importance of the research question stated?	Yes	Provide economic evidence required by decision makers for patients with PCI, regardless of setting and cause.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Payer perspective. Although for Sweden indirect costs were included for the main analysis as a requirement by the Pharma Benefits Board.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	Stated in the model structure diagram
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis. Although Cost/QALY reported so technically a cost-utility study
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	Decision tree and Markov models are described in general but not in relation to why chosen for CE analysis of clopidogrel.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	PCI CURE, PCI CLARITY and CREDO
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
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)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Not clear	QALYs listed as main outcome,
12. Were the methods used to value health states and other benefits stated?	Yes	From literature
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Population with moderate to severe health problems.
14. Were productivity changes (if included) reported separately?	Yes	Indirect costs reported separately for Sweden
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Retrospective and prospective studies obtained from the literature
18. Were currency and price data recorded?	Yes	2006 €
19. Were details of price adjustments for inflation or currency conversion given?	Yes	The exchange rate used is provided with no source
20. Were details of any model used given?	Yes	Decision tree and Markov model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Allows incorporation of short term and long term events
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Until patients reached 100 years of age.
23. Was the discount rate stated?	Yes	3%
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	NA	
26. Were the details of statistical test(s) and	Yes	P-values provided for meta-analysis and confidence

confidence intervals given for stochastic data?		intervals.
27. Was the approach to sensitivity analysis described?	Yes	One way and second order stochastic sensitivity analysis.
28. Was the choice of variables for sensitivity analysis justified?	No	States all possible parameters
29. Were the ranges over which the parameters were varied stated?	Not clear	Distribution provided for stochastic SA. Ranges for One way SA listed in results table but not stated in text.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Not clear	Total costs are reported that are not disaggregated by resource type. However for Sweden costs are reported for including indirect costs and without.
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	Assumptions/Caveats were not reported in same section as conclusions/results
36. Were generalisability issues addressed?	Yes	Non matching populations in the sensitivity analysis. Generalisability of efficacy results across different populations and treatment settings

Berg et al, 2007		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Assess the cost-effectiveness of clopidogrel in short and long term treatment of ST-segment elevation MI (STEMI)
2. Was the economic importance of the research question stated?	Yes	New clinical data on clinical effectiveness of clopidogrel in STEMI patients. Previously shown cost-effectiveness in NSTEMI and UA so can now do so for STEMI
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Payer perspective as mainly direct costs are available. A societal perspective was conducted for Sweden as a requirement by the Pharma Benefits Board.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Not clear	Used comparators investigated in clinical trials Societal perspective stated although following sentence states that healthcare payers in many countries are mainly interested in direct costs.
5. Were the alternatives being compared clearly described?	Yes	Detailed in the model structure. Used alternatives in clinical trials
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	Previous studies have shown clopidogrel to be cost-effective in specific patient populations. This study assesses the cost-effectiveness of clopidogrel in STEMI patients
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CLARITY and COMMIT trials, Swedish Hospital Discharge and Cause of Death register and long-term treatment data from CURE trial.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	CLARITY and COMMIT were detailed in the introduction
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	Yes	Cost of life year gained Also utility and disutility

economic evaluation clearly stated?		values were also stated for health states
12. Were the methods used to value health states and other benefits stated?	Yes	From the literature
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Swedish population with moderate to severe health problems.
14. Were productivity changes (if included) reported separately?		
15. Was the relevance of productivity changes to the study question discussed?	Yes	Included for Sweden due to requirements for Pharmaceutical Benefits Board Excluded for Germany and France as indirect costs not available.
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	2005 €
19. Were details of price adjustments for inflation or currency conversion given?	Yes	CPI from Organisation for Economic Cooperation and Development of Statistics Sweden and exchange rates from Eurostat.
20. Were details of any model used given?	Yes	Combined decision tree and Markov model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	To capture both short term and long term effects
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Not clear	States that patients assumed treatment for 1 year but does not state that this is the model time horizon.
23. Was the discount rate stated?	Yes	3% Costs and benefits
24. Was the choice of rate justified?	No	
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?	Not clear	P values provided for some statistics and 95% CI reported for RR of major bleeding reported in CURE.
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Not clear	The distributions for each parameter for the PSA was stated however the ranges for one-way sensitivity analysis were not stated although details were provided.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	QALYs were not reported despite being detailed in analysis.
33. Was the answer to the study question given?	Yes	Treatment was cost-effective in 3 countries studied.
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	States that practice patterns and outcomes found in the lit may not be identical to those in current practice.

Bruggenjurgen et al, 2007		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Clopidogrel is an expensive alternative and cost effectiveness analysis was conducted to evaluate

		whether or not it is cost-effective
2. Was the economic importance of the research question stated?	Yes	A long term cost-effectiveness analysis not carried out in Germany before.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	German healthcare system – payer perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Comparator in CURE trial and current standard of care.
5. Were the alternatives being compared clearly described?	Not clear	Assumed alternatives through description of CURE trial and adaptation of Swedish economic model. Not explicitly stated.
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Long term evaluation not previously undertaken in Germany
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CURE , Bruggenjurgen 2005, MIR and BHIR
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Some details of CURE and Bruggenjurgen 2005 provided
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	Not based on an overview of a number of studies
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Life years saved
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	Payers perspective
15. Was the relevance of productivity changes to the study question discussed?	Yes	Patients population starting age is 66 which is greater than the German retirement age.
16. Were quantities of resources reported separately from their unit cost?	No	Resource use obtained from Delphi panel although data were not provided
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Not clear	Appears 2005€ although not explicitly stated.
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Markov model was used. Diagram of model structure included as well as detailed description.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Justification not provided anywhere in the model description section
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Until all patients are dead, maximum of 10 years.
23. Was the discount rate stated?	Yes	3% costs and benefits
24. Was the choice of rate justified?	Yes	Recommendation in German healthcare setting
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?	Yes	Confidence intervals provided for relative risk reduction. Statistical tests were not detailed.
27. Was the approach to sensitivity analysis described?	Not clear	Sensitivity analysis is undertaken but does not state method such as one way or multiway or PSA.
28. Was the choice of variables for sensitivity analysis justified?	No	No justification provided other than to prove robustness.
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparing against standard treatment as per the CURE trial and the subsequent Swedish model.

31. Was an incremental analysis reported?	Yes	Incremental cost per life year saved.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Total costs shown as well as incremental LYS. Costs not broken down
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Analysis based on Swedish risk data. Patient group included patients with unstable angina which leads to overestimation of cost per life year saved in Germany
36. Were generalisability issues addressed?	Yes	Generalising Swedish data for Germany was detailed in the Discussion.

Cowper et al, 2005		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Assessing the value of prolonged clopidogrel therapy of patients treated with PCI
2. Was the economic importance of the research question stated?	Yes	Debate surrounding how long clopidogrel therapy should be maintained for as clopidogrel is expensive and may increase bleeding risks.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Societal perspective however not justified
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Standard therapy is one month of clopidogrel. Debate surrounding how long clopidogrel therapy should be maintained for.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Decision tree model.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	No justification for the use of a decision model provided,
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CREDO, DISCC and Framingham Heart Study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Details of the results of CREDO and DISCC were reported but not the study design for CREDO
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	Meta-analysis not required as results from single studies used.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Incremental cost and the Incremental cost per MI prevented. Also incremental cost per life saved
12. Were the methods used to value health states and other benefits stated?	NA	Not Cost-utility analysis, Health states were not valued.
13. Were the details of the subjects from whom valuations were obtained given?	NA	Utilities/QALYs not used in the model.
14. Were productivity changes (if included) reported separately?	No	Reported as societal perspective however no productivity costs reported
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	Costs based on average reimbursement and average length of stay reported for the DRG although these are not stated.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	See above
18. Were currency and price data recorded?	Yes	2000 US$
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Using Producer Price Index for general medical and surgical hospitals
20. Were details of any model used given?	Yes	Diagram of model structure presented as well was

		what was included in the model.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	12 months
23. Was the discount rate stated?	Yes	3% for years of life gained.
24. Was the choice of rate justified?	Not clear	Discount rate stated as “standard”
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?	No	Confidence intervals not reported for all data and statistical tests were not reported.
27. Was the approach to sensitivity analysis described?	Yes	Single and multiway sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	No	Clinical and economic variables included in the sensitivity analysis were stated with no justification provided.
29. Were the ranges over which the parameters were varied stated?	Not clear	Stated in the results section in percentages, although the actual ranges were not reported.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Clopidogrel compared to no clopidogrel in from months 1 to 12. Standard treatment is clopidogrel treatment for 1 month.
31. Was an incremental analysis reported?	Yes	Cost per MI avoided and cost per life year saved
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs were aggregated for hospital, physician and medications.
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Section on study limitations includes issues about generalisability

Crespin et al, 2011		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Comparing two strategies, genotype-driven treatment vs. ticagrelor
2. Was the economic importance of the research question stated?	Yes	No studies evaluating the cost-effectiveness of ticagrelor versus clopidogrel
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Payer perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Clopidogrel coming off patent so will become cheaper and more feasible for patients without a decreased ability to metabolise clopidogrel into its active form
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	PLATO study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	In the model cohort and model probabilities sections
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)?	N/A	

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	QALYs and life-years gained
12. Were the methods used to value health states and other benefits stated?	Yes	The EQ-5D was used for baseline values and a literature search was conducted for health-state utility values
13. Were the details of the subjects from whom valuations were obtained given?	Yes	EQ-5D valuations were obtained from non-institutionalised Americans. Literature search narrowed to American population.
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?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Searches of CEA registry at Tufts University and PubMed
18. Were currency and price data recorded?	Yes	2009 US dollars
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Decision tree and Markov model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Model not justified
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	1-year and 5-year time horizons
23. Was the discount rate stated?	Yes	3%
24. Was the choice of rate justified?	No	
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?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	No	Only ranges for time horizon and treatment duration are stated. Ranges for other variables (e.g., hazard ratios and costs not reported).
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Table 2
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Section about the study not being applicable in other treatment settings or in different subpopulations

Greenhalgh et al, 2009		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		

1. Was the research question stated?	Yes	Cost-effectiveness of prasugrel compared with clopidogrel for the treatment of ACS with PCI
2. Was the economic importance of the research question stated?	Yes	An absence of UK-based economic evaluations of prasugrel for patients with ACS undergoing PCI was noted. A model was required to submit to NICE as part of the STA process.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	UK NHS and Personal Social Services (PSS)
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Clopidogrel is not indicated for use in STEMI patients undergoing PCI according to its EMA license; however, it is in common use in England and Wales for this indication.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	The TRITON-TIMI 38 trial was the key source of clinical evidence. Non-trial sources of clinical evidence were also identified via literature reviews to inform assumptions regarding additional clinical inputs.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	In Chapter 4 of the submission
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)?	Yes	Indirect comparisons were conducted to calculate long-term mortality rates.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per life-year gained and cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	A systematic review identified utility decrements for different health states.
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	TRITON-TIMI 38 included a preplanned economic substudy analysis to evaluate the resource utilitsation associated with serious adverse events over a 12-month period in eight countries.
18. Were currency and price data recorded?	Yes	2006-2007 UK pounds
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	Markov model structure
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?	Yes	Lifetime
23. Was the discount rate stated?	Yes	In the model, costs and benefits were discounted at a rate of 3.5%.
24. Was the choice of rate justified?	Yes	In line with current NICE guidance
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	Confidence intervals were not reported for all data, and statistical tests were not reported.
27. Was the approach to sensitivity analysis described?	Yes	Univariate SA and PSA were conducted by the manufacturer for selected model parameters.
28. Was the choice of variables for sensitivity analysis justified?	Not clear	Selected model parameters
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Incremental costs, life-years, and QALYs
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs, life-years, and QALYs

33. Was the answer to the study question given?	Yes	The baseline ICER was low; estimated over a 40-year period, the incremental cost per QALY gained from prasugrel compared with clopidogrel in the full licensed population was £3,220.
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	The Review Group provided an assessment and critique of the economic model.
36. Were generalisability issues addressed?	Yes	There is limited generalisability to NHS patients in England and Wales owing to differences in the use of clopidogrel in the trial and its current use in UK clinical practice

Heeg et al, 2007		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	To assess the cost effectiveness of oral antiplatelet treatments in the prevention of cardiovascular events in line with current NICE recommendations
2. Was the economic importance of the research question stated?	Not clear	Cost-effectiveness analysis to validate the results of the pharmacoeconomic literature search
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	UK NHS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Recommended and indicated oral antiplatelet treatment in the secondary prevention of cardiovascular events
5. Were the alternatives being compared clearly described?	Yes	Aspirin, clopidogrel, and dipyridamole
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	The authors conducted a review of cost-effectiveness studies relating to antiplatelet treatments and conducted a new updated cost-effectiveness analysis.
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CAPRIE, CHARISMA, (PCI)-CURE, CREDO, COMMIT, CLARITY, ESPS 2 and ESPRIT trials
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Details of studies used are provided in supplementary online file.
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)?	No	Various sources and methods; no formal synthesis undertaken
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Life-year gained
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Not clear	Derived from a number of sources
18. Were currency and price data recorded?	Yes	2006
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Assumed an average 3.5% increase per year
20. Were details of any model used given?	Yes	Details of Markov model and diagram
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Based on a model that had previously been used a number of times, including for the clopidogrel reimbursement application in the Netherlands
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	6-month Markov cycle length and a lifetime horizon
23. Was the discount rate stated?	Yes	Future costs and effects were discounted by 3.5% per year
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	Multivariate probabilistic sensitivity analyses were performed for the various comparisons
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	All alternatives were compared
31. Was an incremental analysis reported?	Yes	Incremental costs and life-years
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	

34. Did conclusions follow from the data reported?	Yes	The cost-effectiveness estimates presented in this article supported the NICE guidelines for the use of antiplatelets for the prevention of cardiovascular events.
35. Were conclusions accompanied by the appropriate caveats?	Yes	The cost-effectiveness of antiplatelets hinges on the patient's initial risk, the risk reduction associated with treatment, and the price of the treatment.
36. Were generalisability issues addressed?	Yes	Differences in cost-effectiveness may vary by subpopulations.

Heller et al, 2003		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Not clear	Study question not clearly defined however assumed to estimate the impact/benefit of the NICE guidelines using population impact measures at individual practice of PCT level.
2. Was the economic importance of the research question stated?	Yes	Use of population impact measures to assess the Impact/Benefit of different guideline recommendations for secondary prevention of MI to aid prioritisation by PCT
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Viewpoint of PCT or individual practices
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Recommendations from the secondary prevention guidelines.
5. Were the alternatives being compared clearly described?	NA	No alternatives used. Study calculated costs of all treatments in secondary prevention guidelines. Costs are not compared between treatments.
6. Was the form of economic evaluation stated?	No	Not CE model or CU model. Used population impact measures to prioritise resource allocation
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Estimate benefits of introduction of NICE's secondary prevention guidelines at practice level or PCT level.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Not clear	Source of relative risk reduction not stated. Sources for Mortality (no reference) risk, costs, population and proportions of existing patients stated in the text.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	Not based on 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	Economic evaluation not based on an overview of a number of studies
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per death prevented
12. Were the methods used to value health states and other benefits stated?	NA	No valuation of health states and benefits. Utilities and QALYs were not used in this economic evaluation
13. Were the details of the subjects from whom valuations were obtained given?	NA	
14. Were productivity changes (if included) reported separately?	NA	Productivity not included nor mentioned
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	NA	Resource use not included although there is an explanation for this.
17. Were the methods for the estimation of	Yes	Details of drug cost calculations explained. Not

quantities and unit costs described?		other costs included
18. Were currency and price data recorded?	No	Currency and cost year not stated. Currency given as € in results tables
19. Were details of price adjustments for inflation or currency conversion given?	No	No details of currency conversion or inflation. Drug costs obtained from MIMS but provided in results section in €.
20. Were details of any model used given?	NA	Model structure not stated or detailed
21. Was there a justification for the choice of model used and the key parameters on which it was based?	NA	No economic model used – study used a methodology to calculate the benefit of guidelines on PCT and practices.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Not clear	1 year assumed as presented in tables and used for mortality rates, although not specifically stated
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	NA	
25. Was an explanation given if cost or benefits were not discounted?	No	No explanation given no discounting
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No confidence intervals or statistical tests reported
27. Was the approach to sensitivity analysis described?	NA	No sensitivity analysis carried out
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?)	Not clear	Incremental analysis was compared to those that are not on treatment
31. Was an incremental analysis reported?	Yes	Incremental analysis compared to those that are not on treatment
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Results presented for a variety of population impact measures(NNT,DIN, PIN, NTP, NEPP).
33. Was the answer to the study question given?	Yes	The impact of population impact measures the new secondary prevention guidelines was stated in the results section
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Detailed in the discussion section
36. Were generalisability issues addressed?	Yes	Discussion section details the impact the assumptions have on the results.

Karnon et al, 2006		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Assess the long term cost-effectiveness of 1 years treatment with clopidogrel in patients with ACS
2. Was the economic importance of the research question stated?	Yes	The economic impact of clopidogrel following NICE recommendation
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	NICE had recently recommended the treatment based on data from CURE trial
5. Were the alternatives being compared clearly described?	Yes	Standard therapy in the UK.
6. Was the form of economic evaluation stated?	Yes	Cost effectiveness and cost-utility model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	Cost-effectiveness and cost-utility based on NICE recommendations
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Details/Design of the CURE study were included along with the PRAIS-UK study and
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	Meta-analysis not used. Results from CURE and PRAIS-UK were used for different inputs.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Incremental cost per life year gained and incremental cost per QALY
12. Were the methods used to value health states and other benefits stated?	No	Utility values were obtained from literature with no information on how they were derived.
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	Resource use quantities were stated for treatment of major bleeding. No other resource quantities were reported.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Drug costs derived from BNF and resource costs derived for NHS ref Costs. Health state costs were obtained from the literature.
18. Were currency and price data recorded?	Yes	2002 GBP
19. Were details of price adjustments for inflation or currency conversion given?	No	Just states costs inflated to 2002 levels. No inflation indices reported
20. Were details of any model used given?	Yes	Model structure (decision tree for 1st year and Markov thereafter) was described including two diagrams
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	No justification on choice of model however justification for key model parameters.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	34 years base case scenario and 1 year
23. Was the discount rate stated?	Yes	6% for costs and 1.5% for benefits
24. Was the choice of rate justified?	Yes	Based on UK guidance at the time of publication
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?	Yes	Confidence intervals were reported for stochastic data but no details of statistical tests were provided.
27. Was the approach to sensitivity analysis described?	Yes	One-way, Two-way and PSA undertaken
28. Was the choice of variables for sensitivity analysis justified?	Yes	Key drivers in the model. Justified relating to bleeding rates and revascularisation
29. Were the ranges over which the parameters were varied stated?	Yes	For bleeding rates and revascularisation in the text and in the results tables
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Compared to UK standard therapy.
31. Was an incremental analysis reported?	Yes	ICER per QALY gained, per LY gained,.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	One years treatment with clopidogrel is a cost-effective intervention compared to standard therapy and should be considered for standard therapy.
35. Were conclusions accompanied by the appropriate caveats?	Not clear	No clear conclusions were stated.
36. Were generalisability issues addressed?	Yes	Assumptions and limitations discussed in the

		discussion

Karnon et al, 2010		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Assess the long term cost-effectiveness of treatment for 1 month and 1 year with clopidogrel in patients with STEMI.
2. Was the economic importance of the research question stated?	Not clear	The introduction mentions that ACS are a common cause of hospital admission and substantial mortality and morbidity but no explicit link between this and the CEA.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Standard therapy chosen so generalisable to UK clinical practice.
5. Were the alternatives being compared clearly described?	No	Clopidogrel vs. standard therapy, although standard therapy not defined
6. Was the form of economic evaluation stated?	Yes	In the abstract it states a cost-utility analysis was conducted.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	Type of economic evaluation only mentioned in abstract
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	Not 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)?	Yes	Calculations and assumptions shown in Table and detailed in text.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Incremental cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	Meta analysis for utility values for stroke states Harvard utilities database for remaining health states
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	NA	Model from healthcare perspective
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Obtained from primary costing study
18. Were currency and price data recorded?	Yes	2006 £
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Figure and description of Markov model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Allows extrapolation of data beyond trial period
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	1 month and 1 year
23. Was the discount rate stated?	Not clear	Range of discount rate stated in sensitivity analysis but base case rate not stated.
24. Was the choice of rate justified?	No	

25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Confidence intervals and P-values were provided although information on what tests were undertaken was not included.
27. Was the approach to sensitivity analysis described?	Yes	Univariate and PSA
28. Was the choice of variables for sensitivity analysis justified?	Not clear	Varying age in sensitivity analysis explained but not other variables.
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Compared to standard therapy
31. Was an incremental analysis reported?	Yes	ICER per LYG and ICER per QALY reported
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	MI, Stroke and number dead reported at 1 year. Costs reported in millions for each treatment and time period
33. Was the answer to the study question given?	Yes	Clopidogrel is cost-effective compared to standard therapy.
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Stated that cost-effective in UK but need to synthesise data from other countries to inform event rates

Kolm et al, 2007		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Cost effectiveness of clopidogrel plus ASA relative to ASA
2. Was the economic importance of the research question stated?	Yes	The objective of the analysis was to determine patient level costs of the therapies used in the trial using the CMG classification system.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Canadian health care system
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Clopidogrel plus ASA already shown to be more effective than ASA alone in the CURE trial.
5. Were the alternatives being compared clearly described?	Yes	Clopidogrel plus ASA vs ASA alone
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CURE and PCI cure
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Both CURE and PCI cure were described in relevant sections
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	Based on single study
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per event prevented and cost per life years gained.
12. Were the methods used to value health states and other benefits stated?	NA	Utilities not used in this model
13. Were the details of the subjects from whom	NA	

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?	Yes	No data available from the trial so excluded
16. Were quantities of resources reported separately from their unit cost?	Yes	Average LOS and number of initial hospitalisations were recorded from Canadian case mix group.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	2004 CAN $
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Inflation index supplied by Statistics Canada to 2004 CAN $
20. Were details of any model used given?	NA	No model was used in the analysis
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?	Yes	One-year
23. Was the discount rate stated?	Yes	3% costs and benefits
24. Was the choice of rate justified?	No	
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?	Yes	P-values for efficacy estimates from CURE trial were shown but not CIs. CIs for life-years were detailed.
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	No	50% and 80% life expectancy and a higher costs of ASA
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparisons same as in CURE trial
31. Was an incremental analysis reported?	Yes	For events prevented and life years gained
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	One year costs were not split by resource use.
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Generalisability issues based on data lacking from CURE trial such as outpatient treatments.

Lamy et al, 2004		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Article is a cost-effectiveness analysis of the use of clopidogrel in the UK, Sweden, France and Canada based on the CURE study.
2. Was the economic importance of the research question stated?	Yes	CURE influenced ACC/AHA guidelines-therefore economic consequences of this o
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Unclear	Stated that direct costs are evaluated from a societal perspective. Authors argue that study is a good proxy for a societal perspective.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Based on CURE study.
5. Were the alternatives being compared clearly	Yes	Treated with clopidogrel and placebo group.

described?		
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness study undertaken
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CURE study data
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Design and result given in summary form for the CURE 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?	Yes	Primary outcome is Cost per primary event 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?	Yes	In discussion
16. Were quantities of resources reported separately from their unit cost?	No	Resources not presented. Costs were not reported at an individual resource level, but instead grouped.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Resource utilisation from CURE study
18. Were currency and price data recorded?	Yes	Currency data for all countries included are 2001 prices
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Currency conversion based on published figures in financial times only. 1 year follow-up so inflation not included.
20. Were details of any model used given?	NA	No model used
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?	Yes	Maximum 1 year follow-up
23. Was the discount rate stated?	NA	Follow-up a maximum of 1 year
24. Was the choice of rate justified?	NA	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Maximum 1 year follow-up
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Boot strap analysis for cost data and ICER and article reports SE and 95% CI
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?)	Yes	As per CURE study
31. Was an incremental analysis reported?	Yes	ICERs for primary event avoided and prevention of first event reported for all 5 countries.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Only for two areas - initial hospitalisation and follow-up and subsequent hospitalisation
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Caveats included for the comparisons drawn against other studies (Table 3)

36. Were generalisability issues addressed?	Yes	For the comparison with other studies. (Table 3)

Latour-Perez et al, 2008		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Assess the incremental ICER of GPIIb/IIIa in patients with NSTE-ACS.
2. Was the economic importance of the research question stated?	Yes	No economic evaluations that represents current clinical practice.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Health care system perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	T New clinical studies available on the use of GPIIb/IIIa
5. Were the alternatives being compared clearly described?	Yes	Three strategies for high risk patients with NSTE-ACS
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness and cost-utility analysis using a Markov model.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	Cost effectiveness and cost utility analysis but no justification.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Systematic review and meta-analysis based on 9 RCT
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
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)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	Obtained from a non-systematic literature review but a footnote describes the methodology
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	Cost and resource use from studies
18. Were currency and price data recorded?	Yes	2006 Euros
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Spanish consumer price index
20. Were details of any model used given?	Yes	Markov model - full description in text and diagram
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Markov model described but no explicit justification why it was used.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Patient life span
23. Was the discount rate stated?	Yes	3%
24. Was the choice of rate justified?	No	
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?	Not clear	P values and CI intervals provided.
27. Was the approach to sensitivity analysis	Yes	One-way and probabilistic

described?		
28. Was the choice of variables for sensitivity analysis justified?	Yes	One- way sensitivity analysis was undertaken for each variable used in the model.
29. Were the ranges over which the parameters were varied stated?	Yes	Basal values and rank of uncertainty values
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and effects were provided for each strategy in a disaggregated form
33. Was the answer to the study question given?	Yes	Using a cost-effectiveness threshold
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Although data refers to a Spanish environment, economic evaluations of strategies have provided similar results

Latour-Perez et al, 2004		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Estimate the CE of clopidogrel, administered for 1 year after hospital admission for non-ST-segment elevation ACS in Spanish public health sphere
2. Was the economic importance of the research question stated?	Yes	Three specific reasons why economic evaluation in Spanish healthcare system is required
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Not clear	States societal but indirect costs are nor included so Spanish health care system
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	As per the CURE study
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Cost per QALY outcome required as cost per event is thought to be ambiguous
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CURE study, Framingham study and Spanish age-sex mortality rates.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	No
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?	Yes	Cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	Based on non-systematic review of the literature
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	Costs are grouped by DRGs
17. Were the methods for the estimation of	Yes	Data from DRG of the Spanish National Institute of

quantities and unit costs described?		Health
18. Were currency and price data recorded?	Yes	1999 Euros
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Markovian decision tree- full description and diagram
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	No explicit justification but implied Markov model due to the time element involved
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	12 months
23. Was the discount rate stated?	Yes	3% for both costs and effects
24. Was the choice of rate justified?	Yes	Following recommendation of experts
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?	Not clear	Models degree of adjustment assessed by Monte Carlo simulation. A table provides ranges for each variable
27. Was the approach to sensitivity analysis described?	Yes	One-way SA and second order Monte Carlo analysis
28. Was the choice of variables for sensitivity analysis justified?	Not clear	All variables in one-way and all but cost of drug and time of administration in Monte Carlo
29. Were the ranges over which the parameters were varied stated?	Yes	Ranges are provided for each variable
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	Using a CE threshold, the use of clopidogrel was cost-effective in 85.3% of cases
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Cost-effectiveness of Clopidogrel depends on a number of factors including duration of administration and strategy
36. Were generalisability issues addressed?	Yes	

Mahoney et al, 2006		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Aims of study clearly stated. Long term CE of clopidogrel use.
2. Was the economic importance of the research question stated?	Not clear	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Societal
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Comparators from the PCI CURE trial.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates	Yes	Patient-level outcomes and resource use from PCI-

used stated?		CURE study data. Life expectancy from external sources
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Overview of PCI-CURE study is provided
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	Single study data source
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per life year gained.
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?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	The clinical events from the trial and associated DRG costs are provided
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	2001 - US Dollars.
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Costs were for 1 year.
20. Were details of any model used given?	NA	No model-economic analysis of a clinical trial
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?	Yes	Life-time for life-expectancy
23. Was the discount rate stated?	Yes	Costs not discounted single year so not applicable. Life expectancy estimates discounted 3% per year after yr 1.
24. Was the choice of rate justified?	No	
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?	Yes	CI for life expectancy gains, cost data and clinical events data taken from the PCI-CURE study.
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	Table I and Table IV
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Compared to standard treatment in PCI-CURE study
31. Was an incremental analysis reported?	Yes	Incremental cost per life year gained
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Life-expectancy displayed by condition and cost-effectiveness by costing source.
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Contained in the Discussion section
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Limitations around application to health systems which differ from the USA.

Mahoney et al, 2010

Study Question	Grade (yes/no/not clear/NA)	Comments
Study design		
1. Was the research question stated?	Yes	Cost-effectiveness analysis of Prasugrel versus Clopidogrel
2. Was the economic importance of the research question stated?	Yes	Economic implication due to potentially large population of patients for new treatment
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	US Healthcare payer perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Economic evaluation of TRITON-TIMI 38 trial so cost-effectiveness of comparators from trial were evaluated.
5. Were the alternatives being compared clearly described?	Yes	Study comparators from TRITON-TIMI 38
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis and secondary cost-utility analysis was evaluated.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Comparing cost-effectiveness of the two treatments compared in the TRITON-TIMI 38 trial
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	TRITON-TIMI 38 trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Refers to the literature of the TRITON-TIMI 38 trial
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?	Yes	Economic primary outcomes was total in-trial costs. In addition incremental cost per life gained was calculated if one treatment was more costly and effective
12. Were the methods used to value health states and other benefits stated?	Yes	Refers to literature – Beaver dam health outcomes study.
13. Were the details of the subjects from whom valuations were obtained given?	No	Cites literature only
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	The type and number of rehospitalisations by treatment are presented
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Cost sections included hospitalisation costs and medication costs.
18. Were currency and price data recorded?	Yes	US dollars. Resource use cost was presented in 2005 dollars and medication in 2009
19. Were details of price adjustments for inflation or currency conversion given?	No	
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?	Yes	Lifetime
23. Was the discount rate stated?	Yes	3% annually in base case
24. Was the choice of rate justified?	No	
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?	Yes	Covered in detail in the statistical analysis section
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	States clinically relevant subgroups – some predetermined and some post hoc

29. Were the ranges over which the parameters were varied stated?	Yes	Online supplementary tables
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparisons were those from the TRITON-TIMI 38trial.
31. Was an incremental analysis reported?	Yes	Incremental cost per year of life gained.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Table 4
33. Was the answer to the study question given?	Yes	Treatment with prasugrel compared with clopidogrel is cost-effective.
34. Did conclusions follow from the data reported?	Yes	Conclusions section included.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Need further studies to understand the optimal duration of treatment and CE in non-ACS settings
36. Were generalisability issues addressed?	Yes	Application of US data countries with different treatment practices highlighted.

Main et al, 2004 (Secondary Report of Manufacturer Submission for Clopidogrel)		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		

1. Was the research question stated?	Yes	Assess the long-term cost-effectiveness of 12 months of treatment with clopidogrel in addition to aspirin, compared with aspirin alone, for patients with non-ST-segment elevation ACS in the UK
2. Was the economic importance of the research question stated?	Yes	Submission to NICE
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	UK NHS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	Clopidogrel in addition to aspirin, compared with aspirin alone
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Cost-effectiveness analysis based on previous analysis/model used in a previous NICE technology assessment report
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Baseline event rates applied in the model were obtained from UK data used in the model report. Baseline event data for the first 6 months were based on data from the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) and an audit of all non-ST-segment elevation ACS patients undergoing acute PCI at Leeds General Infirmary in 2000.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
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)?	No	Various sources and methods; no formal synthesis undertaken
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY or cost per life-year gained
12. Were the methods used to value health states and other benefits stated?	No	Utility values were obtained from a number of different sources
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Not clear	Costs taken from various published sources
18. Were currency and price data recorded?	Yes	UK pounds 2002
19. Were details of price adjustments for inflation or currency conversion given?	No	It is stated that they were inflated, but no source was provided
20. Were details of any model used given?	Yes	Markov model structure and diagram
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Based on the cost-effectiveness model used in a previous NICE technology assessment report on glycoprotein IIb/IIIa antagonists
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits	Yes	The model consisted of a short-term component that

stated?		considered costs and effects over a 12-month period and a longer-term element that extended the analysis over a longer-term time horizon. For the baseline analysis, the expected costs and outcomes of a cohort of patients were evaluated over a time horizon of 40 years.
23. Was the discount rate stated?	Yes	Costs were discounted at 6%, and heath benefits were discounted at 1.5%.
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	Several univariate and multivariate sensitivity analyses were conducted for a 40-year time horizon and probabilistic analyses.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	No	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	Yes	

Mauskopf et al, 2012		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Cost-effectiveness of prasugrel compared with clopidogrel with different characteristics, practice patterns, and adherence patterns compared with clinical trial populations
2. Was the economic importance of the research question stated?	Yes	Applicability of results from clinical trial populations to general practice populations
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	US payer perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	Prasugrel-based therapy compared with clopidogrel-based therapy
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	i3 Vision database and TRITON-TIMI 38
9. Were details of the design and results of the effectiveness study given (if based on a single	No	

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?	Yes	Number of life-years gained, number of CV and bleeding events and number of rehospitalisations
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?	Yes	As part of the results in Table 2
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	2009 US dollars
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Medical care component of the Consumer Price Index
20. Were details of any model used given?	Yes	Disease progression model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	15 months
23. Was the discount rate stated?	Yes	3% for life expectancy
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Confidence intervals were provided but details of statistical tests were not provided
27. Was the approach to sensitivity analysis described?	Yes	One-way and probabilistic sensitivity analyses
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	In the tornado diagram
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	In the limitations section of the discussion
36. Were generalisability issues addressed?	Yes	

NICE, 2009		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		

1. Was the research question stated?	Yes	Cost-effectiveness of prasugrel versus clopidogrel in patients with moderate- to high-risk acute coronary syndromes who were scheduled to have percutaneous coronary intervention. Patients were given aspirin in combination with the drugs studied.
2. Was the economic importance of the research question stated?	Yes	Submission to NICE as part of the STA process
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Not clear	The manufacturer's submission states that in the key categories of estimated costs were related to hospitalisation and drug costs so assume
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Prasugrel was used in the clinical trial TRITON-TIMI 38, on which the economic evaluation was based
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Markov model structure with two phases. The first phase spanned the duration of the TRITON-TIMI 38 trial, and the second phase modelled long-term events.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Patient data from the TRITON-TIMI 38 trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
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)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	A systematic review was conducted to identify HRQoL data relevant to the modelled trial populations.
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Utility reductions for acute coronary syndromes and stroke/MI were taken directly from a US study, with background UK population norms (free of disease) used to determine utility weights for use in the model.
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Not clear	UK pounds but no details of year
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Markov model structure with two phases. The first phase spanned the duration of the TRITON-TIMI 38 trial, and the second phase modelled long-term events. Rather than using data from the trial directly in the model, separate risk equations for primary endpoint events were derived from individual patient data from the TRITON-TIMI 38 trial.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Key parameters based on the TRITON-TIMI 38 trial
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	1 year and 40 years
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	Sensitivity analyses were conducted, but no details are provided.
28. Was the choice of variables for sensitivity analysis justified?	No	Analyses were carried out to explore the impact of: • Preloading of clopidogrel, and • Changing the relative risk for all-cause mortality for the “median” unstable angina and non-ST-segment-elevation MI profile
29. Were the ranges over which the parameters were varied stated?	Yes	For the two variables stated
30. Were relevant alternatives compared? (That is,	Yes	

were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?	Yes	Incremental cost per QALY
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	The Committee, when considering the cost-effectiveness data, agreed that the advantage of prasugrel over clopidogrel was plausible in all patients with ST-segment-elevation MI and in all patients with diabetes mellitus (with ST-segment-elevation MI or non-ST-segment-elevation MI).
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Prasugrel is not cost-effective in all subgroups.

NICE, 2011		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Evaluate the short- and long-term cost-effectiveness of ticagrelor
2. Was the economic importance of the research question stated?	Yes	The economic burden of ACS was discussed.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Direct health service costs were calculated.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	The comparators identified were clopidogrel (standard of care in the UK and used in PLATO) and prasugrel (also used in clinical practice in line with recent NICE guidance)
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	An Excel-based cost-utility model was developed. The model had a two-part construct, with a 1-year decision tree, and a Markov model for long-term extrapolation. A systematic literature search identified a number of papers that modelled cost-effectiveness in an ACS population. A review of these papers showed that the approach of using a short-term decision tree followed by a Markov model was common. In addition, this approach also has been used by independent evidence review groups in the preparation of HTAs commissioned by NICE in the ACS arena.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	The key clinical evidence for ticagrelor comes from a large randomised controlled clinical trial (PLATO)
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	In the clinical effectiveness section of the document
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)?	Yes	Results were taken from a previously published indirect comparison
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Life-years, cost, and QALYs

12. Were the methods used to value health states and other benefits stated?	Yes	The PLATO study included a prespecified Health Economics (HECON) and Quality of Life substudy. This is described in detail.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Subjects from PLATO study
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	A within-trial costing analysis was performed as part of the PLATO HECON substudy; this was used to derive the costs in the decision-analysis model. Costs for the Markov part were taken from published literature.
18. Were currency and price data recorded?	Yes	2008-2009 UK pounds
19. Were details of price adjustments for inflation or currency conversion given?	Yes	The initial costing analysis was undertaken using 2007-2008 costs; however, these have been inflated using the PSSRU inflation indices
20. Were details of any model used given?	Yes	Detailed description and diagram
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Based on previous published economic models in ACS; the approach also has been used by independent evidence review groups in the preparation of HTAs.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	The Markov model is based on a cycle length of 1 year and is run for a period of 40 years (lifetime)
23. Was the discount rate stated?	Yes	3.5% for costs and utilities
24. Was the choice of rate justified?	Yes	NICE reference case
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Mean utilities for the health states and their respective standard errors were provided. Mean costs (95% CI) for Markov states were also reported.
27. Was the approach to sensitivity analysis described?	Yes	One-way sensitivity analysis was conducted using the lower and upper 95% CIs for key variables. PSA was also performed.
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	Explanations were provided for each
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Results were expressed as incremental cost per life-year, incremental costs, and incremental QALYs
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	Ticagrelor is highly cost-effective versus clopidogrel over the 40-year time horizon

34. Did conclusions follow from the data reported?	Yes	Provides the NHS with a new cost-effective option for the treatment of ACS
35. Were conclusions accompanied by the appropriate caveats?	Yes	A list of weaknesses of the evaluation was provided
36. Were generalisability issues addressed?	Yes	The economic evaluation is relevant to all groups of patients who could potentially use the technology per the licensed indication

Rogowski et al, 2009		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Update an existing decision-tree model used in an HTA report that assessed the long-term cost-effectiveness of 12 months of treatment with clopidogrel in addition to aspirin in comparison with aspirin alone in the UK
2. Was the economic importance of the research question stated?	Yes	Update the existing model to provide a more robust approach to evaluating the cost-effectiveness of alternative durations of clopidogrel. The work was also extended to include a formal assessment of the potential value of further research using value of information approaches.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	A series of sensitivity analyses was undertaken in a previous model to explore the potential cost-effectiveness of shorter treatment durations, on the basis that cost-effectiveness may be sensitive to the absolute risk at different follow-up periods.

5. Were the alternatives being compared clearly described?	Yes	The analysis compares five different strategies based on alternative treatment durations with:
		• Lifetime treatment with standard therapy (including aspirin) alone
		• Clopidogrel as an adjunct to aspirin for
		  • 1 month,
		  • 3 months,
		  • 6 months, or
		  • 12 months

6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Updating a previous economic model used in a HTA report
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	The CURE trial remains the primary source of data used in the updated model
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Chapter 3 of the HTA report
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)?	No	No formal synthesis
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Costs and QALYs
12. Were the methods used to value health states and other benefits stated?	No	Taken from published study
13. Were the details of the subjects from whom valuations were obtained given?	No	Taken from published study
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	Costs were taken and updated from previous economic model
18. Were currency and price data recorded?	Yes	2005-2006 UK pounds
19. Were details of price adjustments for inflation or currency conversion given?	No	Stated inflated to 2005/06 but no further details.
20. Were details of any model used given?	No	Details of the previous HTA model structure are provided in Chapter 4 (assessment of cost-effectiveness evidence)
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	This HTA report provides an update of an economic model used in a previous HTA document. Differing scenarios are evaluated.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime horizon (40 years)
23. Was the discount rate stated?	Yes	3.5% for both costs and outcomes
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	95% CI for outcomes reported in CURE
27. Was the approach to sensitivity analysis described?	Not clear	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Scenario were assessed based on treatment duration, which had been found to be sensitive in a previous model.
31. Was an incremental analysis reported?	Yes	Incremental QALY
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	QALY and costs
33. Was the answer to the study question given?	Yes	The updated model reinforced the conclusions from the earlier analysis. That is, a policy of 12 months of

		clopidogrel for patients with NSTE-ACS appears to be cost-effective.
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	In discussion section (Chapter 6)
36. Were generalisability issues addressed?	Yes	Clopidogrel treatment is not cost-effective across all patient risk categories.

SMC, 2007		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Assess the cost-utility of adding clopidogrel to aspirin in a 60-year old patient with ST segment elevation MI
2. Was the economic importance of the research question stated?	Yes	SMC submission
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	No details
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	Clopidogrel plus aspirin vs. aspirin
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	In the "Summary of evidence on comparative efficacy" section; this section describes a pivotal trial and a second larger trial.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	In the "Summary of evidence on comparative efficacy" section
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)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	No	UK pounds; no details of year
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Not clear	Paper states a Markov model was used
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	A sensitivity analysis was conducted, but no details are provided.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Clopidogrel plus aspirin vs. aspirin
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	Using the protocol from the second trial, the cost per QALY was £2,284 for 1 month of treatment and £3,891 for 1 year of treatment. Using the protocol from the pivotal trial, the cost per QALY was £1,857 for 1 month

		of treatment and £2,925 for 1 year of treatment.
34. Did conclusions follow from the data reported?	No	
35. Were conclusions accompanied by the appropriate caveats?	Yes	The SMC listed several scenarios in which the cost per QALY could increase
36. Were generalisability issues addressed?	No	

SMC, 2009		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Cost-utility analysis to assess prasugrel (60 mg loading dose and 10 mg/day maintenance dose) plus aspirin with clopidogrel (300 mg loading dose and 75 mg/day maintenance dose) plus aspirin
2. Was the economic importance of the research question stated?	Yes	SMC submission
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Clopidogrel is licensed in combination with aspirin for the treatment under investigation
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Pivotal phase 3 study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	In the "Summary of evidence on comparative efficacy"
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)?	N/A	QALY and life-years
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Not clear	Disutility estimates for cardiovascular events were derived from a published study
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Disutility estimates were derived from a published study including ACS patients using the EQ 5D and adjusted for UK population norms
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Not clear	UK pounds; no details of year
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Markov model and extrapolation utilising individual patient data from the pivotal phase 3 study. Analysis was performed for a number of patient groups, although cost-effectiveness was assessed for all patients in the phase 3 clinical study
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Key parameters were based on pivotal phase III trial
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	No additional treatment effect was assumed beyond the 12-month maximum duration of prasugrel or clopidogrel treatment, although long-term mortality was extrapolated through to a 40-year time horizon.
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	One-way and a probabilistic sensitivity analysis was conducted.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	The use of the median patient profile for one-way sensitivity analysis for each subgroup was used. Probabilistic sensitivity analysis was based on a single median patient profile, rather than the individual patient data.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when	Yes	

conducting the incremental analysis?)		
31. Was an incremental analysis reported?	Yes	Incremental costs, life-years, and QALYs
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	Using individual patient data, the estimated cost per QALY gained for this patient group was £3,779.
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	The SMC listed several concerns with the analysis.
36. Were generalisability issues addressed?	Yes	The duration of treatment for clopidogrel is much shorter in clinical practice.

SMC, 2011		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Cost-utility analysis comparing ticagrelor to clopidogrel
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Not clear	Clopidogrel is the current standard treatment in Scotland and therefore the relevant comparator. No explanation is provided for using prasugrel.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Clinical data for the comparison with clopidogrel were taken from the pivotal trial and from an indirect comparison evaluating prasugrel. For the Markov phases of the models, the risks of further events were taken from literature sources and published life tables.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	In the clinical effectiveness section of the submission.
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)?	Yes	In the case of the comparison with prasugrel for the decision-tree phase, data were obtained from an indirect comparison using the Bucher method.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	For the decision-tree phase of the model, utility values were estimated directly from EQ-5D data collected from patients in the pivotal trial. For the Markov phase of the model, published values were used.
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Brief details are provided of the subjects in the clinical effectiveness section of the submission.
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	

16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Not clear	The only information provided is that resource use for the decision tree was estimated from patient-level data collected during the pivotal trial and from literature sources for the Markov states.
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	The economic model was structured around a decision tree for the initial year of the model and thereafter a Markov model with health states of MI, post-MI, non-fatal stroke, post-stroke, no event and death.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Clinical data for the comparison with clopidogrel were taken from the pivotal trial and from an indirect comparison evaluating prasugrel. For the Markov phases of the models, the risks of further events were taken from literature sources and published life tables.
23. Was the discount rate stated?	Yes	In the clinical effectiveness section of the submission.
24. Was the choice of rate justified?	Yes	In the case of the comparison with prasugrel for the decision-tree phase, data were obtained from an indirect comparison using the Bucher method.
25. Was an explanation given if cost or benefits were not discounted?	Yes	Cost per QALY
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	For the decision-tree phase of the model, utility values were estimated directly from EQ-5D data collected from patients in the pivotal trial. For the Markov phase of the model, published values were used.
27. Was the approach to sensitivity analysis described?	Not clear	Brief details are provided of the subjects in the clinical effectiveness section of the submission.
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	Not clear	The only information provided is that resource use for the decision tree was estimated from patient-level data collected during the pivotal trial and from literature sources for the Markov states.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	No	
34. Did conclusions follow from the data reported?	Yes	The economic model was structured around a decision tree for the initial year of the model and thereafter a Markov model with health states of MI, post-MI, non-fatal stroke, post-stroke, no event and death.
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	Yes	Clinical data for the comparison with clopidogrel

		were taken from the pivotal trial and from an indirect comparison evaluating prasugrel. For the Markov phases of the models, the risks of further events were taken from literature sources and published life tables.

Shleinitz et al, 2004		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Establish cost-effectiveness of clopidogrel and aspirin as secondary prevention in patients with a prior vascular event
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Societal
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	CAPRIE study comparators
5. Were the alternatives being compared clearly described?	Yes	Clopidogrel versus Aspirin
6. Was the form of economic evaluation stated?	Yes	States Cost-effectiveness analysis but QALYS are calculated so cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CAPRIE Study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Some details of CAPRIE provided along with supplementary data items and reasoning.
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	Single data source used.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	Reference to literature.
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	Not included
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	US Dollars 2002
19. Were details of price adjustments for inflation or currency conversion given?	Yes	GDP deflator used to adjust figures to 2002 levels.
20. Were details of any model used given?	Yes	Markov model used.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Model not justified, key parameters were those from CAPRIE study
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	3% annual
24. Was the choice of rate justified?	Yes	Reference to literature

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?	Not Clear	Ranges and 95% CI for RR
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	Variables mentioned in relation to importance to the model, unclear if this is based on the sensitivity analysis results.
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparators based on the CAPRIE study.
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Clopidogrel provides a quality adjusted life expectancy a cost within societal limits
35. Were conclusions accompanied by the appropriate caveats?	Yes	The conclusion is for patients with PAD or a recent stroke but not in patients with MI
36. Were generalisability issues addressed?	Yes	Covered in introduction section

Shleinitz et al, 2005		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	To determine the cost-effectiveness of clopidogrel plus aspirin compared with aspirin alone.
2. Was the economic importance of the research question stated?	Yes	Adding clopidogrel to aspirin maybe financially unattractive if done in all patients so study assesses high risk
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Societal
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Analysis based on CURE study comparators
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CURE trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
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?	Yes	Lifetime costs, QALYs and incremental cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	Reference to the literature and multiplication for states combining 2 events.
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the	No	

study question discussed?		
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Costs section of model inputs section.
18. Were currency and price data recorded?	Yes	2002 US Dollars
19. Were details of price adjustments for inflation or currency conversion given?	Yes	GDP Deflator
20. Were details of any model used given?	Yes	Markov model produced in TreeAge
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	3% Annually for costs and utilities.
24. Was the choice of rate justified?	No	
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?	Yes	95% CI used for sensitivity analysis and ranges stated in Model inputs table
27. Was the approach to sensitivity analysis described?	Yes	One way, two way and probabilistic.
28. Was the choice of variables for sensitivity analysis justified?	Yes	Performed for all model inputs
29. Were the ranges over which the parameters were varied stated?	Yes	Analysed at both extremes of the 95% confidence interval (see table 'Model Inputs')
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparator treatments in the CURE trial.
31. Was an incremental analysis reported?	Yes	Incremental cost per QALY was reported,
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported for each treatment
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Clopidogrel plus aspirin results in ICER within the traditional limits of cost-effectiveness
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Results may not apply to a number of different types of patients

Weintraub et al, 2005		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Establish long-term cost effectiveness of clopidogrel.
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Not clear	Study states only direct medical costs included which implies the viewpoint is the healthcare provider but conclusion states that study has a societal viewpoint.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	As per the CURE trial
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness
7. Was the choice of form of economic evaluation	Yes	

justified in relation to the questions addressed?		
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	CURE trial data
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Summary of CURE trial design and results provided.
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?	Yes	Costs, life years, incremental cost per life year gained
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	Not included in CURE trial
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Costs associated with diagnosis related groups (DRGs) and Medicare (US) costs
18. Were currency and price data recorded?	Yes	US Dollars – 2001?
19. Were details of price adjustments for inflation or currency conversion given?	No	
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?	Not clear	Study design indicates lifetime time frame (LYG outcome)
23. Was the discount rate stated?	Yes	3%
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	NA	Costs and life-expectancy discounted.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	*P* values and 95% CI stated
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	Life-expectancy and cost of hospitalisations. Major outcomes of interest, but not justified in text.
29. Were the ranges over which the parameters were varied stated?	Not clear	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Not clear	Considered only changes in utility ranges. Not explained clearly.
31. Was an incremental analysis reported?	Yes	Incremental cost per life year gain was reported. In addition, a cost per QALY figure was calculated using assumptions
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	Clopidogrel treatment is both effective and cost-effective
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations section covers key caveats and limitations.
36. Were generalisability issues addressed?	Yes	US costs were applied to trial data and differences in resource use and costs may affect the generalisability

Zhang et al, 2009		
Study Question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Evaluate the long-term cost-effectiveness of clopidogrel in patients with STEMI – this has not been previously investigated.
2. Was the economic importance of the research question stated?	Yes	Whether clopidogrel is cost-effective in STEMI patients. This has not been investigated.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Article states societal but only direct costs are included which implies healthcare provider
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Whether clopidogrel is cost-effective in STEMI patients. Treatments investigated in COMMIT study
5. Were the alternatives being compared clearly described?	Yes	Clopidogrel or matching placebo in addition to Aspirin
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Aim to establish cost-effectiveness in STEMI patients using CEA analysis
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	COMMIT Study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Summary provided from literature
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?	Yes	Life years, cost and Incremental cost per life year gained.
12. Were the methods used to value health states and other benefits stated?	Yes	Assumed utility
13. Were the details of the subjects from whom valuations were obtained given?	No	
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?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Not clear	2003 US Dollars (not clearly stated but indicated by article content)
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Decision model using Tree-age Software
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Up to 1 year
23. Was the discount rate stated?	Yes	3%
24. Was the choice of rate justified?	No	
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?	No	
27. Was the approach to sensitivity analysis described?	Yes	

28. Was the choice of variables for sensitivity analysis justified?	Not clear	Has to be inferred and is not explicitly stated.
29. Were the ranges over which the parameters were varied stated?	No	Values stated but ranges were not.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	Addition of clopidogrel to aspirin in STEMI patients is highly cost effective
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Detailed in the limitations section.
36. Were generalisability issues addressed?	Yes	Trial in China and US costs applied to US –maybe difference in treatment practices and costs

Coleman 2013		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	To determine the cost-effectiveness of using platelet reactivity assays (PRAs) to select a dual-antiplatelet regimen for patients with acute coronary syndrome
2. Was the economic importance of the research question stated?	Yes	Previous economic models evaluating the cost-effectiveness of genotype-driven selection of antiplatelet agents was considered
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	United States payer (or Medicare) perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Replica of Clopidogrel in Unstable angina to prevent Recurrent Events [CURE] study, Trial to assess Improvement in TRITON-TIMI 38 trial and PLATO trial
5. Were the alternatives being compared clearly described?	Yes	Detailed in the model structure. Used alternatives in clinical trials
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	Decision tree and Markov models are described in general but not in relation to why chosen for CE analysis
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Replica of Clopidogrel in Unstable angina to prevent Recurrent Events [CURE] study, TRial to assess Improvement in TRITON-TIMI 38 trial and PLATO trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	Not based on 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)?	Yes	Replica of Clopidogrel in CUREstudy, TRITON-TIMI 38 trial and PLATO trial
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	Yes	From literature
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Taken from published study
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?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	From literature
18. Were currency and price data recorded?	Yes	All costs are expressed in 2011 United States dollars
19. Were details of price adjustments for inflation or currency conversion given?	Yes	When needed, the costs were converted to United States dollars from foreign currency using exchange rates and inflated using the Consumer Price Index for Medical Care
20. Were details of any model used given?	Yes	Markov model was used. Diagram of model structure included as well as detailed description
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Model was simulated with a time horizon of 2, 3, 4, 10, and 40 years
23. Was the discount rate stated?	Yes	The costs and outcomes were discounted at 3% annually
24. Was the choice of rate justified?	Yes	Reference was given for chosen discount rate
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?	No	Confidence intervals not reported for all data and statistical tests were not reported.
27. Was the approach to sensitivity analysis described?	Yes	Single and multiway sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	No	No justification provided other than to prove robustness.
29. Were the ranges over which the parameters were varied stated?	Yes	A 1-way sensitivity analysis for each variable in the model over its plausible range
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparing against standard treatment
31. Was an incremental analysis reported?	Yes	Incremental cost per life year/QALY saved.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported for each treatment
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	PRA-driven selection of antiplatelet therapy appeared to be a cost-effective strategy with the potential to decrease the overall acute coronary syndrome associated healthcare costs
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations section covers key caveats
36. Were generalisability issues addressed?	Yes	US costs were applied to trial data and differences in resource use and costs may affect the generalisability

Coleman 2014		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	To estimate the costeffectiveness of universal compared to PRA-driven selection of ticagrelor or prasugrel for acute coronary syndrome (ACS) patients by EU perspectives

2. Was the economic importance of the research question stated?	Yes	Previous economic models evaluating the cost-effectiveness of genotype-driven selection of antiplatelet agents was considered
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Health care perspective was used.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	TRITON-TIMI 38 trial and PLATO trial were used as the key source of evidence.
5. Were the alternatives being compared clearly described?	Yes	Detailed in the model structure. Used alternatives in clinical trials
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	Decision tree and Markov models are described in general but not in relation to why chosen for CE analysis
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	TRITON-TIMI 38 trial and PLATO trial were used as the key source of evidence in the model.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	Not based on 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)?	Yes	Replica of Clopidogre in TRITON-TIMI 38 trial and PLATO trial
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	Yes	From literature
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Taken from published study
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?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	From literature
18. Were currency and price data recorded?	Yes	All costs are expressed in 2013 United States dollars
19. Were details of price adjustments for inflation or currency conversion given?	Yes	When needed, costs were inflated using the Eurostat HarmonisedIndex of Consumer Prices or consumer price inflationvalues from United Kingdom Office of National Statistics
20. Were details of any model used given?	Yes	Markov model was used. Diagram of model structure included as well as detailed description
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Model was simulated with a time horizon of 5 years
23. Was the discount rate stated?	Yes	Costs and outcomes were discounted at country specific recommended annual rates.
24. Was the choice of rate justified?	Yes	Costs and outcomes were discounted at country specific recommended annual rates.
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?	No	Confidence intervals not reported for all data and statistical tests were not reported.
27. Was the approach to sensitivity analysis	Yes	One way sensitivity analysis was used.

described?		
28. Was the choice of variables for sensitivity analysis justified?	No	No justification provided other than to prove robustness.
29. Were the ranges over which the parameters were varied stated?	Yes	A 1-way sensitivity analysis for each variable in the model over its plausible range
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparing against standard treatment
31. Was an incremental analysis reported?	Yes	Incremental cost per life year/QALY saved.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported for each treatment
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	The universal use of newer P2Y12 inhibitors is not likely cost-effectivecompared to PRA-driven strategies. PRA-driven selection of DAPT appears to be a reasonable strategy to decrease ACS-associatedhealthcare expenditures in these European countries.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations section covers key caveats
36. Were generalisability issues addressed?	No	Genetalisability issues were not addressed.

Theidel 2013		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	To compare the cost-effectiveness of ticagrelor versus clopidogrel within the German health care system
2. Was the economic importance of the research question stated?	Yes	Previous economic models evaluating the cost-effectiveness of antiplatelet agents was considered
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Not clear	Indirect costs were also taken into account
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	PLATO study was considered for chosing appropriate interventions
5. Were the alternatives being compared clearly described?	Yes	Detailed in the model structure. Used alternatives in clinical trials
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	Decision tree and Markov models were described in general but not in relation to why chosen for CE analysis.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	PLATO study was considered for chosing clinical data
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	PLATO study was considered for chosing clinical data
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?	Yes	The primary health outcomes was mean cost and life-years gained (LYG) of treating ACS patients for 1 year with ticagrelor plus ASA compared with clopidogrel plus ASA

12. Were the methods used to value health states and other benefits stated?	Yes	From literature
13. Were the details of the subjects from whom valuations were obtained given?	No	Taken from published study
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?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Unit cost inputs were selected on the basis of best available evidence
18. Were currency and price data recorded?	Yes	Standardized (inflation-adjusted) to the year 2009
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Standardized (inflation-adjusted) to the year 2009
20. Were details of any model used given?	Yes	Markov model was used. Diagram of model structure included as well as detailed description
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The main difference to the already existing multinational model is the used macro-costing approach to generate the cost data
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	All costs and benefit components were subject to a discount rate of 3 % in the base case scenario
24. Was the choice of rate justified?	Yes	Reference was given for chosen discount rate
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?	No	Confidence intervals not reported for all data and statistical tests were not reported.
27. Was the approach to sensitivity analysis described?	Yes	Single and multiway sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	Yes	No justification provided other than to prove robustness
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparing against standard treatment
31. Was an incremental analysis reported?	Yes	Incremental cost per life year/QALY was reported
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported for each treatment
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	12 months of ACS treatment using ticagrelor/ASA instead of clopidogrel/ASA may offer a cost-effective therapeutic option
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations section covers key caveats
36. Were generalisability issues addressed?	No	German costs were applied to trial data and differences in resource use and costs may affect the generalisability

Davies 2013		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		

1. Was the research question stated?	Yes	To assess the long-term cost-effectiveness of 12 months treatment of prasugrel compared to clopidogrel in patients with acute coronary syndrome
2. Was the economic importance of the research question stated?	Yes	Economic burden was considered
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Direct health service costs were calculated
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	TRITON-TIMI 38
5. Were the alternatives being compared clearly described?	Yes	Detailed in the model structure. Used alternatives in clinical trials
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Markov state transition model but not in relation to why chosen for CE analysis
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	TRITON-TIMI 38
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	TRITON-TIMI 38
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?	No	
12. Were the methods used to value health states and other benefits stated?	Yes	From literature
13. Were the details of the subjects from whom valuations were obtained given?	No	Taken from published study
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?	NA	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Costs are modelled over the trial period by assigning the average re-hospitalisation costs for each arm
18. Were currency and price data recorded?	Yes	Spanish diagnosis related groups (DRGs) were inflated to 2013 costs
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Spanish diagnosis related groups (DRGs) were inflated to 2013 costs
20. Were details of any model used given?	Yes	Markov model was used. Diagram of model structure included as well as detailed description
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	All costs and benefit components were subject to a discount rate of 3 % in the base case scenario
24. Was the choice of rate justified?	Yes	Refernce was given for chosen discount rate
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?	No	Confidence intervals not reported for all data and statistical tests were not reported

27. Was the approach to sensitivity analysis described?	Yes	Single and multiway sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	Yes	No justification provided other than to prove robustness
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Comparing against standard treatment
31. Was an incremental analysis reported?	Yes	Incremental cost per life year/QALY was reported
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported for each treatment
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations section covers key caveats
36. Were generalisability issues addressed?	No	

Grima 2014		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Cost-effectiveness of ticagrelor compared to clopidogrel in ACS patients from the perspective of the Canadian publicly funded health care system.
2. Was the economic importance of the research question stated?	Yes	The PLATO study demonstrated a significant reduction in cardiovascular death, myocardial infarction and stroke with ticagrelor compared to clopidogrel in patients with acute coronary syndromes (ACS) treated for up to one year.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Cost-effectiveness analyses of ticagrelor versus clopidogrel based on the PLATO trial have found favorable lifetime incremental cost per quality-adjusted life year (QALY) ratios (range US$2728–US$8443) from public payer perspectives in Germany, Singapore, Australia, and the UK and have resulted in coverage by public plans in several countries.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	TThe extent to which ticagrelor will be used in Canada depends not only on its relative efficacy but also on its economic value.
5. Were the alternatives being compared clearly described?	Yes	Prasugrel and ticagrelor are new antiplatelet agents with comparative clinical trial data with clopidogrel
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Cost-effectiveness analyses of ticagrelor versus clopidogrel based on the PLATO trial have found favorable lifetime incremental cost per quality-adjusted life year (QALY) ratios (range US$2728–US$8443) from public payer perspectives in Germany, Singapore, Australia, and the UK and have resulted in coverage by public plans in several countries.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Analysis was based on PLATO clinical trial data
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	Design and results of the effectiveness study was not given

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)?	No	Details of the methods of synthesis or meta-analysis of estimates were not given
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	Primary outcome was not mentioned
12. Were the methods used to value health states and other benefits stated?	Yes	Details used to value health states and other benefits were stated
13. Were the details of the subjects from whom valuations were obtained given?	No	Details were not provided
14. Were productivity changes (if included) reported separately?	No	Productivity changes were not reported separately
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	Unit cost were reported seperately
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	Canadian drug prices were recorded
19. Were details of price adjustments for inflation or currency conversion given?	Yes	All costs were inflated to reflect 2011 Canadian dollars.
20. Were details of any model used given?	Yes	A two-part model was developed consisting of a one-year decision tree and a lifetime Markov model.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Justification was not provided for model used
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	1 year and life time horizon
23. Was the discount rate stated?	Yes	5% per year
24. Was the choice of rate justified?	No	Tthe choice of discounted rate was not justified
25. Was an explanation given if cost or benefits were not discounted?	No	Explaination was not stated
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Statistical test(s) and confidence intervals were mentioned
27. Was the approach to sensitivity analysis described?	Yes	Univariate and probabilistic sensitivity analyses were conducted.
28. Was the choice of variables for sensitivity analysis justified?	No	Choice of variables was not stated
29. Were the ranges over which the parameters were varied stated?	Yes	Ranges were provided
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	ICER was reported
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported for each treatment
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Ticagrelor is a clinically superior and costeffective option for the prevention of cardiovascular events, including death, among ACS patients in Canada.
35. Were conclusions accompanied by the appropriate caveats?	Not clear	
36. Were generalisability issues addressed?	Not clear	

Straub 2014		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	To assess the clinical impact and cost-effectiveness of selecting P2Y12-inhibitors based on platelet function testing (PFT) in acute coronary syndrome (ACS) patients undergoing PCI
2. Was the economic importance of the research question stated?	Yes	Although some observational studies reported that the measured level of P2Y12-inhibition is predictive for thrombotic events, the clinical and economic benefit of incorporating PFT to personalize P2Y12-receptor directed antiplatelet treatment is unknown
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Not clear	The viewpoint of the analysis was not clear
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	For acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) a dual antiplatelet treatment with aspirin and a P2Y12 receptor inhibitor is considered as standard treatment nowadays. While aspirin is established as an undisputable cornerstone of therapy, the current situation for P2Y12 receptor inhibition is by far more complex with regard to drug selection as both clinical and economic aspects need to be taken into consideration here
5. Were the alternatives being compared clearly described?	Yes	The alternatives being compared clearly described
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	The choice of form of economic evaluation was not justified
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Data was used from TRITON-TIMI 38 trial and PLATO trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	Data was used from TRITON-TIMI 38 trial and PLATO trial
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)?	No	Details were not reported regarding the results
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Not clear	The primary outcome measure for the economic evaluation was not clearly stated
12. Were the methods used to value health states and other benefits stated?	Not clear	The methods used to value health states and other benefits were not stated
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	The details of the subjects from whom valuations were obtained were not given
14. Were productivity changes (if included) reported separately?	No	The productivity changes were not reported separately
15. Was the relevance of productivity changes to the study question discussed?	No	The productivity changes were not discussed
16. Were quantities of resources reported separately from their unit cost?	Yes	The quantities of resources were reported separately from their unit cost
17. Were the methods for the estimation of quantities and unit costs described?	Yes	The methods for the estimation of quantities and unit costs were described
18. Were currency and price data recorded?	Yes	US drug prices and German drug prices were recorded
19. Were details of price adjustments for inflation or currency conversion given?	Yes	The cost information obtained from the literature were transformed to the year 2012 by using the medical component of the U.S consumer price index, reflecting the inflation rate at health services
20. Were details of any model used given?	Yes	A decision tree model was used
21. Was there a justification for the choice of	No	Justification was not provided for model used

model used and the key parameters on which it was based?		
Analysis and interpretation of result		
22. Was the time horizon of cost and benefits stated?	Yes	One year time horizon was used
23. Was the discount rate stated?	Not clear	The discount rates were not stated
24. Was the choice of rate justified?	Not clear	The discount rates were not stated
25. Was an explanation given if cost or benefits were not discounted?	Not clear	The discount rates were not stated
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	The details of the statistical analysis were provided
27. Was the approach to sensitivity analysis described?	Yes	The approach to sensitivity analysis was described
28. Was the choice of variables for sensitivity analysis justified?	Yes	The variables for sensitivity analysis were reported
29. Were the ranges over which the parameters were varied stated?	Not clear	The ranges over which the parameters were varied was not stated
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	The relevant alternatives were compared
31. Was an incremental analysis reported?	Yes	ICER was reported
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Not clear	The major outcomes were not presented in a disaggregated as well as aggregated form
33. Was the answer to the study question given?	Yes	The study question was answered adequately
34. Did conclusions follow from the data reported?	Yes	The conclusions followed from the data reported
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations were discussed.
36. Were generalisability issues addressed?	Not clear	The generalisability issues were not addressed

Lala 2013		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	To evaluate the cost-effectiveness of a CYP2C19*2 genotype-guided strategy of antiplatelet therapy in ACS patients undergoing PCI, compared with two no testing strategies (empiric clopidogrel or prasugrel)
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Payer perspective was used
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	TRITON-TIMI 38 trial was considered for chosing appropriate interventions
5. Were the alternatives being compared clearly described?	No	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	TRITON-TIMI 38 trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	TRITON-TIMI 38 trial was considered for chosing clinical data
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)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	Yes	From literature
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Taken from published study
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?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	All costs were adjusted to 2010 $US
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Model was simulated with a time horizon of 10 years
23. Was the discount rate stated?	Yes	The costs were discounted at 3% annually
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Confidence intervals were reported
27. Was the approach to sensitivity analysis described?	Yes	One-way sensitivity analyses were performed on all variables
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	A 1-way sensitivity analysis for each variable in the model over its plausible range
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Incremental cost per life year/QALY were reported
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported for each treatment
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Among ACS patients undergoing PCI, a genotype-guided strategy yields similar outcomes to empiric approaches to treatment, but is marginally less costly and more effective
35. Were conclusions accompanied by the	Yes	Limitations were discussed.

appropriate caveats?		
36. Were generalisability issues addressed?	No	Generalisability issues were not addressed

Kazi 2014		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design	**Study design**	
1. Was the research question stated?	Yes	The objective of the study was to optimize antiplatelet therapy in acute coronary syndrome
2. Was the economic importance of the research question stated?	No	Economic importance was not mentioned
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Societal perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	Rationale was not mentioned
5. Were the alternatives being compared clearly described?	Yes	Five strategies were examined: generic clopidogrel, prasugrel, ticagrelor, and genotyping for polymorphisms of CYP2C19 with carriers of loss-of-function alleles receiving either ticagrelor (genotyping with ticagrelor) or prasugrel (genotyping with prasugrel) and noncarriers receiving clopidogrel
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	Economic evaluation was not justified
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Data was taken from published studies
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Data was taken from published studies
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)?	No	No methods of synthesis or meta-analysis of estimates were given
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	No primary end point was not provided
12. Were the methods used to value health states and other benefits stated?	No	Methods used to value health states and other benefits were not stated
13. Were the details of the subjects from whom valuations were obtained given?	No	Taken from published study
14. Were productivity changes (if included) reported separately?	No	Productivity changes were not reported separately
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	Quantities of resource swere not reported separately from their unit cost
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	All costs were adjusted to 2009 $US
19. Were details of price adjustments for inflation or currency conversion given?	No	No price adjustment for inflation was mentioned
20. Were details of any model used given?	Yes	Model inputs were provided
21. Was there a justification for the choice of model used and the key parameters on	No	Model used and the key parameters were mentioned

which it was based?		
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Model was simulated with a time horizon of lifetime
23. Was the discount rate stated?	Yes	3% annual discount was provided
24. Was the choice of rate justified?	No	No justification was provided
25. Was an explanation given if cost or benefits were not discounted?	No	No expliantion was provided
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No details were provided
27. Was the approach to sensitivity analysis described?	Yes	Deterministic, probabilistic, and scenario-based sensitivity analyses to account for uncertainty in the input variables
28. Was the choice of variables for sensitivity analysis justified?	No	No justification was provided
29. Were the ranges over which the parameters were varied stated?	No	Ranges were provided
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Five strategies were evaluated: generic clopidogrel; prasugrel; ticagrelor; genotyping for CYP2C19 polymorphisms followed by clopidogrel in patients without reduced-function polymorphisms, and either ticagrelor (the genotyping-ticagrelor strategy) or prasugrel (genotyping-prasugrel strategy)
31. Was an incremental analysis reported?	Yes	Incremental cost per life year/QALY were reported.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Costs and QALYs were not reported for each treatment
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	Genotype-driven personalization of therapy appears to improve clinical outcomes with prasugrel, but not with ticagrelor
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations of the study was provided
36. Were generalisability issues addressed?	Yes	US costs were applied to trial data and differences in resource use and costs may affect the generalisability

Davies 2013		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	The study objective was clearly stated
2. Was the economic importance of the research question stated?	Yes	Economic importance of the research question was discussed
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	National healthcare perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Rationale for the choice of comparator was reported
5. Were the alternatives being compared clearly described?	Yes	Prasugrel vs. clopidogrel
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis (CEA) was conducted
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Markov state transition model was constructed for the analysis assessed the cost-effectiveness of treatment with prasugrel compared with clopidogrel among patientswith an ACS undergoing PCI treatment
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	TRITON-TIMI 38 trial data was used
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	TRITON-TIMI 38 trial data was used
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)?	Yes	Details regarding various estimates were clearly mentioned.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	Not clear	It was unclear whether study considered productivity losses
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Unit costs for drugs and re-hospitalizations were entered in the model in local currencies, but are expressed as Euros based on purchasing power parities
18. Were currency and price data recorded?	Yes	Unit costs for drugs and re-hospitalizations were entered in the model in local currencies, but are expressed as Euros based on purchasing power parities
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Such details were reported
20. Were details of any model used given?	Yes	Markov model was used. Diagram of model structure included as well as detailed description.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The framework for the analysis was a Markovstate transition model constructed to facilitate a time horizonfor the analysis of patients' lifetimes, with assumedmaximum survival duration of 40 years after the index ACS event
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime (40 years) time horizon was applied to the study model
23. Was the discount rate stated?	Yes	3% disocunting was used to cost and outcomes
24. Was the choice of rate justified?	Not clear	
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?	No	Confidence intervals not reported for all data and statistical tests were not reported
27. Was the approach to sensitivity analysis described?	Yes	Deterministic and probabilistic sensitivity analyses were performed
28. Was the choice of variables for sensitivity analysis justified?	Yes	discount rates, utility decrements for haemorrhage, MI and stroke, relative risks for all-cause mortality, DRG costs, and clopidogrel acquisition costs
29. Were the ranges over which the parameters were varied stated?	Yes	Ranges for which parameters were varied were stated
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Prasugrel compared with clopidogrel
31. Was an incremental analysis reported?	Yes	ICER per QALY calculated
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported for each treatment

33. Was the answer to the study question given?	Yes	The study question was appropriately answered
34. Did conclusions follow from the data reported?	Yes	Among patients undergoing PCI for ACS, treatment with prasugrel compared with clopidogrel resulted infavourable cost-effectiveness profiles from these healthcare systems' perspectives
35. Were conclusions accompanied by the appropriate caveats?	Yes	Probabilistic analyses of the whole trial population is impractical due to the number of individual patientprofiles over which population level results are calculated
36. Were generalisability issues addressed?	Yes	The generalisability of the results was discussed

10.12 Appendix 12: Search strategy for section 7.4(Measurement and valuation of health effects)

The following information should be provided.

8. 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.

Please refer to sections 0 and appendix 10, 4 which detail the databases searched to identify economic models, resource use studies and utility studies

9. The date on which the search was conducted.

Please refer to sections sections 0 and appendix 10, 4

10. The date span of the search.

Please refer to sections 0 and appendix 10, 4

11. 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).

Please refer to sections sections 0 and appendix 10, 4

12. Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to sections 0 and appendix 10, 4

13. The inclusion and exclusion criteria.

Please refer to section7.4.5 for the inclusion and exclusion criteria.

14. The data abstraction strategy.

Data were extracted by one reviewer and independently checked for accuracy by a second reviewer.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

15. 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.

Please refer to sections 0 and appendix 10, 4which detail the databases searched to identify economic models, resource use studies and utility studies

16. The date on which the search was conducted.

Please refer to sections 0 and appendix 10, 4

17. The date span of the search.

Please refer to sections 0 and appendix 10, 4

18. 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).

Please refer to sections 0 and appendix 10, 4

19. Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to sections 0 and appendix 10, 4

20. The inclusion and exclusion criteria.

Please refer to section 7.4.5 for the inclusion and exclusion criteria

21. The data abstraction strategy.

Data were extracted by one reviewer and independently checked for accuracy by a second reviewer.

10.14 Appendix 14: Methods used to calculate transition probabilities (section 7.3)

Transition probabilies in the observation period

The likelihood consists of elements about the events and censoring. Log likelihood functions are used to estimate the maximum likelihood and standard error for each event parameter considered. Applying the log likelihood function we find the first and second order derivatives of the Weibull distribution.

$$L = \prod_{i=1}^{Np} \left(S(t_{i-1}) - S(t_i)\right)^{d_i} . \left(0.5 * \left(S(t_{i-1}) + S(t_i)\right)\right)^{c_i}$$

$$S(t) = \exp(-\lambda . t^{\nu})$$

$$Log(L) = \sum_{i=1}^{NP} \left(d_i . \ln\left(\exp(-\lambda . t_{i-1}{}^{\nu}) - \exp(-\lambda . t_i{}^{\nu})\right) + c_i \ln\left(0.5 * \left(\exp(-\lambda . t_{i-1}{}^{\nu}) + \exp(-\lambda . t_{i-1}{}^{\nu})\right)\right)\right)$$

$$\frac{\partial Log(L)}{\partial \lambda} = \sum_{i=1}^{NP} \left(d_i . \frac{-t_{i-1}{}^{\nu} . \exp(-\lambda . t_{i-1}{}^{\nu}) + t_i{}^{\nu} . \exp(-\lambda . t_i{}^{\nu})}{\exp(-\lambda . t_{i-1}{}^{\nu}) - \exp(-\lambda . t_i{}^{\nu})} + c_i \frac{\left(-t_{i-1}{}^{\nu} . \exp(-\lambda . t_{i-1}{}^{\nu}) - t_{i-1}{}^{\nu} \exp(-\lambda . t_{i-1}{}^{\nu})\right)}{\left(\exp(-\lambda . t_{i-1}{}^{\nu}) + \exp(-\lambda . t_{i-1}{}^{\nu})\right)} \right)$$

$$\frac{\partial LogL}{\partial v} = \sum_{i=1}^{NP} \left(d_i . \frac{-\lambda . t_{i-1}{}^{\nu} . \ln(t_{i-1}) . \exp(-\lambda . t_{i-1}{}^{\nu}) + \lambda . t_i{}^{\nu} . \ln(t_i) \exp(-\lambda . t_i{}^{\nu})}{\exp(-\lambda . t_{i-1}{}^{\nu}) - \exp(-\lambda . t_i{}^{\nu})} + c_i \frac{\left(-\lambda . t_{i-1}{}^{\nu} . \ln(t_{i-1}) . \exp(-\lambda . t_{i-1}{}^{\nu}) - \lambda . t_{i-1}{}^{\nu} . \ln(t_{i-1}) \exp(-\lambda . t_{i-1}{}^{\nu})\right)}{\left(\exp(-\lambda . t_{i-1}{}^{\nu}) + \exp(-\lambda . t_{i-1}{}^{\nu})\right)} \right)$$

$$\frac{\partial^2 Log(L)}{\partial \lambda^2} = \sum_{i=1}^{NP} \left(d_i . \frac{te'.ne - ne'te}{'te^2} + c_i \frac{tc'.nc - nc'tc}{'tc^2} \right)$$

$$te = -t_{i-1}{}^{\nu}.\exp(-\lambda.t_{i-1}{}^{\nu}) + t_i{}^{\nu}.\exp(-\lambda.t_i{}^{\nu})$$

$$te' = +t_{i-1}{}^{2.\nu}.\exp(-\lambda.t_{i-1}{}^{\nu}) - t_i{}^{2\nu}.\exp(-\lambda.t_i{}^{\nu})$$

$$ne = \exp(-\lambda.t_{i-1}{}^{\nu}) - \exp(-\lambda.t_i{}^{\nu})$$

$$ne' = te$$

$$tc = +t_{i-1}{}^{\nu}.\exp(-\lambda.t_{i-1}{}^{\nu}) + t_i{}^{\nu}.\exp(-\lambda.t_i{}^{\nu})$$

$$tc' = -t_{i-1}{}^{2.\nu}.\exp(-\lambda.t_{i-1}{}^{\nu}) - t_i{}^{2\nu}.\exp(-\lambda.t_i{}^{\nu})$$

$$nc = \exp(-\lambda.t_{i-1}{}^{\nu}) + \exp(-\lambda.t_i{}^{\nu})$$

$$nc' = tc$$

$$\frac{\partial^2 Log(L)}{\partial v^2} = \sum_{i=1}^{NP}\left(d_i . \frac{te'.ne - ne'te}{'te^2} + c_i \frac{tc'.nc - nc'tc}{'tc^2} \right)$$

$$\sum_{i=1}^{NP}\left(d_i . \frac{-\lambda.t_{i-1}{}^{\nu}.\ln(t_{i-1}).\exp(-\lambda.t_{i-1}{}^{\nu}) + \lambda.t_i{}^{\nu}.\ln(t_i)\exp(-\lambda.t_i{}^{\nu})}{\exp(-\lambda.t_{i-1}{}^{\nu}) - \exp(-\lambda.t_i{}^{\nu})} + c_i \frac{\left(-\lambda.t_{i-1}{}^{\nu}.\ln(t_{i-1}).\exp(-\lambda.t_{i-1}{}^{\nu}) - \lambda.t_{i-1}{}^{\nu}.\ln(t_{i-1})\exp(-\lambda.t_{i-1}{}^{\nu})\right)}{\left(\exp(-\lambda.t_{i-1}{}^{\nu}) + \exp(-\lambda.t_{i-1}{}^{\nu})\right)} \right)$$

$$te = -\lambda.t_{i-1}{}^{\nu}.\ln(t_{i-1}).\exp(-\lambda.t_{i-1}{}^{\nu}) + \lambda.t_i{}^{\nu}.\ln(t_i)\exp(-\lambda.t_i{}^{\nu})$$

$$te' = \left(\lambda.t_{i-1}{}^{\nu}.\ln(t_{i-1})\right)^2.\exp(-\lambda.t_{i-1}{}^{\nu}) - \left(\lambda.t_i{}^{\nu}.\ln(t_i)\right)^2 \exp(-\lambda.t_i{}^{\nu})$$

$$ne = \exp(-\lambda.t_{i-1}{}^{\nu}) - \exp(-\lambda.t_i{}^{\nu})$$

$$ne' = te$$

$$tc = -\lambda.t_{i-1}{}^{\nu}.\ln(t_{i-1}).\exp(-\lambda.t_{i-1}{}^{\nu}) - \lambda.t_{i-1}{}^{\nu}.\ln(t_{i-1})\exp(-\lambda.t_{i-1}{}^{\nu})$$

$$tc' = \left(\lambda.t_{i-1}{}^{\nu}.\ln(t_{i-1})\right)^2.\exp(-\lambda.t_{i-1}{}^{\nu}) + \left(\lambda.t_i{}^{\nu}.\ln(t_i)\right)^2 \exp(-\lambda.t_i{}^{\nu})$$

$$nc = \exp(-\lambda.t_{i-1}{}^{\nu}) + \exp(-\lambda.t_i{}^{\nu})$$

$$nc' = tc$$

Transition probabilities in the extrapolation period

To calculate the long term transition probabilities the increased risk of suffering from both non-fatal and fatal ACS events due to age are incorporated into these calculations. The change in rates of increased risk of events for the clean "event free" health state is explained here as an example.

- In the "event free" health state an individual may suffer from the following:
  - A first non-fatal MI
  - A first non-fatal IS
  - A first non-fatal HS
  - A fatal MI
  - A fatal IS
  - A fatal HS
  - Other cardiovascular death (OCD)

- The probability to remain "event free" is given by:

$$S(t) = \exp(-\lambda_{MI}(t) - \lambda_{Stroke}(t) - \lambda_{Other+}(t))$$

  The exponential function factors in the probabilities of having suffered a event (this is applied to each cycle and is denoted by λ) to provide an estimate to remain "event free".

- The equation presented above can be expanded to incorporate the increased risks of suffering from fatal (denoted by *D*) and non-fatal events (denoted by *S*).

$$S(t) = \exp\left(-\lambda_{MI}(t) - \lambda_{IS}(t) - \lambda_{HS}(t) - \lambda_{Other+}(t)\right) =$$
$$\exp\left(-(\lambda_{MI}^{S} + \lambda_{MI}^{D})(1+r_{MI})^{t} - (\lambda_{IS}^{S} + \lambda_{IS}^{D})(1+r_{IS})^{t} - (\lambda_{HS}^{S} + \lambda_{HS}^{D})(1+r_{HS})^{t} - \lambda_{Other+}(1+r_{other})^{t}\right)$$

  and the probabilities of suffering from each event is given by the following equations:

$$P_{MI}(t) = \frac{(\lambda_{MI}^{S} + \lambda_{MI}^{D})(1+r_{MI})^{t}}{(\lambda_{MI}^{S} + \lambda_{MI}^{D})(1+r_{MI})^{t} + (\lambda_{IS}^{S} + \lambda_{IS}^{D})(1+r_{IS})^{t} + (\lambda_{HS}^{S} + \lambda_{HS}^{D})(1+r_{HS})^{t} + \lambda_{Other+}(1+r_{other})^{t}} .((1-S(t))$$

$$P_{IS}(t) = \frac{(\lambda_{IS}^{S} + \lambda_{IS}^{D})(1+r_{MI})^{t}}{(\lambda_{MI}^{S} + \lambda_{MI}^{D})(1+r_{MI})^{t} + (\lambda_{IS}^{S} + \lambda_{IS}^{D})(1+r_{IS})^{t} + (\lambda_{HS}^{S} + \lambda_{HS}^{D})(1+r_{HS})^{t} + \lambda_{Other+}(1+r_{other})^{t}} .((1-S(t))$$

$$P_{HS}(t) = \frac{(\lambda_{HS}^{S} + \lambda_{HS}^{D})(1+r_{MI})^{t}}{(\lambda_{MI}^{S} + \lambda_{MI}^{D})(1+r_{MI})^{t} + (\lambda_{IS}^{S} + \lambda_{IS}^{D})(1+r_{IS})^{t} + (\lambda_{HS}^{S} + \lambda_{HS}^{D})(1+r_{HS})^{t} + \lambda_{Other+}(1+r_{other})^{t}} .((1-S(t))$$

$$P_{other}(t) = \frac{\lambda_{Other+}(1+r_{other})^{t}}{(\lambda_{MI}^{S} + \lambda_{MI}^{D})(1+r_{MI})^{t} + (\lambda_{IS}^{S} + \lambda_{IS}^{D})(1+r_{IS})^{t} + (\lambda_{HS}^{S} + \lambda_{HS}^{D})(1+r_{HS})^{t} + \lambda_{Other+}(1+r_{other})^{t}} .((1-S(t))$$

- It should be noted that probability of surviving (*S*) and dying (*D*) from an event for example an MI is also needed.
- Within the model this is accounted for by incorporating the notion of mixing the death (*D*) and survival (*S*) of each event and we assume this changes with age.

- The increase risk of suffering from fatal or non-fatal events due to age are fixed values obtained from the model calibration and denoted by *r*.
- We begin with a fixed proportion of survivors (*S*) and decrease this proportion with a fixed percentage (*r)* per cycle.
- The calculation for the transition probabilities is as follows (for the MI example):

$$P_{MI}^{S}(t) = \left(1 - \exp\left(\ln(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}}).\frac{1}{(1 + r_{MI}^{change})^{t}}\right)\right).P_{MI}(t)$$

$$P_{MI}^{D}(t) = \exp\left(\ln(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}}).\frac{1}{(1 + r_{MI}^{change})^{t}}\right).P_{MI}(t)$$

- The same is formaulae is also applied to both types of stroke as presented below:

$$P_{IS}^{S}(t) = \left(1 - \exp\left(\ln(1 - \frac{\lambda_{IS}^{S}}{\lambda_{IS}^{S} + \lambda_{IS}^{D}}).\frac{1}{(1 + r_{IS}^{change})^{t}}\right)\right).P_{IS}(t)$$

$$P_{IS}^{D}(t) = \exp\left(\ln(1 - \frac{\lambda_{IS}^{S}}{\lambda_{IS}^{S} + \lambda_{IS}^{D}}).\frac{1}{(1 + r_{IS}^{change})^{t}}\right).P_{IS}(t)$$

$$P_{HS}^{S}(t) = \left(1 - \exp\left(\ln(1 - \frac{\lambda_{HS}^{S}}{\lambda_{HS}^{S} + \lambda_{HS}^{D}}).\frac{1}{(1 + r_{HS}^{change})^{t}}\right)\right).P_{HS}(t)$$

$$P_{HS}^{D}(t) = \exp\left(\ln(1 - \frac{\lambda_{HS}^{S}}{\lambda_{HS}^{S} + \lambda_{HS}^{D}}).\frac{1}{(1 + r_{HS}^{change})^{t}}\right).P_{HS}(t)$$

- If an individual survives the first event hence the first MI, first IS or first HS, they may suffer from subsequent events of either a MI, IS or HS. Similar formulae to the ones presented above apply in these cases.

- It should be noted that after a second event (either MI, IS or HS) no distinction is made between the subsequent events.

  - Although this assumption may not be relevant to the transition probabilities it is necessary for the changes of increased risk over time. This implies that distribution of having an event either MIs, ISs or HSs should be defined.
    - We can assume that the distribution of MIs, ISs and HSs is identical to patients who do not suffer any further events (hence are "event free") and we define the following equation:

$$\mu = \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{IS}^{S} + \lambda_{HS}^{S}}$$

and

$$S(t) = \exp\left(-(\mu.\lambda^{S} + \lambda_{MI}^{D})(1 + r_{MI})^{t} - ((1-\mu).\lambda^{S} + \lambda_{IS}^{D})(1 + r_{IS})^{t} - ((1-\mu).\lambda^{S} + \lambda_{HS}^{D})(1 + r_{HS})^{t} - \lambda_{Other+}(1 + r_{other})^{t}\right)$$

So the probabilities of suffering from MI, IS and HS is given by:

$$P_{MI}(t) = \frac{(\mu.\lambda^{S} + \lambda_{MI}^{D})(1 + r_{MI})^{t}}{(\mu.\lambda^{S} + \lambda_{MI}^{D})(1 + r_{MI})^{t} + ((1-\mu).\lambda^{S} + \lambda_{IS}^{D})(1 + r_{IS})^{t} + ((1-\mu).\lambda^{S} + \lambda_{HS}^{D})(1 + r_{HS})^{t} + \lambda_{Other+}(1 + r_{other})^{t}}(1 - S(t))$$

$$P_{IS}(t) = \frac{((1-\mu).\lambda^S + \lambda_{IS}^D)(1+r_{MI})^t}{(\mu.\lambda^S + \lambda_{MI}^D)(1+r_{MI})^t + ((1-\mu).\lambda^S + \lambda_{IS}^D)(1+r_{IS})^t + ((1-\mu).\lambda^S + \lambda_{HS}^D)(1+r_{HS})^t + \lambda_{Other+}(1+r_{other})^t}(1-S(t))$$

$$P_{HS}(t) = \frac{((1-\mu).\lambda^S + \lambda_{HS}^D)(1+r_{MI})^t}{(\mu.\lambda^S + \lambda_{MI}^D)(1+r_{MI})^t + ((1-\mu).\lambda^S + \lambda_{IS}^D)(1+r_{IS})^t + ((1-\mu).\lambda^S + \lambda_{HS}^D)(1+r_{HS})^t + \lambda_{Other+}(1+r_{other})^t}(1-S(t))$$

and this implies that the survival and death for multiple events is given by:

$$P^S = \left(1-\exp\left(\ln(1-\frac{\mu\lambda^S}{\mu\lambda^S+\lambda_{MI}^D}).\frac{1}{(1+r_{MI}^{change})^t}\right)\right).P_{MI}(t) + \left(1-\exp\left(\ln(1-\frac{(1-\mu)\lambda^S}{(1-\mu)\lambda^S+\lambda_{IS}^D}).\frac{1}{(1+r_{IS}^{change})^t}\right)\right).P_{IS}(t)$$

$$+\left(1-\exp\left(\ln(1-\frac{(1-\mu)\lambda^S}{(1-\mu)\lambda^S+\lambda_{HS}^D}).\frac{1}{(1+r_{HS}^{change})^t}\right)\right).P_{HS}(t)$$

$$P_{MI}^D(t) = \exp\left(\ln(1-\frac{\mu\lambda^S}{\mu\lambda^S+\lambda_{MI}^D}).\frac{1}{(1+r_{MI}^{change})^t}\right).P_{MI}(t)$$

$$P_{IS}^D(t) = \exp\left(\ln(1-\frac{(1-\mu)\lambda^S}{(1-\mu)\lambda^S+\lambda_{IS}^D}).\frac{1}{(1+r_{IS}^{change})^t}\right).P_{IS}(t)$$

$$P_{HS}^D(t) = \exp\left(\ln(1-\frac{(1-\mu)\lambda^S}{(1-\mu)\lambda^S+\lambda_{HS}^D}).\frac{1}{(1+r_{HS}^{change})^t}\right).P_{HS}(t)$$

Appendix 15: Markov traces

Markov trace - comparator

Time	No Event	MI	IS	HS	MI + MI	IS + IS	HS + HS	MI + IS	MI + HS	IS + HS	3 events	Fatal MI	Fatal IS	Fatal HS	OCD	NCD	Total
0.00	4160.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4160.00
0.25	3934.53	122.12	12.31	1.50	2.05	0.02	0.00	0.20	0.02	0.00	0.00	20.39	20.39	20.39	20.39	5.69	4160.00
0.50	3872.48	152.85	15.81	2.34	3.30	0.03	0.00	0.45	0.07	0.01	0.02	25.66	25.66	25.66	25.66	9.99	4160.00
0.75	3828.51	92.59	10.38	2.33	2.66	0.03	0.00	0.50	0.10	0.01	0.05	29.33	29.33	29.33	29.33	13.85	4160.00
1.00	3793.24	72.46	8.34	2.20	3.18	0.04	0.00	0.64	0.14	0.01	0.08	32.24	32.24	32.24	32.24	17.45	4160.00
1.25	3756.57	58.91	6.92	2.06	2.94	0.04	0.00	0.62	0.15	0.01	0.09	35.29	35.29	35.29	35.29	20.87	4160.00
1.50	3724.47	52.63	6.27	2.02	2.88	0.04	0.00	0.62	0.16	0.01	0.10	37.94	37.94	37.94	37.94	24.15	4160.00
1.75	3695.73	49.23	5.92	2.01	2.90	0.04	0.00	0.64	0.18	0.02	0.11	40.30	40.30	40.30	40.30	27.31	4160.00
2.00	3669.59	43.57	5.28	1.89	2.75	0.04	0.00	0.61	0.18	0.02	0.12	42.43	42.43	42.43	42.43	30.38	4160.00
2.50	3610.83	27.88	3.41	1.28	4.04	0.05	0.01	0.87	0.17	0.02	0.14	46.80	42.89	42.60	57.65	39.63	4160.00
3.00	3550.38	27.95	3.49	1.31	3.97	0.05	0.01	0.89	0.20	0.02	0.21	52.03	43.41	42.79	73.45	49.27	4160.00
3.50	3488.22	27.94	3.56	1.33	4.22	0.05	0.01	0.97	0.24	0.03	0.28	58.28	44.02	43.01	89.96	59.31	4160.00
4.00	3424.37	27.84	3.62	1.36	4.51	0.06	0.01	1.05	0.27	0.03	0.35	65.68	44.72	43.27	107.18	69.75	4160.00
4.50	3358.83	27.66	3.68	1.38	4.78	0.07	0.01	1.14	0.30	0.04	0.43	74.35	45.52	43.56	125.14	80.62	4160.00
5.00	3291.62	27.39	3.73	1.40	5.03	0.07	0.01	1.22	0.33	0.04	0.51	84.42	46.43	43.89	143.86	91.90	4160.00
5.50	3222.75	27.04	3.78	1.42	5.26	0.08	0.01	1.31	0.37	0.05	0.60	96.00	47.47	44.27	163.35	103.62	4160.00
6.00	3152.25	26.61	3.82	1.43	5.46	0.09	0.01	1.39	0.40	0.05	0.69	109.21	48.63	44.70	183.62	115.77	4160.00
6.50	3080.15	26.11	3.85	1.45	5.63	0.09	0.01	1.47	0.43	0.06	0.78	124.15	49.94	45.18	204.68	128.36	4160.00
7.00	3006.50	25.53	3.88	1.46	5.76	0.10	0.01	1.54	0.46	0.06	0.87	140.91	51.40	45.71	226.53	141.39	4160.00
7.50	2931.33	24.90	3.90	1.46	5.86	0.11	0.02	1.60	0.48	0.07	0.96	159.59	53.03	46.31	249.18	154.87	4160.00
8.00	2854.70	24.20	3.91	1.47	5.93	0.11	0.02	1.66	0.51	0.07	1.04	180.25	54.83	46.97	272.63	168.78	4160.00
8.50	2776.69	23.45	3.91	1.47	5.97	0.12	0.02	1.72	0.53	0.08	1.13	202.95	56.81	47.70	296.86	183.13	4160.00
9.00	2697.35	22.66	3.91	1.47	5.97	0.13	0.02	1.77	0.55	0.08	1.20	227.74	58.99	48.50	321.88	197.91	4160.00
9.50	2616.78	21.83	3.89	1.46	5.93	0.13	0.02	1.81	0.57	0.09	1.28	254.64	61.37	49.38	347.65	213.10	4160.00
10.00	2535.06	20.97	3.87	1.46	5.87	0.14	0.02	1.84	0.59	0.09	1.34	283.66	63.97	50.33	374.17	228.70	4160.00

10.50	2452.30	20.08	3.84	1.45	5.77	0.14	0.02	1.86	0.60	0.09	1.40	314.79	66.78	51.37	401.40	244.69	4160.00
11.00	2368.61	19.17	3.80	1.43	5.65	0.15	0.02	1.87	0.61	0.10	1.45	348.00	69.81	52.49	429.30	261.06	4160.00
11.50	2284.10	18.26	3.75	1.41	5.50	0.15	0.02	1.88	0.62	0.10	1.49	383.24	73.07	53.69	457.85	277.77	4160.00
12.00	2198.92	17.33	3.70	1.39	5.33	0.16	0.02	1.88	0.62	0.11	1.52	420.45	76.56	54.98	486.99	294.81	4160.00
12.50	2113.19	16.40	3.63	1.37	5.14	0.16	0.02	1.87	0.62	0.11	1.54	459.52	80.27	56.35	516.68	312.14	4160.00
13.00	2027.08	15.48	3.56	1.34	4.93	0.16	0.03	1.85	0.62	0.11	1.55	500.37	84.22	57.81	546.85	329.74	4160.00
13.50	1940.73	14.57	3.48	1.31	4.70	0.17	0.03	1.82	0.61	0.11	1.55	542.85	88.39	59.35	577.43	347.56	4160.00
14.00	1854.33	13.67	3.40	1.28	4.47	0.17	0.03	1.78	0.61	0.11	1.55	586.82	92.77	60.98	608.37	365.57	4160.00
14.50	1768.04	12.79	3.30	1.25	4.22	0.17	0.03	1.74	0.60	0.12	1.53	632.13	97.36	62.68	639.57	383.73	4160.00
15.00	1682.05	11.93	3.20	1.21	3.97	0.17	0.03	1.69	0.58	0.12	1.50	678.58	102.16	64.46	670.96	401.99	4160.00
15.50	1596.55	11.09	3.10	1.17	3.72	0.17	0.03	1.64	0.57	0.12	1.47	726.00	107.13	66.31	702.45	420.30	4160.00
16.00	1511.73	10.28	2.99	1.13	3.46	0.17	0.03	1.58	0.55	0.12	1.42	774.18	112.28	68.23	733.94	438.62	4160.00
16.50	1427.81	9.50	2.87	1.09	3.21	0.16	0.03	1.51	0.53	0.11	1.37	822.89	117.58	70.20	765.34	456.87	4160.00
17.00	1344.98	8.74	2.75	1.04	2.96	0.16	0.03	1.44	0.50	0.11	1.32	871.92	123.01	72.22	796.55	475.03	4160.00
17.50	1263.45	8.03	2.63	1.00	2.71	0.16	0.03	1.37	0.48	0.11	1.26	921.04	128.54	74.28	827.47	493.01	4160.00
18.00	1183.42	7.34	2.51	0.95	2.47	0.15	0.02	1.29	0.46	0.11	1.19	970.02	134.16	76.38	857.99	510.78	4160.00
18.50	1105.11	6.69	2.38	0.90	2.24	0.15	0.02	1.21	0.43	0.11	1.13	1018.61	139.84	78.50	888.01	528.26	4160.00
19.00	1028.70	6.08	2.25	0.85	2.03	0.14	0.02	1.13	0.40	0.10	1.06	1066.60	145.55	80.64	917.42	545.41	4160.00
19.50	954.39	5.50	2.12	0.80	1.82	0.14	0.02	1.05	0.38	0.10	0.98	1113.76	151.26	82.77	946.13	562.16	4160.00
20.00	882.38	4.96	1.99	0.75	1.62	0.13	0.02	0.97	0.35	0.09	0.91	1159.86	156.95	84.90	974.03	578.46	4160.00
20.50	812.83	4.45	1.86	0.70	1.44	0.12	0.02	0.89	0.32	0.09	0.84	1204.70	162.58	87.01	1001.03	594.26	4160.00
21.00	745.91	3.98	1.73	0.66	1.27	0.11	0.02	0.81	0.29	0.08	0.76	1248.10	168.12	89.09	1027.05	609.50	4160.00
21.50	681.77	3.54	1.60	0.61	1.11	0.11	0.02	0.74	0.27	0.08	0.69	1289.86	173.55	91.13	1052.01	624.15	4160.00
22.00	620.55	3.14	1.48	0.56	0.97	0.10	0.02	0.67	0.24	0.07	0.63	1329.84	178.84	93.11	1075.84	638.16	4160.00
22.50	562.36	2.77	1.36	0.52	0.84	0.09	0.02	0.60	0.22	0.07	0.56	1367.89	183.97	95.04	1098.46	651.49	4160.00
23.00	507.30	2.43	1.24	0.47	0.72	0.08	0.01	0.53	0.19	0.06	0.50	1403.89	188.90	96.89	1119.84	664.12	4160.00
23.50	455.44	2.12	1.13	0.43	0.61	0.08	0.01	0.47	0.17	0.06	0.44	1437.77	193.61	98.67	1139.94	676.02	4160.00
24.00	406.83	1.85	1.02	0.39	0.52	0.07	0.01	0.41	0.15	0.05	0.39	1469.44	198.10	100.36	1158.71	687.16	4160.00
24.50	361.51	1.60	0.92	0.35	0.44	0.06	0.01	0.36	0.13	0.05	0.34	1498.86	202.33	101.95	1176.16	697.54	4160.00
25.00	319.47	1.37	0.82	0.31	0.36	0.06	0.01	0.31	0.12	0.04	0.29	1526.02	206.31	103.45	1192.27	707.16	4160.00
25.50	280.70	1.17	0.73	0.28	0.30	0.05	0.01	0.27	0.10	0.04	0.25	1550.93	210.01	104.85	1207.05	716.01	4160.00
26.00	245.15	1.00	0.65	0.25	0.25	0.04	0.01	0.23	0.08	0.03	0.21	1573.61	213.44	106.14	1220.53	724.11	4160.00

26.50	212.76	0.84	0.57	0.22	0.20	0.04	0.01	0.19	0.07	0.03	0.18	1594.11	216.59	107.33	1232.73	731.46	4160.00
27.00	183.43	0.71	0.50	0.19	0.16	0.03	0.01	0.16	0.06	0.02	0.15	1612.51	219.45	108.41	1243.70	738.10	4160.00
27.50	157.06	0.59	0.43	0.16	0.13	0.03	0.01	0.13	0.05	0.02	0.12	1628.90	222.05	109.39	1253.49	744.05	4160.00
28.00	133.50	0.49	0.37	0.14	0.10	0.02	0.00	0.11	0.04	0.02	0.10	1643.37	224.38	110.27	1262.17	749.34	4160.00
28.50	112.62	0.40	0.32	0.12	0.08	0.02	0.00	0.09	0.03	0.02	0.08	1656.06	226.45	111.06	1269.79	754.01	4160.00
29.00	94.26	0.32	0.27	0.10	0.06	0.02	0.00	0.07	0.03	0.01	0.06	1667.09	228.27	111.75	1276.43	758.09	4160.00
29.50	78.23	0.26	0.22	0.09	0.05	0.01	0.00	0.06	0.02	0.01	0.05	1676.58	229.87	112.36	1282.17	761.63	4160.00
30.00	64.37	0.21	0.19	0.07	0.04	0.01	0.00	0.04	0.02	0.01	0.04	1684.69	231.25	112.88	1287.08	764.68	4160.00
30.50	52.49	0.17	0.15	0.06	0.03	0.01	0.00	0.03	0.01	0.01	0.03	1691.54	232.43	113.33	1291.25	767.28	4160.00
31.00	42.39	0.13	0.13	0.05	0.02	0.01	0.00	0.03	0.01	0.01	0.02	1697.28	233.44	113.71	1294.75	769.48	4160.00
31.50	33.89	0.10	0.10	0.04	0.01	0.01	0.00	0.02	0.01	0.00	0.02	1702.04	234.28	114.03	1297.67	771.32	4160.00
32.00	26.82	0.08	0.08	0.03	0.01	0.00	0.00	0.01	0.01	0.00	0.01	1705.94	234.99	114.30	1300.07	772.84	4160.00
32.50	20.99	0.06	0.06	0.02	0.01	0.00	0.00	0.01	0.00	0.00	0.01	1709.10	235.56	114.52	1302.03	774.08	4160.00
33.00	16.24	0.05	0.05	0.02	0.01	0.00	0.00	0.01	0.00	0.00	0.01	1711.64	236.03	114.70	1303.60	775.09	4160.00
33.50	12.42	0.03	0.04	0.02	0.00	0.00	0.00	0.01	0.00	0.00	0.00	1713.66	236.41	114.84	1304.86	775.89	4160.00
34.00	9.37	0.02	0.03	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1715.23	236.71	114.96	1305.85	776.53	4160.00
34.50	6.98	0.02	0.02	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1716.45	236.95	115.05	1306.61	777.03	4160.00
35.00	5.13	0.01	0.02	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1717.38	237.13	115.11	1307.20	777.41	4160.00
35.50	3.72	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1718.08	237.26	115.17	1307.64	777.70	4160.00
36.00	2.65	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1718.60	237.37	115.21	1307.98	777.92	4160.00
36.50	1.86	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1718.98	237.44	115.24	1308.22	778.08	4160.00
37.00	1.29	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1719.25	237.50	115.26	1308.39	778.20	4160.00
37.50	0.87	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1719.44	237.54	115.27	1308.52	778.28	4160.00
38.00	0.58	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1719.58	237.57	115.28	1308.61	778.34	4160.00
38.50	0.38	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1719.67	237.59	115.29	1308.67	778.38	4160.00
39.00	0.24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1719.73	237.60	115.30	1308.71	778.41	4160.00
39.50	0.15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1719.77	237.61	115.30	1308.73	778.43	4160.00
40.00	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1719.80	237.62	115.30	1308.75	778.44	4160.00

Markov trace- rivaroxaban

Time	Clean	MI	IS	HS	MI + MI	IS + IS	HS+HS	MI + IS	MI + HS	IS + HS	3 events	Fatal MI	Fatal IS	Fatal HS	OCD	NCD	Total
0.00	4104.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4104.00
0.25	3923.39	105.69	14.03	2.99	1.55	0.03	0.00	0.20	0.04	0.01	0.00	12.82	12.82	12.82	12.82	4.79	4104.00
0.50	3872.09	132.88	18.10	4.68	2.51	0.05	0.00	0.45	0.12	0.02	0.02	16.17	16.17	16.17	16.17	8.42	4104.00
0.75	3835.40	81.14	11.96	4.67	2.03	0.04	0.00	0.50	0.17	0.02	0.04	18.51	18.51	18.51	18.51	11.70	4104.00
1.00	3805.78	63.69	9.62	4.42	2.43	0.05	0.01	0.65	0.24	0.03	0.06	20.36	20.36	20.36	20.36	14.75	4104.00
1.25	3770.45	53.60	7.74	3.60	2.35	0.05	0.01	0.63	0.24	0.03	0.07	23.14	23.14	23.14	23.14	18.04	4104.00
1.50	3739.14	49.74	6.74	2.96	2.41	0.04	0.01	0.63	0.24	0.03	0.08	25.61	25.61	25.61	25.61	21.23	4104.00
1.75	3710.83	48.29	6.11	2.40	2.53	0.04	0.01	0.64	0.23	0.02	0.10	27.87	27.87	27.87	27.87	24.33	4104.00
2.00	3684.82	43.09	5.41	2.13	2.43	0.04	0.01	0.62	0.22	0.02	0.10	29.96	29.96	29.96	29.96	27.37	4104.00
2.50	3625.82	27.99	3.43	1.28	3.75	0.05	0.01	0.88	0.20	0.03	0.13	34.31	30.41	30.12	45.12	36.61	4104.00
3.00	3565.11	28.07	3.50	1.31	3.70	0.05	0.01	0.89	0.24	0.03	0.19	39.52	30.94	30.31	60.88	46.24	4104.00
3.50	3502.70	28.06	3.57	1.34	3.95	0.06	0.01	0.97	0.27	0.04	0.26	45.75	31.54	30.54	77.34	56.27	4104.00
4.00	3438.58	27.96	3.64	1.36	4.25	0.07	0.01	1.05	0.30	0.04	0.33	53.13	32.24	30.79	94.51	66.71	4104.00
4.50	3372.77	27.77	3.69	1.38	4.53	0.07	0.01	1.14	0.33	0.04	0.40	61.78	33.04	31.08	112.42	77.56	4104.00
5.00	3305.28	27.51	3.75	1.40	4.79	0.08	0.01	1.23	0.36	0.05	0.48	71.82	33.95	31.42	131.09	88.84	4104.00
5.50	3236.13	27.15	3.79	1.42	5.02	0.09	0.01	1.31	0.40	0.05	0.57	83.37	34.98	31.79	150.53	100.55	4104.00
6.00	3165.33	26.72	3.83	1.44	5.22	0.09	0.01	1.39	0.43	0.06	0.65	96.55	36.14	32.22	170.74	112.69	4104.00
6.50	3092.94	26.22	3.87	1.45	5.40	0.10	0.02	1.46	0.45	0.06	0.74	111.45	37.44	32.70	191.75	125.28	4104.00
7.00	3018.97	25.64	3.89	1.46	5.54	0.11	0.02	1.54	0.48	0.07	0.83	128.17	38.90	33.23	213.54	138.30	4104.00
7.50	2943.49	25.00	3.91	1.47	5.66	0.11	0.02	1.60	0.51	0.07	0.91	146.81	40.52	33.83	236.14	151.77	4104.00
8.00	2866.55	24.30	3.92	1.47	5.73	0.12	0.02	1.66	0.53	0.08	1.00	167.42	42.32	34.49	259.53	165.67	4104.00
8.50	2788.21	23.55	3.93	1.48	5.78	0.13	0.02	1.72	0.55	0.08	1.08	190.07	44.30	35.21	283.71	180.01	4104.00
9.00	2708.55	22.75	3.92	1.47	5.79	0.13	0.02	1.76	0.57	0.09	1.16	214.81	46.47	36.01	308.67	194.78	4104.00
9.50	2627.64	21.92	3.91	1.47	5.76	0.14	0.02	1.80	0.59	0.09	1.23	241.65	48.85	36.89	334.38	209.97	4104.00
10.00	2545.59	21.05	3.89	1.46	5.71	0.14	0.02	1.83	0.61	0.10	1.30	270.61	51.44	37.84	360.84	225.56	4104.00
10.50	2462.48	20.16	3.85	1.45	5.62	0.15	0.02	1.86	0.62	0.10	1.36	301.68	54.24	38.87	388.01	241.55	4104.00

11.00	2378.44	19.25	3.82	1.44	5.51	0.15	0.02	1.87	0.63	0.11	1.40	334.82	57.27	39.99	415.86	257.91	4104.00
11.50	2293.58	18.33	3.77	1.42	5.37	0.16	0.03	1.88	0.63	0.11	1.45	370.00	60.52	41.19	444.35	274.61	4104.00
12.00	2208.04	17.40	3.71	1.40	5.21	0.16	0.03	1.87	0.63	0.11	1.48	407.13	64.00	42.47	473.44	291.64	4104.00
12.50	2121.96	16.47	3.65	1.38	5.03	0.17	0.03	1.86	0.63	0.12	1.50	446.14	67.71	43.85	503.07	308.97	4104.00
13.00	2035.49	15.55	3.58	1.35	4.82	0.17	0.03	1.84	0.63	0.12	1.51	486.92	71.65	45.30	533.18	326.56	4104.00
13.50	1948.79	14.63	3.50	1.32	4.61	0.17	0.03	1.81	0.62	0.12	1.52	529.33	75.81	46.84	563.71	344.39	4104.00
14.00	1862.02	13.73	3.41	1.29	4.38	0.17	0.03	1.78	0.62	0.12	1.51	573.23	80.19	48.47	594.60	362.39	4104.00
14.50	1775.37	12.84	3.32	1.25	4.14	0.17	0.03	1.74	0.60	0.12	1.49	618.47	84.78	50.17	625.75	380.55	4104.00
15.00	1689.03	11.98	3.22	1.22	3.90	0.17	0.03	1.69	0.59	0.12	1.47	664.87	89.56	51.94	657.09	398.81	4104.00
15.50	1603.17	11.13	3.11	1.18	3.65	0.17	0.03	1.63	0.57	0.12	1.44	712.22	94.53	53.79	688.54	417.12	4104.00
16.00	1518.01	10.32	3.00	1.13	3.40	0.17	0.03	1.57	0.55	0.12	1.39	760.34	99.67	55.70	719.99	435.43	4104.00
16.50	1433.74	9.53	2.89	1.09	3.15	0.17	0.03	1.50	0.53	0.12	1.35	808.99	104.96	57.67	751.35	453.69	4104.00
17.00	1350.56	8.78	2.77	1.05	2.91	0.16	0.03	1.43	0.51	0.12	1.29	857.97	110.38	59.69	782.53	471.85	4104.00
17.50	1268.69	8.06	2.64	1.00	2.67	0.16	0.03	1.36	0.48	0.12	1.24	907.04	115.92	61.75	813.41	489.84	4104.00
18.00	1188.34	7.37	2.52	0.95	2.44	0.16	0.03	1.28	0.46	0.11	1.17	955.97	121.53	63.85	843.90	507.61	4104.00
18.50	1109.69	6.72	2.39	0.90	2.21	0.15	0.03	1.21	0.43	0.11	1.11	1004.53	127.21	65.97	873.89	525.09	4104.00
19.00	1032.97	6.10	2.26	0.86	2.00	0.14	0.02	1.13	0.41	0.10	1.04	1052.48	132.91	68.10	903.28	542.25	4104.00
19.50	958.35	5.52	2.13	0.81	1.79	0.14	0.02	1.05	0.38	0.10	0.97	1099.60	138.62	70.23	931.96	559.01	4104.00
20.00	886.04	4.98	2.00	0.76	1.60	0.13	0.02	0.97	0.35	0.10	0.90	1145.68	144.30	72.36	959.84	575.32	4104.00
20.50	816.20	4.47	1.87	0.71	1.42	0.12	0.02	0.89	0.32	0.09	0.82	1190.50	149.93	74.47	986.84	591.13	4104.00
21.00	749.00	3.99	1.74	0.66	1.25	0.12	0.02	0.81	0.30	0.09	0.75	1233.88	155.47	76.55	1012.85	606.38	4104.00
21.50	684.60	3.56	1.61	0.61	1.10	0.11	0.02	0.74	0.27	0.08	0.68	1275.63	160.90	78.58	1037.80	621.04	4104.00
22.00	623.12	3.15	1.48	0.56	0.96	0.10	0.02	0.66	0.24	0.08	0.62	1315.60	166.19	80.57	1061.61	635.06	4104.00
22.50	564.69	2.78	1.36	0.52	0.83	0.09	0.02	0.60	0.22	0.07	0.55	1353.65	171.31	82.49	1084.24	648.41	4104.00
23.00	509.40	2.44	1.25	0.47	0.71	0.09	0.02	0.53	0.20	0.06	0.49	1389.66	176.24	84.35	1105.62	661.05	4104.00
23.50	457.33	2.13	1.13	0.43	0.61	0.08	0.01	0.47	0.17	0.06	0.43	1423.54	180.96	86.12	1125.71	672.96	4104.00
24.00	408.52	1.85	1.03	0.39	0.51	0.07	0.01	0.41	0.15	0.05	0.38	1455.22	185.44	87.81	1144.50	684.11	4104.00
24.50	363.01	1.60	0.92	0.35	0.43	0.06	0.01	0.36	0.13	0.05	0.33	1484.65	189.68	89.41	1161.95	694.51	4104.00
25.00	320.80	1.38	0.83	0.31	0.36	0.06	0.01	0.31	0.12	0.04	0.29	1511.83	193.66	90.91	1178.06	704.14	4104.00
25.50	281.86	1.18	0.73	0.28	0.30	0.05	0.01	0.27	0.10	0.04	0.24	1536.75	197.36	92.31	1192.85	713.01	4104.00
26.00	246.17	1.00	0.65	0.25	0.24	0.04	0.01	0.23	0.08	0.03	0.21	1559.45	200.79	93.60	1206.34	721.12	4104.00
26.50	213.64	0.85	0.57	0.22	0.20	0.04	0.01	0.19	0.07	0.03	0.17	1579.97	203.94	94.79	1218.55	728.48	4104.00

27.00	184.19	0.71	0.50	0.19	0.16	0.03	0.01	0.16	0.06	0.03	0.14	1598.39	206.81	95.88	1229.54	735.14	4104.00
27.50	157.71	0.59	0.43	0.16	0.13	0.03	0.01	0.13	0.05	0.02	0.12	1614.79	209.41	96.86	1239.34	741.09	4104.00
28.00	134.06	0.49	0.37	0.14	0.10	0.02	0.00	0.11	0.04	0.02	0.10	1629.29	211.74	97.74	1248.02	746.39	4104.00
28.50	113.09	0.40	0.32	0.12	0.08	0.02	0.00	0.09	0.03	0.02	0.08	1641.99	213.81	98.52	1255.65	751.07	4104.00
29.00	94.65	0.33	0.27	0.10	0.06	0.02	0.00	0.07	0.03	0.01	0.06	1653.03	215.64	99.22	1262.30	755.16	4104.00
29.50	78.56	0.26	0.23	0.09	0.05	0.01	0.00	0.06	0.02	0.01	0.05	1662.55	217.24	99.82	1268.05	758.72	4104.00
30.00	64.64	0.21	0.19	0.07	0.04	0.01	0.00	0.04	0.02	0.01	0.04	1670.67	218.62	100.35	1272.97	761.77	4104.00
30.50	52.70	0.17	0.15	0.06	0.03	0.01	0.00	0.03	0.01	0.01	0.03	1677.53	219.81	100.80	1277.15	764.38	4104.00
31.00	42.56	0.13	0.13	0.05	0.02	0.01	0.00	0.03	0.01	0.01	0.02	1683.28	220.82	101.18	1280.66	766.58	4104.00
31.50	34.03	0.10	0.10	0.04	0.01	0.01	0.00	0.02	0.01	0.00	0.02	1688.05	221.66	101.50	1283.59	768.42	4104.00
32.00	26.93	0.08	0.08	0.03	0.01	0.00	0.00	0.01	0.01	0.00	0.01	1691.96	222.37	101.77	1285.99	769.94	4104.00
32.50	21.08	0.06	0.06	0.02	0.01	0.00	0.00	0.01	0.00	0.00	0.01	1695.14	222.95	101.99	1287.95	771.19	4104.00
33.00	16.31	0.05	0.05	0.02	0.01	0.00	0.00	0.01	0.00	0.00	0.01	1697.68	223.42	102.17	1289.53	772.20	4104.00
33.50	12.47	0.03	0.04	0.02	0.00	0.00	0.00	0.01	0.00	0.00	0.00	1699.70	223.80	102.31	1290.79	773.01	4104.00
34.00	9.41	0.02	0.03	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1701.28	224.10	102.43	1291.78	773.65	4104.00
34.50	7.01	0.02	0.02	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1702.50	224.33	102.52	1292.55	774.15	4104.00
35.00	5.15	0.01	0.02	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1703.43	224.52	102.59	1293.14	774.53	4104.00
35.50	3.73	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1704.14	224.65	102.64	1293.59	774.83	4104.00
36.00	2.66	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1704.66	224.76	102.68	1293.92	775.05	4104.00
36.50	1.87	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1705.04	224.84	102.71	1294.16	775.21	4104.00
37.00	1.29	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1705.31	224.89	102.73	1294.34	775.32	4104.00
37.50	0.88	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1705.50	224.93	102.75	1294.46	775.41	4104.00
38.00	0.58	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1705.64	224.96	102.76	1294.55	775.47	4104.00
38.50	0.38	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1705.73	224.98	102.77	1294.61	775.51	4104.00
39.00	0.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1705.79	224.99	102.77	1294.65	775.54	4104.00
39.50	0.15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1705.83	225.00	102.77	1294.68	775.55	4104.00
40.00	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1705.86	225.01	102.78	1294.70	775.57	4104.00