

# Health economic evaluation of rivaroxaban in the treatment of patients with chronic coronary artery disease or peripheral artery disease

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Received 18 March 2019; revised 17 July 2019; editorial decision 2 October 2019; accepted 13 November 2019; online publish-ahead-of-print 14 November 2019

**Time for primary review: 31 days**

## Aims

In the COMPASS trial, rivaroxaban 2.5 mg twice daily (bid) plus acetylsalicylic acid (ASA) 100 mg once daily (od) performed better than ASA 100 mg od alone in reducing the rate of cardiovascular disease, stroke, or myocardial infarction (MI) in patients with coronary artery disease (CAD) and peripheral artery disease (PAD). A Markov model was developed to assess the cost-effectiveness of rivaroxaban plus ASA vs. ASA alone over a lifetime horizon, from the UK National Health System perspective.

## Methods and results

The base case analysis assumed that patients entered the model in the event-free health state, with the possibility to experience  $\leq 2$  events, transitioning every three-month cycle, through acute and post-acute health states of MI, ischaemic stroke (IS), or intracranial haemorrhage (ICH), and death. Costs, quality-adjusted life-years (QALYs), life years—all discounted at 3.5%—and incremental cost-effectiveness ratios (ICERs) were calculated. Deterministic and probabilistic sensitivity analyses were conducted, as well as scenario analyses. In the model, patients on rivaroxaban plus ASA lived for an average of 14.0 years with no IS/MI/ICH, and gained 9.7 QALYs at a cost of £13 947, while those receiving ASA alone lived for an average of 12.7 years and gained 9.3 QALYs at a cost of £8126. The ICER was £16 360 per QALY. This treatment was cost-effective in 98% of 5000 iterations at a willingness-to-pay threshold of £30 000 per QALY.

## Conclusion

This Markov model suggests that rivaroxaban 2.5 mg bid plus ASA is a cost-effective alternative to ASA alone in patients with chronic CAD or PAD.

## Keywords

Coronary artery disease • Cost-effectiveness • Peripheral artery disease • Rivaroxaban

## 1. Introduction

Rivaroxaban is a selective direct Factor Xa inhibitor that has been shown to be effective for the prevention and treatment of venous thromboembolism (VTE) and the prevention of stroke or systemic embolism in patients with atrial fibrillation in several large randomized controlled trials.<sup>1–4</sup> Rivaroxaban 2.5 mg or 5 mg twice daily (bid) also reduced the risk of non-fatal and fatal cardiovascular (CV) events in patients with a recent acute coronary syndrome.<sup>5</sup>

In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, rivaroxaban was tested as add-on therapy to standard of care in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).<sup>6</sup> CAD or PAD result from atherosclerosis, and occur when plaque builds up in the arteries.<sup>7–10</sup> Acetylsalicylic acid (ASA) alone is the current standard of care in patients with chronic CAD or PAD and has been shown to reduce the risk of myocardial infarction (MI), stroke, or CV death by one-fifth in patients with CAD, cerebrovascular disease, or PAD.<sup>11</sup>

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In the COMPASS trial, rivaroxaban 2.5 mg bid in combination with ASA 100 mg once daily (od) was superior to ASA 100 mg od alone in reducing the rate of stroke, MI, and CV death in patients with CAD or PAD. However, rivaroxaban 2.5 mg bid in combination with ASA 100 mg od was associated with a higher rate of major bleeding than ASA 100 mg od alone.<sup>12</sup>

In July 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for rivaroxaban 2.5 mg bid in combination with ASA for the prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischaemic events.<sup>13</sup>

An economic model was developed to estimate the costs, quality-adjusted life-years (QALYs), life years (LYs), and cost-effectiveness of rivaroxaban 2.5 mg bid in combination with ASA 100 mg od vs. ASA 100 mg od alone in patients with chronic CAD or PAD in the UK.

## 2. Methods

### 2.1 Model characteristics and approach

A Markov model was developed to assess the comparative costs and outcomes of rivaroxaban 2.5 mg bid in combination with ASA compared with ASA alone in patients with chronic CAD or PAD (Figure 1). The model was developed from the UK National Health System (NHS) perspective. In this context, the ASA dose was considered to be 75 mg od, in line with existing guidelines.<sup>14</sup>

The full list of model health states is presented in [Supplementary material online, Table S1](#).

Patients entered the model in the event-free health state, and continued until death, with up to two events being modelled. Events

considered included MI and stroke, which was divided into ischaemic stroke (IS) and haemorrhagic stroke; the latter was considered part of intracranial haemorrhage (ICH). Patients with events first transitioned to an 'acute' health state, followed by a 'post-acute' health state. This facilitated the differentiation between probabilities of new events, costs and utility, before and after an event.

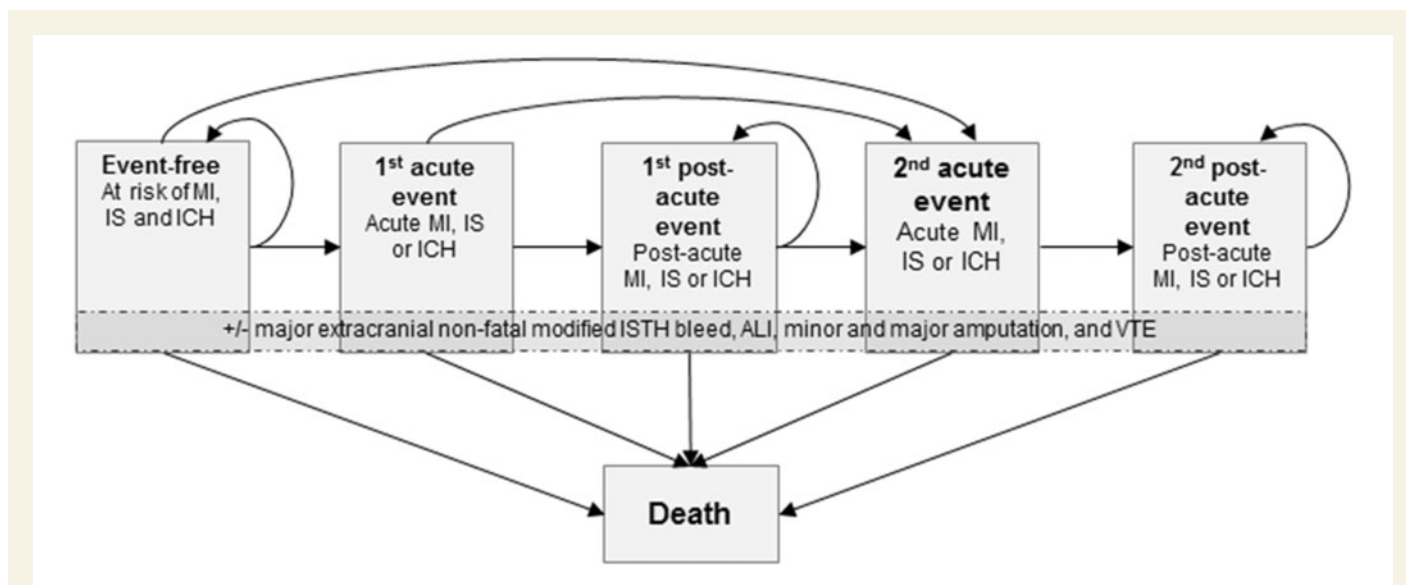
The model also considered the possibility of patients experiencing other events within each health state. Limb events included acute limb ischaemia (ALI; duration of 1 cycle), minor and major amputation (lifetime duration), and VTE (duration of 1 cycle). Major extracranial non-fatal bleeding events (duration of 1 cycle) were also included; the definition was modified compared with that of the International Society on Thrombosis and Haemostasis (ISTH) and included presentation to an acute care facility, with discharge the same day, but without the need for blood transfusion or a drop in Hb >2 g/dL.

Mortality was accounted for, including death due to MI, stroke, fatal bleeding, heart failure, death following a CV procedure or sudden cardiac death, other CV death, and other (background) mortality.

The model simulated patients' treatment over a lifetime horizon (up to 100 years old), accounting for the fact that CV risks and outcomes were relevant for the duration of a patient's life. A three-month cycle length was considered short enough such that the probability of having two events in the same cycle was considered negligible. In order to reduce the difference between real world and simulated costs and QALYs, a half-cycle correction was applied.

### 2.2 Outcomes

The model allowed the calculation of average non-fatal MI events per patient, average non-fatal IS events per patient, average non-fatal ICH events per patient, percentage of patients with CV death, mean number



**Figure 1** Model diagram. The patient enters the model in the event-free health state. When the first event happens, the patient progresses to one of the health states '1st acute event', and experiences one of the three events. Following the '1st acute event' phase, the patient transitions to one of the health states '1st post-acute event'. The patient can remain in the current health state or experience a second event and transition to one of the health states '2nd acute event'. Following the '2nd acute event' phase, the patient transitions to one of the health states '2nd post-acute event'. The patient can transition to the 'Death' state from every state in the model. ALI, acute limb ischaemia; ICH, intracranial haemorrhage; IS, ischaemic stroke; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; VTE, venous thromboembolism.

of years with no event, life expectancy, total deaths by cause, average number of ALI events, major and minor amputations, non-fatal extracranial modified ISTH bleeding events and VTE events, and total QALYs.

Costs considered in this model were direct costs including medication costs, and resource use related to health states and health events. The model provided both cost-utility and cost-effectiveness results, presenting incremental costs per QALY gained, as well as costs per LY saved.

## 2.3 Model inputs

Model inputs are presented in [Supplementary material online, Table S2](#).

### 2.3.1 Transition probabilities (ASA)

For the first 4 years of the ASA arm, transition probabilities were calculated directly from patient-level data from the COMPASS trial for events (MI, IS, and ICH) and CV death and were applied for each health state. Starting year 5, these probabilities were extrapolated over a lifetime horizon, by applying hazard ratios (HRs) from the REACH (REduction of Atherothrombosis for Continued Health) registry.<sup>15</sup> REACH is a prospective registry of outpatient population with known CV disease at entry. Cox regressions, evaluating the impact of age on the risk of next CV event and CV death, were available from the 2-year follow-up data of 50 000 participants from around the world. These HRs for increased risk of next event (MI, IS, and ICH) and CV death, were applied in the model, as the cohort's age was increasing.

Risks of limb events and major bleeding events for the ASA arm were also sourced from COMPASS and assumed to be constant over time.

Background mortality was estimated using a cohort life table generated from the mortality data underlying the life tables (by age and gender) from the Office for National Statistics in the UK, while rates of other types of death were sourced from COMPASS. To avoid double counting, the proportion of deaths attributable to CV disease by gender and age in the UK, as published by the British Heart Foundation,<sup>16</sup> was removed from the background mortality data.

### 2.3.2 Transition probabilities (rivaroxaban 2.5 mg bid in combination with ASA)

Transition probabilities relating to rivaroxaban 2.5 mg bid in combination with ASA were estimated by applying the relevant HRs from the COMPASS trial to the ASA transition probabilities. Several assumptions were made for HRs: treatment was assumed to continue over the patient's lifetime; the comparative effect was assumed to be constant over time; the base case analysis considered HRs even if not statistically significant; and the model did not consider any impact of premature or permanent treatment discontinuation in the base case.

### 2.3.3 Costs and resource use

This cost-effectiveness analysis examined direct costs only. Drug costs were taken from the British National Formulary.<sup>17</sup> No costs were associated with the event-free health state. Resources used in acute health states were calculated based on different inpatient cost categories from the National Schedule of Reference Costs<sup>18</sup> and were averaged using the number of episodes per year. Post-acute event costs, as well as those associated with fatal events, were estimated from the published literature.<sup>19</sup> Costs relating to health states for second events were the maximum of each separate event cost, for both acute and post-acute states. Other costs, including costs associated with occurrences of ALI, amputations (minor and major), VTE, and major non-fatal extracranial modified

ISTH bleeding events, were taken from the national schedule of reference costs.<sup>18</sup> In accordance with National Institute for Health and Care Excellence (NICE) guidelines,<sup>20</sup> future costs, and future QALYs were both discounted at 3.5% per annum.

### 2.3.4 Utilities

For the calculation of QALYs, utility values were sourced from COMPASS EQ-5D-3L analyses, using the UK algorithm.<sup>21</sup> The baseline data informed the event-free utility, and the results of a multivariate regression informed utility values for health states and utility decrements for health events. All values were assumed to be the same in both treatment arms, as there was no evidence to suggest that treatment choice has any impact on quality of life.<sup>22,23</sup> The utility of a health state with a second main event was defined as the lowest utility of the individual included health states.

### 2.3.5 Sensitivity analysis

A deterministic sensitivity analysis was performed to test the parameters set in the model. The ranges for these parameters were taken from the NICE methods guide.<sup>24</sup> A probabilistic sensitivity analysis (PSA) was performed to evaluate the uncertainty of the model parameters on the cost-effectiveness results.<sup>25</sup> In the PSA, transition probabilities were simulated using a Beta or Dirichlet distribution, while log-normal distribution was used for the simulation of relative risks, gamma or log-normal distribution was used for costs, and Beta distribution was used for utilities. The parameters included the percentage of males, health-state costs, health-event costs, all transition probabilities, all health-event probabilities, all HRs relative to treatment effect, HRs increasing risk after the second event, and all utility values and decrements. The effect of the change in the price of rivaroxaban was not considered in the scope of the current analysis, as identified from the British National Formulary.

In addition, several specific scenarios were considered. The impact of a shorter time horizon (15 years) and other discount rates (0% and 5%) was explored; shorter treatment duration was also considered to be of interest. In this scenario, patients treated with rivaroxaban 2.5 mg bid in combination with ASA were switched to ASA alone after 5 years. Other assumptions regarding persistence were considered in two different scenarios. The first scenario considered COMPASS persistence over the 4 years of the trial and assumed that no patient discontinued. In this scenario, only impact on costs was considered as HRs were based on the intention-to-treat data set, which includes treatment interruption and discontinuation. In the second scenario, a lifetime discontinuation rate was considered, with impact on both efficacy and costs. Assumptions regarding the second event valuation of utility and costs were also explored. Finally, the model was run in two subpopulations of the COMPASS trial data: patients with CAD, irrespective of PAD status (91% of the patients), and patients with PAD, irrespective of CAD status (27% of the patients).

## 3. Results

All results are summarized in [Table 1](#).

Over a lifetime horizon used in the model, the rates of non-fatal MI and non-fatal IS were lower for rivaroxaban 2.5 mg bid in combination with ASA (0.233% and 0.086% vs. 0.253% and 0.159%, respectively), while the rate of non-fatal ICH was higher compared with ASA alone (0.025% vs. 0.019%). In addition to a 6% reduction in CV mortality,

**Table 1 Model results**

Model results	Rivaroxaban 2.5 mg bid in combination with ASA	ASA alone	Incremental vs. ASA alone
Events, per patient			
Average non-fatal MIs	0.233	0.253	-0.019
Average non-fatal ischaemic strokes	0.086	0.159	-0.073
Average non-fatal ICHs	0.025	0.019	0.006
Percentage patients with CV death	24.87%	30.90%	-6.03%
Mean no. years with no event	14.03	12.67	1.36
Life expectancy	84.43	83.75	0.68
All deaths	0.974	0.977	-0.004
Additional events, per patient			
Average ALI	0.0229	0.0400	-0.0170
Average minor amputation	0.0181	0.0266	-0.0086
Average major amputation	0.0137	0.0231	-0.0094
Average VTE	0.2536	0.1359	0.1177
Average major extracranial non-fatal bleeds	0.0243	0.0382	-0.0139
QALYs and life years			
QALYs	9.66	9.30	0.36
Life years	12.09	11.69	0.40
Costs			
Drug costs	£8067	£117	£7949
Ongoing medical care	£3841	£5301	-£1460
Non-fatal acute CV events	£1294	£1748	-£454
Mortality	£296	£372	-£76
Additional events	£448	£586	-£138
Total	£13 947	£8126	£5821
Incremental costs			
Per QALY gained	–	–	£16 360
Per life year gained	–	–	£14 380

ALI, acute limb ischaemia; ASA, acetylsalicylic acid; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; QALY, quality-adjusted life-year; VTE, venous thromboembolism.

rivaroxaban 2.5 mg bid in combination with ASA was associated with a longer event-free duration (14.0 years vs. 12.7 years). In terms of the number of health events, more major non-fatal extracranial ISTH bleeding events were simulated with rivaroxaban 2.5 mg bid in combination with ASA, while a reduction in ALI events, amputations, and VTE events was observed. The benefits translated into 0.36 additional QALYs and 0.40 additional LY for rivaroxaban 2.5 mg bid in combination with ASA compared with ASA alone.

Over a lifetime horizon, costs were higher for rivaroxaban 2.5 mg bid in combination with ASA compared with ASA (£13 947 vs. £8126), with incremental costs reaching £5821. This is largely due to higher drug costs (+£7949), although savings were associated with the reduced rates of MI, IS, and CV death.

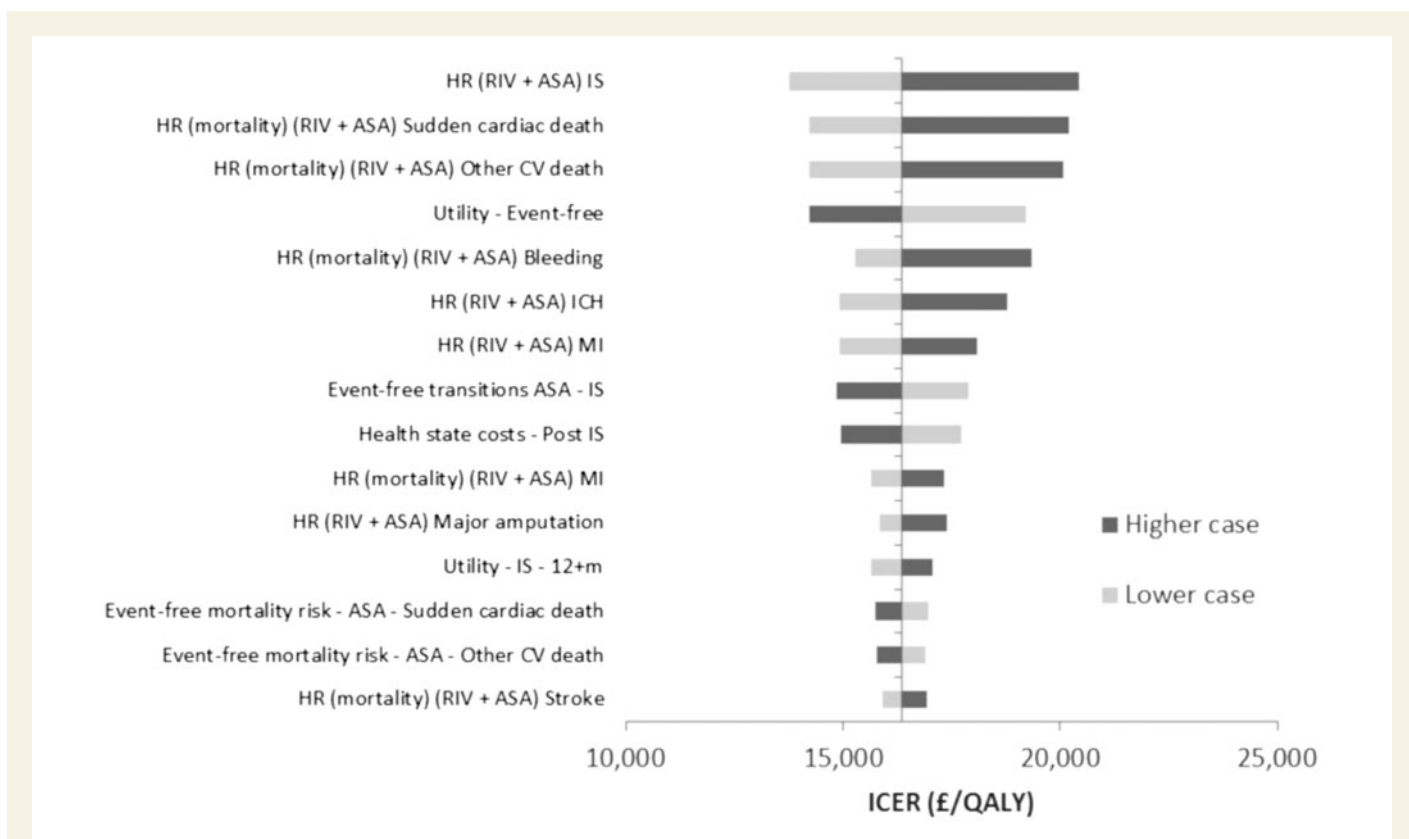
Clinical benefits and associated costs resulted in an incremental cost-effectiveness ratio (ICER) of £16 360 per QALY gained, and £14 380 per LY saved. Considering a NICE threshold of £30 000 per QALY gained, rivaroxaban 2.5 mg bid in combination with ASA is considered cost-effective compared with ASA alone.

The deterministic sensitivity analysis shows that the main ICER drivers included efficacy data related to IS and CV death, and utility for the event-free health state. ICERs resulting from the impact of variations in any other parameter are all below £21 000/QALY. The

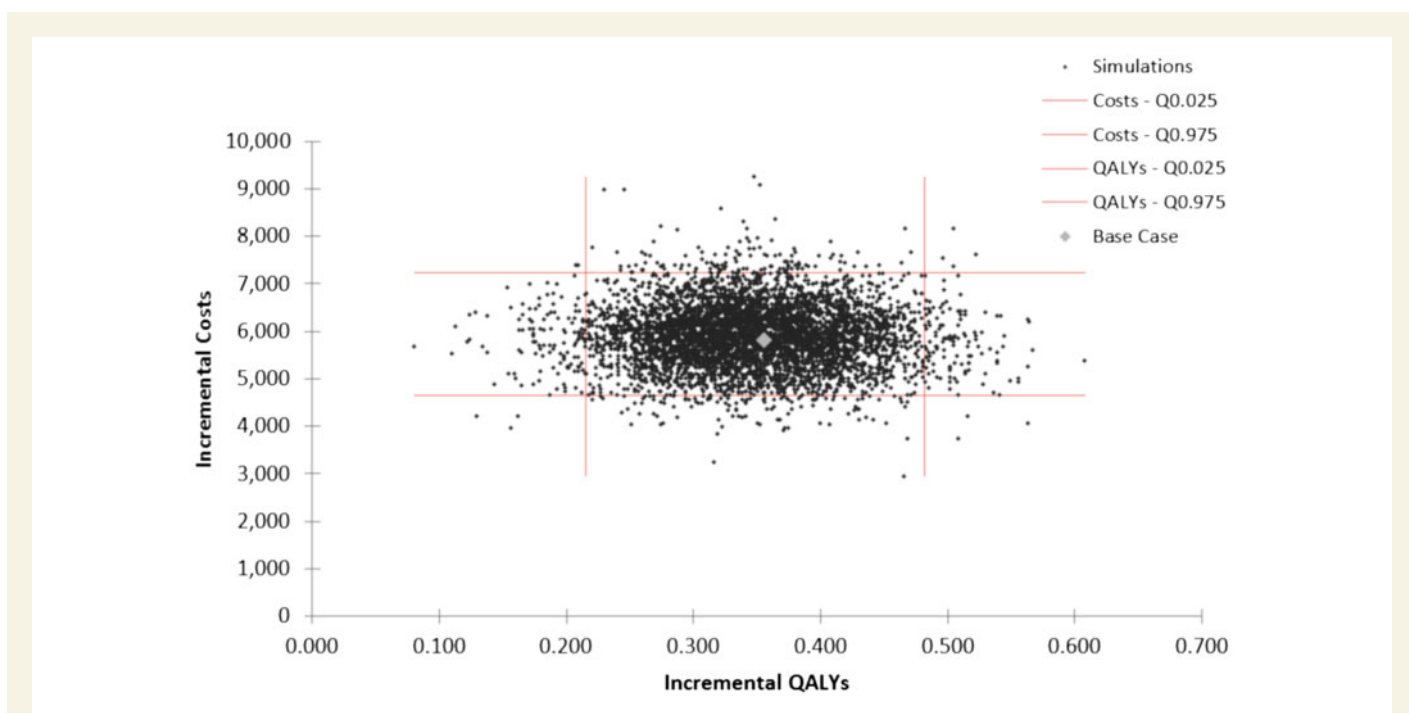
extent of the impact of these variations in parameters is depicted in Figure 2.

Using 5000 simulations, the PSA mean ICER was £16 733/QALY. The probability that rivaroxaban 2.5 mg bid in combination with ASA was cost-effective against ASA alone was around 98%, at a cost-effectiveness threshold of £30 000/QALY (Figure 3).

Table 2 presents the results of the scenario analyses. Taking a shorter time horizon (15 years) increases the ICER by 58%. Incremental costs were reduced due to the shorter duration of treatment, but this was not compensated by a reduction in QALYs. As expected, the scenario analysis considering lower discount rates leads to a lower ICER (-22%) while the scenario with higher discount rates leads to a higher ICER (+10%). A 5-year treatment duration for rivaroxaban 2.5 mg bid in combination with ASA resulted in a similar ICER to the base case (-6%), as costs and QALYs were reduced in parallel with costs dropping to a greater extent than QALYs. Scenarios considering treatment persistence also significantly reduced the ICERs (by 44% and 21%, depending on the scenario). Assumptions regarding the second event valuation of costs and utilities had a limited impact on the results. Finally, the results in the CAD population were similar to that of the base case, while the higher baseline risk in the PAD population translated in a higher treatment benefit, and a reduction of the ICER by 31%.



**Figure 2** Deterministic sensitivity analysis—Tornado diagram on ICER for rivaroxaban 2.5 mg bid in combination with ASA 100 mg od vs. ASA 100 mg od alone. ASA, acetylsalicylic acid; CV, cardiovascular; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; IS, ischaemic stroke; MI, myocardial infarction; QALY, quality-adjusted life-year; RIV, rivaroxaban.



**Figure 3** Probabilistic sensitivity analysis—incremental cost-effectiveness plane for rivaroxaban 2.5 mg bid in combination with ASA 100 mg od vs. ASA 100 mg od alone. q, quartile; QALY, quality-adjusted life-year.

**Table 2 Scenario analyses results**

Scenario	Base case assumption	Scenario assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change
Base case			5821	0.36	16 360	–
Time horizon	Lifetime (33 years)	15 years	5045	0.19	25 926	+58%
Discount rates	3.5%	0%	7590	0.59	12 832	-22%
		5%	5284	0.29	18 059	+10%
Treatment duration	Life time	5 years	2148	0.14	15 325	-6%
Treatment persistence	None	Until 4 years then flat rate (with no impact on efficacy)	3287	0.36	9238	-44%
		Model duration (with impact on efficacy)	2495	0.19	12 992	-21%
Second events assumptions	Maximum cost	Most recent event	5912	0.36	16 618	+2%
		Additive	4932	0.36	13 864	-15%
	Lowest utility	Most recent event	5821	0.35	16 409	0%
		Multiplicative	5821	0.39	14 942	-9%
Population	Patients with chronic CAD or PAD	Patients with chronic CAD	5912	0.35	17 094	+4%
		Patients with PAD	6107	0.55	11 196	-31%

CAD, coronary artery disease; ICER, incremental cost-effectiveness ratio; PAD, peripheral artery disease; QALY, quality-adjusted life-year.

## 4. Discussion

This economic evaluation demonstrated that lifetime treatment with rivaroxaban in combination with ASA is associated with an increase in QALYs of 0.36 and an increase in costs of £5821, in patients with chronic CAD or PAD. From the UK NHS perspective, the cost per QALY is estimated at £16 360. Rivaroxaban 2.5 mg bid in combination with ASA is a cost-effective treatment option for the prevention of atherothrombotic events in patients with chronic CAD or PAD when assuming a willingness to pay at the nominal threshold of £30 000 per QALY.<sup>26</sup>

Exploratory sensitivity and scenario analyses suggested that the model was robust to changes in the majority of input parameters. With acceptable variations to the input parameters, the ICER was likely to remain within the bounds that would typically be considered cost-effective. The ICER of rivaroxaban 2.5 mg bid in combination with ASA compared with ASA alone was found to be most sensitive to efficacy data related to IS and CV death, as well as to the time horizon. Nevertheless, the results of the scenario analysis that considered a shorter time horizon highlight that the benefit of rivaroxaban in combination with ASA consists in lifetime prevention of IS, MI, and CV death; a high proportion of these benefits are observed in the longer term.

The structure specifically incorporated a separation of acute and long-term health states, which reflected real-world observations; risk of a subsequent event is higher, acute costs are higher and utility is lower in the short-term following an event. In addition, tracking for multiple events was possible as a patient could experience more than one non-fatal event (including non-fatal MI, non-fatal IS, and non-fatal ICH).

This model included several conservative assumptions. First, patients could not experience more than one event (MI, IS, or ICH) within a three-month cycle, and more than two events (MI, IS, or ICH) in total, although this is possible in the real world. Second, the base case presumably overestimated total lifetime rivaroxaban costs by not accounting for treatment non-persistence or treatment interruption. Third,

occurrences of limb events were assumed not to have an effect on subsequent risk of MI, IS, ICH, or survival. Finally, probabilities of limb events and the modified ISTH extracranial major non-fatal bleeding events were assumed to be constant disregarding time and health state; it is likely that this probability increases with the number of IS, MI, or ICH in the real world.

Some limitations should be taken into consideration when analysing the results. Several transitions were not possible in the model according to observed data in COMPASS. For example, there were no possible ICH events after an MI or an IS. This is, arguably, unrealistic in real life, but conservative as the treatment benefit was underestimated. Additionally, the base case assumed no treatment discontinuation, for simplicity. Nevertheless, this conservative assumption was challenged with scenarios that did account for discontinuation impact on costs and efficacy, and these resulted in lower ICERs due to reduced treatment costs. Finally, no costs were imputed to the event-free health state, in line with a previous NICE submission.<sup>27</sup> This model supports the use of rivaroxaban 2.5 mg bid in combination with ASA as a cost-effective treatment option in patients with chronic CAD or PAD, compared with ASA alone, in the UK NHS setting.

## Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

## Acknowledgements

The authors thank Monique Jouvilina Dabbous for editorial assistance in the preparation of the manuscript, with funding from Bayer AG.

**Conflict of interest:** J.-B.B. is an employee of Bayer AG. K.B. is an employee of Bayer plc. A.M. and O.C. are employees of Creativ-Ceutical, which received funding from Bayer AG. P.M. received funding from

Creativ-Ceutical P.L., S.M., and M.R.C. received an honorarium to support the development of the model structure and validate the assumptions. A.L. declared no conflict of interest.

## Funding

This work was supported by Bayer AG.

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