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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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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

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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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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)

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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

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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.

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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.

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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

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- 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

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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

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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.

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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).

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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.

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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

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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.

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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.

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- 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.

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		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.

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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

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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).

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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.

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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.

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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:

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- 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.

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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

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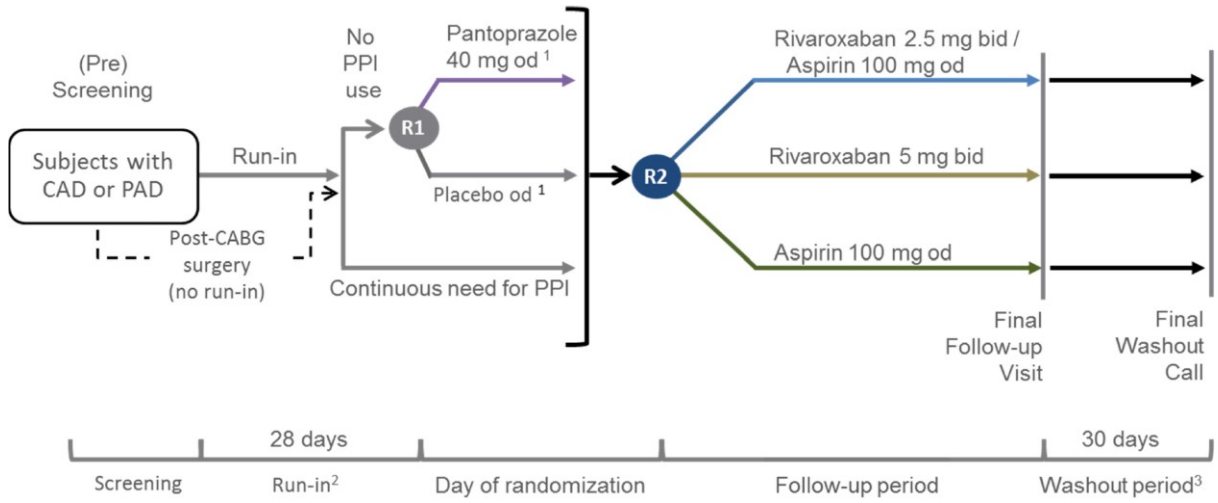
subsequently randomised to one of the three rivaroxaban / aspirin treatment assignments. The COMPASS trial design is reproduced in Figure 1 below.



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.

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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).

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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

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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

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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

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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:

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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).

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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.

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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

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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

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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

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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

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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

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(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

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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

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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).

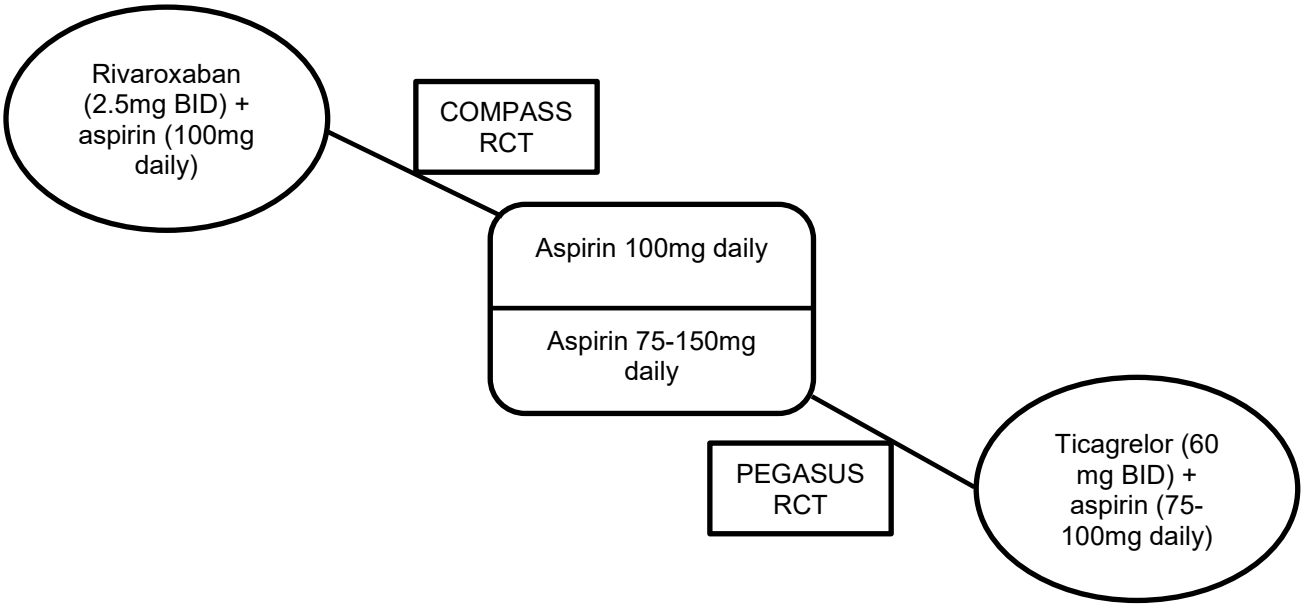

Figure 2 Schematic of the ITC for rivaroxaban + aspirin versus ticagrelor + aspirin

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

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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

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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

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- 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;

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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

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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.

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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

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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).

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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)		

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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)		

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	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)		

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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)		

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	Incidence rate per 100 patient-years (95% CI)	0.45 (0.25-0.76)	0.94 (0.63-1.35)		
CAD+HF		**N=1909**	**N=1912**		
	Crude incidence n (%)	11 (0.6)	31 (1.6)	0.35 (0.18-0.69)	0.00171
	Incidence rate per 100 patient-years (95% CI)	0.32 (0.16-0.58)	0.93 (0.63-1.32)		
CAD+PRF		**N=1824**	**N=1873**		
	Crude incidence n (%)	9 (0.5)	38 (2.0)	0.25 (0.12-0.51)	0.00004
	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		**N=9152**	**N=9126**		
	Crude incidence n (%)	22 (0.2)	40 (0.4)	0.55 (0.32-0.92)	0.02093
	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**		

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	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)		

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	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)		

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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)		

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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,

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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).

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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.

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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

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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.

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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

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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	1.49 (0.67-3.33)	0.32
	Crude incidence n (%)	15 (0.2)	10 (0.1)		
	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	Not calculated	
	Crude incidence n (%)	3 (0.2)	2 (0.1)		
	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	Not calculated	
	Crude incidence n (%)	6 (0.3)	3 (0.2)		
	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)		

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	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

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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.

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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

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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).

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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%).

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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]

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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

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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

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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.

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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.

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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	

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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.

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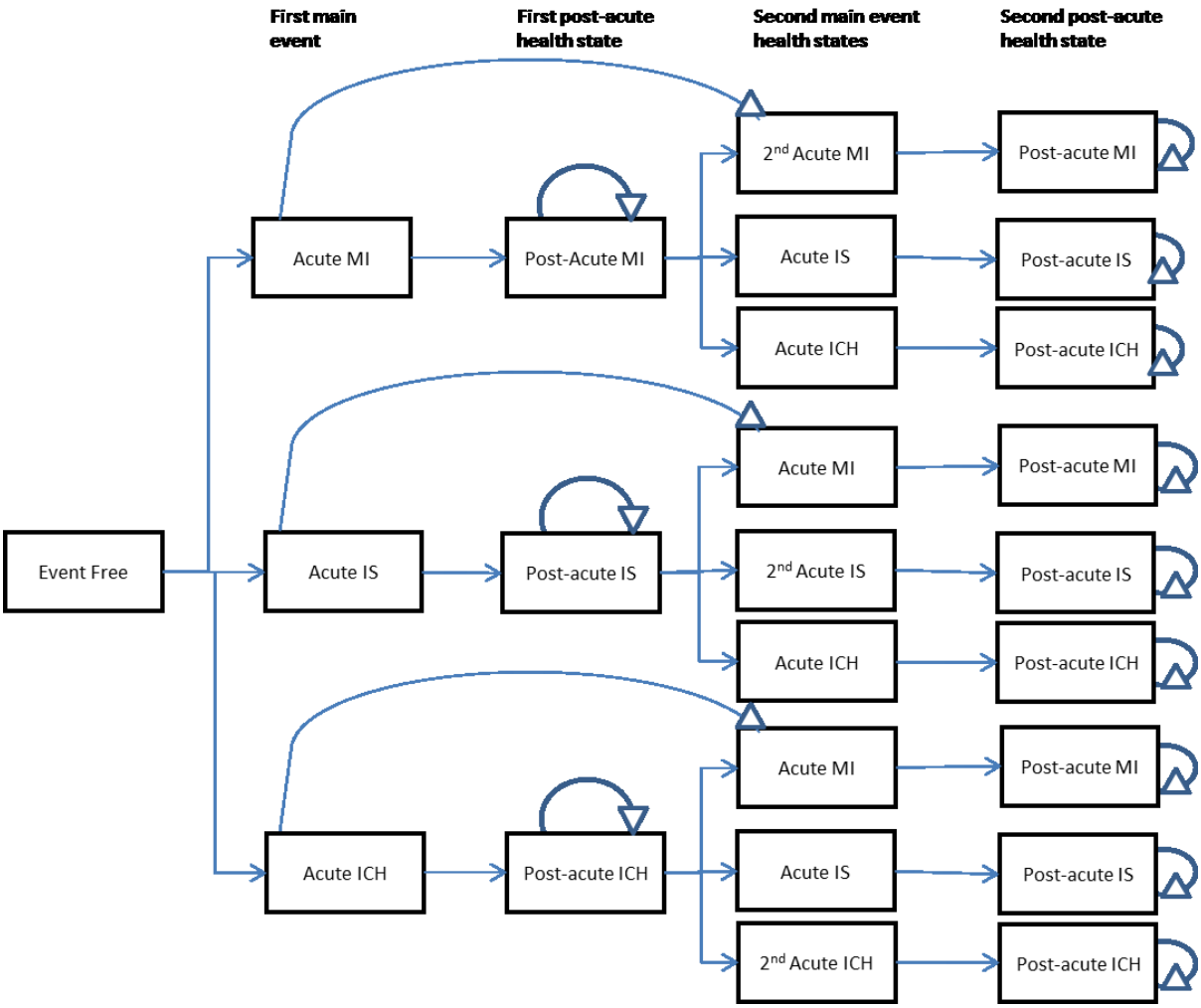

Figure 3 Schematic of the company model

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.

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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

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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

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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

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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]

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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

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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)

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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.

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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.

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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

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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]

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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.

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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.

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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

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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

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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

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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)

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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.

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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.

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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

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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

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(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

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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

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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

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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

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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

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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.

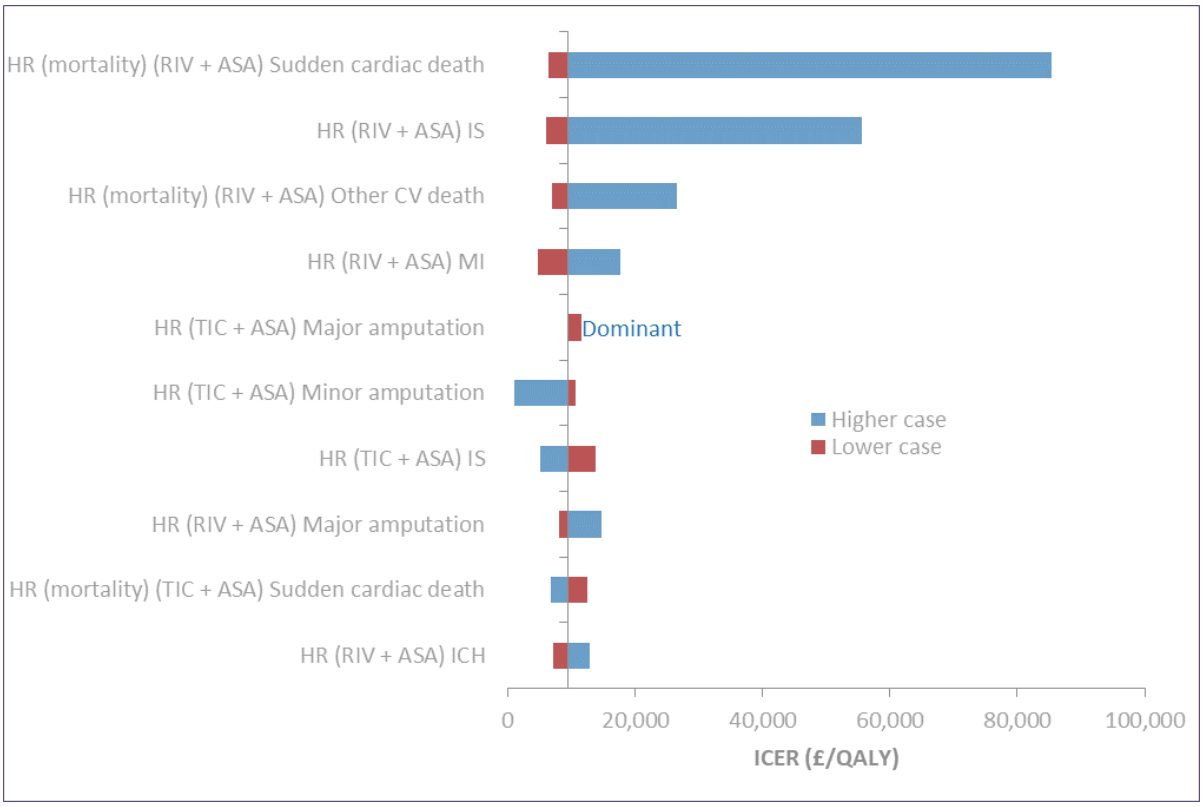

Figure 4 Tornado plot – CAD and PAD subpopulation: rivaroxaban + aspirin vs ticagrelor + aspirin

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

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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

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			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

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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

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	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

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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

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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.

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		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

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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

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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

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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

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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

COMPASS trial	Event rates		HRs	Transition probability
	Rivaroxaban + Aspirin	Aspirin		
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
PEGASUS trial	**Event rates**		**HRs**	**Transition probability**
	Ticagrelor + aspirin, %	**Aspirin**		
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

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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.

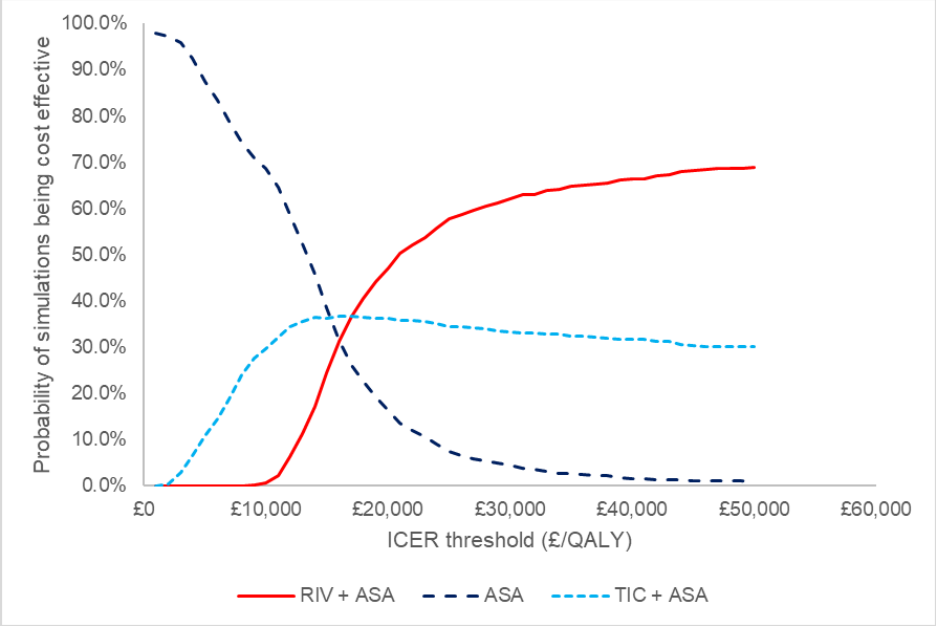

Figure 5 Cost-effectiveness acceptability curve for the COMPASS population for rivaroxaban + aspirin vs its comparators (using updated model) with all CV death varied together

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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

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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

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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

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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*".

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	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).

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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

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