NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [ID1397]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [ID1397]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission summary** from Bayer

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Anticoagulation UK
   b. British Cardiovascular Society
   c. Royal College of Pathologists and British Society for Haematology
   **Royal College of Physicians endorse the response from British Cardiovascular Society*

4. **Expert personal perspectives** from:
   a. Dr Keith Fox, Professor of Cardiology – clinical expert, nominated by Bayer
   b. Dr Jagdeep Singh, Specialty Registrar in Cardiology – clinical expert, nominated by British Cardiovascular Society
   c. Mr Simon Williams – patient expert, nominated by HEART UK

5. **Evidence Review Group report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

6. **Evidence Review Group report – factual accuracy check**

7. **Evidence Review Group – additional analyses**

Post-technical engagement documents

8. **Technical engagement response from Bayer**
   a. Response form
   b. Appendices

9. **Technical engagement responses from experts:**
   a. Dr Keith Fox – clinical expert, nominated by Bayer
   b. Dr Jagdeep Singh – clinical expert, nominated by British Cardiovascular Society

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10. **Technical engagement responses from consultees and commentators:**
    a. Anticoagulation UK
    b. British Cardiovascular Society

11. **Evidence Review Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessments Centre (SHTAC)

12. **Final Technical Report**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [ID1397]

Document A
Company evidence submission summary for committee

Bayer confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

December, 2018

File name	Version	Contains confidential information	Date
Rivaroxaban_ID1397_AppendixA_18Dec18_Final_v1.0	1.0	No	18 Dec 18

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Contents

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Tables and figures

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Submission summary

A.1 Health condition

Cardiovascular disease (CVD) is an umbrella term for conditions affecting the heart or blood vessels. The primary cause is atherosclerosis - a build-up of plaque that progressively accumulates within the inner lining of arterial walls. When plaques rupture they can lead to life-changing atherothrombotic events such as death, MI, stroke, amputation.

The most common type of CVD is coronary artery disease (CAD) (or coronary heart disease [CHD]) - atherosclerotic plaque formation in the arteries supplying the heart. CHD by itself is the most common cause of death in England [53,668 deaths in 2016](1).

There have been few advances in antithrombotic therapy for secondary prevention of CV events over several decades. Despite the widespread use of aspirin, the thrombogenic risk (i.e. residual risk) for clinically important cardiovascular events remains unacceptably high. In the REACH registry – a large international registry of patients with established atherosclerotic disease – the annual incidence of cardiovascular death, MI or stroke was approximately 4.5% in the first year of the register (2). At 3-years the cumulative incidence was 11.6% (3).

Not all patients with CAD are at the same risk of atherothrombotic events. The risk of ischaemic events is determined by a patient's history and the extent of narrowing of their coronary arteries. Patients with CAD who have diffuse atherosclerosis affecting other areas of the body such as peripheral artery disease, have heart failure or poor renal function, are individuals who maintain the greatest risk of further events and who stand to benefit most from antithrombotic treatment.

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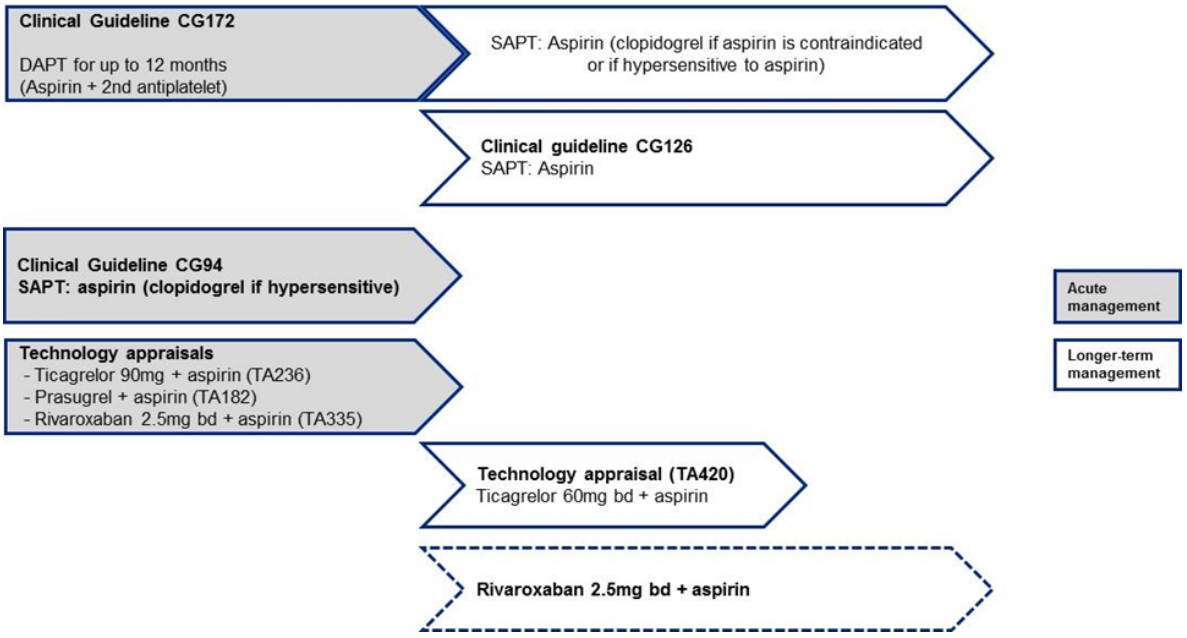
A.2 Clinical pathway of care

The clinical treatment pathway recommended by NICE is presented in Table 1 with the proposed position of rivaroxaban 2.5mg bd + aspirin. Treatment recommendations differ during the acute period (period following an event) and longer-term management. In the acute period patients are recommended to receive dual therapy with low-dose aspirin monotherapy thereafter. Ticagrelor 60mg bd+ aspirin is recommended in patients who experienced an MI 1-2 years earlier.

Table 1. NICE clinical pathway for patients with CAD



DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy

CG172 – Myocardial infarction: cardiac rehabilitation and prevention of further MI

CG126 – Stable angina: management

CG94 – Unstable angina and NSTEMI (early management)

A.3 Equality considerations

None

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A.4 The technology

Table 2 Technology being appraised – B.1.2 (page 29)

UK approved name and brand name	Rivaroxaban (Xarelto®)
Mechanism of action	Rivaroxaban is an oral highly selective direct factor Xa (FXa) inhibitor. FXa plays a central role in blood coagulation, activated by both the intrinsic and extrinsic coagulation pathways, catalysing the conversion of prothrombin to thrombin and ultimately leading to fibrin clot formation and activation of platelets by thrombin. By blocking factor Xa, rivaroxaban decreases the levels of thrombin, which reduces the risk of blood clots forming in the veins and arteries and treats existing clots (4-6). Factor Xa inhibitors (including rivaroxaban) have been shown in other indications to provide more targeted competitive inhibition of coagulation proteins and improved or similar efficacy when compared to warfarin, with lower rates of intracranial bleeding (7-10). The investigated mechanism of action of rivaroxaban has shown synergistic effects with aspirin in secondary prevention for patients with established cardiovascular disease. With the simultaneous inhibition of thromboxane through COX 1 inhibition achieved with aspirin and inhibition of Factor Xa with the vascular dose of rivaroxaban 2.5mg bd (4-6), a dual pathway inhibition of thrombin, in addition to platelet inhibition is achieved. Additionally, as thrombin is a very potent activator of platelets via PAR (protease activated) receptors, there is reason to believe that by inhibiting thrombin formation, factor Xa inhibitors also have an impact on platelet activation (11-16).
Marketing authorisation/CE mark status	Rivaroxaban + aspirin in patients with established CAD or symptomatic PAD has been assessed by the EMA via the EU centralised procedure. Marketing authorisation was received on the 23 August 2018.
Indications and any restriction(s) as described in the summary of product characteristics	Rivaroxaban, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. Restrictions Rivaroxaban is contraindicated in patients with: • hypersensitivity to the active substance or to any of its excipients. • active clinically significant bleeding, or a lesion or condition, considered to be a significant risk for major bleeding (including 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). • concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin,

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	etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban etc.) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. • Concomitant treatment of acute coronary syndrome (ACS) with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) • Concomitant treatment of CAD/PAD with aspirin in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. • hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. • Use is not recommended in patients with creatinine clearance < 15 ml/min. • Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. • Rivaroxaban is also contraindicated in patients who are pregnant or breast feeding. • Not recommended for use in children below 18 years of age. Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended. See Appendix C for SmPC and European public assessment report (EPAR).
Method of administration and dosage	Oral administration with or without food. Rivaroxaban 2.5 mg twice daily in combination with a daily dose of aspirin 75-100mg. Duration of treatment should be determined for each individual patient and should consider the risk for thrombotic events versus the bleeding risks. Note: Other doses and tablet strengths are used in other indications.
Additional tests or investigations	No additional tests or investigations are needed above and beyond normal clinical practice for patients with CAD / PAD. As with other anticoagulants, patients taking rivaroxaban are to be carefully observed for signs of bleeding.
List price and average cost of a course of treatment	2.5mg tablets are available in packs of 56 tablets for £50.40. The treatment period is indefinite.
Patient access scheme (if applicable)	Not applicable

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A.5 Decision problem and NICE reference case

Rivaroxaban, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD), or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

Bayer is not seeking a recommendation for the whole licensed population. The submission focuses on part of the technology's marketing authorisation i.e. we are seeking a recommendation for three subgroups of patients 1) patients with CAD and peripheral artery disease 2) patients with CAD and heart failure 3) patients with CAD and poor renal function (eGFR <60ml/min).

The three subgroups represent a population which is narrower than the population covered by the marketing authorisation.

The populations where we request appraisal are relevant to NHS clinical practice as these three subgroups are at higher baseline risk of thrombotic events compared to the general CAD population and stand to benefit the most from treatment.

- Although rivaroxaban 2.5mg bd + aspirin is cost-effective in the entire licensed population, use in these 3 subgroups optimises the cost-effectiveness of rivaroxaban + aspirin because the relative risk reduction for thrombotic events applies to patients with a higher baseline risk leading to a greater absolute reduction in events (myocardial infarction, stroke, CV death).
- This population reflects where rivaroxaban + aspirin provides the most clinical benefit.

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Table 3 The decision problem – B.1.1 (page 27)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with coronary or peripheral artery disease, excluding people with atrial fibrillation, at high risk of ischaemic events	Evidence is presented for the whole of the licensed population which is in line with the final scope. However, we are not seeking a recommendation for the whole licensed population. We are seeking a recommendation in 3 subgroups (see subgroups below).	Not applicable
Intervention	Rivaroxaban + aspirin	As per the scope	Not applicable
Comparator(s)	In people with stable coronary artery disease: - aspirin - aspirin in combination with ticagrelor In people with peripheral arterial disease: - aspirin - clopidogrel	In line with the final scope for patients with coronary artery disease cost-effectiveness results will be presented against aspirin and ticagrelor 60mg bd + aspirin.	Not applicable
Outcomes	The outcome measures to be considered include: - non-fatal myocardial infarction (STEMI and NSTEMI) - non-fatal stroke - urgent coronary, cerebrovascular or peripheral revascularisation - bleeding events - limb ischemia (including limb amputation) - mortality - adverse effects of treatment - health-related quality of	As per the scope Data on revascularisation was collected in the COMPASS study but was not categorised according to urgency. Data is presented on revascularisations irrespective of urgency.	Data not available

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	life.		
Subgroups to be considered	People with coronary artery disease who also have poor renal function People with coronary artery disease who also have peripheral arterial disease People who have had a previous myocardial infarction People who have had multiple myocardial infarctions	In line with the scope evidence will be presented for: • people with coronary artery disease who also have poor renal function • people with coronary artery disease who also have peripheral arterial disease • people with coronary artery disease who also have heart failure Subgroups not being presented • CAD with prior myocardial infarction • CAD with multiple prior myocardial infarctions	We present evidence for patients with coronary artery disease who also have heart failure. This patient group has not been listed in the scope but represents a group of patients at high risk of thrombotic events who stand to benefit from treatment with rivaroxaban + aspirin. Based on feedback from the medical community, patients defined solely by prior myocardial infarction are not a group of patients where rivaroxaban + aspirin is anticipated to be used.

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A.6 Clinical effectiveness evidence

The evidence for the efficacy and safety of rivaroxaban 2.5mg bd + aspirin in this indication comes from a single RCT i.e. the COMPASS study.

Table 4. Clinical effectiveness evidence

Study title	COMPASS: A randomised controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease (COMPASS- Cardiovascular OutcoMes for People using Anticoagulation StrategieS) Eikelboom JW et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. The New England journal of medicine. 2017;377(14):1319-30.
Study design	Randomised controlled trial
Population	Patients with stable coronary artery and/or peripheral artery disease
Intervention(s)	Rivaroxaban 2.5mg bd + aspirin 100mg daily Rivaroxaban 5mg bd
Comparator(s)	Aspirin 100mg daily
Outcomes specified in the decision problem	- **non-fatal myocardial infarction (STEMI and NSTEMI)** - **non-fatal stroke** - urgent* coronary, cerebrovascular or peripheral revascularisation - **bleeding events** - **limb ischemia (including limb amputation)** **- mortality** **- adverse effects of treatment** **- health-related quality of life** ***** Data on revascularisation was collected in the COMPASS study but was not categorised according to urgency. Data is presented on revascularisations irrespective of urgency.
Reference to section in submission	Section B.2 table 4 page 45

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A.7 Key results of the clinical effectiveness evidence

A.7.1 *Primary efficacy outcome: composite of CV death, stroke, or myocardial infarction*

The primary efficacy outcomes was a composite of CV death, stroke, or myocardial infarction. The results from the COMPASS study are presented in Table 5 for the COMPASS population and for the 3 subgroups where a recommendation is sought.

Rivaroxaban 2.5mg bd + aspirin was superior to aspirin alone for the prevention of the composite primary endpoint of CV death, stroke, or myocardial infarction. The study was stopped early due to superiority of rivaroxaban 2.5mg bd + aspirin after a mean follow-up of 23 months.

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Table 5. Primary efficacy outcomes results (ITT): composite of CV death, stroke, or myocardial infarction

	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
			Hazard Ratio (95% CI)	P value
COMPASS population				
	N=9152	**N=9126**		
Crude incidence n (%)	379 (4.1)	496 (5.4)	0.76 (0.66-0.86)	<0.001
Incidence rate per 100 patient-years (95% CI)	2.18 (1.97-2.41)	2.88 (2.64-3.15)		
CAD and Peripheral artery disease subgroup				
	N=1656	**N=1641**		
Crude incidence n (%)	94 (5.7)	138 (8.4)	0.67 (0.52-0.87)	0.00262
Incidence rate per 100 patient-years (95% CI)	3.06 (2.47-3.75)	4.55 (3.83-5.38)		
CAD and heart failure subgroup				
	N=1909	**N=1912**		
Crude incidence n (%)	105 (5.5)	151 (7.9)	0.68 (0.53-0.87)	0.002
Incidence rate per 100 patient-years (95% CI)	3.12 (2.55-3.78)	4.60 (3.89-5.39)		
CAD and poor renal function subgroup				
	N=1824	**N=1873**		
Crude incidence n (%)	119 (6.5)	165 (8.8)	0.73 (0.57-0.92)	0.007
Incidence rate per 100 patient-years (95% CI)	3.42 (2.84-4.10)	4.71 (4.02-5.48)		

Source: Table 13. Compass primary efficacy outcome results (ITT, All patients), Appendix B, Primary efficacy outcome, Page 80. Table 14. Primary Efficacy outcome results by subgroup (ITT), Appendix B, Page 83

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A.7.2 *Primary safety outcome: major bleeding (modified ISTH criteria)*

As with all anticoagulants, bleeding is the most prominent risk for rivaroxaban. In consequence, primary safety analyses were based on bleeding events adjudicated as major using modified ISTH criteria. Major bleeding was defined as a composite of:

- fatal bleeding, and/or
- symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or
- bleeding into the surgical site requiring re-operation, and/or
- bleeding leading to hospitalisation (with or without an overnight stay)

The results of the primary safety outcome are presented in Table 6 for the COMPASS and for each of the 3 subgroups. Modified ISTH major bleeding was increased with the rivaroxaban 2.5mg bd + aspirin 100mg od compared with aspirin. This was driven by bleeding presenting at hospital, with most major bleeding being gastrointestinal. There was no significant increase in fatal, symptomatic critical organ, or intracranial bleeding events.

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Table 6. Primary safety outcome – modified ISTH major bleeding (ITT)

	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
			Hazard Ratio (95% CI)	P value
COMPASS				
	N=9152	**N=9126**		
Crude incidence n (%)	288 (3.1)	170 (1.9)	1.70 (1.40-2.05)	<0.001
Incidence rate per 100 patient-years (95% CI)	1.67 (1.48-1.87)	0.98 (0.84-1.14)		
CAD and peripheral artery disease subgroup				
	N=1656	**N=1641**		
Crude incidence n (%)	52 (3.1)	36 (2.2)	1.43 (0.93-2.19)	0.09819
Incidence rate per 100 patient-years (95% CI)	1.70 (1.27-2.23)	1.17 (0.82-1.62)		
CAD and heart failure subgroup				
	N=1909	**N=1912**		
Crude incidence n (%)	49 (2.6)	36 (1.9)	1.35 (0.87-2.07)	0.17489
Incidence rate per 100 patient-years (95% CI)	1.46 (1.08-1.92)	1.08 (0.76-1.50)		
CAD and poor renal function				
	N=1824	**N=1873**		
Crude incidence n (%)	75 (4.1)	55 (2.9)	1.41 (1.00-2.00)	0.05058
Incidence rate per 100 patient-years (95% CI)	2.17 (1.71-2.72)	1.55 (1.16-2.01)		

Source: Table 15. COMPASS: primary safety outcome results – modified ISTH major bleeding (ITT, All patients), Appendix B, Primary safety outcome – Major bleeding (modified ISTH criteria), page 90; Table 16. CAD and PAD subgroup: primary safety outcome results (modified ISTH major bleeding), Appendix B, Primary safety outcome – Major bleeding (modified ISTH criteria), page 94; Table 17. CAD and HF subgroup: primary safety outcome results (modified ISTH major bleeding), Appendix B, Primary safety outcome – Major bleeding (modified ISTH criteria), page 96; Table 18. CAD and PRF subgroup: primary safety outcome results (modified ISTH major bleeding), Appendix B, Primary safety outcome – Major bleeding (modified ISTH criteria)

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A.7.3 *Individual components of the primary efficacy outcome*

The individual components of the primary efficacy outcome are presented in Table 7 for COMPASS and for the 3 subgroups.

Table 7. Primary efficacy outcome – individual components: myocardial infarction (ITT)

	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
			Hazard Ratio (95% CI)	P value
COMPASS population				
	N=9152	**N=9126**		
Crude incidence n (%)	178 (1.9)	205 (2.2)	0.86 (0.70-1.05)	0.14
Incidence rate per 100 patient-years (95% CI)	1.02 (0.87-1.18)	1.18 (1.03-1.36)		
CAD and peripheral artery disease subgroup				
	N=1656	**N=1641**		
Crude incidence n (%)	42 (2.5)	57 (3.5)	0.72 (0.49-1.08)	0.116
Incidence rate per 100 patient-years (95% CI)	1.36 (0.98-1.84)	1.87 (1.41-2.42)		
CAD and heart failure subgroup				
	N=1909	**N=1912**		
Crude incidence n (%)	42 (2.2)	51 (2.7)	0.81 (0.54-1.22)	0.304
Incidence rate per 100 patient-years (95% CI)	1.24 (0.90-1.68)	1.54 (1.14-2.02)		
CAD and poor renal function				
	N=1824	**N=1873**		
Crude incidence n (%)	50 (2.7)	68 (3.6)	0.74 (0.51-1.06)	0.099
Incidence rate per 100 patient-years (95% CI)	1.43 (1.06-1.89)	1.92 (1.49-2.43)		

Source: Table 13. Compass primary efficacy outcome results (ITT, All patients), Appendix B, Primary efficacy outcome, Page 80. Table 14. Primary Efficacy outcome results by subgroup (ITT), Appendix B, Page 83

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Table 8. Primary efficacy outcome – individual components: Stroke (ITT)

	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
			Hazard Ratio (95% CI)	P value
COMPASS population				
	N=9152	**N=9126**		
Crude incidence n (%)	83 (0.9)	142 (1.6)	0.58 (0.44-0.76)	<0.001
Incidence rate per 100 patient-years (95% CI)	0.47 (0.38-0.59)	0.82 (0.69-0.96)		
CAD and peripheral artery disease subgroup				
	N=1656	**N=1641**		
Crude incidence n (%)	16 (1.0)	35 (2.1)	0.46 (0.25-0.83)	0.009
Incidence rate per 100 patient-years (95% CI)	0.51 (0.29-0.84)	1.13 (0.79-1.58)		
CAD and heart failure subgroup				
	N=1909	**N=1912**		
Crude incidence n (%)	19 (1.0)	38 (2.0)	0.49 (0.28-0.85)	0.009
Incidence rate per 100 patient-years (95% CI)	0.56 (0.34-0.87)	1.14 (0.81-1.57)		
CAD and poor renal function				
	N=1824	**N=1873**		
Crude incidence n (%)	16 (0.9)	45 (2.4)	0.37 (0.21-0.65)	0.0003
Incidence rate per 100 patient-years (95% CI)	0.45 (0.26-0.74)	1.26 (0.92-1.69)		

Source: Table 13. Compass primary efficacy outcome results (ITT, All patients), Appendix B, Primary efficacy outcome, Page 80. Table 14. Primary Efficacy outcome results by subgroup (ITT), Appendix B, Page 83

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Table 9. Primary efficacy outcome – individual components: CV death (ITT)

	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
			Hazard Ratio (95% CI)	P value
COMPASS population				
	N=9152	**N=9126**		
Crude incidence n (%)	160 (1.7)	203 (2.2)	0.78 (0.64-0.96)	0.02
Incidence rate per 100 patient-years (95% CI)	0.91 (0.77-1.06)	1.16 (1.00-1.33)		
CAD and peripheral artery disease subgroup				
	N=1656	**N=1641**		
Crude incidence n (%)	43 (2.6)	59 (3.6)	0.75 (0.60-0.93)	0.010
Incidence rate per 100 patient-years (95% CI)	1.38 (1.00-1.85)	1.90 (1.44-2.45)		
CAD and heart failure subgroup				
	N=1909	**N=1912**		
Crude incidence n (%)	56 (2.9)	84 (4.4)	0.65 (0.47-0.92)	0.013
Incidence rate per 100 patient-years (95% CI)	1.64 (1.24-2.13)	2.51 (2.00-3.10)		
CAD and poor renal function				
	N=1824	**N=1873**		
Crude incidence n (%)	64 (3.5)	76 (4.1)	0.86 (0.62-1.20)	0.375
Incidence rate per 100 patient-years (95% CI)	1.81 (1.39-2.31)	2.10 (1.66-2.63)		

Source: Table 13. Compass primary efficacy outcome results (ITT, All patients), Appendix B, Primary efficacy outcome, Page 80. Table 14. Primary Efficacy outcome results by subgroup (ITT), Appendix B, Page 83

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A.8 Evidence synthesis

There are two comparators in the economic modelling; aspirin monotherapy and ticagrelor 60mg bd + aspirin. For the comparison with aspirin monotherapy no meta-analysis was conducted as the evidence for rivaroxaban 2.5mg bd + aspirin versus aspirin comes from a single trial i.e. the COMPASS trial.

In respect of a comparison with ticagrelor 60mg bd + aspirin no head to head data are available. A systematic literature review identified a single study for ticagrelor 60mg bd + aspirin in patients with stable CAD i.e. the PEGASUS study which has been reviewed by NICE as part of TA420.

The results of the indirect treatment comparison (using the Bucher method) of rivaroxaban + aspirin versus ticagrelor + aspirin are presented in Table 10 to Table 12. No published evidence was available for the CAD and HF subgroup from the PEGASUS study from which to conduct a comparison.

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Table 10. Summary of results of the indirect comparison of rivaroxaban + aspirin and ticagrelor + aspirin in the COMPASS population

Endpoint	Rivaroxaban + aspirin versus aspirin		Ticagrelor + aspirin versus aspirin		HR [95%CI] for comparison rivaroxaban + aspirin *vs* ticagrelor + aspirin
	No. RCTs	No. patients	No. RCTs	No. patients	
Stroke/MI/CV death	1	18,278	1	14,112	0.90 [0.75, 1.09]
All-cause death	1	18,278	1	14,112	0.92 [0.74, 1.15]
CV death	1	18,278	1	14,112	0.94 [0.71, 1.25]
Stroke	1	18,278	1	14,112	0.77 [0.53, 1.14]
Ischaemic stroke	1	18,278	1	14,112	0.67 [0.44, 1.02]
Myocardial Infarction	1	18,278	1	14,112	1.02 [0.79, 1.32]
Major adverse limb event (MALE)	1	18,278	1	14,112	0.65 [0.36, 1.18]
Amputations	1	18,278	1	14,112	*ITC not feasible*
Acute limb ischaemia (ALI)	1	18,278	1	14,112	0.82 [0.26, 2.60]
Venous thromboembolism (VTE)	1	18,278	1	13,954	1.85 [0.06, 54.97]
Major bleeding	1	18,278	1	13,954	0.73 [0.50, 1.07]
Intracranial bleeding	1	18,278	1	13,954	0.87 [0.40, 1.89]
Haemorrhagic stroke (HS)	1	18,278	1	13,954	1.54 [0.44, 5.34]
Gastrointestinal bleeding	1	18,278	0	0	*ITC not feasible*
Fatal bleeding	1	18,278	1	13,954	1.49 [0.47, 4.69]

Source: Table 32. Summary of results of the indirect comparison of rivaroxaban + aspirin and ticagrelor + aspirin in the COMPASS population, Appendix B, B.2.8 Meta-analysis, Results of the ITC, page 132

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Table 11. Summary of results of the indirect comparison of rivaroxaban + aspirin and ticagrelor + aspirin in the CAD and PAD subgroup

Endpoint	Rivaroxaban + aspirin versus aspirin		Ticagrelor 60mg bd + aspirin versus aspirin		HR [95%CI] for comparison rivaroxaban + aspirin versus ticagrelor + aspirin
	No. RCTs	No. patients	No. RCTs	No. patients	
Stroke/MI/CV death	1	3,297	1	772	0.97 [0.62, 1.53]
All-cause death	1	3,297	1	772	1.46 [0.83, 2.57]
CV death	1	3,297	1	772	1.53 [0.74, 3.19]
Stroke	1	3,297	1	772	1.37 [0.56, 3.31]
Ischaemic stroke	1	3,297	1	772	0.94 [0.33, 2.73]
Myocardial Infarction	1	3,297	0	0	*ITC not feasible*
Major adverse limb event (MALE)	1	3,297	1	772	0.57 [0.25, 1.28]
Amputations	1	3,297	1	772	0.63 [0.04, 11.16]
Acute limb ischaemia (ALI)	1	3,297	1	772	0.91 [0.14, 5.68]
Venous thromboembolism (VTE)	1	3,297	0	0	*ITC not feasible*
Major bleeding	1	3,297	1	762	1.21 [0.28, 5.20]
Intracranial bleeding	1	3,297	0	0	*ITC not feasible*
Haemorrhagic stroke (HS)	1	3,297	0	0	*ITC not feasible*
Gastrointestinal bleeding	1	3,297	0	0	*ITC not feasible*
Fatal bleeding	1	3,297	0	0	*ITC not feasible*

Source: Table 33. Summary of results of the indirect comparison of rivaroxaban + aspirin and ticagrelor + aspirin in the CAD and PAD subgroup, Appendix B, B.2.8 Meta-analysis, Results of the ITC, page 133

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Table 12. Summary of results of the indirect comparison of rivaroxaban + aspirin and ticagrelor + aspirin in the CAD and PRF subgroup

Endpoint	Rivaroxaban + aspirin versus aspirin		Ticagrelor + aspirin versus aspirin		HR [95%CI] for comparison rivaroxaban + aspirin versus ticagrelor + aspirin
	No. RCTs	No. patients	No. RCTs	No. patients	
Stroke/MI/CV death	1	3,697	1	3,196	0.90 [0.66, 1.23]
All-cause death	1	3,697	1	3,196	0.89 [0.63, 1.27]
CV death	1	3,697	1	3,196	0.86 [0.55, 1.35]
Stroke	1	3,697	1	3,196	0.59 [0.27, 1.28]
Ischaemic stroke	1	3,697	0	0	*ITC not feasible*
Myocardial Infarction	1	3,697	1	3,196	0.99 [0.62, 1.57]
Major adverse limb event (MALE)	1	3,697	0	0	*ITC not feasible*
Amputations	1	3,697	0	0	*ITC not feasible*
Acute limb ischaemia (ALI)	1	3,697	0	0	*ITC not feasible*
Venous thromboembolism (VTE)	1	3,697	0	0	*ITC not feasible*
Major bleeding	1	3,697	1	3,196	0.62 [0.31, 1.24]
Intracranial bleeding	1	3,697	0	0	*ITC not feasible*
Haemorrhagic stroke (HS)	1	3,697	0	0	*ITC not feasible*
Gastrointestinal bleeding	0	0	0	0	*ITC not feasible*
Fatal bleeding	0	0	0	0	*ITC not feasible*

Source: Table 34. Summary of results of the indirect comparison of rivaroxaban + aspirin and ticagrelor + aspirin in the CAD and PRF subgroup, Appendix B, B.2.8 Meta-analysis, Results of the ITC, page 134

Hazard ratios used in the economic model

The economic model uses transition probabilities for aspirin and applies hazard ratios for rivaroxaban 2.5mg bd + aspirin versus aspirin to calculate corresponding transition probabilities for rivaroxaban 2.5mg bd + aspirin. The PEGASUS trial also reports hazard ratios for events versus aspirin and these are also used in the model. The hazard ratios used in the model are presented in Table 13 to Table 14.

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Some data were missing for ticagrelor 60mg bd + aspirin. To make a cost-effectiveness comparison possible the following approach was taken:

- If subgroup specific data were missing it was substituted with data from the overall PEGASUS trial (if available).
- For amputations a HR of 1.00 was entered in the case of missing data.
- For major extracranial bleeds the HR for 'major bleeding' (from PEGASUS) was considered a reasonable proxy

Table 13. Hazard ratios used in the economic model for rivaroxaban 2.5mg bd + aspirin versus aspirin

Event	COMPASS	CAD and PAD	CAD and HF	CAD and PRF
Main events				
MI	0.86 (0.70 – 1.05)	0.72 (0.49 – 1.08)	0.81 (0.54-1.22)	0.74 (0.51-1.06)
IS	0.51 (0.38-0.69)	0.49 (0.26-0.92)	0.35 (0.18-0.69)	0.25 (0.12-0.51)
ICH	1.16 (0.67-2.00)	1.16 (0.67-2.00)*	1.44 (0.51-4.06)	1.45 (0.55-3.81)
CV death	0.78 (0.64 – 0.96)	0.72 (0.49-1.07)	0.65 (0.47-0.92)	0.86 (0.62-1.20)
Fatal bleeding (1)	1.49 (0.67-3.33)	1.49 (0.67-3.33)	1.49 (0.67-3.33)	1.49 (0.67-3.33)
Health Events				
Acute limb ischaemia	0.55 (0.32-0.92)	0.48 (0.23-1.02)	0.55 (0.32-0.92)	0.55 (0.32-0.92)
Minor amputation	0.65 (0.35-1.20)	0.66 (0.23-1.86)	0.65 (0.35-1.20)	0.65 (0.35-1.20)
Major amputation	0.57 (0.30-1.09)	0.58 (0.21-1.61)	0.57 (0.30-1.09)	0.57 (0.30-1.09)
Major extracranial non-fatal bleed (modified ISTH criteria)	1.79 (1.46-2.19)	1.61 (1.01-2.56)	1.38 (0.85-2.24)	1.97 (1.55-2.52)
VTE	0.61 (0.37-1.00)	0.57 (0.23-1.46)	0.61 (0.37-1.00)	0.36 (0.13-1.00)

VTE = venous thromboembolism

(1) For fatal bleedings, the HRs are not calculable as per the low rate of events; therefore results from the whole of the COMPASS population are used.

* Number of events to small to calculate a HR for this group – COMPASS value used

Source: Table 56. HR (95% CI) for main events: rivaroxaban + aspirin vs aspirin, Appendix B, B3.3. Clinical parameters and variables, page 191; Table 58. HR (95% CI) for health events: rivaroxaban + aspirin vs aspirin, Appendix B, B3.3. Clinical parameters and variables, Treatment efficacy – Health Events, page 194

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Table 14. Hazard ratios used in the economic model for ticagrelor 60mg bd + aspirin versus aspirin

	COMPASS HR (95%CI)	CAD and PAD HR (95%CI)	CAD and HF HR (95%CI)	CAD and PRF HR (95%CI)
Main events				
MI	0.84 (0.72, 0.98)	0.84 (0.72, 0.98)	0.84 (0.72, 0.98)	0.75 (0.57, 1.00)
IS	0.76 (0.56-1.02)	0.52(0.22-1.22)	0.76 (0.56-1.02)	0.76 (0.56-1.02)
ICH	1.33 (0.77-2.31)	1.33 (0.77-2.31)	1.33 (0.77-2.31)	1.33 (0.77-2.31)
CV death	0.83 (0.68, 1.01)	0.47 (0.25, 0.86)	0.83 (0.68, 1.01)	1.00 (0.74, 1.37)
Fatal bleeding	1.00 (0.44, 2.27)	1.00 (0.44, 2.27)	1.00 (0.44, 2.27)	1.00 (0.44, 2.27)
Health Events				
Acute limb ischaemia	0.67 (0.24, 1.87)	0.53 (0.10, 2.87)	0.67 (0.24, 1.87)	0.67 (0.24, 1.87)
Minor amputation	1.00 (0.51, 1.49)	1.10 (0.07-17.55)	1.00 (0.51, 1.49)	1.00 (0.51, 1.49)
Major amputation	1.00 (0.51, 1.49)	1.10 (0.07-17.55)	1.00 (0.51, 1.49)	1.00 (0.51, 1.49)
Major extracranial non-fatal bleed	2.32 (1.68-3.21)	1.18 (0.29-4.70)	2.32 (1.68-3.21)	2.29 (1.25-4.19)
VTE	0.33 (0.01, 8.22)	0.33 (0.01, 8.22)	0.33 (0.01, 8.22)	0.33 (0.01, 8.22)

PAD = peripheral artery disease; HF = heart failure; PRF = poor renal function

Source: Table 60. Hazard Ratios used in the economic model for ticagrelor + aspirin versus aspirin, Appendix B, B3.3. Clinical parameters and variables, Treatment Efficacy – Health Events, page 196

A.9 Key clinical issues

Rivaroxaban 2.5mg bd + aspirin versus aspirin

The are no key clinical issues in the comparison of rivaroxaban + aspirin versus aspirin.

Rivaroxaban 2.5mg bd + aspirin versus ticagrelor 60mg bd + aspirin

For the comparison of rivaroxaban 2.5mg bd + aspirin and ticagrelor 60mg bd + aspirin there are a couple of clinical issues.

Population recruited to COMPASS versus PEGASUS

There was a degree of between-trial heterogeneity regarding inclusion criteria which resulted in differences in the patients recruited to each trial: 1) PEGASUS recruited patients with prior MI, while in the COMPASS trial the proportion of subjects with a history of MI was 62%. The contribution of patients with PAD in the study

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populations was 5% in the PEGASUS-TIMI 54 trial and 27% in the COMPASS trial. The proportion of patients with PRF was approximately 23% in both trials 2) The time from MI to entry in the studies was different i.e. a mean of 7 years in COMPASS whereas everyone in PEGASUS had an MI 1-3 years earlier.

Definition of major bleeding

The definition of the efficacy and safety outcomes were generally the same in both studies, except the endpoint of major bleeding which were assessed according to different criteria. In COMPASS major bleeding was defined according to the modified ISTH criteria. In the PEGASUS-TIMI 54 trial TIMI criteria were used.

The modification of the ISTH definition of major bleeding was intended to further increase the sensitivity of the ISTH bleeding definition to clinically relevant bleeds. In COMPASS, the modified criteria differed from the standard ISTH definition in a way that it did not consider whether bleeding was associated with a decrease in the haemoglobin level or with blood transfusion. Instead, modified ISTH major bleeding included any bleeding that led to hospitalisation with or without an overnight stay. This mandated revision resulted in the inclusion of refined safety events that would not be considered major bleeds in other antithrombotic trials such as PEGASUS. Relative to other trials the modified ISTH criteria may over-report 'major bleeds'

Overall the trials were considered sufficiently similar for the results from PEGASUS to be used in the economic model to inform the cost-effectiveness comparison against rivaroxaban 2.5mg bd + aspirin.

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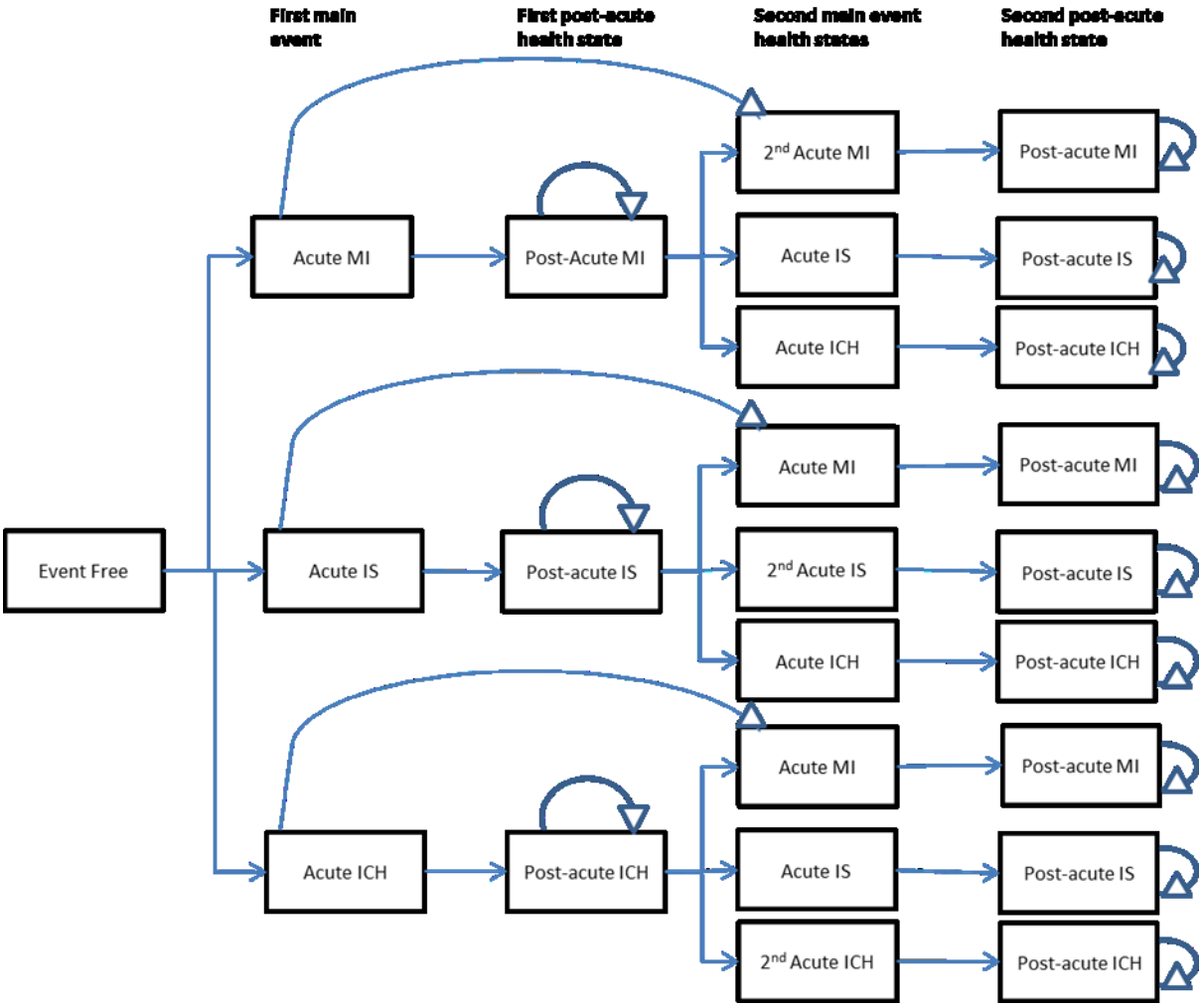
A.10 Overview of the economic analysis

A schematic of the economic model is provided in Table 15.

Table 15. Simplified schematic of the economic model



- For simplicity not all arrows are shown. E.g. the uppermost arrow shows the possible movement from acute MI to acute MI, however, transitions from acute MI to acute ICH or acute IS are also possible
- Secondary health event transitions not shown i.e. patients may experience any of the following from any cycle of the model: major extracranial non-fatal bleed; acute limb ischaemia; minor amputation; major amputation; venous thromboembolism.
- Absorbing state of 'Death' not shown

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Patients enter the model in the ‘event-free’ health state. Patients in this health state have the characteristics of patients from the COMPASS study. Patients can remain in this state or experience a first event including MI, IS, ICH (referred to as ‘main’ events), or death.

Experiencing an event (MI, IS, ICH) is expected to have long-term impacts on costs, QALYs and the risk of a new event, with the effects being greatest just following an event. To best reflect this, the main events have been modelled using ‘acute’ and ‘post-acute’ states, differentiated for each event. Patients can also experience a second main event.

Additionally, patients can experience secondary health events at any timepoint in the model i.e. major extracranial non-fatal bleed; acute limb ischaemia; minor amputation; major amputation; venous thromboembolism.

Cycle length

The cycle length is 3 months. Half-cycle correction has been applied.

Time horizon

Life time

Transition probabilities

Transition probabilities were calculated for the aspirin treatment arm based on the events in the respective subgroups from the COMPASS study. The hazard ratio for rivaroxaban + aspirin versus aspirin for each of these events was used to calculate the transition probability for the rivaroxaban + aspirin arm.

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A.11 Incorporating clinical evidence into the model

The characteristics of patients in the model reflect the COMPASS population or that of the subgroups being assessed.

Efficacy and safety (years 1-4)

For the events in the model transition probabilities for aspirin were calculated from patient-level data from COMPASS. These aspirin transition probabilities are applied as a constant risk for the first four years. Transition probabilities for rivaroxaban 2.5mg bd + aspirin were calculated by applying the applicable HR for each event (rivaroxaban 2.5mg bd + aspirin versus aspirin) to the aspirin transition probabilities.

Efficacy and safety (years 5+)

To capture increasing risk of experiencing a CV event or cardiovascular death with age after the first four years, data from the REACH registry was used. Regression analyses using this registry show a hazard ration of 1.03 for the next CV event for each additional year of age and 1.05 for CV death for each additional year of age (17). These hazard ratios are applied to the transition probabilities for the aspirin arm from year 5 onwards.

Background mortality

Non-cardiovascular mortality is accounted for in the model by using English life tables with CV death removed to avoid double counting. General population annual mortality rates for England were taken from the Office of National Statistics.

Validation of the modelling approach

The model used in this submission was developed with advice from:

- Pr Martin Cowie, Faculty of Medicine, National Heart & Lung Institute, Imperial College, London, England
- Pr Stuart Mealing, YHEC economic evaluation and modelling team, York, England
- Dr Andre Lamy, Dept of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, Hamilton, Ontario, Canada

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- Pr Pierre Levy, Université Paris-Dauphine, PSL Research University, LEDa-LEGOS, Paris, France

During the model development the advisors participated in face to face meetings, teleconferences and email exchange. Prior to model development a literature review was conducted to evaluate other economic models in coronary artery disease. Models were assessed for structure, cycle length, assumptions etc. and the information presented to the advisors.

Over a period of several months input was sought from each advisor on the appropriate model structure and clinical assumptions e.g. treatment duration, persistence, hazard ratios, extrapolation beyond the trial, cycle length, time horizon etc.

Outputs from the economic model were also presented to the advisors with a view to sense checking and, in addition the advisors assessed the appropriateness of different scenario analyses.

Validation of model outputs versus trial results

The outcomes predicted by the model have been compared to those observed from the COMPASS trial. The model replicates the observed data well with no indication of bias towards either rivaroxaban 2.5mg bd + aspirin or aspirin (see Appendices, Appendix J1.1 Clinical Outcomes from the Model [page 566].

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A.12 Key model assumptions and inputs

The key structural and input assumptions incorporated in the model are detailed with justification in Table 16.

Table 16. Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Hazard ratios for rivaroxaban 2.5mg + aspirin versus aspirin for first and second events	HRs apply to both first and second events: this assumes that patient history in terms of the type of event they experienced previously is not considered relevant i.e. that there is no interaction between treatment and event history on the risk of event.	Validated by experts
Treatment discontinuation from year 5+	The rate of discontinuation is half the rate observed in the first years of the COMPASS study	Patients who have reached the 4-year point on treatment are assumed to be those who are most likely to comply with longer term therapy.
Number of events modelled	The model does not consider the possibility of a third event – once a patient is in the second post-event health state they remain there until they die	There were too few patients in the COMPASS study who experienced 3 events from which to estimate HR for thrombotic events. The assumption is conservative (to a minor extent) as the benefits of a reduced rate of events in the rivaroxaban + aspirin arm are not fully accounted for patients who have experienced two events
Utilities	From COMPASS EQ-5D data (UK tariff)	Aligned to reference case
Costs	NHS reference costs	Stated preference by the ERG in the appraisal TA420

Source: Table 87. Key structural and input assumptions, Appendix B, B.3.6. Summary of base case analysis inputs and assumptions, page 251

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A.13 Base-case ICER (deterministic)

A summary of the base-case cost-effectiveness results is provided in Table 17 to Table 20. Rivaroxaban + aspirin is cost-effective in the whole licensed population. In the 3 subgroups where a recommendation is sought the ICER for rivaroxaban 2.5mg bd + aspirin versus aspirin ranges from £5,787/QALY to £10,046/QALY.

Table 17. Base case incremental cost-effectiveness results – COMPASS population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	7039	11.66	9.28	-	-	-	-	-
Ticagrelor + aspirin	8672	11.73	9.35	1633	0.07	0.07	23328	Extendedly dominated
Rivaroxaban 2.5mg bd + aspirin	**10630**	**11.90**	**9.50**	**1958**	**0.17**	**0.15**	**16602**	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Source: Table 88. Base case incremental cost-effectiveness results – COMPASS population, Appendix B, B.3.7. Base-case Results, page 255

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Table 18. Base case incremental cost-effectiveness results – CAD and PAD subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	9292	10.69	8.08	-	-	-	-	-
Ticagrelor + aspirin	10975	11.04	8.35	1683	0.35	0.27	6233	
Rivaroxaban 2.5mg bd + aspirin	**12206**	**11.19**	**8.48**	**1231**	**0.15**	**0.13**	**7416**	**9335**

Source: Table 89. Base case incremental cost-effectiveness results – CAD and PAD subgroup, Appendix B, B.3.7. Base-case Results, page 255

Table 19. Base case incremental cost-effectiveness results – CAD and HF subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	6085	10.41	8.07	-	-	-	-	-
Ticagrelor + aspirin	7713	10.56	8.19	1628	0.15	0.12	13566	Extendedly dominated
Rivaroxaban 2.5mg bd + aspirin	**9779**	**11.22**	**8.71**	**2066**	**0.66**	**0.52**	**5787**	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Source: Table 90. Base case incremental cost-effectiveness results – CAD and HF, Appendix B, B.3.7. Base-case Results, page 256

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Table 20. Base case incremental cost-effectiveness results – CAD and PRF subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	7593	9.59	7.32	-	-	-	-	-
Ticagrelor + aspirin	9010	9.62	7.35	1417	0.03	0.03	47233	Extendedly dominated
Rivaroxaban 2.5mg bd + aspirin	**10226**	**9.91**	**7.59**	**1216**	**0.29**	**0.24**	**10046**	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Source: Table 91. Base case incremental cost-effectiveness results – CAD and PRF, Appendix B, B.3.7. Base-case Results, page 256

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A.14 Probabilistic sensitivity analysis

The are two comparators in this submission (aspirin alone and ticagrelor 60mg bd + aspirin). Bayer is requesting a recommendation in 3 subgroups. Against the main comparator (aspirin) there are therefore 3 associated scatterplots. These are presented in Figure 1 to Figure 3. The PSA results align with those of the deterministic base case analyses and show rivaroxaban + aspirin to be a cost-effective use of NHS resources. The probability of being cost-effective using a 20K threshold was 99% (CAD and PAD subgroup), 100% (CAD and HF subgroup), and 93% (CAD and PRF subgroup).

CAD and PAD subgroup

Table 21. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin vs aspirin (page 265)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	9408	10.79	8.17					
Ticagrelor + aspirin	11488	11.12	8.38	2080	0.33	0.21	9904	Extendedly dominated
Rivaroxaban 2.5mg bd + aspirin	**12455**	**11.27**	**8.55**	**967**	**0.15**	**0.17**	**8138**	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Source: Table 104. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8. Sensitivity analysis, CAD and PAD subgroup, page 273; Table 105. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8. Sensitivity analysis, CAD and PAD subgroup, page 274

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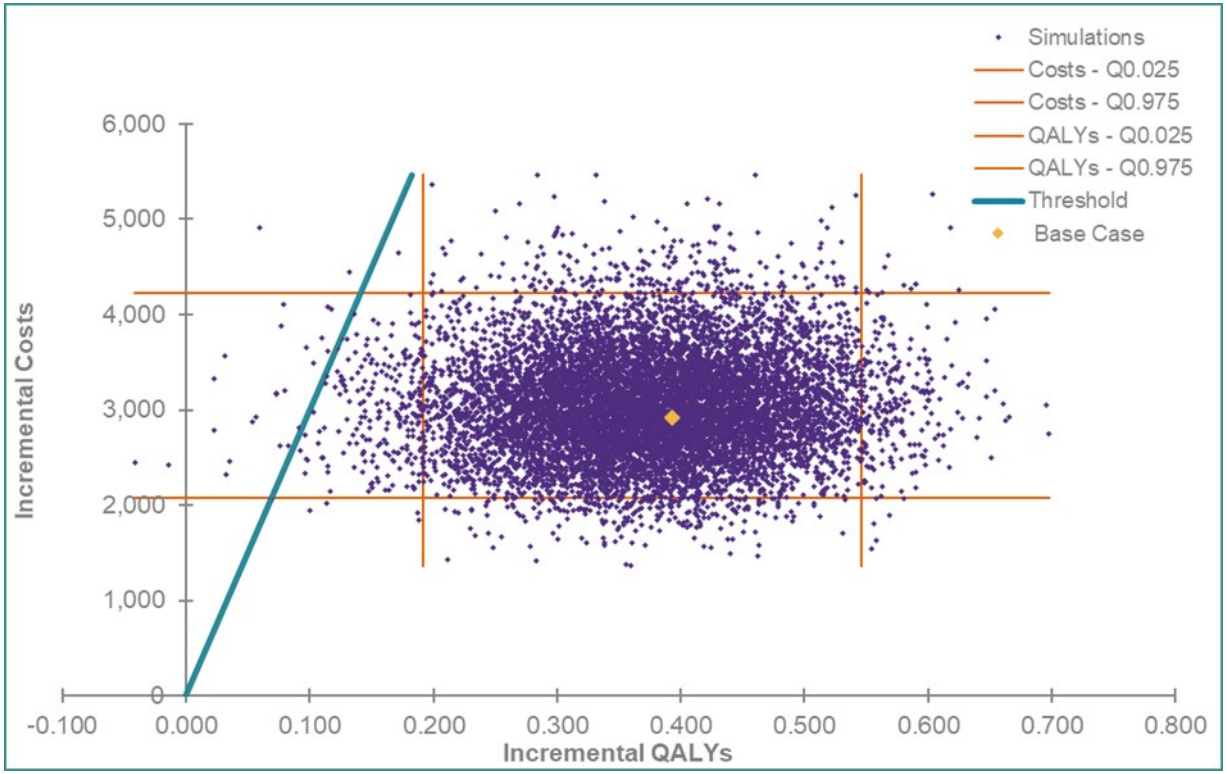
Figure 1. PSA scatterplot – CAD and PAD subgroup – rivaroxaban + aspirin versus aspirin (page 273)



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CAD and HF subgroup

Table 22. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin (page 281, 282)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	6119	10.48	8.13					
Ticagrelor + aspirin	7760	10.62	8.24	1641	0.14	0.11	14918	Extendedly dominated
Rivaroxaban 2.5mg bd + aspirin	**9881**	**11.26**	**8.75**	**2121**	**0.64**	**0.51**	**6085**	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Source: Table 107. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8. Sensitivity analysis, CAD and HF subgroup, page 281; Table 108. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8. Sensitivity analysis, CAD and HF subgroup, page 282

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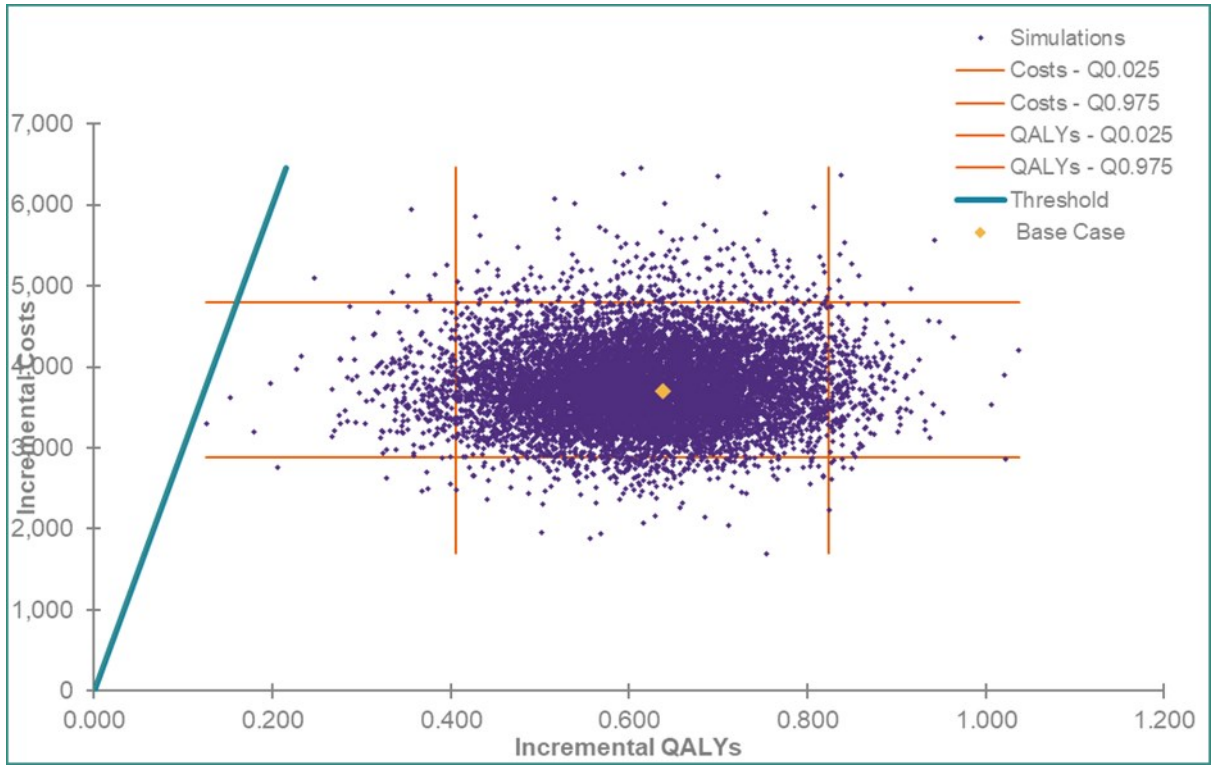
Figure 2. PSA scatterplot – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin (page 281)



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CAD and poor renal function subgroup

Table 23. PSA results – CAD and PRF subgroup – rivaroxaban + aspirin vs aspirin (page 288, 290)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	7714	9.72	7.44					
Ticagrelor + aspirin	9169	9.74	7.46	1455	0.02	0.02	72750	Extendedly dominated
Rivaroxaban 2.5mg bd + aspirin	**10472**	**10.03**	**7.69**	**1303**	**0.29**	**0.25**	**10879**	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Source: Table 110. PSA results – CAD and PRF subgroup – rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8. Sensitivity analysis, Probabilistic Sensitivity analysis, Page 288; Table 111. PSA results – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8. Sensitivity analysis, Probabilistic Sensitivity analysis, Page 290

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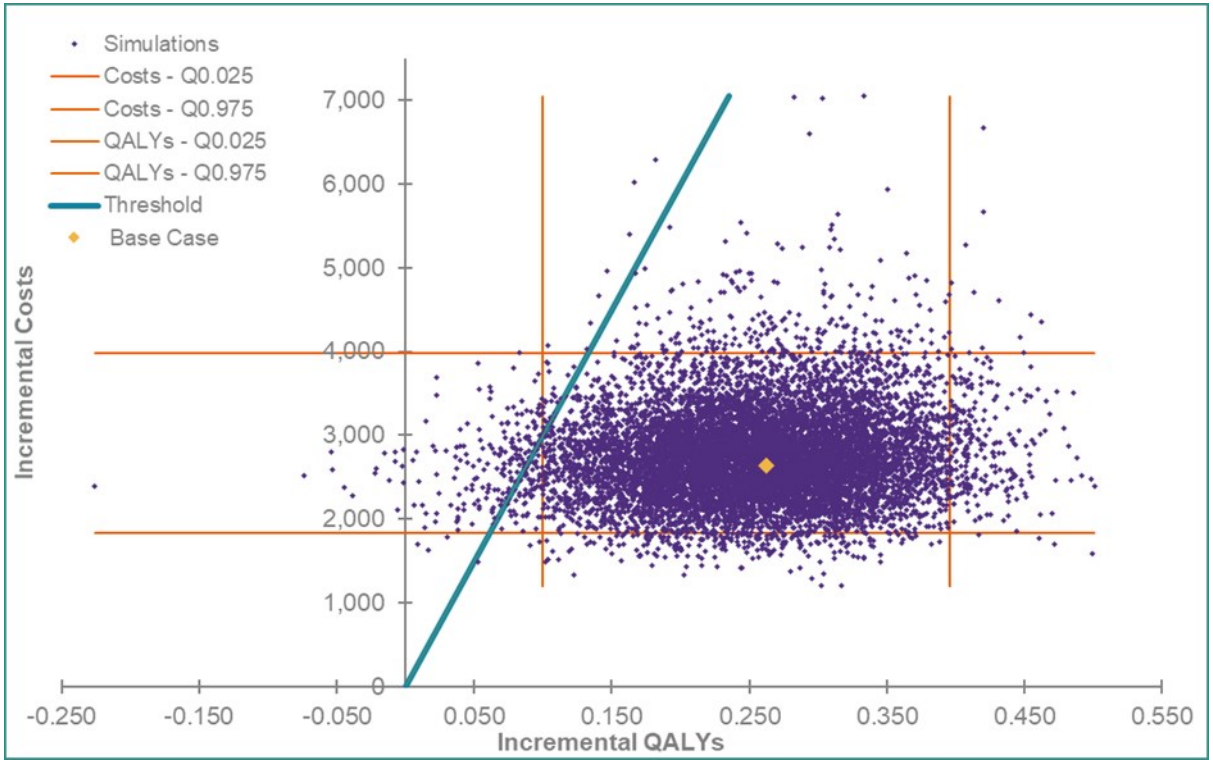
Figure 3. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus aspirin (page 289)



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A.15 Key sensitivity and scenario analyses

One-way sensitivity analyses

A comprehensive set of one-way sensitivity analyses was conducted. The range for each parameter was pre-specified based on the parameter uncertainty, such as 95%CI. In the absence of information, large arbitrary ranges (up to +/- 30%) were used to investigate sensitivity. To explore the uncertainty around age a range of +/- 10% was used.

Tornado diagrams are presented for the 3 subgroups for the comparison against aspirin. Tornado diagrams in the 3 subgroups where ticagrelor + aspirin is the comparator treatment are available in Appendix B: CAD and PAD subgroup - Figure 46 (page 305); CAD and HF subgroup - Figure 48 (page 311); CAD and PRF subgroup - Figure 50 (page 317). The tornado diagrams below presents the top 10 most sensitive analyses.

Figure 4. Tornado diagram – CAD and PAD subgroup: rivaroxaban + aspirin versus aspirin B.3.8 (page 304)

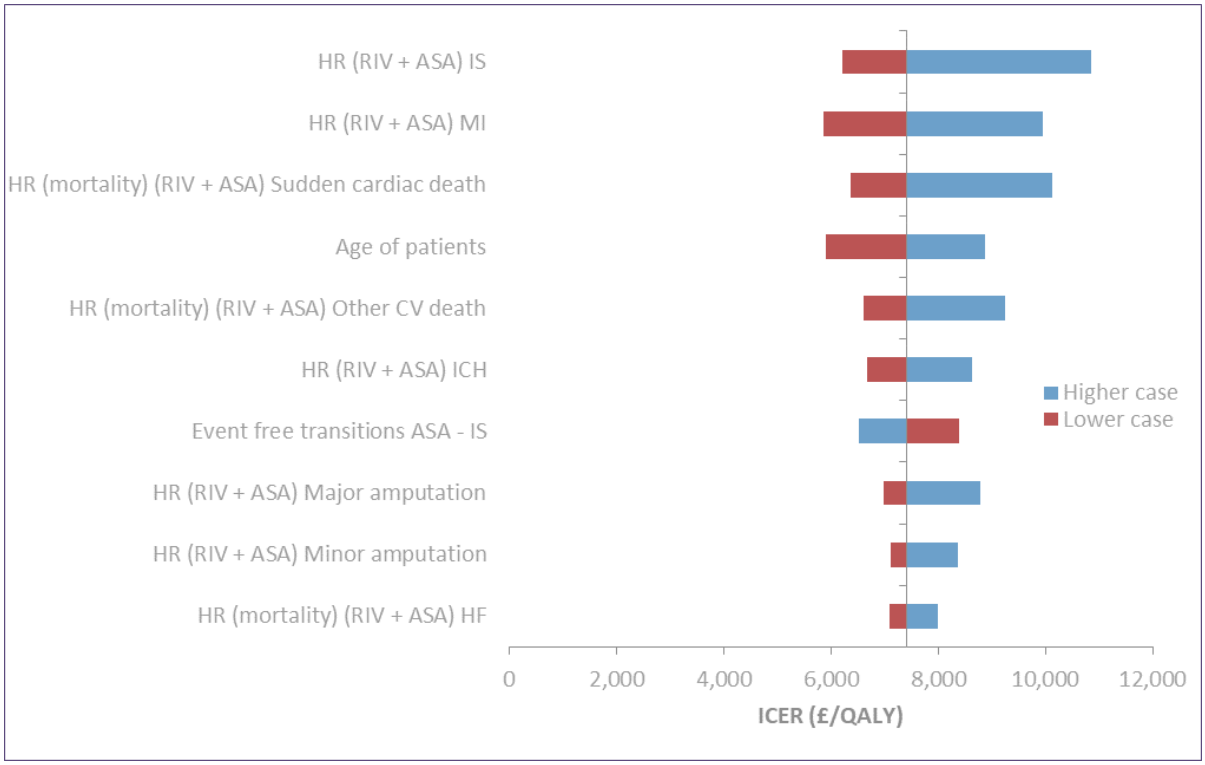

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Figure 4. Tornado diagram – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin B.3.8 (page 310)

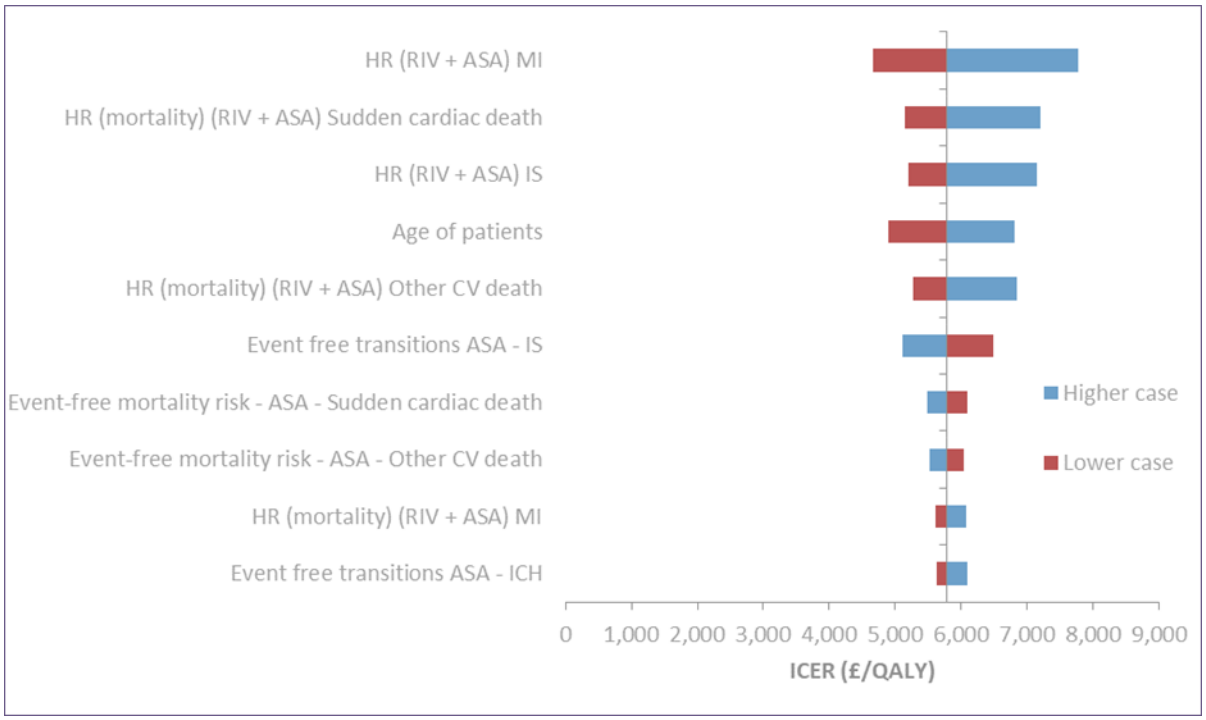

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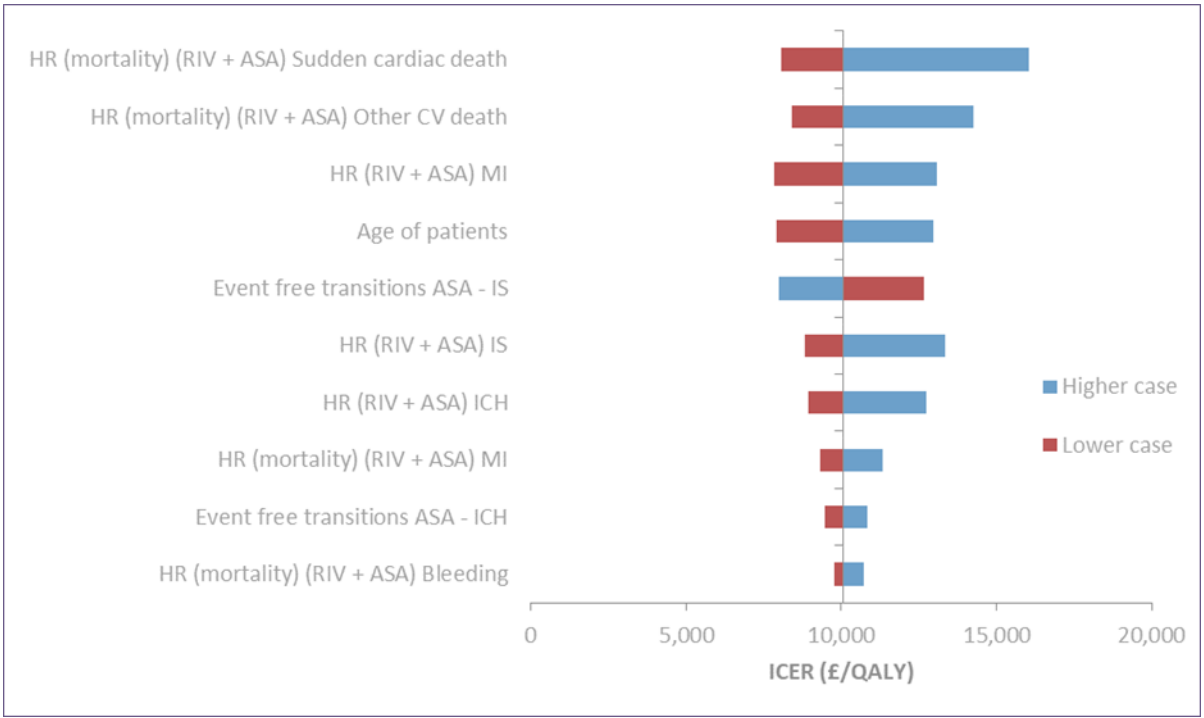
Figure 5. Tornado diagram – CAD and PRF subgroup: rivaroxaban + aspirin versus aspirin B.3.8 (page 316)



Scenario analyses

A comprehensive set of scenario analyses was conducted, considering alternative data sources for certain model parameters to investigate the robustness of the model to different assumption. The scenario analyses conducted are presented in Table 24. As for A.14 and A.15, results are presented for the comparison against aspirin. The full set of results against aspirin and ticagrelor + aspirin are available in Appendix B: CAD and PAD subgroup – Table 126 (page 321); CAD and HF subgroup – Table 127 (page 322); CAD and PRF subgroup – Table 128 (page 323). The results showed the base cases were robust with no scenarios producing costs per QALYs which exceeded 12K in any of the subgroups.

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Table 24. Scenario analyses – input parameters

Model input	Base Case	Rationale	Scenarios
Time horizon	Lifetime	In line with other models, in line with chronic nature of condition, impact on mortality	15 years
Treatment duration	Life time	Consistent with expected label in the population of interest	5 years for RIV+ASA
Treatment discontinuation	Discontinuation for the model duration. Discontinuation rate in the first four years based on COMPASS and discontinuation rate from year 5, half of the discontinuation rate in the first four years. Impact on cost and efficacy.	Validated by clinicians	As per the base case for the first 4 years. From year 5 no further discontinuation from rivaroxaban + aspirin (impact on efficacy and costs)
			Discontinuation rate observed in the first four years is applied for the entire model duration (impact on efficacy and costs)
Treatment interruption	None	Conservative	1 year after an MI, 3 month after an ICH and 1 month after a major bleed
ASA rates	COMPASS data considering null transitions	COMPASS trial data	COMPASS data + null transitions imputed (minimum of transition probabilities for same event independent of previous event history)
Second events assumption - costs			
Cost in the acute state	Costs based on most recent event	Conservative	Additive cost, second event acute cost + first event post-acute cost
Cost in the post-acute state	Costs based on the maximum of the post-acute state costs	Conservative	Costs of the most recent event. Additive cost of both post-acute states
Second event assumptions – utilities			
Utility of second event	Utility of second event based on lowest utility of the individual included health states	Conservative	Based on most recent event utility
			Multiplicative approach
Utilities inputs	EQ-5D COMPASS (GEE results)	COMPASS trial data	RMM analysis COMPASS data
			Ticagrelor utility data
Transition from event free to two events in one cycle	Only one transition permitted	Very low proportion of patients experiencing 2 events in a single cycle	2 transitions permitted
Health states and health events costs	NHS Reference costs	NICE guidelines	Walker et al. 2016
Discount rates	3.5%	NICE guidelines	0%
			5%

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Table 25. Key scenario analyses: ICER – rivaroxaban + aspirin versus aspirin

Model input	Parameter value	CAD and PAD subgroup	CAD and HF subgroup	CAD and PRF subgroup
Base case		**£7,416**	**£5,787**	**£10,046**
Time horizon	15 years	£1806	£1,733	£1,828
Treatment duration	5 years	-£1,058	-£605	-£1,660
Treatment discontinuation	4 years	£454	£155	£616
	Duration of model	-£285	-£115	-£414
Treatment interruption	Yes	-£201	-£104	-£307
ASA transition probabilities	No null transition	-£787	-£285	-£2,455
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	-£9	£0	-£27
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	-£363	-£282	-£1,185
Second event assumptions – utilities	Based on most recent event utility	£0	£0	£0
	Multiplicative approach	-£29	-£57	-£220
Utilities inputs	Repeated measures mixed model	-£13	-£5	-£25
	Ticagrelor TA 420	£17	£43	-£4,000
Transition from event free to two events in one cycle	COMPASS data	-£60	£26	-£17
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£125	£139	£339
Discount rates	0%	-£1,216	-£934	-£1,654
	5%	£578	£444	£777

Source: Table 126. Scenario analysis results – CAD and PAD subgroup. Appendix B, B3.8. Scenario analysis, page 321; Table 127. Scenario analysis results – CAD and HF subgroup, Appendix B, B3.8. Scenario analysis, page 322; Table 128. Scenario analysis results – CAD and PRF subgroup, Appendix B, B3.8. Scenario analysis, page 323

Conclusion

The deterministic base case analyses show that rivaroxaban 2.5mg bd + aspirin is cost-effective. The PSA and scenario analyses confirm the conclusion of cost-effectiveness and show the basecase ICERs to be robust.

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A.16 Innovation

Coronary artery disease remains a leading cause of morbidity and mortality worldwide, with deaths primarily due to major cardiovascular events such as stroke and myocardial infarction. There have been few advances in antithrombotic therapy for secondary prevention of cardiovascular events over several decades.

Aspirin has been the recommended treatment for secondary prevention of CV events for many years with many therapies having failed to show a large enough clinical benefit in relation to their increased risk of bleeding. Importantly, rivaroxaban + aspirin has demonstrated a positive risk-benefit profile in these patients.

In the COMPASS population the benefits of treatment are of similar magnitude to those seen with all other accepted secondary prevention regimens (aspirin, lipid-lowering, blood-pressure lowering, and ACE inhibitors) and are additive to these treatments. The benefit in the 3 subgroups for whom a recommendation is sought is even greater.

A.17 End-of-life criteria

Not applicable

A.18 Budget impact – Document (page 27)

	Company estimate	Cross reference
Number of people in England who would have treatment	12,378 patients in 3rd year	Budget impact template
Average treatment cost per person	£657 per year	Budget impact template
Estimated annual budget impact on the NHS in England	£8,132,346 in 3rd year	Budget impact template

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A.19 Interpretation and conclusions of the evidence

There have been few advances in antithrombotic therapy for secondary prevention of CV events over several decades. Despite the widespread use of aspirin, the risk for clinically important cardiovascular events such as CV death, MI, and stroke remains unacceptably high. In the REACH registry – a large international registry of patients with established atherosclerotic disease – the annual incidence of cardiovascular death, MI or stroke was approximately 4.5% in the first year of the register (2). At 3-years the cumulative incidence was 11.6% (3).

The increased risk of major acute coronary events in the three subgroups where a recommendation is sought is confirmed by the medical literature with the risk shown to be markedly higher for these patients compared to the wider CAD population (18),(2, 3), (19), (20).

The COMPASS trial was stopped earlier than planned due to the superior efficacy of rivaroxaban 2.5mg bd + aspirin versus aspirin across the whole population. However, the greatest benefits are in patients at the highest baseline risk of events.

In COMPASS the benefits of treatment are of similar magnitude to those seen with all other accepted secondary prevention regimens (aspirin, lipid-lowering, blood-pressure lowering, and ACE inhibitors) and are additive to those treatments (Table 26). In the economic analyses rivaroxaban 2.5mg bd + aspirin was shown to be cost-effective in the whole licensed population with a cost per QALY of £16,602. In the 3 subgroups where we are seeking a recommendation the ICER ranged from £5,787/QALY to £10,046/QALY.

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Table 26. Comparison of the effects of guideline indicated secondary prevention pharmacological therapies for patients with vascular disease (21)

Outcomes	Lipid lowering (1 mmol/L reduction in LDL)	BP lowering (10mmHg reduction in systolic BP)	ACE inhibitors	Aspirin	COMPASS rivaroxaban 2.5mg bd + aspirin
MACE[a]	-21%	-20%	-18%	-19%	-24%
Mortality	-9%	-13%	-14%	-9% (NS)	-18%
Stroke	-15%	-27%	-23%	-19%	-42%
MI	-24%	-17%	-18%	-20%[b]	-14% (NS)

ACE=angiotensin-converting enzyme; BP=blood pressure; LDL=low density lipoprotein; MACE=major adverse cardiovascular events; MI=myocardial infarction; NS=non significant

[a]Major coronary event

[b]Non-fatal MI

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Single technology appraisal

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease [ID1397]

Clarification questions

February 2019

File name	Version	Contains confidential information	Date
Rivaroxaban_ID1397_ClarificationQuestions_4Feb19_V1.0	1.0	No	4 Feb 2019

Section A: Clarification on effectiveness data

Indirect and mixed treatment comparisons

A1. Priority question. *It appears that the Bucher indirect comparison does not directly inform the economic model. Please could the company clarify the status of the indirect comparison, e.g. is it for illustrative rather than modelling purposes? The company submission does not appear to provide any discussion or interpretation of the results of the indirect comparison, please provide this.*

The indirect comparison of ticagrelor + aspirin versus rivaroxaban + aspirin was presented in order to provide easily interpretable information on the relative efficacy/safety of both treatments. The rivaroxaban + aspirin versus ticagrelor + aspirin hazard ratios were not used in the economic model as the model uses aspirin as the 'reference' treatment i.e. the economic model is constructed around transition probabilities for aspirin and applies HRs for rivaroxaban + aspirin versus aspirin to calculate transition probabilities for rivaroxaban + aspirin. Similarly, transition probabilities for ticagrelor + aspirin are calculated by applying HRs for ticagrelor + aspirin versus aspirin which have been taken directly from the PEGASUS study.

Interpretation of the results of the indirect comparison

Table 1 summarises the results of the indirect treatment comparison. There were no statistically significant differences in the any endpoint. Out of the 28 comparisons (across the different populations) 20 (71%) numerically favoured rivaroxaban + aspirin and 8 (29%) numerically favoured ticagrelor + aspirin.

Table 1. Summary table for the indirect treatment comparison

Endpoint	COMPASS	CAD and PAD	CAD and PRF
Strokes/MI/CVD	+	+	+
Stroke	+	-	+
IS	+	+	
MI	-		+
CV death	+	-	+
All-cause death	+	-	+
MALE	+	+	
Amputation		+	
ALI	+	+	
VTE	-		
Major bleeding	+	-	+
ICH	+		
Fatal bleeding	-		
GI bleeding			
HS	-		

* ITC in the CAD and HF subgroup not feasible

+	Favours rivaroxaban + aspirin, non-significant (HR <1 and confidence interval contains 1.
-	Favours ticagrelor + aspirin, (HR <1 and confidence interval contains 1).
	Comparison not feasible

A2. Priority question. *In the indirect comparison, sources of between-trial heterogeneity include the patient characteristics of previous myocardial Infarction (MI) and time since previous MI. Additionally the ERG notes that ticagrelor plus aspirin is restricted to patients with a history of MI. Therefore, not all the COMPASS trial population would have been eligible to receive ticagrelor:*

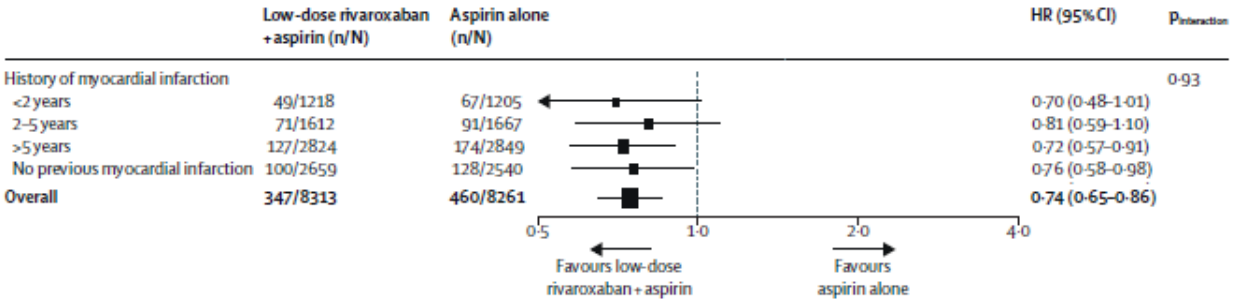
- *Please can the company explain why they did not limit the COMPASS trial population in the indirect comparison to the subgroup with a history of MI?*
- *Please provide a discussion that the potential impact of limiting the trial population in the indirect comparison to the subgroup with a history of MI could have on the outcomes of the indirect comparison.*

As having a 'history of MI' is not effect-modifying we did not consider it necessary to limit the COMPASS population in the indirect comparison.

History of MI

Figure 1 is adapted from Connolly et al (2017) (1) and examines the effect of MI on the primary outcome. The publication states that "*the addition of low-dose rivaroxaban to aspirin resulted in an improvement in the primary efficacy outcome both in patients with a previous MI (HR 0.74, 95% CI 0.63-0.88) and those without a previous MI (0.76, 0.58-0.98, $P_{interaction}$ = 0.91*)." The probability of interaction was not significant indicating that adjusting the populations was not necessary.

Figure 1. Subgroup analysis of primary efficacy outcome (CAD patients)



Adapted from Connolly et al 2017 (1).

Potential impact of limiting the trial population to the subgroup with a history of MI

As presence (absence) of MI is not effect-modifying limiting the trial population would not be expected to influence the ITC results. However, restricting the population to those with a history of MI would substantially lower patients numbers, particularly so with respect to the 3 subgroups, and increase the risk of differences arising purely by chance.

We believe that the comparison conducted was appropriate and that no benefit would be realized by excluding patients without a history of MI from the COMPASS study in the comparison.

A3. If an anchored population-adjusted indirect comparison is feasible, is the PEGASUS trial representative of a real-world population?

Bayer holds patient-level data from COMPASS and therefore an anchored population-adjusted indirect comparison, whereby the population is restricted to patients with a history of MI is feasible. However, as discussed in question A2 this is not considered clinically necessary.

As far as we can tell there were no concerns raised over the generalisability of PEGAGUS in TA420.

Trial differences

A4. Please can the company explain the stated 36 month time of assessment for both the COMPASS and PEGASUS trials as in Tables 139, 140, 141 (pages 398-416 of the company submission appendices). The trials had different duration of follow-up (mean follow up of 23 months in COMPASS and mean follow-up of 32 months in PEGASUS) so this doesn't appear logical.

We apologize, it would have been more accurate if we had described the HRs as being calculated from populations with a mean follow up of 23 months in COMPASS and a mean follow-up of 32 months in PEGASUS. The HRs for both studies utilise data from all participating patients and include patients followed for shorter/longer times than the mean duration of follow-up.

A5. Given there are differences in baseline characteristics between the COMPASS and the PEGASUS trials (which may or may not be prognostic) did the company consider other alternative methods of indirect comparison, such as population adjusted indirect comparisons (as detailed in NICE Decision Support Unit Technical Support Document 18?). Please can you provide a discussion detailing if other methods were considered and the feasibility of these different methods of indirect comparison.

We used the Bucher method for the indirect treatment comparison. The key assumption behind this standard method is that there is no difference between the trials in the distribution of effect-modifying variables. The key difference between COMPASS and PEGASUS is the presence of a history of MI - 100% in PEGASUS and ~62% in COMPASS. However, as the presence (or absence) of MI is not effect-modifying there is nothing to be gained from conducting an adjusted indirect comparison.

Furthermore, TSD 18 states that "*companies deploying MAIC or STC are not only arguing that the treatment effect is dependent on the population, but they are further assuming that the target population is closer to that represented by the competitor trial than in their own trial*". This is not the case for rivaroxaban + aspirin as the 'target' population is not defined by having a history of MI as in PEGASUS and the target population is better represented by the COMPASS trial.

Between trial differences in the distribution of prognostic variables that are not effect-modifiers do not affect inference because the within-trial randomisation means that they do not impact on relative treatment effects (Phillippo DM et al, 2018(2). Patients with multiple comorbidities are at higher baseline risk of cardiovascular events but presence of comorbidities was evenly balanced across treatment arms in both studies.

A6. Did the company conduct a review of prognostic factors for patients with CAD (including the three subgroups), to inform assumptions about heterogeneity of the patients included in the COMPASS and PEGASUS trials? If so, please detail the methodology and prognostic factors identified.

Bayer did not conduct a review of prognostic factors to inform the assumptions about heterogeneity - rather we focused on identification of effect-modifiers which was informed by discussions with experts. The reason for this focus was because between-trial differences in the distribution of prognostic variables that are not effect modifiers do not affect inference because within-trial randomisation means that they do not impact on relative treatment effects (assuming that the sample size is sufficiently large which it is). The COMPASS study was well-balanced at the whole population level and within each of the 3 subgroups.

Clinical experts were consulted with respect to effect-modifiers prior to the conduct of the indirect treatment comparison and before identification of the studies. For completeness these

are outlined briefly below, however, none are applicable in respect of the comparison of PEGASUS and COMPASS.

1) ‘Acute’ versus ‘stable’ disease

Expert advice was that acute and stable patients differ in respect to baseline risk profile, treatment intensity and medical management, which may impact the estimate of relative treatment effects. However, the extent and the direction of this possible association has not been fully elucidated.

In respect of the indirect treatment comparison conducted this was not considered to be an issue as both studies were conducted in ‘stable’ patients.

2) Duration of follow-up

The potential for duration of follow-up having an impact on effect was debated with clinical experts. However, the perspective was considering trials of very short duration (e.g. 3 months) and not in the context of clinical trials which were of much longer durations i.e. PEGASUS and COMPASS. The difference in duration of follow-up between COMPASS and PEGASUS is not expected to affect inference in any way.

A7. Please supply a copy of the final COMPASS trial statistical analysis plan if not already included in the clinical study reports.

Please find attached as a separate file (‘Rivaroxaban_ID1397_SAP_CommercialinConfidence’).

Section B: clarification on cost-effectiveness data

B1. Priority question. *Please provide a comparison of overall survival results for each of the three included subgroups between the COMPASS trial and the outputs of the economic model.*

Table 2 and Table 3 present the comparison between the model outputs and the trial data for all-cause mortality in the CAD and PAD, CAD and HF and CAD and PRF subgroups, for both the aspirin and rivaroxaban + aspirin arms. The results show that the model provides a good estimate of overall mortality compared to the COMPASS study. There is some over (under)estimation in both arms but no indication of bias towards either treatment.

Table 2. Overall mortality - Model predictions versus observed results: aspirin

Cumulative all-cause mortality		Year 1	Year 2	Year 3
CAD and PAD	COMPASS	2.80%	5.91%	10.24%
	Model	2.80%	5.77%	8.88%
	Difference	*0.00%*	*0.14%*	*1.36%*
CAD and HF	COMPASS	2.68%	7.30%	12.52%
	Model	3.07%	6.40%	9.90%
	Difference	*-0.39%*	*0.90%*	*2.62%*
CAD and PRF	COMPASS	3.09%	6.73%	10.87%
	Model	3.44%	7.12%	11.01%
	Difference	*-0.35%*	*-0.39%*	*-0.14%*

Table 3. Overall mortality - Model predictions versus observed results: rivaroxaban + aspirin

Cumulative all-cause mortality		Year 1	Year 2	Year 3
CAD and PAD	COMPASS	2.32%	4.56%	7.85%
	Model	2.30%	4.69%	7.18%
	Difference	*0.02%*	*-0.13%*	*0.67%*
CAD and HF	COMPASS	2.36%	4.65%	8.18%
	Model	2.28%	4.73%	7.30%
	Difference	*0.08%*	*-0.08%*	*0.88%*
CAD and PRF	COMPASS	2.50%	5.48%	10.20%
	Model	3.16%	6.44%	9.86%
	Difference	*-0.66%*	*-0.96%*	*0.34%*

***B2. Priority question**. The ERG is unable to replicate the model results for the validation in Appendix J Table 179-180 using the CAD or PAD population and a reduced model duration. Please explain any other changes to the model that are needed to obtain these results.*

We apologise for this error; the wrong information was presented in the submission.

A comparison of the model outputs and trial data for the overall COMPASS population for both the aspirin and rivaroxaban + aspirin arm is presented below. The results show that the model provides a good estimate of overall mortality compared to the COMPASS study. There is some over (under)estimation in both arms but no indication of bias towards either treatment.

Table 4. Model predictions versus observed results: COMPASS population - rivaroxaban + aspirin

		Year 1	Year 2	Year 3
Cumulative MI	COMPASS	0.99%	1.94%	3.09%
	Model	0.89%	1.80%	2.73%
	Difference	*0.10%*	*0.14%*	*0.36%*
Cumulative Stroke	COMPASS	0.49%	0.85%	1.68%
	Model	0.45%	0.91%	1.36%
	Difference	*0.04%*	*-0.06%*	*0.32%*
Cumulative CV death	COMPASS	0.92%	1.78%	2.99%
	Model	0.87%	1.76%	2.67%
	Difference	*0.05%*	*0.02%*	*0.32%*
Cumulative Major bleed	COMPASS	2.02%	3.21%	4.43%
	Model	1.54%	3.04%	4.52%
	Difference	*0.48%*	*0.17%*	*-0.09%*

Table 5. Model predictions versus observed results: COMPASS population – aspirin

		Year 1	Year 2	Year 3
Cumulative MI	COMPASS	1.21%	2.44%	3.33%
	Model	1.03%	2.10%	3.19%
	Difference	*0.18%*	*0.34%*	*0.14%*
Cumulative Stroke	COMPASS	0.73%	1.55%	2.61%
	Model	0.76%	1.54%	2.32%
	Difference	*-0.03%*	*0.01%*	*0.29%*
Cumulative CV death	COMPASS	1.08%	2.24%	3.67%
	Model	1.10%	2.25%	3.43%
	Difference	*-0.02%*	*-0.01%*	*0.24%*
Cumulative Major bleed	COMPASS	0.87%	1.88%	3.30%
	Model	0.86%	1.70%	2.51%
	Difference	*0.01%*	*0.18%*	*0.79%*

B3. ***Priority question*** *Please state the proportion of patients in the aspirin arm that received dual antiplatelet therapy (please specify treatments) and those who remained only on aspirin after an acute cardiovascular disease (CVD) event in the COMPASS trial.*

'Non-study' medications are captured in the COMPASS CRF (Clinical Research Form) at study visits. If 'non-study' antiplatelet therapy was prescribed the patient was instructed to stop 'study' drug either permanently or temporarily.

Although non-study antiplatelet therapy is captured, the reason for the prescription is not, and therefore it is not possible to conclusively say the therapy was in response to the MI. A further limitation of the data is that as non-study medication is checked at each study visit (every 3/6 months as per the protocol) then medication started and stopped between visits is not captured - leading to possible underreporting of DAPT.

Table 6 reports <u>non-study</u> antiplatelet therapy'. Of the 175 patients who had a post-randomization visit (until and including the final rivaroxaban follow-up visit) following an MI, 103 patients (59%) were receiving non-study DAPT at the time of that visit and 15 patients (9%) reported non-study single antiplatelet use.

Non-study antiplatelet therapy is not recorded for the remaining 57 patients (i.e. 175-103-15).

Table 6. <u>Non-study</u> antiplatelet use in study visit following an MI (COMPASS)

Parameter	Aspirin 100 mg od alone
No of Subjects with MI	205
No of Subjects with visit information available at the first visit after MI	175
Dual antiplatelet therapy at first visit after MI	**103 (100.0%)**
ASPIRIN (NON-STUDY) + CLOPIDOGREL	54 (52.4%)
ASPIRIN (NON-STUDY) + OTHER ANTIPLATELET (NOS)	1 (1.0%)
ASPIRIN (NON-STUDY) + PRASUGREL	11 (10.7%)
ASPIRIN (NON-STUDY) + TICAGRELOR	35 (34.0%)
CLOPIDOGREL + OTHER ANTIPLATELET (NOS)	1 (1.0%)
OTHER ANTIPLATELET (NOS) + TICAGRELOR	1 (1.0%)
Single antiplatelet therapy at first visit after MI	**15 (100.0%)**
ASPIRIN (NON-STUDY)	7 (46.7%)
CLOPIDOGREL	4 (26.7%)
OTHER ANTIPLATELET (NOS)	2 (13.3%)
PRASUGREL	0
TICAGRELOR	2 (13.3%)

B4. Priority question. *In company submission Table 62 (page 207), only a small number of patients had EQ-5D assessments in the one-month visit for acute MI, acute ischaemic stroke (IS) and acute intracranial haemorrhage (ICH). Please clarify whether the utility values for these health states were from this group only or also included other time-points. Please state the total number of patients used to calculate the utility values for each of these health states.*

Utility results were based on data collected from all the timepoints. As an example 236 completed EQ-5D questionnaires informed the estimate for acute MI (12 + 41 + 56 + 40 + 33 + 6 + 48). Table 7 shows the number of values contributing to the estimates for each health state.

Table 7. Number of EQ-5D assessments by study visit and covariate of the multivariate model (ITT analysis set)

Covariate	Category	1 Month visit	6 Month visit	1 Year visit	1 Year 6 month visit	2 Years visit	2 Years 6 Month visit	Final Follow up-visit	Number of EQ-5D questionnaires used for utility analysis
Acute MI	Yes	12 (1.93%)	41 (2.00%)	56 (2.86%)	40 (2.47%)	33 (0.28%)	6 (1.01%)	48 (0.26%)	**236**
	No	609 (98.07%)	2004 (98.00%)	1902 (97.14%)	1577 (97.53%)	11642 (99.72%)	591 (98.99%)	18764 (99.74%)	**37,089**
Post MI	Yes	3 (0.48%)	31 (1.52%)	38 (1.94%)	50 (3.09%)	157 (1.34%)	25 (4.19%)	292 (1.55%)	**596**
	No	618 (99.52%)	2014 (98.48%)	1920 (98.06%)	1567 (96.91%)	11518 (98.66%)	572 (95.81%)	18520 (98.45%)	**36,729**
Acute IS	Yes	5 (0.81%)	23 (1.12%)	23 (1.17%)	15 (0.93%)	16 (0.14%)	8 (1.34%)	23 (0.12%)	**113**
	No	616 (99.19%)	2022 (98.88%)	1935 (98.83%)	1602 (99.07%)	11659 (99.86%)	589 (98.66%)	18789 (99.88%)	**37212**
Post IS	Yes		12 (0.59%)	22 (1.12%)	24 (1.48%)	83 (0.71%)	17 (2.85%)	117 (0.62%)	**275**
	No	621 (100.00%)	2033 (99.41%)	1936 (98.88%)	1593 (98.52%)	11592 (99.29%)	580 (97.15%)	18695 (99.38%)	**37050**
Acute ICH	Yes	2 (0.32%)	3 (0.15%)	2 (0.10%)	4 (0.25%)	3 (0.03%)	2 (0.34%)	5 (0.03%)	**21**
	No	619 (99.68%)	2042 (99.85%)	1956 (99.90%)	1613 (99.75%)	11672 (99.97%)	595 (99.66%)	18807 (99.97%)	**37304**
Post ICH	Yes	1 (0.16%)	5 (0.24%)	3 (0.15%)	5 (0.31%)	19 (0.16%)	6 (1.01%)	27 (0.14%)	**66**
	No	620 (99.84%)	2040 (99.76%)	1955 (99.85%)	1612 (99.69%)	11656 (99.84%)	591 (98.99%)	18785 (99.86%)	**37259**
Any prior major amputation	Yes		12 (0.59%)	7 (0.36%)	9 (0.56%)	15 (0.13%)	5 (0.84%)	21 (0.11%)	**69**
	No	621 (100.00%)	2033 (99.41%)	1951 (99.64%)	1608 (99.44%)	11660 (99.87%)	592 (99.16%)	18791 (99.89%)	**37256**
Any prior minor amputation	Yes	2 (0.32%)	12 (0.59%)	16 (0.82%)	16 (0.99%)	23 (0.20%)	6 (1.01%)	32 (0.17%)	**107**
	No	619 (99.68%)	2033 (99.41%)	1942 (99.18%)	1601 (99.01%)	11652 (99.80%)	591 (98.99%)	18780 (99.83%)	**37218**

Acute ALI	Yes	3 (0.48%)	11 (0.54%)	4 (0.20%)	5 (0.31%)	6 (0.05%)	5 (0.84%)	7 (0.04%)	**41**
	No	618 (99.52%)	2034 (99.46%)	1954 (99.80%)	1612 (99.69%)	11669 (99.95%)	592 (99.16%)	18805 (99.96%)	**37284**
Any prior CLI	Yes	2 (0.32%)	10 (0.49%)	10 (0.51%)	13 (0.80%)	16 (0.14%)	5 (0.84%)	40 (0.21%)	**96**
	No	619 (99.68%)	2035 (99.51%)	1948 (99.49%)	1604 (99.20%)	11659 (99.86%)	592 (99.16%)	18772 (99.79%)	**37229**
Acute VTE	Yes	2 (0.32%)	6 (0.29%)	5 (0.26%)	8 (0.49%)	6 (0.05%)	5 (0.84%)	11 (0.06%)	**43**
	No	619 (99.68%)	2039 (99.71%)	1953 (99.74%)	1609 (99.51%)	11669 (99.95%)	592 (99.16%)	18801 (99.94%)	**37282**
Acute minor bleeding	Yes	170 (27.38%)	266 (13.01%)	180 (9.19%)	128 (7.92%)	148 (1.27%)	42 (7.04%)	159 (0.85%)	**1093**
	No	451 (72.62%)	1779 (86.99%)	1778 (90.81%)	1489 (92.08%)	11527 (98.73%)	555 (92.96%)	18653 (99.15%)	**36232**
Acute major modified ISTH bleeding	Yes	21 (3.38%)	72 (3.52%)	53 (2.71%)	38 (2.35%)	35 (0.30%)	19 (3.18%)	49 (0.26%)	**287**
	No	600 (96.62%)	1973 (96.48%)	1905 (97.29%)	1579 (97.65%)	11640 (99.70%)	578 (96.82%)	18763 (99.74%)	**37038**

Model population

B5. Company submission figure 19 (page 174) shows and the text below the figure states "patients enter the model in the 'event-free' health state". Yet company submission B.3.3 states that the baseline characteristics of patients entering the model are derived from either the whole COMPASS population or one of the subgroups of interest and the COMPASS population are not 'event free'. Company submission table 8 (pages 63-66) shows that some COMPASS participants have experienced either a previous stroke (3.8% of total trial population) or a previous MI (61.8% of total trial population). Please can the company clarify the population cohort characteristics at entry to the economic model?

We apologise for any confusion. Patients enter the model with the baseline characteristics of patients from either the whole of COMPASS or one of the subgroups of interest – consequently many of these patients do have a history of prior events as pointed out. In the context of the decision problem these patients have not had an event since starting treatment with either aspirin or rivaroxaban + aspirin.

B6. Please update table 54 (page 189 of the company submission) and the economic model using 2017 annual background mortality rates.

The model has been updated with the latest ONS life tables for England 2015/2017, also presented in the table below.

Table 8. Background mortality

Age (years)	Annual Mortality (males)	Annual Mortality (females)
65	0.01198	0.00759
66	0.01305	0.00854
67	0.01409	0.00927
68	0.01521	0.01008
69	0.01657	0.01108
70	0.01827	0.01214
71	0.02073	0.01381
72	0.02280	0.01542
73	0.02523	0.01731
74	0.02868	0.01903
75	0.03205	0.02162
76	0.03562	0.02469
77	0.03891	0.02663
78	0.04325	0.03049
79	0.04790	0.03379
80	0.05413	0.03876
81	0.06023	0.04381
82	0.06827	0.04997
83	0.07733	0.05733
84	0.08657	0.06560
85	0.09682	0.07376
86	0.10818	0.08397
87	0.12104	0.09532
88	0.13539	0.10837
89	0.14986	0.12225
90	0.16759	0.13782
91	0.18407	0.15280
92	0.19984	0.16975
93	0.21992	0.18614
94	0.24093	0.20752
95	0.26673	0.23287
96	0.28634	0.25220
97	0.30397	0.26593
98	0.30998	0.28127
99	0.34226	0.31362
100	0.38539	0.33980

Source:
https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables

The implementation of this change has a minor and favourable impact on the ICER (Table 9).

Table 9. Cost-effectiveness using updated life-tables (versus aspirin)

Population	Submitted ICER	Updated ICER
COMPASS	**£16,602**	**£16,420**
CAD and PAD	**£7,416**	**£7,360**
CAD and HF	**£5,787**	**£5,744**
CAD and PRF	**£10,046**	**£9,932**

B7. In table 58 (page 194 of the company submission), we were able to trace the hazard ratios (HRs) for acute limb ischaemia and venous thromboembolism to the sources mentioned in the company submission (Tables 19, 20, 23 and 25); however, we did not find HRs for minor amputations, major amputations and major extracranial non-fatal bleeding. Could you please provide the sources?

Please find below the source tables for HRs for minor and major amputations and major non-fatal extracranial bleeds below. Numbers were too low for calculable HRs for the CAD and HF and CAD and PRF populations in respect of amputations and therefore, for these subgroups, HRs from the whole of COMPASS were used in the economic model.

Whilst providing the source tables we noticed that the HR for Major extracranial non-fatal bleed for the CAD and PRF group was incorrectly reported in table 58 from the submission and should be 1.42 (0.97; 2.08). Implementing this change for the CAD and PRF group has a minor impact on the ICER (Table 10 and Table 11).

Table 10. Base case results – CAD and PRF subgroup: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin monotherapy	£7,593	9.59	7.32				
Rivaroxaban + aspirin	£10,188	9.91	7.59	£2,595	0.315	0.262	£9,892

Table 11. Base case results – CAD and PRF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin monotherapy	£9,010	9.62	7.35				
Rivaroxaban + aspirin	£10,188	9.91	7.59	£1,178	0.287	0.237	£4,971

Table 12. COMPASS – HR for minor/major amputations and major non-fatal extracranial bleeds

Table 2 / 9: Rivaroxaban treatment effect for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date (ITT analysis set)

	Rivaroxaban 2.5 mg bid, Aspirin 100mg od vs Aspirin 100 mg od			Rivaroxaban 5 mg bid vs Aspirin 100 mg od		
Outcome	HR (95% CI)	log-rank p-value	log-rank test statistic	HR (95% CI)	log-rank p-value	log-rank test statistic
Primary Efficacy Outcome	0.76 (0.66;0.86)	0.00004	4.1260	0.90 (0.79;1.03)	0.11490	1.5765
MI	0.86 (0.70;1.05)	0.14458	1.4590	0.89 (0.73;1.08)	0.24392	1.1652
Ischemic stroke (including uncertain stroke)	0.51 (0.38;0.68)	0.00000	4.5884	0.69 (0.53;0.90)	0.00598	2.7487
Hemorrhagic Stroke	1.49 (0.67;3.31)	0.32701	0.9802	2.70 (1.31;5.58)	0.00515	2.7974
CV death	0.78 (0.64;0.96)	0.02053	2.3165	0.96 (0.79;1.17)	0.69006	0.3988
All-cause mortality	0.82 (0.71;0.96)	0.01062	2.5550	0.97 (0.84;1.12)	0.66418	0.4342
Angina	0.95 (0.77;1.17)	0.59957	0.5250	0.87 (0.70;1.08)	0.20995	1.2537
Heart Failure	1.02 (0.84;1.24)	0.84475	0.1958	0.99 (0.81;1.21)	0.94882	0.0642
Venous thromboembolism	0.61 (0.37;1.00)	0.04564	1.9987	0.88 (0.56;1.38)	0.57563	0.5598
Revascularization	0.93 (0.83;1.04)	0.22616	1.2103	0.93 (0.83;1.04)	0.21061	1.2519
Major adverse limb event	0.53 (0.35;0.80)	0.00224	3.0570	0.64 (0.43;0.95)	0.02526	2.2375
Amputation overall	0.64 (0.40;1.00)	0.05040	1.9566	0.64 (0.40;1.01)	0.05300	1.9349
Major Amputation	0.57 (0.30;1.09)	0.08371	1.7295	0.42 (0.21;0.86)	0.01411	2.4546
Minor Amputation	0.65 (0.35;1.20)	0.16471	1.3894	0.81 (0.45;1.44)	0.46615	0.7288
ALI	0.55 (0.32;0.92)	0.02093	2.3092	0.60 (0.36;1.00)	0.04609	1.9945
CLI	0.63 (0.34;1.15)	0.12746	1.5242	0.71 (0.39;1.27)	0.24194	1.1702
Stent thrombosis	1.10 (0.74;1.63)	0.63891	0.4692	1.11 (0.75;1.64)	0.61436	0.5039
Major bleeds modified ISTH	1.70 (1.40;2.05)	0.00000	5.5366	1.51 (1.25;1.84)	0.00003	4.2088
Minor bleeds modified ISTH	1.70 (1.52;1.90)	0.00000	9.5272	1.50 (1.34;1.68)	0.00000	7.1153
Major Intracranial bleeding	1.16 (0.67;2.00)	0.59858	0.5264	1.79 (1.09;2.96)	0.01987	2.3288
Major non-fatal extracranial bleeds modified ISTH	1.79 (1.46;2.19)	0.00000	5.6329	1.51 (1.23;1.87)	0.00011	3.8771
Death within 30 days of acute MI	0.62 (0.33;1.19)	0.14540	1.4560	0.54 (0.28;1.07)	0.07126	1.8038
Death within 30 days of stroke	0.84 (0.38;1.88)	0.67602	0.4179	1.46 (0.72;2.96)	0.28969	1.0588
Death within 14 days of Heart failure	1.13 (0.56;2.26)	0.73457	0.3391	1.07 (0.53;2.16)	0.85591	0.1816
Death within 3 days of a CV procedure	Not calculated	.	.	0.71 (0.23;2.24)	0.55995	0.5829
Sudden cardiac death	0.81 (0.59;1.11)	0.18433	1.3276	1.28 (0.96;1.70)	0.08626	1.7155
Other CV death	0.79 (0.54;1.16)	0.22745	1.2070	0.55 (0.36;0.85)	0.00617	2.7387
Non-CV death	0.87 (0.70;1.08)	0.20357	1.2714	0.98 (0.79;1.21)	0.83451	0.2089
Fatal bleeding other than due to hemorrhagic stroke	Not calculated	.	.	Not calculated	.	.
Malignancy death	0.80 (0.59;1.10)	0.16550	1.3868	0.99 (0.74;1.33)	0.94929	0.0636

Table 2 / 9: Rivaroxaban treatment effect for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date (ITT analysis set)

Outcome	Rivaroxaban 2.5 mg bid, Aspirin 100mg od vs Aspirin 100 mg od			Rivaroxaban 5 mg bid vs Aspirin 100 mg od		
	HR (95% CI)	log-rank p-value	log-rank test statistic	HR (95% CI)	log-rank p-value	log-rank test statistic
Other non-CV death not due to malignancy or bleeding	0.95 (0.69;1.29)	0.72556	0.3510	0.96 (0.71;1.31)	0.81008	0.2403

Table displays unrefuted outcomes = outcome events meeting the definition in the event adjudication plan.
The primary efficacy outcome is composed of the first occurrence of MI, stroke, or CV death. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
Revascularizations, amputations and stent thrombosis are based on investigator assessment.
HR (95% CI): Hazard ratios (95% confidence interval) are based on the stratified Cox proportional hazards model.
Log-rank p-value: p-values (two-sided) are based on the stratified log-rank test.
Log-rank test statistic: test statistic of the stratified log-rank test
MI = myocardial infarction, CV = cardiovascular, p-yrs = patient years; bid = twice daily, od = once daily, CI = confidence interval.
Global rivaroxaban/aspirin outcomes cut-off date = February 06, 2017
Bayer: /var/swan/root/bhc/597939/15786/stat/query22/prod/pgms/t_adtte_trtef_2.sas epspg 23FEB2018 10:49
End of table

Table 13. CAD and PAD subgroup – HR for minor/major amputation and major non-fatal extracranial bleeds

Table 2 / 10: Rivaroxaban treatment effect for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date by CAD/PAD subject (ITT analysis set) (cont.)

CAD and PAD

Outcome	Rivaroxaban 2.5 mg bid, Aspirin 100mg od vs Aspirin 100 mg od			Rivaroxaban 5 mg bid vs Aspirin 100 mg od		
	HR (95% CI)	log-rank p-value	log-rank test statistic	HR (95% CI)	log-rank p-value	log-rank test statistic
Primary Efficacy Outcome	0.67 (0.52;0.87)	0.00262	3.0089	0.83 (0.64;1.06)	0.13365	1.4998
MI	0.72 (0.49;1.08)	0.11155	1.5913	0.89 (0.61;1.30)	0.54494	0.6054
Ischemic stroke (including uncertain stroke)	0.49 (0.26;0.91)	0.02006	2.3252	0.93 (0.56;1.55)	0.78662	0.2707
Hemorrhagic Stroke	Not calculated	.	.	Not calculated	.	.
CV death	0.72 (0.49;1.07)	0.10158	1.6373	0.79 (0.54;1.17)	0.23608	1.1848
All-cause mortality	0.76 (0.56;1.01)	0.06139	1.8707	0.83 (0.62;1.10)	0.19290	1.3020
Angina	0.90 (0.58;1.39)	0.63090	0.4805	1.05 (0.69;1.59)	0.83474	0.2086
Heart Failure	1.02 (0.68;1.52)	0.93204	0.0853	1.00 (0.67;1.50)	0.98117	0.0236
Venous thromboembolism	0.57 (0.23;1.46)	0.23771	1.1807	0.68 (0.28;1.67)	0.39678	0.8474
Revascularization	0.96 (0.78;1.18)	0.70171	0.3830	1.04 (0.85;1.28)	0.69977	0.3856
Major adverse limb event	0.51 (0.29;0.92)	0.02335	2.2676	0.50 (0.28;0.91)	0.02030	2.3208
Amputation overall	0.69 (0.32;1.49)	0.34142	0.9514	0.82 (0.39;1.70)	0.58981	0.5391
Major Amputation	0.58 (0.21;1.61)	0.29330	1.0509	Not calculated	.	.
Minor Amputation	0.66 (0.23;1.86)	0.42764	0.7932	1.03 (0.41;2.60)	0.94384	0.0704
ALI	0.48 (0.23;1.02)	0.04948	1.9644	0.45 (0.20;0.97)	0.03745	2.0808
CLI	0.64 (0.28;1.47)	0.28524	1.0686	0.59 (0.25;1.40)	0.22697	1.2082
Stent thrombosis	1.27 (0.56;2.90)	0.56884	0.5698	0.94 (0.38;2.32)	0.89555	0.1313
Major bleeds modified ISTH	1.43 (0.93;2.19)	0.09819	1.6537	1.71 (1.13;2.59)	0.00989	2.5797
Minor bleeds modified ISTH	1.48 (1.13;1.93)	0.00364	2.9078	1.31 (0.99;1.72)	0.05387	1.9279
Major Intracranial bleeding	Not calculated	.	.	0.78 (0.27;2.25)	0.64271	0.4639
Major non-fatal extracranial bleeds modified ISTH	1.61 (1.01;2.56)	0.04229	2.0307	1.91 (1.21;3.00)	0.00437	2.8505

Table 2 / 10: Rivaroxaban treatment effect for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date by CAD/PAD subject (ITT analysis set) (cont.)

CAD and PAD

Outcome	Rivaroxaban 2.5 mg bid, Aspirin 100mg od vs Aspirin 100 mg od			Rivaroxaban 5 mg bid vs Aspirin 100 mg od		
	HR (95% CI)	log-rank p-value	log-rank test statistic	HR (95% CI)	log-rank p-value	log-rank test statistic
Death within 30 days of acute MI	Not calculated	.	.	Not calculated	.	.
Death within 30 days of stroke	Not calculated	.	.	Not calculated	.	.
Death within 14 days of Heart failure	0.56 (0.19;1.67)	0.29023	1.0576	Not calculated	.	.
Death within 3 days of a CV procedure	Not calculated	.	.	Not calculated	.	.
Sudden cardiac death	0.82 (0.45;1.48)	0.50967	0.6594	0.97 (0.55;1.72)	0.91699	0.1042
Other CV death	0.80 (0.39;1.66)	0.55106	0.5962	0.38 (0.15;0.96)	0.03422	2.1175
Non-CV death	0.80 (0.51;1.25)	0.33149	0.9711	0.87 (0.56;1.35)	0.53194	0.6250
Fatal bleeding other than due to hemorrhagic stroke	Not calculated	.	.	Not calculated	.	.
Malignancy death	0.83 (0.45;1.53)	0.55114	0.5961	0.93 (0.52;1.68)	0.81274	0.2369
Other non-CV death not due to malignancy or bleeding	0.77 (0.40;1.48)	0.43306	0.7840	0.80 (0.42;1.53)	0.50674	0.6639

Table displays unrefuted outcomes = outcome events meeting the definition in the event adjudication plan.
The primary efficacy outcome is composed of the first occurrence of MI, stroke, or CV death. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
Revascularizations, amputations and stent thrombosis are based on investigator assessment.
HR (95% CI): Hazard ratios (95% confidence interval) are based on the stratified Cox proportional hazards model.
Log-rank p-value: p-values (two-sided) are based on the stratified log-rank test.
Log-rank test statistic: test statistic of the stratified log-rank test
MI = myocardial infarction, CV = cardiovascular, p-yrs = patient years; bid = twice daily, od = once daily, CI = confidence interval.
Global rivaroxaban/aspirin outcomes cut-off date = February 06, 2017
Bayer: /var/swan/root/bhc/597939/15786/stat/query22/prod/pgms/t_adtte_trtef_2.sas epspg 23FEB2018 10:49
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Table 14. CAD and HF – HR for minor/major amputations and major non-fatal extracranial bleeds

Table 2 / 13: Rivaroxaban treatment effect for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date by CAD and Heart failure subject (ITT analysis set) (cont.)

CAD and Heart failure

	Rivaroxaban 2.5 mg bid, Aspirin 100mg od vs Aspirin 100 mg od			Rivaroxaban 5 mg bid vs Aspirin 100 mg od		
Outcome	HR (95% CI)	log-rank p-value	log-rank test statistic	HR (95% CI)	log-rank p-value	log-rank test statistic
Primary Efficacy Outcome	0.68 (0.53;0.87)	0.00217	3.0657	0.79 (0.62;1.01)	0.05963	1.8835
MI	0.81 (0.54;1.22)	0.30432	1.0272	0.90 (0.60;1.34)	0.59908	0.5257
Ischemic stroke (including uncertain stroke)	0.37 (0.19;0.69)	0.00126	3.2252	0.55 (0.32;0.97)	0.03575	2.0998
Hemorrhagic Stroke	Not calculated	.	.	Not calculated	.	.
CV death	0.65 (0.47;0.92)	0.01312	2.4806	0.74 (0.53;1.03)	0.06954	1.8149
All-cause mortality	0.64 (0.48;0.84)	0.00153	3.1694	0.75 (0.58;0.99)	0.03872	2.0672
Angina	0.96 (0.65;1.43)	0.84267	0.1985	0.83 (0.55;1.26)	0.38285	0.8727
Heart Failure	0.80 (0.58;1.10)	0.16882	1.3760	0.89 (0.65;1.21)	0.46176	0.7360
Venous thromboembolism	Not calculated	.	.	Not calculated	.	.
Revascularization	1.07 (0.81;1.40)	0.64402	0.4621	1.19 (0.91;1.56)	0.19574	1.2938
Major adverse limb event	Not calculated	.	.	Not calculated	.	.
Amputation overall	0.85 (0.29;2.53)	0.76953	0.2930	0.88 (0.30;2.62)	0.81750	0.2308
Major Amputation	Not calculated	.	.	Not calculated	.	.
Minor Amputation	Not calculated	.	.	Not calculated	.	.
ALI	Not calculated	.	.	Not calculated	.	.
CLI	Not calculated	.	.	Not calculated	.	.
Stent thrombosis	1.09 (0.46;2.57)	0.84454	0.1961	0.91 (0.37;2.25)	0.84463	0.1960
Major bleeds modified ISTH	1.35 (0.87;2.07)	0.17489	1.3567	1.48 (0.97;2.26)	0.07003	1.8117
Minor bleeds modified ISTH	1.81 (1.39;2.37)	0.00001	4.4006	1.57 (1.19;2.08)	0.00125	3.2280
Major Intracranial bleeding	1.44 (0.51;4.06)	0.48417	0.6996	1.00 (0.32;3.11)	0.99608	0.0049
Major non-fatal extracranial bleeds modified ISTH	1.38 (0.85;2.24)	0.19075	1.3084	1.68 (1.05;2.69)	0.02870	2.1876
Death within 30 days of acute MI	Not calculated	.	.	Not calculated	.	.
Death within 30 days of stroke	Not calculated	.	.	0.72 (0.23;2.25)	0.56553	0.5747
Death within 14 days of Heart failure	Not calculated	.	.	0.78 (0.29;2.10)	0.62266	0.4921
Death within 3 days of a CV procedure	Not calculated	.	.	Not calculated	.	.
Sudden cardiac death	0.87 (0.53;1.41)	0.56070	0.5818	1.08 (0.68;1.71)	0.73929	0.3328
Other CV death	0.65 (0.34;1.24)	0.18369	1.3295	0.39 (0.18;0.85)	0.01379	2.4626
Non-CV death	0.61 (0.37;1.00)	0.04682	1.9879	0.79 (0.49;1.26)	0.31190	1.0112
Fatal bleeding other than due to hemorrhagic stroke	Not calculated	.	.	Not calculated	.	.
Malignancy death	0.91 (0.43;1.93)	0.80084	0.2523	0.79 (0.36;1.75)	0.56665	0.5730

Table 2 / 13: Rivaroxaban treatment effect for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date by CAD and Heart failure subject (ITT analysis set) (cont.)

CAD and Heart failure

Outcome	Rivaroxaban 2.5 mg bid, Aspirin 100mg od vs Aspirin 100 mg od			Rivaroxaban 5 mg bid vs Aspirin 100 mg od		
	HR (95% CI)	log-rank p-value	log-rank test statistic	HR (95% CI)	log-rank p-value	log-rank test statistic
Other non-CV death not due to malignancy or bleeding	0.46 (0.23;0.92)	0.02399	2.2574	0.77 (0.43;1.40)	0.39462	0.8513

Table displays unrefuted outcomes = outcome events meeting the definition in the event adjudication plan.
The primary efficacy outcome is composed of the first occurrence of MI, stroke, or CV death. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
Revascularizations, amputations and stent thrombosis are based on investigator assessment.
HR (95% CI): Hazard ratios (95% confidence interval) are based on the stratified Cox proportional hazards model.
Log-rank p-value: p-values (two-sided) are based on the stratified log-rank test.
Log-rank test statistic: test statistic of the stratified log-rank test
MI = myocardial infarction, CV = cardiovascular, p-yrs = patient years; bid = twice daily, od = once daily, CI = confidence interval.
Global rivaroxaban/aspirin outcomes cut-off date = February 06, 2017
Bayer: /var/swan/root/bhc/597939/15786/stat/query22/prod/pgms/t_adtte_trtef_2.sas epspg 23FEB2018 10:49
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Table 15. CAD and PRF – HR for minor/major amputations and major non-fatal extracranial bleeds

Table 2 / 2: Rivaroxaban treatment effect for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date by CAD and eGFR below 60 mL/min (ITT analysis set) (cont.)

CAD and eGFR below 60mL/min

	Rivaroxaban 2.5 mg bid, Aspirin 100mg od vs Aspirin 100 mg od			Rivaroxaban 5 mg bid vs Aspirin 100 mg od		
Outcome	HR (95% CI)	log-rank p-value	log-rank test statistic	HR (95% CI)	log-rank p-value	log-rank test statistic
Primary Efficacy Outcome	0.73 (0.57;0.92)	0.00743	2.6767	0.76 (0.60;0.96)	0.02148	2.2994
MI	0.74 (0.51;1.06)	0.09916	1.6489	0.65 (0.44;0.94)	0.02298	2.2738
Ischemic stroke (including uncertain stroke)	0.27 (0.14;0.53)	0.00003	4.1400	0.56 (0.33;0.92)	0.02142	2.3004
Hemorrhagic Stroke	Not calculated	.	.	Not calculated	.	.
CV death	0.86 (0.62;1.20)	0.37477	0.8876	0.94 (0.68;1.30)	0.71504	0.3651
All-cause mortality	0.84 (0.65;1.08)	0.17800	1.3469	1.03 (0.81;1.31)	0.82336	0.2232
Angina	0.78 (0.50;1.21)	0.26919	1.1049	0.80 (0.52;1.23)	0.30674	1.0221
Heart Failure	0.80 (0.58;1.11)	0.18251	1.3331	0.89 (0.65;1.22)	0.46200	0.7356
Venous thromboembolism	0.36 (0.13;1.00)	0.04078	2.0458	0.58 (0.24;1.39)	0.21757	1.2330
Revascularization	0.80 (0.62;1.03)	0.07672	1.7700	0.88 (0.69;1.13)	0.31343	1.0080
Major adverse limb event	0.65 (0.31;1.40)	0.26888	1.1057	0.36 (0.14;0.91)	0.02478	2.2448
Amputation overall	0.64 (0.25;1.65)	0.35233	0.9301	0.64 (0.25;1.65)	0.34881	0.9369
Major Amputation	Not calculated	.	.	Not calculated	.	.
Minor Amputation	Not calculated	.	.	1.02 (0.36;2.90)	0.97372	0.0329
ALI	Not calculated	.	.	Not calculated	.	.
CLI	1.14 (0.41;3.16)	0.79512	0.2597	0.73 (0.23;2.30)	0.58828	0.5413
Stent thrombosis	0.84 (0.36;1.94)	0.68030	0.4121	1.11 (0.51;2.43)	0.79732	0.2568
Major bleeds modified ISTH	1.41 (1.00;2.00)	0.05058	1.9550	1.14 (0.79;1.64)	0.48712	0.6949
Minor bleeds modified ISTH	1.89 (1.46;2.44)	0.00000	4.9744	1.77 (1.36;2.28)	0.00001	4.3830
Major Intracranial bleeding	1.45 (0.55;3.81)	0.44780	0.7591	1.72 (0.68;4.38)	0.24617	1.1597
Major non-fatal extracranial bleeds modified ISTH	1.42 (0.97;2.08)	0.06859	1.8211	1.07 (0.72;1.60)	0.73853	0.3338
Death within 30 days of acute MI	Not calculated	.	.	Not calculated	.	.
Death within 30 days of stroke	Not calculated	.	.	1.64 (0.53;5.00)	0.38353	0.8714
Death within 14 days of Heart failure	1.52 (0.54;4.27)	0.42597	0.7961	1.33 (0.46;3.84)	0.59406	0.5330
Death within 3 days of a CV procedure	Not calculated	.	.	Not calculated	.	.
Sudden cardiac death	0.90 (0.55;1.49)	0.68553	0.4049	1.02 (0.63;1.65)	0.94372	0.0706
Other CV death	0.97 (0.53;1.79)	0.92615	0.0927	0.76 (0.39;1.45)	0.40001	0.8416
Non-CV death	0.81 (0.55;1.20)	0.30041	1.0356	1.15 (0.80;1.64)	0.45970	0.7393
Fatal bleeding other than due to hemorrhagic stroke	Not calculated	.	.	Not calculated	.	.
Malignancy death	0.80 (0.46;1.40)	0.44168	0.7694	0.99 (0.58;1.67)	0.95616	0.0550

Table 2 / 2: Rivaroxaban treatment effect for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date by CAD and eGFR below 60 mL/min (ITT analysis set) (cont.)

CAD and eGFR below 60mL/min

	Rivaroxaban 2.5 mg bid, Aspirin 100mg od vs Aspirin 100 mg od			Rivaroxaban 5 mg bid vs Aspirin 100 mg od		
Outcome	HR (95% CI)	log-rank p-value	log-rank test statistic	HR (95% CI)	log-rank p-value	log-rank test statistic
Other non-CV death not due to malignancy or bleeding	0.82 (0.47;1.44)	0.48369	0.7004	1.28 (0.77;2.12)	0.33783	0.9585

Table displays unrefuted outcomes = outcome events meeting the definition in the event adjudication plan.
The primary efficacy outcome is composed of the first occurrence of MI, stroke, or CV death. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
Revascularizations, amputations and stent thrombosis are based on investigator assessment.
HR (95% CI): Hazard ratios (95% confidence interval) are based on the stratified Cox proportional hazards model.
Log-rank p-value: p-values (two-sided) are based on the stratified log-rank test.
Log-rank test statistic: test statistic of the stratified log-rank test
MI = myocardial infarction, CV = cardiovascular, p-yrs = patient years; bid = twice daily, od = once daily, CI = confidence interval.
Global rivaroxaban/aspirin outcomes cut-off date = February 06, 2017
Bayer: /var/swan/root/bhc/597939/15786/stat/query22/prod/pgms/t_adtte_trtef_6.sas eppri 10APR2018 14:20
End of table

Transition probabilities

B8. Please explain how the transition probabilities have been inputted (with a rationale) for the scenario analysis for ASA transition probabilities (('Aspirin rate of events' in table 124). In this scenario, it appears null transition probabilities have been inputted; please clarify.

Based on expert advice the economic base case utilises observed results from COMPASS – this includes zero probabilities for some transitions. For example, Table 16 shows a probability of zero for transitioning from the acute IS health state to MI as no patients from COMPASS experienced an MI within 3 months of an IS. However, it is acknowledged that these events may occur outside the relatively short duration of a trial setting. As such, a scenario where non-zero transition probabilities are imputed is considered to explore the impact of this assumption, and is implemented as follows in the model:

- Null event probabilities after a first event

Replaced with the associated probability of the event-free health state e.g. If in the base case the probability of having an MI whilst in acute IS is null, then in the scenario analysis it will be replaced with the probability of having an MI taken from the event free state i.e. 0.00290 (Table 16 and Table 17) – see shaded cells

- Null mortality probabilities after a first event

Replaced with the associated probability of mortality from the event-free health state e.g. If in the base case the probability of dying due to an MI following an IS is null, then in the scenario the probability of dying due to an MI is taken from the event free state – see Table 18 and Table 19)

- Null CV death probabilities after a second event

Imputed the minimum of all probabilities after a second event (i.e. 0.11111 probability of death from MI after a first MI) - Table 20 and Table 21.

Table 16. Aspirin transition probabilities –three-month risk of main events (COMPASS) – BASE CASE

	Risk of MI	Risk of IS	Risk of ICH
Event-free	**0.00290**	0.00176	0.00029
Acute MI	0.00641	0.00641	0
Post-acute MI	0.01852	0.00231	0
Acute IS	0	0.01042	0
Post-acute IS	0.00356	0.01779	0
Acute ICH	0	0	0.07143
Post-acute ICH	0	0.01754	0

Table 17. Aspirin transition probabilities –three-month risk of main events (COMPASS) – SCENARIO

	Risk of MI	Risk of IS	Risk of ICH
Event-free	0.00290	0.00176	0.00029
Acute MI	0.00641	0.00641	0.00029
Post-acute MI	0.01852	0.00231	0.00029
Acute IS	**0.00290**	0.01042	0.00029
Post-acute IS	0.00356	0.01779	0.00029
Acute ICH	0.00290	0.00176	0.07143
Post-acute ICH	0.00290	0.01754	0.00029

Table 18. COMPASS three-month CV death rates in the event free state and after one event – BASE CASE

Health state	Due to MI	Due to stroke	Due to HF	Following CV procedure	Sudden cardiac death	Other CV death	Fatal bleeding
Event-free	0.00033	0.00017	0.00016	0.0001	0.00108	0.00082	0.00004
Acute MI	0	0	0	0	0.00641	0	0
Post-acute MI	0	0	0	0	0	0.00694	0.00231
Acute IS	**0**	0.01042	0	0	0	0.01042	0
Post-acute IS	0	0.00356	0.00356	0	0.01068	0.00356	0
Acute ICH	0	0	0	0	0	0	0
Post-acute ICH	0	0	0	0	0	0	0

Table 19. COMPASS three-month CV death rates in the event free state and after one event – SCENARIO

Health state	Due to MI	Due to stroke	Due to HF	Following CV procedure	Sudden cardiac death	Other CV death	Fatal bleeding
Event-free	0.00033	0.00017	0.00016	0.0001	0.00108	0.00082	0.00004
Acute MI	0.00033	0.00017	0.00016	0.0001	0.00641	0.00082	0.00004
Post-acute MI	0.00033	0.00017	0.00016	0.0001	0.00108	0.00694	0.00231
Acute IS	0.00033	0.01042	0.00016	0.0001	0.00108	0.01042	0.00004
Post-acute IS	0.00033	0.00356	0.00356	0.0001	0.01068	0.00356	0.00004
Acute ICH	0.00033	0.00017	0.00016	0.0001	0.00108	0.00082	0.00004
Post-acute ICH	0.00033	0.00017	0.00016	0.0001	0.00108	0.00082	0.00004

Table 20. COMPASS three-month death rates (all CV death) - 2 events history: base case

First event	Second event					
	Acute MI	Post MI	Acute IS	Post IS	Acute ICH	Post ICH
MI	0.11111	0	0	0	0	0
IS	0	0	0	0	0	0
ICH	0	0	0	0	0	0

Table 21. COMPASS three-month death rates (all CV death) - 2 events history: scenario

First event	Second event					
	Acute MI	Post MI	Acute IS	Post IS	Acute ICH	Post ICH
MI	0.11111	0.11111	0.11111	0.11111	0.11111	0.11111
IS	0.11111	0.11111	0.11111	0.11111	0.11111	0.11111
ICH	0.11111	0.11111	0.11111	0.11111	0.11111	0.11111

B9. The transition probabilities in the model transition matrix worksheet appear the same for the OffTx and OnTx states and the event free- state is not divided between OnTx and OffTx. Please explain how the patients who discontinue rivaroxaban + aspirin accrue the efficacy of the aspirin arm.

The OffTx and OnTx states on the transition matrix worksheet refer to treatment interruption, not treatment discontinuation.

An adjustment has been made for rivaroxaban + aspirin and ticagrelor + aspirin to account for a proportion of patients discontinuing treatment. A composite (weighted) transition probability is calculated, whereby the transitions probability as observed in the rivaroxaban + aspirin or ticagrelor + aspirin arm is applied to the proportion of patients on treatment and the transition probabilities in the aspirin arm are applied to the proportion of patients who have discontinued.

Utility values

B10. The model appears to include age-adjusted utility values. Please explain how this is implemented in the model and provide a reference source for the values used.

An age adjustment is applied on utility scores for each health state based on the UK norms for EQ-5D.

Table 22. EQ-5D index population norms (UK-specific TTO value sets) according to age

18-24	25-34	35-44	45-54	55-64	65-74	75+	Total
0.940	0.927	0.911	0.847	0.799	0.779	0.726	0.856

EuroQol. Self-Reported Population Health: An International Perspective based on EQ-5D. https://eq-5dpublications.euroqol.org/download?id=0_54006&fileId=54415. Accessed June 28, 2018.

Given that patients in COMPASS are aged 68 at entry of the model, a multiplier is considered:

- 1 for all ages until 74
- 0.932 thereafter (0.726/0.779 = 0.932)

Costs and resource use

B11. The scenario for treatment interruption appears to result in higher costs for aspirin and similar costs for rivaroxaban. It is unclear why this should be so, if as stated in the report, treatment is interrupted for 1 year after an MI, 3 months after an acute intracranial haemorrhage and 1 month after a major bleed. Please explain how this scenario has been implemented and comment on whether these results are counter-intuitive.

The treatment interruption scenario is implemented as follows:

- Treatment interruption for one year following an MI - Patients switch to dual antiplatelet therapy (ticagrelor + aspirin) for one year, in all arms.

- Treatment interruption of 3 months after an ICH - Patients receive aspirin only, for three months. (Patients in the aspirin arm continue on aspirin).

- Treatment interruption of 1 month after a major bleed event - Patients receive aspirin only, for one month. (Patients in the aspirin arm continue on aspirin).

No adjustment on transition probabilities is considered as the transition probabilities in the aspirin arm and the HRs were calculated using the ITT dataset which already accounts for periods off-treatment.

The treatment interruption following an ICH and major bleed event do not have any impact in the aspirin arm and have a small impact, decreasing overall drug costs, in the rivaroxaban + aspirin arm as per the short interruption period. The changes in drugs acquisition costs are driven by the one-year switch to DAPT following an MI. This leads to an important per cycle cost increase in the aspirin arm (£180 per cycle for DAPT vs. £2 per cycle for aspirin) while the impact is minor in the rivaroxaban + aspirin arm (£166 vs. £180). Furthermore, the increase in the rivaroxaban + aspirin arm is somewhat offset by the decrease due to ICH and major bleed interruption as explained above. This explains the increase in costs in the aspirin arm while the costs in the rivaroxaban + aspirin arm are similar between the base case and the scenario.

B12 Please update Table 78 (page 237 of the company submission)_and the model by inflating with 2018 Personal Social Services Research Unit (PSSRU) costs.

In our submission we used 2017 PSSRU costs as the 2018 costs were not available until after the submission date. Table 23 provides the adjusted costs as requested. The updated costs are marginally lower than those using 2017 PSSRU inflation indices as a result of different methodology used by the PSSRU in the 2018 version.

Table 23. Table 78 from the submission updated using PSSRU 2018. Cost of fatal events (113)

	Value	Source
Fatal MI	£2,213.69	Walker et al. 2016. Table A5. Cost of Fatal CVD events
Fatal IS	£2,213.69	Walker et al. 2016. Table A5. Cost of Fatal CVD events
Fatal ICH	£2,213.69	Walker et al. 2016. Table A5. Cost of Fatal CVD events
Bleeding death and heart failure death	£2,213.69	Walker et al. 2016. Table A5. Cost of Fatal CVD events
CV procedure death and other CV death	£2,213.69	Walker et al. 2016. Table A5. Cost of Fatal CVD events
All CV death	£2,213.69	Walker et al. 2016. Table A5. Cost of Fatal CVD events
Sudden cardiac death	£2,213.69	Walker et al. 2016. Table A5. Cost of Fatal CVD events
Non-CV death	£1,856.68	Walker et al. 2016. Table A5. Cost of Fatal non-CVD events

B13. Please update the model and the following tables (and any other relevant table) using NHS reference costs 2017/18 – Tables 75, 76, 77, 79, 80, 81, 82, 83, 84 and 85.

Costs have been updated to use 2017/2018 NHS Reference costs and PSSRU 2018 HCHS index. The submission did not use 2017/2018 NHS Reference costs as these only became available a few days before the submission deadline.

The effect on the ICER is presented in Table 34 – to Table 41. There is a small decrease in the ICER for all analyses. Please note that the updated life tables (question B6), and corrected HR for CAD and PRF (question B7) are also incorporated in these analyses.

Table 24. Submission Table 75. Rehabilitation costs taken from England and Wales NHS Reference costs 2016/17

Event	HRG code	Description	Source	Number of days for rehabilitation	Average cost (per day)
MI	VC38Z	Rehabilitation for myocardial infarction and other cardiac disorders	REHAB	5	£279.44
IS	VC04Z	Rehabilitation for stroke	REHAB	14	£387.61
HS/ICH	VC04Z	Rehabilitation for stroke	REHAB	28	£387.61

Table 25. Submission Table 76. Cost items per health state

Code	Description	Activity	National Average Unit Cost	Source
Acute MI				
EB10A	Actual or Suspected Myocardial Infarction, with CC Score 13+	9,294	£3,408.31	NHS Reference costs 2017/18
EB10B	Actual or Suspected Myocardial Infarction, with CC Score 10-12	12,599	£2,531.37	NHS Reference costs 2017/18
EB10C	Actual or Suspected Myocardial Infarction, with CC Score 7-9	13,622	£2,130.51	NHS Reference costs 2017/18
EB10D	Actual or Suspected Myocardial Infarction, with CC Score 4-6	13,959	£1,855.95	NHS Reference costs 2017/18
EB10E	Actual or Suspected Myocardial Infarction, with CC Score 0-3	9,922	£1,617.18	NHS Reference costs 2017/18
Weighted average			**£2,265.21**	
VC38Z	Rehabilitation for Acute Myocardial Infarction or Other Cardiac Disorders	5	£279.44	NHS Reference costs 2017/18
Total cost			***£3,662.42***	
Post-acute MI				
			£514.14	Walker et al, 2016 Table A5 – cost in subsequent 90-day periods
Acute IS				
AA22C	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 14+	2,068	£6,543.53	NHS Reference costs 2017/18
AA22D	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 11-13	1,781	£4,369.08	NHS Reference costs 2017/18
AA22E	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 8-10	2,136	£3,650.54	NHS Reference costs 2017/18
AA22F	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 5-7	2,802	£3,206.64	NHS Reference costs 2017/18

Code	Description	Activity	National Average Unit Cost	Source
AA22G	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 0-4	4,662	£2,364.26	NHS Reference costs 2017/18
Weighted average			**£3,652.18**	
		Number of visits		
VC04Z	Rehabilitation for Stroke	14	£387.61	NHS Reference costs 2017/18
Total cost			***£9,078.69***	
Post-acute IS				
			£478.87	Walker et al, 2016 Table A5 – cost in subsequent 90-day periods
Acute ICH				
AA23C	Haemorrhagic Cerebrovascular Disorders with CC Score 14+	1,224	£6,961.88	NHS Reference costs 2017/18
AA23D	Haemorrhagic Cerebrovascular Disorders with CC Score 10-13	1,541	£4,426.03	NHS Reference costs 2017/18
AA23E	Haemorrhagic Cerebrovascular Disorders with CC Score 6-9	2,160	£3,492.05	NHS Reference costs 2017/18
AA23F	Haemorrhagic Cerebrovascular Disorders with CC Score 3-5	1,522	£3,017.29	NHS Reference costs 2017/18
AA23G	Haemorrhagic Cerebrovascular Disorders with CC Score 0-2	994	£3,040.75	NHS Reference costs 2017/18
Weighted average			**£4,098.84**	
		Number of visits		

Code	Description	Activity	National Average Unit Cost	Source
VC04Z	Rehabilitation for Stroke	28	£387.61	NHS Reference costs 2017/18
Total cost			***£14,951.87***	
Post-acute ICH				
			£716.16	Walker et al, 2016 Table A5 – cost in subsequent 90-day periods

Table 26. Submission Table 77. Cost of revascularisation

Currency Code	Currency Description	Activity	National Average Unit Cost
EY40A	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	752	£7,461.97
EY40B	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	1,335	£5,295.52
EY40C	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	3,165	£4,363.42
EY40D	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	3,061	£3,712.94
EY41A	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	1,307	£6,525.55
EY41B	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	2,802	£4,488.03
EY41C	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	9,037	£3,492.95
EY41D	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	10,510	£3,050.64
Weighted average		**58.9%**	£3,834.62
ED22A	Complex, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 11+	113	£17,687.26
ED22B	Complex, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 6-10	81	£16,330.70
ED22C	Complex, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 0-5	33	£13,254.26
ED23A	Standard, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 11+	230	£16,183.49
ED23B	Standard, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 6-10	239	£12,550.98
ED23C	Standard, Coronary Artery Bypass Graft with Single Heart Valve Replacement or Repair, with CC Score 0-5	134	£11,399.10
Weighted average		**5.5%**	£14,467.72
Total cost			**£3,055.96**

Table 27. Submission Table 79. Cost of major non-fatal extracranial bleed

Code	Description	Activity	National Average Unit Cost
FE02A	Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 3+	695	£3,479.92
FE02B	Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 1-2	2,194	£1,054.65
FE02C	Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 0	4,141	£790.77
FF52A	Intermediate Therapeutic General Abdominal Procedures, 19 years and over, with CC Score 3+	892	£4,663.58
FF52B	Intermediate Therapeutic General Abdominal Procedures, 19 years and over, with CC Score 1-2	1,269	£3,171.61
FF52C	Intermediate Therapeutic General Abdominal Procedures, 19 years and over, with CC Score 0	2,592	£2,041.77
FD03A	Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+	1,123	£5,586.36
FD03B	Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4	1,026	£3,613.00
FD03C	Gastrointestinal Bleed with Single Intervention, with CC Score 8+	1,576	£3,800.54
FD03D	Gastrointestinal Bleed with Single Intervention, with CC Score 5-7	2,385	£2,748.21
FD03E	Gastrointestinal Bleed with Single Intervention, with CC Score 0-4	5,986	£2,199.31
FD03F	Gastrointestinal Bleed without Interventions, with CC Score 9+	4,516	£1,890.35
FD03G	Gastrointestinal Bleed without Interventions, with CC Score 5-8	16,126	£1,260.48
FD03H	Gastrointestinal Bleed without Interventions, with CC Score 0-4	57,795	£783.00
FF05Z	Intermediate Upper Gastrointestinal Tract Procedures, 19 years and over	26,996	£280.21

FE22Z	Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over	202,176	£438.05
FE20Z	Therapeutic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over	24,038	£667.19
FF04A	Major, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 7+	488	£7,777.46
FF04B	Major, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 4-6	674	£5,751.38
FF04C	Major, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 2-3	1,248	£4,801.89
FF04D	Major, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 0-1	2,503	£3,816.97
Weighted average			**£739.86**
Total	**Includes cost of reversal agents – see Miscellaneous costs and resource use (page 246)** **Prothrombin complex (HICD0308 £391) for 2.1% of patients**		**£747.90**

Table 28. SubmissionTable 80. Cost of acute limb ischaemia

Currency Code	Currency Description	Activity	National Average Unit Cost
YR23A	Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 5+	780	£5,095.24
YR23B	Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4	862	£3,031.79
YR10A	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 6+	795	£5,741.83
YR10B	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 3-5	613	£2,564.35
YR10C	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 0-2	574	£1,811.28
YR11A	Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 9+	1,725	£6,706.58
YR11B	Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 6-8	1,729	£3,133.92
YR11C	Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 3-5	3,652	£2,076.15
YR11D	Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 0-2	3,842	£1,465.59
YR12Z	Percutaneous Transluminal Angioplasty with Insertion of Stent Graft into Peripheral Blood Vessel	530	£5,808.86
YR13Z	Percutaneous Transluminal Angioplasty with Insertion of, Drug-Eluting, Coated or Embolic Protection Stent, into Peripheral Blood Vessel	909	£3,992.99
YR14A	Percutaneous Transluminal Angioplasty with Insertion of Multiple Metal Stents into Peripheral Blood Vessels, with CC Score 3+	918	£5,211.82
YR14B	Percutaneous Transluminal Angioplasty with Insertion of Multiple Metal Stents into Peripheral Blood Vessels, with CC Score 0-2	469	£2,882.42
YR15A	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 6+	1,111	£5,916.03

YR15B	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 3-5	1,421	£2,825.97
YR15C	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 0-2	1,458	£2,097.43
YQ13A	Bypass to Tibial Arteries with CC Score 7+	216	£10,583.82
YQ13B	Bypass to Tibial Arteries with CC Score 0-6	267	£8,726.18
Weighted average			**£3,432.47**

Table 29. Submission Table 81. Major amputation inpatient procedure costs

Currency Code	Currency Description	Activity	National Average Unit Cost
YQ20A	Amputation of Multiple Limbs with CC Score 10+	355	£23,911.71
YQ20B	Amputation of Multiple Limbs with CC Score 0-9	176	£16,444.54
YQ21A	Amputation of Single Limb with Other Blood Vessel Procedure, with CC Score 10+	354	£19,650.16
YQ21B	Amputation of Single Limb with Other Blood Vessel Procedure, with CC Score 0-9	304	£15,547.76
YQ22A	Amputation of Single Limb with CC Score 10+	1,549	£12,658.72
YQ22B	Amputation of Single Limb with CC Score 0-9	1,696	£8,355.37
YQ23A	Multiple, Amputation Stump or Partial Foot Amputation Procedures, for Diabetes or Arterial Disease, with CC Score 8+	323	£12,049.28
YQ23B	Multiple, Amputation Stump or Partial Foot Amputation Procedures, for Diabetes or Arterial Disease, with CC Score 0-7	199	£5,412.48
Weighted average			£12,472.49
VC14Z	Rehabilitation for Amputation of Limb		£438.49
Total			**£12,910.98**

Table 30. Submission Table 82. Estimated cost for major amputation equipment

Equipment type	Utilisation rate		Unit cost		Cost
	Value	Source	Value	Source	
Wheelchair	79.20%	NCEPOD Report (115) (Table 8.5 and 8.14)	£429.78	NHS reference costs 2017/2018 (116) (community health service_ WC01 and WC05)	£340.39 (utilisation rate x unit value)
Prosthesis	20.80%	Assumption (100-79.20)	£3,383.03	Wright 2013(117) Appendix Table 11	£703.67 (utilisation rate x unit value)

Table 31. Submission Table 83. Estimated rehabilitation costs

Equipment	% of patients benefiting		Number of contacts		Unit cost		Cost
	Value	Source	Value	Source	Value	Source	
Physiotherapy	95.7%	NCEPOD Report(115) Table 8.5	24	Guidelines (118) Page 13	£54.91	NHS reference costs (1)	£1,1261.16
Occupational therapy	90.9%	NCEPOD Report(115) Table 8.5	5	Guidelines (118) Page 13	£73.25	NHS reference costs (2)	£332.93

(1) NHS reference costs 2017/2018(116) (total outpatient attendances _ 650)

(2) NHS reference costs 2017/2018(116) (total outpatient attendances _ 651)

NCEPOD – National Confidential Enquiry into Patient Outcome and Death

The total cost of a major amputation is estimated at £15,549.12.

Table 32. Submission Table 84. Minor amputation costs

Currency Code	Currency Description	Activity	National Average Unit Cost
YQ24B	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with Other Open Blood Vessel Procedure, with CC Score 0-7	191	£11,282.53
YQ25A	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with Imaging Intervention, with CC Score 8+	440	£12,776.19
YQ25B	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with Imaging Intervention, with CC Score 0-7	202	£8,315.79
YQ26A	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with CC Score 8+	2,639	£6,440.11
YQ26B	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with CC Score 5-7	1,610	£4,003.05
YQ26C	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with CC Score 0-4	2,010	£2,809.41
Weighted average			**£5,434.80**

Table 33. Submission Table 85. VTE costs

Currency Code	Currency Description	Activity	National Average Unit Cost
DZ09J	Pulmonary Embolus with Interventions, with CC Score 9+	877	£5,073.26
DZ09K	Pulmonary Embolus with Interventions, with CC Score 0-8	785	£3,110.40
DZ09L	Pulmonary Embolus without Interventions, with CC Score 12+	3,366	£2,973.37
DZ09M	Pulmonary Embolus without Interventions, with CC Score 9-11	5,549	£2,029.93
DZ09N	Pulmonary Embolus without Interventions, with CC Score 6-8	10,079	£1,531.01
DZ09P	Pulmonary Embolus without Interventions, with CC Score 3-5	15,985	£1,083.96
DZ09Q	Pulmonary Embolus without Interventions, with CC Score 0-2	14,366	£767.41
Weighted average	**Pulmonary Embolus**	**51,007**	**£1,410.51**
YQ51A	Deep Vein Thrombosis with CC Score 12+	4,081	£1,276.12
YQ51B	Deep Vein Thrombosis with CC Score 9-11	4,479	£861.93
YQ51C	Deep Vein Thrombosis with CC Score 6-8	6,302	£804.41
YQ51D	Deep Vein Thrombosis with CC Score 3-5	10,783	£611.38
YQ51E	Deep Vein Thrombosis with CC Score 0-2	17,361	£382.53
Weighted average	**Deep Vein Thrombosis**	**43,006**	**£636.46**
Weighted average	**VTE (PE+DVT)**		**£1,056.42**

COMPASS population

Table 34. Submission Table 92. Base case results – COMPASS population: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin monotherapy	£7,260	11.74	9.35	-			
Rivaroxaban + aspirin	£10,842	11.99	9.57	£3,582	0.247	0.219	£16,326

Table 35. Submission Table 93. Base case results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor + aspirin	£8,889	11.82	9.41	-			
Rivaroxaban + aspirin	£10,842	11.99	9.57	£1,953	0.170	0.155	£12,581

CAD and PAD subgroup

Table 36. submission Table 94. Base case results – CAD and PAD subgroup: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin monotherapy	£9,571	10.76	8.13	-			
Rivaroxaban + aspirin	£12,476	11.26	8.53	£2,905	0.498	0.398	£7,309

Table 37. Submission Table 95. Base case results – CAD and PAD subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor + aspirin	£11,257	11.11	8.39	-			
Rivaroxaban + aspirin	£12,476	11.26	8.53	£1,219	0.148	0.135	£9,047

CAD and HF

Table 38. Submission Table 96. Base case results – CAD and HF subgroup: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin monotherapy	£6,256	10.45	8.09	-			
Rivaroxaban + aspirin	£9,925	11.26	8.74	£3,668	0.812	0.643	£5,702

Table 39. Submission Table 97. Base case results – CAD and HF: rivaroxaban + aspirin vs ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor + aspirin	£7,872	10.60	8.21	-			
Rivaroxaban + aspirin	£9,925	11.26	8.74	£2,053	0.662	0.524	£3,920

CAD and PRF

Table 40. Submission Table 98. Base case results – CAD and PRF subgroup: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin monotherapy	£7,855	9.68	7.39	-			
Rivaroxaban + aspirin	£10,431	10.00	7.65	£2,576	0.321	0.267	£9,661

Table 41. Submission Table 99. Base case results – CAD and PRF: rivaroxaban + aspirin vs ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor + aspirin	£9,263	9.71	7.41	-			
Rivaroxaban + aspirin	£10,431	10.00	7.65	£1,168	0.292	0.241	£4,841

References

1. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanas F, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England). 2017.
2. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. Med Decis Making. 2018;38(2):200-11.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [ID1397]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Anticoagulation UK
3. Job title or position	Project Manager (Consultant)
4a. Brief description of the organisation (including who funds it). How many members does it have?	Independent charity organisation (reg 1090250) Founded in 2000 Subscribers – fee to join, network of supporters, volunteer regional contacts and Telephone helpline ACUK aims include the prevention of thrombosis and provision of information, education and support to people on anticoagulation therapy ACUK work with patients, medical professionals, other charities, government and industry. ACUK provides the secretariat for the All Party Parliamentary Thrombosis Group which hold an annual meeting and chaired by Lyn Brown MP
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Patient education days, helpline activity. Direct approach to ACUK, emails, letters. HealthUnlocked forum(dedicated ACUK platform)** **ACUK provide representatives to speak at various healthcare conferences throughout the year e.g National Training Centre for Anticoagulation courses run at Warwick Medical School, Course Director Professor David Fitzmaurice**

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients diagnosed with PAD or CAD will naturally be concerned about their risk of heart attack or stroke and these health issues can be challenging to manage and require the patient, family or carer to consider making significant adjustments to lifestyle, diet and exercise to reduce risk along with taking medications long term to prevent recurrences and worsening of the diseases.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	We have no specific knowledge on patient's viewpoint in PAD or CAD as difficult to elicit. We do hear from patients who are placed on anticoagulation therapy and have questions or concerns around their treatment, commonly around choice of ac on offer, side effects and whether it will be necessary for short or long term. Most common worries are blood clots and stroke risk. From our experience, patients rely on their healthcare professionals to present the best options for prevention and treatment of their conditions and are guided by them. The majority of patients we interact with are unaware of the NICE guidelines for the management of their treatments and we would always suggest that they look at these and discuss with their clinician if they had any questions. With PAD and CAD and the current treatment regimes, the key factors must be that patients understand why they are being prescribed dual therapy and how the different drugs work. This can assist with drug compliance.
8. Is there an unmet need for patients with this condition?	Men who appear at higher risk of CHD and our aging population

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We have not solicited feedback directly from patients or carers. ACUK General view point Having reviewed ' Rivaroxaban with or with or without aspirin in patients with stable coronary artery disease: an international, randomised, doubleblind, placebo –controlled trial' - Connolly et al, Lancet 2018; 391:205 18, it appears that in patients with stable coronary artery disease, the addition of rivaroxaban lowered major vascular events giving added protection for high risk patients, potentially reducing morbidity and mortality in a disease area which is one of the leading causes of death in the UK and with a significant population size of 1.8 million having CHD diagnosis. Reducing serious health outcomes such as stroke and heart attacks which can greatly affect individuals across every aspect of their wellbeing and continued health should be considered as will also reduce burden to families, carers and NHS related costs
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We note that the study outcomes indicate that there is an increased bleeding risk but no significant increase in iantracranial bleeding or other critical organ bleeding. **This would need to be discussed appropriately with patients to ensure risk and benefit fully explained.** Patients will reduced kidney function may not be suitable? Dosing and adherence – 2.5mg bd. Patients would need to be educated as to importance of taking these medications as directed due to the short half life and effectiveness Not suitable for people with hepatic disease?

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All those it appears noted in the final scope. We are an aging population and therefore anyone presenting with CHD and is eligible for treatments should be able to access
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Raising awareness of CAD and PAD and promoting healthy lifestyle and exercise to combat are key to encouraging the population to manage their CHD risk.** Treatment is key when diagnosis made and should be complemented throughout by pathways to support patients at risk in making adjustments to lifestyle if assessed as being a contributor to CHD

Other issues	
13. Are there any other issues that you would like the committee to consider?	None at this point. Our representations are based on our general opinion around this area.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission:	

- A treatment pathway which can reduce life threatening events caused by CAD or PAD
- Rivaroxaban as an anticoagulant does not need regular monitoring
- Patient reassurance for protection against stroke/heart attack
- Add to medication regime – ensuring emphasis on compliance need
- Patient needs to understand bleeding risk v benefits

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [ID1397]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Jagdeep S. Singh**
2. Name of organisation	**British Cardiovascular Society**

3. Job title or position	**Cardiology Specialist Registrar** Member of BCS Guidelines and Practice Committee
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**We represent the majority of UK consultant cardiologists, registrars, GPs with special interest, nursing and other professionals with interest in cardiovascular medicine. We are affiliated with 18 unique organisations that work in various areas of cardiovascular medicine including research. We are funded by**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To reduce major adverse cardiovascular (CV) events in patients with stable coronary artery disease (CAD) or peripheral arterial disease (PAD). These events include ischaemic stroke, CV death, myocardial infarction (MI) and major adverse limb events including major amputations.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	With regard to CV outcomes, one would consider at least 20% relative risk reduction (an arbitrary figure based around the risk reductions of other CV drugs). Importantly, these effects should also be seen in important components of composite outcomes. These improvements should not be at the cost of potential complications. In this particular case, one would expect to see reductions in risk of MI and CV death and this should not be at the cost of increased major bleeding events. Will also expect to see a healthy difference between numbers needed to treat vs numbers needed to harm.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Current guideline-directed therapies for stable CAD are very efficacious, therefore any new therapy may only add an incremental benefit. On the other hand, patients with PAD have high risk of disability and loss of limb with limited treatment options so there may be an area of unmet need in this particular group of patients.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Using oral medications such as an antiplatelet agent (aspirin / clopidogrel / ticagrelor / prasugrel), statins, beta-blockers and ACE-inhibitors.
• Are any clinical guidelines used in the treatment of the	Yes. CG 172, CG 147 and CG 126.

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway is very well established and accepted. There is little variation in current practice, mainly around individualising therapy for particular patient risks / tolerances / co-morbidity. *Note this author practices medicine in Scotland.
• What impact would the technology have on the current pathway of care?	This technology will add another medication to be considered. It will not change the structure of the pathway *per se,* however there will be additional considerations around risk (e.g. bleeding risk / liver disease), patient selection (high vs low risk), timing of drug initiation (mean start time in clinical trial was 7 years after initial diagnosis) and by extension, who will start the drug (GP vs cardiologist).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Will likely be used in the same way but will depend on the restrictions / limitations placed if this drug is eventually licenced for use.
• How does healthcare resource use differ between the technology and current care?	There should not be any difference.
• In what clinical setting should the technology be used? (For example,	Considering this drug is aimed at patients with stable CAD and PAD, it will likely be used mainly in primary care or specialist clinics. However, given the potentially serious bleeding risks involved, one suspects GPs may be reluctant to start this medication without support / advice from specialists.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment may be required around training and disseminating information on indications and patient selection criteria and education about potential risks. It is also important to note that unlike in ATLAS TIMI 51 which used aspirin doses between 75-100mg, the COMPASS trial used only 100mg doses of Aspirin. This means patients being considered for this drug will require a different dose of aspirin than currently being used. This may require substantial costs in procurement and stocking.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	No Benefits are negligible and primarily driven by reduction in ischaemic stroke. (?High proportion of occult atrial fibrillation may have contributed) Number needed to treat is 77 vs number needed to harm of 83. (based on main COMPASS publication - Eikelboom et al. NEJM, Oct 2017)
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Not in patients with CAD, however there may be quality of life improvements in patients with PAD. 56% relative risk reduction in major adverse limb events including major amputation.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As above, patients with PAD may derive more meaningful benefit.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Yes, the following issues can be anticipated: • Polypharmacy and associated compliance issues. Patients will already be on multiple medications for CAD, this technology adds a further tablet twice a day. • Patients may have to be switched to 100mg doses of aspirin instead of 75mg. This will add complexity / confusion. May also require addition of proton pump inhibitors, especially in patients >75 yrs in whom a doubling of major bleeding risk was seen (Figure S2, supplementary index Eikelboom et al. NEJM, Oct 2017) • Deciding who (GP / Cardiologist) will start this drug, when and in whom may be difficult to organise.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. There should be clear guidance on which group of patients this should be started on. It should not require any additional testing.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No all potential benefits will be included in QALY calculations.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Not with regard to CAD. Current evidence-based therapy is very effective. The incremental benefits seen do not justify the increased risk of complication, cost and complexity in delivering this technology. Additionally, the trial underpinning the evidence was stopped early due to efficacy benefits and the authors accept that in such situations the treatment effect may be overestimated. There may, however, be a case to be made for benefits in patients with PAD.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	It may potentially address the increased risk of CV / limb events in patients with PAD.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects of this technology – major bleeding – may have significant effects on the patient's quality of life. Although there was no difference in fatal bleeding, there was an 88% increase in 'other major bleeding' which are bleeding events into critical organs and / or requiring at least 2 units of transfusion. Importantly, this measure was not included in the calculation of net clinical benefit. These events cause significant morbidity (hospitalisation and additional procedures) and may result in permanent disability (non-fatal but large intracranial haemorrhage)
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, except for the use of 100mg aspirin rather than 75mg.

• If not, how could the results be extrapolated to the UK setting?	It could be argued that both 75mg and 100mg represent low dose aspirin and there should not be much resistance to this argument.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Rates of major adverse cardiovascular and limb events and their component categories. Yes, all these important outcomes were measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance?	
21. How do data on real-world experience compare with the trial data?	There is limited real world experience. This technology has not been approved by the FDA for use in the indication being considered. It was only recently approved by the EMC. Noting that previous approvals by EMC and NICE for the use of this technology in ACS (TA 335) has not been widely adopted by the clinical community, one suspects there is very limited experience in this particular indication of CAD.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Evidence suggests negligible benefit for patients with coronary artery disease but potentially larger benefit for those with peripheral arterial disease • Potential side-effects may confer significant morbidity and permanent disability and this risk may have been underestimated in the clinical trial • Implementation may require investment around training and potential changes to current pathways / practice • Patient selection and risk stratification may be difficult and complex • This technology will contribute to polypharmacy and may result in reduced compliance

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [ID1397]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists and British Society for Haematology**

3. Job title or position	**Consultant Haematologist & Honorary senior lecturer**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation, whose mission is to maintain the internationally renowned standards and reputation of British pathology, through training, assessments, examinations and professional development, to the benefit of the public. It is a registered charity with over 11,000 members work in hospital laboratories, universities and industry worldwide. The British Society for Haematology is the UK professional organisation for doctors specialising in haematology. In addition to representing the interests of its members, it publishes the British Journal of Haematology and issues BSH Guidelines on haematological conditions
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Prevention of thrombotic complications from cardiovascular disease

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in deaths and number of thrombotic events
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Coronary artery disease and peripheral vascular disease are two important disease conditions that affect many people with increasing age. Prevention of major cardiovascular events and complications in these patients is an important clinical need. Although there are several therapies available for use in this situation, many patients continue to have complications and have adverse clinical outcome
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently many patients are on single or dual antiplatelet treatment. In addition to life style modification such as regular exercise, dietary changes and help to stop smoking for people who smoke, NICE clinical guideline 172 recommends that everyone who has an acute myocardial infarction should be offered treatment with a combination of an angiotensin-converting enzyme inhibitor, dual antiplatelet therapy (aspirin plus a second antiplatelet agent), a beta-blocker and a statin. The guideline recommends that aspirin should be offered indefinitely after a myocardial infarction. NICE technology appraisal guidance 420 also recommends ticagrelor in combination with aspirin for people who

	had a myocardial infarction and who are at high risk of a further event. Ticagrelor should be offered for a maximum of 3 years. NICE clinical guideline 172 also recommends clopidogrel monotherapy as an alternative for people with aspirin hypersensitivity. People with lower limb PAD are considered separately in NICE clinical guideline 147. The recommendations align with NICE clinical guideline 172 and additionally recommend clopidogrel as an option to prevent occlusive vascular events, in line with NICE technology appraisal guidance 210. Some patients may be on warfarin instead of dual antiplatelet treatment and some high-risk patients on aspirin and warfarin
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines i.e NICE clinical guidelines (147, 172, technology appraisal guidance 420 etc)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. Fairly well defined but there is uncertainty about what to do for patients who also require anticoagulation for Atrial Fibrillation
• What impact would the technology have on the current pathway of care?	1. Might improve outcome (efficacy) 2 Simplify the pathway and potentially no longer difference in patients with and without AF

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Rivaroxaban in combination with aspirin will offer an additional treatment option for prevention of major adverse cardiovascular events If licensed in patients with CAD or PAD.
• How does healthcare resource use differ between the technology and current care?	As above. This will be an additional treatment option for prevention of major adverse cardiovascular events if licensed in patients with CAD or PAD.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	There are larger number of patients in primary and secondary care including specialist clinics who will benefit from this
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Financial investment (it is an addition to existing treatment) and education
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Those patients who continue have complications with aspirin alone may have reduced or no complications with combination with low dose rivaroxaban

• Do you expect the technology to increase length of life more than current care?	Yes, probably by reducing life threatening the thromboembolic events
• Do you expect the technology to increase health-related quality of life more than current care?	Yes By reducing thrombotic /ischaemic events (i.e MI, stroke, peripheral ischemia)
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Technology will be beneficial to patients on aspirin alone rather than in patients on dual antiplatelet treatment or patients on antiplatelet treatment and anticoagulant already
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	It may be potentially more difficult unless the drug specific antidote for rivaorxaban is approved and available in UK. Reversing dual antiplatelet is already difficult and it is not clear there is any effective strategy. The cost of the drug specific antidote for rivaorxaban would need to be considered.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients at high risk of bleeding or on dual antiplatelet treatment should not be started the rivaroxaban Patients with moderate renal impairment may need regular renal function assessment and patients with severe heart failure and severe renal impairment should not be given technology drug (rivaroxaban)
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This may have substantial benefit to patients on aspirin alone by reducing or preventing thromboembolic complications
• Is the technology a 'step-change' in the management of the condition?	Yes in a selected group of patients with the condition
• Does the use of the technology address any particular unmet need of the patient population?	Yes, patients on low dose aspirin alone with recurrent events and unable to take dual antiplatelet treatment
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Rivaroxaban low dose may cause increase risk of bleeding in some patients especially those with moderate renal impairment.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Clinical trials may differ from standard clinical practice as the patients for the trials are selected more carefully than the clinically practice and there are sets of inclusion and exclusion criteria. In clinical practice sometime, we may have to deviate from these on individual patient risk and benefits. However, in majority of the cases, clinical trials reflect the UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Safety (mainly clinically relevant bleeding and major bleeding) and efficacy (recurrent thrombotic events : myocardial infarction (MI), stroke)or cardiovascular death
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	-
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	-

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	-
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease Eikenboom N Engl J Med 2017; 377:1319-30.
21. How do data on real-world experience compare with the trial data?	-
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	-
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to	

be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Efficacy by reducing the thromboembolic complications
- Simplifying pathways
- Management of bleeding events related to technology drug including the cost
- Patient exclusion from the technology drug (Patients with severe heart failure and severe renal impairment
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease [ID1397]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Keith AA Fox**

2. Name of organisation	**Professor of Cardiology, University of Edinburgh (Emeritus), former President of the British Cardiovascular Society, former Chair of the Clinical and Scientific Programme of the European Society of Cardiology, Current President of ASH Scotland (Action on Smoking and Health).** **I am Co-Chair, with Salim Yusuf, of the Steering Committee of the COMPASS Trial.**
3. Job title or position	**Professor of Cardiology, University of Edinburgh (Emeritus)**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? **X** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission?	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X** other I know that a submission has been made by Bayer, the sponsor of the COMPASS Trial. However, that submission has not been shared with me.
6. If you wrote the organisation submission and/ or do not	☐ Not applicable, I did not write that submission.

have anything to add, tick here.	
The aim of treatment for this condition	
7. What is the main aim of treatment?	Context: for a population with documented vascular disease and features of higher risk, to reduce the burden of major cardiovascular adverse outcome events. To qualify for inclusion, the patients had to have had documented coronary and/or peripheral arterial disease. The primary outcome was the composite of cardiovascular death or myocardial infarction or stroke. The main aim was to test the hypothesis that rivaroxaban 2.5mg bd plus aspirin (or rivaroxaban 5mg bd alone) was superior to aspirin in the above population. Only the "dual pathway" therapy (rivaroxaban 2.5mg bd plus aspirin) was superior to aspirin alone.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	By design, the primary aim was to reduce cardiovascular death or myocardial infarction or stroke (the primary composite endpoint of the COMPASS trial). The trial was terminated early by the DSMB (at a mean of 23 months) because the primary endpoint showed greater than a four standard deviation benefit (the predefined stopping rule). At completion a highly significant 24% relative risk reduction (1.4% absolute risk reduction) in the primary endpoint was demonstrated. The major impact was on stroke reduction (42% relative risk reduction, 0.7% absolute risk reduction) and the impacts on cardiovascular mortality and on total mortality were also statistically significant, and of clinical importance (Eikelboom JW et al N Engl J Med. 2017 Oct 5;377(14):1319-1330). In addition to the reduction in cardiovascular death, the stroke reduction is of major clinical significance as it impacts on disability and personal independence. It is important to note that the outcomes achieved were on top of a high standard of guideline indicated secondary prevention (90% were on lipid lowering therapy, 71% on ACE/ARB, 70% were on a beta blocker). Although 75% of the study population had prior hypertension, the mean blood pressure at randomisation was 136/77 and mean total cholesterol at randomisation was 4.2mmol/L (NEJM 2017 377, 1319-30). Thus by modern guideline indicated standards these were a well-treated population. The key point is that the outcomes achieved were on top of a standard that most clinicians would previously have judged to be highly acceptable. Additional pre-specified endpoints included the impact on major adverse limb events (MALE) and on amputations, especially relevant in the population with peripheral artery disease. Both of these additional endpoints were reduced by the dual pathway COMPASS regimen (rivaroxaban 2.5mg bd plus aspirin, R+A) versus aspirin alone (Anand SS et al Lancet. 2018 Jan 20;391(10117):219-229).

	Although these peripheral artery outcomes were infrequent, they are of major significance for patients with peripheral arterial disease as they impact on the independence and disability in affected individuals. Consistent with the findings of prior trials of more intensive anti-thrombotic therapy, or dual anti-platelet therapy, there was an increase in major bleeding (ISTH modified; a more inclusive definition 3.1% R+A versus 1.9% aspirin, hazard ratio 1.70). There was no significant excess in fatal bleeding, nor in intracranial bleeding. The predefined outcome of net clinical benefit (CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ) occurred significantly less often in the R+A group versus aspirin alone (4.7% versus 5.9% respectively, a 20% relative risk reduction (NEJM 2017 377, 1319-30).
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	As demonstrated in the previous REACH registry, there is an overlap between patients with just clinically manifest coronary disease and those with peripheral arterial disease (including carotid disease). In addition many patients will have occult vascular disease in more than one vascular territory. Approximately 5 to 10% of the REACH registry patients had recurrent cardiovascular events after one year and patients continue to accrue events over time (JAMA 2010;304:1350-7). The frequency of cardiovascular events was increased in those with concomitant risk factors for vascular disease, or disease manifest in more than one territory. Large-scale data from England, France Sweden and the US in CAD populations have demonstrated similarly increased rates of cardiovascular events over time (adjusted for baseline risk) across these four countries. Beyond the first year after myocardial infarction, there is a further 20% mortality rate in the subsequent 3 years (Eur Heart J – QCCO (2016) 2, 172–183). Even in very well treated trial populations (with some higher risk patients excluded) there remains a 15% rate of death or MI at 3 years, despite very high rates of secondary prevention (TIMI 52 Trial JAMA. 2014;312(10):1006-1015). Thus, despite current guideline indicated secondary prevention measures, patients with coronary or peripheral artery disease continue to accrue serious adverse cardiovascular events. A recent review by Fox KAA (myself), Metra M, Morais JJ and Atar D has challenged the previously accepted concept of stable coronary disease ("The Myth of stable coronary artery disease", Nature Reviews Cardiology, in press March 2019) as such higher risk patients continue to experience adverse cardiovascular complications. In summary, there is substantial evidence from large scale registries and from clinical trials that cardiovascular events continue to accrue among patients with vascular disease, despite current secondary prevention therapy and lifestyle advice and guidance.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	For patients with documented coronary artery disease (NICE CG172) or peripheral artery disease the guideline based standard of care for anti-thrombotic therapy is single anti-platelet therapy (low dose aspirin is the standard of care in the NHS and internationally, and for PAD clopidogrel alone is an option in some guidelines).
Are any clinical guidelines ...?	Yes, anti-thrombotic for coronary artery disease secondary prevention (NICE CG 172) recommends aspirin indefinitely. Aspirin (100mg daily) was the comparator in the double blind COMPASS Trial.
Is the pathway of care well defined ...?	Yes, the pathways of care for acute myocardial infarction and for established coronary or peripheral artery disease are well defined. For coronary disease this is based on multiple randomised trials. Immediately after myocardial infarction a patient is usually managed with dual anti-platelet therapy (DAPT) and such patients were not eligible for the COMPASS trial. Such a patient would only have been eligible for the COMPASS regimen once they no longer required DAPT. The existing pathways for CAD are widely implemented in the UK as seen in the evidence from registry studies including NICOR (National Cardiac Audit Programme report 2018) https://www.nicor.org.uk/national-cardiac-audit-programme/
What impact would the technology have on the current pathway of care?	The COMPASS regimen (rivaroxaban 2.5mg bd plus aspirin) would be substituted for aspirin alone in suitable patients with documented vascular disease. Implementation of the COMPASS dual pathway regimen could be done at out patient review, or secondary prevention review, in suitable patients. Such higher risk vascular patients could be identified in advance, at the time of presentation with a vascular event or an elective vascular procedure. For a patient requiring DAPT for a period of time (after acute coronary syndrome or after stent placement), the patient would only become eligible for the COMPASS regimen at the end of DAPT treatment. Patients requiring full anticoagulation (for example for atrial fibrillation or for prosthetic valves or rheumatic heart disease, or thrombo-embolic disease) would not be eligible.

11. Will the technology be used in the same way as current care ...	Yes, rivaroxaban 2.5mg bd plus aspirin would be used in place of aspirin alone. As higher rates of bleeding were observed with this therapy, compared with aspirin alone, the patients would be reviewed at the same time as their reviews for the remainder of secondary prevention therapy (eg statins, ACE/ARB, beta blocker). Patients should be advised, in advance, about the steps that the patient should take in the event of a bleeding complication.
How does healthcare resource ...	Rivaroxaban 2.5mg bd plus aspirin would be used in place of aspirin alone (see also comments above).
In what clinical setting should the technology be used?	Implementation of the COMPASS dual pathway regimen could be done at out patient review, or secondary prevention review, in suitable patients. Such higher risk vascular patients could be identified in advance, at the time of presentation with a vascular event or an elective vascular procedure. For a patient requiring DAPT for a period of time (after acute coronary syndrome or after stent placement), the patient would only become eligible for the COMPASS regimen at the end of DAPT treatment. Patients requiring full anticoagulation (for example for atrial fibrillation or for prosthetic valves or rheumatic heart disease, or thrombo-embolic disease) would not be eligible.
• What investment is needed to introduce the technology?	No additional facilities are required as the therapy would be implemented alongside current secondary prevention measures. Additional patient education would be required, as for any new therapy, and specific guidance given about how bleeding events should be handled.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the trial evidence suggests that substantial benefits are expected in higher risk coronary or peripheral artery disease patients (please also see response to item 8). In a recent overview we have placed the results of COMPASS in the context of other anti-thrombotic options and of accepted secondary prevention measures (Fox KAA et al European Heart Journal (2018) 0, 1–8 doi:10.1093/eurheartj/ehy347). While observations across different trials must be viewed with caution, the COMPASS regimen is the only anti-thrombotic therapy to reduce cardiovascular deaths, and it has the largest impact on stroke reduction (see table 1 below). Increases in bleeding were seen for each of the intensified anti-thrombotic therapies, and with similar hazard ratios (table 2 below). Examining the COMPASS results in the context of other guideline recommended secondary prevention therapies, the results are at least as marked as for 1mmol/L LDL reduction, 10mmHg BP reduction or ACE/ARB therapy (see table 3 below). It must be noted that the COMPASS results were achieved on top of high rates of statin therapy, BP control and use of ACE/ARB inhibition and beta blockers, and against the reference anti-thrombotic therapy, aspirin.

Table 1 Efficacy: anti-thrombotic secondary prevention strategies in stable vascular disease

	CAPRIE[32] clopidogrel	CHARISMA[14] clopidogrel + aspirin	PEGASUS[18] ticagrelor 90 + aspirin	PEGASUS[18] ticagrelor 60 + aspirin	TRA2P[34] vorapaxar	COMPASS[1–3] rivaroxaban + aspirin
CV death/MI/stroke	-9%[a]	-7% (NS)	-15%	-16%	-13%	-24%
CV death	-8% (NS)	+4% (NS)	-13% (NS)	-17% (NS)	-11% (NS)	-22%
Stroke	–	-21%	-18% (NS)	-25%	-3% (NS)	-42%
MI	–	-6% (NS)	-19%	-16%	-17%	-14% (NS)
Major adverse limb events	–	-26% (NS)	-29%[b]	-10%[c] (NS)	-29%[d]	-47%
Amputations	+10.6%	-29% (NS)	-29% (NS)	-5% (NS)	-10% (NS)	-52%

Table 2 Bleeding: anti-thrombotic secondary prevention strategies in stable vascular disease

	CAPRIE[14] clopidogrel	CHARISMA[14] clopidogrel + aspirin	PEGASUS[18] ticagrelor 90 + aspirin	PEGASUS[18] ticagrelor 60 + aspirin	TRA2P[34] vorapaxar	COMPASS[1–3] rivaroxaban + aspirin
Major bleeds	-27%[a]	+43%[b]	+169%[c]	+132%[c]	+46%[d]	+70%
Severe bleed GUSTO		+25% (NS)	Not reported	Not reported	+66%[e]	+9% (NS)
Fatal bleed		+53% (NS)	+42% (NS)	0% (NS)	+46% (NS)	+49% (NS)
ICH	-29%[a]	+4% (NS)	+44% (NS)	+33% (NS)	+94%	+16% (NS)

Table 3 Comparison of the effects of guideline indicated secondary prevention pharmacological therapies for patients with vascular disease

Outcomes	Lipid lowering[41,42] (1 mmol/L reduction in LDL)	BP lowering[43] (10 mmHg reduction in systolic BP)	ACE inhibitors[44]	Aspirin[40]	COMPASS[1–3] rivaroxaban + aspirin
MACE[a]	-21%	-20%	-18%	-19%	-24%
Mortality	-9%	-13%	-14%	-9% (NS)	-18%
Stroke	-15%	-27%	-23%	-19%	-42%
MI	-24%	-17%	-18%[b]	-20%	-14% (NS)

Do you expect the technology to increase length of life?	Yes, the evidence from the trial shows reduced mortality and cardiovascular mortality with the COMPASS dual pathway regimen compared with the guideline standard, aspirin.
Do you expect the technology	Yes, however the evidence is not yet published. The reduction in strokes and major adverse limb events and amputations will all lead to improvements in health related quality of life. The increase in bleeding is mainly reversible bleeding (predominantly GI or GU) so

to increase health-related quality of life more than current care?	should not lead to long term adverse quality of life effects. Interestingly, the GI and GU bleeding events were shown to have revealed underlying GU and GI malignancies (a hundred fold increase in the diagnosis of GU and a 20 fold increase in the diagnosis of GI cancers with the respective major bleeds). Non-GI and GU bleeds were not associated with revealing more cancers, and there is no evidence that there was an absolute increase in the frequency of cancers. (These data have been presented ESC 2018 and the manuscript is under review). With the limited data, a difference in outcomes for cancers diagnosed earlier has not yet been shown.
Are there any groups of people for whom the technology would be more or less effective?	The evidence supports the use of the COMPASS dual pathway regimen in chronic vascular patients at increased risk of vascular complications. In a recent paper (Anand SS JACC 2019 in press) we have shown that patients with vascular disease in more than one territory, or patients with CAD plus at least one key risk factor (diabetes or chronic heart failure or renal dysfunction) have the most benefit. Symptomatic peripheral arterial disease patients are already at higher risk. Patients at high bleeding irreversible risk and those who did not meet the "risk enrichment" criteria of the COMPASS would not be expected to have the same benefit.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care?	The dual pathway COMPASS regimen would replace the use of aspirin alone, in suitable patients. It would not be more difficult to initiate, but additional patient education and precautions are needed in relation to the risk of bleeding events. The patients would be reviewed as for his/her secondary prevention therapies. The very low dose non-vitamin K antagonist (rivaroxaban 2.5mg bd) is a quarter of the full anticoagulation dose used for patients with atrial fibrillation and stroke risk. However, any use of even a very low dose of anti-coagulant for secondary prevention in these vascular risk patients, in sinus rhythm, will require both clinician and patient education and guidance. Routine use of a protein pump inhibitor (PPI) was not done in the trial (it was tested in a factorial design and the PPI did not change the primary outcome, but it did reduce bleeding). Clinicians may judge that a PPI is indicated in specific patients in relation to bleeding risk, after having addressed reversible causes of bleeding (for example use of NSAIDS).
15. Will any rules be used to start or stop	No formal rules other than avoiding this therapy in patients that need full anticoagulation and those with high bleeding risk. For patients requiring DAPT with a potent P2Y12 antagonist (ticagrelor or prasugrel) I would advise initiation after the DAPT treatment has been completed. DAPT with clopidogrel and aspirin plus 2.5mg bd of rivaroxaban bd was tested in the ATLAS trial after ACS and is approved by the EMA, but not widely used.

treatment testing?	
16. Do you consider that the use of the technology ...	The impact of stroke, not only on the patient, but also on their carers is of major significance and would not be counted in direct QALY calculations. The impact of avoiding major adverse limb events in patients with peripheral arterial disease will also affect carers and so have indirect benefits on quality of life.
17. Do you consider the technology to be innovative in its potential to make a significant ...	Yes, this is the first anti-thrombotic therapy for secondary prevention that reduces cardiovascular and total mortality. The reduction in stroke was on top of high standards of secondary prevention and hypertension management (please see response to point 8). In my view, and this consistent with the view of international experts in the field, that the COMPASS regimen provides a step change in secondary prevention for higher vascular risk patients. The benefits were achieved on top of a high standard of guideline indicated secondary prevention.
• Is the technology a 'step-change' in the management of the condition?	(As above) Yes, this is the first anti-thrombotic therapy for secondary prevention that reduces cardiovascular and total mortality. The reduction in stroke was on top of high standards of secondary prevention and hypertension management (please see response to point 8). In my view, and this consistent with the view of international experts in the field, that the COMPASS regimen provides a step change in secondary prevention for higher vascular risk patients. The benefits were achieved on top of a high standard of guideline indicated secondary prevention.
Does the use of the technology address ...	Yes, please see the response to point 9. There are continuing risks of adverse cardiovascular and peripheral arterial events in patients at higher vascular risk and documented coronary or peripheral arterial disease. These are unmet needs, as the COMPASS patients were well treated with secondary prevention measures, by any international standard.

18. How do any side effects or adverse effects ...	Consistent with the findings of prior trials of more intensive anti-thrombotic therapy, or dual anti-platelet therapy, there was an increase in major bleeding (ISTH modified, using a more inclusive definition: 3.1% R+A versus 1.9% aspirin, hazard ratio 1.70). There was no significant excess in fatal bleeding, nor in intracranial bleeding. (Please also see response to point 12, above). Major bleeding was significantly increased in the first year of treatment with R+A, but not thereafter (manuscript under review). The predefined outcome of net clinical benefit (CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ) occurred significantly less often in the R+A group versus aspirin alone (4.7% versus 5.9% respectively, a 20% relative risk reduction (NEJM 2017 377, 1319-30).
Sources of evidence	
19. Do the clinical trials on the technology ...	Yes, the reference standard for antithrombotic therapy in chronic coronary vascular disease in the UK is aspirin (NICE CG 172). Clopidogrel and other agents may also be used in PAD patients depending on the clinical setting.
If not, ...	Not applicable
What, in your view, are the most important ...	The composite of cardiovascular death or MI or stroke (the primary endpoint of the COMPASS trial), the individual endpoints, and major adverse limb events and amputations were measured in the COMPASS trial. Net clinical benefit was also pre-specified and reported (NEJM 2017 Eikelboom et al).
If surrogate ...	Not applicable
Are there any adverse effects ...	None reported and none known to me

20. Are you aware ...	No, not aware of such evidence
21. Are you aware of any new evidence ...	No, not regarding ticagrelor for secondary prevention after MI (TA420), or clopidogrel (TA210). However, there are 2 more recent and relevant studies. In EUCLID (13.885 symptomatic PAD patients treated with ticagrelor versus clopidogrel) there was no benefit for ticagrelor versus clopidogrel despite the high vascular risk population (N Engl J Med 2017;376:32-40). In the SOCRATES trial (13,199 patients treated for acute stroke or TIA with aspirin versus ticagrelor), ticagrelor was not found to be superior to aspirin (N Engl J Med 2016; 375:35-43). These findings, and the results of the CHARISMA and COMPASS trials suggest that combined anti-platelet and low dose anticoagulation may be more effective than more intensive anti-platelet therapy for a number of vascular conditions.
22. How do data on real-world...	Analysis of the REACH registry suggests that about 53% of the REACH population would have been eligible for the COMPASS trial, and 68% of the PAD patients (European Heart Journal (2017) 00, 1–9 doi:10.1093/eurheartj/ehx658). The XATOA prospective registry is analysing management and outcomes of vascular risk patients treated in the "real world" with the COMPASS dual pathway regimen. The prospective XATOAis currently recruiting (NCT03746275).
Equality	
23a. Are there any potential equality issues	None known
23b. Consider whether ...	None known
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Registry and trial data demonstrate that chronic CAD and PAD patients are at risk of adverse cardiovascular and limb outcomes despite the application of guideline indicated secondary prevention, and despite the current standards of care seen in well developed healthcare systems.
- The dual pathway COMPASS regimen (rivaroxaban 2.5mg bd plus low dose aspirin) significantly reduced cardiovascular death/MI/ stroke and adverse limb events, on top of high standards of secondary prevention therapy and the largest impact was on stroke reduction. This regimen was compared (double blind) with the same low dose of aspirin and it also reduced total mortality.
- PAD patients and CAD patients with one or more additional risk factor (e.g. diabetes, chronic heart failure, renal dysfunction) have the most to gain in absolute terms, although the proportional benefits of the COMPASS regimen were similar across the range of patients included in the COMPASS trial.
- The bleeding risks of the dual pathway COMPASS regimen are mainly manifest in the first year of treatment, whereas the benefits continue to accrue over time. These bleeding risks are of similar risk magnitude to those seen with dual antiplatelet therapy.
- The dual pathway COMPASS regimen is the only antithrombotic secondary prevention therapy to reduce cardiovascular and all cause mortality and the findings present the opportunity for a "step change" to improve outcomes among patients with vascular disease and markers of vascular risk.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease [ID1397]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Jagdeep S. Singh**
2. Name of organisation	**British Cardiovascular Society**

3. Job title or position	**Cardiology Specialist Registrar** **Member of BCS Guidelines and Practice Committee**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☒ yes

rest of this form will be deleted after submission.)	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease [ID1397]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Simon Williams, HEART UK- The Cholesterol Charity**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ x a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	HEART UK- The Cholesterol Charity
4. Did your nominating organisation submit a submission?	☐ **x** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ **x** yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ **x** I am drawing on others' experiences. Please specify how this information was gathered: From the Cholesterol Helpline and other communications with patients
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CAD can lead to heart failure, heart attacks and strokes resulting in disability and death. Patients with each of these conditions will lifelong care from the NHS and others and often patients often fear that a heart attack or stroke will lead to another, which will be more disabling and potentially fatal. PAD can be a painful condition that gets worse when walking, thus limiting the mobility of patients. PAD can potentially also lead to amputation of lower limbs, if the condition is poorly managed.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	
10. Is there an unmet need for patients with this condition?	Patients, particularly with PAD are often from hard to reach groups and underserved by the NHS. Patients are often from a lower socio economic group and have inequitable access to services.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Patients want access to treatments that help manage their risk better and lower their chances of a condition deteriorating further.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Patients will need to understand the risks associated with any treatment and balance this with the benefits. Communicating risk and benefit can be challenging and should be addressed with this treatment in a manner that is clear and understandable to different patients with different needs.
Patient population	
13. Are there any groups of patients who might benefit	

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**CAD has a higher prevalence in less affluent areas and is an indicator for deprivation, highlighting many health inequality issues. Patients, particularly those with PAD are often from lower socio economic groups and have had access to support to make healthier choices throughout their lives.**
Other issues	
15. Are there any other issues that you would like the committee to consider?	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- The benefit and risks of treatment ought to be communicated effectively to patients to make informed choices
- Additional support for patients to reinforce healthier choices and lifestyles will help manage CAD and PAD more effectively, but may often be very challenging to change behaviour.

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Thank you for your time.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease

Post-factual error check

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Declared competing interests of the authors

None declared

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Rider on responsibility for report

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

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Contributions of authors

Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanna Picot critically appraised the clinical effectiveness systematic review, and drafted the report; Olu Onyimadu critically appraised the

health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report, project managed the report and is the project guarantor. Joanne Lord critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the clinical effectiveness systematic review, and drafted the report.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AE	Adverse event
ALI	Acute limb ischaemia
ASA	Acetylsalicylic acid
Bd	Twice daily
BNF	British National Formulary
BSC	Best supportive care
CABG	Coronary artery bypass graft
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CVD	Cardiovascular disease
DIC	Deviance information criteria
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EPAR	European Public Assessment Report
ERG	Evidence Review Group
EQ-5D	EuroQol 5-Dimension
FDA	Food and Drug Administration
GEE	Generalised estimating equation
GFR	Glomerular filtration rate
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
ICH	Intracranial haemorrhage
IS	Ischaemic Stroke
ISTH	International Society on Thrombosis and Haemostasis
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSTEMI	Non–ST-segment elevation myocardial infarction
od	*omne in die* (once a day)

OS	Overall survival
ORR	Objective response rate
PAD	Peripheral Artery Disease
PAS	Patient access scheme
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PD	Progressed disease
PF	Progression free
PFS	Progression free survival
PH	Proportional hazards
PRF	Poor renal function
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
STEMI	ST-elevation myocardial infarction
TEAE	Treatment emergent adverse events
TIMI	Thrombosis in Myocardial Infarction
TTD	Time to treatment discontinuation
VTE	Venous thromboembolism
WTP	Willingness-to-pay

SUMMARY

Scope of the company submission

The marketing authorisation for rivaroxaban in this indication is "adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events". The company's submission (CS) focuses on three specific patient subpopulations:

1. People with CAD and PAD (CAD+PAD)
2. People with CAD and poor renal function (estimated Glomerular Filtration Rate (GFR) < 60 ml per minute) (CAD+PRF)
3. People with CAD and heart failure (CAD+HF)

Although the CS focuses on the three subpopulations listed above the company also presents data for the whole of the licensed population. The company is only seeking a NICE recommendation for the three subpopulations.

The NICE scope defines the population for this appraisal as "Adults with coronary or peripheral artery disease, excluding people with atrial fibrillation, at high risk of ischaemic events". The NICE scope includes the first two of the subpopulations listed above, but the third, CAD+HF, is not mentioned. Expert clinical advice to the ERG indicates that all three subpopulations are clinically important, and that there is unmet clinical need in these groups. The NICE scope includes two other subpopulations which have not been included in the CS:

- People with previous myocardial infarction (MI)
- People with multiple prior MIs

The comparator treatments listed in the NICE scope are:

- For people with stable CAD, aspirin or aspirin in combination with ticagrelor
- For people with PAD, aspirin or clopidogrel.

The company's decision problem includes as comparators:

- aspirin (described in the CS as the "main comparator")
- ticagrelor + aspirin (described in the CS as the "secondary comparator")

The CS does not explicitly include patients with PAD only (i.e. PAD without concomitant CAD) as a separate subpopulation. Clopidogrel, one of the comparator treatments for this group of patients, is omitted from the CS.

The outcomes included in the CS generally match those listed in the NICE scope.

Summary of submitted clinical effectiveness evidence

The company's systematic review of clinical effectiveness identified one relevant randomised controlled trial (RCT) of rivaroxaban: the COMPASS trial. The ERG believes the company has identified all the relevant RCTs of rivaroxaban.

The COMPASS trial is an international, multicentre, phase III superiority trial of 27,395 patients, sponsored by the company, with a double-blind, double-dummy design. It enrolled patients with a history of stable atherosclerotic vascular disease (either CAD or PAD). The enrolled patients were at high risk of ischaemic events. Patients were randomised to one of three rivaroxaban / aspirin treatment assignments. For this appraisal the relevant comparison is:

- Rivaroxaban 2.5 mg twice daily + aspirin 100mg once daily (n = 9,152 patients) versus aspirin 100 mg once daily (n = 9,126 patients).

Patient characteristics and baseline demographics were well balanced between the two trial arms. Results from the third trial arm (5 mg rivaroxaban twice daily) are not presented in the CS. The results were not significant for the primary efficacy outcome and the 5mg rivaroxaban dose is not licenced for this indication.

The company presents results for the intention-to-treat (ITT) population and the three subpopulations shown in Table 1.

Table 1 Numbers of patients in the ITT and subpopulations for which the CS presents results

	Rivaroxaban 2.5 mg + aspirin 100mg	Aspirin 100 mg	Total[a]
ITT population	9,152	9,126	18,278 (100%)
CAD+PAD patient subpopulation	1,656	1,641	3,297 (18.0%)
CAD+HF patient subpopulation	1,909	1,912	3,821 (20.9%)
CAD+PRF patient subpopulation	1,824	1,873	3697 (20.2%)

[a] This is the total of the two arms relevant for this appraisal. The third trial arm, rivaroxaban 5mg twice daily (n=9117), has not been included in the CS.

The primary efficacy outcome was a composite measure of time from randomisation to the first occurrence of a primary efficacy outcome event: cardiovascular death, stroke (ischaemic, haemorrhagic or stroke of uncertain cause) or MI.

The primary safety outcome was defined as time from randomisation (in days) to the first occurrence of the primary safety outcome event, major bleeding. The components of major bleeding were:

- fatal bleeding, and/or
- symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or
- bleeding into the surgical site requiring re-operation, and/or
- bleeding leading to hospitalisation (with or without an overnight stay)

Of these, the bleeding events that inform the economic model are fatal bleeding, and major extracranial non-fatal bleeding.

Secondary outcomes include two further composite efficacy measures, as well as net clinical benefit and all-cause mortality. Tertiary outcomes include all the individual components of the composite outcomes, plus arterial revascularisation, limb amputation, and venous thromboembolism (VTE). Health-related quality of life (HRQoL) and adverse events were also reported.

There are no head-to-head RCTs of rivaroxaban + aspirin versus ticagrelor + aspirin. Therefore, an indirect treatment comparison (ITC) was used to estimate the relative efficacy of rivaroxaban and ticagrelor. The company's systematic review identified the PEGASUS RCT, which compared ticagrelor (60 mg twice a day) + aspirin (75-150 mg daily) to aspirin alone. The COMPASS and PEGASUS RCTs, which the ERG has judged to be at a low risk of bias, allow the comparison of rivaroxaban + aspirin to ticagrelor + aspirin through the common comparator of aspirin alone.

There are some important differences between the population of patients enrolled in the COMPASS RCT and those enrolled in the PEGASUS RCT:

- In the COMPASS RCT 62% of patients had a prior MI but this was 100% in the PEGASUS RCT
- In COMPASS a patient's MI could have happened any time within the past 20 years, but the time elapsed since the prior MI was restricted to between one and three years in the PEGASUS RCT

- In the COMPASS RCT 27% of patients had PAD but only 5% had PAD in the PEGASUS RCT

Ticagrelor (NICE TA420 'ticagrelor for preventing atherothrombotic events after myocardial infarction') is an option for preventing atherothrombotic events in adults who had a MI and who are at high risk of a further event. Thus, for the approximately 38% of patients in the COMPASS trial who had not experienced a previous MI, ticagrelor is not a relevant comparator.

There were also some differences between the COMPASS and PEGASUS trials in how outcomes were defined:

- major bleeding was defined by modified International Society on Thrombosis and Haemostasis (ISTH) criteria in the COMPASS RCT but by the Thrombosis in Myocardial Infarction (TIMI) criteria in the PEGASUS RCT.
- the definition of MI in the COMPASS RCT excluded sudden cardiac death (instead sudden cardiac death was assessed as a CV-related death) whereas in PEGASUS, sudden unexpected cardiac deaths were included in the definition of a MI.

The CS states that the difference in major bleeding definition would be anticipated to bias the analysis against rivaroxaban + aspirin against ticagrelor + aspirin in the ITC.

An adjusted ITC of rivaroxaban + aspirin versus ticagrelor + aspirin using the Bucher et al method was performed for 13 outcomes in the ITT population. In the subpopulations the ITC was only possible for CAD+PAD (9 outcomes) and CAD+PRF (6 outcomes). No data were presented in the PEGASUS trial for a CAD+HF population therefore an ITC was not possible for this subpopulation. The results of the ITC were not used in the economic model.

The primary outcomes (efficacy and safety) and outcomes that are included in the economic model are presented in the ERG report and summarised below.

COMPASS trial results

For the primary composite efficacy outcome of cardiovascular death, stroke or MI the HR was 0.76 (95% CI 0.66 to 0.86), indicating a 24% reduction in the risk of having the composite outcome in the rivaroxaban + aspirin arm ($p<0.001$). In the three subpopulations the incidence rate of the primary efficacy outcome per 100 patient years is higher than it is in the ITT

population in both trial arms with the differences between arms favouring rivaroxaban + aspirin in all three subpopulations:

- The CAD+PAD subpopulation demonstrated the greatest reduction in risk (33%) with a HR of 0.67 (95% CI 0.52 to 0.87, p=0.00262),
- There was a very similar result for the CAD+HF subpopulation (HR 0.68, 95% CI 0.53 to 0.87, p=0.002).
- The result for the CAD+PRF subpopulation was closer to that of the ITT population (HR 0.73, 95% CI 0.57 to 0.92, p=0.007).

The results from the ITC for the primary efficacy outcome in the ITT population and the CAD+PAD and CAD+PRF subpopulations produced HRs of 0.90, 0.97 and 0.90 respectively with the 95% confidence intervals for all three crossing one indicating that there were no statistically significant differences in these populations between rivaroxaban + aspirin versus ticagrelor + aspirin.

The CS provides the results for the individual components of the primary efficacy composite endpoint.

- For MI, the reduction in incidence in the rivaroxaban + aspirin arm was not statistically different to that of the aspirin only arm in the ITT population nor in any of the three subpopulations. Experiencing an MI is one of the health states in the company's economic model.
- For stroke however, there was a statistically significant reduction in the rivaroxaban + aspirin arm in comparison to the aspirin only arm which was greatest in the CAD+PRF subpopulation (HR 0.37, 95% CI 0.21 to 0.65, p=0.0003) followed by the CAD+PAD and CAD+HR subpopulations (HR 0.46 and 0.49 respectively). The reduction in the risk of stroke was greater in all subpopulations (albeit with wider 95% confidence intervals) than in the ITT population (HR 0.58, 95% CI 0.44 to 0.76, p<0.01).
- For the final component of the primary efficacy endpoint, cardiovascular deaths, there was a statistically significant reduction (based on reported p-values) in favour of rivaroxaban + aspirin in the ITT population and in the CAD+PAD (despite the 95% CI crossing one) and CAD+HF subpopulations. In the CAD+PRF subpopulation, although the HR of 0.86 was in favour of the rivaroxaban + aspirin arm than in the aspirin alone arm, the confidence interval spanned one and the p-value indicated the difference was

not statistically significant (p=0.375). Cardiovascular deaths are taken into account in the company's economic model as part of the absorbing state of death.

In agreement with the results from the ITC for the primary efficacy outcome, the indirect comparisons for the individual components of the primary outcome also indicated that there were no statistically significant differences between rivaroxaban + aspirin versus ticagrelor + aspirin.

Ischaemic stroke, acute limb ischaemia, VTE and amputation were outcomes each of which contributed data to the economic model. Results for ischaemic stroke were similar to those for the overall outcome of stroke reported above, with a statistically significant reduction in the risk of ischaemic stroke in favour of rivaroxaban + aspirin. The CAD+PRF subpopulation experienced the greatest reduction in risk, followed by the CAD+HR and then the CAD+PAD subpopulation. For acute limb ischaemia, VTE and amputation, numerical results were in favour of the rivaroxaban + aspirin arm. However, the numbers of events were often low (particularly in the subpopulations) and HRs could not always be calculated. Confidence intervals were typically wide and often spanned 1.

The primary safety outcome of the COMPASS trial was the composite outcome of major bleeding. In common with other antithrombotic medicines, bleeding is the most prominent safety risk for rivaroxaban. Major bleeding events occurred more often in the rivaroxaban + aspirin arm than the aspirin only arm (incident rate per 100 patient years 1.67 vs 0.98 in the aspirin only arm; HR 1.70 (95% CI 1.40 to 2.05), p<0.001). A consistent pattern of more major bleeding events in the rivaroxaban + aspirin arm than in the aspirin only arm was observed in the CAD+PAD, CAD+HF and CAD+PRF subpopulations. The CS states that the most common site for bleeding was the gastrointestinal tract. Results were also presented for each of the components of the primary safety composite outcome.

HRQoL was assessed using the EQ-5D instrument in the ITT population of the COMPASS RCT. There was very little change between the mean values at baseline and the mean values at the two-year and final visits and mean values were very similar in the two arms of the trial. It was apparent that there was a high proportion of missing data (57% at year 2 and 31% at the final visit) and no imputation of missing values was performed.

In addition to presenting results for the three key subpopulations (which are subgroups of the ITT population) results for the primary efficacy and safety outcome were presented (in an appendix to the CS) for subgroups defined by other patient demographic and prognostic characteristics. Results were broadly consistent with those for the ITT population.

Summary of submitted cost effectiveness evidence

The CS includes a review of published cost-effectiveness evidence and a economic model developed for this appraisal.

Systematic review of the published economic evidence

The company conducted a systematic literature review for published cost-effectiveness evidence for CAD and / or PAD. They reported that 41 studies (in 42 publications) were identified for full review. Most of these studies used Markov models with health states for MI, and CV death. The ERG notes that many of the included studies do not include the three treatments relevant to this appraisal. Five studies were conducted in the UK. The company did not find any cost-effectiveness studies of rivaroxaban 2.5mg in this current indication. However, the ERG found two additional studies after the company's searches were completed (company search up to March 2018). These studies estimated the cost-effectiveness of rivaroxaban + aspirin versus aspirin in people with stable cardiovascular disease (Ademi et al) and CAD + PAD (Zomer et al) in Australia.

Description of the company model

The submitted model consists of a Markov model with **main health states** for MI, ischaemic stroke, intracranial haemorrhage and death. Patients can have up to two cardiovascular events. The model uses a lifetime horizon and is from the perspective of NHS England and Personal Social Services. Discounting is applied to cost and outcomes at 3.5% per annum. The submission includes analyses for the whole COMPASS population and the three subpopulations.

Patients move between health states according to the transition probabilities which were derived from the COMPASS trial. In addition to the acute main events, patients can also experience secondary **"health events"** at any time-point in the model (i.e. extracranial non-fatal bleed, acute limb ischaemia, minor amputation, major amputation, VTE).

Patients are assumed to be treated with rivaroxaban + aspirin or aspirin indefinitely unless treatment is discontinued (e.g. for an adverse event). Treatment with ticagrelor + aspirin is set to a maximum of three years to reflect the recommendation from NICE TA420. Patients discontinue treatment according the discontinuation rate observed in the COMPASS trial. Patients who discontinue rivaroxaban or ticagrelor receive aspirin alone and subsequently only accrue the costs and efficacy of the aspirin arm. In the base case, the model assumes there are no treatment interruptions for invasive procedures, such as percutaneous coronary intervention and those who had an MI, major bleeds or had a stroke.

As stated earlier, the ITC does not inform the economic model. Instead, the transition probabilities for rivaroxaban + aspirin and ticagrelor + aspirin are calculated by applying HRs to the transition probabilities for the aspirin only group. The HRs apply for both first and second events and are constant over time. The HRs for rivaroxaban + aspirin vs. aspirin are from the COMPASS trial whilst those for ticagrelor + aspirin vs aspirin are from the PEGASUS trial. In the cases where there are no data for subgroups, assumptions have been made.

The model uses health utilities estimated from the COMPASS trial for the main event states and the health events. The model uses resource costs associated with drug acquisition, cost of fatal and non-fatal events, cost of health events, and costs of follow-up care. NHS reference costs are used to estimate the unit costs of health events and follow-up care. The company updated the costs and background mortality in their clarification response (questions B6, B12). Updated results are shown in Tables 34-40 of the clarification response document.

Company's base case results

The company base case cost effectiveness results are shown in Table 1, Table 2 and Table 3 and Table 4 for the whole COMPASS population, CAD+PAD, CAD+HF, CAD+PRF subpopulations, respectively.

Table 2 Incremental base case cost effectiveness results for COMPASS population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER: rivaroxaban versus comparator (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	£7,260	9.35	-	-	£16,326	-
Ticagrelor + aspirin	£8,889	9.41	£1,629	0.06	£12,581	Extendedly dominated
Rivaroxaban + aspirin	£10,842	9.57	£1,953	0.155	NA	£16,326

Table 3 Incremental base case cost effectiveness results for CAD+PAD subpopulation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER: rivaroxaban versus comparator (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	£9,571	8.13	-	-	£7,309	-
Ticagrelor + aspirin	£11,257	8.39	£1,686	0.26	£9,047	£6,485
Rivaroxaban + aspirin	£12,476	8.53	£1,219	0.14	NA	£9,047

Table 4 Incremental base case cost effectiveness results for CAD+HF subpopulation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER: rivaroxaban versus comparator (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	£6,256	8.09	-	-	£5,702	-
Ticagrelor + aspirin	£7,872	8.21	£1,616	0.12	£3,920	Extendedly dominated
Rivaroxaban + aspirin	£9,925	8.74	£2,053	0.52	NA	£5,702

Table 5 Incremental base case cost effectiveness results for CAD+PRF subpopulation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER: rivaroxaban versus comparator (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	£7,855	7.39	-	-	£9,861	-
Ticagrelor + aspirin	£9,263	7.41	£1,408	0.02	£4,841	Extendedly dominated
Rivaroxaban + aspirin	£10,431	7.65	£1,168	0.24	NA	£9,861

The company conducted deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses (PSA). In deterministic sensitivity analyses, the ICERs were most sensitive to changes in the HR for MI, IS and sudden cardiac death. The company stated that for the subpopulation of patients with CAD+PAD, the ICERs remained below £20,000/QALY in all scenarios and for the other two subpopulations the results were largely insensitive to the different scenarios.

Commentary on the robustness of submitted evidence

Strengths

- The ERG considers that the company's systematic review of clinical effectiveness has been well conducted. The literature search strategies are fit for purpose and it is unlikely that any relevant studies will be been omitted.
- The pivotal phase III trial of rivaroxaban, the COMPASS RCT, is a well-conducted study which is likely to be at a low risk of bias. The statistical procedures used in the COMPASS trial are, overall, appropriate.
- The structure of the company's economic model is appropriate and correctly implemented and includes relevant and comprehensive health states.
- The COMPASS trial provides a robust source of HRQoL, using the EQ-5D instrument (though there was a large amount of missing data for this measure in the trial).
- The approach taken by the company for estimating health care resources and costs is reasonable and in line with previous NICE technology appraisals.

Weaknesses and areas of uncertainty

- The company has omitted clopidogrel as a comparator from the CS which is a relevant comparator for the people with PAD. The omission of clopidogrel may be tied to the fact that the company is not seeing reimbursement for the PAD only population in their CS. Expert clinical advice to the ERG is that clopidogrel would be given to patients with stable CAD and PAD, which is one of the patient subpopulations included in the CS.
- The CAD+PAD, CAD+HF and CAD+PRF subpopulations each comprise around 20% of the randomised population and will be statistically underpowered for efficacy and safety outcomes.
- The ITC of rivaroxaban + aspirin to ticagrelor + aspirin was conducted using an appropriate statistical method but the ERG is concerned about the impact of important differences between the patients enrolled in the two trials. Specifically, 62% of patients in the COMPASS trial had a previous MI, whereas all patients in the PEGASUS trial had experienced an MI (in the last two years). Ticagrelor + aspirin would only be a treatment option for those patients in the COMPASS trial with a history of MI within the past three years.
- The two key clinical trials included in the company's indirect comparison of rivaroxaban + aspirin versus ticagrelor + aspirin use differing classifications of major bleeding. The ISTH classification is more sensitive and captures more major bleeding events leading to hospitalisation. The extent to which this might bias the results of the ITC is unclear.
- The company's base case analysis uses zero transition probabilities in transitions where there were no events in the COMPASS trial. The ERG is of the opinion that for some transitions the transition probabilities appear counter-intuitive, for example where an individual's chance of experiencing another MI is lower after experiencing an MI than before experiencing an MI.
- There are several missing values for the HRs, particularly for the main events and adverse events in the PEGASUS trial for the subpopulations. Assumptions have had to be made for these missing values. These introduce further uncertainty into the model results.
- The company has not include the full uncertainty around the model results as in the deterministic sensitivity analyses and PSA, CV death was stratified into cause of death, and the mortality hazard ratios for each of these were varied independently.

- The utility values from the event-free health states appeared higher than utility values collected for the general UK population.

Summary of additional work undertaken by the ERG

The ERG did not find any errors in the company's model. We ran the model for an ERG base case, which included changes to some of the model assumptions regarding the HRs for ticagrelor, the values used for the transition probabilities, treatment interruption, and the utility values. Details are shown in Table 6.

Table 6 ERG base case

Model aspect	Company analysis	ERG base case	Justification
Hazard ratios for ticagrelor + aspirin vs aspirin	Main events: Where HRs were not available for subpopulations, HRs from the PEGASUS whole trial population were used. Adverse events: For amputations, HR =1 vs. aspirin, for non-fatal bleeds HR for major bleeding used; where HR were not available HRs from the whole PEGASUS whole trial population were used.	Main events: no change from company base case. Adverse events: For all adverse events, HRs for ticagrelor vs. aspirin are the same as rivaroxaban vs. aspirin.	Main events: reasonable to use HRs from PEGASUS whole trial population in the absence of subgroup interactions. Adverse events: Data from PEGASUS trial highly uncertain for adverse events as these data were not collected / reported or were defined differently. Unclear whether there are any differences between adverse events for rivaroxaban and ticagrelor (CS Tables 32-33).
Null transition probabilities	Use null transition probabilities for aspirin, as observed in the COMPASS trial.	Use company scenario for imputed values for aspirin transition probabilities. Null event probabilities after a first-event replaced with the probabilities from the event-free health state. Null CV death probabilities after a second-event imputed using the minimum of	Imputed values are more similar to expected real-life values.

		all probabilities after a second event.	
Treatment interruption	No interruption for rivaroxaban + aspirin was explicitly considered after the main events (MI, ICH or IS).	Treatment interruption: 1 year after an MI, patients switch to dual antiplatelet therapy (ticagrelor + aspirin) for one year, in all arms. 3 months after an ICH, patients receive aspirin only for 3 months. 1 month after a major bleed, patients receive aspirin only for one month.	More similar to clinical practice.
Utility values for event-free health state	Values taken from COMPASS trial. For combined health states, company uses lowest utility of the two health states.	Use age-adjusted population utility norms for COMPASS population, with subgroups adjusted according to disutility seen in COMPASS. For combined health states use multiplicative utility values. Utility values for the event-free state shown in Table 65.	Unrealistic for patients with multi-vessel disease and subgroups to have utility higher than general population norm. NICE Decision Support Unit (DSU) guide states that correct approach is to use multiplicative utility values.
Monitoring costs for event-free health state	No costs incurred for monitoring for event-free health state.	Use monitoring costs from TA317, updated to 2017/18: £167.66.	Patients will be monitored whilst in the event free state.

The effects of the ERG changes to the company model only have a marginal effect on the model results (Table 7) and are favourable to rivaroxaban.

Table 7 ERG base case results for the COMPASS whole trial population

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; vs aspirin
Aspirin	£13,387	8.39		£17,024
Ticagrelor + aspirin	£14,647	8.40	Extendedly dominated	£11,453
Rivaroxaban + aspirin	£16,885	8.60	£17,024	NA

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from Bayer on the clinical effectiveness and cost effectiveness of rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 18th January 2019. A response from the company via NICE was received by the ERG on 5th February 2019 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The CS provides a brief overview of the epidemiology and natural history of cardiovascular disease, and indicates that coronary artery disease (CAD) is the most common type of cardiovascular disease. Peripheral artery disease (PAD) is not defined or discussed, apart from being listed among the factors which increase the risk of thrombotic events.

2.2 Critique of company's overview of current service provision

Current management guidelines for CAD are cited, and a NICE clinical pathway is provided for CAD (CS Figure 1). This incorporates NICE clinical guidelines and NICE appraisal guidance for management of acute coronary syndromes and longer-term management. The pathway shows that acute management of a coronary event would comprise dual antiplatelet therapy, including ticagrelor 90mg and aspirin (NICE TA236[1]); or prasugrel and aspirin (NICE TA182[2]); or rivaroxaban 2.5mg + aspirin (NICE TA335[3]). Expert clinical opinion to the ERG concurs with this, but notes that clopidogrel is also an option for patients with an acute event who have a stent fitted. Choice of anti-platelet therapy in the acute setting varies between geographical areas. The NICE guideline "Peripheral arterial disease: diagnosis and management" (CG147[4]) is not cited. The omission of PAD-specific background information may be because the company is not seeking a recommendation for patients with PAD only (as discussed below).

The anticipated place of rivaroxaban therapy in longer-term management is specified in the CS: in selected stable CAD patients at high risk of ischaemic events (see subpopulations below). The CS cites the 2013 European Society of Cardiology (ESC) guidelines on the management of stable CAD[5] in support of this.

2.3 Critique of company's definition of decision problem

The decision problem (CS Table 1) is narrower than the marketing authorisation and differs from the NICE scope, primarily in terms of patient population. The marketing authorisation states: "Rivaroxaban, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events" (CS page 29). The decision problem focuses on three subpopulations of patients where the risk of ischaemic events is considered high and in whom the company is seeking a recommendation from the NICE appraisal committee:

1. People with CAD and PAD (CAD+PAD)
2. People with CAD and poor renal function (CAD+PRF) (estimated Glomerular Filtration Rate (GFR) <60ml/min);
3. People with CAD and heart failure (CAD+HF)

The NICE scope includes the first two subpopulations, but does not mention the third. Expert clinical advice to the ERG is that these are clinically important subpopulations who currently have unmet need, and that it is unlikely that there are any other clinically important subpopulations omitted from the CS. One clinical expert commented that patients with diabetes would be a potentially important subpopulations, but these patients may be covered by the CAD+PAD subpopulation (The ERG notes that each of the three subpopulations in the pivotal phase III trial of rivaroxaban – the COMPASS trial - included around 40% of diabetic patients).

The NICE scope includes two further subpopulations which have not been included in the CS:

- people with previous MI;
- people with multiple MIs.

The ERG notes that approximately 62% of the COMPASS trial ITT population had experienced a previous MI, though the proportion of this population who had multiple MI is not reported.

Although people with a previous MI is not a subpopulation considered in the CS, in the three subpopulations of people the CS considers to be at high risk of further ischemic events (as listed above) the proportion of people with a previous MI in the trial ranges between approximately 60% to 80%.

The CS also covers the whole of the licensed population, though as mentioned, the company is not seeking a NICE recommendation in this whole population. The CS also does not explicitly include patients with PAD only (i.e. PAD without concomitant CAD). This is one of the populations included in the NICE scope. One of the comparators for this group of patients, clopidogrel, is omitted from the CS. Expert clinical advice to the ERG is that clopidogrel would be given to patients with stable CAD and PAD.

The decision problem includes the comparators aspirin (described in the CS as the "main comparator"), and ticagrelor + aspirin (described in the CS as the "secondary comparator"). The ERG notes that NICE's guidance on ticagrelor (TA420[6]) is that it is an option for preventing atherothrombotic events in adults who had a MI and who are at high risk of a further event. Thus, for the approximately 38% of patients in the COMPASS trial, who had not experienced a previous MI, ticagrelor is not a relevant comparator (we discuss this in more detail below in section 3.1.7). The ERG is not aware of other relevant comparators that have been omitted from the NICE scope or the decision problem.

The decision problem matches the NICE scope in all other respects.

In terms of dose, rivaroxaban 2.5mg is indicated for twice daily combination with a daily dose of aspirin 75-100mg. The 2.5mg dose of rivaroxaban is already indicated for treatment of acute coronary syndrome (NICE TA335[3]). The COMPASS trial used an aspirin dose of 100mg per day. The recommended dose in the UK is 75mg (a 100mg tablet is not available). NICE TA335 states that patients should take a daily dose of 75–100 mg aspirin. CS appendix T provides evidence on the similarity between aspirin doses of 75mg and 100mg in terms of mechanism of action and efficacy. Clinical experts to the ERG agreed that the two doses provide similar efficacy in practice.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS reports separate literature searches for clinical effectiveness studies (dated June 2018); cost-effectiveness studies (dated March 2018); health-related quality of life (HRQoL) (dated April 2018) and costs and healthcare resources (dated July 2018). All of the searches are appropriately structured with transparent documentation. The searches contain a balanced selection of free text and index terms, correctly linked sets, appropriate search filters and are executed on an acceptable range of databases (e.g. Medline, Embase, and the Cochrane Central Register of Controlled Trials). The ERG elected to update the clinical effectiveness searches which were seven months out of date. These were focused on rivaroxaban and ticagrelor co-administered with aspirin and were run on Medline, Embase and the Cochrane Central Register of Controlled Trials. The ERG decided that update searches were not necessary for cost effectiveness, healthcare resource use nor for HRQoL. Ongoing trials were documented in the CS as searched for on clinicaltrials.gov. The ERG checked the UK Clinical Trials Gateway and no additional ongoing RCTs were found. Overall the searches are considered fit for purpose.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

CS Appendix D provides details on the processes and methods used by the company to identify and select relevant clinical effectiveness evidence. The company states they conducted their systematic review following the Cochrane Collaboration guidelines for systematic review. The systematic review therefore included the use of a predefined protocol (not included in the CS), clearly stated inclusion and exclusion criteria, a PRISMA flow diagram, quality assessment of and summary details of the identified evidence.

The systematic review utilises a search strategy the company had devised previously with a multi-country perspective. Consequently, the search included comparators not relevant to the current UK appraisal (non-UK comparators were excluded during screening of retrieved full texts). The search was updated and the results were screened against the eligibility criteria presented in CS Appendix D Table 129. In brief, key criteria were:

- Population – adults with CAD and/or PAD. The population is in line with the final scope and that defined in the company's decision problem.
- Intervention/Comparators – Rivaroxaban + aspirin; ticagrelor 60 mg BID + aspirin; aspirin monotherapy (note that no doses were specified by the company for rivaroxaban or aspirin). Although the intervention and comparators match those in the decision problem, the ERG notes that the comparator of clopidogrel for patients with PAD is not included. For the population described for the inclusion criteria of the systematic review clopidogrel is a relevant comparator, however the ERG presumes that it has been omitted because a decision had already been made not to seek reimbursement for the PAD only population prior to the systematic review being undertaken.
- Outcomes – three composite outcomes (stroke/MI/cardiovascular death; coronary heart disease death/MI/ischemic stroke/acute limb ischaemia; cardiovascular death/MI/ischemic stroke/acute limb ischemia), individual components of composite outcomes, eight other clinical outcomes, nine safety outcomes. All the outcomes listed in the final scope (with the exception of HRQoL for which separate searches were conducted as described in CS B.3.4) and company decision problem were included.

The inclusion and exclusion criteria for the systematic review therefore reflect the decision problem stated in the submission, and the licensed indication for rivaroxaban.

RCTs (including pragmatic trials, subgroup analyses of eligible RCTs and extension of RCTs) were eligible for inclusion. No limits were placed relating to the quality of RCTs. Conference abstracts published in 2015 or later were included. There were no language restrictions or geographic restrictions. Although systematic reviews were excluded four systematic reviews, stated to be the most relevant and up to date, identified by the searches were retrieved and used as an additional source of references.

A flow diagram (CS Appendix D Figure 51) shows the flow of studies thorough the states of inclusion and exclusion screening. Two independent reviewers screened titles and abstracts (when available) and the retrieved full text papers of potentially relevant articles. A third reviewer resolved any disagreements about the inclusion or exclusion of full text papers. The primary reason for exclusion of references was documented at both screening stages.

ERG conclusion

The ERG believes the company's systematic review will have identified relevant evidence for the use of rivaroxaban in the appropriate population. However, the company has omitted clopidogrel as a comparator from the systematic review which is a relevant comparator for the population described. The omission of clopidogrel may be tied to the fact that the company is not seeing reimbursement for the PAD only population in their CS.

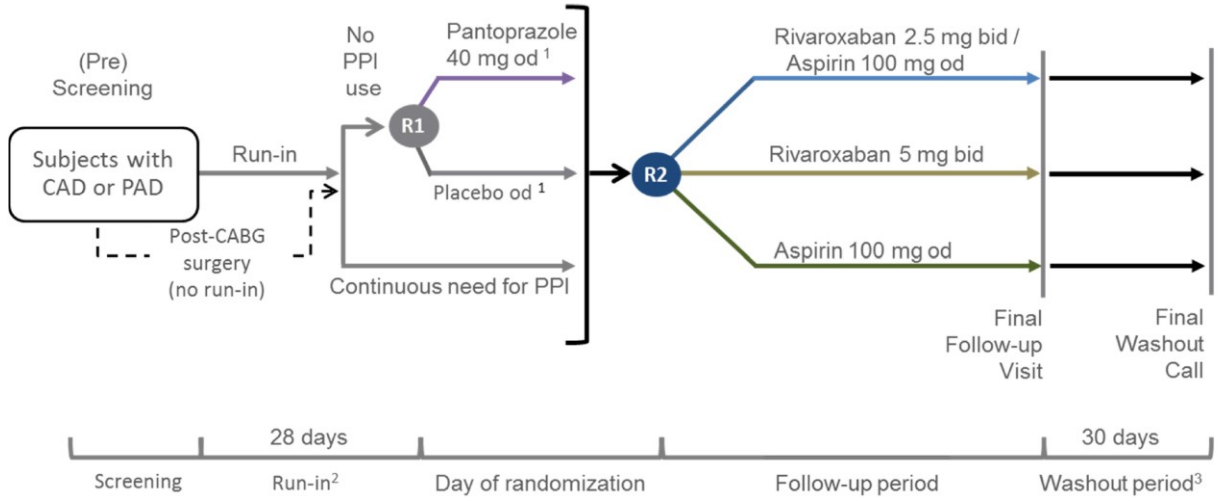
3.1.3 Identified studies

The systematic review identified two RCTs (reported by 13 publications). One, the COMPASS RCT provides evidence for rivaroxaban + aspirin and is the focus of the submission. The other, the PEGASUS-TIMI 54 trial provides evidence for ticagrelor + aspirin and contributes data to an indirect treatment comparison to enable the comparative efficacy of rivaroxaban and ticagrelor to be explored because there are no head to head comparisons of these interventions in the population of interest. The COMPASS RCT is described below, the PEGASUS-TIMI 54 trial is described in Section 3.1.7. No non-randomised evidence was included in the submission.

The COMPASS RCT is an international, multicentre, phase 3 superiority trial with a double-blind, double-dummy design. It was sponsored by the company and enrolled patients with a history of stable atherosclerotic vascular disease (either CAD or PAD). Patients were at high risk of ischaemic events but did not have an indication of dual antiplatelet therapy or full dose anticoagulation (e.g. atrial fibrillation) and they were not at a high risk for bleeding which would contraindicate the use of long-term anticoagulant therapy. The CS states patients with any history of haemorrhagic or lacunar stroke or a recent stroke were excluded from the trial because previous trials of other antithrombotic agents have found that this group of patients has a higher risk of intracranial haemorrhage.

The COMPASS RCT randomised patients in a 3-by-2 partial factorial design in which patients who had a continuous need for use of a proton pump inhibitor at baseline underwent only a single randomisation (to one of three arms: rivaroxaban 2.5 mg bd + aspirin 100 mg od; rivaroxaban 5 mg bd + aspirin placebo; rivaroxaban placebo + aspirin 100 mg od). Patients who did not have a continuous need for treatment with a proton pump inhibitor first entered a proton-pump inhibitor randomisation (to one of two arms: pantoprazole or placebo) and were

subsequently randomised to one of the three rivaroxaban / aspirin treatment assignments. The COMPASS trial design is reproduced in Figure 1 below.



Source: ERG reproduction of CS Figure 3

bid = twice daily; CABG = coronary artery bypass graft; CAD = coronary artery disease; od = once daily; PAD = peripheral artery disease; PHRI = Population Health Research Institute; PPI = proton pump inhibitor; R = randomisation. [1] Topline results for the pantoprazole/placebo arms of the trial are reported in CS Appendix P. [2] Aspirin 100 mg od and rivaroxaban placebo as run-in medication. [3] Patients treated according to local standard of care.

Figure 1 COMPASS trial design

For the purposes of this STA only the results from the second randomisation to rivaroxaban/aspirin are relevant. Furthermore, as stated in CS section B.2.3, the CS focusses on the 2.5mg twice daily dose of rivaroxaban because this is the dose licenced for this indication (the results for the 5 mg dose twice daily were not significant for the primary efficacy outcome). The relevant comparison is therefore: Rivaroxaban 2.5 mg twice daily + aspirin 100mg once daily (n = 9,152) versus aspirin 100 mg once daily (n = 9,126).

A flow-chart showing the numbers of patients randomised to antithrombotic treatment, treated, and who completed treatment to the global cut-off, final follow-up and who completed follow-up and washout is presented in CS Appendix D Figure 57. Flow-charts were not provided for the three subpopulations of interest.

As stated earlier in Section 2.3, the company's decision problem is narrower than the NICE scope and the marketing authorisation (specifically patients with PAD are excluded, unless they also have CAD). The company presents four sets of results from the COMPASS trial as shown in Table 8.

Table 8 Numbers of patients in the ITT and subpopulations for which the CS presents results

	Rivaroxaban 2.5 mg + aspirin 100mg	Aspirin 100 mg	Total[a]
ITT population	9,152	9,126	18,278 (100%)
CAD+PAD patient subpopulation	1,656	1,641	3,297 (18.0%)
CAD+HF patient subpopulation	1,909	1,912	3,821 (20.9%)
CAD+PRF patient subpopulation	1,824	1,873	3,697 (20.2%)

[a] This is the total of the two arms relevant for this appraisal. The third trial arm, rivaroxaban 5mg twice daily (n=9117), has not been included in the CS.

The company presents baseline characteristics for the ITT population and the three subpopulations in CS Table 8. In the ITT population, and also in the CAD+PAD, CAD+HF and CAD+PRF subpopulations, patient characteristics and baseline demographics were well balanced between the two study arms (Table 9).

Table 9 Key baseline demographic and disease characteristics for the ITT COMPASS study population and three subpopulations

Data presented as number (%) or mean ± S.D	Rivaroxaban 2.5mg bd + aspirin 100mg od				Aspirin 100mg od			
		Subpopulation				Subpopulation		
	COMPASS ITT N=9152	CAD+PAD N=1656	CAD+HF N=1909	CAD+PRF N=1824	COMPASS ITT N=9126	CAD+PAD N=1641	CAD+HF N=1912	CAD+PRF N=1873
Sex – Male	7093 (77.5)	1259 (76.0)	1459 (76.4)	1314 (72.0)	7137 (78.2)	1266 (77.1)	1486 (77.7)	1301 (69.5)
Age (yr)	68.3 ± 7.9	68.2 ± 8.2	65.7 ± 9.1	71.8 ± 7.3	68.2 ± 8.0	68.1 ± 8.1	65.6 ± 8.9	71.7 ± 7.3
Race, White	5673 (62.0)	1113 (67.2)	1207 (63.2)	1103 (60.5)	5682 (62.3)	1113 (67.8)	1177 (61.6)	1155 (61.7)
Cholesterol (mg/dL)	167 ± 178	168 ± 153	187 ± 342	162 ± 132	167 ± 180	169 ± 216	179 ± 270	167 ± 189
Systolic BP (mmHg)	136 ± 17	138 ± 18	133 ± 17	136 ± 18	136 ± 18	138 ± 18	133 ± 16	135 ± 18
Diastolic BP (mmHg)	77 ± 10	77 ± 10	78 ± 10	76 ± 10	78 ± 10	78 ± 10	78 ± 10	76 ± 10
Baseline ABI <0.9	1190 (13.0)	842 (50.8)	228 (11.9)	248 (13.6)	1233 (13.5)	879 (53.6)	236 (12.3)	247 (13.2)
Estimated GFR 30 - <60 ml/min	1977 (21.6)	437 (26.4)	446 (23.4)	1762 (96.6)	2028 (22.2)	441 (26.9)	469 (24.5)	1799 (96.0)
Fragile subject [a]	2308 (25.2)	477 (28.8)	444 (23.3)	1122 (61.5)	2284 (25.0)	445 (27.1)	458 (24.0)	1148 (61.3)
Smoker (current)	1944 (21.2)	417 (25.2)	575 (30.1)	223 (12.2)	1972 (21.6)	400 (24.4)	566 (29.6)	253 (13.5)
Previous stroke	351 (3.8)	100 (6.0)	80 (4.2)	77 (4.2)	335 (3.7)	88 (5.4)	85 (4.4)	93 (5.0)
Previous MI	5654 (61.8)	990 (59.8)	1511 (79.2)	1248 (68.4)	5721 (62.7)	1002 (61.1)	1536 (80.3)	1281 (68.4)
Heart failure	1963 (21.4)	408 (24.6)	1909 (100)	467 (25.6)	1979 (21.7)	408 (24.9)	1912 (100)	500 (26.7)
CAD†	8313 (90.8)	1656 (100)			8261 (90.5)	1641 (100)		
PAD‡	2492 (27.2)	1656 (100)	408 (21.4%)	459 (25.2%)	2504 (27.4)	1641 (100)	408 (21.3%)	466 (24.9%)
Symptomatic PAD	2026 (22.1)	1190 (71.9)	295 (15.5)	330 (18.1)	2039 (22.3)	1176 (71.7)	295 (15.4)	344 (18.4)

Source: CS Table 8 but with multiple characteristics deleted to enable a more compact table showing key characteristics only

ABI - ankle brachial index; bd - twice daily; BP – blood pressure; CAD - coronary artery disease; GFR - estimated glomerular filtration rate; HF - heart failure; ITT - intention - to - treat; MI – myocardial infarction; od - once daily; PAD - peripheral artery disease; PRF - poor renal function i.e. GFR <60ml/min; S.D. - standard deviation; yr - year;

The GFR was calculated by means of the Chronic Kidney Disease Epidemiology Collaboration formula. Data on GFR were missing for four patients in the rivaroxaban - plus - aspirin group and four in the rivaroxaban - alone group (COMPASS ITT)

[a] Fragility = yes; includes patients with age >75 years or weight ≤50 kg or baseline eGFR <50 mL/min

† shown are patients with a history of coronary artery disease irrespective of whether it met the inclusion criteria for the trial

‡ shown are patients with a history of peripheral arterial disease irrespective of whether it met the inclusion criteria for the trial

Inevitably there are differences in baseline demographics between the ITT population and each of the subpopulations, predominantly as a consequence of the types of patient included in each subpopulation. For example, 71.9% of the CAD+PAD subpopulation had symptomatic PAD whereas only 15.5% to 22.1% of the ITT, CAD+HF and CAD+PRF subpopulation had symptomatic PAD. The ERG noted that the CAD+PRF subpopulation had a higher proportion of patients who are fragile. Expert clinical advice to the ERG is that patients with poor renal function are often older and likely to be more frail.

The company identified one relevant ongoing study from a search of clinicaltrials.gov, which is actually the pantoprazole sub-study from within the COMPASS RCT. The ERG has searched the UK Clinical Trials Gateway but did not find anything additional.

3.1.4 Description and critique of the approach to validity assessment

The CS quality assessed the COMPASS RCT and also the PEGASUS RCT which contributed data to the indirect comparison using NICE's suggested criteria. The ERG's assessment is compared with the company's assessment of the COMPASS RCT in Table 10 (see Section 3.1.7 for ERG assessment of PEGASUS).

Table 10 Company and ERG assessment of trial quality

Trial quality assessment criteria	CS response	ERG response
1. Was randomisation carried out appropriately?	Yes	Yes
2. Was concealment of treatment allocation adequate?	Yes	Yes
3. Were groups similar at outset in terms of prognostic factors?	Yes	ITT: Yes CAD+PAD subpopulation: Yes CAD+HF subpopulation: Yes CAD+PRF subpopulation: Yes
4. Were care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
5. Were there any unexpected imbalances in drop-outs between groups?	No	No
6. Is there any evidence that authors measured more outcomes than reported?	No	No
7. Did the analysis (a) include an ITT analysis? (b) If so, was this appropriate and (c) were appropriate methods used to account for missing data?	(a) Yes (b) Yes (c) Yes	(a) Yes (b) Yes (c) Yes

ERG conclusion

The ERG agrees with the company's assessment of the COMPASS RCT finding it to be a well-conducted study which is likely to be at a low risk of bias.

3.1.5 Description and critique of company's outcome selection

The outcomes included in the CS match the NICE scope, with the exception of urgent coronary, cerebrovascular or peripheral revascularisation. The COMPASS trial collected data on revascularisation, but this was not categorised according to urgency. The CS therefore presents revascularisation irrespective of urgency.

The CS reports a number of outcomes as measured in the COMPASS trial. CS Table 7 lists these outcomes and provides a definition of each measure and timing of assessment for all except the EQ-5D health-related quality of life measure which is defined but the timing of assessments is not stated.

3.1.5.1 Primary outcomes

The primary efficacy outcome was a composite measure of time from randomisation to the first occurrence of a primary efficacy outcome event: cardiovascular death, stroke (ischaemic, haemorrhagic or stroke of uncertain cause) or MI. The definitions of the individual events appear to be standard, though the CS highlights a difference in definition of MI between the COMPASS trial and the PEGASUS trials – namely in COMPASS sudden cardiac death was not included in the definition of MI but assessed as CV-related death. In contrast, the definition of MI adopted in the PEGASUS-TIMI 54 trial included both confirmed MI and sudden unexpected cardiac deaths. The CS comments that it is not expected that the different definitions of MI between the two trials would have any meaningful impact on the results of the indirect comparison (see section 3.1.7 of this report for a critique of the indirect comparison).

The ERG notes that this composite outcome has been included in other RCTs of other antithrombotic agents, as featured in previous NICE appraisals of rivaroxaban for acute coronary syndrome (TA335) and ticagrelor for preventing atherothrombotic events after MI (TA420).

The individual components of the composite outcome (MI, ischaemic stroke and cardiovascular death) are included in as main (first) events in the economic model. However, the trial was not

statistically powered for these events individually (we provide a critique of the trial's statistical procedures in section 3.1.6 of this report).

The primary safety outcome was defined as time from randomisation (in days) to the first occurrence of the primary safety outcome event, major bleeding. The components of major bleeding included:

- fatal bleeding, and/or
- symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or
- bleeding into the surgical site requiring re-operation, and/or
- bleeding leading to hospitalisation (with or without an overnight stay)

The bleeding events that inform the economic model are fatal bleeding, and major extracranial non-fatal bleeding.

Major bleeding was defined according to modified International Society on Thrombosis and Haemostasis (ISTH) criteria (stated in the CS to be a "mandated revision"). These criteria were modified for the COMPASS trial to increase the sensitivity of the ISTH bleeding definition to clinically relevant bleeds. The CS reports that the modified ISTH included any bleeding that led to hospitalisation with or without an overnight stay. It is stated that these events would not be considered major bleeds in other antithrombotic trials, and that this may introduce potential over-reporting of hospitalisation due to local practices, physicians' experience, and local in-and out-patient policies. The modified ISTH criteria, in contrast to the original ISTH criteria, did not consider whether bleeding was associated with a decrease in the haemoglobin level or with blood transfusion.

The ERG notes that the bleeding classification used in the PEGASUS RCT of ticagrelor (which is used in the company's indirect comparison of rivaroxaban versus ticagrelor –see section 3.1.7 of this report) is the Thrombosis in Myocardial Infarction (TIMI) criteria. These two sets of criteria differ from each other in respect of major bleeding definitions. In contrast to the ISTH criteria above, the TIMI criteria classifies major bleeding as:

1. Any intracranial* bleeding, OR
2. Clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hb) of ≥5 g/dL (or, when haemoglobin is not available, a fall in haematocrit of ≥15%),
   OR
3. Fatal bleeding (a bleeding event that directly led to death within 7 days). (PEGASUS trial appendix[7])

Expert clinical advice to the ERG is that the ISTH classification is more detailed than the TIMI classification. In clinical practice a range of classification systems are used, including the HAS-BLED instrument. The experts commented that the ISTH classification is not routinely used in practice but HAS-BLED and TIMI are.

3.1.5.2 Secondary outcomes

The CS reports two secondary efficacy composite outcomes from the COMPASS trial, both are variants of the primary efficacy composite outcome:

- time (in days) from randomisation to the first occurrence of *coronary heart disease death*, MI, ischaemic stroke or acute limb ischaemia.
- time (in days) from randomisation to the first occurrence of *cardiovascular death*, MI, ischaemic stroke or acute limb ischaemia.

The first of the two composite outcomes includes *coronary heart disease death* which is a narrower definition of death from underlying cardiovascular disease than *cardiovascular death* which was included in the second of the two composite outcomes above. Cardiovascular death includes death due to acute MI, sudden cardiac death, or death due to a cardiovascular procedure. Cardiovascular death is used as an event in the economic model as part of the absorbing state death which also includes deaths due to fatal bleeding and background all-cause mortality (non-CV deaths). Both of the secondary efficacy composite outcomes include ischaemic stroke which is a subgroup of the over-arching stroke outcome included in the composite primary efficacy outcome. Ischaemic stroke is included as a health state in the economic model separately to intracranial haemorrhage. Both secondary efficacy composite outcomes also include acute limb ischaemia which is a severe clinical manifestation in patients with peripheral artery disease, and is included in the economic model as a 'health event' (defined as a clinical outcome that patients may experience within each health state. These events differ from 'main events' as they do not affect the subsequent risk of main events or survival).

The CS includes the outcome of net clinical benefit, a composite of cardiovascular death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ. The CS states that this outcome balances the lower risk of cardiovascular death, stroke, or MI (the primary efficacy outcome) against the most serious bleeding events (components of the primary safety outcome). All of the individual components of this composite outcome inform the economic model (as main events) except symptomatic bleeding into a critical organ.

All-cause mortality was measured as any death for which definite evidence of a primary non-CV cause existed.

3.1.5.3 Tertiary outcomes

All of the individual components of the primary and secondary composite outcomes were tertiary outcomes.

Health-related quality of life (HRQoL) was measured in the COMPASS trial using the EQ-5D instrument (5 dimension, 3 levels) (see section 4.3.6 of this report for further details of how this informed the economic model).

The other tertiary outcomes reported in the CS included arterial revascularisation, limb amputation, and venous thromboembolism (VTE). Of these, limb amputation (major / minor) and VTE are included in the economic model as health events.

3.1.5.4 Safety outcomes

Adverse events were measured in the COMPASS trial and classified by the Medical Dictionary for Regulatory Activities (MedDRA) version 2.0. Events were measured by laboratory tests (e.g. including cardiac biomarkers), and physical measurements. Definitions for adverse event and serious adverse event are provided in CS Table 7.

ERG conclusion

The CS reports a comprehensive range of efficacy and safety measures, based on those included in the COMPASS trial. The primary efficacy composite outcome includes appropriate major health events (MI, stroke, and cardiovascular death), which individually inform the economic model as main events. This composite outcome has been used in other RCTs of antithrombotic agents and in previous NICE appraisals.

The primary safety composite outcome of major bleeding includes fatal bleeding, and/or symptomatic bleeding in a critical area or organ, bleeding into the surgical site requiring re-operation, and/or bleeding leading to hospitalisation (with or without an overnight stay). The two key clinical trials included in the company's indirect comparison of rivaroxaban + aspirin versus ticagrelor + aspirin use differing classifications of major bleeding. The ISTH classification is more sensitive and captures more major bleeding events leading to hospitalisation. We discuss this further in section 3.1.7 of this report.

3.1.6 Description and critique of the company's approach to trial statistics

3.1.6.1 Hypothesis and statistical power sample size calculation

The COMPASS trial's main hypothesis was that rivaroxaban 2.5mg bd + aspirin 100mg or rivaroxaban 5mg bd alone would be more effective than aspirin 100mg alone in reducing the risk of recurrent cardiovascular events (i.e. the primary efficacy composite outcome).

The trial was event driven with a target sample size of 27,400 patients (27,395 were subsequently randomised). This sample size was based on a primary efficacy outcome expected event-rate of 3.3 per 100 person-years in the aspirin only arm. The trial was designed to continue until at least 2200 participants had a confirmed primary efficacy outcome, providing 90% power to detect a 20% relative risk reduction in each of the two comparisons of rivaroxaban versus aspirin. The planned study duration was five years.

Two formal interim analyses of efficacy were planned, when 50% and 75% of primary efficacy events had occurred, respectively. The trial was stopped after a mean follow-up of 23 months when 1324 of the planned 2200 events had occurred (i.e. a total of 1324 patients across the three trial arms had experienced a primary efficacy outcome event). The independent data and safety monitoring board recommended stopping the trial after the planned first interim analysis for efficacy (stated as 50% of planned events in the CS, though the ERG notes that 1324/2200 is approximately 60%) demonstrated a consistent difference in the primary efficacy outcome in favour of rivaroxaban 2.5mg bd + aspirin 100mg od.

An early stop of the trial for efficacy had not been anticipated by the study investigators, and therefore a strategy for formal testing of secondary outcomes at the interim analysis was not

pre-specified. The CS does not comment on the implications of this. The ERG presumes that the planned strategy for testing secondary outcomes at the final follow-up were implemented.

The CS notes that one of the consequences of early study termination is the occurrence of fewer primary events "which affects statistical power for comparisons" (CS page 153). The ERG concurs with this assertion but notes the relative risk reduction achieved for the comparison between rivaroxaban + aspirin versus aspirin alone exceeded the 20% threshold in the power calculation (24% - see section 3.3. of this report for a summary of the trial results). Furthermore, the confidence interval for the primary efficacy outcome HR for this comparison was relatively narrow and did not cross one (HR=0.76; 95% CI 0.66-0.86; two-sided p<0.01). This suggests that there was sufficient statistical power despite fewer planned events occurring by the time of early trial termination. However, the power calculation was based on the whole trial population and statistical power will be further reduced in the three subpopulations of particular interest included in the CS (see below).

The CS also discusses the possibility of over-estimation of treatment effects in trials that are stopped early. The CS suggests that the modified Haybittle–Peto rule which was used as the stopping boundary for the interim analyses, required substantial evidence to meet it i.e. a difference of four standard deviations (SDs) at the first interim analysis that was consistent over a period of three months, and a consistent difference of three SD at the second interim analysis. The pre-specified conservative stopping boundary was chosen to make it difficult to stop the trial early for efficacy reasons.

The ERG notes that there has been debates in the literature about the impact of early stopping of trials on the effect estimates.[8] A simulation study showed that in trials with a well-designed interim-monitoring plan, stopping the trial when 50% or greater of the information has been collected has a negligible impact on estimation.[9] Early interim analyses (<or=25% of the required information) raises concerns about the inflation of the treatment effect. Given that COMPASS had accumulated over 50% of primary efficacy outcome events at the first interim analysis it is reasonable to assume that the effect estimates are less likely to be over-estimated in this trial.

The results and analyses of all efficacy and safety outcomes are presented for events occurring up to the global rivaroxaban / aspirin outcomes cut-off date of 6th February 2017 that were

adjudicated to have met their definition i.e. 'unrefuted by adjudication (see below for details of adjudication).

3.1.6.2 Statistical testing procedures

Kaplan–Meier (KM) estimates of the cumulative risk were used to evaluate time to event occurrences. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were obtained from stratified Cox proportional-hazards models. CS Appendix O provides a plot of the log of the negative log of the KM estimates of the survival function versus the log of time, to verify the assumption of proportional hazards. The plot is provided for the primary efficacy outcome only and visual inspection of the plots shows that the survival curves become more parallel over time as more events occur. The CSR reports that a time-treatment interaction generated a p=0.1967 for the interaction in the comparison of rivaroxaban 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg "indicating a trend for an interaction" (CSR page 258). The CS does not report details of whether the proportional hazard assumption was supported for other trial outcomes. The KM survival curves for rivaroxaban 2.5mg + aspirin and aspirin alone presented in the CS for secondary outcomes appear parallel based on visual inspection by the ERG.

Multiplicity can be a problem in statistical testing, whereby running multiple statistical tests increases the probability of finding statistically significant results by chance even if there is no underlying effect. In the COMPASS trial a mixture gatekeeping procedure based on the Hochberg test was used to address the potential for multiplicity related to testing two primary and six secondary hypotheses. The Hochberg-based gatekeeping procedure is based on an extension of the general mixture methodology developed in Dmitrienko and Tamhane.[10, 11] The trial statistical analysis plan (SAP) reports that the methodology has been used in multiple phase III clinical trials. Further detail of this procedure is given in CS Appendix M.

The Hochberg-based procedure was used to protect the Type I error rate (incorrect rejection of the null hypothesis) with respect to eight null hypotheses at a single decision point. The eight null hypotheses were grouped into four families, each family containing a comparison of rivaroxaban + aspirin versus aspirin and a comparison of rivaroxaban versus aspirin on one for the primary and one for each of the three secondary outcomes. A null hypotheses was to be tested only if the preceding null hypothesis was rejected. Each rivaroxaban treatment arm was

first compared with the aspirin only arm on the primary efficacy outcome, followed by the same comparisons on the three ordered secondary efficacy outcomes:

- Composite of coronary heart disease death, ischaemic stroke, MI, or acute limb ischaemia.
- Composite of cardiovascular death, ischaemic stroke, MI, or acute limb ischaemia.
- Mortality (all cause).

The Hochberg-based approach is an established methodology to adjust for multiple testing and the ERG considers its use in COMPASS to be acceptable albeit it is limited to selected outcomes and excludes subgroup analysis.

3.1.6.3 Missing data

The results and analyses of all efficacy and safety outcomes are presented in the CS for events occurring up to the 'global rivaroxaban / aspirin outcomes cut-off date of 6th February 2017' (i.e. at the early termination of the trial at the first interim analysis). Time to event outcomes were censored at the earliest of the global cut-off date and the patient's last contact date during the treatment portion of the trial. The number of non-completers (patients lost to follow-up or who withdrew consent) was small in the trial: a total of 20 patients (0.2%) in the rivaroxaban 2.5mg + aspirin arm and 24 patients (0.2%) in the aspirin arm at the global cut-off date. The CS reports that final follow-up visits were planned after the decision to terminate the study was made and nearly all patients (>99% of patients with completed follow-up visits) completed this visit by May 2017. The ERG notes that data for this final follow-up visit are not reported in the CS though were included in sensitivity analyses of the primary efficacy outcome. The results of the sensitivity analysis were similar to those based on the global cut-off date of February 2017 – see CS section B.2.4 and CS Appendix N).

CS table 10 provides further details of procedures followed to handle missing data.

The EQ-5D instrument was administered at baseline, as well as at year two and at the final rivaroxaban/aspirin follow-up visit (by May 2017). The CSR reports that EQ-5D questionnaire were analysed as available, with no imputation of missing values. The ERG notes from CS Table 28 that at baseline EQ-5D data are presented for 9089/9152 (99%) patients in the rivaroxaban 2.5mg and aspirin arm and 9067/9126 (99%) patients in the aspirin arm. This outcome therefore is not based on an ITT analysis. Final data were available for 6281 and 6222

patients in the respective trial arms, indicating a significant amount of missing data for this outcome (approximately 31% of patients missing).

3.1.6.4 Data analysis sets

The trial had two analysis populations:

- Full analysis set, based on the intention-to-treat principle including all randomised patients up to the global cut-off date (6th February 2017).
- Safety analysis set, based on all randomised patients who received at least one dose of study medication (overall 27,351/27,395 randomised patients; 99.8%).

The ITT population was used for the analysis of all efficacy outcomes as well as the primary safety outcome of major bleeding (though, as commented above, EQ-5D was analysed by ITT). The CS does not explicitly state whether under the definition of ITT patients were analysed in the trial arms to which they had been randomised (i.e. in cases of patient crossover). The ERG assumes patients were analysed within their randomised trial arms. The safety analysis set was used for the analysis of adverse events. A sensitivity analysis explored treatment-emergent major bleeding events based on the safety analysis set, which produced similar results to those based on the full analysis set (CS Appendix N).

3.1.6.5 Subgroups

The CS presents results of the primary efficacy outcome and the primary safety outcome for a number of subgroups in CS appendix L. All of these are based on the ITT population. The subgroups include demographic characteristics (e.g. age, sex, race, geographical region) and prognostic factors (e.g. estimated GFR, hypertension, CAD, PAD). These subgroups are amongst a number of subgroups pre-specified in the trial's SAP, though not all of the subgroups in the SAP are reported in the CS or associated journal publications.

The ERG notes that only one of the three subpopulations of interest in the CS was pre-specified in the SAP: patients with both CAD and PAD. The other two subpopulations of interest in the CS (i.e. CAD+PRF and CAD+HF) were not pre-specified in the SAP. A subgroup based on estimated GFR was pre-specified (≤60ml/min, >60ml/min) but this was not restricted to CAD patients. Likewise, history of heart failure was a pre-specified subgroup in the SAP but was not restricted to CAD patients (NB. Results for the subgroup of patients by heart failure are not presented in the CS). However, all three subpopulations were specified in an additional SAP

(dated July 2017) describing additional analyses related to health economics and outcomes research.

CS Appendix E also reports subgroup analyses for each of the three respective subpopulations of interest to the CS (CS Figures 59, 60, 61, 63, 64 and 65). The subgroup variables include demographic factors and selected prognostic factors (e.g. MI history, diabetes, hypertension etc). Caution is required in the interpretation of these analyses as they do not appear to be pre-specified and they will be underpowered due to relatively small sample sizes.

The SAP reports assessing treatment-subgroup interactions using a stratified Cox proportional hazards model. The SAP also states that no interactions with any of the subgroups were expected. P values for the interaction tests are reported for the subgroup results in the CS (Appendix E) and the main trial journal publication for the primary efficacy outcome and the primary safety outcome.

One of the trial journal publications reports outcomes restricted to the subpopulation of patients with CAD (approximately 90% of the ITT population).[12] The publication states that a sample size calculation was not planned in advance for this subpopulation but given the majority of the enrolled patients were expected to have CAD, statistical power to detect a 20% relative risk reduction was expected to be greater than 80% (as stated above, the statistical power was 90% for the sample size calculation in the whole trial population). The publication reports outcomes for number of subgroups of the CAD subpopulation, based on demographic and prognostic factors (the latter including PAD).

3.1.6.6 Outcome adjudication

An adjudication process was undertaken by an event adjudication committee to verify that investigator-reported events accurately met the trial's pre-specified event definitions. The adjudication committee comprised members with clinical and methodological expertise. A list of the names of the committee members is published in the supplementary appendix to the primary trial journal publication,[13] though their affiliations and relationship with the company are not specified.

Outcomes that underwent adjudication were MI, stroke, death, severe limb ischaemia, angina, heart failure, VTE, cancer, bleeding and gastrointestinal events. CS Appendix L provides an

overview of the adjudication process, whereby an algorithm was followed until events were ultimately classified as 'unrefuted final', or 'refuted'. Efficacy and safety results presented in the CS were based on unrefuted events (i.e. those which were judged to meet pre-specified event definitions).

Table S3 in the supplement to the trial journal publication provides a sensitivity analysis of investigator-reported and adjudicated results for the primary and secondary composite outcomes.[13] CS Appendix N (Table 200) also provides this information for the three subpopulations of interest in the CS. There were slightly fewer adjudicated events compared to investigator-reported events for each outcome, but HRs were similar between the investigator and adjudicated results.

ERG conclusion

The statistical procedures used in the COMPASS trial are, overall, appropriate. The trial was stopped at the first interim analysis for meeting pre-defined efficacy stopping criteria, when approximately 60% of the events required in the statistical power calculation had occurred. The primary efficacy outcome was statistically significant for the comparison of 2.5mg bd + aspirin vs aspirin 100mg alone, with a relatively narrow confidence interval, suggesting adequate statistical power. ITT analyses were used for the majority of efficacy outcomes, and missing data was low (loss to follow-up/consent withdrawal less than 1%). Only one of the three subpopulations of interest in the CS was pre-specified in the trial (CAD+PAD), thus the other two subpopulations (CAD+HF and CAD+PRF) are post-hoc trial analyses (though requested by the NICE scope of the appraisal). These subpopulations comprise around 20% of the randomised population and they will be statistically underpowered for efficacy and safety outcomes.

3.1.7 Description and critique of the company's approach to the evidence synthesis

The CS presents data supported by a narrative review of the single RCT, the COMPASS RCT, which assessed rivaroxaban + aspirin in a population of adults with stable CAD and/or PAD at a high risk of ischaemic events. As only one trial was available, no meta-analysis was undertaken.

The trial evidence compares rivaroxaban + aspirin to aspirin alone. No direct evidence was identified by the company's systematic review for comparisons of rivaroxaban + aspirin with

ticagrelor + aspirin. The company therefore conducted an indirect treatment comparison (ITC) to estimate the relative efficacy of rivaroxaban and ticagrelor. The company were asked to clarify the status of the ITC as it does not directly inform the economic model (Clarification question A1). The company explained that the indirect comparison was presented to provide "easily interpretable information on the relative efficacy/safety of both treatments" but that the rivaroxaban + aspirin versus ticagrelor + aspirin hazard ratios were not used in the economic model (see section 4.3.5 of this report for a discussion of treatment effectiveness in the model).

The ITC is underpinned by the company's systematic review reported in CS Appendix D. This systematic review identified two trials to include in the indirect comparison, the COMPASS RCT (3 references) and the PEGASUS RCT (10 references). As already summarised (Section 3.1.3) the COMPASS RCT compared rivaroxaban (2.5 mg twice a day) + aspirin (100 mg daily) to aspirin alone (100 mg daily). The PEGASUS RCT compared ticagrelor (60 mg twice a day) + aspirin (75-150 mg daily) to aspirin alone. These two RCTs therefore allow the comparison of rivaroxaban + aspirin to ticagrelor + aspirin through the common comparator of aspirin alone (Figure 2).

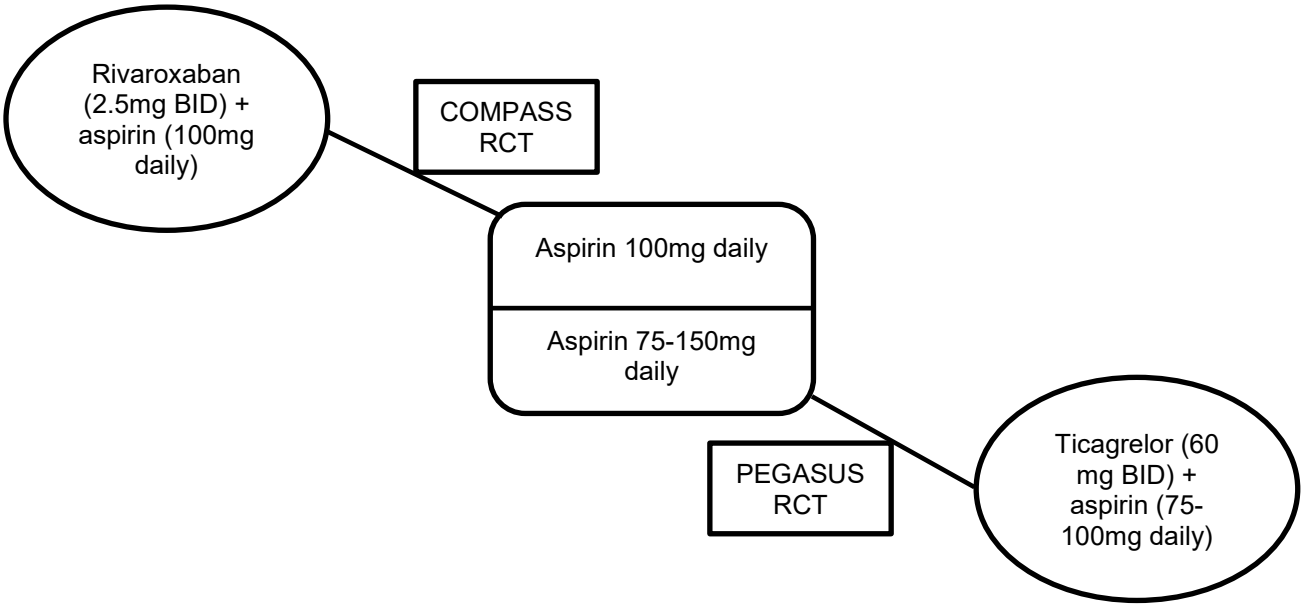


Figure 2 Schematic of the ITC for rivaroxaban + aspirin versus ticagrelor + aspirin

The ERG has quality assessed the COMPASS RCT and the PEGASUS RCT using NICE's suggested criteria (Table 11).

Table 11 Company and ERG assessment of the COMPASS and PEGASUS RCTs

		COMPASS	PEGASUS
1. Was randomisation carried out appropriately?	CS:	Yes	Yes
	ERG:	Yes	Yes
2. Was concealment of treatment allocation adequate?	CS:	Yes	Yes
	ERG:	Yes	Yes
3. Were groups similar at outset in terms of prognostic factors?	CS:	Yes	Yes
	ERG:	ITT: Yes CAD+PAD subpopulation: Yes; CAD+HF subpopulation: Yes; CAD+PRF subpopulation: Yes	ITT: Yes CAD+PAD and CAD+PRF subpopulation: data not available for separate trial arms; CAD+HF subpopulation: no data available
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS:	Yes	Yes
	ERG:	Yes	Yes
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No	No
	ERG:	No	Yes
Comment: CS Appendix D Figure 57 shows the progress of patients though the COMPASS study (ITT set). Proportions of patients who were study non-completers is very low and similar between the two study arms. For PEGASUS paper states that the proportions of patients in each group who discontinued treatment prematurely over the duration of the trial were 28.7% in the 60 mg of ticagrelor twice daily arm, and 21.4% in the placebo arm (P<0.001). The paper states that the majority of the premature discontinuations in the ticagrelor group were due to adverse events.			
6. Is there any evidence that authors measured more outcomes than reported?	CS:	No	No
	ERG:	No	No
7. Did the analysis (a) include an ITT analysis? (b) If so, was this appropriate and (c) were appropriate methods used to account for missing data?	CS:	(a) Yes (b) Yes (c) Yes	Yes
	ERG:	(a) Yes (b) Yes (c) Yes	(a) Yes (b) Yes (c) Yes

As stated above, the ERG agrees with the company's assessment of the COMPASS RCT. However, for the assessment of the PEGASUS trial the ERG disagreed with the company for one issue, of whether there were any unexpected drop-outs between groups. The company judged that there were no unexpected drop-outs between groups but the ERG notes that a statistically significantly greater proportion of patients discontinued treatment prematurely in the ticagrelor 60mg arm (28.7%) compared to the placebo arm (21.4%, p<0.001). The published PEGASUS paper[7] states that the majority of the premature discontinuations in the ticagrelor group were due to adverse events. ITT analyses were conducted which should have minimised the impact of any attrition bias due to the uneven proportions between groups of patients

discontinuing treatment prematurely, and the ERG also notes that patients who dropped out of treatment were expected to continue attending scheduled follow-up visits.

Overall the ERG believes the PEGASUS RCT is a well conducted study which is likely to be at a low risk of bias.

An ITC was conducted using the Bucher et al method[14] which compares the magnitude of the treatment effects in the RCTs whilst preserving randomisation. Indirect comparisons were conducted for the ITT populations and results reported for 13 outcomes (composite outcome of stroke/MI/CV death; all-cause death; cardiovascular death; all strokes; ischaemic stroke; MI; major adverse limb event; acute limb ischaemia; VTE; major bleeding; intracranial bleeding; haemorrhagic stroke; fatal bleeding). An ITC was not possible for two outcomes (amputations; gastrointestinal bleeding).

For the subpopulations ITCs were possible for fewer outcomes (CAD+PAD: 9 outcomes; CAD+PRF: 6 outcomes; CAD+HF ITC not possible as not data available for this subpopulation from the PEGASUS RCT).

The ERG has considered the methods, assumptions and reporting of the ITC using the criteria suggested by Donegan and colleagues[15] and the findings are reported in Appendix 9.1. The analysis used an appropriate method, but the key area of concern regarding the ITC is that there are some important differences between the patients enrolled in the COMPASS RCT and those enrolled in the PEGASUS RCT:

- the proportion of patients with a prior MI was 62% in the COMPASS RCT but 100% in the PEGASUS RCT
- the time elapsed since the prior MI differed because this was restricted to between one and three years in the PEGASUS RCT but in COMPASS patients could have had an MI at any time within the past 20 years
- the proportion of patients with PAD differed, being 27% in the COMPASS RCT but only 5% in the PEGASUS RCT

There were also some differences in how outcomes were defined:

- major bleeding was defined by the modified ISTH criteria in the COMPASS RCT but by the TIMI criteria in the PEGASUS RCT

- the definition of MI in the COMPASS RCT excluded sudden cardiac death (instead sudden cardiac death was assessed as a CV-related death) whereas in PEGASUS, sudden unexpected cardiac deaths were included in the definition of a MI.

The only one of these population and outcome definition differences that the company comments on is that of the major bleeding definition, which the CS states would be anticipated to bias the analysis against rivaroxaban + aspirin in the ITC against ticagrelor + aspirin. The company does not discuss the potential impacts of the other differences between the trials. In the ERG's view the population in the PEGASUS trial aligns more closely to trials of secondary prevention after acute coronary syndrome whereas the focus of the current STA is a secondary prevention in people with CAD and/or PAD. However, the ERG is aware that there does not appear to be any other source of data to enable a rivaroxaban versus ticagrelor comparison in the CAD and/or PAD population.

The ERG and NICE asked the company to clarify why they did not limit the COMPASS trial population in the ITC to the subgroup with a history of MI (Clarification question A2). The company responded that adjusting the population of COMPASS to a subgroup with a history of MI was not necessary because for the primary efficacy composite outcome of the trial having a 'history of MI' is not effect-modifying. The ERG is concerned that, whilst 'history of MI' may not be effect-modifying for the primary efficacy outcome, this may not be the case for other outcomes. For example, in a secondary publication of the trial[12] although the p-value for the interaction test of the subgroup analysis by history of MI for major bleeding is not significant (p=0.54), the confidence intervals for the history of MI <2 years and 2-5 years are wide and cross 1 (Figure 4B) (NB. This subgroup analysis is restricted to the subpopulation of patients with CAD). Furthermore, in addition to the hazard ratios, the underlying event rates for key outcomes according to 'history of MI' are important and have an impact on costs and utilities in the economic modelling. For these reasons the ERG believe that effect of limiting the COMPASS population to those with a history of MI should have been explored. The ERG has conducted a scenario analysis for the subgroup of patients with a prior MI (see section 4.4 of this report). Finally, as discussed earlier in this report, "People who have had a previous myocardial infarction" is a subgroup of interest listed in the NICE scope for this appraisal. Expert clinical advice to the ERG is that patients with a prior MI are at risk of recurrent MIs/other events.

The differences between the ITT populations of COMPASS and PEGASUS are likely to feed through in the three subpopulations of particular interest in this STA (CAD+PAD; CAD+HF;

CAD+PRF). However, because PEGASUS baseline trial data were not available separately for each arm of the trial for these subpopulations (only for all treatment groups combined which included a ticagrelor 90mg arm that is not included in the ITC) it is difficult to be certain how similar population characteristics are between the trials for these subpopulations.

ERG conclusion

No direct evidence compares rivaroxaban + aspirin with ticagrelor + aspirin. Therefore the company conducted an ITC, underpinned by a systematic review, to estimate the relative efficacy of rivaroxaban and ticagrelor. The two RCTs included in the ITC, COMPASS (rivaroxaban + aspirin versus aspirin) and PEGASUS (ticagrelor + aspirin versus aspirin) were both well conducted studies likely to be at a low risk of bias. An appropriate method was used for the ITC but the ERG is concerned about the impact of important differences between the patients enrolled in the two trials. In particular, a history of MI should have been explored because:

i) ticagrelor + aspirin would only be a treatment option for the patients in the COMPASS trial with a history of MI

ii) whilst 'history of MI' may not be effect-modifying for the primary efficacy outcome, this may not be the case for the other outcomes included in the economic model or subgroups.

iii) it is important to use a subgroup by 'history of MI' in the economic model because the event rates for key outcomes have an impact on costs and utilities in the economic modelling.

iv) "People who have had a previous myocardial infarction" is a subgroup of interest listed in the NICE scope for this appraisal.

3.2 Summary statement of company's approach to systematic review

Table 12 below provides a quality assessment of the company's systematic review of effectiveness, using criteria from the Centre for Reviews and Dissemination, University of York. In summary, the ERG consider that the systematic review has been well conducted.

Table 12 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments

1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research? ie all studies identified	Yes
3. Is the validity of included studies adequately assessed?	Yes, using the NICE recommended criteria
4. Is sufficient detail of the individual studies presented?	Yes, characteristics and results of the trials are presented in CS appendix.
5. Are the primary studies summarised appropriately?	Yes, narrative synthesis of the COMPASS trial. Meta-analysis not possible as only one rivaroxaban trial was identified.

3.3 Summary of submitted evidence

In the following subsections we summarise the results of the COMPASS RCT as presented in the CS, focusing on the primary outcomes (efficacy and safety) and outcomes that are included in the economic model. For each outcome, data from the ITT population are presented, followed by the data for the three subpopulations (CAD+PAD, CAD+HF and CAD+PRF). The primary safety outcome data are presented in section 3.3.12 of this report. Outcomes that are not reported here but which can be found in the CS are:

- Secondary outcome composite of ischaemic stroke, MI, acute limb ischaemia or death from coronary heart disease (CS Tables 19-22)
- Secondary outcome composite of ischaemic stroke, MI, acute limb ischaemia or cardiovascular death (CS Tables 19-22)
- death from any cause (CS Tables 19-22)
- death from coronary heart disease (CS Tables 19-22)
- deep vein thrombosis and pulmonary embolism (CS Tables 23 and 25)
- revascularisation (CS Table 24)
- haemorrhagic stroke (CS Table 27)

Finally, it should be noted that for composite outcomes and each component part of the composite outcomes, only the first event after randomisation has been reported by the company. Subsequent events of the same type are not shown and consequently the events in the component parts of a composite outcome may sum to a higher value than that shown for the composite outcome.

3.3.1 Primary efficacy outcome: Composite of cardiovascular death, stroke or MI

In the ITT population both the crude incidence and the incidence rate per 100 patient-years of the composite primary efficacy outcome of cardiovascular death, stroke or MI was higher in the aspirin arm than in the rivaroxaban + aspirin arm. The absolute difference in the incidence rate per 100 patient-years was 0.7. The HR of 0.76 (95% CI 0.66 to 0.86), indicating a 24% reduction in the risk of having the composite outcome in the rivaroxaban + aspirin arm, was statistically significant (p<0.001) (Table 13).

Table 13 Primary efficacy outcome results

Population	Outcome: composite of CV death, stroke, or MI	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT		**N=9152**	**N=9126**	0.76 (0.66-0.86)	<0.001
	Crude incidence n (%)	379 (4.1)	496 (5.4)		
	Incidence rate per 100 patient-years (95% CI)	2.18 (1.97-2.41)	2.88 (2.64-3.15)		
CAD+PAD		**n=1656**	**n=1641**	0.67 (0.52-0.87)	0.00262
	Crude incidence n (%)	94 (5.7)	138 (8.4)		
	Incidence rate per 100 patient-years (95% CI)	3.06 (2.47-3.75)	4.55 (3.83-5.38)		
CAD+HF		**n=1909**	**n=1912**	0.68 (0.53-0.87)	0.002
	Crude incidence n (%)	105 (5.5)	151 (7.9)		
	Incidence rate per 100 patient-years (95% CI)	3.12 (2.55-3.78)	4.60 (3.89-5.39)		
CAD+PRF		**n=1824**	**n=1873**	0.73 (0.57-0.92)	0.007
	Crude incidence n (%)	119 (6.5)	165 (8.8)		
	Incidence rate per 100 patient-years (95% CI)	3.42 (2.84-4.10)	4.71 (4.02-5.48)		

Source: CS tables 13 and 14
bd – twice a day; od – once a day

In the three subpopulations the company is focussing on, the incidence rate per 100 patient-years of the primary efficacy outcome is higher than it is in the ITT population in both the trial arms. The absolute differences in the primary efficacy outcome between the two arms of the trial again favour the rivaroxaban + aspirin arm (difference in the incidence rate per 100 patient years of 1.5 for the CAD+PAD subpopulation, 0.9 for the CAD+HF subpopulation and 1.3 for the CAD+PRF subpopulation). The HR for the subpopulations are all less than that of the ITT population (but with wider confidence intervals). This indicates a greater and statistically significant reduction in risk of having the composite outcome in the rivaroxaban + aspirin arm of the subpopulations in comparison to the ITT population. The CAD+PAD subpopulation demonstrated the greatest reduction in risk (33%) with a HR of 0.67 (95% CI 0.52 to 0.87, p=0.00262), with a very similar result for the CAD+HF subpopulation (HR 0.68, 95% CI 0.53 to 0.87, p=0.002) whereas the result for the CAD+PRF subpopulation was closer to that of the ITT population (HR 0.73, 95% CI 0.57 to 0.92, p=0.007) (Table 13).

3.3.2 Individual components of the primary efficacy composite outcome

In addition to presenting the results of the primary composite outcome, the CS also provides the results for the individual components of the primary efficacy outcome, which were classed as tertiary endpoints.

3.3.2.1 Myocardial infarction

The reduction in the incidence of MI in rivaroxaban + aspirin arm of the ITT population was not statistically different to that of the aspirin only arm (HR 0.86, 95% CI 0.7 to 1.05, p=0.14). The incidence of MI in the three subpopulations from the trial was higher in both study arms but the reduction in the incidence in the rivaroxaban + aspirin arm in comparison to the aspirin alone arm was not statistically significant in any subpopulation (Table 14). Experiencing an MI is one of the health states in the company's economic model.

3.3.2.2 Stroke

There was a statistically significant reduction in the risk of stroke for patients in the rivaroxaban plus + group in comparison to the aspirin alone group in the ITT population and the three subpopulations (Table 15). The greatest reduction in the risk of stroke was observed in the CAD+PRF subpopulation (HR 0.37, 95% CI 0.21 to 0.65, p=0.0003) followed by the CAD+PAD and CAD+HR subpopulations (HR 0.46 and 0.49 respectively). The reduction in the risk of stroke was greater in all subpopulations (albeit with wider 95% confidence intervals) than in the ITT population (HR 0.58, 95% CI 0.44 to 0.76, p<0.01).

Table 14 Tertiary outcome of MI (component of the primary efficacy composite outcome)

Population	Outcome: MI	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT		N=9152	N=9126	0.86 (0.70-1.05)	0.14
	Crude incidence n (%)	178 (1.9)	205 (2.2)		
	Incidence rate per 100 patient-years (95% CI)	1.02 (0.87-1.18)	1.18 (1.03-1.36)		
CAD+PAD		N=1656	N=1641	0.72 (0.49-1.08)	0.116
	Crude incidence n (%)	42 (2.5)	57 (3.5)		
	Incidence rate per 100 patient-years (95% CI)	1.36 (0.98-1.84)	1.87 (1.41-2.42)		
CAD+HF		N=1909	N=1912	0.81 (0.54-1.22)	0.304
	Crude incidence n (%)	42 (2.2)	51 (2.7)		
	Incidence rate per 100 patient-years (95% CI)	1.24 (0.90-1.68)	1.54 (1.14-2.02)		
CAD+PRF		N=1824	N=1873	0.74 (0.51-1.06)	0.099
	Crude incidence n (%)	50 (2.7)	68 (3.6)		
	Incidence rate per 100 patient-years (95% CI)	1.43 (1.06-1.89)	1.92 (1.49-2.43)		

Source: CS tables 13 and 14
bd – twice a day; od – once a day

Table 15 Tertiary outcome of stroke (component of the primary efficacy outcome)

Population	Outcome: stroke	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT		N=9152	N=9126	0.58 (0.44-0.76)	<0.001
	Crude incidence n (%)	83 (0.9)	142 (1.6)		
	Incidence rate per 100 patient-years (95% CI)	0.47 (0.38-0.59)	0.82 (0.69-0.96)		
CAD+PAD		N=1656	N=1641	0.46 (0.25-0.83)	0.009
	Crude incidence n (%)	16 (1.0)	35 (2.1)		
	Incidence rate per 100 patient-years (95% CI)	0.51 (0.29-0.84)	1.13 (0.79-1.58)		

CAD+HF	**Crude incidence n (%)**	**N=1909**	**N=1912**	0.49 (0.28-0.85)	0.009
		19 (1.0)	38 (2.0)		
	Incidence rate per 100 patient-years (95% CI)	0.56 (0.34-0.87)	1.14 (0.81-1.57)		
CAD+PRF	**Crude incidence n (%)**	**N=1824**	**N=1873**	0.37 (0.21-0.65)	0.0003
		16 (0.9)	45 (2.4)		
	Incidence rate per 100 patient-years (95% CI)	0.45 (0.26-0.74)	1.26 (0.92-1.69)		

Source: CS tables 13 and 14
bd – twice a day; od – once a day

3.3.2.3 Cardiovascular deaths

A statistically significant reduction in the risk of cardiovascular deaths in the rivaroxaban + aspirin group in comparison to the aspirin alone group was apparent in the ITT population and in the CAD+PAD and CAD+HF subpopulations (Table 16). In the CAD+PRF subpopulation, although the incidence rate of cardiovascular deaths was lower in the rivaroxaban + aspirin arm than in the aspirin alone arm, the p-value for the HR of 0.86 indicated the difference was not statistically significant (p=0.375). Cardiovascular deaths (due to either a MI, stroke, heart failure, subsequent to a cardiovascular procedure, a sudden cardiac death or any other type of cardiovascular death) is taken into account in the company's economic model as part of the absorbing state of death (which also includes fatal bleeding and non-cardiovascular deaths).

Table 16 Tertiary outcome of cardiovascular deaths (component of the primary efficacy outcome)

Population	Outcome: CV death	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT	**Crude incidence n (%)**	**N=9152**	**N=9126**	0.78 (0.64-0.96)	0.02
		160 (1.7)	203 (2.2)		
	Incidence rate per 100 patient-years (95% CI)	0.91 (0.77-1.06)	1.16 (1.00-1.33)		
CAD+PAD	**Crude incidence n (%)**	**N=1656**	**N=1641**	0.72 (0.49-1.07)	0.0102
		43 (2.6)	59 (3.6)		

	Incidence rate per 100 patient-years (95% CI)	1.38 (1.00-1.85)	1.90 (1.44-2.45)		
CAD+HF	**Crude incidence n (%)**	**N=1909**	**N=1912**	0.65 (0.47-0.92)	0.013
		56 (2.9)	84 (4.4)		
	Incidence rate per 100 patient-years (95% CI)	1.64 (1.24-2.13)	2.51 (2.00-3.10)		
CAD+PRF	**Crude incidence n (%)**	**N=1824**	**N=1873**	0.86 (0.62-1.20)	0.375
		64 (3.5)	76 (4.1)		
	Incidence rate per 100 patient-years (95% CI)	1.81 (1.39-2.31)	2.10 (1.66-2.63)		

Source: CS tables 13 and 14
bd – twice a day; od – once a day

3.3.3 Non-cardiovascular deaths

In addition to the outcome of cardiovascular deaths presented in section 3.3.2.3 above, the company also reported non-cardiovascular deaths (Table 17). The cardiovascular and the non-cardiovascular deaths data were combined by the company and presented as 'deaths from any cause' which is not reproduced in this ERG report (it can be found in CS Tables 19, 20, 21 and 22). Non-cardiovascular deaths were a secondary outcome and are implemented in the model as part of the absorbing model state of death.

Table 17 Secondary outcome of non-cardiovascular deaths

Population	**Outcome: Non-CV death**	**Rivaroxaban 2.5mg bd + aspirin 100mg od**	**Aspirin 100mg od**	**Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg**	
				HR (95% CI)	**P value**
ITT	**Crude incidence n (%)**	**N=9152**	**N=9126**	0.87 (0.70-1.08)	0.20
		153 (1.7)	175 (1.9)		
	Incidence rate per 100 patient-years (95% CI)	0.87 (0.74-1.02)	1.00 (0.86-1.16)		
CAD+PAD	**Crude incidence n (%)**	**N=1656**	**N=1641**	0.80 (0.51-1.25)	0.3315
		35 (2.1)	44 (2.7)		
	Incidence rate per 100 patient-years (95% CI)	1.12 (0.78-1.56)	1.42 (1.03-1.90)		

CAD+HF	**Crude incidence n (%)**	**N=1909**	**N=1912**	0.61 (0.37-1.00)	0.04682
		25 (1.3)	40 (2.1)		
	Incidence rate per 100 patient-years (95% CI)	0.73 (0.47-1.08)	1.19 (0.85-1.62)		
CAD+PRF	**Crude incidence n (%)**	**N=1824**	**N=1873**	0.81 (0.55-1.20)	0.30041
		45 (2.5)	56 (3.0)		
	Incidence rate per 100 patient-years (95% CI)	1.27 (0.93-1.70)	1.55 (1.17-2.01)		

Source: CS Tables 19, 20, 21, 22

3.3.4 Ischaemic stroke

Experiencing an ischaemic stroke is one of the health states in the economic model and was a tertiary endpoint in the COMPASS RCT. The results for ischaemic stroke were similar to those of the overall outcome of stroke (reported above in section 3.3.2.2) in that a statistically significant reduction in the risk of ischaemic stroke for patients in the rivaroxaban + aspirin group in comparison to the aspirin alone group was observed in the ITT population and the three subpopulations (Table 18). However, there was a minor change in the degree to which the risk of ischaemic stroke was reduced in the different subpopulations in comparison to overall stroke. The CAD+PRF subpopulation experienced the greatest reduction in risk, followed by the CAD+HR and then the CAD+PAD subpopulations (whereas for overall stroke the CAD+PAD subpopulation had a lower risk than the CAD+HR subpopulation).

Table 18 Tertiary outcome of ischaemic stroke

Population	**Outcome: Ischaemic stroke**	**Rivaroxaban 2.5mg bd + aspirin 100mg od**	**Aspirin 100mg od**	**Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg**	
				HR (95% CI)	**P value**
ITT	**Crude incidence n (%)**	**N=9152**	**N=9126**	0.51 (0.38-0.69)	<0.001
		64 (0.7)	125 (1.4)		
	Incidence rate per 100 patient-years (95% CI)	0.36 (0.28-0.47)	0.72 (0.60-0.86)		
CAD+PAD	**Crude incidence n (%)**	**N=1656**	**N=1641**	0.49 (0.26-0.92)	0.0244
		14 (0.8)	29 (1.8)		

	Incidence rate per 100 patient-years (95% CI)	0.45 (0.25-0.76)	0.94 (0.63-1.35)		
CAD+HF	**Crude incidence n (%)**	**N=1909**	**N=1912**	0.35 (0.18-0.69)	0.00171
		11 (0.6)	31 (1.6)		
	Incidence rate per 100 patient-years (95% CI)	0.32 (0.16-0.58)	0.93 (0.63-1.32)		
CAD+PRF	**Crude incidence n (%)**	**N=1824**	**N=1873**	0.25 (0.12-0.51)	0.00004
		9 (0.5)	38 (2.0)		
	Incidence rate per 100 patient-years (95% CI)	0.25 (0.12-0.48)	1.06 (0.75-1.46)		

Source: CS Tables 19, 20, 21, 22

3.3.5 Acute limb ischaemia

Acute limb ischaemia was tertiary outcome and one of the health events captured in the company's economic model. The incidence rate per 100 patient-years was lower in the rivaroxaban + aspirin arm than in the aspirin only arm in the ITT population and in the three subpopulations (Table 19). The number of events was low in the CAD+HF and the CAD+PRF subpopulation so no HR was calculated (this had implications for the economic model as described in Section 4.3.5.5 of this report). In the ITT population the HR was 0.55 (95% CI 0.32 to 0.92, p=0.02093) indicating a 45% reduction in the risk of acute limb ischaemia in the rivaroxaban group. In the CAD+PAD subpopulation the point estimate for the HR indicated a greater reduction in risk than in the ITT population but there was greater uncertainty as indicated by the wider 95% confidence intervals and the result is on the boundary of conventional statistical significance (HR 0.48, 95% CI 0.23 to 1.02, p=0.0495).

Table 19 Tertiary outcome of acute limb ischaemia

Population	**Outcome: Acute limb ischaemia**	**Rivaroxaban 2.5mg bd + aspirin 100mg od**	**Aspirin 100mg od**	**Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg**	
				HR (95% CI)	**P value**
ITT	**Crude incidence n (%)**	**N=9152**	**N=9126**	0.55 (0.32-0.92)	0.02093
		22 (0.2)	40 (0.4)		
	Incidence rate per 100 patient-years (95% CI)	0.12 (0.08-0.19)	0.23 (0.16-0.31)		
CAD+PAD		**N=1656**	**N=1641**		

	Crude incidence n (%)	10 (0.6)	21 (1.3)	0.48 (0.23-1.02)	0.0495
	Incidence rate per 100 patient-years (95% CI)	0.32 (0.15-0.59)	0.68 (0.42-1.04)		
CAD+HF		**N=1909**	**N=1912**		
	Crude incidence n (%)	3 (0.2)	9 (0.5)	Not calculated	
	Incidence rate per 100 patient-years (95% CI)	0.09 (0.02-0.26)	0.27 (0.12-0.51)		
CAD+PRF		**N=1824**	**N=1873**		
	Crude incidence n (%)	4 (0.2)	12 (0.6)	Not calculated	
	Incidence rate per 100 patient-years (95% CI)	0.11 (0.03-0.29)	0.33 (0.17-0,58)		

Source: CS Tables 19, 20, 21, 22

3.3.6 Venous thromboembolism (VTE)

VTE was a tertiary outcome and has been included here because it is one of the health events captured in the company's economic model. The overall number of events, and consequently the incident rate per 100 patient-years was low, and there were no events in the rivaroxaban arm of the CAD+HF subpopulation so a HR was not calculated by the company. Although the point estimates for the HR of venous thrombotic events in the rivaroxaban + aspirin arm compared to the aspirin alone arm of the trial was in favour of rivaroxaban + aspirin the confidence intervals around the estimate were wide reaching or exceeding a value of one in all cases (Table 20).

Table 20 Tertiary outcome of venous thromboembolism

Population	**Outcome: Venous thromboembolism (adjudicated)**	**Rivaroxaban 2.5mg bd + aspirin 100mg od**	**Aspirin 100mg od**	**Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg**	
				HR (95% CI)	**P value**
ITT		**N=9152**	**N=9126**		
	Crude incidence n (%)	25 (0.3)	41 (0.4)	0.61 (0.37-1.00)	0.05
	Incidence rate per 100 patient-years (95% CI)	0.14 (0.09-0.21)	0.23 (0.17-0.32)		
CAD+PAD		**N=1656**	**N=1641**	0.57 (0.23-1.46)	0.23771
	Crude incidence n (%)	7 (0.4)	12 (0.7)		

	Incidence rate per 100 patient-years (95% CI)	0.22 (0.09-0.46)	0.39 (0.20-0.68)		
CAD+HF	**Crude incidence n (%)**	**N=1909**	**N=1912**	Not calculated	
		0	9 (0.5)		
	Incidence rate per 100 patient-years (95% CI)	0	0.27 (0.12-0.51)		
CAD+PRF	**Crude incidence n (%)**	**N=1824**	**N=1873**	0.36 (0.13-1.00)	0.04078
		5 (0.3)	14 (0.7)		
	Incidence rate per 100 patient-years (95% CI)	0.14 (0.05-0.33)	0.39 (0.21-0.65)		

Source: CS Tables 23 and 25

3.3.7 Amputation

Amputation is another outcome that contributes data to the company's economic model. In addition to this overall outcome of amputation the company also reported separately on amputation for cardiovascular reasons and amputations for other reasons (CS tables 24 and 26). The overall incidence of amputations was low, but as would be expected amputations among people in the CAD+PAD subpopulation occurred at a higher incidence rate than in either of the other two subpopulations or the ITT population (Table 21). The incidence rate of amputations was lower in the rivaroxaban + aspirin arm than in the aspirin only arm but the difference was not statistically significant.

Table 21 Tertiary outcome of limb amputation

Population	**Outcome: Amputation**	**Rivaroxaban 2.5mg bd + aspirin 100mg od**	**Aspirin 100mg od**	**Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg**	
				HR (95% CI)	**P value**
ITT	**Crude incidence n (%)**	**N=9152**	**N=9126**	0.64 (0.40-1.00)	0.05040
		30 (0.3)	47 (0.5)		
	Incidence rate per 100 patient-years (95% CI)	0.17 (0.12-0.24)	0.27 (0.20-0.36)		
CAD+PAD	**Crude incidence n (%)**	**N=1656**	**N=1641**	0.69 (0.32-1.49)	0.34142
		11 (0.7)	16 (1.0)		
	Incidence rate per 100 patient-years (95% CI)	0.35 (0.18-0.63)	0.52 (0.30-0.84)		

CAD+HF	**Crude incidence n (%)**	**N=1909**	**N=1912**	0.85 (0.29-2.53)	0.76953
		6 (0.3)	7 (0.4)		
	Incidence rate per 100 patient-years (95% CI)	0.18 (0.06-0.38)	0.21 (0.08-0.43)		
CAD+PRF	**Crude incidence n (%)**	**N=1824**	**N=1873**	0.64 (0.25-1.65)	0.35233
		7 (0.4)	11 (0.6)		
	Incidence rate per 100 patient-years (95% CI)	0.20 (0.08-0.41)	0.31 (0.15-0.55)		

Source: CS Tables 24 and 26

3.3.8 Net clinical benefit

The company presents results for net clinical benefit (Table 22) to provide an indication of the balance between rivaroxaban + aspirin in reducing the risk of the primary efficacy outcome (composite of cardiovascular death, stroke or MI) and the increase in risk from fatal bleeding or symptomatic bleeding in a critical area or organ which were two components of the primary safety outcome [the other two components of the safety outcome which are not included were bleeding into the surgical site requiring re-operation and bleeding leading to hospitalisation (with or without an overnight stay)].

Table 22 Composite outcome of net clinical benefit

Population	Outcome: Net clinical benefit (composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ)	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT	**Crude incidence n (%)**	**N=9152**	**N=9126**	0.80 (0.70-0.91)	<0.001
		431 (4.7)	534 (5.9)		
	Incidence rate per 100 patient-years (95% CI)	2.49 (2.26-2.73)	3.11 (2.85-3.39)		
CAD+PAD	**Crude incidence n (%)**	**N=1656**	**N=1641**	0.68 (0.53-0.88)	0.00327
		101 (6.1)	145 (8.8)		
	Incidence rate per 100 patient-years (95% CI)	3.30 (2.69-4.01)	4.80 (4.05-5.65)		
CAD+HF	**Crude incidence n (%)**	**N=1909**	**N=1912**	0.70 (0.55-0.88)	0.00296
		113 (5.9)	159 (8.3)		
	Incidence rate per 100 patient-years (95% CI)	3.37 (2.78-4.05)	4.85 (4.12-5.66)		

CAD+PRF		**N=1824**	**N=1873**		
	Crude incidence n (%)	133 (7.3)	176 (9.4)	0.76 (0.61-0.95)	0.01771
	Incidence rate per 100 patient-years (95% CI)	3.85 (3.22-4.56)	5.04 (4.32-5.84)		

Source: CS Tables 29 and 30

3.3.9 Summary of health related quality of life (HRQoL)

The company presents evidence in the CS on HRQoL using the EQ-5D instrument in the ITT population of the COMPASS RCT. It is apparent from the values presented in Table 23 that there were missing EQ-5D data (approximately 0.7% missing at baseline, 57% at year 2 and 31% at the final visit) and no imputation of missing values was performed. There was very little change between the mean values at baseline and the mean values at the 2-year and final visits. Final visits took place after the decision to terminate the study (outcomes cut-off date of 6th February 2017) and more than 99% of these visits were completed by 15th May 2017. Mean values were very similar in the two arms of the trial.

Table 23 EQ-5D Index score change from baseline in the COMPASS ITT population

Visit	**Rivaroxaban 2.5mg bd + aspirin 100mg od N=9152**				**Aspirin 100mg od N=9126**				**p-value**
	n	**Mean ± SD**	**Median**	**Min-Max**	**n**	**Mean ± SD**	**Median**	**Min-Max**	
Baseline value	9089	0.83±0.195	0.85	-0.59-1.00	9067	0.84±0.191	0.85	-0.59-1.00	
Year 2 value	3906	0.83±0.200	0.85	-0.59-1.00	3904	0.84±0.196	0.85	-0.43-1.00	
Year 2 change from baseline	3901	-0.01±0.190	0.00	-1.59-1.13	3897	-0.01±0.193	0.00	-1.43-1.32	0.1485
Final value	6281	0.84±0.202	0.85	-0.59-1.00	6222	0.84±0.203	0.85	-0.59-1.00	0.7858
Final change from baseline	6256	0.00±0.197	0.00	-1.59-1.12	6197	0.00±0.199	0.00	-1.07-1.59	

Source: CS Table 28

3.3.10 Sub-group analyses results

Results for the three key subpopulations the company presents for this appraisal (CAD+PAD, CAD+HF, CAD+PRF) have been presented alongside those of the ITT population in sections 3.3.1 to 3.3.8 above. For subgroups defined by other patient characteristics (e.g. age, sex,

renal function, diabetes) results for the primary efficacy outcome and the primary safety outcome in the ITT population and the three key subpopulations for the appraisal are presented in CS Appendix E. CS Appendix E also presents a short narrative summary of the subgroup analyses for the secondary efficacy outcomes, for other subgroup analyses of net clinical benefit including the net clinical benefit in people with a history of stroke. Inevitably some of the subgroups defined by patient characteristics were small (e.g. only 76 participants were Black) and consequently some of the confidence intervals around the HRs were wide.

For the primary efficacy outcome the central HR estimates for subpopulations of the ITT population favoured rivaroxaban + aspirin rather than aspirin alone. In the CAD+PAD, CAD+HF and CAD+PRF subpopulations, further analysis by subgroups of other patient characteristics were broadly consistent with the analysis in the ITT population. However, due to low numbers of events, some HRs were not calculated and some confidence intervals lay at or over the line of no effect.

The NICE scope for this appraisal identified four subgroups to be considered if the evidence allowed. Two of these are two of the key subpopulations the company is focussing on (CAD+PAD and CAD+PRF) but the other two, people who have had a previous MI and people who have had multiple MIs, are not commented on by the company. Data are available for the CAD only population defined as 'History of myocardial infarction' (either <2 years, 2-5 years or >5 years) or 'No previous myocardial infarction' in the publication by Connolly et al.[12] Data are also presented for the CAD+PAD, CAD+PRF and CAD+HF subpopulations, defined as 'MI history: Yes' and 'MI history: No', in CS appendix E. These data are presented below in Table 24.

The data presented in Table 24 should be interpreted cautiously, particularly for the CAD+PAD, CAD+HR and CAD+PRF subpopulations. In the CAD only subgroup, results for the primary efficacy outcome for the four subgroups by history of MI are similar (in terms of the HR central estimates). In the CAD+PAD, CAD+HR and CAD+PRF subpopulations the HRs suggest that those with a history of MI may gain more benefit from treatment with rivaroxaban + aspirin than those without a history of MI (HR central estimates are lower and confidence intervals do not cross one in the subgroup with a history of MI).

Table 24 Subgroup analyses for the primary efficacy outcome by history of MI

Population	Subgroups	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	$P_{interaction}$
CAD	History of MI				0.93
	<2 years	49/1218 (4.02%[a])	67/1205 (5.56%[a])	0.70 (0.48-1.01)	
	2-5 years	71/1612 (4.40%[a])	91/1667 (5.46%[a])	0.81 (0.59-1.10)	
	>5 years	127/2824 (4.50%[a])	174/2849 (6.11%[a])	0.72 (0.57-0.91)	
	No previous MI	100/2659 (3.76%[a])	128/2540 (5.04%[a])	0.76 (0.58-0.98)	
CAD+PAD	MI History				NR
	Yes	58/990 (5.86%)	91/1002 (9.08%)	0.63 (0.46-0.88)	
	No	36/666 (5.41%)	47/639 (7.36%)	0.74 (0.48-1.14)	
CAD+HF	MI History				NR
	Yes	86/1511 (5.69%)	128/1536 (8.33%)	0.67 (0.51-0.87)	
	No	19/398 (4.77%)	23/376 (6.12%)	0.78 (0.42-1.44)	
CAD+PRF	MI History				NR
	Yes	82/1248 (6.57%)	126/1281 (9.84%)	0.65 (0.49-0.86)	
	No	37/576 (6.42%)	39/592 (6.59%)	0.97 (0.62-1.53)	

Source: Connolly et al.[12] and CS Appendix E Figures 59, 60 and 61
[a] Percentages calculated by the ERG

3.3.11 Indirect treatment comparison (ITC) results

Indirect treatment comparisons between the COMPASS RCT and PEGASUS RCT were undertaken to enable a comparison of rivaroxaban + aspirin versus ticagrelor + aspirin in the ITT population and the CAD+PAD and CAD+PRF subpopulations. The PEGASUS trial publications did not present any evidence for a CAD+HF subpopulation so it is not possible to conduct an indirect comparison for this subpopulation.

In this section, we present the ITC results for the outcomes presented in sections 3.3.1 to 3.3.7 with the exception of non-cardiovascular deaths (section 3.3.3) for which no ITC was undertaken. In addition to the outcomes presented here, results from ITCs for all-cause death (composite of cardiovascular deaths and non-cardiovascular deaths), major adverse limb event, intracranial bleeding, haemorrhagic stroke and gastrointestinal bleeding are available in the CS (CS Table 32- 34).

The results for the ITCs conducted for the primary efficacy outcome and each of its component parts are reproduced in Table 25. The HRs for the rivaroxaban + aspirin versus ticagrelor + aspirin lay between 0.77 and 1.37 with the confidence intervals for all HRs crossing one indicating that there were no statistically significant differences for any of the outcomes.

Table 25 Indirect comparison results for the primary efficacy composite outcome and its component parts

Outcome	Population	Rivaroxaban + aspirin vs aspirin		Ticagrelor + aspirin vs aspirin		HR [95%CI][a]
		No. RCTs	No. patients	No. RCTs	No. patients	
Stroke/MI/CV death	**ITT**	1	18,278	1	14,112	0.90 [0.75, 1.09]
	CAD+PAD	1	3,297	1	772	0.97 [0.62, 1.53]
	CAD+PRF	1	3,697	1	3,196	0.90 [0.66, 1.23]
MI	**ITT**	1	18,278	1	14,112	1.02 [0.79, 1.32]
	CAD+PAD	1	3,297	0	0	*ITC not feasible*
	CAD+PRF	1	3,697	1	3,196	0.99 [0.62, 1.57]
Stroke	**ITT**	1	18,278	1	14,112	0.77 [0.53, 1.14]
	CAD+PAD	1	3,297	1	772	1.37 [0.56, 3.31]
	CAD+PRF	1	3,697	1	3,196	0.59 [0.27, 1.28]
CV death	**ITT**	1	18,278	1	14,112	0.94 [0.71, 1.25]
	CAD+PAD	1	3,297	1	772	1.53 [0.74, 3.19]
	CAD+PRF	1	3,697	1	3,196	0.86 [0.55, 1.35]

Source: CS Tables 32-34

[a] for comparison rivaroxaban + aspirin vs ticagrelor + aspirin

The results from the ITCs conducted for the tertiary outcomes that contribute data to the economic model were similar to those of the primary efficacy outcome in that there were no statistically significant differences (Table 26). An ITC was not feasible for the CAD+HF subpopulation for any of these outcomes.

Table 26 Indirect comparison results for tertiary outcomes that contribute data to the economic model

Outcome	Population	Rivaroxaban + aspirin vs aspirin		Ticagrelor + aspirin vs aspirin		HR [95%CI][a]
		No. RCTs	No. patients	No. RCTs	No. patients	
Ischaemic stroke	**ITT**	1	18,278	1	14,112	0.67 [0.44, 1.02]
	CAD+PAD	1	3,297	1	772	0.94 [0.33, 2.73]
	CAD+PRF	1	3,697	0	0	*ITC not feasible*
Acute limb ischaemia (ALI)	**ITT**	1	18,278	1	14,112	0.82 [0.26, 2.60]
	CAD+PAD	1	3,297	1	772	0.91 [0.14, 5.68]
	CAD+PRF	1	3,697	0	0	*ITC not feasible*
Venous thromboembolism (VTE)	**ITT**	1	18,278	1	13,954	1.85 [0.06, 54.97]
	CAD+PAD	1	3,297	0	0	*ITC not feasible*
	CAD+PRF	1	3,697	0	0	*ITC not feasible*
Amputations	**ITT**	1	18,278	1	14,112	*ITC not feasible*
	CAD+PAD	1	3,297	1	772	0.63 [0.04, 11.16]
	CAD+PRF	1	3,697	0	0	*ITC not feasible*

Source: CS Tables 32-34

[a] for comparison rivaroxaban + aspirin versus ticagrelor + aspirin

3.3.12 Summary of adverse events

In the CS the primary safety outcome was reported in the main clinical effectiveness section (CS Section B.2.6) with other adverse events reported in CS Section B.2.10. Bleeding is the most prominent safety risk for rivaroxaban (in common with other antithrombotic medicines) and hence 'Major bleeding' was the primary safety outcome.

3.3.12.1 Primary safety outcome: Major bleeding (composite outcome, modified ISTH criteria)

Bleeding events were adjudicated and categorised as 'major' using the modified ISTH criteria as described earlier (section 3.1.5).

Major bleeding events occurred more often in the rivaroxaban + aspirin arm than the aspirin only arm (incident rate per 100 patient years 1.67 vs 0.98 in the aspirin only arm; HR 1.70 (95% CI 1.40 to 2.05), p<0.001). A consistent pattern of more major bleeding events in the rivaroxaban arm than in the aspirin only arm was also observed in the CAD+PAD, CAD+HF and CAD+PRF subpopulations (Table 27). The CS states that the most common site for bleeding was the gastrointestinal tract.

Table 27 Primary safety outcome results

Population	Outcome: Major bleeding (composite outcome, modified ISTH criteria)	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT		N=9152	N=9126	1.70 (1.40-2.05)	<0.001
	Crude incidence n (%)	288 (3.1)	170 (1.9)		
	Incidence rate per 100 patient-years (95% CI)	1.67 (1.48-1.87)	0.98 (0.84-1.14)		
CAD+PAD		N=1656	N=1641	1.43 (0.93-2.19)	0.09819
	Crude incidence n (%)	52 (3.1)	36 (2.2)		
	Incidence rate per 100 patient-years (95% CI)	1.70 (1.27-2.23)	1.17 (0.82-1.62)		
CAD+HF		N=1909	N=1912	1.35 (0.87-2.07)	0.17489
	Crude incidence n (%)	49 (2.6)	36 (1.9)		
	Incidence rate per 100 patient-years (95% CI)	1.46 (1.08-1.92)	1.08 (0.76-1.50)		
CAD+PRF		N=1824	N=1873	1.41 (1.00-2.00)	0.05058
	Crude incidence n (%)	75 (4.1)	55 (2.9)		
	Incidence rate per 100 patient-years (95% CI)	2.17 (1.71-2.72)	1.55 (1.16-2.01)		

Source: CS Tables 15, 16, 17 and 18

3.3.12.2 Individual components of the primary safety outcome

In addition to presenting the results of the primary composite safety outcome the CS also provides the results for the individual components of the primary safety composite outcome. The individual components of the primary safety outcome measure were regarded as tertiary endpoints.

3.3.12.2.1 Fatal bleeding

Fatal bleeding was a rare event in the COMPASS trial (Table 28). Although more fatal bleeding events occurred in the rivaroxaban + aspirin arm than the aspirin alone arm in the ITT population the 95% confidence interval for the HR spans 1.0 indicating no statistically significant difference between the trial arms (HR 1.49, 95% CI 0.67 to 3.33; p=0.32). In the population subpopulations the incidence rate per 100 patient-years seems slightly higher than in the ITT population but caution is needed in interpreting this due to the small numbers of events. The company did not calculate HRs for fatal bleeding in the subpopulations. Fatal bleeding is a component of the economic model.

Table 28 Tertiary outcome of fatal bleeding

Population	Outcome:	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT		N=9152	N=9126		
	Crude incidence n (%)	15 (0.2)	10 (0.1)	1.49 (0.67-3.33)	0.32
	Incidence rate per 100 patient-years (95% CI)	0.09 (0.05-0.14)	0.06 (0.03-0.10)		
CAD+PAD		N=1656	N=1641		
	Crude incidence n (%)	3 (0.2)	2 (0.1)	Not calculated	
	Incidence rate per 100 patient-years (95% CI)	0.10 (0.02-0.28)	0.06 (0.01-0.23)		
CAD+HF		N=1909	N=1912		
	Crude incidence n (%)	6 (0.3)	3 (0.2)	Not calculated	
	Incidence rate per 100 patient-years (95% CI)	0.18 (0.06-0.38)	0.09 (0.02-0.26)		
CAD+PRF		N=1824	N=1873	Not calculated	
		5 (0.3)	4 (0.2)		

	Crude incidence n (%)				
	Incidence rate per 100 patient-years (95% CI)	0.14 (0.05-0.33)	0.11 (0.03-0.28)		

Source: CS Tables 15 to 18

3.3.12.2.2 Symptomatic bleeding in a critical area or organ

Although there were more events of symptomatic bleeding in a critical area or organ in the rivaroxaban + aspirin arm than the aspirin alone arm in the ITT population no statistically significant difference between the trial arms was demonstrated (Table 29). There was also no statistically significant difference for this outcome between the trial arms in any of the subpopulations.

Table 29 Tertiary outcome of symptomatic bleeding in a critical area or organ

Population	**Outcome:**	**Rivaroxaban 2.5mg bd + aspirin 100mg od**	**Aspirin 100mg od**	**Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg**	
				HR (95% CI)	**P value**
ITT		**N=9152**	**N=9126**		
	Crude incidence n (%)	63 (0.7)	49 (0.5)	1.28 (0.88-1.86)	0.19679
	Incidence rate per 100 patient-years (95% CI)	0.36 (0.28-0.46)	0.28 (0.21-0.37)		
CAD+PAD		**N=1656**	**N=1641**		
	Crude incidence n (%)	9 (0.5)	12 (0.7)	0.74 (0.31-1.75)	0.4878
	Incidence rate per 100 patient-years (95% CI)	0.29 (0.13-0.55)	0.39 (0.20-0.68)		
CAD+HF		**N=1909**	**N=1912**		
	Crude incidence n (%)	11 (0.6)	12 (0.6)	0.90 (0.40-2.03)	0.79388
	Incidence rate per 100 patient-years (95% CI)	0.32 (0.16-0.58)	0.36 (0.19-0.63)		
CAD+PRF		**N=1824**	**N=1873**		
	Crude incidence n (%)	19 (1.0)	16 (0.9)	1.21 (0.62-2.36)	0.56702
	Incidence rate per 100 patient-years (95% CI)	0.54 (0.322-0.84)	0.45 (0.25-0.72)		

Source: CS Tables 15 to 18

3.3.12.2.3 Bleeding into the surgical site requiring re-operation

The number of events of bleeding into the surgical site requiring re-operation was very low and consequently a HR was only calculated for the ITT population. No statistically significant difference was observed between the study arms (Table 30).

Table 30 Tertiary outcome of bleeding into the surgical site requiring re-operation

Population	Outcome:	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT		N=9152	N=9126		
	Crude incidence n (%)	10 (0.1)	8 (<0.1)	1.24 (0.49-3.14)	0.65119
	Incidence rate per 100 patient-years (95% CI)	0.06 (0.03-0.10)	0.05 (0.02-0.09)		
CAD+PAD		N=1656	N=1641		
	Crude incidence n (%)	2 (0.1)	3 (0.2)	Not calculated	
	Incidence rate per 100 patient-years (95% CI)	0.06 (0.01-0.23)	0.10 (0.02-0.28)		
CAD+HF		N=1909	N=1912		
	Crude incidence n (%)	1 (<0.1)	1 (<0.1)	Not calculated	
	Incidence rate per 100 patient-years (95% CI)	0.03 (0.00-0.16)	0.03 (0.00-0.17)		
CAD+PRF		N=1824	N=1873		
	Crude incidence n (%)	5 (0.3)	3 (0.2)	Not calculated	
	Incidence rate per 100 patient-years (95% CI)	0.14 (0.05-0.33)	0.08 (0.02-0.24)		

Source: CS Tables 15 to 18

3.3.12.2.4 Bleeding leading to hospitalisation

Bleeding leading to hospitalisation (with or without an overnight stay) is the part of the composite outcome of 'Major bleeding' using the modified ISTH criteria that differs from major bleeding events reported in other antithrombotic trials. As noted previously the CS states that the inclusion of this outcome may introduce potential over-reporting of hospitalisation.

In the ITT population the incidence rate per 100 patient-years of bleeding leading to hospitalisation was higher in the rivaroxaban + aspirin arm than in the aspirin only arm and this was a statistically significant difference (HR 1.91, 95% CI 1.51 to 2.41, p<0.00001). A similar result was obtained from the analysis in the CAD+PAD population (HR 1.87, 95% CI 1.10 to 3.18, p=0.01788) but in the CAD+HF and CAD+PRF populations the difference in events of bleeding leading to hospitalisation was not statistically significant (Table 31).

Table 31 Tertiary outcome of bleeding leading to hospitalisation

Population	Outcome:	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg od vs. aspirin 100mg	
				HR (95% CI)	P value
ITT		N=9152	N=9126	1.91 (1.51-2.41)	<0.00001
	Crude incidence n (%)	208 (2.3)	109 (1.2)		
	Incidence rate per 100 patient-years (95% CI)	1.20 (1.04-1.37)	0.63 (0.51-0.76)		
CAD+PAD		N=1656	N=1641	1.87 (1.10-3.18)	0.01788
	Crude incidence n (%)	40 (2.4)	21 (1.3)		
	Incidence rate per 100 patient-years (95% CI)	1.30 (0.93-1.77)	0.68 (0.42-1.04)		
CAD+HF		N=1909	N=1912	1.37 (0.80-2.34)	0.24529
	Crude incidence n (%)	32 (1.7%)	23 (1.2%)		
	Incidence rate per 100 patient-years (95% CI)	0.95 (0.65;1.34)	0.69 (0.44;1.04)		
CAD+PRF		N=1824	N=1873	1.35 (0.87-2.08	0.17733
	Crude incidence n (%)	47 (2.6)	36 (1.9)		
	Incidence rate per 100 patient-years (95% CI)	1.35 (0.99-1.80)	1.01 (0.70-1.39)		

Source: CS Tables 15 to 18

3.3.12.3 Other adverse events

As bleeding events and some other safety outcomes (e.g. cardiovascular death and all-cause mortality) for COMPASS were reported as efficacy outcomes (and reported within the efficacy

section of the CS), these were not reported as adverse events in the COMPASS RCT (and were not reported in CS Section B.2.10 on adverse events). The impact of this was to reduce the overall number of adverse events reported in COMPASS.

A summary of all the adverse events reported in COMPASS (including in the rivaroxaban 5 mg trial arm which is not included in this appraisal) is presented in Table 32. For all except one of the types of adverse event reported in Table 32 the proportion of events was slightly lower in the aspirin only arm than in either of the two rivaroxaban study arms (the exception being 'AE with outcome death') but all but one of the differences was less than 1%. The exception was a difference of approximately 1.4% between 'Study drug-related TEAE – antithrombotic study medication' which was 4.6% in the rivaroxaban + aspirin arm and 3.1% in the aspirin only arm.

Table 32 Overall summary of the number of all patients with AEs (SAF)*

	Rivaroxaban 2.5mg bd + aspirin 100mg od	Rivaroxaban 5mg bd	Aspirin 100mg od
	N=9134 (100%)	**N=9110 (100%)**	**N=9107 (100%)**
Any AE	1344 (14.7%)	1329 (14.6%)	1254 (13.8%)
TEAE	1219 (13.3%)	1211 (13.3%)	1140 (12.5%)
Post-treatment AE	252 (2.8%)	242 (2.7%)	214 (2.3%)
Pre-discontinuation AE	410 (4.5%)	378 (4.1%)	331 (3.6%)
Serious AE	784 (8.6%)	772 (8.5%)	713 (7.8%)
Serious TEAE	641 (7.0%)	624 (6.8%)	582 (6.4%)
AE with outcome death	203 (2.2%)	210 (2.3%)	204 (2.2%)
Study drug-related TEAE – antithrombotic study medication	417 (4.6%)	369 (4.1%)	286 (3.1%)
Study drug-related TESAE – antithrombotic study medication	53 (0.6%)	41 (0.5%)	20 (0.2%)
Permanent discontinuation of antithrombotic study medication due to TEAE	312 (3.4%)	307 (3.4%)	238 (2.6%)
Permanent discontinuation of antithrombotic study medication due to TESAE	75 (0.8%)	74 (0.8%)	64 (0.7%)

Source: Reproduction of CS Table 35
AE=adverse event; bd=twice daily; od=once daily; SAE=serious adverse event; SAF=safety analysis set; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event;
Only AEs that occurred after randomisation are taken into account.
'All patients' includes both Japan and non-Japan patients.
Pre-discontinuation AE: all events that started during the 30 days period before premature permanent discontinuation of any antithrombotic study treatment but not earlier than the day of randomisation.
* Includes events of special interest (ESI).

For the remainder of the CS reporting of adverse events patients from Japan were not included. This is because the Japanese Pharmaceuticals and Medical Devices Agency required different safety reporting criteria such that certain outcomes had to be reported as an AE or an SAE. Consequently, the safety data from patients in Japan were not directly comparable with the safety data from majority of the COMPASS trial population.

The CS summarises the most frequent (≥0.1%) treatment-emergent adverse events (TEAEs) among the non-Japan COMPASS population (CS Table 36). The majority of the TEAEs were of either moderate or severe maximum intensity (Table 33). The most frequent TEAEs were categorised as 'gastrointestinal disorders' and amongst these the three most common in the rivaroxaban + aspirin trial arm were:

- 'abdominal pain upper' (rivaroxaban 2.5mg + aspirin: 0.3%, rivaroxaban 5mg: 0.2%, aspirin: 0.2%)
- 'gastritis' (rivaroxaban 2.5mg + aspirin: 0.2%,, rivaroxaban 5mg: <0.1%, aspirin 100mg od: 0.2%)
- 'diarrhoea' (rivaroxaban 2.5mg + aspirin: 0.2%, rivaroxaban 5mg: 0.4%, aspirin 100mg od: 0.2%)

Among the other categories of TEAE the most frequently occurring events in the rivaroxaban + aspirin trial arm were (data presented for the three trial arms rivaroxaban 2.5mg + aspirin vs rivaroxaban 5mg vs aspirin 100mg od in each case):

- 'acute kidney injury' (0.3% vs. 0.3% vs. 0.2%)
- 'atrial fibrillation' (0.2% vs. 0.2% vs. 0.2%)
- 'sepsis' (0.2% vs. 0.2% vs. 0.2%)
- anaemia (0.2% vs. 0.1% vs. <0.1%)
- urinary tract infection (0.2% vs. 0.1% vs. <0.1%)
- lung neoplasm malignant (0.2% vs. 0.1% vs. 0.1%)
- dizziness (0.2% vs. 0.1% vs. 0.1%)

The most common drug related TEAEs (≥0.2% patients) were 'atrial fibrillation', 'abdominal pain upper' (both reported in the paragraphs above) and pruritus (<0.1% vs 0.2% vs <0.1%).

Table 33 TEAEs in the non-Japan COMPASS trial population

	Rivaroxaban 2.5mg bd + aspirin 100mg od	Rivaroxaban 5mg bd	Aspirin 100mg od
	N=8617	**N=8593**	**N=8588**
Number of non-Japan trial participants with at least one TEAE	765 (8.9%)	767 (8.9%)	689 (8.0%)
Maximum intensity - Moderate	4.1%	4.1%	3.4%
Maximum intensity - Severe	3.1%	2.9%	2.9%

In addition to the adverse events described above the CS provides short commentaries at the end of CS Section B.2.10 on:

- drug-related TEAEs
- AEs of special interest
- Treatment-emergent serious adverse events
- Adverse events leading to premature permanent discontinuation of any antithrombotic study drug
- Laboratory values and vital signs
- Summary of AEs for non-Japan patients by the mutually exclusive subgroups 'CAD only', 'PAD only' or 'CAD and PAD'.

3.3.12.4 Indirect treatment comparisons on adverse event data

ITCs could be undertaken for the outcomes of Major bleeding in the ITT population and in the CAD+PAD and the CAD+PRF subpopulations. For fatal bleeding the ITC could only be made for the ITT population. There was no statistically significant difference between rivaroxaban + aspirin versus ticagrelor + aspirin (Table 34).

Table 34 Indirect comparison results for major bleeding and fatal bleeding

Outcome	Population	Rivaroxaban + aspirin vs aspirin		Ticagrelor + aspirin vs aspirin		HR [95%CI][a]
		No. RCTs	No. patients	No. RCTs	No. patients	
Major bleeding	**ITT**	1	18,278	1	13,954	0.73 [0.50, 1.07]
	CAD+PAD	1	3,297	1	762	1.21 [0.28, 5.20]
	CAD+PRF	1	3,697	1	3,196	0.62 [0.31, 1.24]

Fatal bleeding	**ITT**	1	18,278	1	13,954	1.49 [0.47, 4.69]
	CAD+PAD	1	3,297	0	0	*ITC not feasible*
	CAD+PRF	0	0	0	0	*ITC not feasible*

Source: CS Tables 32-34
[a] for comparison rivaroxaban + aspirin versus ticagrelor + aspirin

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations for pharmacological interventions for adult patients with CAD and/or PAD.

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of rivaroxaban + aspirin compared with aspirin, and compared with ticagrelor + aspirin is estimated for the whole COMPASS trial population and for the subpopulations of patients with CAD+PAD, CAD+HF, and CAD+PRF.

4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify economic evaluations of interventions for CAD and / or PAD. See section 3.1.1 of this report for the ERG critique of the search strategy.

The inclusion and exclusion criteria for the systematic review are listed in Table 160 in CS Appendix J. The inclusion criteria state that economic studies of interventions for patients with CAD and/or PAD would be included. Studies published after 2007 and conference abstracts published after 2014 are included.

Ninety seven studies were identified from screening 2145 titles and abstracts. Of these, 56 studies were excluded, mainly because they were published before 2007. Forty one studies were included (42 publications) for full review. The CS stated that no cost-effectiveness studies of rivaroxaban 2.5mg in the indication in this current NICE appraisal were retrieved. A summary of the included studies is shown in CS Table 39. The CS states that three quarters of the studies used Markov models and included health states for MI, stroke and CV death and adverse events for major bleeding, intracranial haemorrhage (ICH), gastrointestinal bleeding and neutropenia. Five studies were conducted in the UK.

The ERG notes that many of the included studies do not include the three treatments relevant to this appraisal. The most relevant studies to the current appraisal are those studies which were either conducted in the UK for ticagrelor or aspirin or those that included rivaroxaban. We have

tabulated the two studies that meet these criteria in Table 35. The study by Pouwels et al.[16] is a summary of the ERG report for the NICE technology appraisal of ticagrelor + aspirin vs. aspirin in patients with a history of MI (TA420).[6]

Table 35 Summary of the cost-effectiveness analyses identified by the systematic literature review

Study/year / country	Population and age	Summary of model	Intervention	Comparator	Incremental QALYs	Incremental costs (currency)	ICER (per QALY gained)
Begum[17] 2015 Sweden	CAD (ACS) 62 years	Markov model; Time horizon 40 years; Cycle length: 12 weeks (0-2 years) and 6 months (2-40 years)	Rivaroxaban 2.5 mg BID in combination with standard antiplatelet therapy	Standard antiplatelet therapy alone	0.14	10,000 SEK (€1129)	71,246 SEK/QALY (€8045/QALY)
Pouwels[16] 2018 UK	CAD 65 years	Health state transition model; Time horizon 40 years; Cycle length 3 months	Ticagrelor + aspirin	Aspirin	0.058	£1439	£24711/QALY

SEK = Swedish Krona; ICER = Incremental cost-effectiveness ratio; ACS = Acute coronary syndrome

The ERG identified two additional studies published after the company's searches were completed: Ademi et al.[18] and Zomer et al.[19] Ademi et al.[18] developed a Markov model to estimate the cost-effectiveness of rivaroxaban + aspirin versus aspirin in people with stable cardiovascular disease in Australia, based on results from the COMPASS trial. The model had annual cycles and a lifetime time horizon and had health states for i) alive with no recurrent CVD, ii) alive with recurrent CVD and iii) dead. Compared to aspirin alone, rivaroxaban + aspirin was estimated to cost an additional AUD$12,156 (discounted) per person, but led to 0.386 quality adjusted life years (QALYs) gained (discounted), over 20 years. These costs and QALYs equated to an incremental cost-effectiveness ratio (ICER) of AUD$31,436/QALY gained.

Zomer et al.[19] developed a Markov model to estimate the cost-effectiveness of rivaroxaban + aspirin versus aspirin in people with peripheral or carotid artery disease in Australia, based on results from the COMPASS trial. The model had the same structure as reported above for Ademi et al. For a population of 1000 patients, there was an additional 256 QALYs gained, at an additional cost of AUD$6,858,103 and the ICER was AUD$26,769 per QALY for rivaroxaban.

The ERG also notes that there are two relevant NICE technology appraisals with cost-effectiveness models: TA335 (Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome)[3] and TA420 (Ticagrelor for preventing atherothrombotic events after myocardial infarction).[6] In TA335, a Markov model was developed comparing rivaroxaban with clopidogrel or aspirin. The model consisted of sixteen health states corresponding to whether the patient suffered an acute coronary syndrome (ACS) event or not. The ACS events considered in the model were: MI, ischaemic stroke (IS), haemorrhagic stroke or intracranial haemorrhage (HS/ICH); a bleeding event measured on the TIMI scale; and revascularisation. In TA420, reported in Pouwels et al.,[16] a Markov model was developed to assess the cost effectiveness of ticagrelor + aspirin compared with aspirin alone in patients who had had an MI. Health states were included for no event, non-fatal MI, non-fatal stroke, and death (CV event, other fatal event). Non-fatal MI and stroke had acute and stable health states.

4.3 Critical appraisal of the company's submitted economic evaluation

The methods and results of a de novo economic model developed by the company for this appraisal are reported in Sections B.3.2 to B.3.11 of the CS.

4.3.1 NICE reference case

The ERG's assessment to determine whether the company's submitted economic evaluation complies with the NICE reference case is shown in Table 36 below. The ERG is of the view that the company's analysis broadly matches the reference case, although we note variations from the decision problem as defined in the NICE scope. These differences are discussed in the following section.

Table 36 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Partly	The company's economic evaluation does not address all the subgroups listed in the final scope issued by NICE. Subgroups not addressed include people who have had a previous MI and people who have had multiple MIs. The subpopulation of people with PAD only was not addressed. See CS B.3.9.
Comparator: As listed in the scope developed by NICE	Partly	As mentioned above, not all comparators are included. Specifically, clopidogrel should be a comparator in people with PAD (though PAD only is not included in the decision problem).
Perspective on costs: NHS and PSS	Yes	See CS Table 40
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	See CS Table 40
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	See CS Table 40
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	See CS appendix D.
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	See CS Table 40
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes	See CS Table 40
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Yes	See CS section B.3.4
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	

ERG conclusion: We are of the opinion that the company's model and economic evaluation do not fully meet the NICE scope, as some subpopulations and comparators of interest are not included. However, the methods used to estimate cost-effectiveness appear reasonable and data inputs in the company's model conform to the NICE methodological guidance. The company's presentation of results also meets the NICE methods guidance to companies.

4.3.2 Model structure

The company developed a de novo Markov model and described the key features and assumptions of their economic model in Section B3.2 of the CS. The model has three month cycles and a lifetime horizon. The perspective is that of NHS England and Personal Social Services (PSS). Discounting is applied to cost and outcomes at 3.5% per annum. The CS states that the model consists of five **main event health states**: 1) event-free, 2) non-fatal MI, 3) ischaemic stroke (IS), 4) intracranial haemorrhage (ICH), 5) death. The main event health states (MI, IS, ICH) are sub-divided into acute event (0-3 months after acute event) or post-event (3+ months after acute event). In addition, there are health states for a second acute event. The company states that the model does not consider the possibility of a third event as few patients in the COMPASS trial experienced a third event. A schematic of the model structure is reproduced in Figure 3.

Patients enter the model in the 'Event-free' health states. Each patient cohort has the characteristics of patients in the COMPASS trial. Note, that 'Event-free' does not mean that patients have not previously had an ACS event, as more than half the patients in COMPASS had had a previous MI. Patients move between health states according to the transition probabilities which were derived from the COMPASS trial. In addition to the acute main events, patients can also experience secondary health events at any time-point in the model, i.e. extracranial non-fatal bleed, acute limb ischaemia, minor amputation, major amputation, venous thromboembolism. Death is included in the model as an absorbing state. For patients in the event-free state and also after one event, death is stratified according to the reason for death (MI, stroke, heart failure, CV procedure, sudden cardiac death, other CV death, fatal bleeding, non-CV death). For patients who have had two events, the model uses all CVD death only, due to the low number of patients having two events in the COMPASS trial.

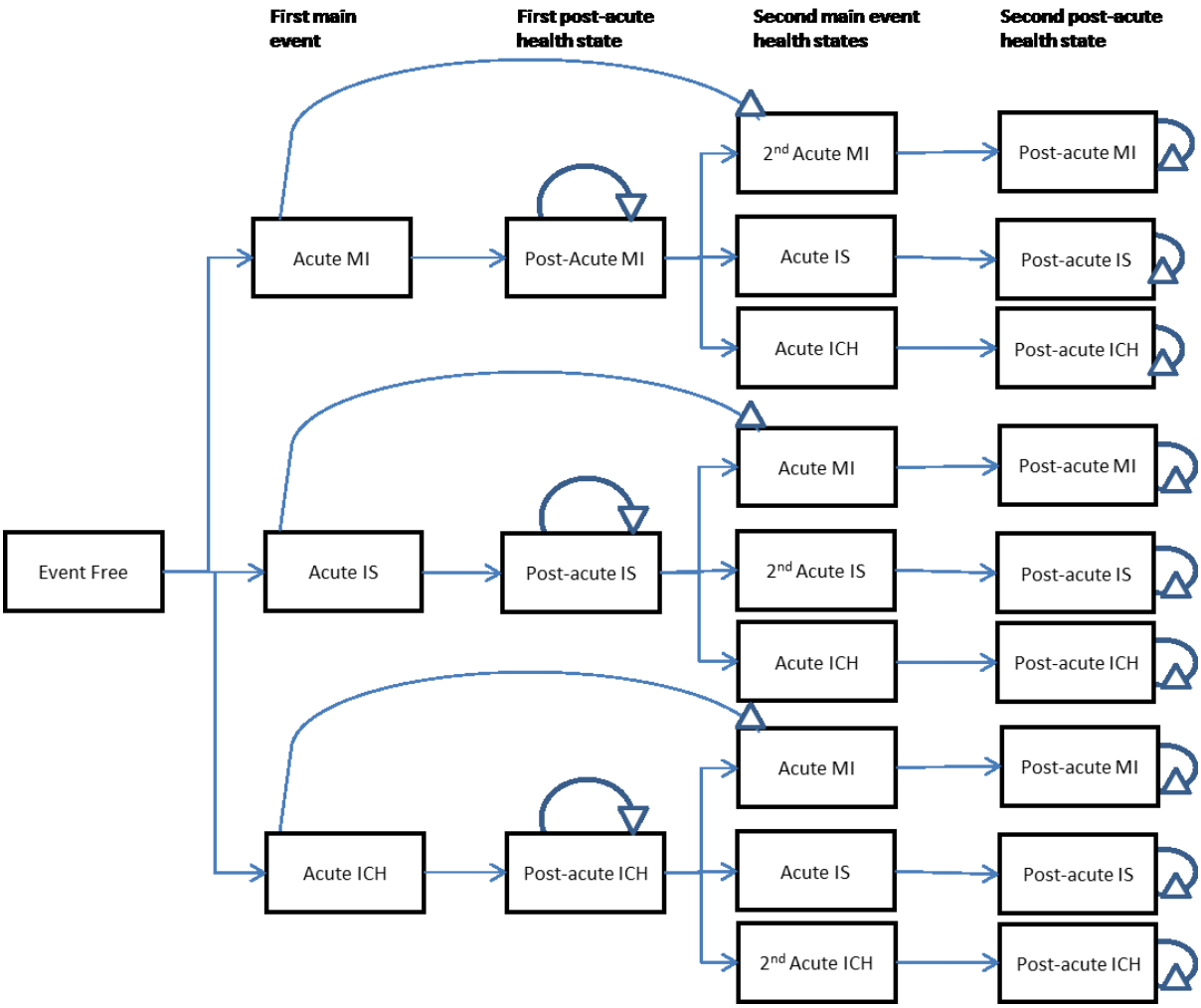


Figure 3 Schematic of the company model

Source: reproduced from CS Figure 19

Patients are assumed to be treated with rivaroxaban + aspirin or aspirin indefinitely unless treatment is discontinued (e.g. for adverse events). Treatment with ticagrelor + aspirin is set to a maximum of three years to reflect the recommendation from NICE TA420.[6] Patients discontinue treatment according to the discontinuation rate observed in the COMPASS trial. Patients who discontinue rivaroxaban or ticagrelor receive aspirin alone and subsequently only accrue the costs and efficacy of the aspirin arm. In the base case, the model assumes there are no treatment interruptions for invasive procedures, such as percutaneous coronary intervention or for those who had an MI, major bleeds or had a stroke. The CS includes a scenario analysis that includes treatment interruption following an event (section 4.3.10). Treatment discontinuation is discussed in more detail in section 4.3.5 of this report.

The key assumptions in the company's base case are shown in Table 37 together with ERG comments on these assumptions.

Table 37 Key assumptions in the company's base case

Area	Company base case assumption	ERG comment
Model structure	Markov model with 26 health states. CS states that majority of models for CAD were Markov and included health states for MI, stroke and cardiovascular death.	We agree that a Markov model is appropriate for this disease area and the health states included are comprehensive and reasonable.
Time horizon	Lifetime horizon. The model runs until the cohort reaches age 100 years. CS states this is in line with standard modelling approaches of treatments that have an effect on survival	We agree that the time horizon is reasonable and is long enough to reflect all important differences in costs or outcomes between the technologies being compared.
Cycle length	3 months with half-cycle correction. CS states this is appropriate as it reflects the COMPASS data and is short enough that it is unlikely that patients will experience two events in one cycle.	The cycle length is appropriate and the half-cycle correction is correctly applied.
Treatment discontinuation	Whilst on treatment the benefits observed in the COMPASS trial are modelled. If treatment is stopped then the subsequent time periods are modelled without treatment effects and patients are assumed to continue low-dose aspirin. CS states this assumption is appropriate because the effect over time was constant.	We agree that the company's approach to treatment discontinuation and treatment effect are reasonable and appropriate.
Treatment interruption following an event	No interruption for rivaroxaban + aspirin was explicitly considered after the main events (MI, ICH or IS).	In clinical practice, after an MI for instance, patients may be initiated on dual antiplatelet therapy during the acute period. ERG considers it more realistic to include treatment interruption.

The model structure used by the company in this appraisal differs from that used in the NICE technology appraisal TA420[6] for ticagrelor + aspirin vs. aspirin in two key ways. Firstly, the company's model includes ICH as a main event which was not included in the model used in

TA420. Secondly, the company explicitly models up to two non-fatal events, whereas in TA420 only the first non-fatal event is modelled and thereafter patients remain in this health state. Subsequent non-fatal events are modelled by a temporary (three months) impact on costs and quality of life but no impact on survival. This approach was criticised by the ERG assessing the company submission in TA420.

> **ERG conclusion:** The structure of the company's model is appropriate and correctly implemented and includes relevant and comprehensive health states. The time horizon is in line with NICE's reference case and the company has included a half-cycle correction.

4.3.3 Population

The patient population described in the final scope is "Adults with coronary or peripheral artery disease (CAD or PAD), excluding people with atrial fibrillation, at high risk of ischaemic events". The company presents analysis and results for the population in the COMPASS trial, which matches the population in the NICE final scope. Baseline characteristics of the patients in the COMPASS population are summarised in Table 9 of this report. In addition, the company reports three subpopulations for whom they seek a NICE recommendation:

- Patients with CAD and PAD (CAD+PAD)
- Patients with CAD who also have heart failure (CAD+HF)
- Patients with CAD who also have poor renal function (GFR) < 60 ml per minute) (CAD+PRF)

These subpopulations comprise around 20% of the randomised population and they are statistically underpowered for efficacy and safety outcomes.

4.3.4 Interventions and comparators

In the CS, rivaroxaban 2.5mg bd + aspirin 75mg od is compared against aspirin 75mg od and also against ticagrelor 60mg bd + aspirin 75mg od, with results presented in both incremental and in a pairwise fashion.

The PEGASUS trial is used as a source of clinical effectiveness data for ticagrelor + aspirin, as previously used in NICE TA420.[6] The ERG regards the PEGASUS trial to be of low risk of bias and an appropriate source of evidence for ticagrelor + aspirin. However, the patient group

comprises people who had an MI in the previous three years, in contrast to the COMPASS trial in which only 62% of patients had a previous MI. An ITC of the COMPASS and PEGASUS trials was conducted by the company but is not used directly to inform the economic model (see section 3.1.7 of this report for a critique of the ITC). Instead, the respective COMPASS and PEGASUS trial-based HRs (compared to aspirin) were used in the economic model. We discuss this further in section 4.3.5 of this report.

The NICE scope specifies clopidogrel as a comparator in patients with PAD, however, the CS does not report cost-effectiveness analyses for this comparator and subgroup. The ERG notes that a previous NICE appraisal (TA210)[20] recommends clopidogrel as an option to prevent occlusive events in people who have PAD, or who have had an IS or who have multi-vascular disease, or for people who have had a MI only if aspirin is contraindicated or not tolerated.

> **ERG conclusion:** We consider the COMPASS and PEGASUS trials, used to inform the economic model, to be of good methodological quality, however, we note important clinical heterogeneity between the two trials.

4.3.5 Treatment effectiveness and extrapolation

4.3.5.1 Overview

Patients move between health states in the economic model according to three-monthly (per cycle) transition probabilities. Transition probabilities are presented in the CS section B3.3 for the cohort receiving aspirin only. Transition probabilities for the cohorts receiving rivaroxaban + aspirin, and ticagrelor + aspirin are estimated by applying a HR to the aspirin cohort transition probabilities.

4.3.5.2 Transition probabilities for main events

The transition probabilities for the first four years of the model are based upon patient-level data from the COMPASS trial and are constant for the first four years of the model. From the fifth year transition probabilities are informed by data from the REACH registry.[21] The REACH registry is a large international, prospective, observational registry with 24 months of clinical follow-up of patients with established CAD, cerebrovascular disease, or PAD enrolled between 2003-4 (CS Appendix Q). Regression analysis of these data show a HR of 1.03 for the next CV

event for each year of age and 1.05 for CV death for each additional year of age. These HRs are applied to the transition probabilities for aspirin for year five onwards.

Transition probabilities for these main events (fatal or non-fatal) are shown in Table 38 (CS Table 42) for the COMPASS population and in CS Tables 43-45 for the other subpopulations. The CS notes that for some of the transitions, there were no events recorded in the COMPASS trial and these events have been assigned zero transition probabilities. The company took this approach on the advice of their clinical experts. The company has included a scenario analysis whereby zero transitions have been replaced with non-zero values from the event-free probabilities to reflect the real-life risk (section 4.3.10).

Table 38 Aspirin transition probabilities: three-monthly rates, years 1 - 4 (COMPASS trial)

		TO		
		First event		
		MI	**IS**	**ICH**
FROM	**Event-free**	0.00290	0.00176	0.00029
		TO		
		Second event		
		MI	**IS**	**ICH**
	First event			
	- Acute MI	0.00641	0.00641	0
	- Post-acute MI	0.01852	0.00641	0
	- Acute IS	0	0.01042	0
	- Post-acute IS	0.00356	0.01779	0
	- Acute ICH	0	0	0.07143
	- Post-acute ICH	0	0.01754	0

Source: Reproduced from CS Table 42

The ERG considers that including zero transition probabilities is unrealistic as some of the transition probabilities are inconsistent. For example, those patients in the acute MI state may have lower probabilities of an event that those in the event-free state. However, expert clinical advice to the ERG is that the risk of another event during the three months after an event is higher than for those in the event-free group. Therefore, the ERG suggests that the company should use the scenario which imputes non-zero transition probabilities from transition probabilities from other health states, and we have used this in the ERG base case (section 4.4). An alternative approach would have been to have used transition probabilities for these events from another source, such as from the REACH registry.[21]

4.3.5.3 Mortality

Death is included in the model as CV death, fatal bleeding and non-CV death. In the event-free and first event health states, the model tracks the cause of death (MI, stroke, heart failure, CV procedure, sudden cardiac death, other CV death), but in the health states where they have had two previous events the cause of death is captured as 'all CV death'. Table 39 (CS Table 46) shows the CV death rates from the event-free and first-event health states for the COMPASS population for patients receiving aspirin only. CS Tables 47-49 shows these transition probabilities for the three subpopulations.

Table 39 Aspirin - three-monthly CV death rates: from 'event-free' and 'first-event' health states (COMPASS)

Health state	Due to MI	Due to stroke	Due to HF	Following CV procedure	Sudden cardiac death	Other CV death	Fatal bleeding
Event-free	0.00033	0.00017	0.00016	0.00010	0.00108	0.00082	0.00004
Acute MI	0	0	0	0	0.00641[a]	0	0
Post-acute MI	0	0	0	0	0	0.00694	0.00231
Acute IS	0	0.01042[a]	0	0	0	0.01042[a]	0
Post-acute IS	0	0.00356	0.00356	0	0.01068	0.00356	0
Acute ICH	0	0	0	0	0	0	0
Post-acute ICH	0	0	0	0	0	0	0

[a] Values from company economic model, incorrectly reported in CS Table 46
Source: reproduced from CS Table 46

Table 40 (CS Table 50) shows the transition probabilities from second events for the COMPASS population for those patients who received aspirin only. CS Tables 51-53 shows these transition probabilities for the subpopulations.

Table 40 Aspirin - three-monthly death rates (all CV death): from second event (COMPASS)

	Second event					
First event	**Acute MI**	**Post MI**	**Acute IS**	**Post IS**	**Acute ICH**	**Post ICH**
- MI	0.11111	0	0	0	0	0
- IS	0	0	0	0	0	0
- ICH	0	0	0	0	0	0

Source: reproduced from CS Table 50

Background mortality is included within the model by using the general population mortality rates for England from the Office for National Statistics and removing the proportion of deaths attributable to CV disease. The general population mortality statistics are shown in CS Table 54

and the proportion of deaths attributable to CV disease are shown in CS Table 55. The CS states that this approach avoids double counting. The ERG agrees with the approach used for mortality. In response to a clarification question (B6), the company updated the general population mortality statistics to those data from 2016/2017.

4.3.5.4 Hazard ratios for main events

The transition probabilities for rivaroxaban + aspirin and ticagrelor + aspirin are calculated by applying COMPASS and PEGASUS trial HRs respectively to the transition probabilities for the aspirin only group. The HRs apply to both first and second main events and are constant over time.

The CS justifies the use of a constant hazard by exploring the proportional hazards assumption (CS appendix O). The company states that the proportional hazard assumption is considered valid, as the curves of the log of the negative log of the Kaplan-Meier versus the log of time are parallel by visual inspection. This assumption is also supported by the horizontal nature of the smoothed plot of the Schoenfeld Residuals and the non-significant time-treatment interactions in the Cox model.

The ERG agrees within the company's assumption of a constant hazard based upon the evidence provided. However, we note that this evidence is for a short time duration only as the trial has only 23 months mean follow-up and it is unclear whether the constant hazard would continue to apply over the longer term.

Table 41 (CS table 56) shows the HRs for the main events implemented in the model for rivaroxaban + aspirin. The ERG notes the high uncertainty in some of the HRs shown by the wide 95% confidence intervals, particularly for the subpopulations. This is principally for ICH and fatal bleeding. It is also notable that rivaroxaban + aspirin is not shown to be more effective than aspirin only for MI for all groups and CV death (CAD+PAD and CAD+PRF) (results not statistically significant).

Table 41 HR (95% CI) for main events: rivaroxaban + aspirin vs aspirin

Event	COMPASS population	CAD+PAD	CAD+HF	CAD+PRF
MI	0.86 (0.70-1.05)	0.72 (0.49-1.08)	0.81 (0.54-1.22)	0.74 (0.51-1.06)
IS	0.51 (0.38-0.69)	0.49 (0.26-0.92)	0.35 (0.18-0.69)	0.25 (0.12-0.51)

ICH	1.16 (0.67-2.00)	1.16 (0.67-2.00)[a]	1.44 (0.51-4.06)	1.45 (0.55-3.81)
CV death	0.78 (0.64-0.96)	0.72 (0.49-1.07)	0.65 (0.47-0.92)	0.86 (0.62-1.20)
Fatal bleeding[b]	1.49 (0.67-3.33)	1.49 (0.67-3.33)	1.49 (0.67-3.33)	1.49 (0.67-3.33)

[a] Number of events too small to calculate a HR for this group – COMPASS whole trial value used
[b] For fatal bleedings, the HRs in the subpopulations are not calculable due to the low rate of events; therefore results from the whole of the COMPASS population are used.
Source: reproduced from CS Table 56

For the transition probabilities for those treated with ticagrelor + aspirin, the HRs were taken directly from the PEGASUS trial (Table 42), rather than from the ITC as discussed in section 3.1.7 of this report. The CS does not give a rationale for using an alternative method to indirectly compare rivaroxaban and ticagrelor in the model, but the ERG believes that the two methods provide the same results and therefore the method in the model is appropriate. This is based on a comparison between the results of the COMPASS trial (Table 41) and the PEGASUS trial (Table 42) with the results of the ITC presented earlier in Table 25 of this report. The ERG also notes it is possible to replicate the ITC HRs using the HRs in Table 41 and Table 42 by dividing the HR for rivaroxaban + aspirin vs aspirin by the HR for ticagrelor + aspirin vs aspirin.

The CS notes that there are several missing HRs in the PEGASUS trial for the subpopulations. For these missing inputs, the HRs for the overall PEGASUS trial were used. The ERG notes that for the subpopulation with CAD+HF there are no HRs available and all have been taken from the overall PEGASUS trial population.

Table 42 Available HRs for ticagrelor + aspirin versus aspirin (from PEGASUS trial)

	COMPASS population HR (95%CI)	CAD+PAD HR (95%CI)	CAD+HF HR (95%CI)	CAD+PRF HR (95%CI)
Main events				
MI	0.84 (0.72, 0.98)	NA	NA	0.75 (0.57, 1.00)
IS	0.76 (0.56-1.02)	0.52(0.22-1.22)	NA	NA
ICH	1.33 (0.77-2.31)	NA	NA	NA
CV death	0.83 (0.68, 1.01)	0.47 (0.25, 0.86)	NA	1.00 (0.74, 1.37)
Fatal bleeding	1.00 (0.44, 2.27)	NA	NA	NA

Source: Reproduced from CS Table 59

The ERG agrees that it is reasonable to assume that for the main events, the HRs would be similar between the main trial population and the subpopulations, in the absence of evidence. The ERG notes that in the PEGASUS trial,[7] none of the subgroups were significantly different to the whole trial population for the composite end point of cardiovascular death, MI or stroke.

4.3.5.5 Adverse events

The adverse events, or **health events** as the company calls them, are different from main events discussed above in that they do not change the future risk of a main event or survival. In the company's model, these events only affect costs and QALYs. These health events are as follows:

- Major non-fatal extracranial bleed
- Acute limb ischaemia (ALI)
- Major amputation
- Minor amputation
- Venous thromboembolism (VTE)

In this section, we summarise and critique the company's approach to handling the risk of these adverse events in each model cycle.

The CS describes a two-step approach where for each subpopulation, baseline risks (three-monthly transition probabilities) of the events are first estimated from the aspirin arm of the COMPASS population; then, transition probabilities for the other treatment arms are calculated by applying the HRs reported in CS Table 57.

Table 43 (CS Table 57) below shows the three-month probabilities of having any of the adverse events by population for the aspirin only arm.

Table 43 Aspirin only three-monthly transition probabilities for adverse health events

	COMPASS	CAD+PAD	CAD+HF	CAD+PRF
ALI	0.0006393	0.0019101	0.0007233	0.0006916
Minor amputation	0.0004262	0.0009550	0.0003616	0.0005533
Major amputation	0.0003694	0.0007163	0.0002893	0.0004150
Major extracranial non-fatal bleed (modified ISTH criteria)	0.0021738	0.0023876	0.0023868	0.0036655
VTE	0.0006109	0.0011142	0.0007233	0.0010374

Source: Reproduced from CS Table 57

These three-monthly event risks are constant probabilities estimated from a mean event rate during the four year follow-up of the COMPASS trial. The company argues that an assumption of constant risk is justified because events do not demonstrate consistent patterns of increasing or decreasing rates over time. CS Figures 20 and 21 are reported to justify this assumption.

They show the three-monthly event rates over a period of 30 months. The ERG finds this assumption of constant hazard to be reasonable.

The HRs applied to the rivaroxaban + aspirin and ticagrelor + aspirin arms are reported in CS Tables 58 and 59. Both tables are reproduced below (Table 44 and Table 45 respectively).

Table 44 Available hazard ratios for health events: rivaroxaban + aspirin vs aspirin (from COMPASS trial)

	COMPASS HR (95%CI)	CAD+PAD HR (95%CI)	CAD+HF HR (95%CI)	CAD+PRF HR (95%CI)
Health events				
ALI	0.55 (0.32-0.92)	0.48 (0.23-1.02)	0.55 (0.32-0.92)	0.55 (0.32-0.92)
Minor amputation	0.65 (0.35-1.20)	0.66 (0.23-1.86)	0.65 (0.35-1.20)	0.65 (0.35-1.20)
Major amputation	0.57 (0.30-1.09)	0.58 (0.21-1.61)	0.57 (0.30-1.09)	0.57 (0.30-1.09)
Major extracranial non-fatal bleed (modified ISTH criteria)	1.79 (1.46-2.19)	1.61 (1.01-2.56)	1.38 (0.85-2.24)	1.97 (1.55-2.52)
VTE	0.61 (0.37-1.00)	0.57 (0.23-1.46)	0.61 (0.37-1.00)	0.36 (0.13-1.00)

Source: Reproduced from CS Table 58
VTE = venous thromboembolism; ALI = acute limb ischaemia

Table 45 Available hazard ratios for health events: ticagrelor + aspirin versus aspirin (from PEGASUS trial)

	COMPASS HR (95%CI)	CAD+PAD HR (95%CI)	CAD+HF HR (95%CI)	CAD+PRF HR (95%CI)
Health events				
ALI	0.67 (0.24, 1.87)	0.53 (0.10, 2.87)	NA	NA
Minor amputation	NA	1.10 (0.07-17.55)[a]	NA	NA
Major amputation	NA	1.10 (0.07-17.55)[a]	NA	NA
Major extracranial non-fatal bleed	NA	NA	NA	NA
VTE	0.33 (0.01, 8.22)	NA	NA	NA

Source: Reproduced from CS Table 59
[a] calculated from the available data for amputations. Overall amputations HR assumed to apply to minor and major amputations
NA = not available

The ERG was unable to find HRs for minor amputations, major amputations and major extracranial non-fatal bleeding in the sources cited in the CS. We raised this issue with the company in clarification question B7 and the company provided source tables for all the adverse events. The company notes that the incidence of adverse events for the subpopulations were too low to calculate HRs and their approach was to use HRs from the whole COMPASS population. In the absence of more robust data, we consider this assumption to be reasonable

but note that it introduces uncertainties in the cost-effectiveness results for the affected subpopulations. The company also spotted an error in CS Table 58, where the HR for the CAD+PRF subpopulation was incorrectly reported (clarification question B7). The company has included the correct value in their updated model.

Table 45 (CS Table 59) reports the HRs from the PEGASUS trial (ticagrelor + aspirin vs aspirin) for the main events and adverse events. There are several missing values, particularly in the CAD+HF population and the CAD+PRF population. The company's approach for handling missing values are as follows:

- Use data from the overall PEGASUS trial where subgroup specific trial data are missing
- Use a HR of 1.00 for amputations, if data are missing
- Use HR for major bleeding from the PEGASUS trial as a proxy for extracranial bleeds

Firstly, the ERG notes the high level of uncertainty in the HRs of adverse events. Secondly, we observe that the ITC HR estimates for bleeds (rivaroxaban + aspirin vs ticagrelor + aspirin) reported in CS Table 32 go in counter-intuitive directions (see Table 46 below). For instance, while rivaroxaban + aspirin is more favourable in major and intracranial bleeds, ticagrelor + aspirin is preferable when considering haemorrhagic stroke and fatal bleeds. The wide confidence intervals around some of these endpoints may be 'noise' due to a poorly powered sample size.

The ERG's preference for the base case analysis is to use the same adverse event HRs for ticagrelor + aspirin as for rivaroxaban + aspirin (see section 4.4 of this report).

Table 46 Summary of results of the indirect comparison of rivaroxaban + aspirin and ticagrelor + aspirin in the COMPASS population

Endpoint	Rivaroxaban + aspirin versus aspirin		Ticagrelor + aspirin versus aspirin		HR [95%CI] for comparison rivaroxaban + aspirin *vs* ticagrelor + aspirin
	No. RCTs	No. patients	No. RCTs	No. patients	
Stroke/MI/CV death	1	18,278	1	14,112	0.90 [0.75, 1.09]
All-cause death	1	18,278	1	14,112	0.92 [0.74, 1.15]
CV death	1	18,278	1	14,112	0.94 [0.71, 1.25]
Stroke	1	18,278	1	14,112	0.77 [0.53, 1.14]
Ischaemic stroke	1	18,278	1	14,112	0.67 [0.44, 1.02]
Myocardial Infarction	1	18,278	1	14,112	1.02 [0.79, 1.32]

Major adverse limb event (MALE)	1	18,278	1	14,112	0.65 [0.36, 1.18]
Amputations	1	18,278	1	14,112	*ITC not feasible*
Acute limb ischaemia (ALI)	1	18,278	1	14,112	0.82 [0.26, 2.60]
Venous thromboembolism (VTE)	1	18,278	1	13,954	1.85 [0.06, 54.97]
Major bleeding	1	18,278	1	13,954	0.73 [0.50, 1.07]
Intracranial bleeding	1	18,278	1	13,954	0.87 [0.40, 1.89]
Haemorrhagic stroke (HS)	1	18,278	1	13,954	1.54 [0.44, 5.34]
Gastrointestinal bleeding	1	18,278	0	0	*ITC not feasible*
Fatal bleeding	1	18,278	1	13,954	1.49 [0.47, 4.69]

Source: CS Table 32

4.3.5.6 Treatment duration

In the base case, treatment with rivaroxaban + aspirin and aspirin continues over the patients' lifetime. Treatment with ticagrelor + aspirin is for a maximum of three years to reflect the recommendation of NICE TA420.[6] The company varies the length of the treatment duration in a scenario analysis (section 4.3.10).

In COMPASS, 16.9% of patients on rivaroxaban + aspirin and 15.9% of patients on aspirin only discontinued treatment over the course of the study (CS Figure 12). In the base case, patients discontinue at the rate observed in COMPASS. Those patients who discontinue rivaroxaban + aspirin receive aspirin only. The CS states that those who discontinue rivaroxaban + aspirin receive the costs and efficacy of the aspirin only arm. In the clarification response (question B9), the company stated that an adjustment is made in the model for rivaroxaban + aspirin and ticagrelor + aspirin to account for the proportion of patients who discontinue treatment. A composite (weighted) transition probability is calculated whereby the transition probabilities as observed in the rivaroxaban + aspirin or ticagrelor + aspirin arm are applied to the proportion of patients on treatment and the transition probability for the aspirin arm are applied to the proportion of patients who have discontinued treatment. The ERG considers that the company's approach to modelling the treatment effect for those who discontinue treatment is reasonable and appropriate.

The base case assumes that after four years, the discontinuation rate is half the rate observed for the first four years, based on the rationale that by this time most patients would remain on treatment in the longer term. The company varies this assumption in the scenario analyses, which we report in section 4.3.10.

In the base case, there was no modelling of treatment after the main events (MI, IS, ICH). The CS states that in clinical practice, patients may be initiated on dual platelet therapy during the acute phase after an MI. The CS states that their approach is conservative as i) the model is based on ITT results so any effects of discontinued treatment is already accounted for in the efficacy and safety results and ii) the cost of therapy is applied to each patient, even those who may have interrupted therapy and so the costs in the rivaroxaban + aspirin arm are overestimated (clarification question B11). The company varies this assumption in a scenario analysis (section 4.3.10). The ERG considers that the scenario that includes treatment interruption is more similar to clinical practice and we have therefore included this in the ERG base case (section 4.4).

> **ERG conclusion:** The key issues with treatment effectiveness relate to missing data and the assumptions applied in data imputation. For the main events, the ERG considers that zero transition probabilities computed from the company's analysis of the COMPASS trial do not reflect reality, as experiencing an event would normally be a risk factor for future events. We address this in our preferred analysis. Missing values are also a major problem with the PEGASUS trial, both with main events and adverse events. We discuss our preferred approach in section 4.4.

4.3.6 Health related quality of life

The company conducted two sets of systematic literature searches to identify utility values relevant to the health states and adverse events. The first search focused on utility studies used in previous submissions to NICE and yielded six primary studies for data extraction. Details of the company's prioritisation process for eligible literature can be found in the CS Appendix H. The utility estimates vary widely, reflecting differences in population and duration over which the values apply. The second search focused on utility studies, published since 2007, not previously used in NICE submissions. A description of the company's methods can be found in CS Appendix H. The identified utility values also vary widely, reflecting differences in population and severity of disease.

The company concluded that there was a significant variation in the range of utility values for events and that it was challenging to choose a set of utility values from the multiple sources. In addition, they are of the opinion that values estimated from the COMPASS trial are more robust.

They have, therefore, used the COMPASS trial values in their base case and used utility values from the PEGASUS study for sensitivity analysis. We consider that the company's approach is justified.

Utility values were elicited in the COMPASS trial using EQ-5D-3L data collected at seven measurement time points. The model assumes that patients will experience different HRQoL at the onset of a main event (the acute phase) and with the passing of time (the post-acute phase). This assumption was made in a previous STA (TA420)[6] and the ERG finds it reasonable.

Hence the company estimates two sets of utility values for each main event:

- Main events
    i. acute MI (in the last 3 months)
    ii. post MI (more than 3 months after MI)
    iii. acute IS
    iv. post IS
    v. acute ICH
    vi. post ICH

Adverse events, otherwise described as health events in the CS (see section 4.3.5.5 for details), are each assigned a single utility score or disutility.

- Adverse events (health events)
    i. any minor amputation (toe and foot)
    ii. any major amputation (above foot)
    iii. acute limb ischaemia (ALI, in the last 3 months)
    iv. acute venous thromboembolism (VTE, in the last 3 months)
    v. major non-fatal extracranial by modified ISTH criteria

The company explored two types of multivariate models: a Generalised Estimating Equation Model (GEE) and a Repeated Measures Mixed Model. Factors included in both models include the dummy variables for all main events and adverse events of interest, gender, age and baseline EQ-5D. Residuals from both models were plotted against the observed and predicted EQ-5D values to test for normality and assess model quality (CS Figures 23-26). The plots are right skewed with fewer values around the utility lower limit. We consider that both models give

comparable outputs and are of good standard. In the base case, the company uses utility values from the GEE model and uses the mixed repeated measures model results in a scenario analysis.

For this analysis, the company assumes that the antithrombotic side effects from both treatment arms are negligible and therefore all the treatment arms were pooled together. This is consistent with the COMPASS trial.

CS Table 62 shows the number of clinic visits by health state in the multivariate analysis of EQ-5D data. The estimated mean utility values for the COMPASS population and subpopulations are summarised below in Table 47. The company uses the event-free health state utility values for each subpopulation from their GEE model and then calculates the utility for each of the health states by adjusting by the same disutility for each subpopulation. The disutilities for adverse events in the COMPASS population are assumed to be the same for all subpopulations.

The company assumes that patients who have acute limb ischaemia, major bleed or venous thromboembolism have a reduced quality of life for three month only. For amputation, the disutility is applied for the remainder of the model duration (or until death). Our experts consider that these assumptions are reasonable.

In the company's model, utility values in Table 47 are adjusted for age using utility multipliers. The ERG notes that the baseline utility score for the event-free population of the COMPASS trial and the three subpopulations are higher than that of the UK general population for the 64-75 age group (0.779).[22] This appears unrealistic to the ERG. In our scenario analysis, we scale down the baseline event-free utilities, so that these utilities are no higher than the UK general population (section 4.4).

Table 47 Summary of utility values for cost-effectiveness analysis

Health state/Event	Utility value / disutility (mean)	Utility value / disutility (mean)	Utility value / disutility (mean)	Utility value / disutility (mean)
	COMPASS	**CAD+PAD**	**CAD+PRF**	**CAD+HF**
Event free	0.835	0.796	0.813	0.8
MI (acute)	0.784	0.745	0.762	0.749
MI (post-acute)	0.807	0.768	0.785	0.772

Health state/Event	Utility value / disutility (mean)	Utility value / disutility (mean)	Utility value / disutility (mean)	Utility value / disutility (mean)
	COMPASS	**CAD+PAD**	**CAD+PRF**	**CAD+HF**
IS (acute)	0.647	0.608	0.625	0.612
IS (post-acute)	0.743	0.704	0.721	0.708
ICH (acute)	0.702	0.663	0.68	0.667
ICH (post-acute)	0.755	0.716	0.733	0.72
ALI (acute)	-0.157	-0.157	-0.157	-0.157
Minor amputation (acute)	-0.10	-0.10	-0.10	-0.10
Minor amputation (post-acute)	-0.10	-0.10	-0.10	-0.10
Major amputation (acute)	-0.175	-0.175	-0.175	-0.175
Major amputation (post-acute)	-0.175	-0.175	-0.175	-0.175
Major extracranial non-fatal bleed (modified ISTH criteria) (acute)	-0.019	-0.019	-0.019	-0.019
VTE (acute)	-0.111	-0.111	-0.111	-0.111

Source: reproduced from CS Table 70

The company's approach following transition to another main event is to use the lowest utility of the two health states. In scenario analysis, they test a multiplicative assumption (where utilities of the two health states are multiplied) and an assumption using the utility score of the most recent event. The ERG uses the multiplicative approach in our base case. We are of the opinion that the multiplicative approach is a better representation of reality in the event of comorbidities, as stated in the Decision Support Unit's (DSU) guide to disutilities.[23]

The company uses the disutilities derived from the NICE appraisal of ticagrelor (TA420[6]) in a scenario analysis. In the PEGASUS trial-based submission (TA420)[6] the utility decrements are estimated for four adverse events including grade 1-2 and grade 3-4 dyspnoea, which are not relevant to the COMPASS trial, and categorise bleeds using different definitions (ISTH in COMPASS; TIMI in PEGASUS). The only adverse event included in TA420, which is also in the current economic model is major non-fatal bleeds. We note that these differences could potentially increase the uncertainty around the cost-effectiveness results for rivaroxaban vs ticagrelor but we are of the opinion that these differences do not affect model results significantly.

ERG conclusion: The company's approach to estimating HRQoL uses EQ-5D data from the COMPASS trial. The use of the COMPASS utility data is preferable, given the good quality of the trial, to other estimates of utility that may not be representative of the

population modelled. There are issues surrounding the choice of disutilities for adverse events and that the COMPASS trial was not powered for subpopulations. However, the company applies disutilities from the COMPASS trial to the subpopulations and we deem this to be reasonable. We have applied the multiplicative assumption in cases where patients suffer a second major event. We believe this is more appropriate than the company's base case assumption.

4.3.7 Resource use and costs

The company performed a systematic literature review of cost-effectiveness studies which identified six UK based alternative sources of costs (see CS Appendix G). These studies are summarised in CS Table 71. The company concluded that these studies do not provide appropriate alternatives to NHS reference costs which have informed most costs and resource use estimates in the model. One exception is the cost of ongoing care following an event, which is not available from NHS reference costs. The company expanded its search criteria to identify these follow-on costs and the method is described in CS Appendix I. This pragmatic search located a study conducted by the Centre for Health Economics from the University of York (Walker et al[24]). Walker et al estimated the long-term healthcare resource use and costs of patients with stable coronary artery disease in England who were followed from 2001-2010. Costs from Walker et al[24] are summarized in CS Table 72. The ERG considers that the company's search methods are appropriate and that NHS reference costs are of better quality and relevance compared to the identified studies. We also consider that the costs from Walker et al[24] provide appropriate estimates for follow-on care costs.

In Table 48 below, we summarise the different components of cost incorporated into the model.

Table 48 Summary of costs included in the company's model

Cost
Medication costs
Cost of main event (non-fatal) - Acute cycle - Subsequent cycles
Cost of main event (fatal)
Cost of fatal events (non-cardiovascular)

Cost of adverse events

Source: Adapted from CS Table 73

In the company's model, patients do not incur any costs while in the 'no event' state. We are of the view that all patients will incur a health state cost, for example for outpatient consultations, regardless of their health state. The previous NICE appraisal of ticagrelor (TA420)[6] applied a cost of £160.31 per cycle to individuals in the 'no event' health state. The ERG inflated this cost to a 2018 estimate (£167.66) and applied it in the ERG analysis.

Medication costs representing all treatments included in the company's analysis are listed below in Table 49 below. These costs are up to date and appropriately sourced from the British National Formularly.[25]

Table 49 Medication costs

Drug	Daily dose	Pack size	Pack price	Daily cost	Source
Aspirin	75mg od	28	£0.63	£0.02	BNF (cost of 28 tablets (GSL) [25]
Rivaroxaban	2.5mg bd	56	£50.40	£1.80	BNF[25]
Ticagrelor	60mg bd	56	£54.60	£1.95	BNF[25]

Source: Reproduced from CS Table 74. BNF online, accessed November 2018

The ERG noted that, apart from medication costs, the company used 2016/17 NHS Reference costs, instead of the more recent 2017/18 source.[26] Costs from Walker et al 2016[24] were also not uprated to 2018 estimates. In clarification questions B11 to B13, we requested the most recent NHS reference estimates from the company. The company updated their costs in their response and provided a revised model reflecting these updates. We note that these cost updates do not make any significant difference to the cost-effectiveness results.

Non-fatal main events costs are split into the acute phase and the post-acute phase. The acute phase costs consist of inpatients costs, procedure costs and rehabilitation costs. Inpatient costs are estimated from relevant inpatient categories in the NHS reference costs and weighted based on the number of episodes. These inpatient costs are reported in CS Table 76.

Procedure costs consist of weighted costs of percutaneous coronary intervention and CABG estimated from the NHS reference costs. The proportion of patients who underwent a percutaneous coronary intervention (58.9%) or CABG (5.5%) following an MI in the COMPASS study was applied to these procedure costs to derive the revascularisation costs reported in CS Table 77. A revascularisation cost of £3,055.96 is re-estimated in the company clarification document Table 26.

The company applies a specific number of days for individual acute event rehabilitation costs to calculate the average costs per day. The company sourced rehabilitation costs from NHS reference costs and the average number of days for rehabilitation from a previous NICE submission TA335.[3] The company assumes that rehabilitation practices has not changed over the past five years and our clinical experts agree that this is a reasonable assumption.

In Table 50, we present sum totals of costs accruing to each health state (main event) and their sources. These include costs for rehabilitation in the acute phases of health states and costs for individual post-acute phases.

Table 50 Summary of costs for resources per health state

Health state	Total cost	Source
Acute MI	£6,718.37	NHS Reference costs 2017/18
Post-acute MI	£514.14	Walker et al, 2016[24] Table A5 – cost in subsequent 90-day periods
Acute IS	£9,078.69	NHS Reference costs 2017/18
Post-acute IS	£478.87	Walker et al, 2016[24] Table A5 – cost in subsequent 90-day periods
Acute ICH	£14,951.87	NHS Reference costs 2017/18
Post-acute ICH	£716.16	Walker et al, 2016[24] Table A5 – cost in subsequent 90-day periods

Source: company clarification document table 27 (using NHS reference costs for 2017/18)

The company applies the costs of fatal main events or health states from Walker et al[24] to account for overestimations that could occur from using the total costs of main events reported in Table 50 above for the fatal events. The ERG deems this assumption a reasonable control for overestimation. In the company clarification document Table 23, the company presents the costs of fatal events from Walker et al used in the model uprated to 2017/2018. These costs are the same for all CV fatal events (£2,213.69). Company clarification document Table 23 also includes a cost of £1,856.68 for non-cardiovascular death.

If a patient experiences a second non-fatal event (e.g. an MI followed by a stroke), they incur the more expensive of the follow-on costs of the two events We find this assumptions gives a conservative estimate of cost-effectiveness and is therefore reasonable. The company has explored a scenario where the costs of acute events and post-acute events are additive, i.e. the sum of the costs of both non-fatal events. A further scenario using only the cost of the most recent post-acute event was also explored by the company.

The company's model includes the costs for the five adverse events (health events) described in the previous section. The company submitted updated costs for these events in the company clarification Tables 27 (CS Table 79 to CS Table 83). These costs only apply in the cycles where the adverse events occur. For major bleeds, the company uses gastrointestinal (GI) bleeds as a proxy. A cost of £747.90 was estimated by taking a weighted average of NHS reference costs for long-stay, short-stay and day case admissions.

For acute limb ischaemia, the weighted average costs of a range of interventions including surgery, thrombolysis and angioplasty were estimated to give £3,432.47. For major amputations, the company estimates three costs separately: procedure costs, equipment costs and rehabilitation costs. The updated versions of these costs are reported in Tables 81 to 83 of the company clarifications document. Minor amputations and venous thromboembolisms are estimated from weighted averages of relevant Healthcare Resource Group costs. They amount to £5,434.80 and £1,056.42 respectively.

> **ERG conclusion:** The company's methods for estimating resource use and costs are mostly satisfactory. The company has addressed the issues we raised in the clarification questions, regarding using up to date sources of NHS reference costs and uprating relevant costs. In the company's model, patients do not incur any costs while in the 'no event' state. We are of the opinion that patients will incur some costs and in our analysis, we apply a maintenance cost to patients for each cycle they spend in the 'no event' state.

4.3.8 Model validation

In line with the recommendations developed by a task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision

Making (SMDM)[27] for model quality assurance, the ERG checked the economic model for transparency and validity. The outcome of these checks are discussed below.

4.3.8.1 Model transparency

The CS clearly described the model structure, parameter values and their sources, data identification methods, and assumptions used in the model. The model was technically transparent and the visual basic code used within the model was accessible. In general, the CS described the analyses clearly and provided adequate information to assess the model.

4.3.8.2 Internal consistency

The CS states that the model has undergone review from clinical and health economics experts during the model development. Four of these reviewers are named in the CS (Prof Martin Cowie, Prof Stuart Mealing, Dr Andre Larny, Prof Pierre Levy). The model structure was developed in consultation with the experts and based upon previous economic model included in the company's literature review. The internal validity of the model was tested at two modelling agencies to ensure the calculations were correct and that the results were logical and consistent.

The ERG also tested the internal validity of the company model. Below is a summary of the checks conducted by the ERG to assess the internal validity of the model:

i) Individual equations were checked for their mathematical correctness. However, due to time constraints, the ERG was not able to check all cells in the model. The ERG did not identify any errors in the equations in the company model.

ii) The visual basic programming code within the model was checked and appeared to be correct.

iii) The ERG checked for consistency of the parameters reported in the technical document and those utilised within the model. The ERG conducted a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed.

Based on the checks conducted as stated above, the ERG has not identified any technical internal errors in the company model.

4.3.8.3 External consistency

The company has presented validity of the model outcomes in relation to those observed in the COMPASS trial. These are presented in CS Table 179 (rivaroxaban + aspirin) and CS Table 180

(aspirin only) respectively in CS Appendix J. CS Tables 179 and 180 were updated in the clarification response (question B2), in Tables 4-5 which are reproduced below in Table 51 and Table 52.

Table 51 Model predictions versus observed results: COMPASS population – rivaroxaban + aspirin

		Year 1	Year 2	Year 3
Cumulative MI	COMPASS	0.99%	1.94%	3.09%
	Model	0.89%	1.80%	2.73%
	Difference	*0.10%*	*0.14%*	*0.36%*
Cumulative Stroke	COMPASS	0.49%	0.85%	1.68%
	Model	0.45%	0.91%	1.36%
	Difference	*0.04%*	*-0.06%*	*0.32%*
Cumulative CV death	COMPASS	0.92%	1.78%	2.99%
	Model	0.87%	1.76%	2.67%
	Difference	*0.05%*	*0.02%*	*0.32%*
Cumulative Major bleed	COMPASS	2.02%	3.21%	4.43%
	Model	1.54%	3.04%	4.52%
	Difference	*0.48%*	*0.17%*	*-0.09%*

Source: reproduced from company clarification response document Table 4

Table 52 Model predictions versus observed results: COMPASS population – aspirin

		Year 1	Year 2	Year 3
Cumulative MI	COMPASS	1.21%	2.44%	3.33%
	Model	1.03%	2.10%	3.19%
	Difference	*0.18%*	*0.34%*	*0.14%*
Cumulative Stroke	COMPASS	0.73%	1.55%	2.61%
	Model	0.76%	1.54%	2.32%
	Difference	*-0.03%*	*0.01%*	*0.29%*
Cumulative CV death	COMPASS	1.08%	2.24%	3.67%
	Model	1.10%	2.25%	3.43%
	Difference	*-0.02%*	*-0.01%*	*0.24%*
Cumulative Major bleed	COMPASS	0.87%	1.88%	3.30%
	Model	0.86%	1.70%	2.51%
	Difference	*0.01%*	*0.18%*	*0.79%*

Source: reproduced from company clarification response document Table 5

The CS states that there is some small overestimation and underestimation of some events in both arms but overall the model replicates the observed data well with no indication of bias towards either treatment. The ERG agrees that the model provides a reasonable fit to the events for the COMPASS trial.

The ERG requested that the company also compare the model results for the subpopulations with the observed outcomes in the COMPASS trial. The company provided this information in response to clarification question B1 in Tables 2-3 for the outcome of overall mortality. The

company stated that there was some under and overestimation in both arms but no indication of bias towards either treatment and that the model provides a good estimate of overall mortality compared to the COMPASS study. The ERG notes that the fit for the subpopulations is not as good as for the whole COMPASS population, particularly for the year three results and for the CAD+PAD and CAD+HF subpopulation results for aspirin only. This may be due to the uncertainty of the data at this time point in the study and is conservative, i.e. underestimates the benefit of rivaroxaban.

In addition, the company has attempted to compare the model results for ticagrelor + aspirin versus aspirin with those from TA420 by using the cost and utility inputs and starting age from TA420 in their model. The results are shown in Table 182 of CS Appendix J and reproduced in Table 53.

Table 53 Comparative results against TA420 for the rivaroxaban model using TA420 inputs

	TA420				Rivaroxaban model		
Cost	**Ticagrelor + aspirin**	**Aspirin**	**Difference**		**Ticagrelor + aspirin**	**Aspirin**	**Difference**
Drug costs	£1,571	£132	£1,439		£1,843	£76	£1,767
Other costs	£12,872	£12,887	-£5		£6,981	£7,415	-£433
Total	£14,443	£13,019	£1,434		£8,824	£7,491	£1,333

	TA420				Rivaroxaban model		
Health outcomes	**Ticagrelor + aspirin**	**Aspirin**	**Difference**		**Ticagrelor + aspirin**	**Aspirin**	**Difference**
Life years	12.34	12.25	0.0909		13.67	13.58	0.0901
QALYs	9.27	9.20	0.0708		10.33	10.26	0.0709

	TA420		Rivaroxaban model
Cost per life year gained	£15,776 (calculated)		£14,790
ICER (£/QALYs)	£20,098		£18,794

The CS states that the results were reasonably well aligned to those from TA420. However, the CS states that there are structural and input differences that remain between the company's model and the model used in TA420. For instance, the transition probabilities are from different trials and it was not possible to change some of the costs as there was no equivalent cost in TA420 or vice versa. The ERG notes that the starting population would differ between analyses

as all patients in TA420 start after a recent MI, whereas those from the rivaroxaban appraisal do not. This may explain, in part, why the costs are higher in TA420 than in the company's model. Nevertheless, the ERG agrees that the incremental differences in costs and utilities are similar between analyses.

4.3.9 Cost effectiveness results

Results from the economic model are presented in CS tables 89 – 91 as incremental cost per QALY gained for rivaroxaban + aspirin compared with aspirin and rivaroxaban + aspirin compared with ticagrelor + aspirin. These are presented for the whole COMPASS population and also for the subpopulations for CAD+PAD, CAD+HF and CAD+PRF. Life years gained are also reported. As stated earlier, the company updated the costs and background mortality in their clarification response (questions B6, B12). Updated results are shown in Tables 34-40 of the clarification response and are summarised below.

For the COMPASS population, an incremental cost per QALY gained of £16,326 for rivaroxaban + aspirin versus aspirin is reported (Table 54). For CAD+PAD, an incremental cost per QALY gained of £9,047 is reported (see Table 55) for rivaroxaban + aspirin versus ticagrelor + aspirin. For CAD+HF, an incremental cost per QALY gained of £5,702 is reported (see Table 56) for rivaroxaban + aspirin versus aspirin. For CAD+PRF, an incremental cost per QALY gained of £9,861 is reported (see Table 57) for rivaroxaban + aspirin versus aspirin.

Table 54 Incremental base case cost effectiveness results for the COMPASS population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER: rivaroxaban versus comparator (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	£7,260	9.35	-	-	£16,326	-
Ticagrelor + aspirin	£8,889	9.41	£1,629	0.06	£12,581	Extendedly dominated
Rivaroxaban + aspirin	£10,842	9.57	£1,953	0.155	NA	£16,326

Table 55 Incremental base case cost effectiveness results for the CAD and PAD subpopulation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER: rivaroxaban versus comparator (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	£9,571	8.13	-	-	£7,309	-
Ticagrelor + aspirin	£11,257	8.39	£1,686	0.26	£9,047	£6,485
Rivaroxaban + aspirin	£12,476	8.53	£1,219	0.14	NA	£9,047

Table 56 Incremental base case cost effectiveness results for the CAD and HF subpopulation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER: rivaroxaban versus comparator (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	£6,256	8.09	-	-	£5,702	-
Ticagrelor + aspirin	£7,872	8.21	£1,616	0.12	£3,920	Extendedly dominated
Rivaroxaban + aspirin	£9,925	8.74	£2,053	0.52	NA	£5,702

Table 57 Incremental base case cost effectiveness results for the CAD and PRF subpopulation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER: rivaroxaban versus comparator (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	£7,855	7.39	-	-	£9,861	-
Ticagrelor + aspirin	£9,263	7.41	£1,408	0.02	£4,841	Extendedly dominated
Rivaroxaban + aspirin	£10,431	7.65	£1,168	0.24	NA	£9,861

In deterministic sensitivity analyses, the ICERs were most sensitive to changes in the HR for MI, IS and sudden cardiac death. The company stated that for the subpopulation of patients with

CAD+PAD, the ICERs remained below £20,000/QALY in all scenarios and for the other two subpopulations the results were largely insensitive to the different scenarios.

The results of the PSA run by the ERG using the updated model are shown in Table 63. These are similar to those reported in the CS section B3.8. For the COMPASS population there was 84.3% and 91.6% probability of rivaroxaban + aspirin being cost-effective, relative to aspirin only and relative to ticagrelor + aspirin respectively, at a willingness-to-pay threshold of £20,000 per QALY gained.

4.3.10 Assessment of uncertainty

The company assessed methodological, structural and parameter uncertainties associated with the base-case analyses by conducting a range of deterministic sensitivity, probabilistic sensitivity and scenario analyses, details of which are discussed below.

Deterministic sensitivity analyses

Deterministic sensitivity analyses (DSA) were conducted on model parameter inputs. The parameters and their ranges are shown in Table 58. With the exception of HRs for CV death (discussed below), the choice of parameters included and the ranges for variation is reasonable. The input variables and their ranges are shown in the CS in Table 112 for the COMPASS population, Table 115 for the CAD+PAD subpopulation, Table 118 for the CAD+HF subpopulation, and Table 121 for the CAD+PRF subpopulation. The company ran pairwise DSA for rivaroxaban + aspirin against both aspirin and ticagrelor + aspirin.

Table 58 Parameters and their ranges used for deterministic sensitivity analyses

Parameters	Range
Transition probabilities	95% confidence interval; +/-20% of the mean values
Hazard ratios	95% confidence intervals
Disease management costs / event costs	+/- 30% of the mean values
Terminal care/ end of life costs	+/- 30% of the mean values
Discontinuation rate	95% confidence interval; +/-20% of the mean values
Health state utilities	95% confidence intervals

The company produced tornado plots for rivaroxaban + aspirin against both aspirin only and ticagrelor + aspirin for each of the subpopulations that showed the parameters with the most impact on the model results (CS Figures 43 -50). The model was most sensitive to changes to the HR parameters for sudden cardiac death, MI and IS across the three subpopulations. The DSA results in the CS are shown in Tables 116-117,119-120,122-123. For all DSAs, except the one for CAD+PAD subpopulation comparing rivaroxaban + aspirin versus ticagrelor + aspirin, the ICERs remained below £20,000 per QALY. In the DSA for CAD+PAD subpopulation comparing rivaroxaban + aspirin versus ticagrelor + aspirin, the parameters for HR sudden cardiac death, HR IS and HR Other CV death produced ICERs of more than £20,000 per QALY. The tornado plot for this DSA is shown in Figure 4.

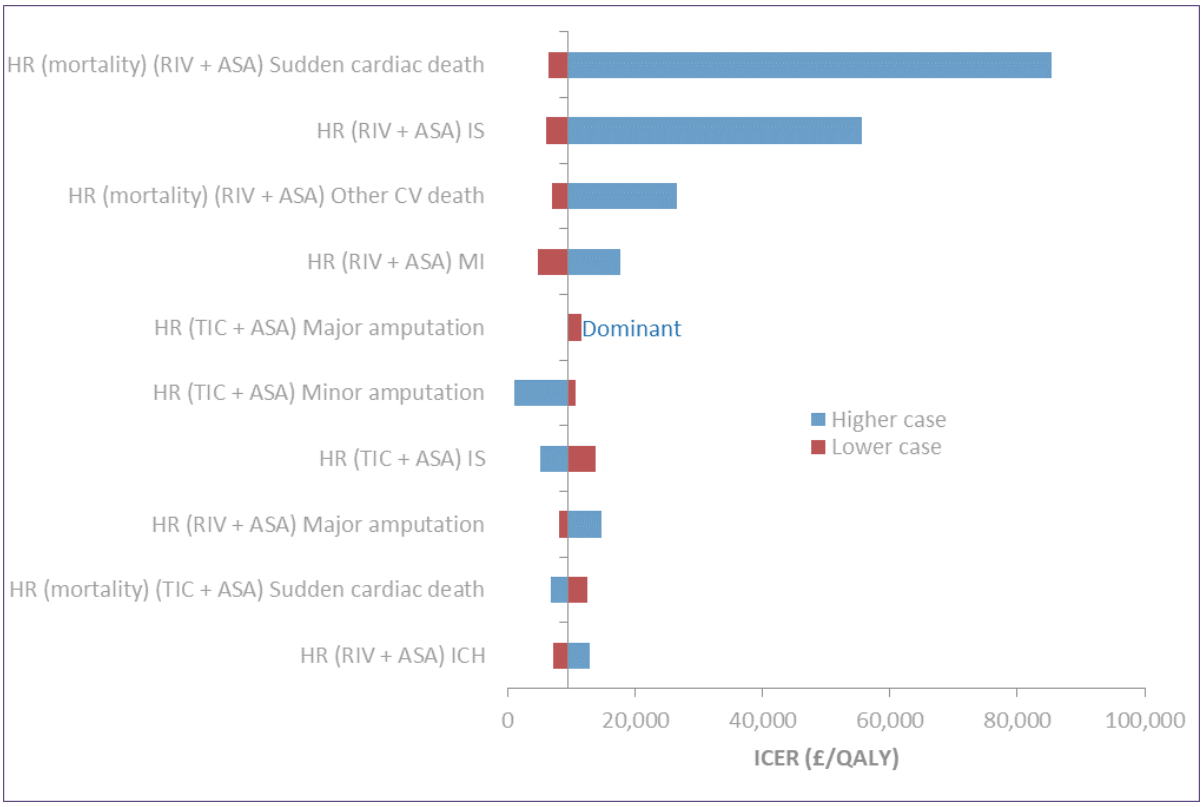


Figure 4 Tornado plot – CAD and PAD subpopulation: rivaroxaban + aspirin vs ticagrelor + aspirin

Source: reproduced from CS Figure 46

In CS Table 56, the HRs are reported for all CV deaths. In the model, CV death is stratified by death due to MI, stroke, CV procedure, sudden cardiac death, 'other CV death' and 'all CV death'. The HRs for these death events are assumed to be the same for CV death in CS Table

56. In the DSA, the company has varied each of these mortality HRs separately. However, the ERG suggests that a better approach is to vary only the HR for all CV death as the HR has been calculated for all CV deaths. By varying the HR for each mortality event separately, the company has underestimated the uncertainty around the model results. The ERG ran the DSA (using the updated economic model) by varying the HR for all CV death in section 4.4.

Scenario analysis

The company conducted scenario analyses to assess structural, methodological and parameters uncertainties. The scenario analyses are detailed in CS Table 124, reproduced below in Table 59. The company ran pairwise scenarios for rivaroxaban + aspirin separately against both aspirin and against ticagrelor + aspirin. The ERG considers that the scenario analyses are appropriate and reasonable.

Table 59 Scenario analyses – input parameters

Model input	Base Case	Rationale	Scenarios
Time horizon	Lifetime (33 years)	In line with other models, in line with chronic nature of condition, impact on mortality	15 years
Treatment duration	Life time	Consistent with licence	5 years for rivaroxaban + aspirin
Treatment discontinuation	Discontinuation rate in the first four years based on the rate observed in COMPASS. Discontinuation rate from year 5 assumed to be half the rate of the first four years. Impact on cost and efficacy.	Patients who have reached the 4-year timepoint on treatment are those who are most likely to be compliant in the longer term	As per the base case for the first 4 years. From year 5 no further discontinuation from rivaroxaban + aspirin (impact on efficacy and costs)
			Discontinuation rate observed in the first four years is applied for the entire model duration (impact on efficacy and costs)
Treatment interruption	None	Conservative	1 year after an MI, patients switch to dual antiplatelet therapy (ticagrelor + aspirin) for one year, in all arms. 3 month after an ICH, patients receive aspirin only for 3 months. 1 month after a major

			bleed, patients receive aspirin only for one month.
Aspirin rate of events	As observed in COMPASS trial i.e. null transitions inputted	COMPASS trial data	Null transitions changed to minimum of transition probabilities for same event independent of previous event history. Additional detail from clarification response (question B11): Null event probabilities after a first event replaced with the associated probability of the event-free health state. Null CV death probabilities after a second event imputed the minimum of all probabilities after a second event.
Efficacy for health states and health events	Neutral HRs vs aspirin for comparator when no evidence	No evidence	Replaced by rivaroxaban + aspirin HRs vs aspirin
Second events assumption - costs			
Cost in the acute state	Costs based on most recent event	Conservative	Additive cost, second event acute cost + first event post-acute cost
Cost in the post-acute state	Costs based on the maximum of the post-acute state costs	Conservative	Costs of the most recent event
			Additive cost of both post-acute states
Second event assumptions – utilities			
Utility of second event	Utility of second event based on lowest utility of the individual included health states	Conservative	Based on most recent event utility
			Multiplicative approach
Utilities inputs	EQ-5D COMPASS (GEE model)	COMPASS trial data	Repeated measures mixed model analysis results
			Ticagrelor utility data (TA420)
Transition from event free to two events in one cycle	Not possible	Very low proportion of patients experiencing such transition, very low impact on the ICER	2 events in a single cycle allowed
Health states and health events costs	NHS Reference costs	NICE guidelines	Walker et al. 2016: follow-on costs for the first 90-day period used following an event
Discount rates	3.5%	NICE guidelines	0%
			5%

Source: reproduced from CS Table 124

The results for the scenario analyses are shown for the CAD+PAD, CAD+HF, CAD+PRF subpopulations in CS tables 126-128 respectively. The CS states that in the CAD+PAD subpopulation, the ICERs remained below £20,000/QALY for all scenarios. For the CAD+HF and CAD+PRF subpopulations, the results were largely insensitive to the different scenarios. The ERG concurs. The scenario analysis results for the CAD+PAD subpopulation are shown in Table 60 (reproduced from CS Table 126 and updated using the most recent version of the model).

Table 60 Scenario analysis results – COMPASS population (using updated model)

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		£16,326	£12,581
Time horizon	15 years	£22,505	£17,695
Treatment duration	5 years	£14,008	£3,738
Treatment discontinuation	4 years	£17,022	£14,370
	Duration of model	£15,843	£11,077
Treatment interruption	Yes	£16,077	£12,312
ASA transition probabilities	No null transition	£15,638	£9,538
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	£16,326	£13,254
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£16,341	£12,623
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£15,296	£11,451
Second event assumptions – utilities	Based on most recent event utility	£16,380	£12,625
	Multiplicative approach	£15,873	£12,169
Utilities inputs	Repeated measures mixed model	£16,278	£12,535
	Ticagrelor TA 420	£16,646	£12,873
Transition from event free to two events in one cycle	COMPASS data	£16,308	£10,964
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal	£16,668	£13,244

	MI/IS/ICH Cost in first 90-day periods		
Discount rates	0%	£13,004	£15,666
	5%	£17,888	£7,463

Probabilistic sensitivity analysis (PSA)

The company conducted PSA on their base case analysis to assess parametric uncertainty (CS section B3.8) for the COMPASS population and the three subpopulations. The company ran pairwise PSA for rivaroxaban + aspirin separately against both aspirin alone and ticagrelor + aspirin. The ERG considers it would be better if results were presented together for all three treatments. The PSA was run for 10,000 iterations and took about an hour and a half to run. The input parameters and distributions are shown in CS Table 100 for the COMPASS population, CS Table 103 for the CAD+PAD subpopulations, CS Table 106 for the CAD+HF subpopulation, and CS Table 109 for the CAD+PRF subpopulation. Table 61 shows the parameters and distributions used in the PSA. The ERG considers that all appropriate parameters are included in the PSA and the ranges and distributions used are appropriate. The PSA has been implemented using a visual basic macro which makes it difficult for a non-specialist to assess or make changes to the PSA.

As with the deterministic sensitivity analyses, the company has underestimated the uncertainty by varying difficult CV mortality HRs separately, rather than varying these mortality HRs together.

Table 61 List of parameters and associated distributions included in the PSA

Parameter	Distribution
Population	Beta / Normal
Transition probabilities	Beta
AE rates (incidence)	Beta / lognormal
Hazard ratios	Lognormal
Costs	Gamma
Utilities	Beta
Treatment discontinuation	Normal

The CS presented the results for each of the subpopulations and these are presented in CS Tables 104-105, 107-108 and 110-111. The PSA results for each subpopulation compared to

the deterministic ICERs are shown in Table 62 using the updated economic model. In general the deterministic ICERs were similar to the PSA ICERs, with the exception of the comparison between rivaroxaban + aspirin with ticagrelor + aspirin for the CAD+PAD subpopulation. For this analysis, the PSA ICER was about 40% lower than the deterministic ICER.

Table 62 Comparison of the ICERs obtained from the deterministic and PSA analyses (using updated economic model)

	ICER (£/QALY)							
ICER	**COMPASS**		**CAD+PAD**		**CAD+HF**		**CAD+PRF**	
	vs aspirin	vs TIC+ aspirin	vs aspirin	vs TIC+ aspirin	vs aspirin	vs TIC+ aspirin	vs aspirin	vs TIC+ aspirin
Deterministic	£16,326	£12,581	£7,309	£9,047	£5,702	£3,920	£9,661	£4,841
PSA	£16,557	£12,837	£7,973	£5,919	£5,857	£4,035	£10,348	£5,261

TIC = Ticagrelor

The probability of rivaroxaban + aspirin being cost-effective at different willingness-to-pay thresholds are tabulated in Table 63. At a willingness-to-pay threshold of £20,000 per QALY, the probability of rivaroxaban being cost effective was 100% vs aspirin and ticagrelor + aspirin for the CAD+HF subpopulation. For CAD+PAD, the probability of rivaroxaban being cost-effective was 80% versus ticagrelor + aspirin and 99% versus aspirin. For CAD+PRF, the probability of rivaroxaban being cost-effective ranged between 93% and 97% against aspirin and ticagrelor + aspirin respectively.

Table 63 Probability of rivaroxaban + aspirin being cost-effective at different willingness-to-pay thresholds (using updated model)

	Probability of being cost-effective (%)							
WTP threshold (per QALY)	**COMPASS**		**CAD+PAD**		**CAD+HF**		**CAD+PRF**	
	vs aspirin	vs ticagrelor + aspirin	vs aspirin	vs ticagrelor + aspirin	vs aspirin	vs ticagrelor + aspirin	vs aspirin	vs ticagrelor + aspirin
£20,000	84.3	91.6	98.8	79.7	100	100	95.6	98.7
£30,000	99	98.4	100	84.3	100	100	99.0	99.6

WTP = Willingness-to-pay

4.4 Additional work undertaken by the ERG

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost-effectiveness analyses.

The ERG did not discover any errors or discrepancies in the economic model. We firstly ran the model for our preferred base case. Our base case is explained and justified in Table 64. Results are shown for the effect of each of the individual changes on the COMPASS whole trial population (Table 66) and then the effect of all the changes together for the COMPASS whole trial population (Table 67) and the subpopulations (Table 68 - Table 70). We conduct additional analyses by exploring the uncertainty in the economic model by varying all CV mortality HRs together and investigating a best and worst case bleeding scenario. We also include a scenario analysis restricted to patients with a previous MI.

Table 64 ERG base case

Model aspect	Company analysis	ERG base case	Justification
Hazard ratios for ticagrelor + aspirin vs aspirin	Main events: Where HRs were not available for subpopulations, HRs from the PEGASUS whole trial population were used. Adverse events: For amputations, HR =1 vs. aspirin, for non-fatal bleeds HR for major bleeding used; where HR were not available HRs from the whole PEGASUS whole trial population were used.	Main events: no change from company base case. Adverse events: For all adverse events, HRs for ticagrelor vs. aspirin are the same as rivaroxaban vs. aspirin.	Main events: reasonable to use HRs from PEGASUS whole trial population in the absence of subgroup interactions. Adverse events: Data from PEGASUS trial highly uncertain for adverse events as these data were not collected / reported or were defined differently. Unclear whether there are any differences between adverse events for rivaroxaban and ticagrelor (CS Tables 32-33).
Null transition probabilities	Use null transition probabilities for aspirin, as observed in the COMPASS trial.	Use company scenario for imputed values for aspirin transition probabilities. Null event probabilities after a first-event replaced with the probabilities from the	Imputed values are more similar to expected real-life values.

		event-free health state. Null CV death probabilities after a second-event imputed using the minimum of all probabilities after a second event.	
Treatment interruption	No interruption for rivaroxaban + aspirin was explicitly considered after the main events (MI, ICH or IS).	Treatment interruption: 1 year after an MI, patients switch to dual antiplatelet therapy (ticagrelor + aspirin) for one year, in all arms. 3 months after an ICH, patients receive aspirin only for 3 months. 1 month after a major bleed, patients receive aspirin only for one month.	More similar to clinical practice.
Utility values for event-free health state	Values taken from COMPASS trial. For combined health states, company uses lowest utility of the two health states.	Use age-adjusted population utility norms for COMPASS population, with subgroups adjusted according to disutility seen in COMPASS. For combined health states use multiplicative utility values. Utility values for the event-free state shown in Table 65.	Unrealistic for patients with multi-vessel disease and subgroups to have utility higher than general population norm. NICE Decision Support Unit (DSU) guide [23] states that correct approach is to use multiplicative utility values.
Monitoring costs for event-free health state	No costs incurred for monitoring for event-free health state.	Use monitoring costs from TA317, updated to 2017/18: £167.66.	Patients will be monitored whilst in the event free state.

Table 65 Utility values used in ERG base case for the event-free health state

Event-free health state	COMPASS	CAD+PAD	CAD+HF	CAD+PRF
Company model	0.835	0.796	0.800	0.813
ERG base case	0.779	0.743	0.783	0.792

The ERG changes to the company model only have a marginal effect on the model results (Table 66).

Table 66 ERG analyses for the COMPASS population

Model aspect	ICER vs aspirin	ICER vs ticagrelor + aspirin
Company base case	*£16,326*	*£12,581*
HRs for ticagrelor + aspirin vs aspirin	£16,326	£13,328
Null transition probabilities	£15,638	£9,538
Treatment interruption	£16,077	£12,312
Utility values for event-free health state	£16,856	£12,892
Monitoring costs for event-free health state	£17,606	£13,843

Table 67 ERG base case analyses for the COMPASS population

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; rivaroxaban vs comparator
Aspirin	£13,387	8.39		£17,024
Ticagrelor + aspirin	£14,647	8.40	Extendedly dominated	£11,453
Rivaroxaban + aspirin	£16,885	8.60	£17,024	NA

Table 68 ERG base case CAD+PAD subpopulation

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; rivaroxaban vs comparator
Aspirin	£14,040	7.11		£7,731
Ticagrelor + aspirin	£15,774	7.36	£6,911	£8,922
Rivaroxaban + aspirin	£17,316	7.53	£8,922	NA

Table 69 ERG base case CAD+HF subpopulation

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; rivaroxaban vs comparator
Aspirin	£12,158	7.70		£6,327
Ticagrelor + aspirin	£13,487	7.77	Extendedly dominated	£4,710
Rivaroxaban + aspirin	£16,097	8.32	£6,327	NA

Table 70 ERG base case CAD+PRF subpopulation

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; rivaroxaban vs comparator
Aspirin	£12,043	6.67		£8,355
Ticagrelor + aspirin	£13,269	6.71	Extendedly dominated	£5,217
Rivaroxaban + aspirin	£14,799	7.00	£8,355	NA

As can be seen from Table 67 - Table 70, the changes to the company's assumptions in the ERG base case have only a small effect on company's base case results.

4.4.1.1 ERG scenario analyses

4.4.1.1.1 CV death

The ERG ran the company DSA (using the updated economic model) by varying the HRs for all CV death and assuming the same HRs for all the CV mortality events. The HRs for mortality due to MI, stroke, HF, CV procedure, sudden cardiac death, other CV death and all CV death were set to the lower and higher 95%CI of the HR for all CV death. These results are shown in Table 71 and show that the model results are more sensitive to changes in the all CV death HR than shown in the company DSA. Using the upper bound for the HR for all CV death, ICERs are more than £20,000 per QALY for the COMPASS population and the subpopulations for CAD+PAD and CAD+PRF.

Table 71 One-way sensitivity analysis results for HR CV death using same ranges for all CV death

Population	Comparator	Model input	Lower/Upper bound	Lower bound	Upper bound
COMPASS	Aspirin	HR CV death	0.64/0.96	£11,512	£38,018
COMPASS	Ticagrelor + aspirin	HR CV death	0.64/0.96	£8,060	£69,249
CAD+PAD	Aspirin	HR CV death	0.49/1.07	£5,275	£25,346
CAD+PAD	Ticagrelor + aspirin	HR CV death	0.49/1.07	£4,399	Dominated
CAD+HF	Aspirin	HR CV death	0.47/0.92	£4,380	£12,170
CAD+HF	Ticagrelor + aspirin	HR CV death	0.47/0.92	£3,006	£11,060
CAD+PRF	Aspirin	HR CV death	0.62/1.20	£6,088	Dominated
CAD+PRF	Ticagrelor + aspirin	HR CV death	0.62/1.20	£3,252	Dominated

4.4.1.2 Bleeding

The ERG investigated the uncertainty around the bleeding events by conducting best / worse case scenarios for bleeding. We varied the bleeding event transition probabilities and HRs for bleeding from their lower 95% CI and higher 95% CI for all bleeding inputs together. The inputs varied are shown in Table 72. The results are shown in Table 73 for the COMPASS population and show that the model results are less sensitive to changes in the bleeding parameters than for the CV death HR. This is because the event rate for fatal bleeding is low and the impact of major bleeding is relatively low in terms of additional costs and disutilities. The results were not run for the subpopulations as full data are not available for these groups.

Table 72 Inputs used for the one-way sensitivity analysis results for bleeding

Event	Model input	Mean	Lower bound	Upper bound
Fatal bleed event free	Transition probability	0.00004	0.000009	0.0001
Fatal bleed – Patients with 1 MI history	Transition probability	0.00231	0.00185	0.00278
Major bleed	Transition probability	0.00217	0.00184	0.00253
Fatal bleed	Hazard ratio	1.49	0.67	3.33
Major bleed	Hazard ratio	1.79	1.46	3.19

Table 73 One-way sensitivity analysis results for bleeding scenario

Population	Comparator	Model input	Company base case	Lower bound	Upper bound
COMPASS	Aspirin	HR CV death	£16,326	£15,412	£23,562
COMPASS	Ticagrelor + aspirin	HR CV death	£12,581	£11,657	£22,136

4.4.1.2.1 MI subgroup

As noted earlier in our report (section 3.1.7), there are differences between the COMPASS and PEGASUS trial populations in terms of the proportion who had experienced a previous MI, with 62% of patients in COMPASS having a previous MI and all patients in PEGASUS having a previous MI. The ERG has attempted to conduct a comparison between rivaroxaban + aspirin and ticagrelor + aspirin for patients with a prior MI. We have used the HRs for MI, stroke and CV death from subgroup analyses in patients with a previous MI from the COMPASS trial and transition probabilities derived from the PEGASUS trial for MI (for the event-free group) (Table 74). Note the transition probabilities from the PEGASUS trial for stroke and CV death are in proportion to those seen in the COMPASS trial. Also note that the potential time period during which a previous MI could occur was much longer in the COMPASS trial than in the PEGASUS

trial (up to 20 years and 1-3 years, respectively). HRs stratified by the time period of the previous MI in the COMPASS trial (e.g. <1 year ago; 1-2 years, etc) were not available to the ERG. These would have provided data more comparable to the PEGASUS trial.

Table 74 Event rates and transition probabilities for previous MI subgroup in COMPASS with 23 month follow-up and PEGASUS with 36 month follow-up

	Event rates			
COMPASS trial	**Rivaroxaban + Aspirin**	**Aspirin**	**HRs**	**Transition probability**
Composite efficacy outcome	4.4%	5.8%	0.76	
MI	2.1%	2.5%	**0.84**	0.002625
Stroke	1.0%	1.6%	**0.63**	0.00125
CV death	1.7%	2.5%	**0.68**	0.002125
	Event rates			
PEGASUS trial	**Ticagrelor + aspirin, %**	**Aspirin**	**HRs**	**Transition probability**
Composite efficacy outcome	7.8%	9%	0.87	
MI	4.5%	5.2%	0.87	**0.004333**
Stroke	1.5%	1.9%	0.79	0.001583
CV death	2.9%	3.4%	0.85	0.002833

Values shown in bold are those used in this scenario.

The results of the scenario analysis are shown in
Table **75**. These show that in this scenario rivaroxaban is more cost-effective than in the company base case. However, it is important to note that the comparison is only illustrative as the HRs are not restricted to those who had a MI in the last two years, as is the case in the PEGASUS trial. We note that a subgroup analysis[12] of CAD patients in COMPASS with an MI in the previous two years showed a more favourable effect on the primary composite efficacy outcome compared to patients whose previous MI occurred longer ago. We therefore speculate that HRs for patients with an MI in the previous two years were available for all outcomes, the cost-effectiveness results are likely to be more favourable to rivaroxaban than in our analysis.

Table 75 ERG scenario analysis for patients with previous MI in the COMPASS population

Population	Comparator	Model inputs	Company base case	ERG scenario analysis
COMPASS	Aspirin	HR MI, stroke, CV death	£16,326	£13,056
COMPASS	Ticagrelor + aspirin	HR MI, stroke, CV death	£12,581	£9,719

4.4.1.3 ERG probabilistic sensitivity analyses

The ERG has run the PSA by setting all CV mortality HRs to vary together, rather than independently. In addition, rivaroxaban + aspirin is compared to aspirin and to ticagrelor + aspirin, rather than in a pairwise analyses. The results are shown below in Table 76. As stated above, these demonstrate higher uncertainty for rivaroxaban compared to its comparators than shown in the company results.

Table 76 Probability of rivaroxaban + aspirin being cost-effective at different WTP thresholds (using updated model) with all CV death varied together

	Probability of being cost-effective (%)			
WTP threshold (per QALY)	**COMPASS**	**CAD+PAD**	**CAD+HF**	**CAD+PRF**
	vs aspirin and ticagrelor + aspirin	vs aspirin and ticagrelor + aspirin	vs aspirin and ticagrelor + aspirin	vs aspirin and ticagrelor + aspirin
£20,000	47.1%	61.6%	87.7%	67.5%
£30,000	62.1%	64.3%	90.2%	71.2%

WTP = willingness-to-pay

The cost-effectiveness acceptability curve for the COMPASS population is shown in Figure 5.

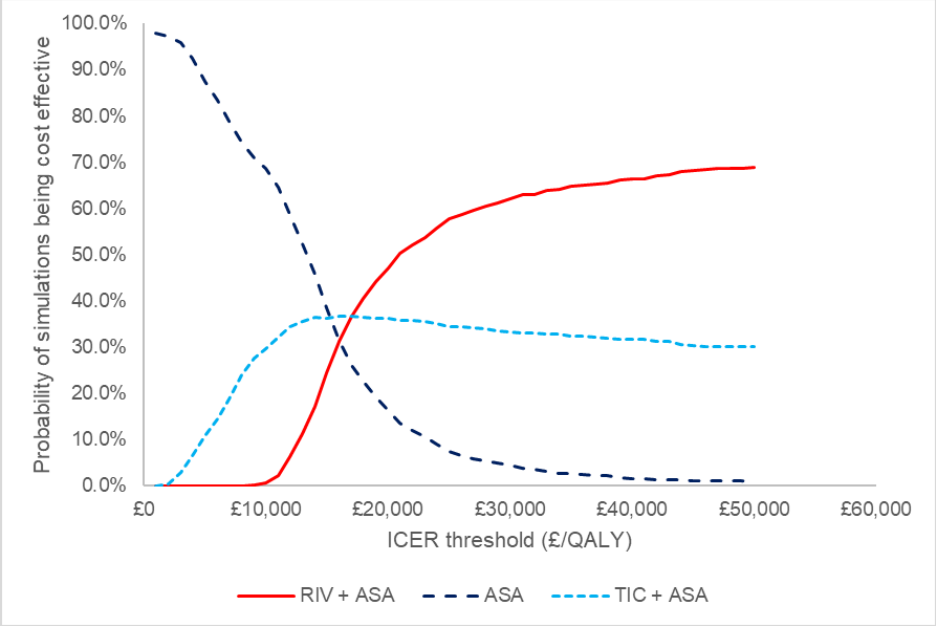


Figure 5 Cost-effectiveness acceptability curve for the COMPASS population for rivaroxaban + aspirin vs its comparators (using updated model) with all CV death varied together

5 End of life

The CS does not mention whether rivaroxaban should be considered under NICE's end of life criteria.

6 Innovation

The CS provides only a very brief statement in support of rivaroxaban + aspirin as an innovative treatment for secondary prevention of cardiovascular disease (CS section B.2.12). It is stated that there have been few new available antithrombotic treatments for this condition for several decades. The results of the COMPASS trial are stated to be of a similar magnitude to those seen with all other secondary prevention treatments (including aspirin, lipid lowering, blood pressure lowering and ACE inhibitors). The CS does not provide a biological or pharmacokinetic rationale for rivaroxaban + aspirin to be considered a treatment innovation.

Expert clinical advice to the ERG is that rivaroxaban is not an innovative treatment in terms of its mechanism of action, as it is similar to other drugs that have been used in the management of CAD for a number of years (e.g. anticoagulation and antiplatelet properties). However, one of the clinical experts commented that the additional benefit of rivaroxaban added to aspirin as shown in the COMPASS trial is regarded as an important clinical effectiveness innovation.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The ERG regards the COMPASS trial to be a well-conducted trial which is likely to be at a low risk of bias. The trial measured an appropriate range of relevant outcomes. The composite primary efficacy outcome (cardiovascular death, stroke (ischaemic, haemorrhagic or stroke of uncertain cause) or MI) has been used in previous trials of antithrombotic treatments, as featured in previous NICE appraisals.

The primary safety outcome was major bleeding, which is a composite of specific bleeding events, including fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding into the surgical site requiring re-operation and bleeding leading to hospitalisation (with or without an overnight stay). The bleeding events that inform the economic model are fatal bleeding, and

major extracranial non-fatal bleeding. Major bleeding was defined according to modified ISTH criteria which, it stated in the CS, increases the sensitivity of the ISTH bleeding definition to clinically relevant bleeds. In contrast, the PEGASUS RCT of ticagrelor (used in the company's ITC of rivaroxaban versus ticagrelor) uses the TIMI criteria. These two sets of criteria differ from each other in respect of major bleeding definitions. The CS states that the differences in bleeding criteria would likely bias the analysis against rivaroxaban + aspirin in the ITC. The ERG observes that the confidence intervals for bleeding events in the ITC are wide and cross 1 and it is therefore difficult to definitely assess the degree of any bias due to this imprecision around the treatment effect.

The trial was statistically powered for the primary composite efficacy outcome, but not for the individual components of this outcome, which inform the economic model.

Only one of the three subpopulations of interest in the CS was pre-specified in the trial protocol (3rd July 2014): patients with both CAD and PAD. The other two subpopulations of interest in the CS (i.e. CAD+PRF and CAD+HF) were only specified in a later health economics outcomes research statistical analysis plan (18th July 2017). Expert clinical advice to the ERG is that these are clinically relevant subpopulations. The COMPASS trial was not statistically powered to identify significant treatment effects in these subpopulations.

The NICE scope includes two further subpopulations which have not been included in the CS: people with previous MI; and people with multiple MIs. The ERG notes that approximately 62% of the COMPASS trial ITT population had experienced a previous MI, though the proportion of this population who had multiple MI is not reported. NICE's guidance on ticagrelor (TA420[6]) is that it is an option for preventing atherothrombotic events in adults who had a MI and who are at high risk of a further event. Thus, for the approximately 38% of patients in the COMPASS trial, who had not experienced a previous MI, ticagrelor is not a relevant comparator. The company did not conduct an ITC restricting the patients in the COMPASS trial to those with a previous MI (and those with an MI within the previous two years), to more closely align with the patients in the PEGASUS trial, all of whom had a previous MI. The company states that previous MI is not an effect modifier based on the COMPASS trial analysis. Expert advice to the ERG is that a previous MI is prognostic of recurrent events. Based purely on COMPASS subgroup trial data alone it appears that it is not an effect modifier, but whether this applies more widely is

uncertain. As this is a significant source of heterogeneity between the two trials it is appropriate to explore this as a subgroup analysis.

7.2 Summary of cost effectiveness issues

7.2.1.1 Comparators

The intervention (rivaroxaban 2.5mg bd + aspirin 75mg od) is compared against aspirin 75mg od and against ticagrelor 60mg bd + aspirin 75mg od. The NICE scope specifies clopidogrel as a comparator in patients with PAD, however, the CS does not report cost-effectiveness analyses for this comparator and subgroup.

7.2.1.2 Model assumptions

The company developed a de novo Markov model, which has three-month cycles and a lifetime horizon. The structure of the company's model is appropriate and correctly implemented and includes relevant and comprehensive health states. The time horizon is in line with NICE's reference case and the company has included a half-cycle correction.

7.2.1.3 Treatment effectiveness and extrapolation

The transition probabilities for the first four years of the model are based upon patient-level data from the COMPASS trial and subsequently adjusted from data from the REACH registry. The main issues with treatment effectiveness have to do with missing data and assumptions applied in data imputation. For the main events, the ERG considers that zero transition probabilities computed from the company's analysis of the COMPASS trial do not reflect reality as experiencing an event would normally be a risk factor for future events. We address this in our preferred analysis.

7.2.1.4 Health utility

The company's approach to estimating HRQoL uses data from the COMPASS trial. The use of the COMPASS utility data is preferable, given the good quality of the trial, to other estimates of utility that may not be representative of the population modelled. We find the use of COMPASS trial data to be consistent with the NICE reference case. We note that the COMPASS trial was not powered for the three patient subpopulations. We have applied the multiplicative assumption

in cases where patients suffer a second major event, as we believe this is more appropriate than the company's base case assumption.

7.2.1.5 Health resources and costs

The approach taken by the company for estimating health care resources and costs is reasonable and in line with previous NICE technology appraisals. The company has addressed the issues we raised in the clarification questions, regarding using up to date sources of NHS reference costs and uprating relevant costs.

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9 APPENDICES

9.1 ERG appraisal of the indirect comparison methods, assumptions and reporting using the criteria suggested by Donegan and colleagues[15]

Indirect comparison method	**Judgement (Yes, No, Unclear, Not applicable)**
Is the method applied to undertake the indirect comparison adequate?	Yes, used the 'adjusted' method of Bucher et al.
If an adequate method is used, is a treatment effect estimate and measure of precision reported?	Yes
Similarity	
Is the assumption of similarity stated?	No
Is a method described to assess the similarity assumption within the review methods section?	
Is a reasonable approach used to assess the assumption of similarity?	No. Although meta-regression was planned, using standardised network meta-regression techniques, this was not feasible because only two trials were available to include. Patient and trial characteristics of the two trials were compared and differences highlighted but the potential impact of these differences on the indirect treatment comparison was not always discussed.
Are patient or trial characteristics reported for all trials in the indirect comparison?	Yes
Are patient or trial characteristics compared across the two trial sets involved in the indirect comparison?	Yes
Are patient or trial characteristics reported to be comparable for the two trial sets involved in the indirect comparison?	No. The following differences were reported for the ITT population but, with the exception of the impact of a difference in the definition of major bleeding, the potential impacts of the differences on the indirect comparison were not discussed: Proportion of patients with prior MI was 62% in the COMPASS RCT but 100% in the PEGASUS RCT. Time since prior MI was restricted to between 1 and 3 years earlier in the PEGASUS RCT but in COMPASS patients could have had an MI within the past 20 years. Proportion of patients with PAD was 27% in the COMPASS RCT but only 5% in the PEGASUS RCT. Premature discontinuation was statistically significantly different between the two arms of the PEGASUS RCT but discontinuations occurred at a similar rate in the two arms of the COMPASS RCT. Definition of major bleeding was by the modified ISTH criteria in the COMPASS RCT but by the TIMI criteria in the PEGASUS RCT. The CS (Appendix D) states that "*The net effect of the different definitions of 'major bleeds' is an anticipated bias against rivaroxaban + aspirin in the ITC against ticagrelor + aspirin*".

	Other differences were reported and were stated to either be non-significant differences or to not have an impact on the results of the indirect comparison: Aspirin dose of 100 mg daily in COMPASS and 75-150mg daily in PEGASUS were stated to not differ significantly. Note that the dose typically used in the UK is 75mg daily. Duration of follow-up in the COMPASS RCT at the outcomes cut-off date of 6th February 2017 was a mean of 23 months whereas in the PEGASUS RCT the longest follow-up was a mean of 36 months. As part of the response to clarification question A6 the company stated that "the difference in duration of follow-up between COMPASS and PEGASUS is not expected to affect inference in any way". Myocardial infarction definition in the COMPASS RCT excluded sudden cardiac death (instead sudden cardiac death was assessed as a CV-related death) whereas in PEGASUS sudden unexpected cardiac deaths were included in the definition of a myocardial infarction. The ERG finds that in addition to the differences between the two trials reported above, additional minor differences are apparent: Mean age was approximately 3 years older in the COMPASS RCT. White participants formed a higher proportion of the PEGASUS RCT (approximately 86%) than the COMPASS RCT (approximately 62%) Current smokers were more common in the COMPASS RCT (approximately 21%) than in the PEGASUS RCT (approximately 17%) Diabetes at baseline was more common among COMPASS participants (approximately 38%) than PEGASUS participants (approximately 32%). Coronary artery disease was present in all PEGASUS participants (who as already noted had all had a previous MI) and was present in approximately 90% of COMPASS participants. NSAID use at randomisation was almost universal in PEGASUS (99.9%) but only reported for approximately 5% of COMPASS participants. The ERG also notes that, as can be seen in CS Appendix D Table 132, several baseline characteristics reported for the COMPASS RCT were not reported for the PEGASUS RCT (or were reported in a different format) and therefore the similarity between the two trial on some characteristics cannot be ascertained. In addition to the differences between the ITT populations of the COMPASS and PEGASUS RCTs there were likely similar differences in the CAD+PAD and CAD+PRF subpopulations. However, subgroup data from PEGASUS were not available separately for each arm of the trial, only for all treatment groups combined (which included a Ticagrelor 90mg arm that is not included in the indirect comparison).

Homogeneity across trials within each of the two trial sets involved in the indirect comparison	
Is the method used to determine the presence of statistical heterogeneity adequate?	Not applicable: only one trial in each trial set
Is the homogeneity assumption satisfied or is statistical heterogeneity accounted for if present?	Not applicable: only one trial in each trial set
If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each trial set involved in the indirect comparison investigated by an adequate method?	Not applicable: only one trial in each trial set
Consistency	
Is consistency of effects assessed?	Not applicable: both indirect and direct evidence are not presented for the same comparison
If the direct and indirect evidence is reported to be consistent, is the evidence combined and the result presented?	Not applicable: both indirect and direct evidence are not presented for the same comparison
If inconsistency is reported, is this accounted for by not combining the direct and indirect evidence?	Not applicable: both indirect and direct evidence are not presented for the same comparison
Are patient or trial characteristics compared between direct and indirect evidence trials?	Not applicable: both indirect and direct evidence are not presented for the same comparison
Are patient or trial characteristics for direct and indirect evidence trials reported to be comparable?	Not applicable: both indirect and direct evidence are not presented for the same comparison
Are any included 3-arm trials correctly analysed?	Not applicable: both indirect and direct evidence are not presented for the same comparison
Is justification given for using indirect evidence and direct evidence?	Not applicable: both indirect and direct evidence are not presented for the same comparison
Does the review present results from all trials providing direct evidence ?	Not applicable: both indirect and direct evidence are not presented for the same comparison
Interpretation	
Is a distinction made between direct comparisons and indirect comparisons?	Not applicable: both indirect and direct evidence are not presented for the same comparison
Does the review state that more trials providing direct evidence are needed?	No
Reporting	
Does the review present both of the meta-analysis results from each of the two trial sets involved in the indirect comparison?	Not applicable: both indirect and direct evidence are not presented for the same comparison
Was it highlighted which results were from indirect evidence?	Yes
Are the individual trials' treatment effect estimates reported?	Yes

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease [ID1397]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre (SHTAC) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Friday 15 March 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Description of two subgroups (CAD + HF, CAD + PRF) as being post-hoc analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report states that only one of the 3 submitted subgroups was pre-specified (CAD + PAD) and that 2 subgroups were post-hoc analyses i.e. CAD HF, CAD + PRF). The statement is not correct as all 3 subgroups were pre-specified. The pages where these statements are made are: Pages 20, 42, 43, 44, 82, 121	References to CAD + PAD being the only pre-specified subgroup should be removed. References to CAD + HF and CAD + PRF being post-hoc analyses should be removed	Each of the 3 subgroups were pre-specified for analysis	We have updated the report to reflect the fact that these subgroups were specified in the health economics and outcomes research statistical analysis plan dated 18th July 2017.

Issue 2 Statement that the positioning requested in the CS excludes stable patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 of ERG report states: *The anticipated place of rivaroxaban therapy in longer-term management is specified in the CS: in selected CAD patients at high risk of ischaemic events (see subpopulations below), but rivaroxaban is not to be recommended for stable CAD patients. The CS cites the 2013 European Society of Cardiology (ESC) guidelines on the management of stable CAD [5] in support of this.* The first part of this statement is correct but not the second - Bayer is requesting that rivaroxaban be recommended in the 3 subgroups presented in the CS. However we have not stated that rivaroxaban is not recommended for 'stable' CAD patients. Patients within the 3 high-risk subgroups might be described as 'stable', yet still high-risk, from a medical perspective.	Remove the statement "*but rivaroxaban is not to be recommended for stable CAD patients".*	Patients in the 3 requested subgroups can dually be described as 'high-risk' and 'stable'.	Change made as requested

The ESC guidelines (2013) relate to dual antiplatelet therapy and conclude that combined antiplatelet [DAPT] therapy may be beneficial only in selected patients at high risk of ischaemic events, but are not to be recommended systematically in stable CAD patients. The requested positioning is stated correctly elsewhere in the ERG report and we think the statement has mixed the company positioning and ESC 2013 guidelines by mistake.			

Issue 3 Incorrect specification of subgroup for which an indirect treatment comparison was not possible

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 65 it states that "an ITC was not feasible for the CAD + PRF subpopulation". An ITC was feasible for the CAD + PRF subpopulation but not the CAD + HF subpopulation.	Replace "CAD + PRF" with "CAD + HF"	The statement relates to CAD + HF and not CAD + PRF	Change made as requested

Issue 4 Marking of CIC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 15, 40, 41 and 61 information has been marked as CIC. Bayer appreciates the ERG erring on the side of caution in their highlighting of this newly presented information as CIC. We are however happy for the CIC marking to be removed.	Remove formatting which indicated the information is commercial in confidence	Bayer does not consider the information to be CIC.	CIC marking lifted as requested.

(please cut and paste further tables as necessary)

Deterministic sensitivity analyses

The deterministic sensitivity analyses for rivaroxaban vs aspirin and rivaroxaban vs ticagrelor are shown below in Tables 3-10 for the COMPASS population and the subpopulations for the 5 most influential model inputs.

The main driver of the results is changes to HR for sudden cardiac death. Other parameters that have an effect on model results are HR for MI and HR for IS. However, these parameters only have a small impact on model results, (change in ICER <£5,000), except for the comparison between rivaroxaban vs ticagrelor for the CAD + PAD population (change in ICER £47,037).

The reason that changes to the HR for stroke have only a small effect on the model results is that the 95% CIs for HR for stroke are narrow (see Table 1 and 2) and the stroke is a relatively rare event (8-10% stroke incidence over patient lifetime for rivaroxaban and aspirin respectively).

Table 1 HR (95% CI) for main events: rivaroxaban + aspirin vs aspirin

Event	COMPASS population	CAD+PAD	CAD+HF	CAD+PRF
IS	0.51 (0.38-0.69)	0.49 (0.26-0.92)	0.35 (0.18-0.69)	0.25 (0.12-0.51)

Table 2 HR (95% CI) for main events: rivaroxaban + aspirin vs ticagrelor + aspirin

	COMPASS population	CAD+PAD	CAD+HF	CAD+PRF
IS	0.76 (0.56-1.02)	0.52 (0.22-1.22)	0.76 (0.56-1.02)	0.76 (0.56-1.02)

Table 3 Deterministic sensitivity analysis COMPASS population, rivaroxaban vs aspirin

Model input	Lower bound	Upper bound	Difference
Base case	£16,326		
HR (mortality) (RIV + ASA) Sudden cardiac death	£11,512	£38,018	£26,506
Age of patients	£12,277	£20,174	£7,897
HR (RIV + ASA) MI	£14,344	£18,843	£4,498
HR (RIV + ASA) IS	£14,714	£18,865	£4,151
HR (mortality) (RIV + ASA) Bleeding	£15,332	£19,140	£3,808

Table 4 Deterministic sensitivity analysis COMPASS population, ticagrelor vs aspirin

Model input	Lower bound	Upper bound	Difference
Base case	£12,581		
HR (mortality) (RIV + ASA) Sudden cardiac death	£8,060	£69,249	£61,189
HR (mortality) (TIC + ASA) Sudden cardiac death	£16,897	£9,721	£7,176
HR (RIV + ASA) MI	£10,059	£15,929	£5,869
HR (RIV + ASA) IS	£10,682	£15,786	£5,104

Age of patients	£10,699	£14,909	£4,210

Table 5 Deterministic sensitivity analysis CAD + PAD, rivaroxaban vs aspirin

Model input	Lower bound	Upper bound	Difference
Base case	£7,309		
HR (mortality) (RIV + ASA) Sudden cardiac death	£5,275	£25,346	£20,072
HR (RIV + ASA) IS	£6,116	£10,739	£4,623
HR (RIV + ASA) MI	£5,742	£9,855	£4,113
Age of patients	£5,749	£8,678	£2,929
HR (RIV + ASA) ICH	£6,545	£8,560	£2,015

Table 6 Deterministic sensitivity analysis CAD + PAD, ticagrelor vs aspirin

Model input	Lower bound	Upper bound	Difference
Base case	£9,047		
HR (mortality) (RIV + ASA) Sudden cardiac death	£4,398	Dominated	-
HR (RIV + ASA) IS	£5,707	£52,745	£47,037
HR (mortality) (TIC + ASA) Sudden cardiac death	£23,173	£4,839	£18,334
HR (RIV + ASA) MI	4469.47	17210.70	£12,741
HR (TIC + ASA) Major amputation	£11,202	Dominant	£11,202

Table 7 Deterministic sensitivity analysis CAD + HF, rivaroxaban vs aspirin

Model input	Lower bound	Upper bound	Difference
Base case	£5,702		
HR (mortality) (RIV + ASA) Sudden cardiac death	£4,380	£12,170	£7,790
HR (RIV + ASA) MI	£4,566	£7,700	£3,134
HR (RIV + ASA) IS	£5,109	£7,074	£1,965
Age of patients	£4,822	£6,687	£1,864
Event free transitions ASA - IS	£6,404	£5,028	£1,376

Table 8 Deterministic sensitivity analysis CAD + HF, ticagrelor vs aspirin

Model input	Lower bound	Upper bound	Difference
Base case	£3,820		
HR (mortality) (RIV + ASA) Sudden cardiac death	£3,006	£11,060	£8,054
HR (RIV + ASA) MI	£2,715	£6,173	£3,458
HR (RIV + ASA) IS	£3,323	£5,378	£2,055
Event free transitions ASA - IS	£4,546	£3,321	£1,225
HR (mortality) (TIC + ASA) Sudden cardiac death	£4,458	£3,454	£1,003

Table 9 Deterministic sensitivity analysis CAD + PRF, rivaroxaban vs aspirin

Model input	Lower bound	Upper bound	Difference
Base case	£9,661		
HR (mortality) (RIV + ASA) Sudden cardiac death	£6,088	Dominated	-
HR (RIV + ASA) MI	£7,462	£12,695	£5,233
Age of patients	£7,634	£12,277	£4,643
Event free transitions ASA - IS	£12,209	£7,648	£4,561
HR (RIV + ASA) IS	£8,456	£12,880	£4,424

Table 10 Deterministic sensitivity analysis CAD + PRF, ticagrelor vs aspirin

Model input	Lower bound	Upper bound	Difference
Base case	£4841		
HR (mortality) (RIV + ASA) Sudden cardiac death	£3,252	Dominated	-
HR (RIV + ASA) MI	£2,499	£8,123	£5,624
HR (RIV + ASA) ICH	£3,514	£8,069	£4,555
HR (mortality) (TIC + ASA) Sudden cardiac death	£7,380	£3,474	£3,906
HR (RIV + ASA) IS	£4,012	£7,161	£3,149

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease [ID1397]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Friday 10 May 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bayer Plc Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Should the focus be on the whole population or 'high risk' subgroups?	
Should rivaroxaban be considered for the whole population for whom it is licensed, or only for people considered to be at higher risk of ischaemic events?	The rationale for the three subgroups was based on feedback from the medical community that, although rivaroxaban is effective in the whole population, prescribing would be focussed in those patients at the greatest baseline risk of ischaemic events. Evidence for these groups having a high baseline risk is well published (section B1.3 of Company Submission – page 35 (1),(2, 3), (4), (5)). We acknowledge that other combinations of risk factors may combine to produce baseline risk levels comparable to those of the three subgroups presented – for example patients with diabetes who may have already experienced an ischaemic event. Such patients may also be considered for treatment but may not be captured within the three subgroups. We do believe however that the large majority of patients who would be considered for treatment are captured within our submission. Certainly, we have received no indication that rivaroxaban would be considered for patients whose baseline risk is not high.
Are the subgroups presented by the company clinically relevant and do they represent a population at high baseline risk of thrombotic events as suggested by the company?	The subgroups presented are clinically relevant. The increased risk of major acute coronary events in the subgroups is expected and confirmed by the medical literature with the risk shown to be markedly higher for patients with concomitant PAD, HF or PRF than the wider CAD population (1),(2, 3), (4), (5). • Patients with CAD and PAD have an increased risk of CV events and CV death compared with those with CAD only. Analysis of the REACH registry showed that at 1 year the rate of CV events was 3.2% in patients with CAD and PAD versus 1.6% in those with CAD alone. The incidence of CV death at 1 year was 4.6% versus 2.4% (2) • Patients with CAD and HF have a 1.7 fold increase in risk of CV events compared to those with CAD only (6)

	• Patients with CAD and PRF have an increased risk of CV events compared to those with CAD and normal renal function; in the REACH registry at 1 year the rate of CV events was 3.1% versus 2.5% (5) The clinical experts consulted by the ERG indicate that the subgroups presented are clinically relevant. The ERG report contains the statement that "*expert clinical advice to the ERG is that these [the 3 subgroups requested by Bayer] are clinically important subpopulations who currently have unmet need, and that it is unlikely that there are any other clinically important subpopulations omitted from the CS. One clinical expert commented that patients with diabetes would be a potentially important subpopulations, but these patients may be covered by the CAD+PAD subpopulation (The ERG notes that each of the three subpopulations in the pivotal phase III trial of rivaroxaban – the COMPASS trial - included around 40% of diabetic patients).*"
If high risk subgroups are appropriate, should treatment effects be based on the hazard ratios for the whole population, or is it appropriate to accept different treatment effects in the different groups?	We believe that the approach of using subgroup-specific HRs is appropriate as it uses the observed data from the trial. However, to reduce uncertainty we have repeated the whole analysis set presented in the original company submission using a fixed HR approach. These analyses incorporate all the ERG preferences summarised in Appendix 1. As the information runs to over 30 pages we have provided a summary of the base case results (Table 1 to Table 4) and attached the full set of results in Appendix 2. These results are for the implementation of a fixed HR prior to the identification of a coding error in the model (see 'Identification of an error in the model' below). However these results are presented to see the impact of implementing a fixed HR in isolation of the subsequent correction. The same results, but with the error corrected, are presented in Table 5 to Table 8.

Table 1. Base case incremental cost-effectiveness results – COMPASS population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	13387	11.27	8.39					
Ticagrelor + aspirin	14647	11.26	8.40	1260	-0.01	0.01	124752	Extendedly dominated
Rivaroxaban + aspirin	16885	11.52	8.60	2237	0.25	0.20	17024	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 88. Base case incremental cost-effectiveness results – COMPASS population, Appendix B, B.3.7. Base-case Results, page 255

Table 2. Base case incremental cost-effectiveness results – CAD and PAD subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	14040	10.03	7.11					
Ticagrelor + aspirin	15774	10.37	7.36	1734	0.34	0.25	6911	
Rivaroxaban + aspirin	17382	10.48	7.44	1609	0.11	0.08	10079	19923

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 89. Base case incremental cost-effectiveness results – CAD and PAD subgroup, Appendix B, B.3.7. Base-case Results, page 255

Table 3. Base case incremental cost-effectiveness results – CAD and HF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12158	10.13	7.70					
Ticagrelor + aspirin	13487	10.20	7.77	1329	0.07	0.07	19418	Extendedly dominated
Rivaroxaban + aspirin	15911	10.62	8.09	2425	0.42	0.32	9624	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 90. Base case incremental cost-effectiveness results – CAD and HF, Appendix B, B.3.7. Base-case Results, page 256

Table 4. Base case incremental cost-effectiveness results – CAD and PRF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12043	8.93	6.68					
Ticagrelor + aspirin	13269	8.97	6.71	1225	0.04	0.04	33556	Extendedly dominated
Rivaroxaban + aspirin	15058	9.31	6.96	1790	0.33	0.25	10500	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 91. Base case incremental cost-effectiveness results – CAD and PRF, Appendix B, B.3.7. Base-case Results, page 256

Identification of an error in the model

The results of the fixed HR analyses using the ERG preferences produced an unexpected result, prompting further investigation i.e. a negative LYG for ticagrelor versus aspirin – see Table 1.

We identified a coding error in the calculation of the proportion of patients in "Post IS Post IS" state in the aspirin arm of the model, specifically in the transition matrix whereby some patients in the aspirin arm were not transitioning to the death state as intended [(a)]. A coding error in the calculation of the non-fatal event rates for the Post IS Acute ICH and Post IS Post ICH states was also identified and corrected [(b)].
These errors were not identified in the original submission as their impact did not affect the base case but only the scenario analysis where null transitions were replaced with non-zero values.

[(a)] Sheet ASA trace, column AK, Cells 7 to 210, =(AJ6*(INDEX(ASA_eventprob_ageadj,D7,**67**)-INDEX(ASAdeath,D7,**33**)))+(AK6*(INDEX(ASA_eventprob_ageadj,D7,**68**)-INDEX(ASAdeath,D7,**34**)))
[(b)] Sheet Non-fatal event rate, Cell E36 **p_Mort_Stroke_FromICH** (to replace p_Mort_Stroke_FromIS), Cell G36 **p_Mort_Stroke_From3ICH** (to replace p_Mort_Stroke_From3IS)

Model results for fixed HRs with the correction

The fixed HR analyses have been repeated but with the corrections above also applied. Results are summarised in Table 5 to Table 8. The full analysis set is provided in Appendix 3.

Table 5. Base case incremental cost-effectiveness results – COMPASS population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12974	11.16	8.32					
Ticagrelor + aspirin	14662	11.26	8.40	1688	0.10	0.08	20849	Extendedly dominated
Rivaroxaban + aspirin	16896	11.51	8.60	2234	0.25	0.20	14193	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 88. Base case incremental cost-effectiveness results – COMPASS population, Appendix B, B.3.7. Base-case Results, page 255

Table 6. Base case incremental cost-effectiveness results – CAD and PAD subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	13976	10.02	7.10					
Ticagrelor + aspirin	15774	10.37	7.36	1797	0.35	0.26	6966	
Rivaroxaban + aspirin	17382	10.48	7.44	1609	0.11	0.08	10054	19923

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 89. Base case incremental cost-effectiveness results – CAD and PAD subgroup, Appendix B, B.3.7. Base-case Results, page 255

Table 7. Base case incremental cost-effectiveness results – CAD and HF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	11801	10.03	7.63					
Ticagrelor + aspirin	13535	10.20	7.76	1734	0.17	0.14	12808	Extendedly dominated
Rivaroxaban + aspirin	15952	10.62	8.09	2417	0.42	0.32	9105	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 90. Base case incremental cost-effectiveness results – CAD and HF, Appendix B, B.3.7. Base-case Results, page 256

Table 8. Base case incremental cost-effectiveness results – CAD and PRF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	11793	8.88	6.64					
Ticagrelor + aspirin	13297	8.97	6.71	1504	0.09	0.07	21094	Extendedly dominated
Rivaroxaban + aspirin	15080	9.30	6.96	1783	0.33	0.25	10216	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

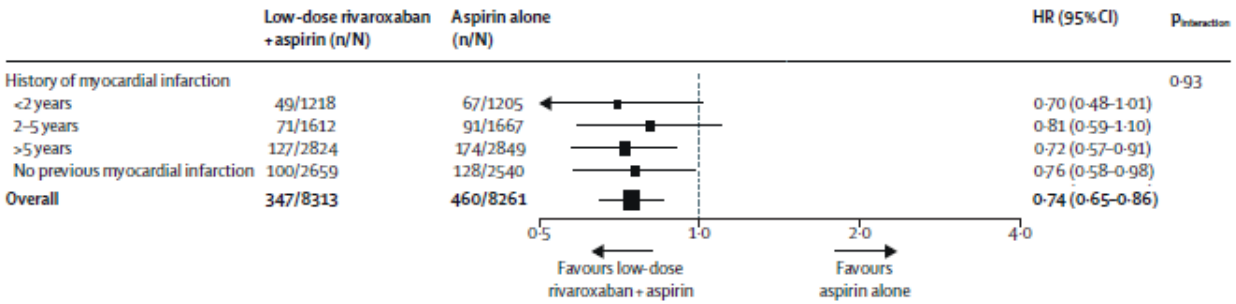
Refers to CS Table 91. Base case incremental cost-effectiveness results – CAD and PRF, Appendix B, B.3.7. Base-case Results, page 25

	Summary of the results With the ICERs remaining well below the £20K/QALY threshold, using a fixed HR does not alter the conclusion of rivaroxaban being cost-effective.
Issue 2: Exclusion of clopidogrel as a comparator for people with PAD	
Is it reasonable to exclude clopidogrel as a relevant comparator for the overall COMPASS trial population and the subgroup of people with CAD and PAD?	A recommendation is requested for three subgroups of patients - all of whom have CAD in combination with an additional comorbidity which infers a higher baseline risk i.e. concomitant PAD or heart failure or poor renal function. In patients with CAD the applicable NICE recommendations are from CG126 (Stable angina) and CG172 (Myocardial infarction) which recommend patients be maintained long-term with aspirin 75mg daily for secondary prevention of cardiovascular disease, always taking into account the risk of bleeding and comorbidities. In these guidelines clopidogrel is only recommended if aspirin is contraindicated or if there is hypersensitivity to aspirin. Rivaroxaban cannot be added to aspirin if the patient has a contraindication or hypersensitivity, this means that clopidogrel is only an option where rivaroxaban is not – it therefore cannot be considered a comparator.
Is clopidogrel used in clinical practice in the NHS to treat people with stable CAD and/or PAD at high risk of ischaemic events or the subgroup of people with CAD and PAD?	In stable CAD patients aspirin monotherapy is the preferred treatment if the patient does not have a contraindication or hypersensitivity. Clopidogrel monotherapy is used in stable patients in the NHS but in patients who cannot use aspirin. In acute patients dual antiplatelet therapy (aspirin + clopidogrel) is used. However rivaraxoban + aspirin, in this indication, is not being used in acute patients.

Issue 3: Comparison with ticagrelor + aspirin in people with history of MI	
Is the subgroup of people with MI clinically relevant and important?	Patients with MI are 'clinically' relevant. However, according to advice received by Bayer from the medical community in the UK, having a history of MI in isolation (i.e. without other factors predisposing the patient to higher baseline risk of events) is insufficient reason alone to warrant the addition of rivaroxaban to ongoing treatment with aspirin.
Would limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population reduce the uncertainty in the treatment effect of rivaroxaban+ aspirin when comparing to ticagrelor + aspirin?	In our submission we provided cost-effectiveness estimates for rivaroxaban + aspirin versus ticagrelor + aspirin. The inputs for the analysis were taken from two studies, one for rivaroxaban (COMPASS) and one for ticagrelor (PEGASUS). As described in our submission (and highlighted by the ERG) there are differences between the patients enrolled in the two trials. The main difference was that in PEGASUS 100% of patients had a history of MI (one to three years prior) compared to 62% in COMPASS (up to 20 years prior). In our comparison no adjustment was made for this difference i.e. restricting the COMPASS population to those with a history of MI 1-3 years prior as it was not considered necessary. For the reasons outlined below Bayer does not consider adjusting the COMPASS population to match PEGASUS inclusion criteria to be necessary (bullets 1 – 3); and furthermore considers that uncertainty is increased rather than decreased by any such adjustment (bullet 4): **1. There is no interaction for the primary outcome according to history of MI indicating that presence/absence of MI is not effect-modifying** Figure 1 is adapted from Connolly et al (2017) (7) and examines the effect of MI on the primary outcome. The publication states that "*the addition of low-dose rivaroxaban to aspirin resulted in an improvement in the primary efficacy outcome both in patients with a previous MI (HR 0.74, 95% CI 0.63-0.88) and those without a previous MI (0.76, 0.58-0.98, $P_{interaction}$ = 0.91)*." The probability of interaction was not significant indicating that adjusting the populations is not necessary.

Figure 1. Subgroup analysis of primary efficacy outcome (CAD patients)

Adapted from Connolly et al 2017 (7).



2. **The requirement to have a history of 'recent' MI is a restriction to the license for ticagrelor - not rivaroxaban. As such ticagrelor is, at most, a minor comparator i.e. in only a subset of patients (those specifically with recent MI) and for a limited period of time (1-3 years following an MI). Rivaroxaban has neither of these restrictions to its license.**

Technical Support Document 18 states that "*companies deploying [adjusted comparisons] are not only arguing that the treatment effect is dependent on the population, but they are further assuming that the target population is closer to that represented by the competitor trial than in their own trial*". This is not the case for rivaroxaban + aspirin as the 'target' population is not defined by having a history of recent MI.

3. **The approach of using subgroup specific hazard ratios is in conflict with using trial specific hazard ratios (see issue 1)**

In issue 1 the use of fixed hazard ratios appears to be preferred as the ERG states that "…none of the statistical tests for interaction for the primary endpoint results was significant. Therefore, there is no reason to hypothesise that treatment effects differ between subgroups. Consequently, it might be more appropriate to use the whole trial (ITT) estimates of hazard ratio for estimating treatment effects in

subgroups". Using subgroup-specific HRs in the comparison with ticagrelor would be to diverge from the position implied in issue 1.

4. **Restricting the COMPASS population as suggested subdivides the population twice: once by MI and secondly by time since MI. This is not a pre-specified analysis and increases rather than decreases uncertainty in the results, especially as there is no indication from the results that presence (or absence) of MI is effect-modifying.**

   In summary, Bayer does not consider adjustment of the COMPASS population to be necessary or to reduce uncertainty. However, we have conducted an analysis whereby the comparison of rivaroxaban with ticagrelor has been restricted to patients with a recent (prior 1-3 years) history of MI. This analysis has been conducted for the whole of the COMPASS population. The analysis has not been conducted for the three subgroups where a recommendation is sought as this would have required the population be 'cut' three times i.e. by MI, by time since MI and within the subgroup of interest.

The following parameters have been updated and for all other inputs in the model, data from the overall COMPASS population was used.

Transition probabilities

- Event and mortality risks in the aspirin arm of the model have been derived from the COMPASS trial data, using a subgroup restricted to patients having had an MI one to three years prior to enrollment in the trial – see Appendix 5 for details.
- Null transitions are imputed as per ERG preferences (Appendix 1).
    - Because of the small sample size, some mortality events (mortality due to HF and CV proc) in the event-free state and mortality after two events are not observed. Given the ERG's critique around the lack of transition and preference for replacing null transitions with non-zero values, mortality risks from the overall COMPASS population have been used for these events.

Hazard ratios

- For HRs for rivaroxaban vs. aspirin, two approaches have been taken

	○ HRs specific to the subgroup with recent MI ○ HR are considered to be equal to HR for the overall COMPASS population as per the ERG's comment on issue 1. • For HRs for ticagrelor vs. aspirin, the data from PEGASUS was implemented as 100% of patients enrolled in the PEGASUS trial have had an MI prior to the trial. *Age* Updated to 67 years. *Model errors as identified in issue 1* The corrections described have been implemented. Table 9 presents results using HRs specific to the CAD + recent MI population; Table 10 presents results for the CAD + recent MI population but using fixed HRs. In summary rivaroxaban + aspirin remained below the £20k/QALY threshold in both analyses.

Table 9. Base case incremental cost-effectiveness results – CAD with recent MI: subgroup specific HRs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12604	11.41	8.57					
Ticagrelor + aspirin	14336	11.52	8.66	1733	0.11	0.08	20859	Extendedly dominated
Rivaroxaban + aspirin	16950	11.73	8.81	2614	0.21	0.15	18297	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 10. Base case incremental cost-effectiveness results – CAD with recent MI population – Fixed HR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12604	11.41	8.57					
Ticagrelor + aspirin	14336	11.52	8.66	1733	0.11	0.08	20859	Extendedly dominated
Rivaroxaban + aspirin	16688	11.80	8.86	2351	0.27	0.21	14109	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

	Clinical results for the CAD + recent MI subgroup are presented in Appendix 4.
Is the (modified) ISTH classification used in clinical practice in the NHS to define major bleeds?	Bleeding classification scores (TIMI or ISTH) are not used in clinical practice. These tools are used in clinical trials for regulatory purposes.
Are the ISTH and TIMI classification methods used to define major bleeds sufficiently similar and able to identify the same number of major bleeds in the same population?	The modified ISTH (used in COMPASS) has a broader definition of 'major' bleed in comparison to TIMI (used in PEGASUS). Consequently some bleeds that would not be classified as major using TIMI would be classified as such using modified ISTH. Therefore, had TIMI been used in the COMPASS trial there would have been fewer bleeds defined as major. However, the respective classification methods were also used in the comparator arms of both studies and therefore the more pertinent question might be whether use of either scoring method would affect the respective hazard ratios of either treatment versus aspirin. This is important as it is the HRs that are used in the economic model. In this respect Bayer is not aware of any evidence that this would be the case and believes it is reasonable to rely on the inputs as used.
Issue 4: Transition probabilities for main events (MI, stroke, CV death) in the economic model	
What is the preferred source for calculating the probability of experiencing a main event in each cycle of the model when there are no events recorded in the COMPASS trial? Would probabilities calculated using REACH registry data be more appropriate or imputing non-zero values from transition probabilities from other health states (ERG preferred method)?	We agree that substituting transition probabilities with zero values, for non-zero values, is more clinically plausible. The scenario analysis we presented (and preferred by the ERG) replaced zero values with other values from the COMPASS study and, as expected, showed a small but favourable effect on the ICER. As discussed during the technical engagement call scenario analysis using transition probabilities taken from other sources, such as the REACH registry, might be informative. We have done this and describe the approach below.

Bhatt et la. (2010) (6), using the REACH registry, found that:

- Patients with *an ischaemic event in the past year* had a significantly higher rate of cardiovascular death, myocardial infarction, or stroke than those with no ischaemic event (HR, 1.71; 95% CI, 1.57-1.85; *P*.001) (6).
- Patients with *an ischaemic event more than a year ago* had a significantly higher rate of cardiovascular death, myocardial infarction, or stroke than those with no ischemic event (HR, 1.41; 95% CI, 1.32- 1.51; *P*.001).

Based on this evidence, another approach is implemented as follows:

- Null event probabilities after a first event are imputed with the associated probability of the event-free health state, increased using a 1.71 multiplier

	Risk of MI after a first event	
	Base case	**Null transition imputed**
Event-free	0.00290	0.00290
Acute MI	0.00641	0.00641
Post-acute MI	0.01852	0.01852
Acute IS	0	0.00508 (0.00290*1.71)
Post-acute IS	0.00356	0.00356
Acute ICH	0	0.00508 (0.00290*1.71)
Post-acute ICH	0	0.00508 (0.00290*1.71)

- Null death probabilities after a first event are imputed with the associated probability of the event-free health state, increased using a 1.41 multiplier

- Null CV death probabilities after a first event are imputed using the maximum of all probabilities

NB – all ERG preferences are applied and subgroup specific HRs are used. These analyses apply the corrections identified in issue 1.

Deterministic results are presented below. In summary this scenario analysis showed improved ICERs versus the base case presented in issue 1.

Table 11. Base case incremental cost-effectiveness results – COMPASS population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12942	11.14	8.31					
Ticagrelor + aspirin	14631	11.25	8.39	1689	0.10	0.08	20833	Extendedly dominated
Rivaroxaban + aspirin	16863	11.50	8.59	2232	0.25	0.20	14185	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 12. Base case incremental cost-effectiveness results – CAD and PAD population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	13854	9.94	7.05					
Ticagrelor + aspirin	15656	10.29	7.31	1802	0.35	0.26	6930	
Rivaroxaban + aspirin	17191	10.54	7.48	1535	0.25	0.18	7624	8639

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 13 .Base case incremental cost-effectiveness results – CAD and HF population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	11785	10.01	7.62					
Ticagrelor + aspirin	13521	10.18	7.75	1735	0.17	0.14	12756	Extendedly dominated
Rivaroxaban + aspirin	16120	10.91	8.31	2599	0.73	0.56	6270	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 14. Base case incremental cost-effectiveness results – CAD and PRF population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	11769	8.86	6.62					
Ticagrelor + aspirin	13276	8.95	6.70	1507	0.09	0.07	20788	Extendedly dominated
Rivaroxaban + aspirin	14785	9.34	6.99	1508	0.39	0.29	8215	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Issue 5: Underestimation of impact of CV death on the incremental cost effectiveness ratio (ICER)	
As each death rate only has a fraction of the CV deaths, is it reasonable to vary the HR for all CV deaths in the DSA to adequately capture the uncertainty around this parameter?	As described by the ERG, the company submission varied the HR for each component of CV death individually in its deterministic sensitivity analyses. This approach implicitly assumes each component is independent of the others. In contrast, varying all the components together assumes that they are perfectly correlated. It is likely that neither approach is entirely realistic i.e. neither are the components completely independent nor are they perfectly correlated. It could be argued (as the ERG have done) that the company submission underestimates uncertainty, however, it is equally valid to argue that the ERG approach overestimates uncertainty. In this context we believe that the results presented by the ERG should be viewed in the context of representing a worst-case view of uncertainty. Given the lack of data to estimate the extent of correlation we have not attempted to provide any 'middle-ground' analysis and leave both analysis for consideration by the committee.

References:

1. Khoury H, Lavoie L, Welner S, Folkerts K. The Burden of Major Adverse Cardiac Events and Antiplatelet Prevention in Patients with Coronary or Peripheral Arterial Disease. Cardiovasc Ther. 2016;34(2):115-24.
2. Steg PG, Bhatt DL, Wilson PW, D'Agostino R, Sr., Ohman EM, Rother J, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA. 2007;297(11):1197-206.
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4. Lavoie L, Khoury H, Welner S, Briere JB. Burden and Prevention of Adverse Cardiac Events in Patients with Concomitant Chronic Heart Failure and Coronary Artery Disease: A Literature Review. Cardiovasc Ther. 2016;34(3):152-60.
5. Dumaine RL, Montalescot G, Steg PG, Ohman EM, Eagle K, Bhatt DL, et al. Renal function, atherothrombosis extent, and outcomes in high-risk patients. Am Heart J. 2009;158(1):141-8 e1.
6. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA. 2010;304(12):1350-7.
7. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanas F, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England). 2017.

All references were provided as part of the original submission data package..

APPENDICES

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease [ID1397]

Technical Engagement Response

Contents

List of Tables

List of figures

Appendix 1 – ERG preferences

ERG preferences have been implemented:

- HR for ticagrelor vs. aspirin for health events are the same as HR for rivaroxaban vs. aspirin

- Null transitions are imputed

    1. Null event probabilities after a first event are imputed with the associated probability of the event-free health state

	Risk of MI after a first event	
	Base case	**Null transition imputed**
Event-free	0.00290	0.00290
Acute MI	0.00641	0.00641
Post-acute MI	0.01852	0.01852
Acute IS	0	0.00290
Post-acute IS	0.00356	0.00356
Acute ICH	0	0.00290
Post-acute ICH	0	0.00290

    2. Null death probabilities after a first event are imputed with the associated probability of the event-free health state

	Mortality risk of Stroke after a first event	
	Base case	**Null transition imputed**
Event-free	0.00017	0.00017
Acute MI	0	0.00017
Post-acute MI	0	0.00017
Acute IS	0.01042	0.01042
Post-acute IS	0.00356	0.00356
Acute ICH	0	0.00017
Post-acute ICH	0	0.00017

    3. Null CV death probabilities after a first event would be imputed the maximum of all probabilities (i.e. 0.11111)

	Mortality risk after two events	
	Base case	**Null transition imputed**
Acute MI	0.11111	0.11111
Post-acute MI	0	0.11111
Acute IS	0	0.11111
Post-acute IS	0	0.11111
Acute ICH	0	0.11111
Post-acute ICH	0	0.11111

- Treatment interruption included
  An interruption of one year after MI is implemented in order to allow patients to take dual antiplatelet therapy (TIC+ASA). Additionally, a three-month interruption after ICH and a one-month interruption after major bleed are implemented. After an ICH and a major bleed, the treatment cost is omitted during the interruption. No impact on transition probabilities is considered, as per the use of the ITT data set to calculate HRs.

- Utility values in the event free state are adjusted based on EQ5D UK norms. A multiplicative approach is taken to calculate utility value of subsequent events.

- Monitoring cost in the event free state is included based on TA317, inflated to 2017/2018 pounds £167.66.

Appendix 2 – Fixed HR results (without coding error corrected)

Base case results

Table 1. Base case incremental cost-effectiveness results – COMPASS population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	13387	11.27	8.39					
Ticagrelor + aspirin	14647	11.26	8.40	1260	-0.01	0.01	124752	Extendedly dominated
Rivaroxaban + aspirin	16885	11.52	8.60	2237	0.25	0.20	17024	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Refers to CS Table 88. Base case incremental cost-effectiveness results – COMPASS population, Appendix B, B.3.7. Base-case Results, page 255

Table 2. Base case incremental cost-effectiveness results – CAD and PAD subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	14040	10.03	7.11					
Ticagrelor + aspirin	15774	10.37	7.36	1734	0.34	0.25	6911	
Rivaroxaban + aspirin	17382	10.48	7.44	1609	0.11	0.08	10079	19923
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Refers to CS Table 89. Base case incremental cost-effectiveness results – CAD and PAD subgroup, Appendix B, B.3.7. Base-case Results, page 255

Table 3. Base case incremental cost-effectiveness results – CAD and HF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12158	10.13	7.70					
Ticagrelor + aspirin	13487	10.20	7.77	1329	0.07	0.07	19418	Extendedly dominated
Rivaroxaban + aspirin	15911	10.62	8.09	2425	0.42	0.32	9624	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Refers to CS Table 90. Base case incremental cost-effectiveness results – CAD and HF, Appendix B, B.3.7. Base-case Results, page 256

Table 4. Base case incremental cost-effectiveness results – CAD and PRF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12043	8.93	6.68					
Ticagrelor + aspirin	13269	8.97	6.71	1225	0.04	0.04	33556	Extendedly dominated
Rivaroxaban + aspirin	15058	9.31	6.96	1790	0.33	0.25	10500	
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Refers to CS Table 91. Base case incremental cost-effectiveness results – CAD and PRF, Appendix B, B.3.7. Base-case Results, page 256

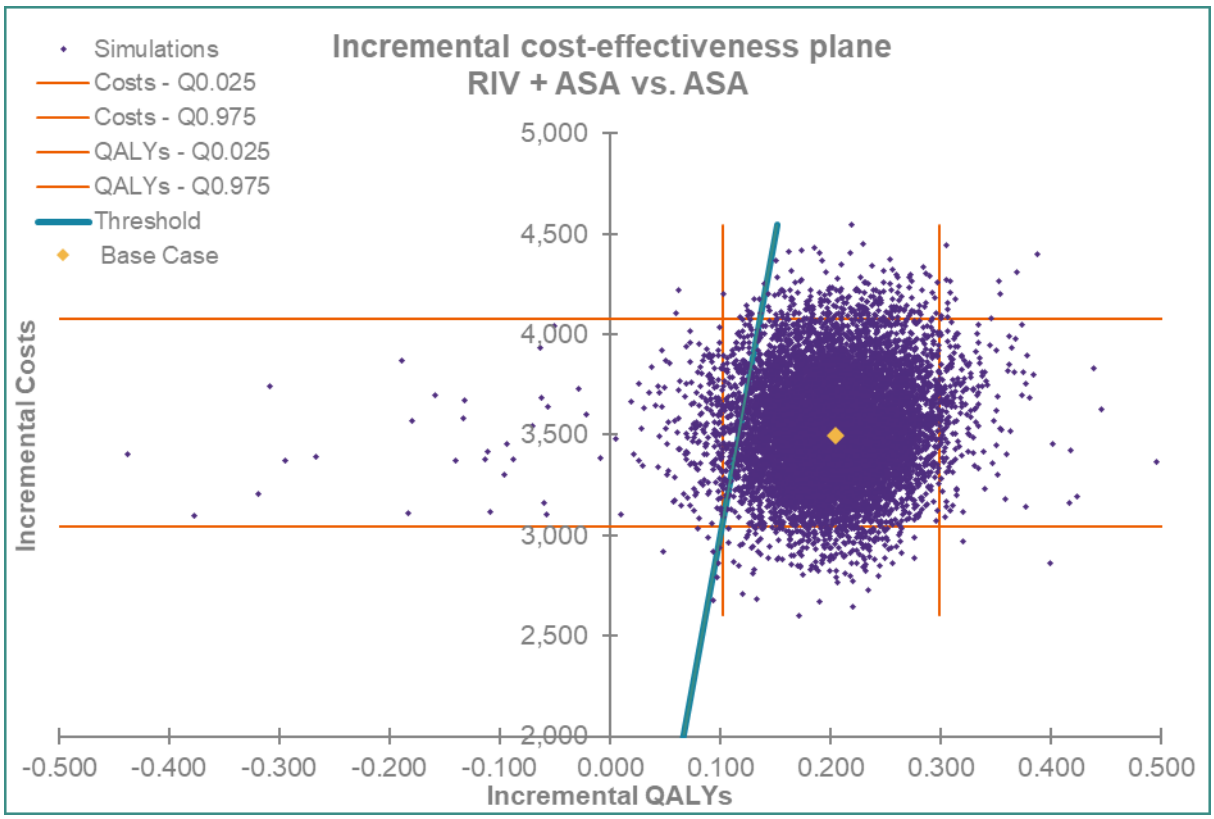
Probabilistic sensitivity analysis results

Table 5. PSA results - COMPASS population: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin	13520	11.38	8.50				
Rivaroxaban + aspirin	17052	11.62	8.69	3532	0.241	0.189	18664
P(cost-effectiveness):20K	71.60%						
P(cost-effectiveness):30K	95.75%						

Refers to CS Table 101. PSA results - COMPASS population: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 265

Figure 1. PSA scatterplot – COMPASS population: rivaroxaban + aspirin vs aspirin (WTP threshold =£30,000/QALY)



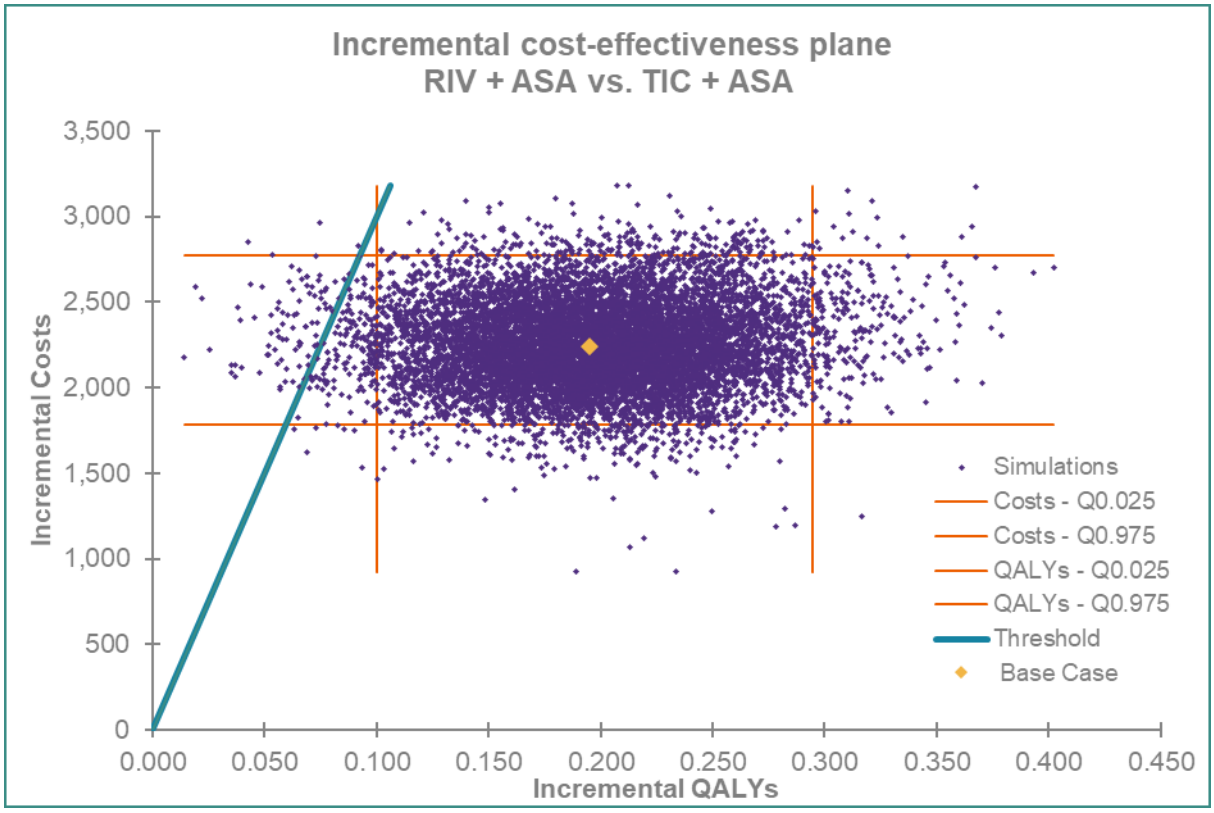
Refers to CS Figure 27. PSA scatterplot – COMPASS population: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 265

Table 6. PSA results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor	14800	11.37	8.49				
Rivaroxaban + aspirin	17052	11.62	8.69	2252	0.255	0.197	11430
P(cost-effectiveness):20K	94.96%						
P(cost-effectiveness):30K	99.11%						

Refers to CS Table 102. PSA results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 266

Figure 2. PSA scatterplot – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin (WTP threshold =£30,000/QALY)



Refers to CS Figure 29. PSA scatterplot – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 267

Figure 3. CEAC – COMPASS population

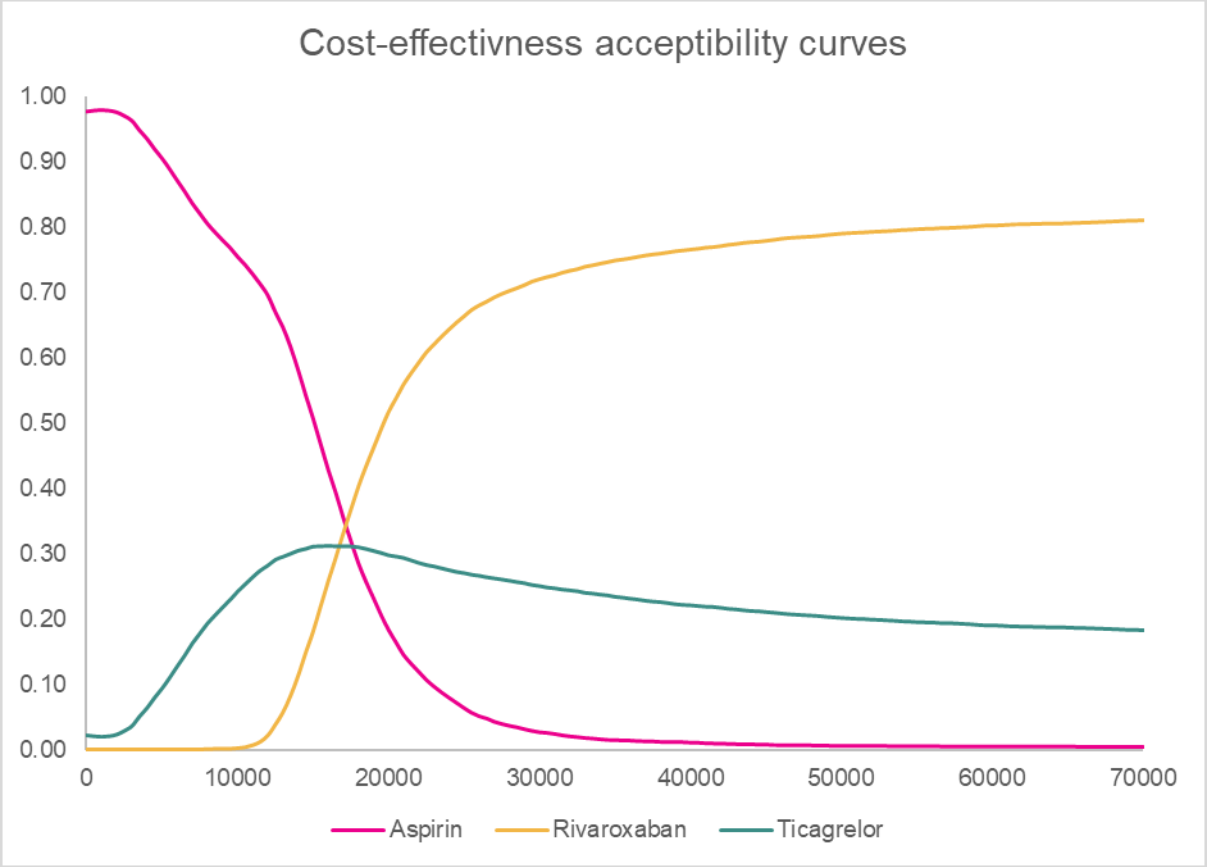
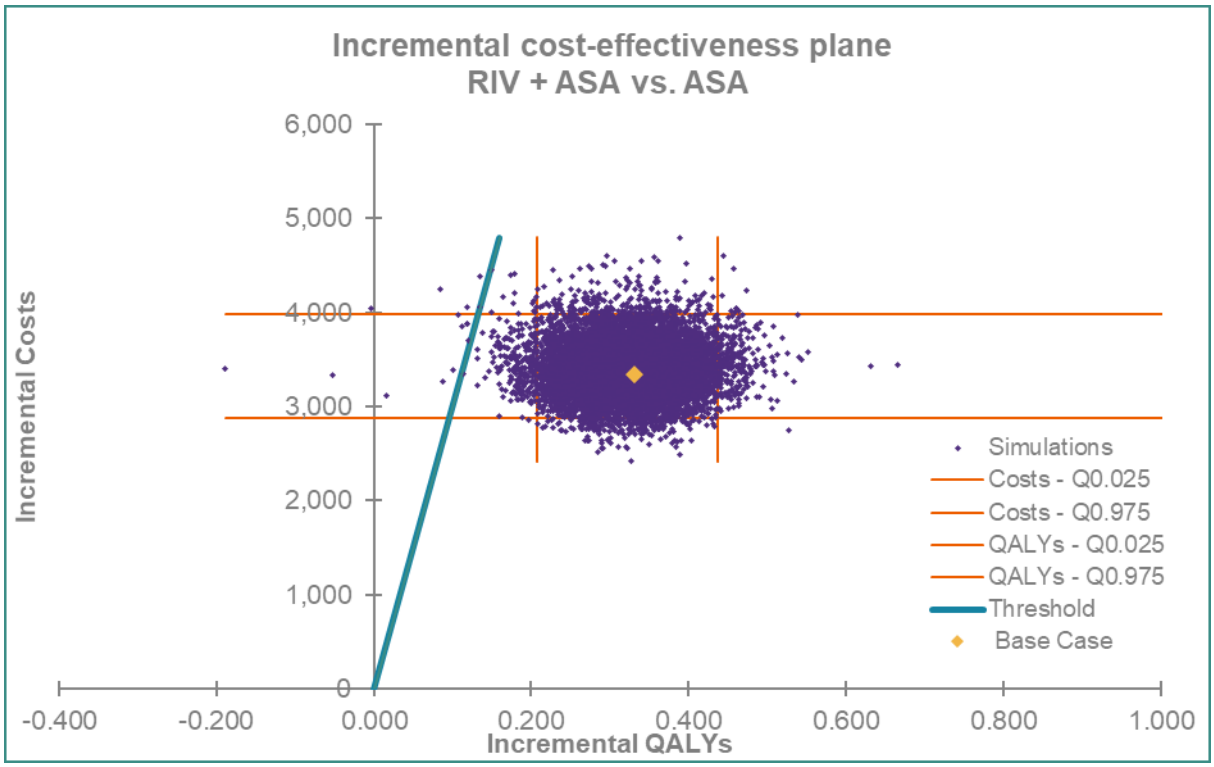


Table 7. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin	14148	10.11	7.18				
Rivaroxaban + aspirin	17546	10.55	7.50	3398	0.438	0.323	10530
P(cost-effectiveness):20K	99.14%						
P(cost-effectiveness):30K	99.85%						

Refers to CS Table 104. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 273

Figure 4. PSA scatterplot – CAD and PAD subgroup – rivaroxaban + aspirin versus aspirin



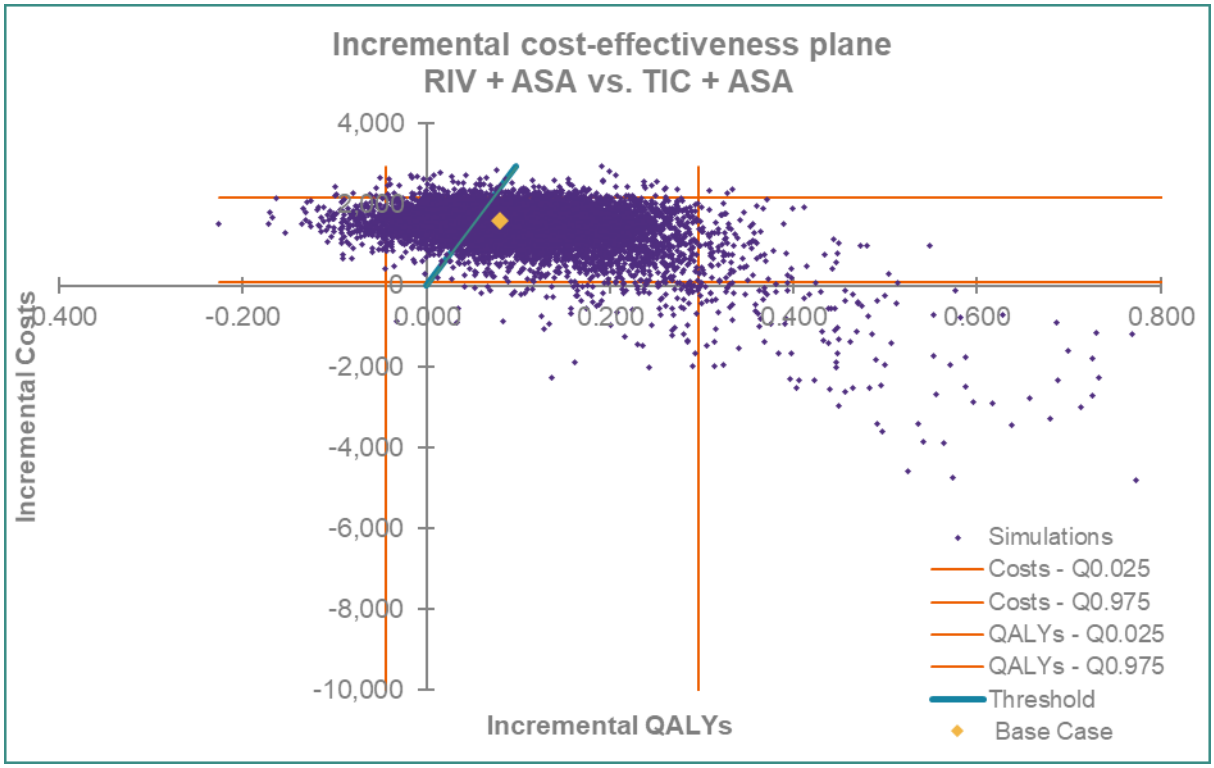
Refers to CS Figure 31. PSA scatterplot – CAD and PAD subgroup – rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 273

Table 8. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor	16131	10.44	7.39				
Rivaroxaban + aspirin	17546	10.55	7.50	1415	0.116	0.111	12787
P(cost-effectiveness):20K	67.72%						
P(cost-effectiveness):30K	77.41%						

Refers to CS Table 105. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 274

Figure 5. PSA scatterplot – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin



Refers to CS Figure 33. PSA scatterplot – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 275

Figure 6. CEAC – CAD and PAD subgroup

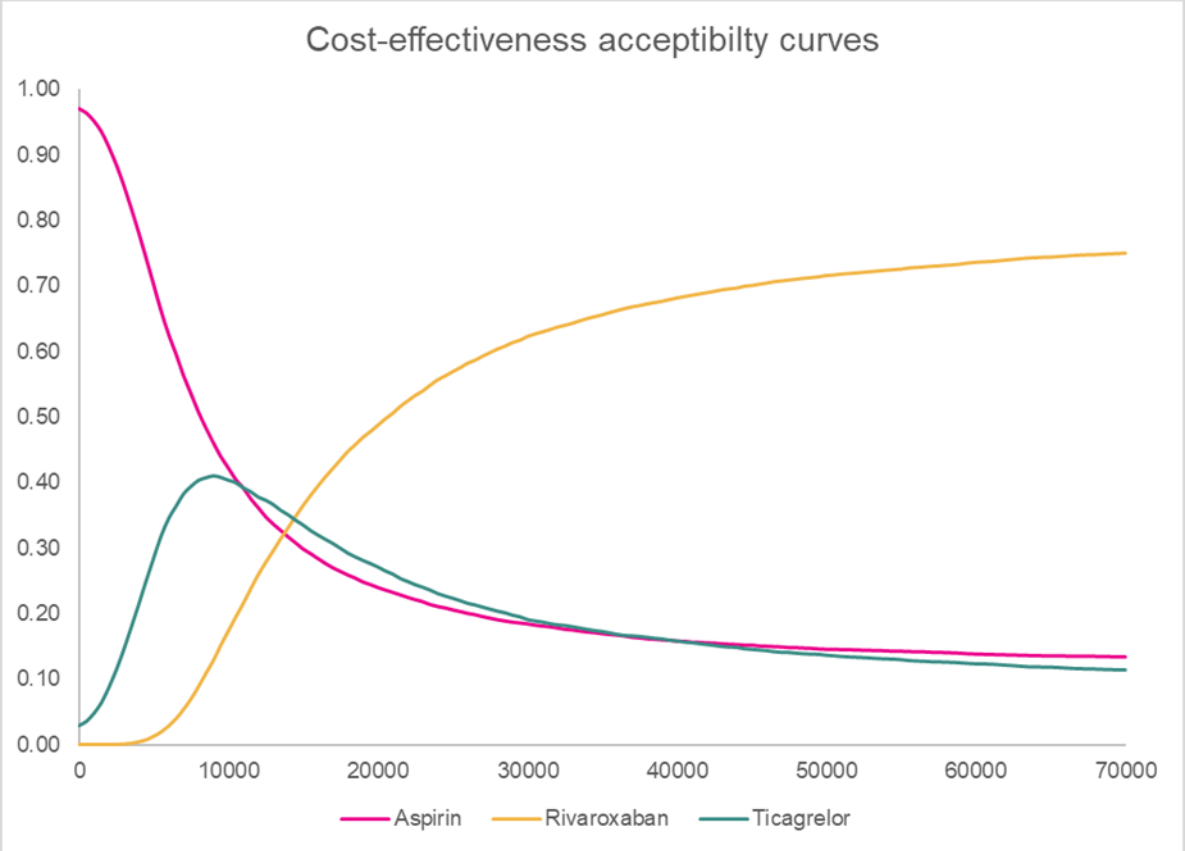
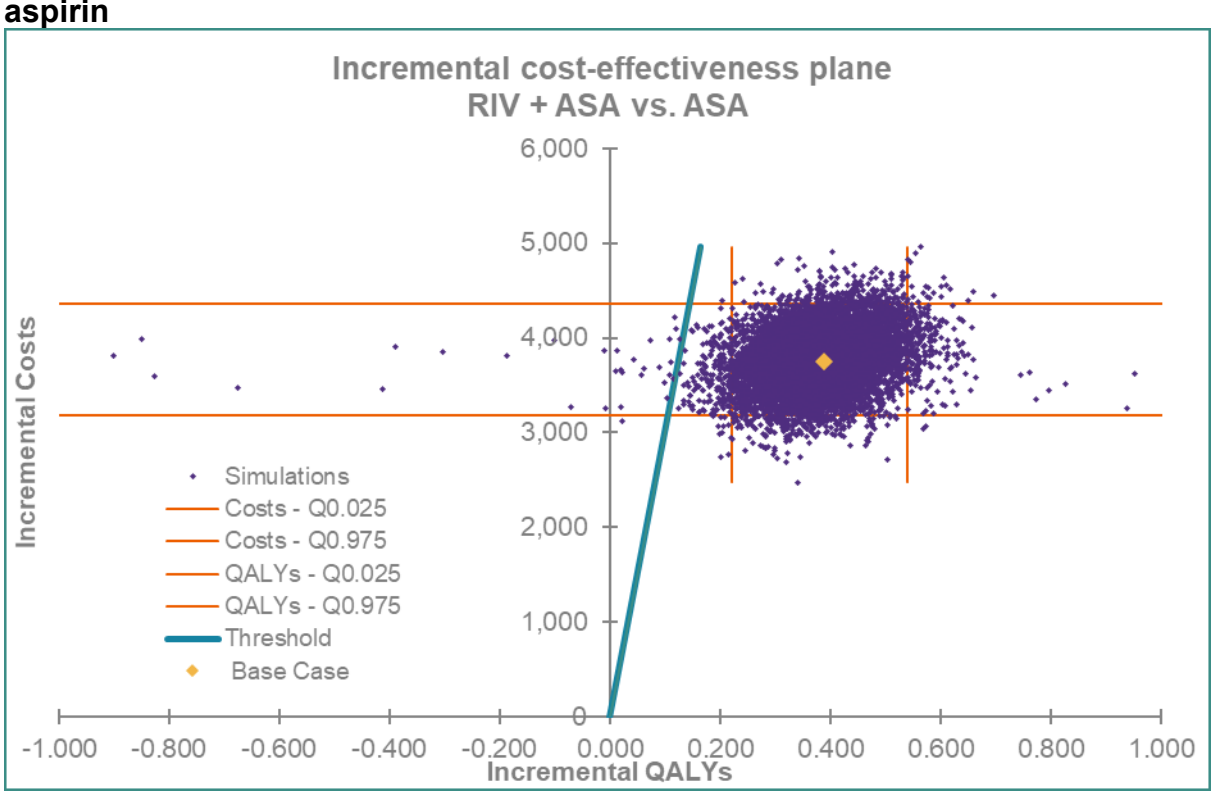


Table 9. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin	12217	10.19	7.75				
Rivaroxaban + aspirin	15983	10.66	8.13	3766	0.476	0.379	9934
P(cost-effectiveness):20K	98.90%						
P(cost-effectiveness):30K	99.61%						

Refers to CS Table 107. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 281

Figure 7. PSA scatterplot – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin



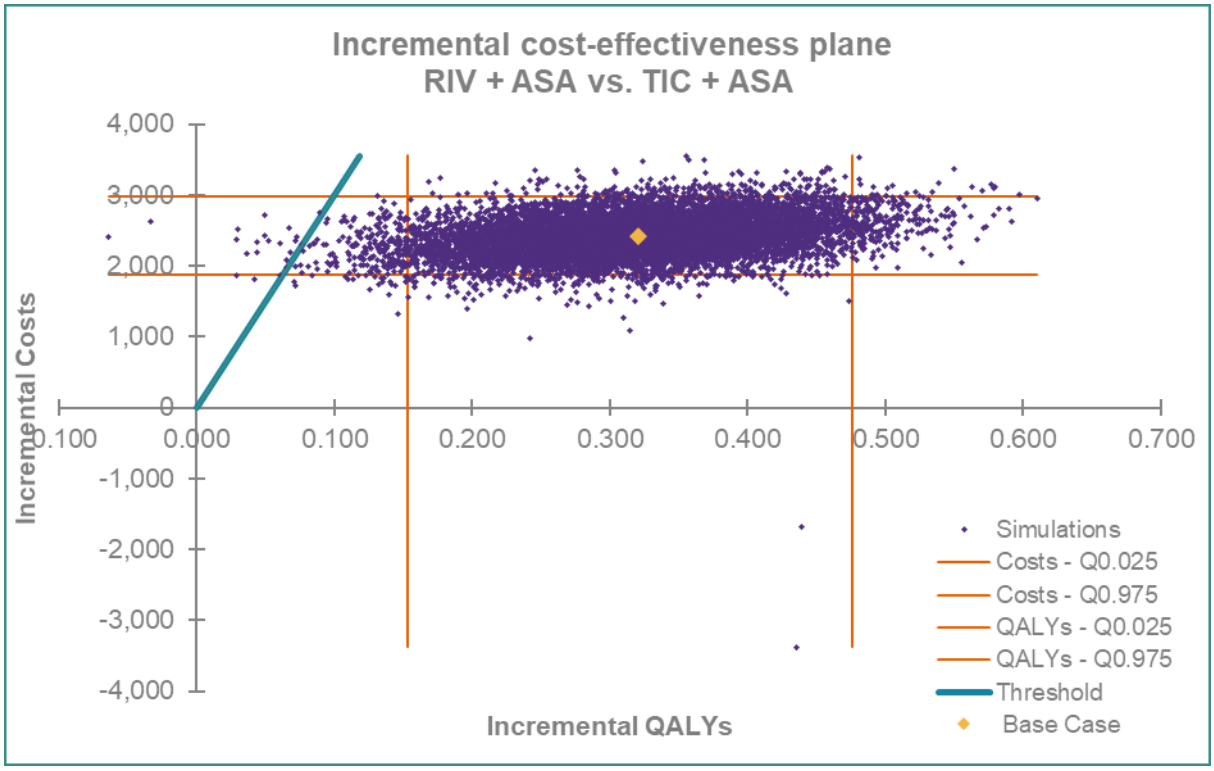
Refers to CS Figure 35. PSA scatterplot – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 281

Table 10. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor	13562	10.25	7.81				
Rivaroxaban + aspirin	15983	10.66	8.13	2421	0.317	0.413	7643
P(cost-effectiveness):20K	99.19%						
P(cost-effectiveness):30K	99.78%						

Refers to CS Table 108. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 282

Figure 8. PSA scatterplot – CAD and HF subgroup – rivaroxaban + aspirin versus ticagrelor + aspirin



Refers to CS Figure 37. PSA scatterplot – CAD and HF subgroup – rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 283

Figure 9. CEAC – CAD and HF subgroup

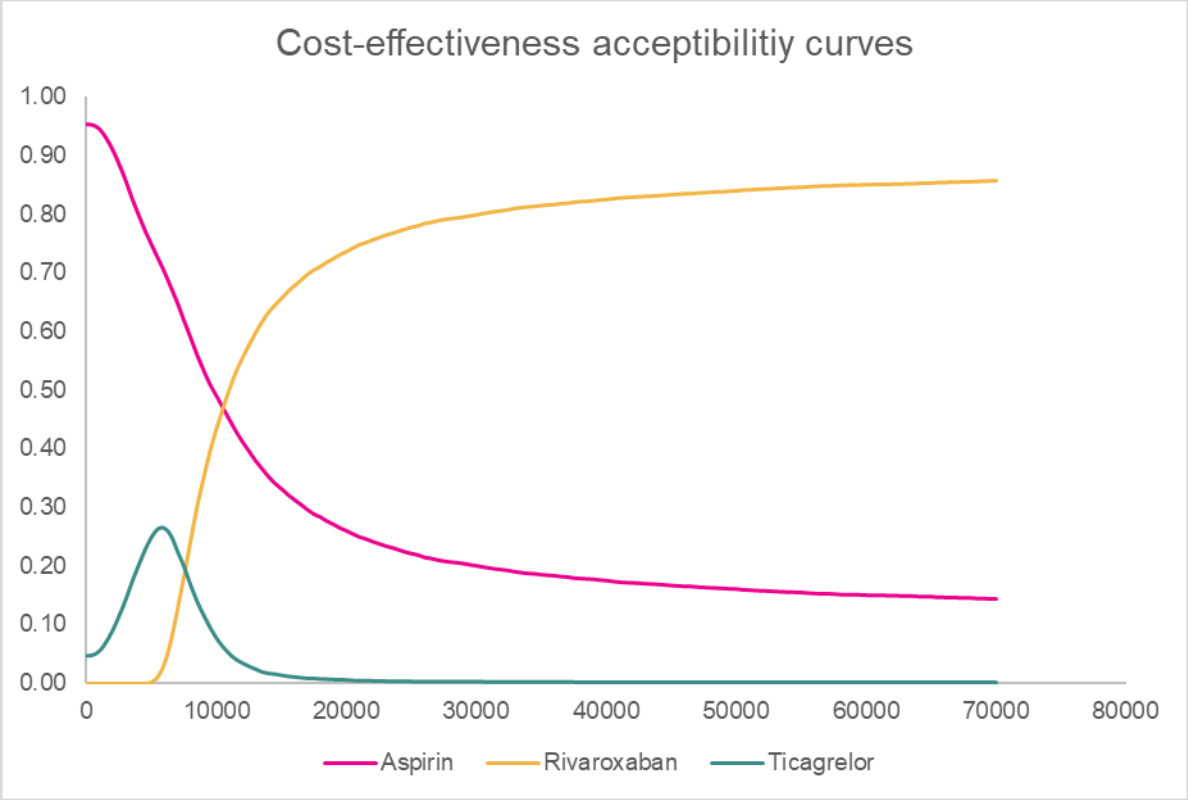
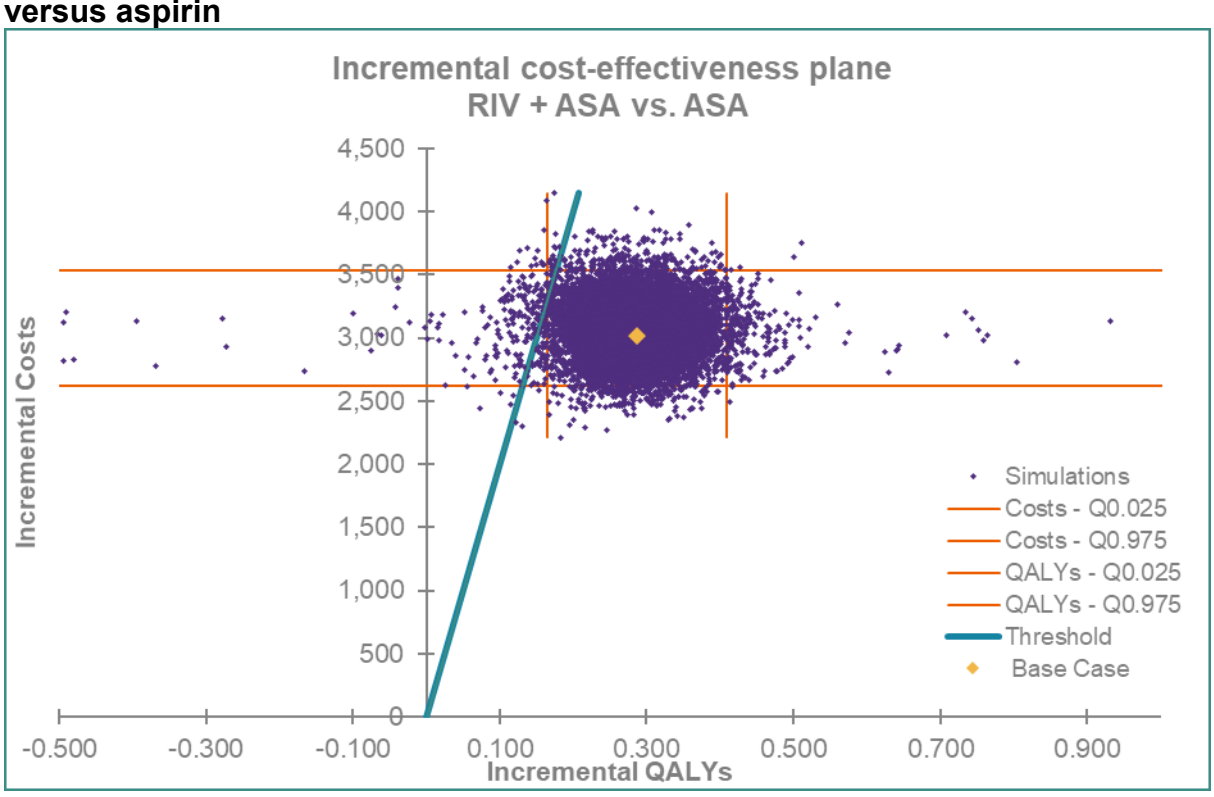


Table 11. PSA results – CAD and PRF subgroup – rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin	12177	9.04	6.78				
Rivaroxaban + aspirin	15237	9.41	7.06	3060	0.373	0.286	10689
P(cost-effectiveness):20K	97.77%						
P(cost-effectiveness):30K	99.34%						

Refers to CS Table 110. PSA results – CAD and PRF subgroup – rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 288

Figure 10. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus aspirin



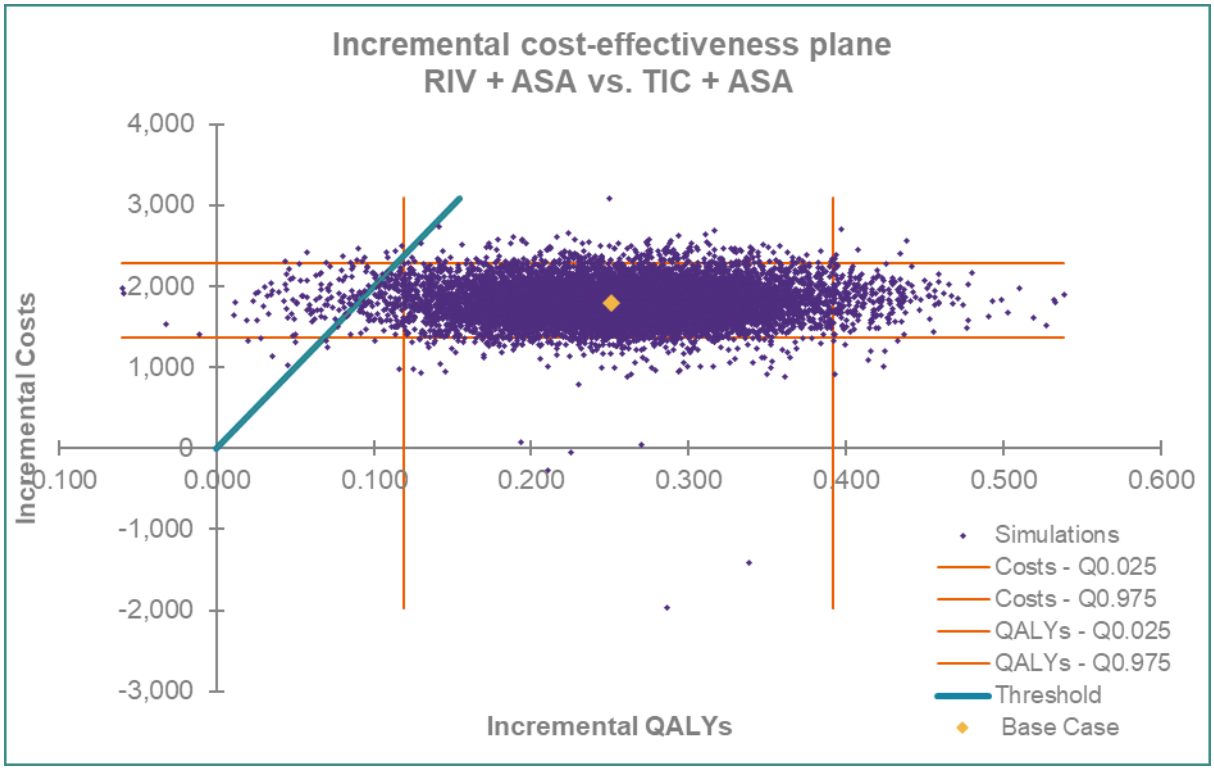
Refers to CS Figure 39. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 289

Table 12. PSA results – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor + aspirin	13432	9.07	6.81				
Rivaroxaban + aspirin	15237	9.41	7.06	1806	0.339	0.257	7035
P(cost-effectiveness):20K	98.79%						
P(cost-effectiveness):30K	99.50%						

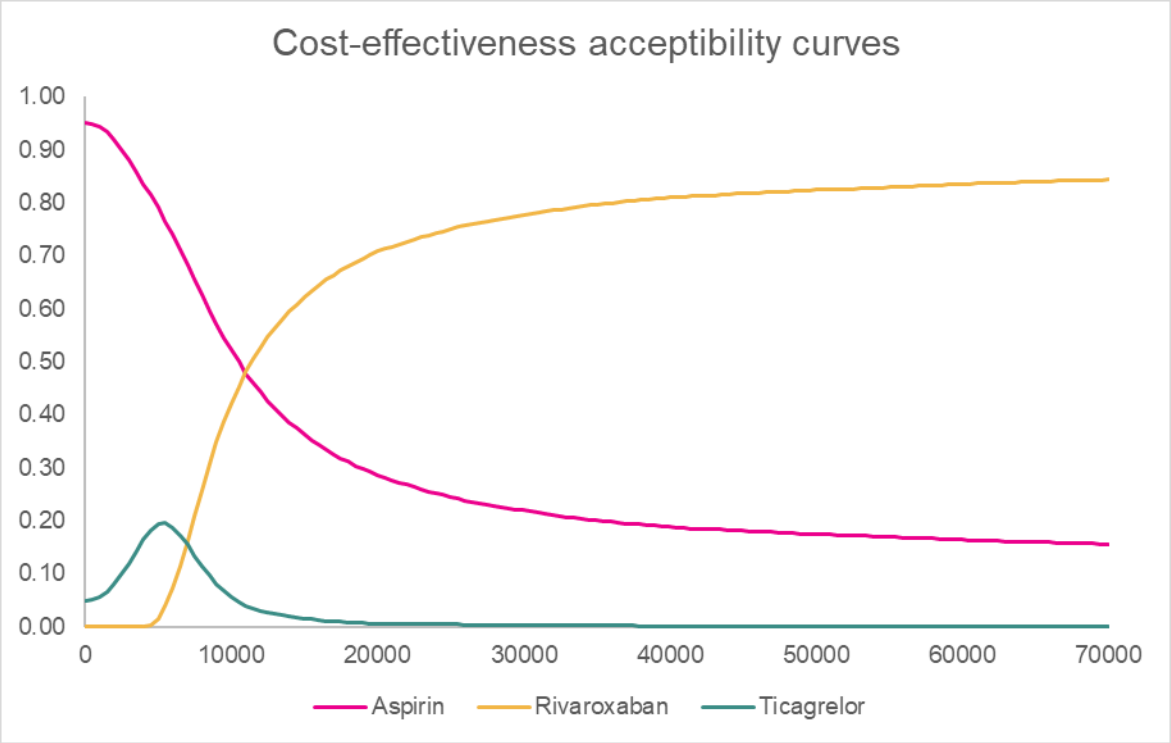
Refers to CS Table 111. PSA results – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 290

Figure 11. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin



Refers to Cs Figure 41. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 290

Figure 12. CEAC – CAD and PRF subgroup



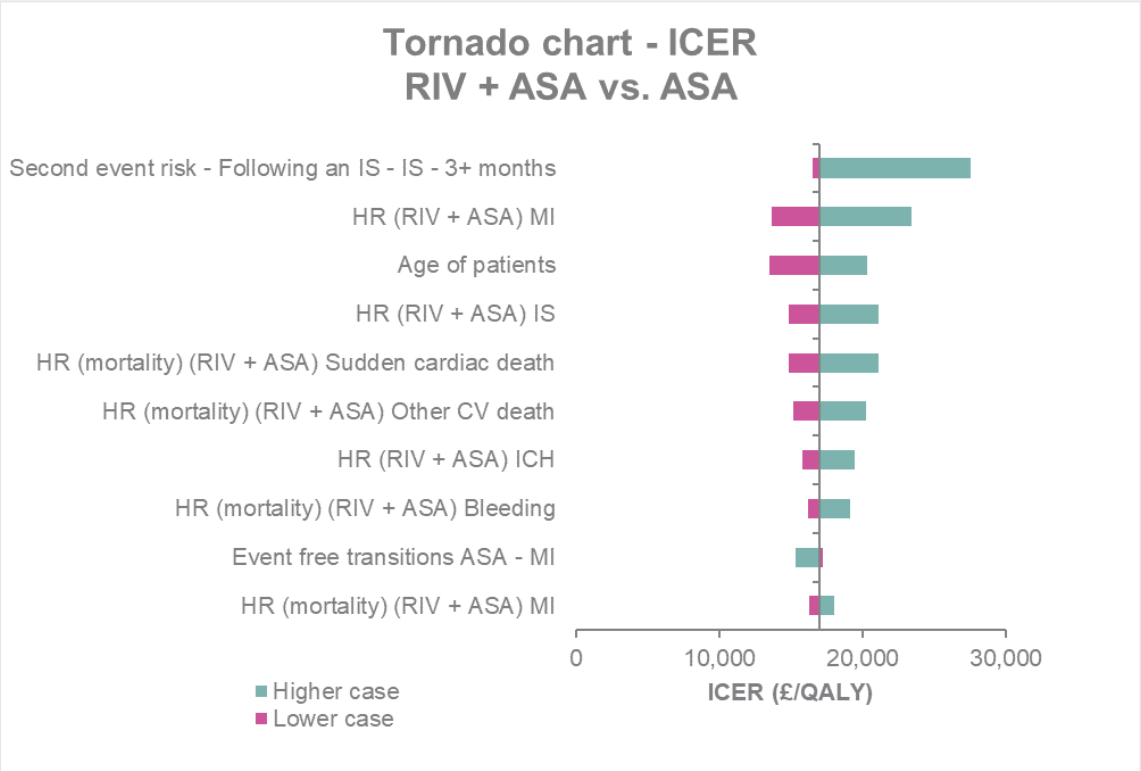
Deterministic sensitivity analysis results

Table 13. One-way sensitivity analysis results – COMPASS population: rivaroxaban + aspirin vs aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	Second event risk - Following an IS - IS - 3+ months	0.01423/0.02135	16565	27575
2	HR (RIV + ASA) MI	0.70/1.05	13677	23451
3	Age of patients	61.20/74.80	13512	20370
4	HR (RIV + ASA) IS	0.38/0.69	14849	21171
5	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	14850	21142
6	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	15188	20263
7	HR (RIV + ASA) ICH	0.67/2.00	15837	19444
8	HR (mortality) (RIV + ASA) Bleeding	0.67/3.33	16226	19163
9	Event free transitions ASA - MI	0.00251/0.00332	17253	15345
10	HR (mortality) (RIV + ASA) MI	0.64/0.96	16317	18039

Refers to CS Table 113 One-way sensitivity analysis results – COMPASS population: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 297

Figure 13. Tornado diagram – COMPASS population: rivaroxaban + aspirin vs aspirin



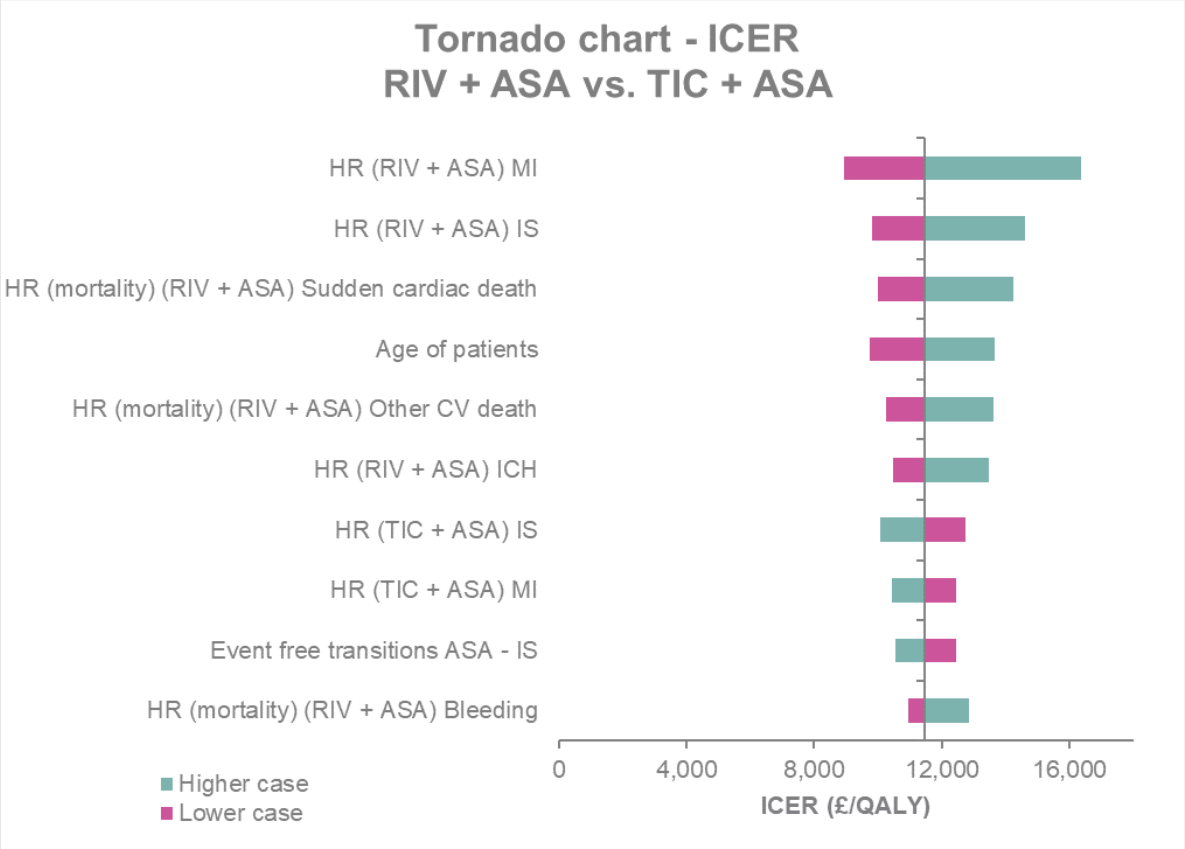
Refers to CS Figure 43. Tornado diagram – COMPASS population: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 298

Table 14. One-way sensitivity analysis results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	8941	16383
2	HR (RIV + ASA) IS	0.38/0.69	9832	14593
3	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	10016	14233
4	Age of patients	61.20/74.80	9734	13658
5	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	10241	13627
6	HR (RIV + ASA) ICH	0.67/2.00	10464	13465
7	HR (TIC + ASA) IS	0.56/1.02	12745	10064
8	HR (TIC + ASA) MI	0.72/0.98	12440	10443
9	Event free transitions ASA - IS	0.00146/0.00209	12439	10539
10	HR (mortality) (RIV + ASA) Bleeding	0.67/3.33	10943	12836

Refers to CS Table 114. One-way sensitivity analysis results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 298

Figure 14. Tornado diagram – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin



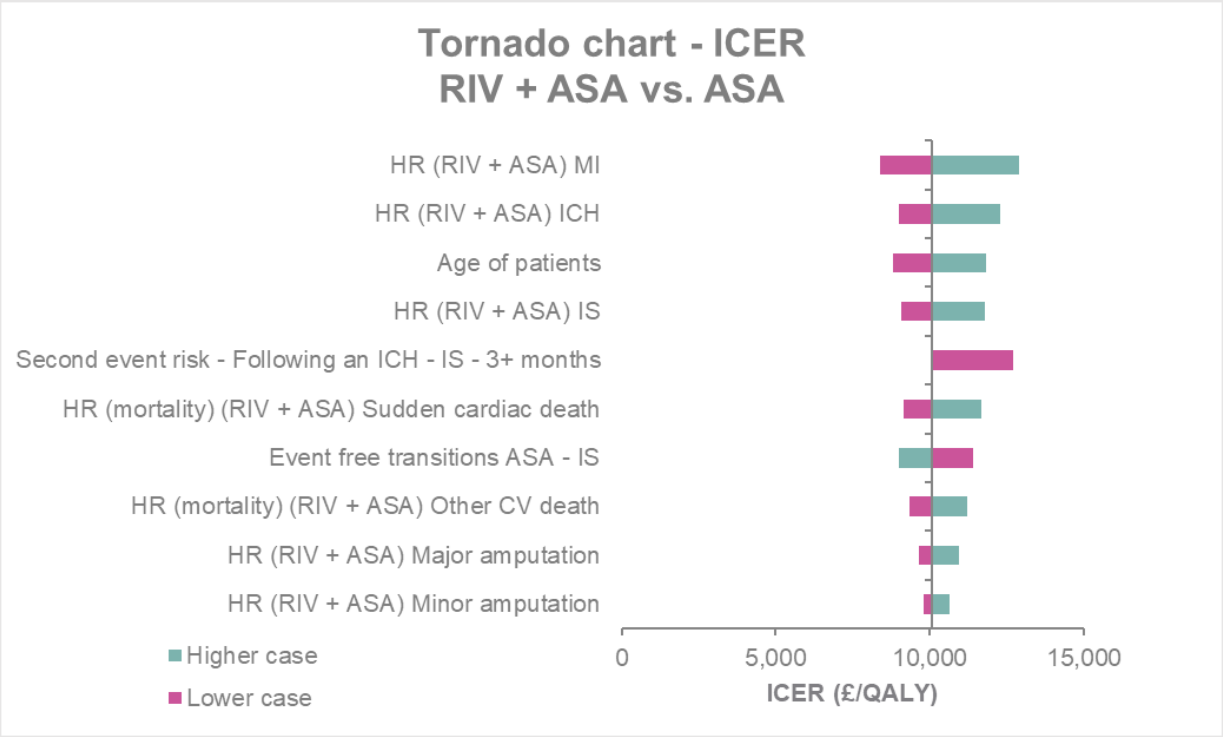
Refers to CS Figure 44. Tornado diagram – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 299

Table 15. One-way sensitivity analysis results – CAD and PAD subgroup: Rivaroxaban + aspirin vs aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	8380	12913
2	HR (RIV + ASA) ICH	0.67/2.00	8991	12297
3	Age of patients	61.20/74.80	8806	11827
4	HR (RIV + ASA) IS	0.38/0.69	9097	11801
5	Second event risk - Following an ICH - IS - 3+ months	0.02424/0.03636	12716	10115
6	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	9151	11690
7	Event free transitions ASA - IS	0.00158/0.00329	11413	8998
8	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	9362	11227
9	HR (RIV + ASA) Major amputation	0.30/1.09	9657	10941
10	HR (RIV + ASA) Minor amputation	0.35/1.20	9793	10629

Refers to CS Table 116. One-way sensitivity analysis results – CAD and PAD subgroup: Rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 304

Figure 15. Tornado diagram – CAD and PAD subgroup : rivaroxaban + aspirin vs aspirin



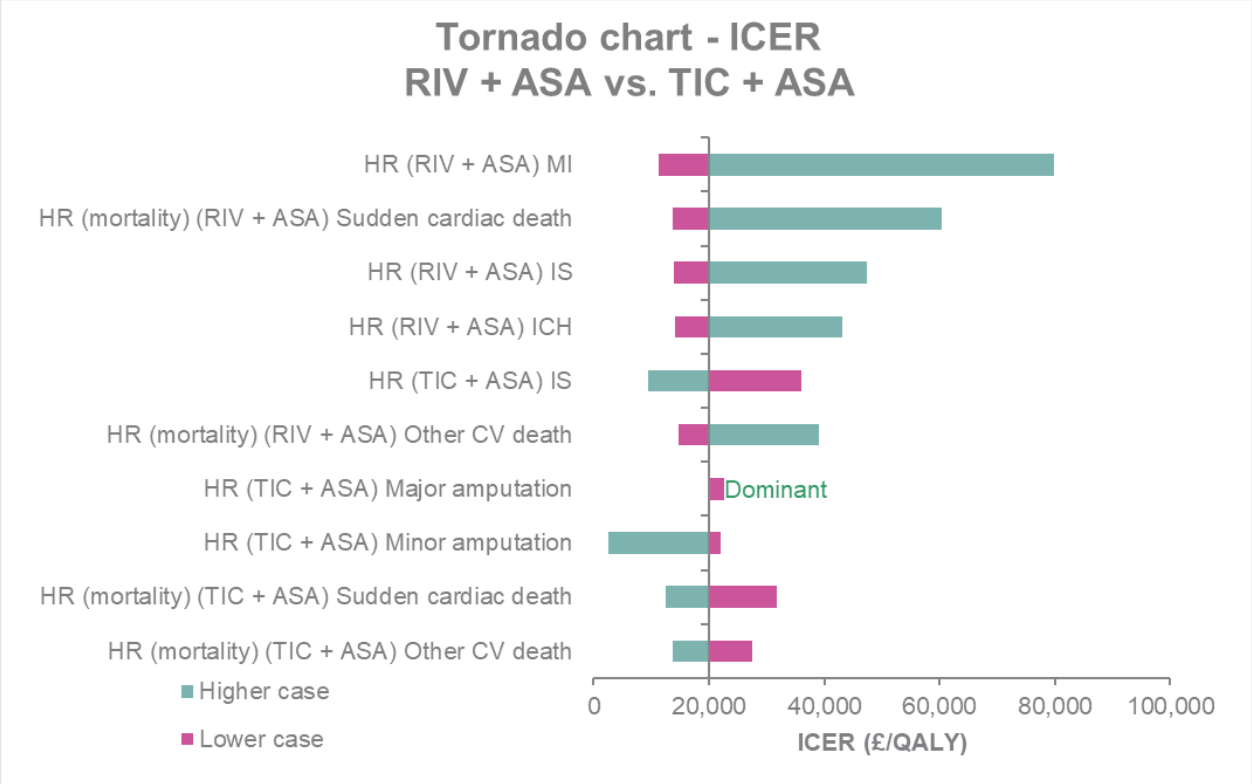
Refers to CS Figure 45. Tornado diagram – CAD and PAD subgroup : rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 304

Table 16. One-way sensitivity analysis results – CAD and PAD subgroup: Rivaroxaban + aspirin vs ticagrelor + aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	11268	79849
2	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	13652	60402
3	HR (RIV + ASA) IS	0.38/0.69	13883	47370
4	HR (RIV + ASA) ICH	0.67/2.00	14087	43130
5	HR (TIC + ASA) IS	0.22/1.22	36017	9483
6	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	14784	38980
7	HR (TIC + ASA) Major amputation	0.070/17.55	22556	Dominant
8	HR (TIC + ASA) Minor amputation	0.070/17.55	21928	2571
9	HR (mortality) (TIC + ASA) Sudden cardiac death	0.25/0.86	31713	12506
10	HR (mortality) (TIC + ASA) Other CV death	0.25/0.86	27410	13761

Refers to CS Table 117. One-way sensitivity analysis results – CAD and PAD subgroup: Rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 305

Figure 16. Tornado diagram – CAD and PAD subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin



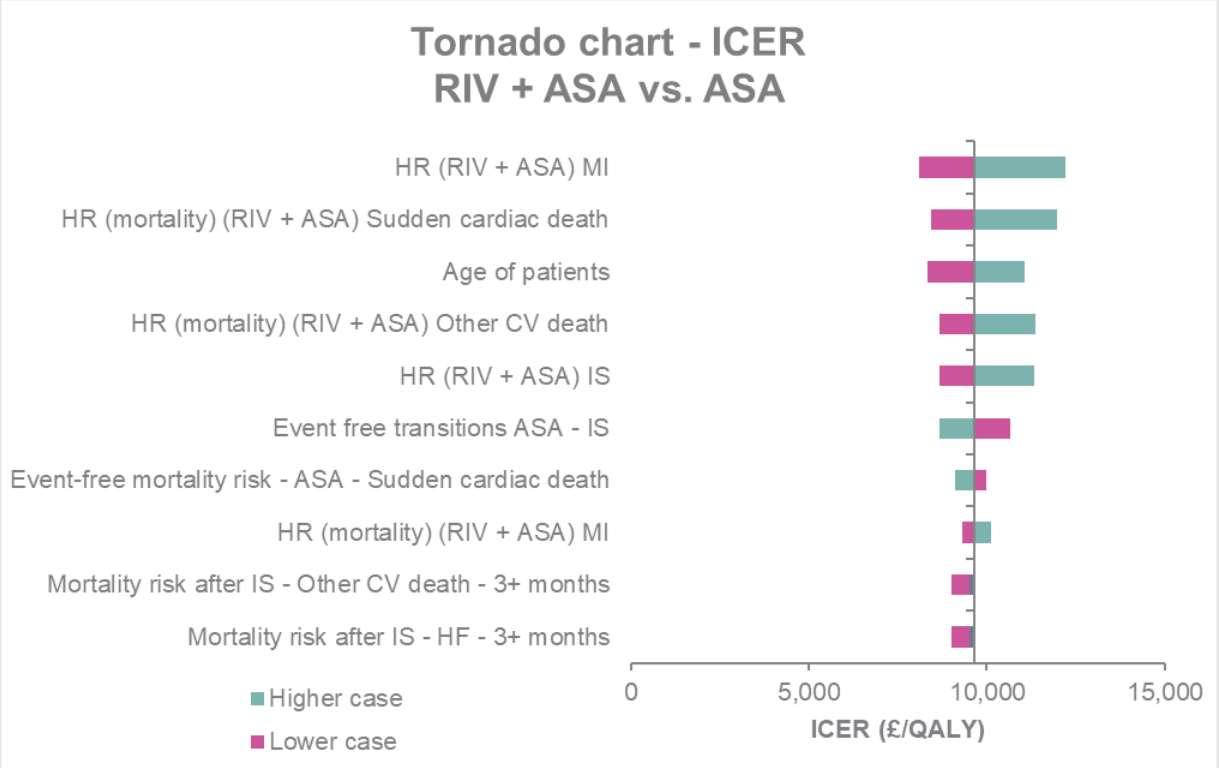
Refers to CS Figure 46. Tornado diagram – CAD and PAD subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 305

Table 17. One-way sensitivity analysis results – CAD and HF subgroup: rivaroxaban + aspirin vs aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	8105	12230
2	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	8437	11970
3	Age of patients	58.50/71.50	8333	11066
4	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	8670	11362
5	HR (RIV + ASA) IS	0.38/0.69	8666	11339
6	Event free transitions ASA - IS	0.00173/0.00341	10654	8671
7	Event-free mortality risk - ASA - Sudden cardiac death	0.0016/0.0032	9978	9105
8	HR (mortality) (RIV + ASA) MI	0.64/0.96	9308	10115
9	Mortality risk after IS - Other CV death - 3+ months	0.01013/0.01519	9001	9527
10	Mortality risk after IS - HF - 3+ months	0.01013/0.01519	9001	9527

Refers to CS Table 119. One-way sensitivity analysis results – CAD and HF subgroup: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 310

Figure 17. Tornado diagram – CAD and HF subgroup : rivaroxaban + aspirin vs aspirin



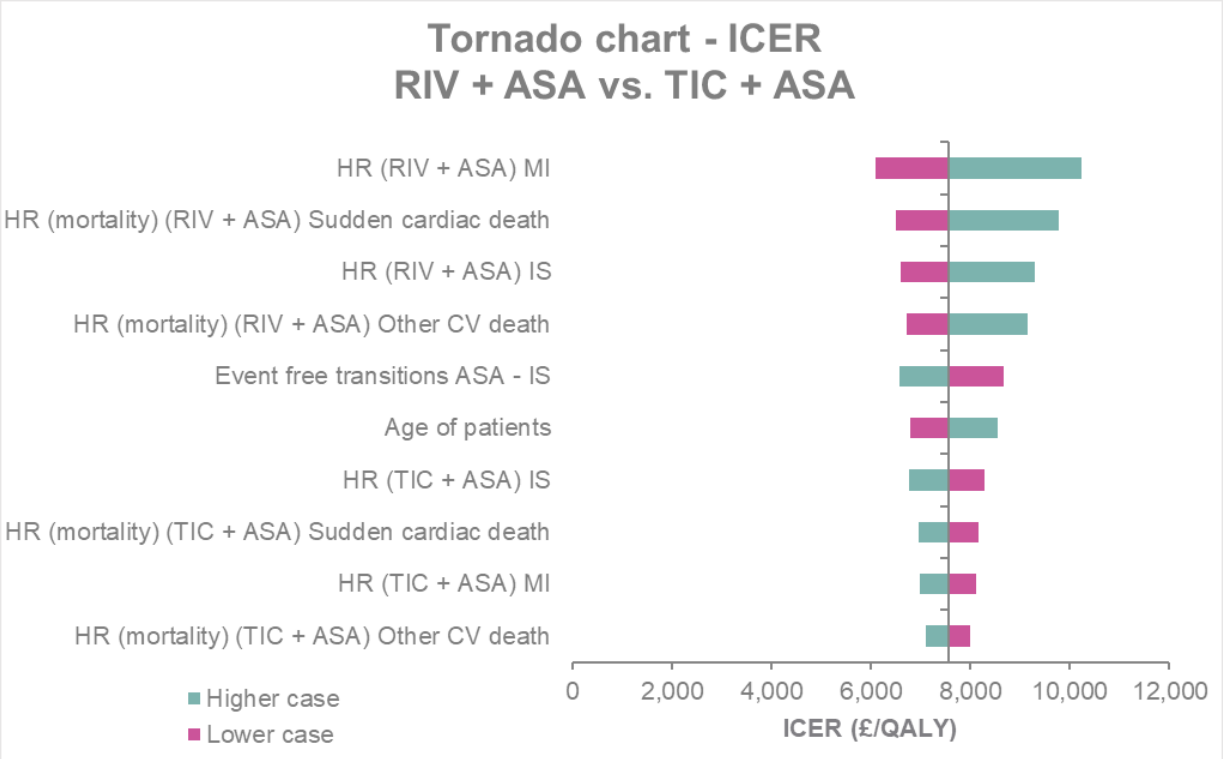
Refers to CS Figure 47. Tornado diagram – CAD and HF subgroup : rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 310

Table 18. One-way sensitivity analysis results – CAD and HF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	6084	10244
2	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	6514	9777
3	HR (RIV + ASA) IS	0.38/0.69	6608	9294
4	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	6719	9157
5	Event free transitions ASA - IS	0.00173/0.00341	8678	6568
6	Age of patients	58.50/71.50	6804	8555
7	HR (TIC + ASA) IS	0.56/1.02	8276	6763
8	HR (mortality) (TIC + ASA) Sudden cardiac death	0.68/1.01	8163	6961
9	HR (TIC + ASA) MI	0.72/0.98	8115	6980
10	HR (mortality) (TIC + ASA) Other CV death	0.68/1.01	7995	7105

Refers to CS Table 120. One-way sensitivity analysis results – CAD and HF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 311

Figure 18. Tornado diagram – CAD and HF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin



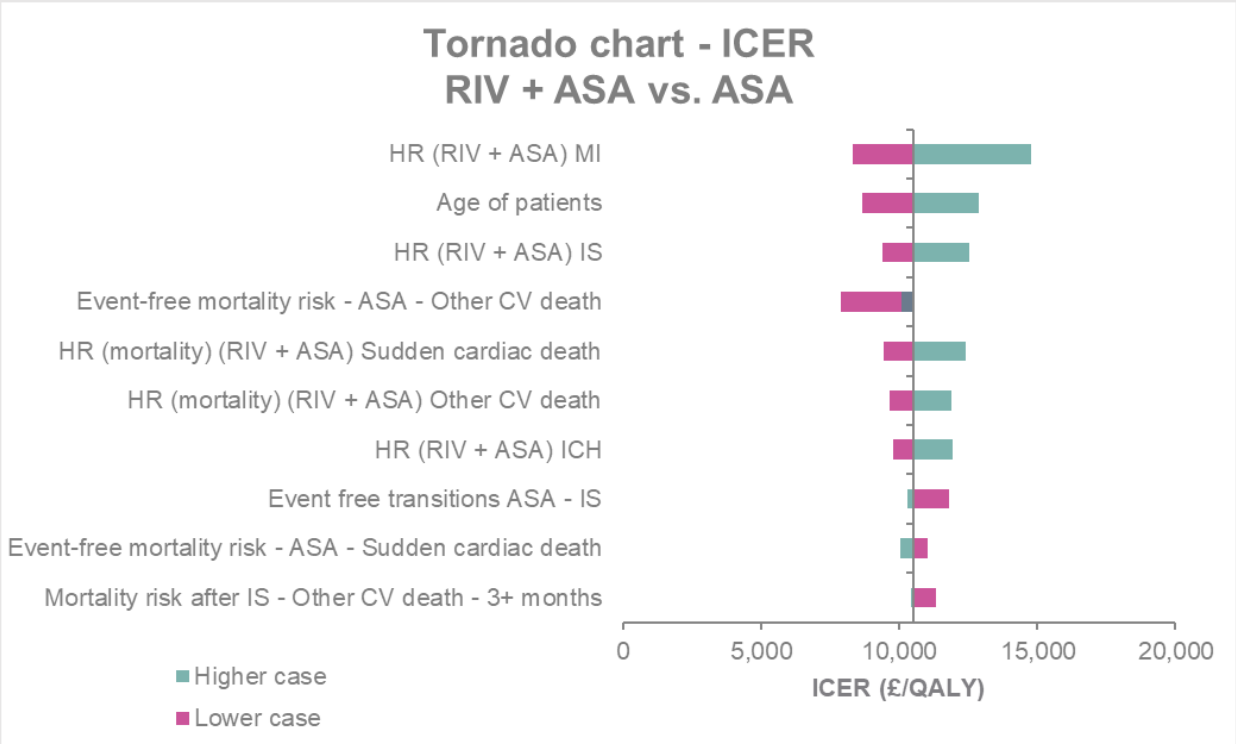
Refers to CS Figure 48. Tornado diagram – CAD and HF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 311

Table 19. One-way sensitivity analysis results – CAD and PRF subgroup: rivaroxaban + aspirin vs aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	8310	14780
2	Age of patients	64.80/79.20	8645	12855
3	HR (RIV + ASA) IS	0.38/0.69	9366	12522
4	Event-free mortality risk - ASA - Other CV death	0.0009/0.0021	7879	10066
5	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	9430	12403
6	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	9663	11867
7	HR (RIV + ASA) ICH	0.67/2.00	9758	11926
8	Event free transitions ASA - IS	0.00179/0.00345	11790	10309
9	Event-free mortality risk - ASA - Sudden cardiac death	0.0013/0.0027	11041	10053
10	Mortality risk after IS - Other CV death - 3+ months	0.00808/0.01212	11335	10421

Refers to CS Table 122. One-way sensitivity analysis results – CAD and PRF subgroup: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 316

Figure 19. Tornado diagram – CAD and PRF subgroup : rivaroxaban + aspirin vs aspirin



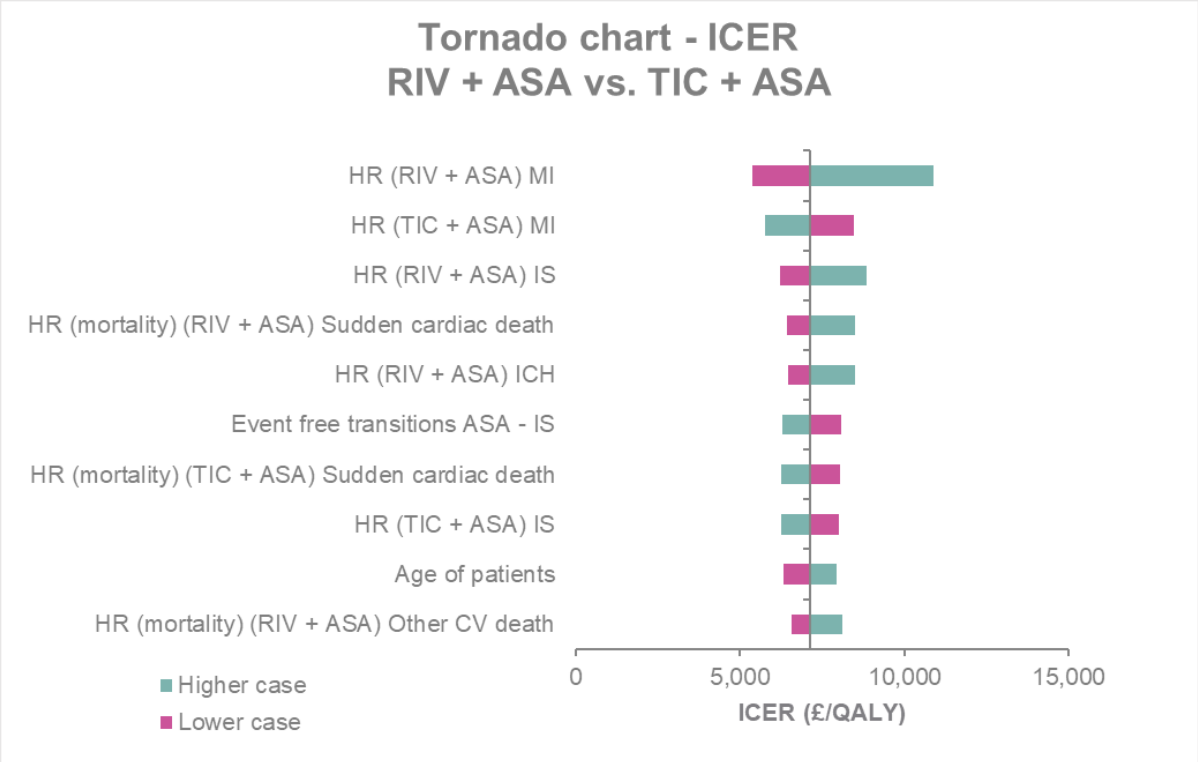
Refers to CS Figure 49. Tornado diagram – CAD and PRF subgroup : rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 316

Table 20. One-way sensitivity analysis results – CAD and PRF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	5355	10894
2	HR (TIC + ASA) MI	0.57/1.00	8448	5765
3	HR (RIV + ASA) IS	0.38/0.69	6223	8845
4	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	6414	8504
5	HR (RIV + ASA) ICH	0.67/2.00	6457	8479
6	Event free transitions ASA - IS	0.00179/0.00345	8088	6283
7	HR (mortality) (TIC + ASA) Sudden cardiac death	0.74/1.37	8035	6236
8	HR (TIC + ASA) IS	0.56/1.02	7986	6246
9	Age of patients	64.80/79.20	6332	7946
10	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	6565	8117

Refers to CS Table 123. One-way sensitivity analysis results – CAD and PRF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 317

Figure 20. Tornado diagram – CAD and PRF subgroup : rivaroxaban + aspirin vs ticagrelor + aspirin



Refers to CS Figure 50. Tornado diagram – CAD and PRF subgroup : rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 317

Scenario analyses results

Table 21. Scenario analysis results – COMPASS population

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		**£17,024**	**£11,453**
Time horizon	15 years	£22,031	£16,374
Treatment duration	5 years	£18,015	£5,523
Treatment discontinuation	4 years	£16,674	£12,424
	Duration of model	£17,356	£10,585
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	-	£11,386
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£17,023	£11,454
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£15,925	£11,377
Second event assumptions – utilities	Based on most recent event utility	£17,793	£11,492
Utilities inputs	Repeated measures mixed model	£16,981	£11,439
	Ticagrelor TA 420	£17,633	£11,577
Transition from event free to two events in one cycle	COMPASS data	£17,004	£11,135
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£17,383	£11,783
Discount rates	0%	£13,855	£9,942
	5%	£18,498	£12,105

Refers to CS Table 125. Scenario analysis results – COMPASS population, Appendix B, B.3.8 Sensitivity analysis, Scenario analysis, page 320

Table 22. Scenario analysis results – CAD and PAD subgroup

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		**£10,079**	**£19,923**
Time horizon	15 years	£12,285	£50,744
Treatment duration	5 years	£9,024	Dominated
Treatment discontinuation	4 years	£10,371	£16,040
	Duration of model	£9,871	£27,463
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	-	£19,980
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£10,077	£19,925
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£10,024	£19,877
Second event assumptions – utilities	Based on most recent event utility	£10,100	£19,946
Utilities inputs	Repeated measures mixed model	£10,066	£19,866
	Ticagrelor TA 420	£10,142	£20,203
Transition from event free to two events in one cycle	COMPASS data	£10,243	£18,985
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£10,221	£20,552
Discount rates	0%	£8,522	£14,513
	5%	£10,804	£23,312

Refers to CS Table 126. Scenario analysis results – CAD and PAD subgroup, Appendix B, B.3.8 Sensitivity analysis, Scenario analysis, page 321

Table 23. Scenario analysis results – CAD and HF subgroup

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		**£9,642**	**£7,557**
Time horizon	15 years	£12,380	£9,954
Treatment duration	5 years	£9,327	£4,173
Treatment discontinuation	4 years	£9,678	£8,022
	Duration of model	£9,614	£7,135
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	-	£7,532
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£9,642	£7,557
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£9,092	£7,528
Second event assumptions – utilities	Based on most recent event utility	£9,857	£7,572
Utilities inputs	Repeated measures mixed model	£9,631	£7,553
	Ticagrelor TA 420	£9,819	£7,610
Transition from event free to two events in one cycle	COMPASS data	£9,452	£7,397
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£9,882	£7,790
Discount rates	0%	£8,014	£6,745
	5%	£10,396	£7,899

Refers to CS Table 127. Scenario analysis results – CAD and HF subgroup, Appendix B, B.3.8 Sensitivity analysis, Scenario analysis, page 322

Table 24. Scenario analysis results – CAD and PRF subgroup

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		**£10,500**	**£7,141**
Time horizon	15 years	£12,053	£8,040
Treatment duration	5 years	£9,703	£3,899
Treatment discontinuation	4 years	£10,690	£7,939
	Duration of model	£10,358	£6,500
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	-	£7,141
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£10,498	£7,140
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£10,211	£7,172
Second event assumptions – utilities	Based on most recent event utility	£10,623	£7,141
Utilities inputs	Repeated measures mixed model	£10,493	£7,139
	Ticagrelor TA 420	£9,184	£7,465
Transition from event free to two events in one cycle	COMPASS data	£10,479	£7,062
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£10,744	£7,319
Discount rates	0%	£8,951	£6,755
	5%	£11,213	£7,281

Refers to CS Table 128. Scenario analysis results – CAD and PRF subgroup, Appendix B, B.3.8 Sensitivity analysis, Scenario analysis, page 323

Appendix 3 – Fixed HR results with coding error corrected

Base case results

Table 25. Base case incremental cost-effectiveness results – COMPASS population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	12974	11.16	8.32					
Ticagrelor + aspirin	14662	11.26	8.40	1688	0.10	0.08	20849	Extendedly dominated
Rivaroxaban + aspirin	16896	11.51	8.60	2234	0.25	0.20	14193	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 88. Base case incremental cost-effectiveness results – COMPASS population, Appendix B, B.3.7. Base-case Results, page 255

Table 26. Base case incremental cost-effectiveness results – CAD and PAD subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	13976	10.02	7.10					
Ticagrelor + aspirin	15774	10.37	7.36	1797	0.35	0.26	6966	
Rivaroxaban + aspirin	17382	10.48	7.44	1609	0.11	0.08	10054	19923

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 89. Base case incremental cost-effectiveness results – CAD and PAD subgroup, Appendix B, B.3.7. Base-case Results, page 255

Table 27. Base case incremental cost-effectiveness results – CAD and HF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	11801	10.03	7.63					
Ticagrelor + aspirin	13535	10.20	7.76	1734	0.17	0.14	12808	Extendedly dominated
Rivaroxaban + aspirin	15952	10.62	8.09	2417	0.42	0.32	9105	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 90. Base case incremental cost-effectiveness results – CAD and HF, Appendix B, B.3.7. Base-case Results, page 256

Table 28. Base case incremental cost-effectiveness results – CAD and PRF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	11793	8.88	6.64					
Ticagrelor + aspirin	13297	8.97	6.71	1504	0.09	0.07	21094	Extendedly dominated
Rivaroxaban + aspirin	15080	9.30	6.96	1783	0.33	0.25	10216	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Refers to CS Table 91. Base case incremental cost-effectiveness results – CAD and PRF, Appendix B, B.3.7. Base-case Results, page 25

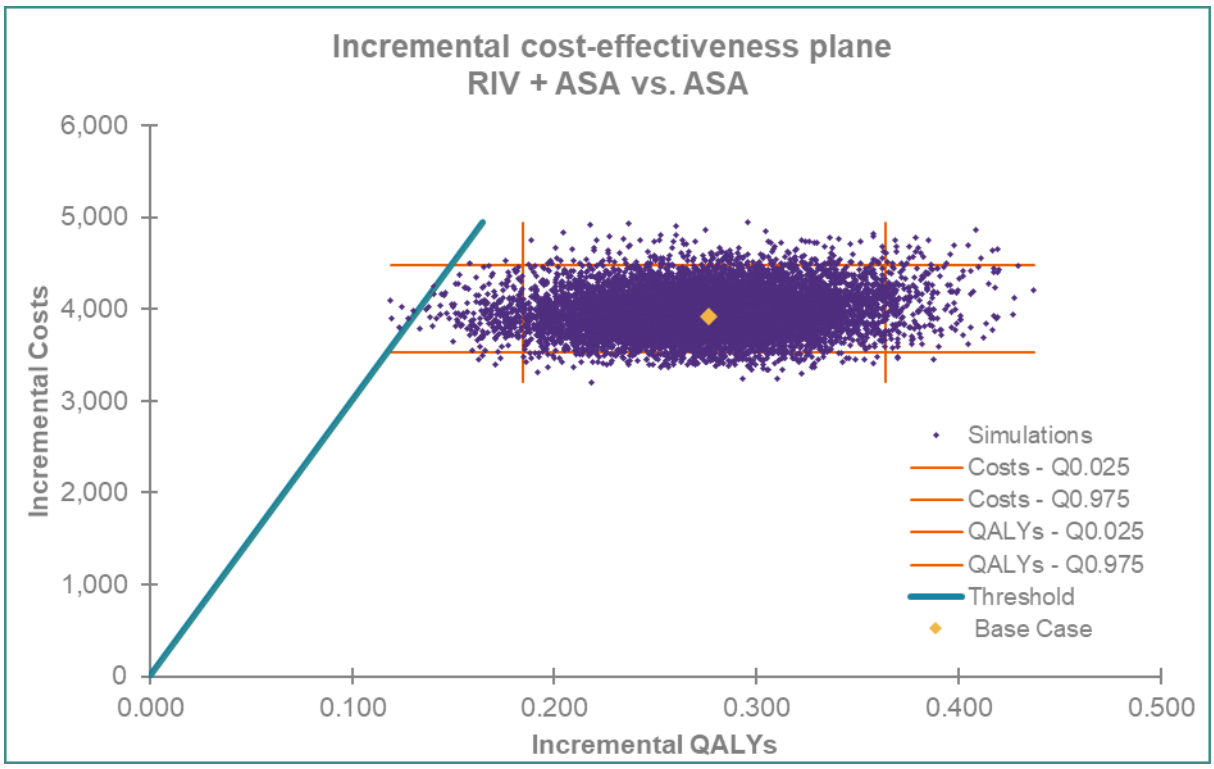
Probabilistic sensitivity analysis results

Table 29. PSA results - COMPASS population: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin	13097	11.27	8.41				
Rivaroxaban + aspirin	17074	11.62	8.69	3977	0.353	0.275	14462
P(cost-effectiveness):20K	94.88%						
P(cost-effectiveness):30K	99.93%						

Refers to CS Table 101. PSA results - COMPASS population: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 265

Figure 21. PSA scatterplot – COMPASS population: rivaroxaban + aspirin vs aspirin (WTP threshold =£30,000/QALY)



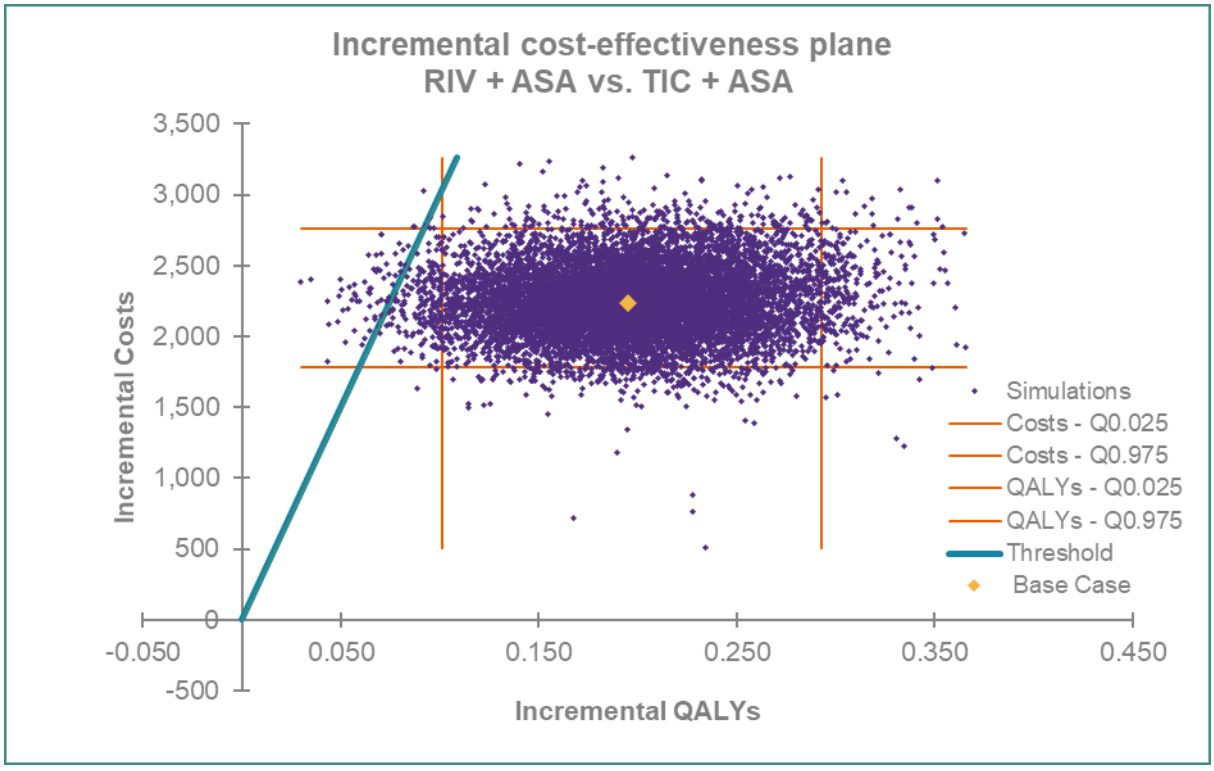
Refers to CS Figure 27. PSA scatterplot – COMPASS population: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 265

Table 30. PSA results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor	14820	11.37	8.49				
Rivaroxaban + aspirin	17074	11.62	8.69	2255	0.255	0.198	11403
P(cost-effectiveness):20K	95.62%						
P(cost-effectiveness):30K	99.37%						

Refers to CS Table 102. PSA results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 266

Figure 22. PSA scatterplot – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin (WTP threshold =£30,000/QALY)



Refers to CS Figure 29. PSA scatterplot – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 267

Figure 23. CEAC – COMPASS population

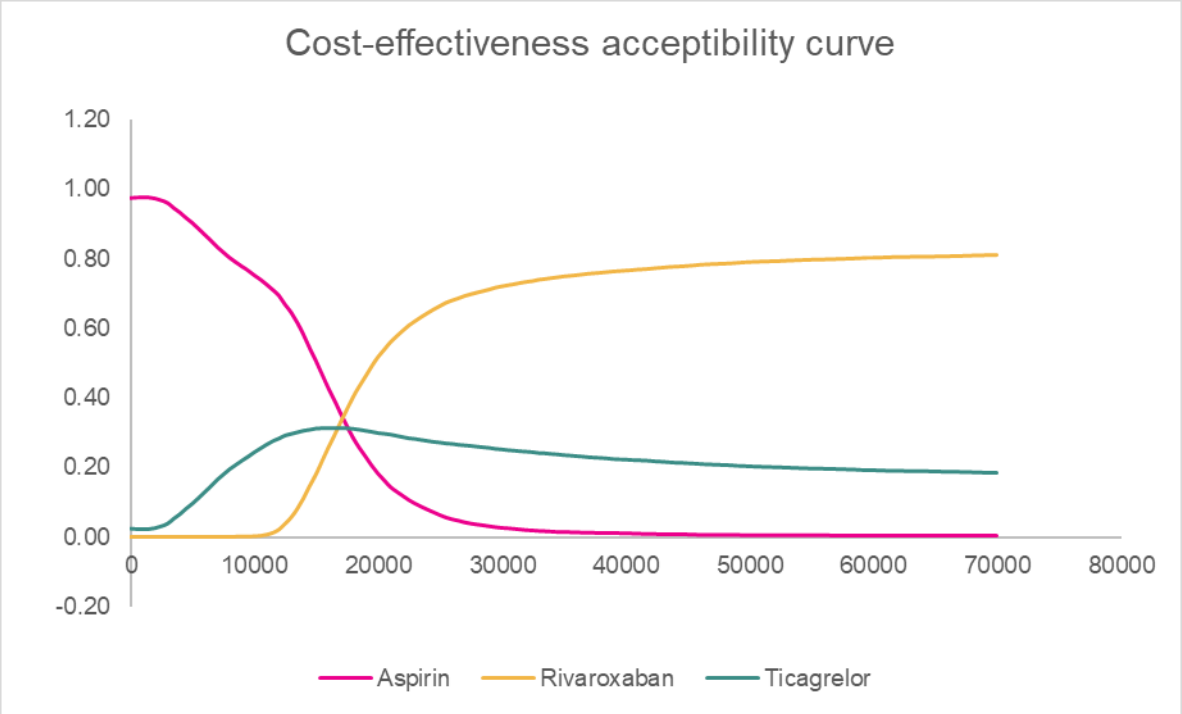
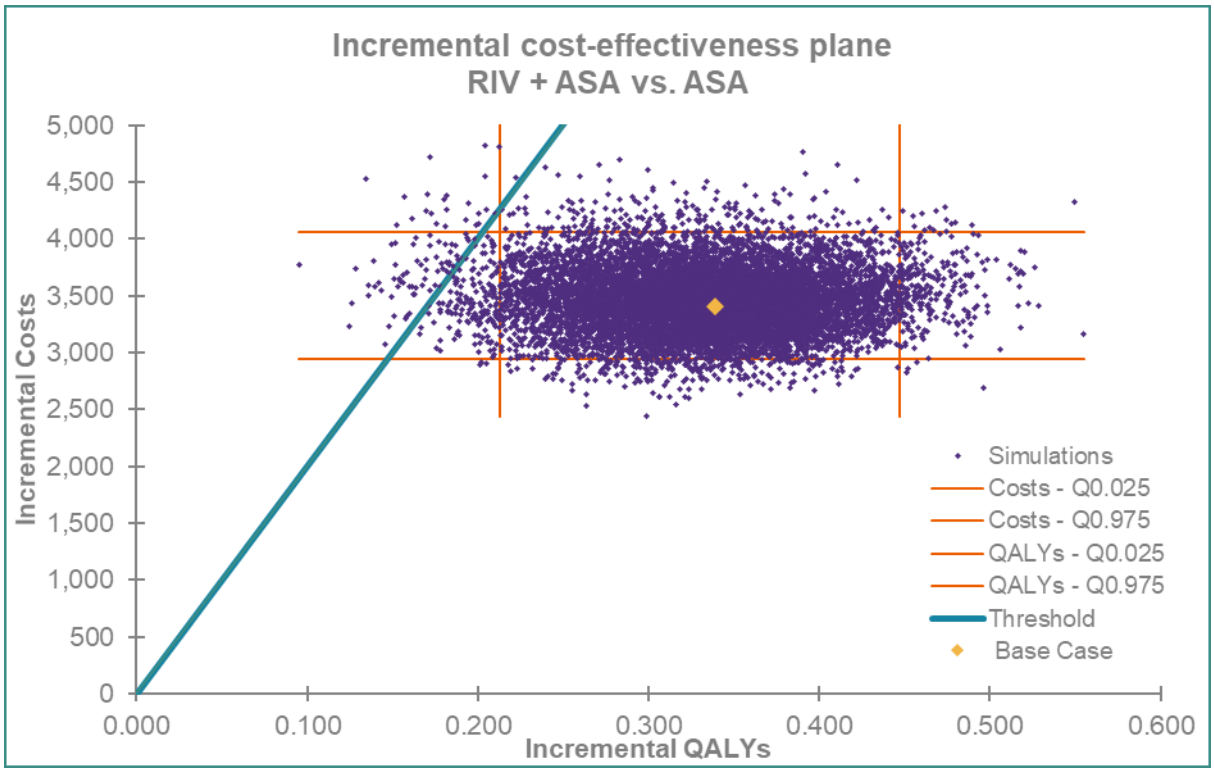


Table 31. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin	14076	10.10	7.17				
Rivaroxaban + aspirin	17539	10.55	7.50	3463	0.448	0.331	10455
P(cost-effectiveness):20K	99.07%						
P(cost-effectiveness):30K	99.97%						

Refers to CS Table 104. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 273

Figure 24. PSA scatterplot – CAD and PAD subgroup – rivaroxaban + aspirin versus aspirin



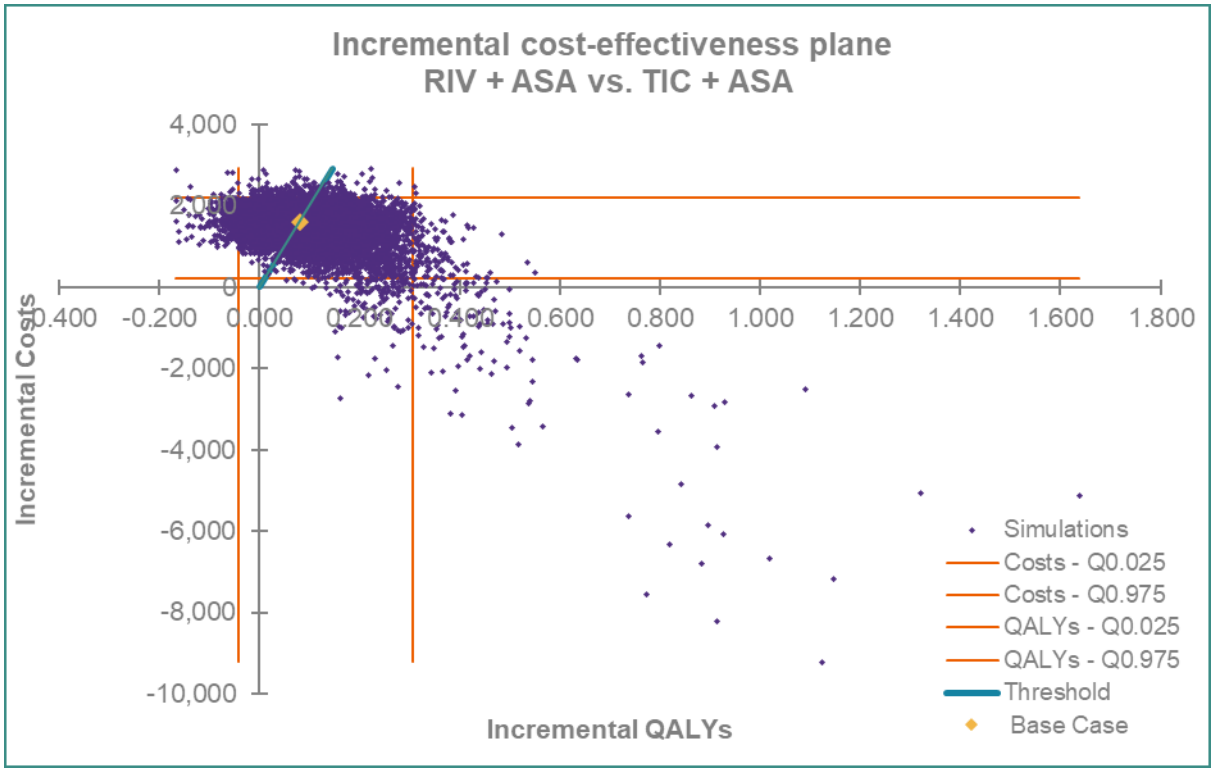
Refers to CS Figure 31. PSA scatterplot – CAD and PAD subgroup – rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 273

Table 32. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor	16107	10.43	7.39				
Rivaroxaban + aspirin	17539	10.55	7.50	1432	0.117	0.111	12884
P(cost-effectiveness):20K	67.69%						
P(cost-effectiveness):30K	76.97%						

Refers to CS Table 105. PSA results – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 274

Figure 25. PSA scatterplot – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin



Refers to CS Figure 33. PSA scatterplot – CAD and PAD subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 275

Figure 26. CEAC – CAD and PAD subgroup

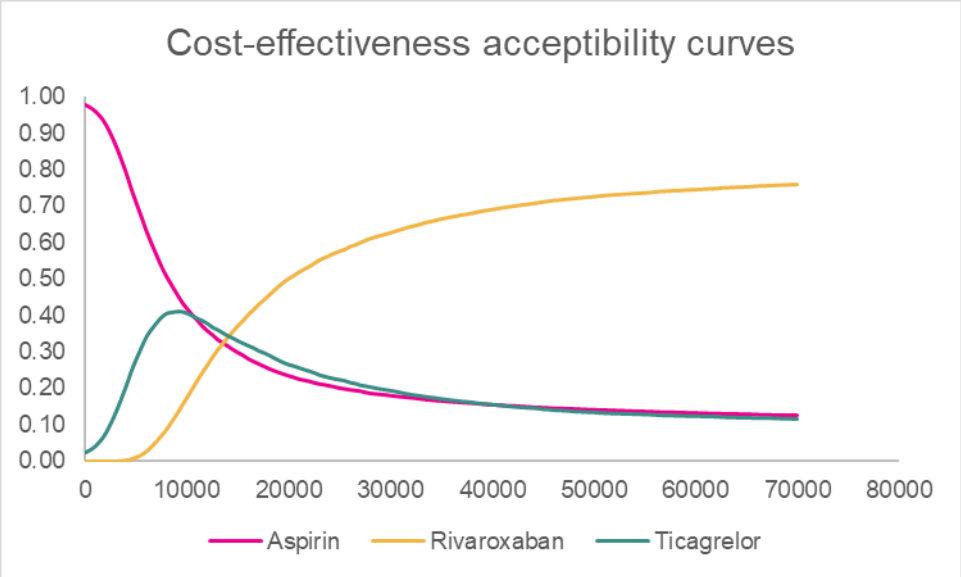
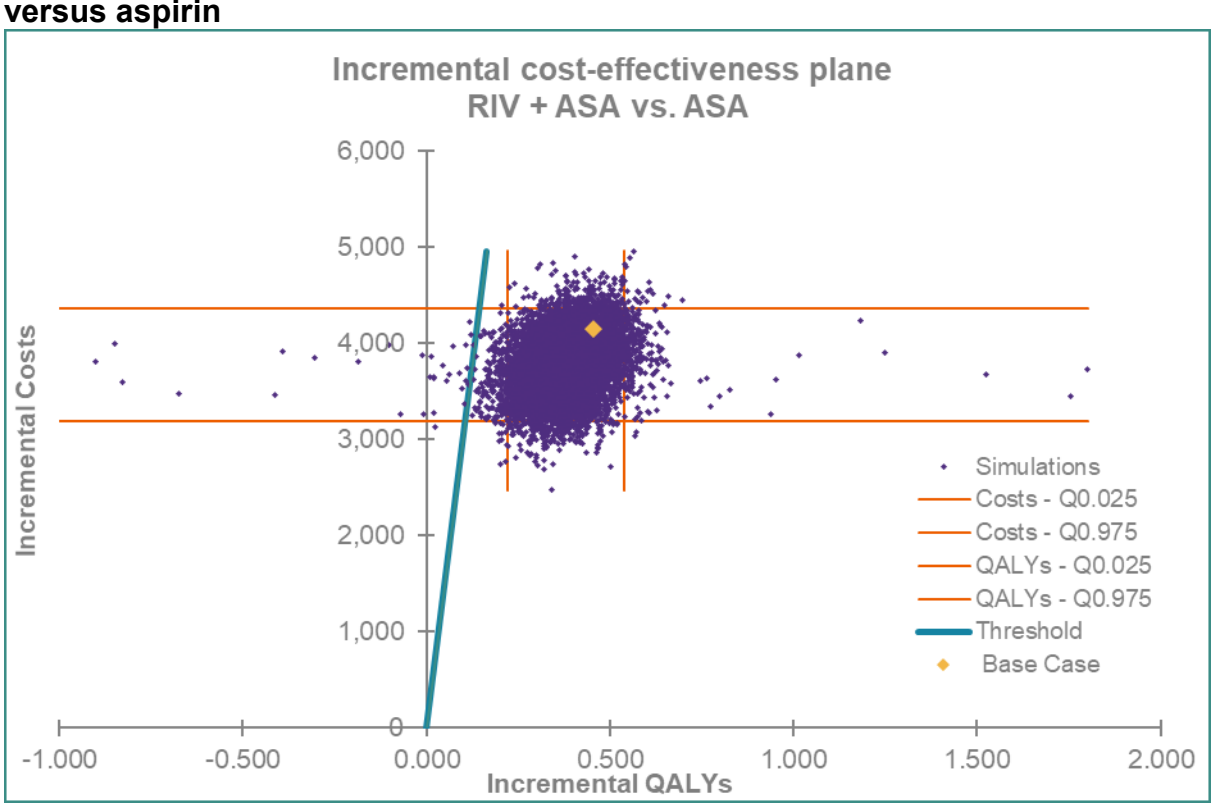


Table 33. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin	11852	10.07	7.67				
Rivaroxaban + aspirin	16023	10.65	8.12	4172	0.580	0.448	9306
P(cost-effectiveness):20K	99.85%						
P(cost-effectiveness):30K	99.99%						

Refers to CS Table 107. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 281

Figure 27. PSA scatterplot – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin



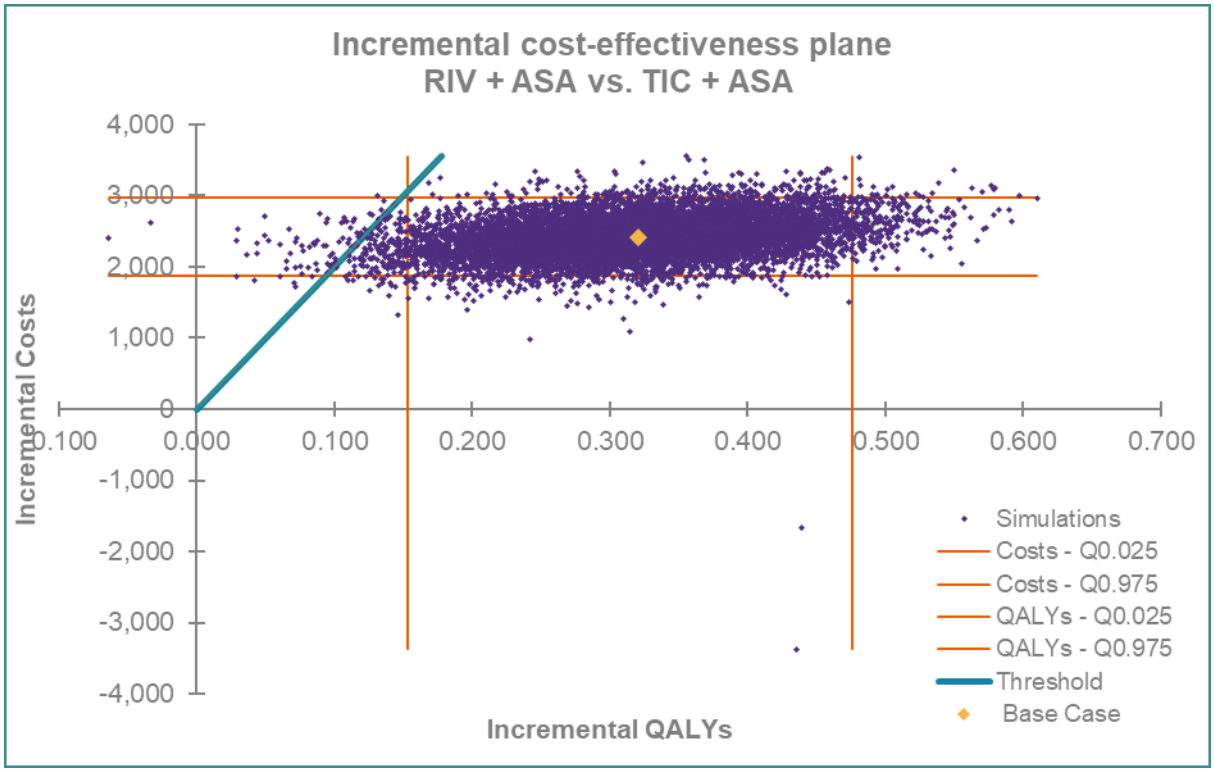
Refers to CS Figure 35. PSA scatterplot – CAD and HF subgroup: rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 281

Table 34. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor	13610	10.24	7.80				
Rivaroxaban + aspirin	16023	10.65	8.12	2413	0.413	0.317	7601
P(cost-effectiveness):20K	99.29%						
P(cost-effectiveness):30K	99.79%						

Refers to CS Table 108. PSA results – CAD and HF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 282

Figure 28. PSA scatterplot – CAD and HF subgroup – rivaroxaban + aspirin versus ticagrelor + aspirin



Refers to CS Figure 37. PSA scatterplot – CAD and HF subgroup – rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 283

Figure 29. CEAC – CAD and HF subgroup

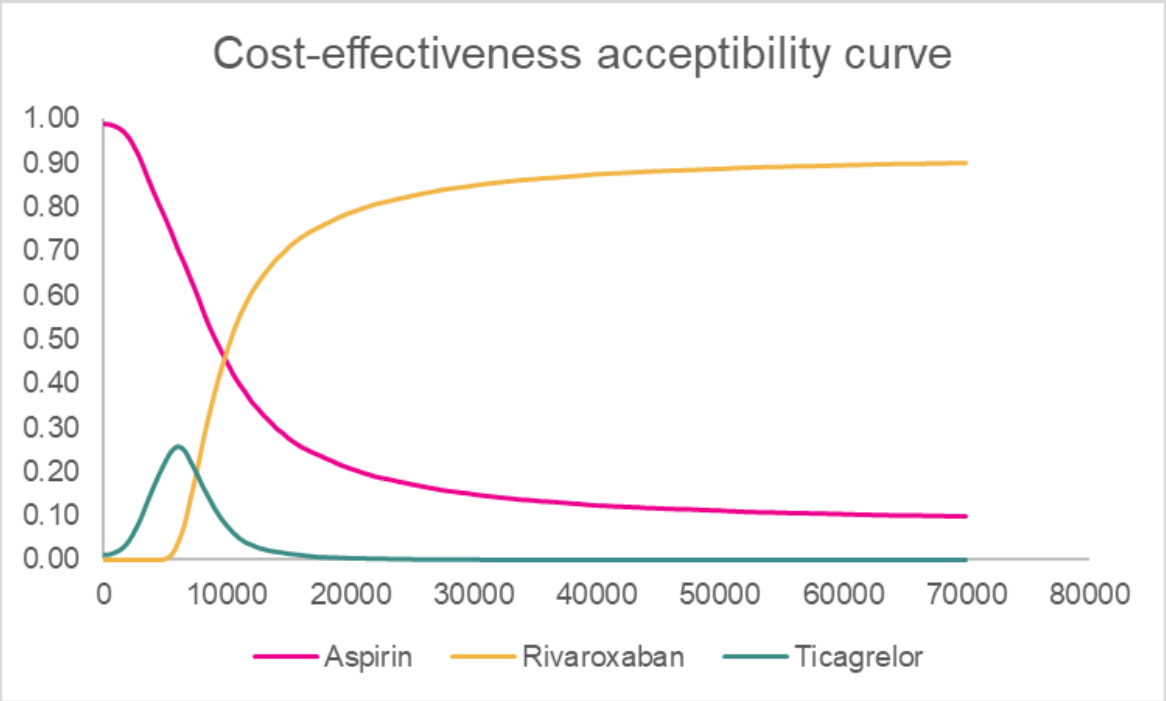
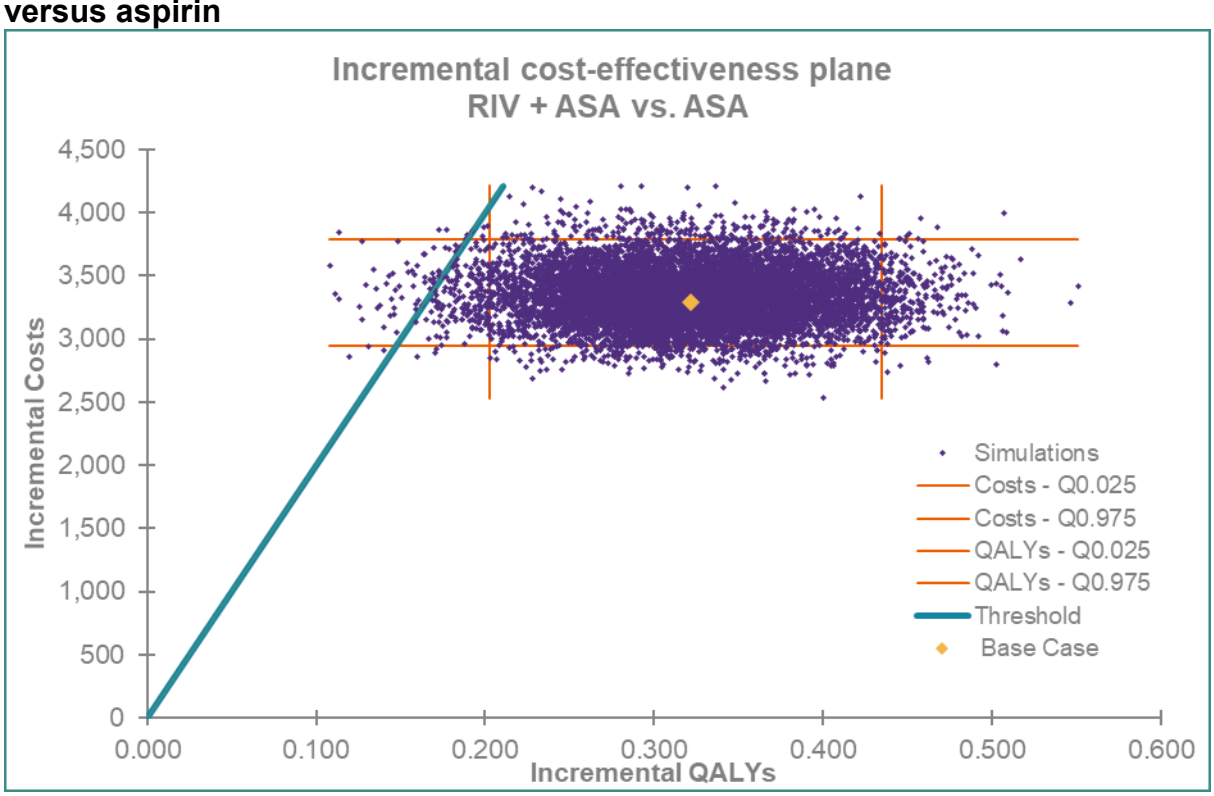


Table 35. PSA results – CAD and PRF subgroup – rivaroxaban + aspirin vs aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Aspirin	11915	8.98	6.73				
Rivaroxaban + aspirin	15256	9.40	7.05	3341	0.419	0.321	10421
P(cost-effectiveness):20K	99.38%						
P(cost-effectiveness):30K	99.97%						

Refers to CS Table 110. PSA results – CAD and PRF subgroup – rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 288

Figure 30. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus aspirin



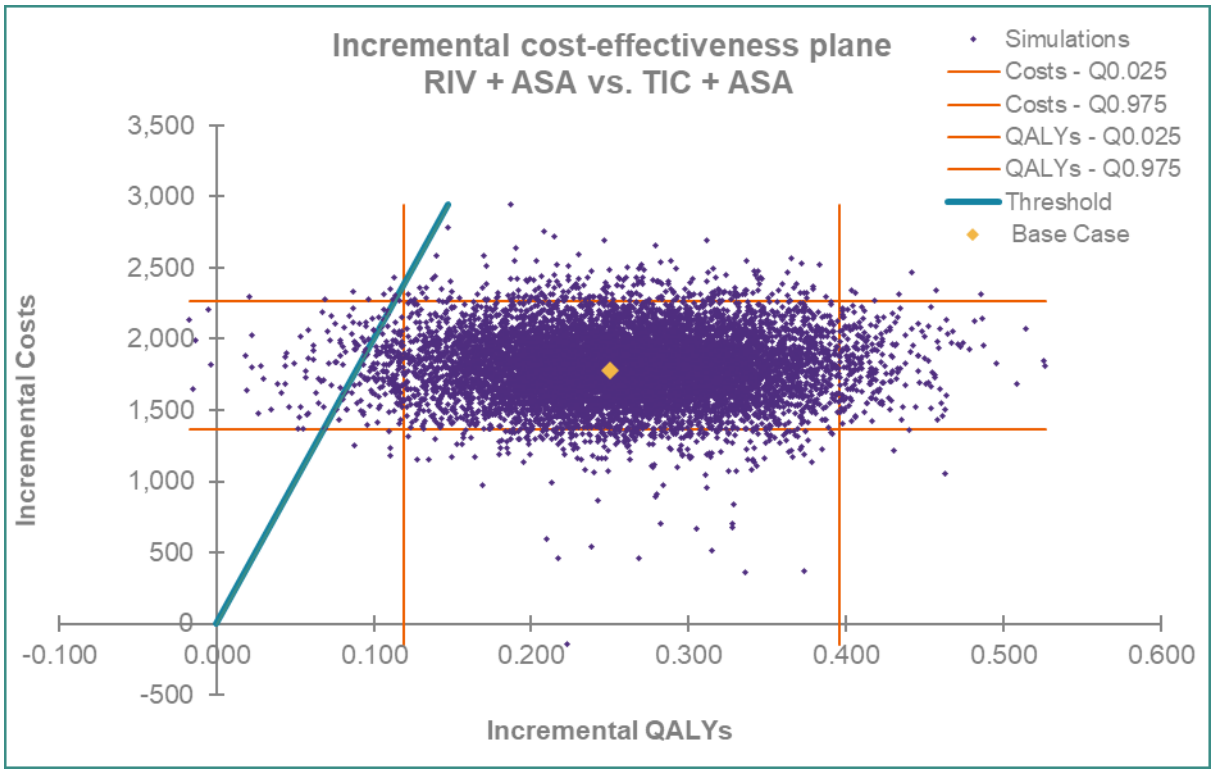
Refers to CS Figure 39. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 289

Table 36. PSA results – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
Ticagrelor + aspirin	13454	9.06	6.80				
Rivaroxaban + aspirin	15256	9.40	7.05	1802	0.341	0.258	6976
P(cost-effectiveness):20K	99.07%						
P(cost-effectiveness):30K	99.68%%						

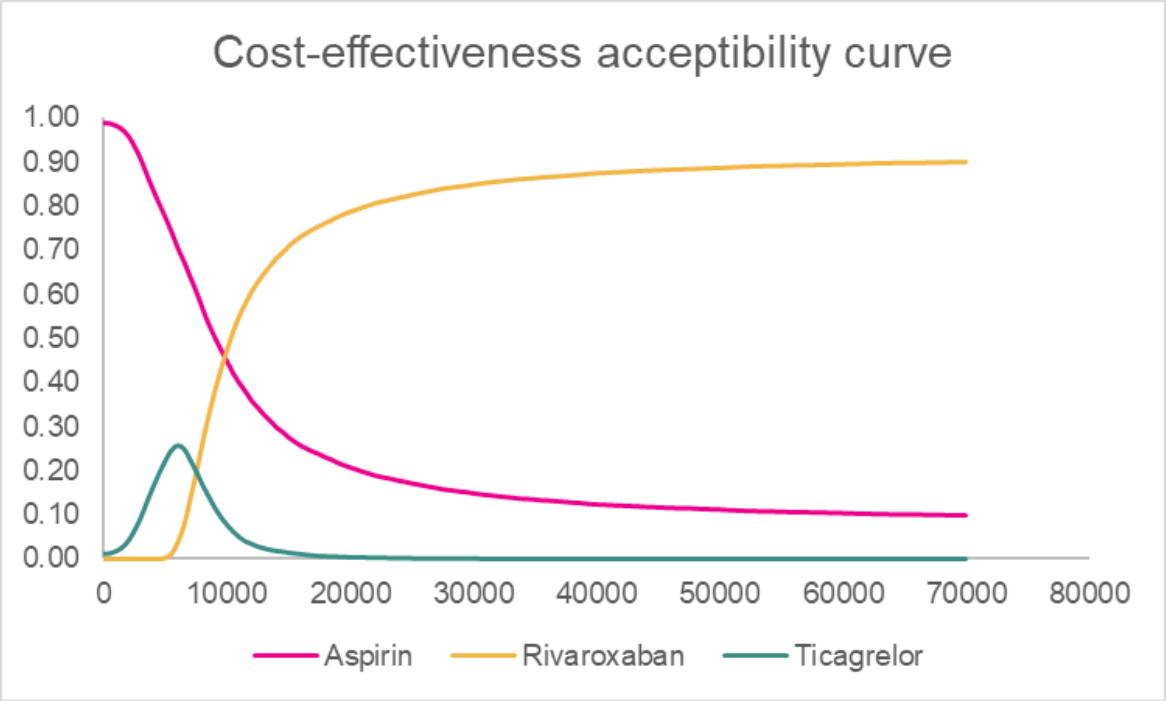
Refers to CS Table 111. PSA results – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 290

Figure 31. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin



Refers to CS Figure 41. PSA scatterplot – CAD and PRF subgroup: rivaroxaban + aspirin versus ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Probabilistic sensitivity analysis, page 290

Figure 32. CEAC – CAD and PRF subgroup



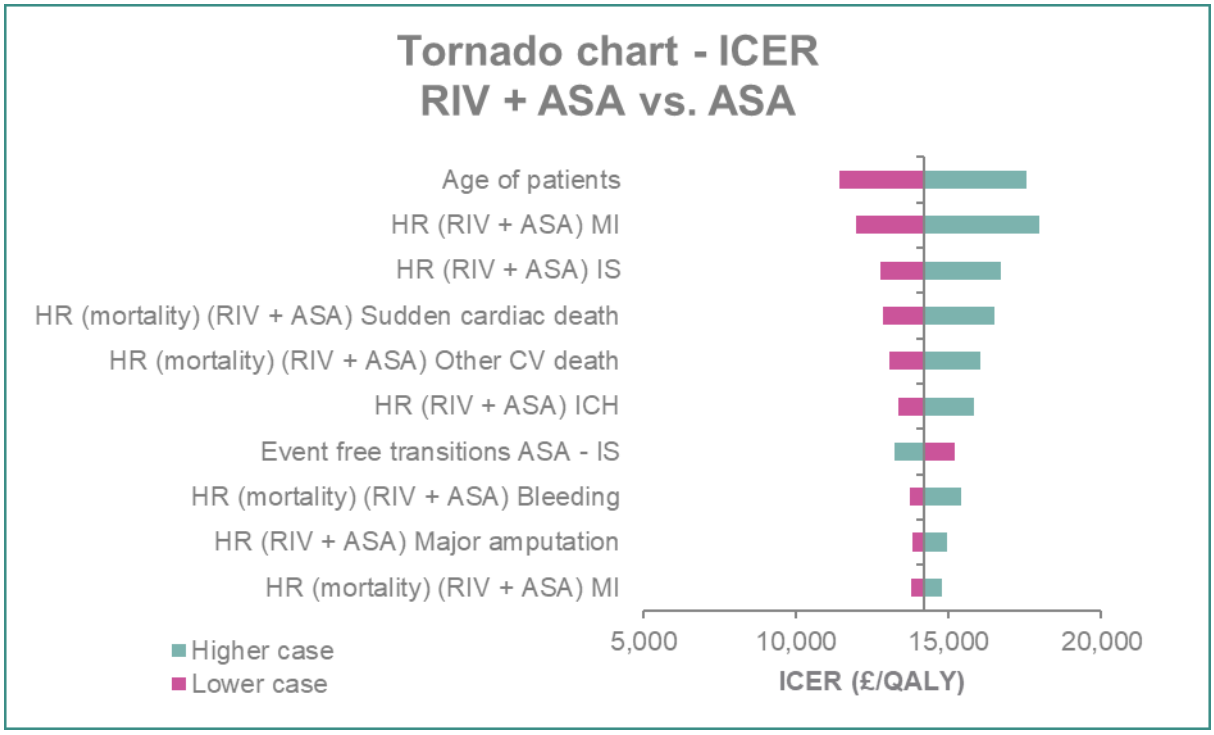
Deterministic sensitivity analysis results

Table 37. One-way sensitivity analysis results – COMPASS population: rivaroxaban + aspirin vs aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	Age of patients	61.20/74.80	11440	17532
2	HR (RIV + ASA) MI	0.70/1.05	11964	17965
3	HR (RIV + ASA) IS	0.38/0.69	12760	16711
4	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	12831	16517
5	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	13050	16046
6	HR (RIV + ASA) ICH	0.67/2.00	13367	15818
7	Event free transitions ASA - IS	0.00146/0.00209	15219	13227
8	HR (mortality) (RIV + ASA) Bleeding	0.67/3.33	13711	15421
9	HR (RIV + ASA) Major amputation	0.30/1.09	13823	14940
10	HR (mortality) (RIV + ASA) MI	0.64/0.96	13760	14797

Refers to CS Table 113 One-way sensitivity analysis results – COMPASS population: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 297

Figure 33. Tornado diagram – COMPASS population: rivaroxaban + aspirin vs aspirin



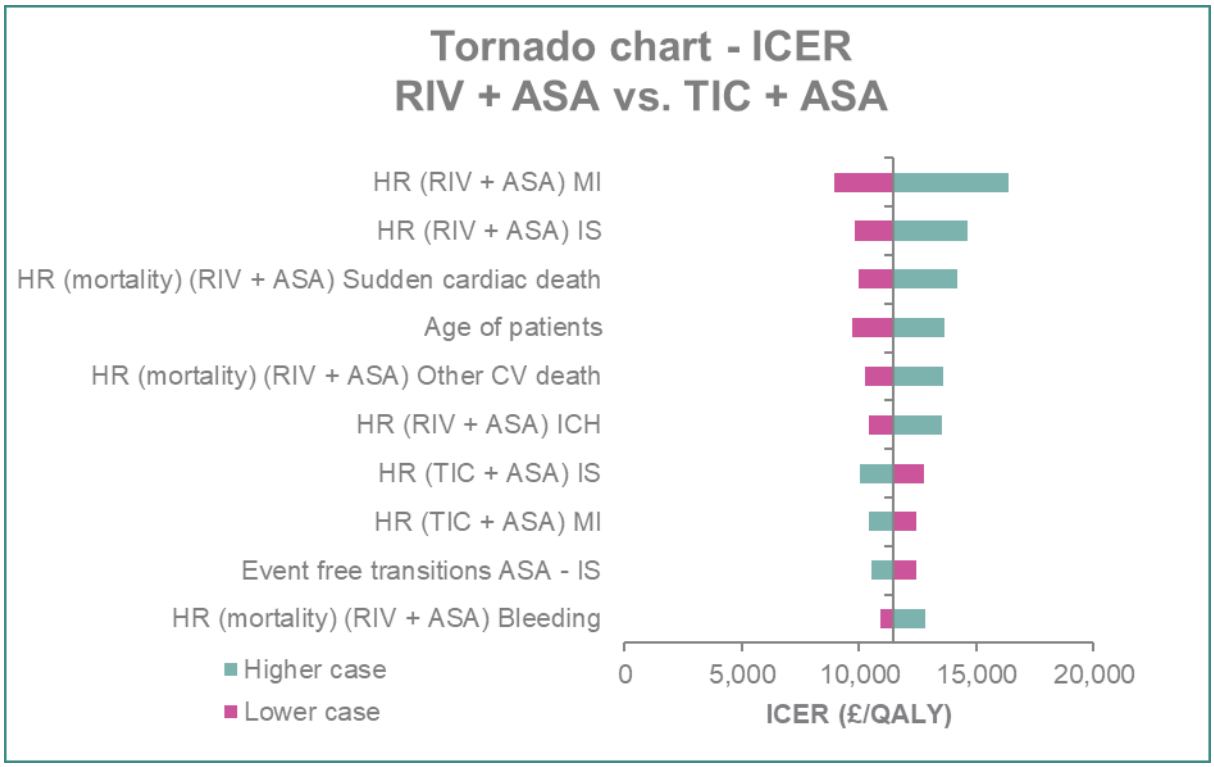
Refers to CS Figure 43. Tornado diagram – COMPASS population: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 298

Table 38. One-way sensitivity analysis results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	8928	16353
2	HR (RIV + ASA) IS	0.38/0.69	9803	14602
3	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	10003	14202
4	Age of patients	61.20/74.80	9721	13631
5	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	10227	13601
6	HR (RIV + ASA) ICH	0.67/2.00	10415	13519
7	HR (TIC + ASA) IS	0.56/1.02	12738	10036
8	HR (TIC + ASA) MI	0.72/0.98	12420	10427
9	Event free transitions ASA - IS	0.00146/0.00209	12422	10519
10	HR (mortality) (RIV + ASA) Bleeding	0.67/3.33	10925	12814

Refers to CS Table 114. One-way sensitivity analysis results – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 298

Figure 34. Tornado diagram – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin



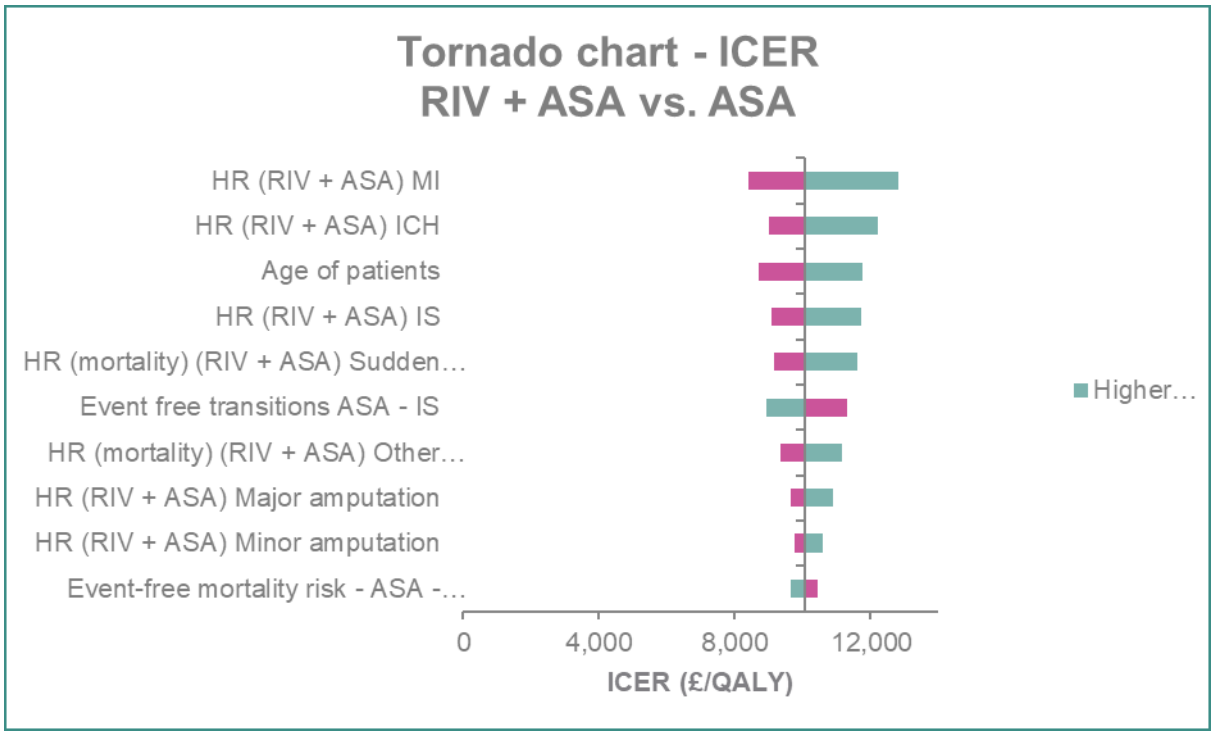
Refers to CS Figure 44. Tornado diagram – COMPASS population: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 299

Table 39. One-way sensitivity analysis results – CAD and PAD subgroup: Rivaroxaban + aspirin vs aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	8390	12811
2	HR (RIV + ASA) ICH	0.67/2.00	8989	12216
3	Age of patients	61.20/74.80	8687	11755
4	HR (RIV + ASA) IS	0.38/0.69	9093	11730
5	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	9146	11619
6	Event free transitions ASA - IS	0.00158/0.00329	11319	8913
7	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	9353	11171
8	HR (RIV + ASA) Major amputation	0.30/1.09	9642	10896
9	HR (RIV + ASA) Minor amputation	0.35/1.20	9775	10591
10	Event-free mortality risk - ASA - Sudden cardiac death	0.0012/0.0027	10438	9646

Refers to CS Table 116. One-way sensitivity analysis results – CAD and PAD subgroup: Rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 304

Figure 35. Tornado diagram – CAD and PAD subgroup: rivaroxaban + aspirin vs aspirin



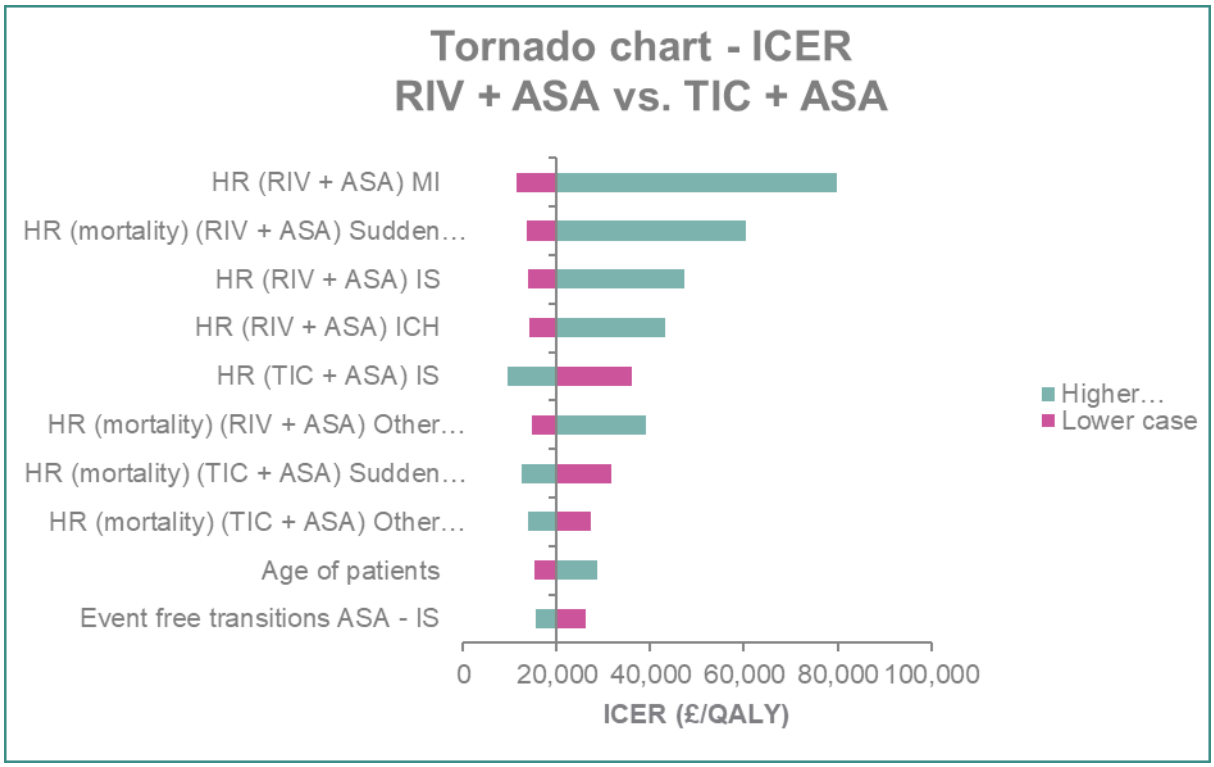
Refers to CS Figure 45. Tornado diagram – CAD and PAD subgroup : rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 304

Table 40. One-way sensitivity analysis results – CAD and PAD subgroup: Rivaroxaban + aspirin vs ticagrelor + aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	11268	79849
2	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	13652	60402
3	HR (RIV + ASA) IS	0.38/0.69	13883	47370
4	HR (RIV + ASA) ICH	0.67/2.00	14087	43130
5	HR (TIC + ASA) IS	0.22/1.22	36017	9483
6	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	14784	38980
7	HR (mortality) (TIC + ASA) Sudden cardiac death	0.25/0.86	31713	12506
8	HR (mortality) (TIC + ASA) Other CV death	0.25/0.86	27410	13761
9	Age of patients	61.20/74.80	15125	28759
10	Event free transitions ASA - IS	0.00158/0.00329	26178	15597

Refers to CS Table 117. One-way sensitivity analysis results – CAD and PAD subgroup: Rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 305

Figure 36. Tornado diagram – CAD and PAD subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin



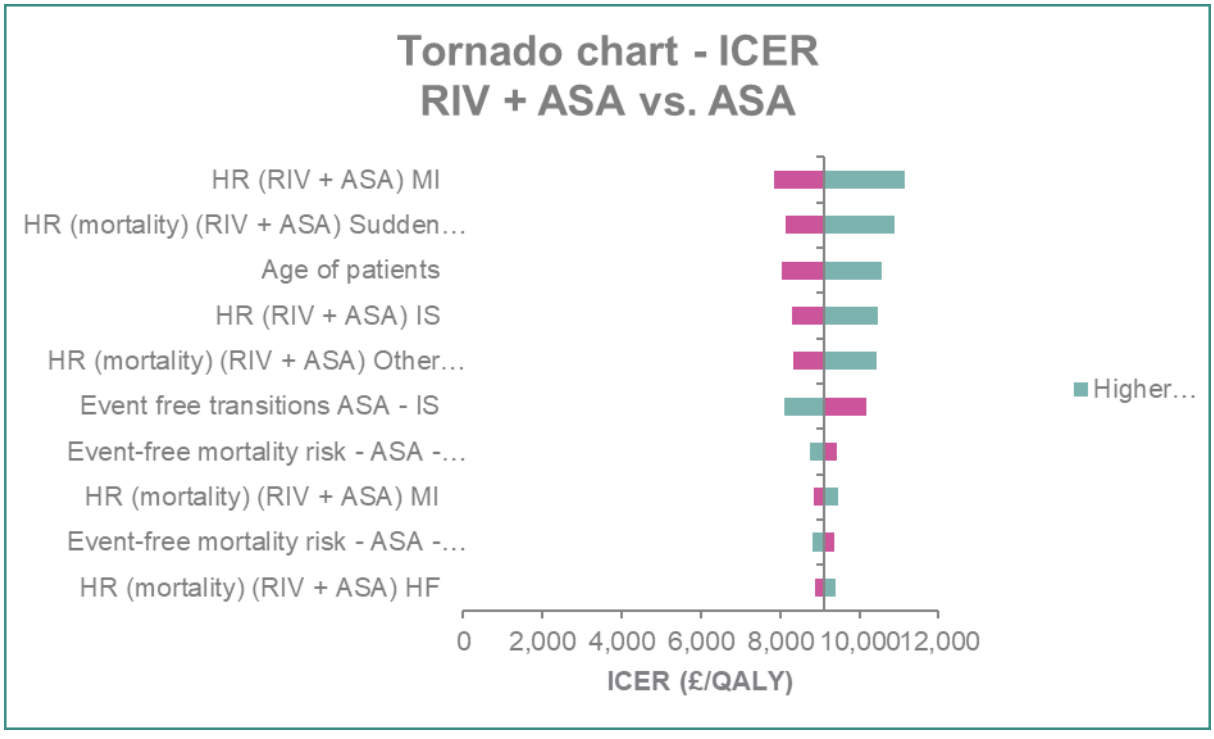
Refers to CS Figure 46. Tornado diagram – CAD and PAD subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 305

Table 41. One-way sensitivity analysis results – CAD and HF subgroup: rivaroxaban + aspirin vs aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	7832	11137
2	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	8127	10876
3	Age of patients	58.50/71.50	8032	10561
4	HR (RIV + ASA) IS	0.38/0.69	8287	10480
5	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	8321	10424
6	Event free transitions ASA - IS	0.00173/0.00341	10193	8116
7	Event-free mortality risk - ASA - Sudden cardiac death	0.0016/0.0032	9440	8759
8	HR (mortality) (RIV + ASA) MI	0.64/0.96	8838	9478
9	Event-free mortality risk - ASA - Other CV death	0.0011/0.0025	9381	8805
10	HR (mortality) (RIV + ASA) HF	0.64/0.96	8888	9404

Refers to CS Table 119. One-way sensitivity analysis results – CAD and HF subgroup: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 310

Figure 37. Tornado diagram – CAD and HF subgroup : rivaroxaban + aspirin vs aspirin



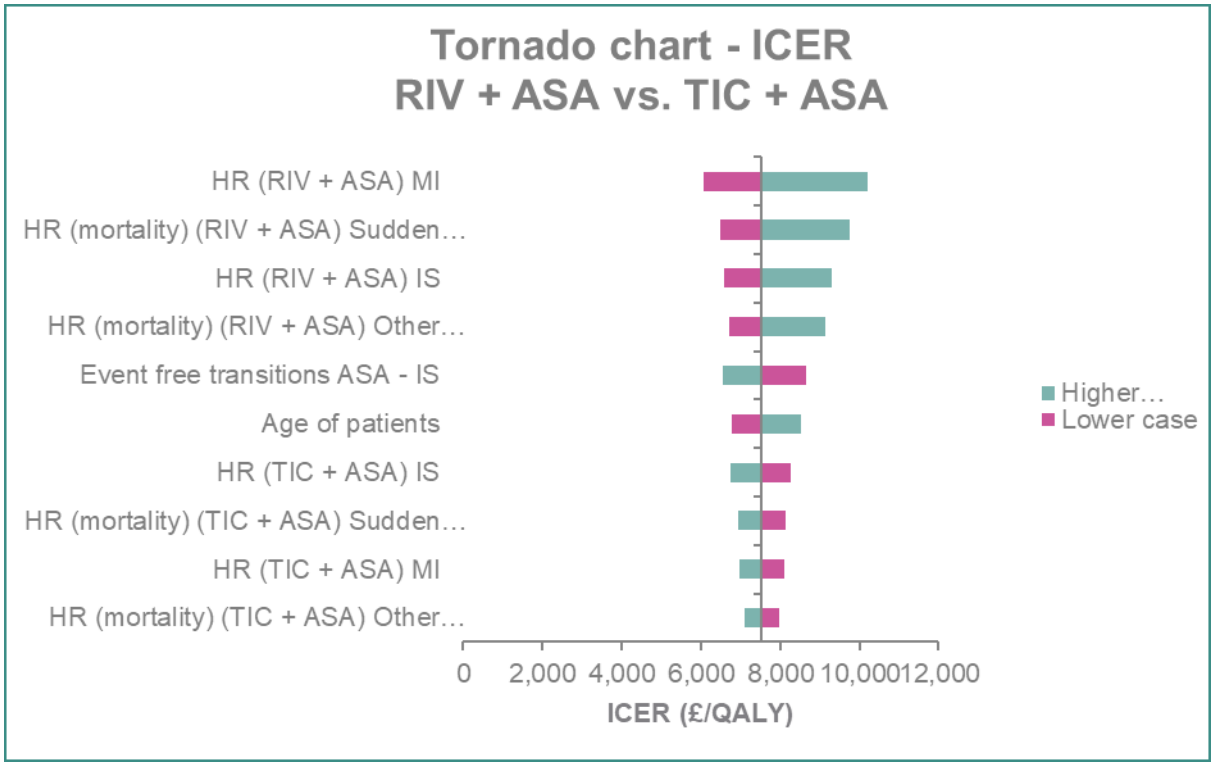
Refers to CS Figure 47. Tornado diagram – CAD and HF subgroup : rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 310

Table 42. One-way sensitivity analysis results – CAD and HF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	6071	10222
2	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	6504	9749
3	HR (RIV + ASA) IS	0.38/0.69	6575	9311
4	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	6708	9132
5	Event free transitions ASA - IS	0.00173/0.00341	8666	6548
6	Age of patients	58.50/71.50	6792	8533
7	HR (TIC + ASA) IS	0.56/1.02	8274	6734
8	HR (mortality) (TIC + ASA) Sudden cardiac death	0.68/1.01	8145	6948
9	HR (TIC + ASA) MI	0.72/0.98	8098	6966
10	HR (mortality) (TIC + ASA) Other CV death	0.68/1.01	7978	7091

Refers to CS Table 120. One-way sensitivity analysis results – CAD and HF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 311

Figure 38. Tornado diagram – CAD and HF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin



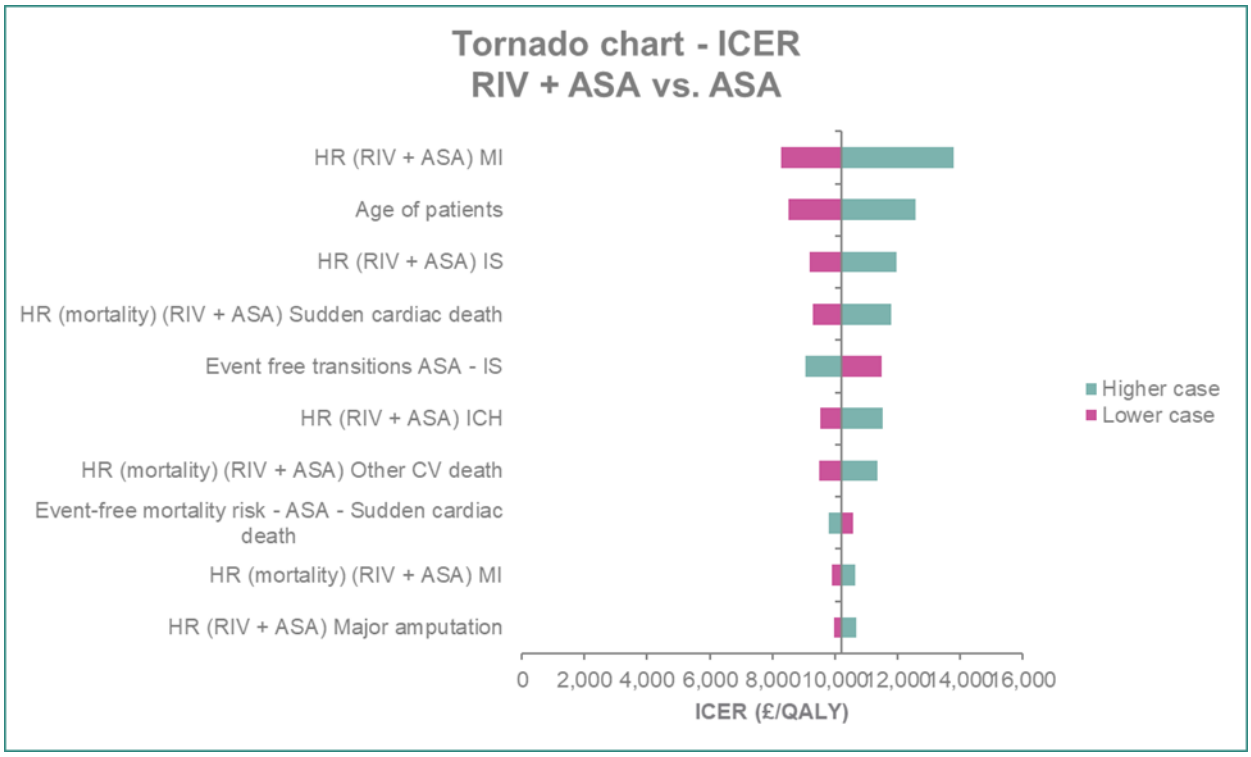
Refers to CS Figure 48. Tornado diagram – CAD and HF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 311

Table 43. One-way sensitivity analysis results – CAD and PRF subgroup: rivaroxaban + aspirin vs aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	8271	13809
2	Age of patients	64.80/79.20	8533	12594
3	HR (RIV + ASA) IS	0.38/0.69	9205	11972
4	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	9285	11812
5	Event free transitions ASA - IS	0.00179/0.00345	11491	9063
6	HR (RIV + ASA) ICH	0.67/2.00	9534	11517
7	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	9488	11374
8	Event-free mortality risk - ASA - Sudden cardiac death	0.0013/0.0027	10596	9813
9	HR (mortality) (RIV + ASA) MI	0.64/0.96	9896	10666
10	HR (RIV + ASA) Major amputation	0.30/1.09	9987	10670

Refers to CS Table 122. One-way sensitivity analysis results – CAD and PRF subgroup: rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 316

Figure 39. Tornado diagram – CAD and PRF subgroup: rivaroxaban + aspirin vs aspirin



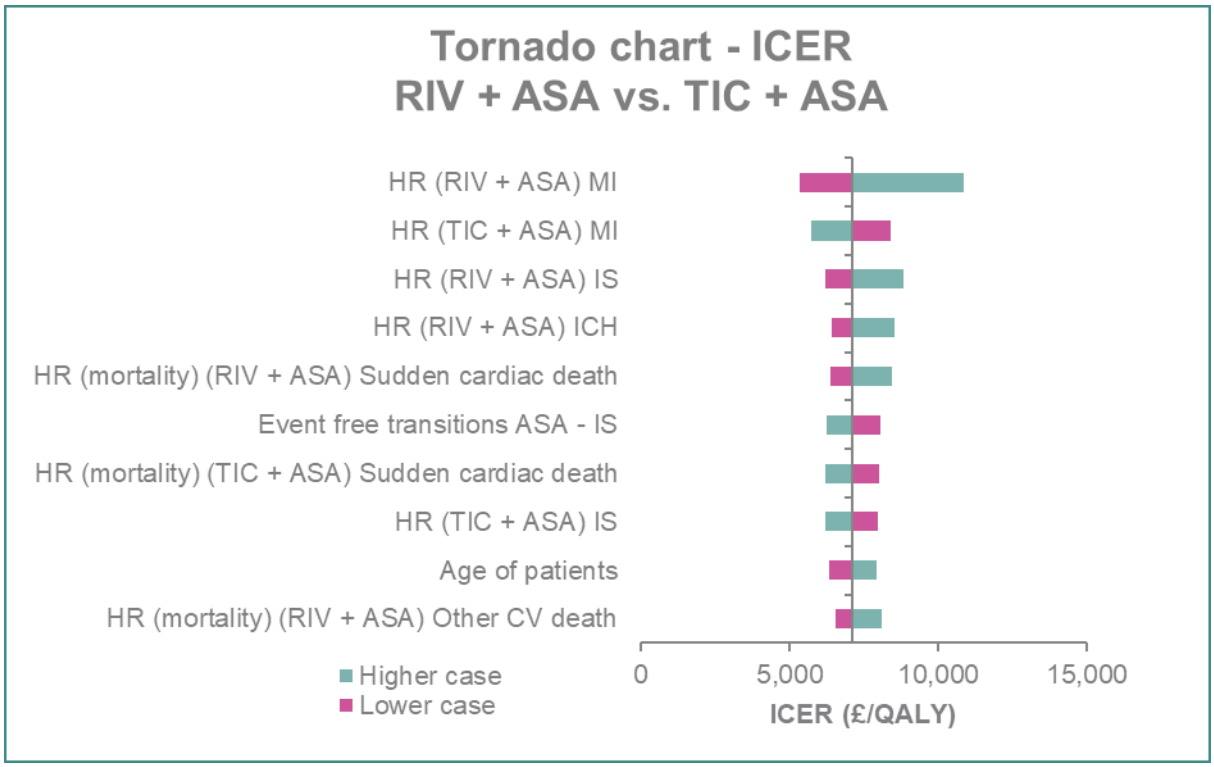
Refers to CS Figure 49. Tornado diagram – CAD and PRF subgroup : rivaroxaban + aspirin vs aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 316

Table 44. One-way sensitivity analysis results – CAD and PRF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin

Rank	Model input	Lower/Upper bound	Lower bound	Upper bound
1	HR (RIV + ASA) MI	0.70/1.05	5338	10863
2	HR (TIC + ASA) MI	0.57/1.00	8423	5747
3	HR (RIV + ASA) IS	0.38/0.69	6189	8850
4	HR (RIV + ASA) ICH	0.67/2.00	6407	8522
5	HR (mortality) (RIV + ASA) Sudden cardiac death	0.64/0.96	6399	8469
6	Event free transitions ASA - IS	0.00179/0.00345	8072	6256
7	HR (mortality) (TIC + ASA) Sudden cardiac death	0.74/1.37	8008	6220
8	HR (TIC + ASA) IS	0.56/1.02	7976	6214
9	Age of patients	64.80/79.20	6315	7916
10	HR (mortality) (RIV + ASA) Other CV death	0.64/0.96	6547	8089

Refers to CS Table 123. One-way sensitivity analysis results – CAD and PRF subgroup: rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 317

Figure 40. Tornado diagram – CAD and PRF subgroup : rivaroxaban + aspirin vs ticagrelor + aspirin



Refers to CS Figure 50. Tornado diagram – CAD and PRF subgroup : rivaroxaban + aspirin vs ticagrelor + aspirin, Appendix B, B.3.8 Sensitivity analysis, Deterministic sensitivity analysis, page 317

Scenario analyses results

Table 45. Scenario analysis results – COMPASS population

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		**£14,193**	**£11,434**
Time horizon	15 years	£19,778	£16,330
Treatment duration	5 years	£12,920	£5,488
Treatment discontinuation	4 years	£14,436	£12,412
	Duration of model	£14,015	£10,562
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	-	£11,368
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£14,193	£11,436
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£14,115	£11,355
Second event assumptions – utilities	Based on most recent event utility	£14,234	£11,473
Utilities inputs	Repeated measures mixed model	£13,272	£10,690
	Ticagrelor TA 420	£13,406	£10,811
Transition from event free to two events in one cycle	COMPASS data	£13,827	£11,117
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£14,465	£11,770
Discount rates	0%	£11,408	£9,930
	5%	£15,527	£12,084

Refers to CS Table 125. Scenario analysis results – COMPASS population, Appendix B, B.3.8 Sensitivity analysis, Scenario analysis, page 320

Table 46. Scenario analysis results – CAD and PAD subgroup

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		**£10,054**	**£19,923**
Time horizon	15 years	£12,254	£50,744
Treatment duration	5 years	£9,020	Dominated
Treatment discontinuation	4 years	£10,345	£16,040
	Duration of model	£9,848	£27,463
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	-	£19,980
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£10,052	£19,925
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£10,055	£19,877
Second event assumptions – utilities	Based on most recent event utility	£10,053	£19,946
Utilities inputs	Repeated measures mixed model	£9,399	£18,680
	Ticagrelor TA 420	£9,454	£18,977
Transition from event free to two events in one cycle	COMPASS data	£9,889	£18,985
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£10,193	£20,552
Discount rates	0%	£8,533	£14,513
	5%	£10,766	£23,312

Refers to CS Table 126. Scenario analysis results – CAD and PAD subgroup, Appendix B, B.3.8 Sensitivity analysis, Scenario analysis, page 321

Table 47. Scenario analysis results – CAD and HF subgroup

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		**£9,105**	**£7,541**
Time horizon	15 years	£11,790	£9,920
Treatment duration	5 years	£8,489	£4,120
Treatment discontinuation	4 years	£9,221	£8,012
	Duration of model	£9,013	£7,114
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	-	£7,517
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£9,105	£7,541
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£9,063	£7,507
Second event assumptions – utilities	Based on most recent event utility	£9,121	£7,555
Utilities inputs	Repeated measures mixed model	£8,911	£7,380
	Ticagrelor TA 420	£8,968	£7,436
Transition from event free to two events in one cycle	COMPASS data	£8,965	£7,381
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£9,316	£7,781
Discount rates	0%	£11,790	£6,736
	5%	£7,625	£7,880

Refers to CS Table 127. Scenario analysis results – CAD and HF subgroup, Appendix B, B.3.8 Sensitivity analysis, Scenario analysis, page 322

Table 48. Scenario analysis results – CAD and PRF subgroup

Model input	Parameter value	ICER Rivaroxaban + aspirin vs. aspirin	ICER Rivaroxaban + aspirin vs. ticagrelor + aspirin
Base case		**£10,216**	**£7,119**
Time horizon	15 years	£11,859	£8,010
Treatment duration	5 years	£9,413	£3,860
Treatment discontinuation	4 years	£10,430	£7,922
	Duration of model	£10,060	£6,474
Hazard ratios	Replaced by RIV+ASA HRs vs ASA	-	£7,119
Second event assumptions - costs	Acute state and Post-acute state – cost of most recent event	£10,215	£7,119
	Acute state – cost of acute state second event + post-acute cost first event Post-acute state – sum of both events post-acute costs	£10,213	£7,146
Second event assumptions – utilities	Based on most recent event utility	£10,219	£7,120
Utilities inputs	Repeated measures mixed model	£9,953	£6,936
	Ticagrelor TA 420	£9,475	£7,248
Transition from event free to two events in one cycle	COMPASS data	£10,127	£7,041
Health states and health events costs	Walker et al. 2016 Table A5 - Incremental cost of non-fatal MI/IS/ICH Cost in first 90-day periods	£10,441	£7,305
Discount rates	0%	£8,755	£6,738
	5%	£10,893	£7,257

Refers to CS Table 128. Scenario analysis results – CAD and PRF subgroup, Appendix B, B.3.8 Sensitivity analysis, Scenario analysis, page 323

Appendix 4 – Clinical results for CAD + recent MI subgroup

Table 49. Recent MI (1-3 years prior) subgroup: Number of subjects and incidence rates (ITT population) – efficacy and safety endpoints

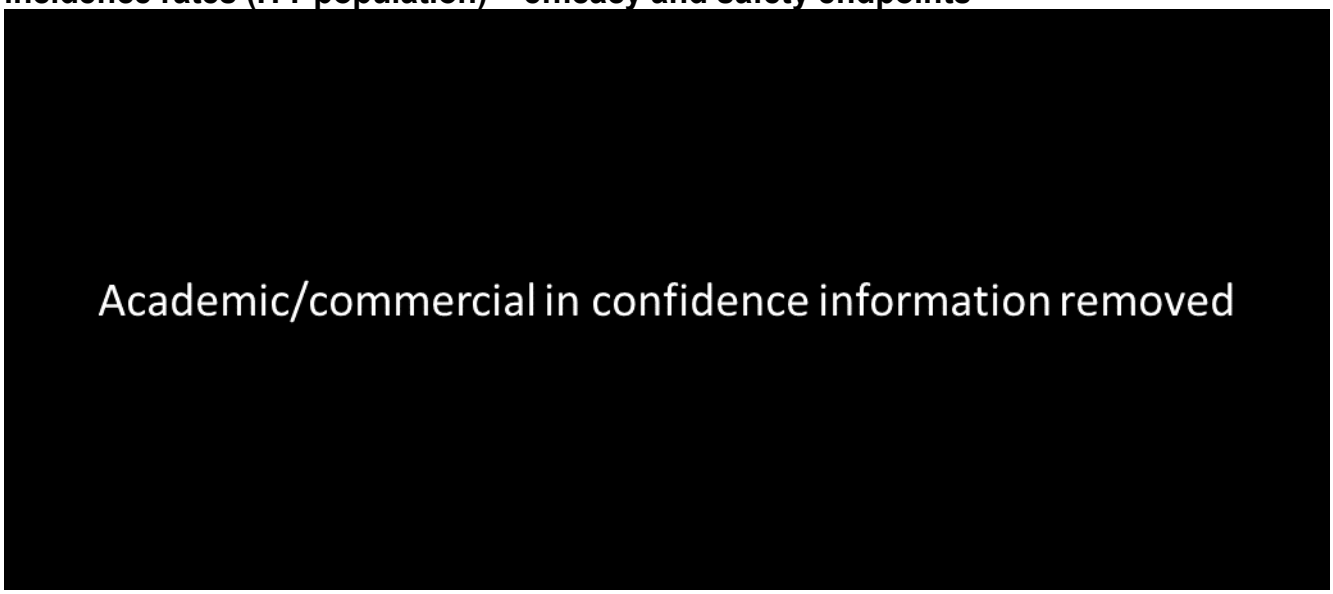
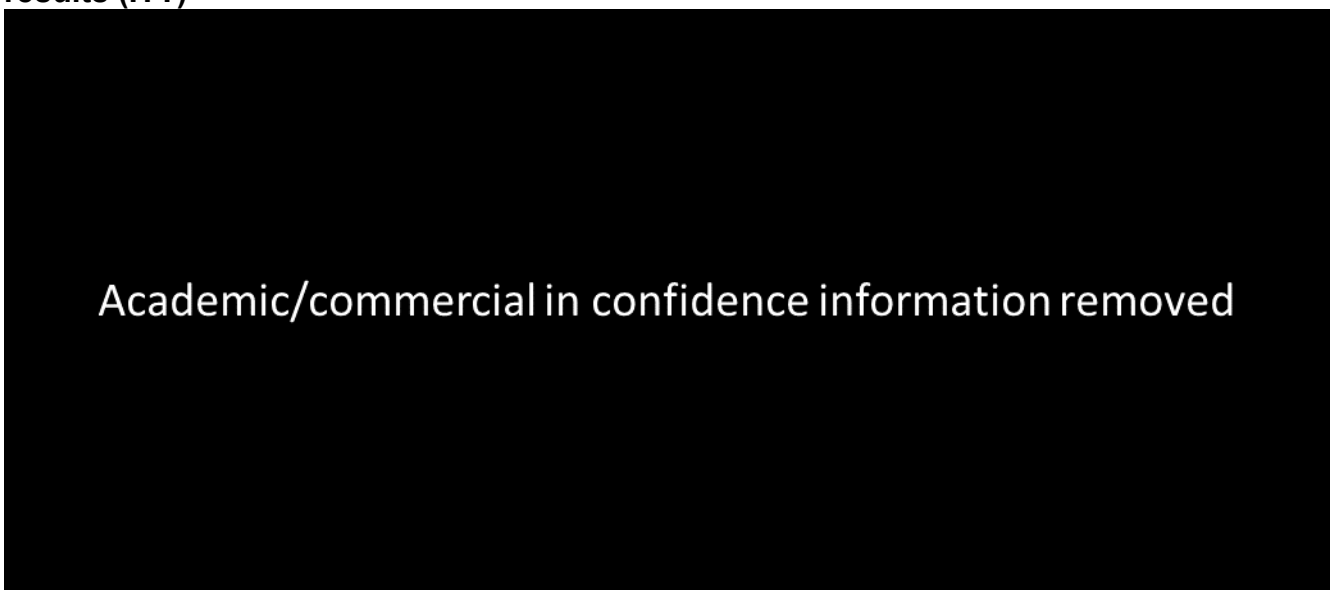


Table 50. Recent MI (1-3 years prior): primary and secondary efficacy/safety results (ITT)



Appendix 5 – Transition probabilities for CAD + recent MI patients

Table 51. Aspirin transition probabilities - three-month risk of main events in patients with no modelled history of main events

Initial health state	Final health state	Three-month risk
Event free	MI	0.00233
	IS	0.00184
	ICH	0.00029

Table 52. Aspirin transition probabilities - three-month risk of second main events applied to those with one modelled main event

	Time since first event	
	0-3 months	**3+ months**
Following a first MI3-6 months		
MI	0.0000	0.0357
IS	0.0000	0.0000
ICH	0.0000	0.0000
Following a first IS		
MI	0.0000	0.0000
IS	0.0000	0.0200
ICH	0.0000	0.0000
Following a first IC		
MI	0.0000	0.0000
IS	0.0000	0.0000
ICH	0.0000	0.0000

Table 53. COMPASS three-month death rates considered in the model (except combined health states)

	Three-month mortality risk in event-free patients (ASA arm)
Death due to MI	0.00019
Death due to stroke (HS or IS)	0.00010
Death due to HF	0.00000[1]
Death following CV procedure	0.00000[2]
Sudden cardiac death	0.00097
Other CV death	0.00682
Fatal bleeding	0.00010

	Three-month mortality risk after a first event (ASA arm)	
	Acute	**Post-acute**
	0-3 months	**3+ months**
	Three-month mortality risk in patients with one MI since the model commenced	
Death due to MI	0.00000	0.00000
Death due to stroke (HS or IS)	0.00000	0.00000
Death due to HF	0.00000	0.00000
Death following CV procedure	0.00000	0.00000
Sudden cardiac death	0.00000	0.00000
Other CV death	0.00000	0.01786
Fatal bleeding	0.00000	0.00000
	Three-month mortality risk in patients with one IS since the model commenced	
Death due to MI	0.00000	0.00000
Death due to stroke (HS or IS)	0.00000	0.00000
Death due to HF	0.00000	0.02000
Death following CV procedure	0.00000	0.00000
Sudden cardiac death	0.00000	0.02000
Other CV death	0.00000	0.00000
Fatal bleeding	0.00000	0.00000
	Three-month mortality risk in patients with one ICH since the model commenced	
Death due to MI	0.00000	0.00000
Death due to stroke (HS or IS)	0.00000	0.00000
Death due to HF	0.00000	0.00000
Death following CV procedure	0.00000	0.00000
Sudden cardiac death	0.00000	0.00000
Other CV death	0.00000	0.00000
Fatal bleeding	0.00000	0.00000

[1] Overall COMPASS data used in the model – Three-month rate of mortality for HF in the event free state 0.00016

[2] Overall COMPASS data used in the model – Three-month rate of mortality for CV procedure in the event free state 0.00010

Table 54. COMPASS three-month death rates (all CV death) considered in the model (health states for second events)

Health state	Acute state	Post-acute states
	0-3 months	3+ months
2 MIs	0.00000[3]	0.00000
2 IS	0.00000	0.00000
2 ICH	0.00000	0.00000
MI then IS	0.00000	0.00000
MI then ICH	0.00000	0.00000
IS then MI	0.00000	0.00000
IS then ICH	0.00000	0.00000
ICH then MI	0.00000	0.00000
ICH then IS	0.00000	0.00000

Table 55. Aspirin health event three-month probabilities

	Three-month probability
Major extracranial non-fatal bleed (modified ISTH criteria)	0.000477
ALI	0.000095
Minor amputation	0.000095
Major amputation	0.002098
VTE	0.004960

[3] Overall COMPASS data used – Three month death rate after two events 0.11111

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Technical engagement response form

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- Do not use abbreviations.
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About you

Your name	**Keith AA Fox (Professor of Cardiology)**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No past or current, direct or indirect links to, or funding from, the tobacco industry**

Questions for engagement

Issue 1: Should the focus be on the whole population or 'high risk' subgroups?	

Should rivaroxaban be considered for the whole population for whom it is licensed, or only for people considered to be at higher risk of ischaemic events?	**The COMPASS trial included patients at elevated cardiovascular risk, based on evidence of peripheral and/or coronary artery disease. Those with coronary artery disease and below 65 yrs of age were required to have additional risk enrichment factors:**
	• **Age <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors**
	  ○ **Current smoker**
	  ○ **Diabetes mellitus**
	  ○ **Renal dysfunction (eGFR<60 ml/min)**
	  ○ **Heart failure**
	  ○ **Non-lacunar ischaemic stroke ≥1 month ago**
	The results of the COMPASS trial demonstrate consistent benefits for the rivaroxaban + aspirin strategy across the full included population. No heterogeneity of effects is seen.
	Thus the evidence supports treatment for the whole population in line with the enrichment criteria. Clinicians will judge the combination of risk features, and bleeding risks to decide on whether the COMPASS regimen is appropriate. I do not believe that it should be restricted to the heart failure, poor renal function or disease in 2 vascular beds as patients with other risk features have similar benefits, For example those with previous MI, those with prior (non-lacunar) ischaemic stroke and those with diabetes.
	In other related settings (PEGASUS regimen of ticagrelor 1 to 3 years after MI, plus aspirin)

	clinicians in the NHS have chosen to implement this therapy in only a selected small proportion of the potentially eligible population. This suggests that clinicians will likely also weigh up risks and benefits across the COMPASS eligible population and choose patients to treat based on a combination of risk factors (ie not necessarily only those proposed by the company).
Are the subgroups presented by the company clinically relevant and do they represent a population at high baseline risk of thrombotic events as suggested by the company?	**As indicated above, those patients with peripheral artery disease and those patients with coronary artery disease and markers of higher risk (see above) show clear and consistent evidence of benefit. No heterogeneity of effects of the COMPASS regimen was seen. For the reasons listed above I do not believe that it is appropriate to restrict use to only the subgroups (CAD + PAD or CAD plus poor renal function or heart failure) as other higher risk groups were included in the COMPASS inclusion criteria and demonstrated similar benefit. Clinicians are likely to weigh up all the risk factors that were enrichment factors in COMPASS, and the bleeding risks, before making their recommendations in discussion with the patient.**
If high risk subgroups are appropriate, should treatment effects be based on the hazard ratios for the whole population, or is it appropriate to accept different treatment effects in the different groups?	**In my view the treatment should not be restricted to the 3 "high risk subgroups" identified by the company as consistency of treatment effects was demonstrated across the included population without evidence of heterogeneity. I believe that clinicians can weigh up risks and potential benefits in deciding who should be treated, as they currently do for prolonged dual anti-platelet therapy (for example the PEGASUS regimen beyond a year after MI).**
Issue 2: Exclusion of clopidogrel as a comparator for people with PAD	
Is it reasonable to exclude clopidogrel as a relevant comparator for the overall COMPASS trial population and the subgroup of people with CAD and PAD?	**Clopidogrel has not been tested in the COMPASS trial. As all the guidelines (UK and ESC) recommend aspirin as the antiplatelet agent for patients with chronic CAD, clopidogrel is only recommended in chronic CAD patients who cannot tolerate aspirin (for example due to true hypersensitivity to aspirin). Therefore such patients intolerant of aspirin would not be eligible for the COMPASS regimen. I believe that this indicates that clopidogrel is not a**

	relevant comparator.
Is clopidogrel used in clinical practice in the NHS to treat people with stable CAD and/or PAD at high risk of ischaemic events or the subgroup of people with CAD and PAD?	**Clopidogrel is not first line guideline treatment for patients with chronic coronary artery disease. Based on guidelines clopidogrel is an option for treatment of patients with peripheral artery disease. However, in the CAPRIE study, clopidogrel showed a modest 8.7% relative (0.5% absolute) risk reduction compared with aspirin. By comparison, the rivaroxaban plus aspirin treatment in COMPASS shows a substantially greater 28% relative (2% absolute) risk reduction (unlike the CAPRIE trial, in COMPASS this was on top of well treated secondary prevention) and it also reduced acute limb events and amputations. (Anand et al Lancet 2017). Thus for patients with CAD plus PAD, for whom aspirin was the prior anti-platelet of choice, then the COMPASS regimen is a relevant option.**
Issue 3: Comparison with ticagrelor + aspirin in people with history of MI	
Is the subgroup of people with MI clinically relevant and important?	**Patients with prior MI are part of the CAD cohort, but COMPASS is not a "post MI study". Only 34% patients with prior MI had the MI within 5 years of randomisation into COMPASS, and only 5% in the first year after MI. Thus COMPASS should not be considered as just a post-MI trial.**
Would limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population reduce the uncertainty in the treatment effect of rivaroxaban+ aspirin when comparing to ticagrelor + aspirin?	**It is not appropriate to align with the PEGASUS population as in PEGASUS 100% of patients were included (1 to 3 yrs after MI) and after one year of treatment with a P2Y12 antagonist (usually ticagrelor or clopidogrel) + aspirin. Such dual antiplatelet therapy is recommended by guidelines and commenced immediately after MI. Only 5% of the COMPASS CAD patients had their MI within the prior year (Connolly et al Lancet 2017). If a patient had an indication for dual antiplatelet therapy they were not eligible for inclusion in COMPASS. Thus, the COMPASS regimen could be considered after dual anti-platelet therapy, but not an alternative to dual anti-platelet therapy (for example in the early period after MI or after stent). Approaches to "align" the COMPASS and PEGASUS populations are hazardous not only because of the differences in baseline characteristics and duration after MI, but also because the PEGASUS population was exposed to dual antiplatelet**

	therapy during the first year after MI (they were not naive to dual anti-platelet therapy and hence those with bleeding complications during the first year after MI would not likely be included in PEGASUS). The median time since MI (in those that had prior MI) in COMPASS was 7 years so the situation was different and patients were on just aspirin at baseline. If they required dual anti-platelet therapy, or if they were on an antiplatelet other than aspirin they were not eligible for COMPASS (Canadian Journal of Cardiology 33 (2017) 1027e1035).
Is the (modified) ISTH classification used in clinical practice in the NHS to define major bleeds?	**The modified ISTH classification is not widely used in the NHS. This modified ISTH classification for major bleeds is broader than the original ISTH definition as it includes patients that attended a clinical facility for a bleed but could be discharged without hospital admission and without transfusion or surgical procedures. Thus with rivaroxaban plus aspirin there were 3.1% major bleeds with the modified ISTH definition but only 2.3% with the original ISTH definition (Eikelboom et al 2019 under review)**
Are the ISTH and TIMI classification methods used to define major bleeds sufficiently similar and able to identify the same number of major bleeds in the same population?	**No, ISTH and TIMI major bleeds are not sufficiently similar. TIMI major bleeds (these have more severe BARC criteria) were associated with increased one year mortality whereas ISTH bleeds were not (Published by the Academic Research Consortium J Am Coll Cardiol. 2014 May 13;63(18):1866-75).**
Issue 4: Transition probabilities for main events (MI, stroke, CV death) in the economic model	
What is the preferred source for calculating the probability of experiencing a main event in each cycle of the model when there are no events recorded in the COMPASS trial? Would probabilities calculated using REACH registry data be more appropriate or imputing non-zero values from transition probabilities from other health states (ERG	**Not my area of expertise**

preferred method)?	
Issue 5: Underestimation of impact of CV death on the incremental cost effectiveness ratio (ICER)	
As each death rate only has a fraction of the CV deaths, is it reasonable to vary the HR for all CV deaths in the DSA to adequately capture the uncertainty around this parameter?	**Not my area of expertise**

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Technical engagement response form

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About you

Your name	**Jagdeep S. Singh**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Cardiovascular Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**

Questions for engagement

Issue 1: Should the focus be on the whole population or 'high risk' subgroups?	
Should rivaroxaban be considered for the whole population for whom it is licensed, or only for people considered to be at higher risk of ischaemic events?	**Strict adherence to the evidence would mean it should be considered for the entire population. However, it is reasonable to limit the use of the drug to subgroups with increased risk of ischaemic events. Other groups that are of high thrombotic risk include patients with previous MI / stroke / TIA, multi-vessel coronary disease or extensive stenting. It is important to note that there were no significant interactions for patients with PAD or PRF.** **It seems a little counter-intuitive that the company is seeking to drop PAD indication where that subgroup seemed to derive the most benefit.**
Are the subgroups presented by the company clinically relevant and do they represent a population at high baseline risk of thrombotic events as suggested by the company?	**Yes, the 3 subgroups identified; CAD plus PAD/HF/PRF are clinically relevant and represent patients who are at higher risk of thrombotic events.**
If high risk subgroups are appropriate, should treatment effects be based on the hazard ratios for the whole population, or is it appropriate to accept different treatment effects in the different groups?	**The appraisal should consider the entire ITT population as presented in the publication, however it is reasonable to take into account the treatment effects of each subgroup. I agree with the technical team's assessment that there is no between-group heterogeneity, therefore the whole-group treatment effects should be applied. Expert statistical input may be required in this regard.**

Issue 2: Exclusion of clopidogrel as a comparator for people with PAD	
Is it reasonable to exclude clopidogrel as a relevant comparator for the overall COMPASS trial population and the subgroup of people with CAD and PAD?	**Clopidogrel should be included as a comparator for the overall COMPASS analysis as it is frequently used in this population (see below). This analysis should be the performed regardless of the company's licencing strategy.** **Clopidogrel *must* be included as a comparator for the PAD subgroup as it is the current anti-platelet of choice for the condition.**
Is clopidogrel used in clinical practice in the NHS to treat people with stable CAD and/or PAD at high risk of ischaemic events or the subgroup of people with CAD and PAD?	**Yes, it is. Clopidogrel is the drug of choice for PAD and is also used certain subgroups of patients with CAD. These include patients with aspirin allergies or intolerances, it may also be given, instead of aspirin, in patients with concomitant stroke / TIA or PAD.**
Issue 3: Comparison with ticagrelor + aspirin in people with history of MI	
Is the subgroup of people with MI clinically relevant and important?	**Yes, this is a very relevant subgroup. The company is pursuing a primarily CAD indication (with other 'high thrombotic risk' features) for this drug and the previous MI subgroup, arguably, has the highest risk.**
Would limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population reduce the uncertainty in the treatment effect of rivaroxaban+ aspirin when comparing to ticagrelor + aspirin?	**It would certainly help to reduce (but not eliminate) the heterogeneity, especially since only approximately 60% of COMPASS patients had a history of MI, with the majority being more than 2 years old (approx. 30% at least 5 years old). While PEGASUS was an exclusively post-MI trial with a median post-MI duration of 1.7 years. I would expect to see this analysis performed by the company.**
Is the (modified) ISTH classification used in clinical practice in the NHS to define major bleeds?	**No. The various bleeding classifications - ISTH / TIMI / GUSTO are primarily research tools used to define and classify a bleeding event as a major / minor / non-bleeding end-point. In clinical practice, factors such as the site of bleeding, haemodynamic compromise, other comorbidities and organ involvement (eg. Concurrent type II MI with a GI bleed), speed and**

	amount of blood loss are some of the factors considered to define a bleeding as a major bleed requiring active intervention.
Are the ISTH and TIMI classification methods used to define major bleeds sufficiently similar and able to identify the same number of major bleeds in the same population?	**No. The 'modified' ISTH criteria used in COMPASS is far more sensitive than the TIMI criteria and would result in more outcomes.**
Issue 4: Transition probabilities for main events (MI, stroke, CV death) in the economic model	
What is the preferred source for calculating the probability of experiencing a main event in each cycle of the model when there are no events recorded in the COMPASS trial? Would probabilities calculated using REACH registry data be more appropriate or imputing non-zero values from transition probabilities from other health states (ERG preferred method)?	N/A
Issue 5: Underestimation of impact of CV death on the incremental cost effectiveness ratio (ICER)	
As each death rate only has a fraction of the CV deaths, is it reasonable to vary the HR for all CV deaths in the DSA to adequately capture the uncertainty around this parameter?	N/A

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Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Anticoagulation UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**

Questions for engagement

Issue 1: Should the focus be on the whole population or 'high risk' subgroups?	
Should rivaroxaban be considered for the whole population for whom it is licensed, or only for people considered to be at higher risk of ischaemic events?	We note that the SMC has recommended use for the broader population: coronary artery disease or symptomatic peripheral artery disease and… at high risk of ischaemic events. We would suggest that the whole population would be a consistent approach
Are the subgroups presented by the company clinically relevant and do they represent a population at high baseline risk of thrombotic events as suggested by the company?	Our observation is that if these subgroups show significant benefit over other sub populations, priority for access to treatment would provide benefits to patient outcomes
If high risk subgroups are appropriate, should treatment effects be based on the hazard ratios for the whole population, or is it appropriate to accept different treatment effects in the different groups?	Unable to comment
Issue 2: Exclusion of clopidogrel as a comparator for people with PAD	
Is it reasonable to exclude clopidogrel as a relevant comparator for the overall COMPASS trial population and the subgroup of people with CAD and PAD?	Unable to comment
Is clopidogrel used in clinical practice in the NHS to treat people with stable CAD and/or PAD at high risk of ischaemic events or the subgroup of people with CAD and PAD?	Unable to comment

Issue 3: Comparison with ticagrelor + aspirin in people with history of MI	
Is the subgroup of people with MI clinically relevant and important?	Unable to comment
Would limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population reduce the uncertainty in the treatment effect of rivaroxaban+ aspirin when comparing to ticagrelor + aspirin?	Unable to comment
Is the (modified) ISTH classification used in clinical practice in the NHS to define major bleeds?	Unable to comment
Are the ISTH and TIMI classification methods used to define major bleeds sufficiently similar and able to identify the same number of major bleeds in the same population?	Unable to comment
Issue 4: Transition probabilities for main events (MI, stroke, CV death) in the economic model	
What is the preferred source for calculating the probability of experiencing a main event in each cycle of the model when there are no events recorded in the COMPASS trial? Would probabilities calculated using REACH registry data be more appropriate or imputing non-zero values from transition probabilities from other health states (ERG preferred method)?	Unable to comment
Issue 5: Underestimation of impact of CV death on the incremental cost effectiveness ratio (ICER)	
As each death rate only has a fraction of the CV deaths, is it reasonable to vary the HR for all CV deaths in the DSA to adequately capture the	Unable to comment

uncertainty around this parameter?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease [ID1397]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Friday 10 May 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to

the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Cardiovascular Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

Questions for engagement

Issue 1: Should the focus be on the whole population or 'high risk' subgroups?	
Should rivaroxaban be considered for the whole population for whom it is licensed, or only for people considered to be at higher risk of ischaemic events?	**Yes to both.**
Are the subgroups presented by the company clinically relevant and do they represent a population at high baseline risk of thrombotic events as suggested by the company?	**I'd be worried that picking post hoc subgroups where the benefit seemed greater is statistically suspect. Such benefits are in my mind hypothesis generating and would need studied in a prospective RCT before the purported benefits could be assumed to be correct rather than the play of chance in a trial looking at loads of subgroups.** It's not clear to me for example why the presence or absence of renal impairment or heart failure would be something that would be a mechanism to explain increased benefit of rivaroxaban in preventing ischemic events. Patients with both CAD and PAD would be expected to have more ischemic events, since they have more clinically extensive atherosclerotic disease, so that subgroup makes some sense.
If high risk subgroups are appropriate, should treatment effects be based on the hazard ratios for the whole population, or is it appropriate to accept different treatment effects in the different groups?	**I think safer to use the more modest ratios from the whole population, which was the primary endpoint for the trial, for which it was adequately powered.**
Issue 2: Exclusion of clopidogrel as a comparator for people with PAD	
Is it reasonable to exclude clopidogrel as a relevant comparator for the overall COMPASS trial population and the subgroup of people with CAD and PAD?	**Clopidogrel is not often used longterm for patients with CAD only. It is commonly used in those with CAD and PAD and those with PAD alone. If one subgroup that is being**

	considered is the CAD+PAD group, then I would have thought clopidogrel was the obvious comparator.
Is clopidogrel used in clinical practice in the NHS to treat people with stable CAD and/or PAD at high risk of ischaemic events or the subgroup of people with CAD and PAD?	**Yes- As above**
Issue 3: Comparison with ticagrelor + aspirin in people with history of MI	
Is the subgroup of people with MI clinically relevant and important?	**It is common in the UK for patients with an MI in the last year to be on ticagrelor (and Aspirin) although many are still treated with Asp +clopidogrel. Beyond 12 months, it is less common to be on ticagrelor, although there is likely to be a significant minority that are and that this number is likely to be rising in view of PEGASUS. They should all have finished taking ticagrelor by three years following their MI.** I think most cardiologists would be reluctant to coprescribe Aspirin and ticagrelor AND rivaroxaban (for fear of high bleeding risks in an untested combination) so it is likely that there would be a choice between a rivaroxaban containing combination and a ticagrelor containing one.
Would limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population reduce the uncertainty in the treatment effect of rivaroxaban+ aspirin when comparing to ticagrelor + aspirin?	**I suppose, but not sure how valid it is to compare subgroups of different trials.**
Is the (modified) ISTH classification used in clinical practice in the NHS to define major bleeds?	**In clinical practice, we don't classify bleeds at all as far as I'm aware. It's only done in the context of trials. I sit on a different NICE committee (ACS) and they have gone for a hierarchy of bleeding definitions – you could speak to them about it.**
Are the ISTH and TIMI classification methods used to define major bleeds sufficiently similar and able to identify the same number of major bleeds in the same population?	**Doubt it. Bleeding definitions are sometimes quite different and you'd need to check carefully the exact wording used in the two definitions.**

Issue 4: Transition probabilities for main events (MI, stroke, CV death) in the economic model	
What is the preferred source for calculating the probability of experiencing a main event in each cycle of the model when there are no events recorded in the COMPASS trial? Would probabilities calculated using REACH registry data be more appropriate or imputing non-zero values from transition probabilities from other health states (ERG preferred method)?	Don't know to be honest
Issue 5: Underestimation of impact of CV death on the incremental cost effectiveness ratio (ICER)	
As each death rate only has a fraction of the CV deaths, is it reasonable to vary the HR for all CV deaths in the DSA to adequately capture the uncertainty around this parameter?	Don't know

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease

ERG critique of company updated analyses in response to the NICE Technical Engagement Report

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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1. Introduction

This document is the ERG's review and critique of the response by the company (Bayer Plc Ltd) to technical report issued by NICE to experts on 5th April 2019. The ERG received the company's response on 13th May 2019.

The company updated their analyses in respect of some of the questions for engagement below, with tabulated results in their response document and separate appendix. The company also provided an accompanying updated economic model.

Below we take each of the key issues for consideration and comment on the company's response to them.

2. Key issues for consideration

Issue 1 – Should the focus be on the whole population or 'high risk' subgroups?

Questions for engagement	ERG comments
a. Should rivaroxaban be considered for the whole population for whom it is licensed, or only for people considered to be at higher risk of ischaemic events?	The company maintain their position, citing feedback from the medical community that prescribing would be focused on patients at the greatest risk of ischaemic events. The company believes that the large majority of patients who would be considered for treatment with rivaroxaban are captured within their submission. Comments from other experts responding to the technical engagement suggest that there may be other high risk patient subgroups for whom treatment would be considered (e.g. those with previous MI; those with diabetes). They suggested that clinicians are likely to choose patients to treat based on a combination of the individual patient's risk factors (not necessarily only those chosen by the company).
b. Are the subgroups presented by the company clinically relevant and do they represent a population at high baseline risk of thrombotic events as suggested by the company?	The company maintains their rationale for the clinical relevance of the three subgroups, citing literature to support their position (e.g. from the REACH registry). Comments from other experts responding to the technical engagement generally support the clinical relevance of the three subgroups chosen by the company, but note that there are other high risk patient subgroups who would derive similar benefit from rivaroxaban and aspirin.

c. If high risk subgroups are appropriate, should treatment effects be based on the hazard ratios for the whole population, or is it appropriate to accept different treatment effects in the different groups?	The company considers use of subgroup-specific HRs appropriate as this is based on empirical data from the COMPASS trial. As requested during the technical engagement teleconference, the company has produced results using a "fixed hazard ratio (HR) approach", i.e. using the HR from the total COMPASS trial population for the subgroup analyses. These analyses incorporate all the ERG preferences (Appendix 1 of the of the company's Technical engagement response form). The analyses are shown before and after correcting a coding error in of the company's Technical engagement response form (results with coding error in Tables 1 to 4; corrected results Tables 5 to 8). The ERG has checked and verified the analyses and the coding error. The coding error resulted in negative transition probabilities and the ERG agrees with the correction made by the company. The ERG notes the following with regard to the analyses: • In tables 5-8 of the company's Technical engagement response form, the total QALYs for ticagrelor + aspirin and rivaroxaban + aspirin have been transposed. • The company has only used fixed HRs for the rivaroxaban + aspirin arm. For the ticagrelor + aspirin arm, HRs for the three respective subgroups of the PEGASUS trial are used. For consistency, the ERG considers that fixed HRs should also be used for the ticagrelor + aspirin arm (i.e. the HR for the whole PEGASUS trial population). We present analyses using fixed HRs for rivaroxaban + aspirin (COMPASS trial) and the ticagrelor + aspirin arm (PEGASUS trial) in Tables 1-3 below. These changes only alter the results for ticagrelor + aspirin. The ERG notes that the results are similar for the HR fixed analyses to those with subgroup specific HR analyses.

Table 1 Base case incremental cost-effectiveness results – CAD and PAD subgroup using fixed HRs (with code correction)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	13976	7.10				
Ticagrelor + aspirin	15578	7.21	1602	0.11	7807	
Rivaroxaban + aspirin	17382	7.44	1804	0.23	10054	14878

Table 2 Base case incremental cost-effectiveness results – CAD and HF, using fixed HRs (with code correction)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	11801	7.63				
Ticagrelor + aspirin	13542	7.76	1741	0.14	12869	Extendedly dominated
Rivaroxaban + aspirin	15952	8.09	2409	0.32	9105	

Table 3 Base case incremental cost-effectiveness results – CAD and PRF (with code correction)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Aspirin monotherapy	11793	6.64				
Ticagrelor + aspirin	13439	6.75	1646	0.11	14792	Extendedly dominated
Rivaroxaban + aspirin	15079	6.96	1640	0.21	10216	

Issue 2 – Exclusion of clopidogrel as a comparator for people with PAD

Questions for engagement	ERG comments
a. Is it reasonable to exclude clopidogrel as a relevant comparator for the overall COMPASS trial population and the subgroup of people with CAD and PAD?	The company cites NICE clinical guidelines which recommend long-term maintenance with aspirin for secondary prevention of cardiovascular disease. Clopidogrel is only recommended if aspirin is contraindicated or there is hypersensitivity to aspirin. If rivaroxaban is to be added to aspirin then clopidogrel cannot be considered as a comparator.
b. Is clopidogrel used in clinical practice in the NHS to treat people with stable CAD and/or PAD at high risk of ischaemic events or the subgroup of people with CAD and PAD?	The company states that clopidogrel monotherapy is used in stable CAD patients in the NHS who are unable to take aspirin. Comments from other experts responding to the technical engagement suggest that clopidogrel is used in patients with CAD and PAD, and PAD alone.

Issue 3 – Comparison with ticagrelor + aspirin in people with history of MI

Questions for engagement	ERG comments
a. Is the subgroup of people with MI clinically relevant and important?	The company acknowledges that patients with MI are clinically relevant but, based on medical advice, history of MI alone (i.e. without other risk factors) is insufficient to warrant an additional treatment to aspirin such as rivaroxaban.
b. Would limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population reduce the uncertainty in the treatment effect of rivaroxaban+ aspirin when comparing to ticagrelor + aspirin?	The company reiterates their rationale for not including people with a history of MI as a subgroup. Namely, absence/presence of MI was not effect-modifying for the primary outcome of the COMPASS trial; and the requirement for a recent MI is a feature of the marketing authorisation for ticagrelor, but not rivaroxaban, thus they consider ticagrelor to be a “minor comparator”. The company also points out that using MI subgroup-specific HRs conflicts with the recommendation to use fixed (whole trial) HRs for subgroup analyses (see Issue 1). Furthermore, such a subgroup analysis would be post-hoc and based on a

	subset of patients who had a previous MI *and* restricted to MI in the last three years. The ERG acknowledges this as a limitation, and thus any MI subgroup analysis should only be considered to be illustrative rather than confirmatory. Comments from other experts responding to the technical engagement note the heterogeneity between patients in the COMPASS and PEGASUS trials (in terms of prior treatment history in those with a previous MI). This heterogeneity makes comparisons between the two trials problematic. Despite the above reservations. The company has provided analyses using a subgroup restricted to patients having had an MI one to three years prior to enrolment in the trial. The company has produced two analyses: MI subgroup-specific HRs (Table 9) and fixed HRs (from the whole COMPASS population) using transition probabilities for the subgroup who had a previous MI (Table 10). The ICERs in Table 9 are slightly higher than the ERG MI subgroup scenario analysis previously reported in the ERG report (Table 75), and the results in Table 10 are similar to those produced for fixed HRs (Table 5 – corrected company base case). The results of the company's analyses show that the ICERs for rivaroxaban and aspirin remained below £20,000 per QALY gained for the recent MI patient subgroup. The ERG has attempted to reproduce these analyses using the transition probabilities in Appendix 5 of the of the company's Technical engagement response form and hazard ratios in Appendix 4 but is unable to replicate the results shown in Table 9 and 10 of the company's Technical engagement response form.
c. Is the (modified) ISTH classification used in clinical practice in the NHS to define major bleeds?	The company states that this classification score is used in clinical trials but not used in clinical practice. This concurs with comments from other experts responding to the technical

	engagement and expert clinical advice to the ERG (stated in the ERG report).
d. Are the ISTH and TIMI classification methods used to define major bleeds sufficiently similar and able to identify the same number of major bleeds in the same population?	The company notes (as per their original submission to NICE) that the modified ISTH criteria has a broader definition of major bleeds compared to TIMI and therefore the ISTH would classify more bleeds as major than TIMI. This reflects the views of the experts responding to the technical engagement. The company also states that they are not aware of any evidence that the different classification schemes used in the COMPASS trial and the PEGASUS trial (modified ISTH and TIMI, respectively) would affect the respective hazard ratios versus aspirin (which are used in the economic model).

Issue 4 – Transition probabilities for main events (MI, stroke, CV death) in the economic model

Questions for engagement	ERG comments
a. What is the preferred source for calculating the probability of experiencing a main event in each cycle of the model when there are no events recorded in the COMPASS trial? Would probabilities calculated using REACH registry data be more appropriate or imputing non-zero values from transition probabilities from other health states (ERG preferred method)?	The company agrees that it is more clinically plausible to substitute zero transition probabilities with non-zero values. The company have adjusted the transition probabilities from other sources (i.e. the REACH registry). The ERG has checked the company analyses in Tables 11-14 of the company's Technical engagement response form. The ERG was not able to replicate these results exactly but obtained very similar results. Including the adjustment from the REACH registry for some of the transition probabilities does not significantly change the results for the whole COMPASS population but the results for the subgroups become more cost-effective for rivaroxaban + aspirin by about £2-3,000 per QALY. The ERG agrees with the approach taken by the company and considers that adjusting transition probabilities according to the HR observed in the REACH registry is appropriate.

Issue 5 – Underestimation of impact of CV death on the incremental cost effectiveness ratio (ICER)

Questions for engagement	ERG comments
a. As each death rate only has a fraction of the CV deaths, is it reasonable to vary the HR for all CV deaths in the DSA to adequately capture the uncertainty around this parameter?	The ERG report states that the company has underestimated uncertainty by varying each component of CV death individually. The company comments that "*it is equally valid to argue that the ERG approach overestimates uncertainty. In this context we believe that the results presented by the ERG estimated the extent of context of representing a worst-case view of uncertainty" (*page 20 company technical engagement response form). The company has not provided any alternative analyses and leave both analyses for consideration by the committee. The ERG disagrees with the company's comment and maintain that the standard approach would be to vary the HRs observed in the COMPASS trial, i.e. Total CV death rather than vary the components of CV death individually.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report-updated after technical engagement

Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease

1. Summary of the post-engagement technical report

1.1 This document is the post-engagement version of the technical report for this appraisal. It has been prepared by the **technical team** with input from the lead team and chair of the appraisal committee.

The post-engagement technical report issued by the appraisal committee to help it make decisions at the appraisal committee meeting. A draft version of this technical report was sent out for consultation between 11th March and 8th April 2019. The draft report included a list of issues that have an impact on the certainty of the company's estimates of clinical or cost effectiveness. The aim of the consultation was to seek feedback from consultees and commentators on these issues to help inform the technical team's preferred modelling assumptions.

The aim of the post-engagement version of the technical report is to:

- summarise the feedback that was received on the issues that were identified originally
- explain how the feedback has or has not been helpful in resolving areas of uncertainty

Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the **technical team**
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the **company**, consultees and their nominated clinical experts and patient experts and
- the evidence review group (**ERG**) report.

The technical report should be read with the full supporting documents for this appraisal.

1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. The issues that were considered at technical engagement are described in detail in section 2 below, along with the feedback that was received. The following table summarizes the current status of each issue in terms of the technical team's view on the level of outstanding uncertainty.

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 1 – should the focus be on the whole population or 'high risk' subgroups?	Whether it is appropriate to consider the whole population with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events (marketing authorisation for rivaroxaban) or the 3 subgroups presented by company reportedly at higher baseline risk of thrombotic events. Unclear if there is evidence of between-subgroup heterogeneity in relative treatment effects, therefore should hazard ratios for the whole ITT population be applied to the 'higher-risk' subgroups.	Feedback during engagement was consistent and noted that in order to reduce uncertainty and ensure consistency of approach, the whole COMPASS population should be considered rather than the 3 subpopulations put forward by the company. and aspirin. Additionally, there is little evidence to suggest heterogeneity of treatment effect between the subgroups.	For discussion
Issue 2 – exclusion of clopidogrel as a comparator for people with PAD	Company does not present clinical and cost-effectiveness results versus clopidogrel for the subpopulation of people with combined CAD/PAD, or the overall COMPASS population, despite the NICE scope specifying that clopidogrel is a comparator for people with PAD. There is concern that omitting clopidogrel from analyses will exclude valid comparisons of clopidogrel with rivaroxaban + aspirin in clinically relevant groups of people.	Clopidogrel is a valid comparator for people with PAD (with or without concomitant CAD) based on existing NICE guidance. Clopidogrel is not a valid comparator for the overall COMPASS population because aspirin remains the antiplatelet of choice in people with stable CAD unless it is contraindicated, for example, as a result of hypersensitivity. The committee needs to decide whether it is content to make a recommendation that would include people eligible for clopidogrel in the absence of clinical and cost-effectiveness analysis covering this group.	For discussion

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 3 – comparison with ticagrelor + aspirin in people with history of MI	Whether estimating the relative efficacy of rivaroxaban + aspirin compared with ticagrelor + aspirin with an indirect treatment comparison using the COMPASS and PEGASUS trials is appropriate. There are differences in the 2 trial populations particularly in the proportion of people with a previous MI and expert opinion on whether limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population could reduce the uncertainty in the treatment effect of rivaroxaban+ aspirin when comparing to ticagrelor + aspirin is required.	Feedback during engagement suggested that people with a history of MI represent a subgroup that is at high risk of further ischaemic events. However, limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population would increase uncertainty in the results of the indirect treatment comparison, rather than decrease due to considerable heterogeneity between patients in the COMPASS and PEGASUS trials which makes comparisons between the two trials problematic. Such analyses would be post-hoc and subdivide the COMPASS population twice.	For discussion
Issue 4 – transition probabilities for main events (MI, stroke, CV death) in the economic model	Transition probabilities included in the company model were inconsistent and meant that patients in the acute MI state may have lower probabilities of an event that those in the event-free state. This raised concerns about the face validity of the model as experiencing an event would normally be a risk factor for future events.	Company agreed that that it is more clinically plausible to substitute zero transition probabilities with non-zero values and present scenario analyses using values for transition probabilities from other sources such as the REACH registry. Results incorporated all ERG preferences and used subgroup specific HRs as well as rectified a coding error. The ERG noted that adjustment from the REACH registry for some of the transition probabilities does not significantly change the results for the whole COMPASS population but the results for the subgroups become more cost-effective for rivaroxaban + aspirin by about £2-3,000 per QALY	Agreed

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 5 – underestimation of impact of CV death on the incremental cost effectiveness ratio (ICER)	The economic model underestimates the impact of varying the stratified mortality outcome of 'CV death'. An ERG scenario analysis shows that the model results are more sensitive to changes in the all CV death HR than shown in the company deterministic sensitivity analysis (DSA). The same issue has led to an underestimation of parameter uncertainty in the PSA. The technical team consider that the correct approach is to vary the HR for "all CV deaths" as in the ERG scenario analysis	The company notes that the ERG approach implicitly assumes each component is independent of the others whereas varying all the components together assumes that they are perfectly correlated. It is likely that neither approach is entirely realistic, and the ERG approach may overestimate uncertainty. Therefore, it should be viewed as a worst-case view of uncertainty and both results by the company and ERG be considered by the committee. As the company have not provided alternative analyses, the technical team maintain their original position that the correct approach is to vary the HR for "all CV deaths" between 95% confidence intervals as in the ERG scenario analysis.	Agreed

1.3 Prior to technical engagement the technical team noted that the following issues also have an impact on the company's estimates of clinical and cost effectiveness. However, the technical team did not seek feedback on these points specifically because it was recognised that consultation comments were unlikely to resolve these uncertainties:

- Different classification criteria for the primary safety outcome (major bleeding) used in COMPASS and PEGASUS
- Subgroup analyses are statistically underpowered for efficacy and safety outcomes

- Missing data for the subpopulations in the PEGASUS trial

1.4 No equality issues were identified by the company, consultees and their nominated clinical experts and patient experts.

2. Key issues for consideration

Issue 1 – Should the focus be on the whole population or 'high risk' subgroups?

Background/description of issue	- Rivaroxaban, co-administered with aspirin, has a marketing authorisation "for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events". - The **company** presents evidence for the overall licensed population (people with stable CAD and/or PAD at high risk of ischaemic events) but the submission focuses on 3 subpopulations as follows: **i.** patients with CAD and PAD **ii.** patients with CAD and HF **iii.** patients with CAD and poor renal function (PRF) with eGFR<60ml/min - The NICE scope stated that "If the evidence allows subgroups defined as having a higher risk of a major cardiovascular event will be considered" - Only one of the subpopulations was pre-specified as a subgroup of interest in the COMPASS trial and none of the statistical tests for interaction was significant. Therefore, it might be more appropriate to use the whole trial estimates of hazard ratio for estimating treatment effects in subgroups.
Why this issue is important	It is important to know if the subgroups presented by the company are clinically relevant. Do they represent the people at highest risk of ischaemic events? It is also important to consider how treatment-effects should be estimated for subgroups.
Questions for engagement	a. Should rivaroxaban be considered for the whole population for whom it is licensed, or only for people considered to be at higher risk of ischaemic events? b. Are the subgroups presented by the company clinically relevant and do they represent a population at high baseline risk of thrombotic events as suggested by the company?

	c. If high risk subgroups are appropriate, should treatment effects be based on the hazard ratios for the whole population, or is it appropriate to accept different treatment effects in the different groups?
Technical team preliminary scientific judgement and rationale	- The **technical team** would welcome feedback on whether the appraisal should focus on the whole population with CAD or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events (the marketing authorisation). - The **company** argues that the 3 subgroups they have presented are at higher baseline risk of thrombotic events and stand to benefit the most from treatment with rivaroxaban. Clinical expert opinion on the validity of this statement would be appreciated. - The **technical team** is not convinced that there is evidence of between-subgroup heterogeneity in relative treatment effects and that, therefore, hazard ratios for the whole ITT population should be applied to the 'higher-risk' subgroups.
Summary of comments	Comments from experts: - The subgroups identified by the company are clinically relevant and do represent people who are at greater risk of thrombotic events. Although it would be reasonable to limit the use of rivaroxaban to only these subgroups of people that are at high risk of ischaemic events, there is no between group heterogeneity in treatment effects, therefore the overall population treatment effects should be applied. Furthermore, in order to ensure consistency in approach and to reduce uncertainty arising from using results from subgroups which are small, treatment with rivaroxaban should not be restricted to the 3 high risk subgroups as there is no between group heterogeneity. - Clinicians in the NHS have been prescribing ticagrelor+ aspirin in a smaller and select population than the population recommended by NICE. This suggests that clinicians will also likely select patients to treat with rivaroxaban + aspirin based on a combination of individual patient risk factors and weigh up the bleeding risks and treatment benefits for the whole COMPASS population, rather than considering only the subgroups proposed by the company. - Other groups that are of high thrombotic risk include people with previous MI / stroke, multi-vessel coronary disease, extensive stenting and diabetes. People with risk factors other than the 3 subgroups proposed by the company were included in the COMPASS trial and showed similar treatment benefits Comments from professional organisations: - The whole population should be considered to ensure consistency of approach and to reduce uncertainty.

	Comments from company: - Rationale for the 3 subgroups proposed is based on feedback from clinical experts that prescribing would be focused on patients at the greatest risk of ischaemic events. Literature (for example, from the REACH registry) also supports the clinical relevance of the subgroups. Therefore, although there may be some people with baseline risks that may not be captured within the 3 subgroups, most patients who would be considered for treatment with rivaroxaban would be captured within these subpopulations. - Subgroup-specific hazard ratios (HRs) are appropriate as this is based on observed data from the COMPASS trial. However, to reduce uncertainty, analyses using a "fixed HR approach, that is, using the HR from the overall COMPASS population were presented (also taking into account a coding error which resulted in negative transition probabilities). The analyses showed that using a fixed HR does not produce ICER's in excess of £20,000 per QALY gained. Critique from the ERG: - After checking and verifying the analyses by the company shown in table 1-4 above and the coding error, the ERG agrees with the correction made by the company. However, they note: o The total QALYs for ticagrelor + aspirin and rivaroxaban + aspirin have been transposed in the updated cost-effectiveness results tables provided by the company. o The company has only used fixed HRs for the rivaroxaban + aspirin arm in the updated analyses provided. For the ticagrelor + aspirin arm, HRs for the three respective subgroups of the PEGASUS trial are used. The ERG considers that fixed HRs should also be used for the ticagrelor + aspirin arm (that is, the HR for the whole PEGASUS trial population) for consistency. Analyses using fixed HRs for rivaroxaban + aspirin (COMPASS trial) and the ticagrelor + aspirin arm (PEGASUS trial) show that using fixed HRs only alter the results for ticagrelor + aspirin.
Technical team scientific judgement after engagement	- The experts responding to technical engagement noted that in order to reduce uncertainty and ensure consistency of approach, the whole COMPASS population should be considered rather than the 3 subpopulations put forward by the company. Expert opinion suggests that there may be high-risk groups other than those presented by the company for whom treatment would be considered (for example, those with previous MI; those with diabetes) that would derive similar benefit from rivaroxaban and aspirin. Additionally, there is little evidence to suggest heterogeneity of treatment effect between the subgroups.

Issue 2 – Exclusion of clopidogrel as a comparator for people with PAD

Background/description of issue	- The **company** does not present clinical and cost-effectiveness results versus clopidogrel for the subpopulation of people with combined CAD/PAD, or the overall COMPASS population, despite the NICE scope specifying that clopidogrel is a comparator for people with PAD. - The **company** omitted clopidogrel from its systematic review and did not present any clinical or cost-effectiveness evidence for it. The ERG notes that the omission of clopidogrel may be tied to the fact that the company is not seeking a recommendation for the PAD only population in their CS. Clinical expert advice to the **ERG** shows that clopidogrel is used to treat people with stable CAD and PAD.
Why this issue is important	Although clopidogrel is not relevant for the CAD and HF or CAD and PRF subgroups, it might be considered relevant for the overall COMPASS trial population and for the CAD and PAD subgroup
Questions for engagement	a. Is it reasonable to exclude clopidogrel as a relevant comparator for the overall COMPASS trial population and the subgroup of people with CAD and PAD? b. Is clopidogrel used in clinical practice in the NHS to treat people with stable CAD and/or PAD at high risk of ischaemic events or the subgroup of people with CAD and PAD?
Technical team preliminary scientific judgement and rationale	The **technical team** is concerned that omitting clopidogrel from analyses will exclude valid comparisons of rivaroxaban + aspirin with clopidogrel in clinically relevant groups of people. The company states that it is not seeking a recommendation for the PAD only population. As a consequence, the decision problem set out in the scope is not adequately addressed. Clinical opinion would be valued to determine if clopidogrel is a valid comparator for people with stable CAD and/or PAD at high risk of ischaemic events and subgroup of people with CAD and PAD.

Summary of comments	Comments from experts: - One clinical expert considers that clopidogrel should be included as a comparator for the overall COMPASS population (adult patients with CAD or symptomatic PAD at high risk of ischaemic events) as it is frequently used in this population. It is the current anti-platelet treatment of choice for people with PAD and is also used to treat certain subgroups of people with CAD such as people with aspirin allergies or intolerances. Clopidogrel may also be given instead of aspirin, in patients with concomitant stroke / transient ischaemic attack or PAD. - Another expert does not consider clopidogrel to be a comparator for the overall COMPASS population as clopidogrel is only recommended in chronic CAD patients who cannot tolerate aspirin. People intolerant of aspirin were not be eligible for the COMPASS trial which indicates that clopidogrel is not a relevant comparator for the overall COMPASS population. - Clopidogrel is not often used long-term for patients with CAD only. It is commonly used in those with CAD and PAD and those with PAD alone. In the CAD+PAD subgroup, clopidogrel is an obvious comparator. Comments from company: - NICE guidelines recommend people with stable CAD be maintained long-term with aspirin 75mg daily for secondary prevention of cardiovascular disease. In these guidelines clopidogrel is only recommended if aspirin is contraindicated or if there is hypersensitivity to aspirin. Rivaroxaban cannot be added to aspirin if the patient has a contraindication or hypersensitivity which means that clopidogrel is only an option where rivaroxaban is not – it therefore cannot be considered a comparator. - In the acute setting, patients with CAD may be treated with clopidogrel and aspirin (people with stable CAD treated in the long term are not). Rivaroxaban + aspirin is not being used in acute patients, therefore clopidogrel is not a valid comparator in the long-term.
Technical team scientific judgement after engagement	- Clopidogrel is a valid comparator for people with PAD (with or without concomitant CAD) based on existing NICE guidance. This is in line with the scope for this appraisal. One expert suggests that the benefit of clopidogrel over aspirin is modest in this population. - Clopidogrel is not a valid comparator for the overall COMPASS population because aspirin remains the antiplatelet of choice in people with stable CAD. Clopidogrel is only recommended where aspirin is unsuitable.

Issue 3 – Comparison with ticagrelor + aspirin in people with history of MI

Background/description of issue	- To estimate the relative efficacy of rivaroxaban + aspirin compared with ticagrelor + aspirin, the company carried out an indirect treatment comparison (ITC). The 2 trials included were COMPASS and PEGASUS. The **ERG** notes that although the ITC is methodologically sound, there are some important differences between the patients enrolled in the 2 trials: o the proportion of patients with a prior MI was 100% in PEGASUS but 62% in COMPASS o time elapsed since an MI was restricted to between 1-3 years in PEGASUS whereas patients could have had an MI at any time within the past 20 years in COMPASS o the proportion of patients with PAD was only 5% in PEGASUS but 27% in COMPASS o The primary safety outcome (major bleeding) was defined by the TIMI criteria in PEGASUS but modified ISTH criteria in COMPASS o PEGASUS included sudden unexpected cardiac deaths in the definition of a MI whereas COMPASS excluded (assessed as a CV-related death instead) - The company did not use the results of the ITC in their economic model. Instead HRs from the COMPASS and PEGASUS trials were applied to the transition probabilities for the aspirin only group to calculate transition probabilities for rivaroxaban + aspirin and ticagrelor + aspirin. - NICE guidance TA420 states that ticagrelor is an option for preventing atherothrombotic events in adults who had a MI and who are at high risk of a further event. Thus, for the approximately 38% of patients in the COMPASS trial, who had not experienced a previous MI, ticagrelor is not a relevant comparator. This number may be even smaller as the proportion in the 38% who would have had an MI in the last 2 years is unknown. - Most of the differences in the COMPASS and PEGASUS population relate to the proportion of people with an MI. When queried why the COMPASS trial population in the ITC was not limited to the subgroup with a history of MI, the company said that adjusting the COMPASS population to a subgroup with a history of MI was not necessary because having a 'history of MI' is not effect-modifying for the primary efficacy composite outcome - A scenario analysis by the **ERG** comparing rivaroxaban + aspirin and ticagrelor + aspirin for the subgroup of patients with a prior MI showed rivaroxaban + aspirin is more cost-effective than the company's base case. The **ERG** used HRs for MI, stroke and CV death from subgroup analyses in patients with a previous MI from COMPASS and transition probabilities derived from PEGASUS for MI (for the event-free group).

	The time period for an MI was much longer in COMPASS than in PEGASUS (up to 20 years and 1-3 years, respectively) and the HRs are not restricted to those who had a MI in the last two years in COMPASS (as is the case for people in PEGASUS) so comparison is only illustrative. (see ERG report section 4.4.1.2.1 for more information). - Similarly, a subgroup analysis of people with CAD in COMPASS with an MI in the previous two years showed a more favourable effect on the primary composite efficacy outcome (cardiovascular death, stroke or MI) compared to patients whose previous MI occurred longer ago. The **ERG** speculates that if HRs for patients with an MI in the previous two years were available for all outcomes, the cost-effectiveness results are likely to be more favourable to rivaroxaban than in the **ERG's** scenario analysis. However, given the lack of evidence of heterogeneity in treatment effects, it may be inappropriate to use subgroup specific hazard ratios for these analyses (see issue 1 above).
Why this issue is important	- "People who have had a previous MI" is a subgroup of interest listed in the NICE scope and expert clinical advice to the ERG suggests patients with a prior MI are at risk of recurrent MIs/other events. - A scenario analysis by the ERG shows that rivaroxaban + aspirin may potentially be more cost-effective than the company's base case for the subgroup of patients with a prior MI.
Questions for engagement	a. Is the subgroup of people with MI clinically relevant and important? b. Would limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population reduce the uncertainty in the treatment effect of rivaroxaban+ aspirin when comparing to ticagrelor + aspirin? c. Is the (modified) ISTH classification used in clinical practice in the NHS to define major bleeds? d. Are the ISTH and TIMI classification methods used to define major bleeds sufficiently similar and able to identify the same number of major bleeds in the same population?
Technical team preliminary scientific judgement and rationale	The **technical team** is of the view that analyses limiting the COMPASS population to people with a previous MI (and those with an MI within the previous two years) should be explored by the company in order to align the COMPASS population to that of PEGASUS, all of whom had a previous MI.
Summary of comments	Comments from experts: - One expert notes that as the company is seeking a recommendation for a population of people with primarily CAD at high risk of ischaemic events, people with a history of MI represent a subgroup that may arguably be at highest risk. Limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population would help to reduce the heterogeneity in the 2 trials.

	- In contrast, another expert noted that COMPASS was not designed as a post-MI trial and it would not be appropriate to align it with the PEGASUS population as 100% of patients in PEGASUS had an MI in the previous 1 to 3 years and had had treatment with a P2Y12 antagonist (usually ticagrelor or clopidogrel) + aspirin for a year whereas only 5% of the COMPASS CAD patients had their MI within the prior year. o Patients with an indication for dual antiplatelet therapy were not eligible for inclusion in the COMPASS trial. Therefore. although rivaroxaban +aspirin can be considered as a treatment option after dual anti-platelet therapy, it is not an alternative to dual anti-platelet therapy in the acute setting after an MI. o It is not appropriate to limit the COMPASS population to align with PEGASUS because there are not only differences in baseline characteristics and duration after MI between the two trial populations, but also because the PEGASUS population was exposed to dual antiplatelet therapy during the first year after MI. This means that patients in PEGASUS were not naive to dual anti-platelet therapy and people with bleeding complications during the first year after MI would not likely have been eligible for inclusion in the trial. In contrast, the median time since MI (in COMPASS patients that had prior MI) was 7 years with patients on long term maintenance treatment with aspirin. The baseline bleeding risk in this population would naturally be higher compared to the PEGASUS population. - The modified ISTH classification criteria used to classify bleeds is not widely used in the NHS and is more sensitive than the TIMI classification criteria for bleeds as it includes patients that attended a clinical facility for a bleed but could be discharged without hospital admission and without transfusion or surgical procedures. Comments from the company: - Although people who have had previous MI are a clinically relevant subgroup, clinical expert advice shows that having a history of MI in isolation (that is, without other factors predisposing the patient to higher baseline risk of events) is insufficient reason alone to warrant the addition of rivaroxaban to ongoing treatment with aspirin. Adjusting the COMPASS population to match PEGASUS is not necessary and increases uncertainty: o absence/presence of MI was not effect-modifying for the primary outcome of the COMPASS trial according to a subgroup analysis of the primary efficacy outcome in CAD patients. This showed that there was no significant interaction for the primary outcome according to history of MI. o the requirement for a recent MI is a restriction in the marketing authorisation for ticagrelor. Rivaroxaban does not have this restriction and its target population is not defined by having a history of MI

	○ using MI subgroup-specific HRs conflicts with the preference for fixed (whole trial population) HRs for subgroup analyses (as discussed in Issue 1). ○ subgroup analysis would be post-hoc and would involve subdividing the COMPASS population twice to a subset of patients who had a previous MI *and* restricted to MI in the last three years. This would increase uncertainty in the results rather than decreasing it - Despite these reservations, analyses for the overall COMPASS population restricted to a subgroup of people who had an MI 1-3 years prior to enrolment in the trial are provided (not for the 3 subpopulations proposed by the company). - Results using HRs specific to the CAD + recent MI population and for the CAD + recent MI population but using fixed HRs from the overall COMPASS trial population show that the ICERs for rivaroxaban and aspirin remained below £20,000 per QALY gained for subgroup of people with previous MI. - The TIMI or ISTH bleeding classification scores are not used in clinical practice in the NHS and are tools used in clinical trials for regulatory purposes. The modified ISTH criteria has a broader definition of major bleeds compared to TIMI and would classify more bleeds as major. IMI or ISTH bleeding classification scores are not used in clinical practice in the NHS and are tools used in clinical trials for regulatory purposes. The modified ISTH criteria has a broader definition of major bleeds compared to TIMI and would classify more bleeds as major. - The company also states that they are not aware of any evidence that the different classification scores used in the COMPASS trial and the PEGASUS trial (modified ISTH and TIMI, respectively) would affect the respective hazard ratios versus aspirin. This is important as it is the HRs that are used in the economic model. Critique from the ERG: - The ERG acknowledges that a subgroup analysis restricting the COMPASS population to people with a previous MI would be post-hoc analyses that subdivides the population twice which increases uncertainty in the results. Thus, any MI subgroup analysis should only be considered to be illustrative rather than confirmatory. - The ERG notes that the ICERs in table 8 above are slightly higher than the ERG MI subgroup scenario analysis previously reported in the ERG report (Table 75). The results in table 10 are similar to those produced for fixed HRs (Table 1 – corrected company base case above for the overall COMPASS population). - The ERG was unable to replicate the results of these analyses using data provided by the company

Technical team scientific judgement after engagement	- The technical team is of the view that analyses based on limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population are highly uncertain and are not useful for decision making. - Ticagrelor, in combination with aspirin, is recommended as an option for preventing atherothrombotic events in adults who had a MI in the previous 1-2 years. Given that only 5% of the COMPASS trial population with CAD had had their MI within the prior year, ticagrelor is a valid treatment option for only a small proportion of the overall trial population. Taking this as well the uncertainty in the results of the ITC into account, the committee should discuss the relevance of ticagrelor as a valid comparator for the overall COMPASS population and consider whether the key comparator in this appraisal is aspirin.

Issue 4 – Transition probabilities for main events (MI, stroke, CV death) in the economic model

Background/description of issue	- The transition probabilities (which is the probability of a patient experiencing a main event in each cycle of the model) for the first 4 years of the model are based upon patient-level data from COMPASS and are constant for this period. From the 5th year transition probabilities are informed by data from the REACH registry. - For some transitions from health states other than 'event-free', there were no events recorded in COMPASS. When this was the case, the **company** assigned a probability of having such events to zero, that is, it was assumed that the cohort in certain health states was not at risk of experiencing events. The **company** took this approach on the advice of clinical experts but included a scenario analysis in its submission in which zero transitions had been replaced with non-zero values from the event-free probabilities to reflect the real-life risk. - Furthermore, some of the non-zero probabilities were considered unrealistically low. For example, people in the 'acute MI' health state had a lower probability of MI than those who were event-free. This seems implausible in the light of clinical advice that people who have had a first MI are at higher risk of a second during the first 3 months after the event. **ERG** considers including zero transition probabilities is unrealistic and notes that for some transitions, the transition probabilities appear counter-intuitive, for example where an individual's chance of experiencing another MI is lower after experiencing an MI than before experiencing an MI. - The **ERG** prefers imputing non-zero transition probabilities from transition probabilities from other health states and have incorporated this in their base case based on clinical expert advice demonstrating that the risk of another event during the three months after an event is higher than for those in the event-free group.

	Alternatively, the **ERG** suggests that transition probabilities for events where none was recorded in the trial could be calculated using data from another source, such as the REACH registry. - The **ERG** also highlights that as COMPASS was not powered to detect differences between the subpopulations, some of the HRs used to calculate the TPs for main events particularly for the 3 subpopulations are highly uncertain with wide 95% confidence intervals (principally for intracranial haemorrhage and fatal bleeding).
Why this issue is important	The transition probabilities included in the company model are inconsistent and mean that those patients in the acute MI state may have lower probabilities of an event that those in the event-free state. This raises concerns about the face validity of the model as experiencing an event would normally be risk factor for future events.
Questions for engagement	a. What is the preferred source for calculating the probability of experiencing a main event in each cycle of the model when there are no events recorded in the COMPASS trial? Would probabilities calculated using REACH registry data be more appropriate or imputing non-zero values from transition probabilities from other health states (ERG preferred method)?
Technical team preliminary scientific judgement and rationale	- The technical team agree with the ERG that it is implausible to assume zero risks. Some of the transition probabilities appear counter-intuitive, for example where an individual's chance of experiencing another MI is lower after experiencing an MI than before experiencing an MI. - The technical team would welcome scenario analyses where alternative approaches to calculating TPs for main events (MI, stroke, CV death) are explored. This may include imputing non-zero TPs from TPs from other health states or using other sources such as the REACH registry.
Summary of comments	Comments from company: - Agree that it is more clinically plausible to substitute zero transition probabilities with non-zero values and present scenario analyses using values for transition probabilities from other sources such as the REACH registry. Results incorporate all ERG preferences and use subgroup specific HRs. These analyses also rectify the coding error identified in issue 1. The scenario analysis shows improved ICERS compared to the base case reported in issue 1: Critique from the ERG: - The ERG checked the company scenario analyses results presented in table 10-13 above and could not replicate the results presented by the company although similar results were obtained. - Including the adjustment from the REACH registry for some of the transition probabilities does not significantly change the results for the whole COMPASS population but the results for the subgroups become more cost-effective for rivaroxaban + aspirin by about £2-3,000 per QALY. ERG agrees that adjusting transition probabilities according to the HR observed in the REACH registry is appropriate.

Technical team scientific judgement after engagement	- The technical team agrees with the approach proposed by the ERG and taken by the company to substitute zero transition probabilities values with non-zero values taken from REACH registry.

Issue 5 – Underestimation of impact of CV death on the incremental cost effectiveness ratio (ICER)

Background/description of issue

- The **company's** deterministic sensitivity analyses (DSA) underestimates the impact of varying the stratified mortality outcome of 'CV death'. This has the largest effect on the ICER in scenario analyses carried out by the **ERG**.
- The mortality outcome cardiovascular (CV) death is stratified by death due to MI, stroke, CV procedure, sudden cardiac death, 'other CV death' and 'all CV death'. However, the HR estimates from COMPASS, are for "all CV death" and the same HR is assumed for all stratified death events in the model as for "all CV death". In its DSA (and PSA), the **company** has varied each of these mortality HRs separately. As each death rate only has a fraction of the CV deaths, the effect of varying the HRs individually in the DSA and PSA is small.
- The **ERG** considers that a better approach is to set all CV mortality HRs to vary together, rather than independently. In a scenario analysis, the HRs for all CV death were varied whilst assuming the same HRs for all the CV mortality events. The HRs for mortality due to MI, stroke, HF, CV procedure, sudden cardiac death, other CV death and all CV death were set to the lower and higher 95%CI of the HR for all CV death. These results are shown below and show that the model results are more sensitive to changes in the all CV death HR than shown in the company DSA. Using the upper bound for the HR for all CV death, ICERs are more than £20,000 per QALY for the COMPASS population and the subpopulations for CAD+PAD and CAD+PRF.

One-way sensitivity analysis results for HR CV death using same ranges for all CV death

Population	Comparator	Model input	Lower/Upper bound	Lower bound	Upper bound
COMPASS	Aspirin	HR CV death	0.64/0.96	£11,512	£38,018
COMPASS	Ticagrelor + aspirin	HR CV death	0.64/0.96	£8,060	£69,249
CAD+PAD	Aspirin	HR CV death	0.49/1.07	£5,275	£25,346

CAD+PAD	Ticagrelor + aspirin	HR CV death	0.49/1.07	£4,399	Dominated
CAD+HF	Aspirin	HR CV death	0.47/0.92	£4,380	£12,170
CAD+HF	Ticagrelor + aspirin	HR CV death	0.47/0.92	£3,006	£11,060
CAD+PRF	Aspirin	HR CV death	0.62/1.20	£6,088	Dominated
CAD+PRF	Ticagrelor + aspirin	HR CV death	0.62/1.20	£3,252	Dominated

Source: Table 71 (page 116) of ERG report

This issue also impacted on the company's probabilistic sensitivity analysis (PSA), leading the ERG to argue that parameter uncertainty had been underestimated in the PSA.

Why this issue is important	The economic model underestimates the impact of varying the stratified mortality outcome of 'CV death'. . An ERG scenario analysis shows that the model results are more sensitive to changes in the all CV death HR than shown in the company DSA. The same issue has led to an underestimation of parameter uncertainty in the PSA
Questions for engagement	a. As each death rate only has a fraction of the CV deaths, is it reasonable to vary the HR for all CV deaths in the DSA to adequately capture the uncertainty around this parameter?
Technical team preliminary scientific judgement and rationale	The **technical team** consider that the correct approach is to vary the HR for "all CV deaths" between 95% confidence intervals as in the ERG scenario analysis
Summary of comments	Comments from company: - The approach taken by the ERG implicitly assumes each component is independent of the others. In contrast, varying all the components together assumes that they are perfectly correlated. It is likely that neither approach is entirely realistic that is, none of the components are completely independent nor are they perfectly correlated. - It could be argued that the company analysis underestimates uncertainty, however, it is equally valid to argue that the ERG approach overestimates uncertainty. Therefore, the scenario analysis presented by the ERG should be viewed in the context of representing a worst-case view of uncertainty. The company note that no attempt to provide a 'middle-ground' analysis has been taken given the lack of data to estimate the extent of correlation and both the company results and that of the ERG scenario analysis should be considered by the committee.

	Critique from ERG: - The ERG disagrees with the company's comment and maintain that the standard approach would be to vary the HRs observed in the COMPASS trial that is, total CV death rather than vary the components of CV death individually.
Technical team scientific judgement after engagement	As the company has not provided alternative analyses, the technical team maintains its original position that the correct approach is to vary the HR for "all CV deaths" between 95% confidence intervals as in the ERG scenario analysis.

3. Issues for information

Table 1: List of ICERs and impact of changes on the cost-effectiveness estimate

Alteration	**Technical team rationale**	**rivaroxaban + aspirin vs. aspirin**	**rivaroxaban + aspirin vs. ticagrelor + aspirin**
		ICER	**ICER**
Updated company base case for overall COMPASS population (using subgroup specific HRs, incorporating ERG preferences such as using transition probabilities from REACH registry and model corrections)	**–**	**£14,185***	**Ticagrelor + aspirin is extendedly dominated by the combination of aspirin and rivaroxaban + aspirin.**
Updated company base case for the CAD and PAD population	-	£7,624	£8,639
Updated company base case for the CAD and HF population	-	£6,270	Ticagrelor + aspirin is extendedly dominated by the combination of aspirin and rivaroxaban + aspirin.
Updated company base case for the CAD and PRF population	-	£8,215	Ticagrelor + aspirin is extendedly dominated by the combination of aspirin and rivaroxaban + aspirin.

Using a fixed HR approach and model error correction (overall COMPASS population)	There is little evidence to suggest heterogeneity of treatment effect between the subgroups and experts responding to technical engagement agreed that the whole COMPASS population should be considered rather than the 3 subpopulations put forward by the company	£14,193	Ticagrelor + aspirin is extendedly dominated by the combination of aspirin and rivaroxaban + aspirin.
Using a fixed HR approach and model error correction (CAD + PAD population)	As above	£10,054	£19,923 **
Using a fixed HR approach and model error correction (CAD + HF population)		£9,105	Ticagrelor + aspirin is extendedly dominated by the combination of aspirin and rivaroxaban + aspirin.
Using a fixed HR approach and model error correction (CAD + PRF population)		£10,216	Ticagrelor + aspirin is extendedly dominated by the combination of aspirin and rivaroxaban + aspirin.

*The ERG was not able to replicate this ICER exactly but obtained very similar result.

** The ERG noted that the company only applied fixed HRs for the rivaroxaban + aspirin arm of the COMPASS trial when presenting results using a fixed HR approach. For the ticagrelor + aspirin arm, HRs for the three respective subgroups of the PEGASUS trial were used. The ERG considered that fixed HRs should have been used for the ticagrelor + aspirin arm as well (that is, the HR for the whole PEGASUS trial population) for consistency. When the analyses were repeated using fixed HRs for rivaroxaban + aspirin (COMPASS trial) and the ticagrelor + aspirin arm (PEGASUS trial), results for ticagrelor + aspirin only were altered. The ICER for rivaroxaban+ aspirin compared to ticagrelor + aspirin in the CAD + PAD population decreased to £14,878 per

QALY gained with ticagrelor+ aspirin remaining extendedly dominated in the overall COMPASS population and remaining 2 subgroups.

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Different classification criteria for the primary safety outcome (major bleeding) used in COMPASS and PEGASUS	Major bleeding was defined according to modified ISTH criteria in COMPASS. The modified ISTH is more sensitive and included any bleeding that led to hospitalisation with or without an overnight stay. The **company** noted that these events may not be considered major bleeds in other antithrombotic trials, and therefore may introduce potential over-reporting of hospitalisations The bleeding classification criteria used in PEGASUS is the Thrombosis in Myocardial Infarction (TIMI) criteria. Clinical expert advice to the **ERG** suggests that although the ISTH is more detailed than the TIMI classification, it is used less frequently in clinical practice in the NHS compared to the TIMI and HAS-BLED classifications. The use of two different classification criteria to define the primary safety outcome of rivaroxaban for the comparison against ticagrelor as the ISTH criteria is more sensitive and can lead to over-reporting of hospitalisation due to local practices, physicians' experience, and local in-and out-patient policies.	Effect on the cost-effectiveness estimate is unknown

	As major bleeding events in both arms of each trial were categorised using the same bleeding criteria, the relative effect of using 2 different criteria's is unknown and may possibly not be significant.	
Subgroup analyses	Subpopulations comprise around 20% of the randomised population and will be statistically underpowered for efficacy and safety outcomes.	Effect on the cost-effectiveness estimate is unknown
Missing data for the subpopulations in the PEGASUS trial	The **company** notes that there are several missing HRs in the PEGASUS trial for the 3 subpopulations and states that HRs for the overall PEGASUS trial population were used for these missing inputs. The **ERG** notes that for the subpopulation with CAD+HF there are no HRs available and all have been taken from the overall PEGASUS trial population. It agrees that in the absence of evidence, it is reasonable to assume that for the main events, the HRs would be similar between the main trial population and the subpopulations. The **ERG** further notes that none of the subgroups were significantly different to the whole trial population in PEGASUS for the composite end point of cardiovascular death, MI or stroke.	Uncertainty in the cost-effectiveness results for the affected subpopulations is unknown

Table 3: Other issues for information

Issue	Comments
No event state health cost	In the **company's** model, patients do not incur any costs while in the 'no event' state. The **ERG** considers that all patients will incur a health state cost, for example for outpatient consultations, regardless of their health state. Previous NICE appraisal of ticagrelor (TA420) applied a cost of £160.31 per cycle to individuals in the 'no event' health state. The **ERG**

	inflated this cost to a 2018 estimate (£167.66) and applied it in the ERG base case analysis and the **technical team** agrees with this approach.
Uncertainty around health- related quality of life due to high proportion of missing data	**1. Utility for event free population** The utility values in the company's model were adjusted for age using utility multipliers. The **ERG** notes that the baseline utility score for the event-free population of COMPASS and the three subpopulations are higher than that of the UK general population for the 64-75 age group (0.779). In the **ERG b**ase case, the **ERG** scales down the baseline event-free utilities, so that these utilities are no higher than the UK general population. **2. The multiplicative assumption (for utility values) in the economic model's health states** The COMPASS trial was not powered for the 3 subpopulations the company is seeking recommendation for. The **company** explored a multiplicative assumption in a scenario analysis in which utilities of two health states are multiplied and an assumption using the utility score of the most recent event is used. The **ERG** also favoured this multiplicative approach to calculate utility values for the subpopulations in cases where patients suffer a second major event. The **ERG** considered this more appropriate than the company's approach of using the lowest utility of the two health states following transition to another main event and considered it a better representation of reality in the event of comorbidities. The **technical team** agrees with the amendments made by the ERG in its base case analysis.
Treatment Interruption	In the **company's** base case, no treatment interruption for rivaroxaban + aspirin was explicitly considered after a main event (MI, stroke, CV death). However, in clinical practice, people may be initiated on dual antiplatelet therapy after an MI during the acute period. The company considers its approach is conservative and overestimates costs in the rivaroxaban + aspirin arm. The **ERG** also notes that it is not reflective if clinical practice. The **ERG** included treatment interruption in their base case which showed that the model was not sensitive to this change and did not have any significant impact on the ICER. However, the **technical teams'** preference is for treatment interruption to be included in the base case analysis as this is reflective of clinical practice.
Equality considerations	No equalities issues were identified.
Innovation	The **company** states that there have been few advances in antithrombotic therapy for secondary prevention of cardiovascular events over several decades. In the COMPASS overall population, the benefit of rivaroxaban+ aspirin treatment is of a similar magnitude to other accepted secondary prevention regimens such as aspirin, lipid-lowering, blood-pressure

	lowering, and ACE inhibitors. The benefit is even greater in the subgroups for whom the company seeks recommendation The **ERG** notes rivaroxaban is not an innovative treatment in terms of its mechanism of action, as it is similar to other drugs used in the management of CAD for a number of years. One clinical expert consulted by the **ERG** commented that the additional benefit of rivaroxaban added to aspirin as shown in the COMPASS is regarded as an important clinical effectiveness innovation.

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