Cost-effectiveness of rivaroxaban in the treatment of patients with chronic CAD or PAD in the UK

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BACKGROUND

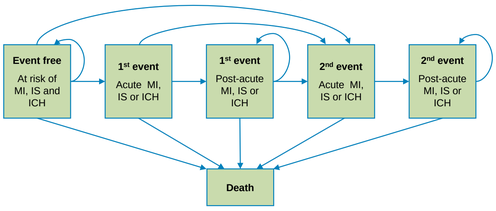
- Chronic coronary artery disease (CAD) and peripheral artery disease (PAD) result from atherosclerosis, and occur when plaque builds up in the arteries. Acetylsalicylic acid (ASA) alone is the current standard of care in patients with chronic CAD or PAD.
- Rivaroxaban is a selective direct Factor Xa inhibitor. In the COMPASS trial[1], rivaroxaban 2.5 mg bid in combination with ASA was superior to ASA alone in reducing the rate of stroke, myocardial infarction (MI) and cardiovascular (CV) death in these patients. However, the combination was associated with a higher rate of major bleeding.

OBJECTIVE

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

METHODS

- A Markov model was developed from the UK NHS perspective. The model simulated patients' treatment over a lifetime horizon, and considered a three-month cycle length.
- In accordance with NICE guidelines, future costs and future QALYs were both discounted at 3.5% per annum.



Model structure

- Patients entered the model in the event-free health state, and continued until death, with up to 2 events being modelled.
- Events considered included MI, ischaemic stroke (IS) and intracranial haemorrhage (ICH). Patients with events first transitioned to an 'acute' health state, followed by a 'post-acute' health state.
- Patients could also experience other events within each health state, including acute limb ischaemia (ALI; duration of 1 cycle), minor and major amputation (lifetime duration), venous thromboembolism (VTE, duration of 1 cycle) and major extracranial non-fatal bleeding events (duration of 1 cycle).
- Mortality included CV death and background non-CV death.

Model inputs and assumptions

Model inputs	
Patients characteristics	• Age and gender (required to calculate background mortality rates)
Transition probabilities (MI, IS, ICH and CV death)	• ASA arm - first 4 years : calculated directly from the COMPASS trial • ASA arm – subsequent years: extrapolated using HRs from the REACH registry for increased risk of next event (MI, IS and ICH) and CV death, based on increasing age • RIV+ASA arm: estimated by applying the relevant HRs to the ASA transition probabilities
Risk of other events	• ASA arm : calculated directly from the COMPASS trial • RIV+ASA arm: estimated by applying the relevant HRs to the ASA risks • No impact on transition probabilities
Background mortality	• UK life table (by age and gender) from Office for National Statistics • % of CV deaths (by gender and age), published by British Heart Foundation, removed to avoid double counting

Direct costs	• Drug costs: British National Formulary
	• Event costs:
	  • No costs associated with the event-free health state
	  • Acute health states: different inpatient cost categories from National Schedule of Reference Costs, and averaged using number of episodes per year
	  • Post-acute event costs and fatal events: published literature
	  • Second events: maximum of each separate event cost
	  • Other events: National Schedule of Reference Costs

Utilities	• Calculations on EQ-5D-3L from the COMPASS trial:
	  • Event-free utility: baseline data
	  • Health states and utility decrements for health events: multivariate regression
	• All values assumed to be the same in both treatment arms (no evidence to suggest that treatment has any impact on utility)
	• Second event: minimum of each separate event cost

Model assumptions	
Treatment duration	• Lifetime assumed for both treatments
Treatment effect	• HRs constant over time, for the duration of the COMPASS trial, as well as thereafter (i.e. no efficacy waning) • HRs applied for both first and second events (i.e. no interaction between treatment and event history on the risk of event) • HRs applied independently of significance level
Treatment persistence	• No impact of treatment premature permanent discontinuation on efficacy (although not realistic, conservative as it considers that drug costs are accounted for the whole model simulation)
Treatment interruption	• No impact of rivaroxaban treatment interruption (although not realistic, conservative as it considers that drug costs are accounted for the whole model simulation – could be expected in real life: interruption of ≥1 year after an MI, of 3 months after an ICH and of 1 month after a major bleed)

Sensitivity analyses

- A deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA) were performed.
- Several scenarios were conducted to evaluate the impact of main model assumptions.

RESULTS

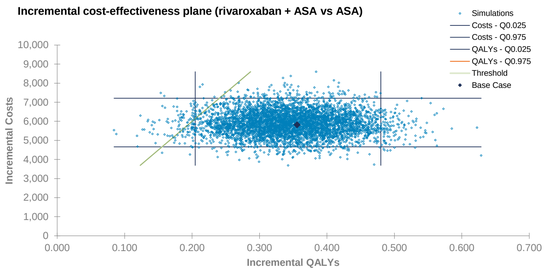
Base case

- Clinical benefits and associated costs resulted in an ICER of £16,360 per QALY gained, and £14,380 per LY saved.

	Rivaroxaban + ASA	ASA	Incremental vs ASA
Events, per patient			
Average non-fatal MI	0.233	0.253	-0.019
Average non-fatal IS	0.086	0.159	-0.073
Average non-fatal ICH	0.025	0.019	0.006
% patients with CV death	24.87%	30.90%	-6.03%
Mean 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	9.64	9.28	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	-	-	**£16,054**
Per life year gained	-	-	**£14,380**

Sensitivity analyses

- The DSA showed that the main ICER drivers included efficacy data related to IS and CV death, as well as utility in the event-free state. All ICERs remain below a £20,000 threshold.
- Using 5000 simulations, the PSA mean ICER was £16,733/QALY. The probability that rivaroxaban in combination with ASA was cost-effective against ASA alone was around 98%, at a cost-effectiveness threshold of £30,000/QALY.



- Impact of scenarios was as expected.

	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	% change
Base case	**5821**	**0.36**	**16,360**	**-**
15 years time horizon	5045	0.19	25,926	+58%
0% discount rate	7590	0.59	12,832	-22%
5% discount rate	5284	0.29	18,059	+10%
5 years treatment duration	2148	0.14	15,325	-6%

Model limitations

- Patients could not experience >1 event (MI, IS or ICH) within a cycle, and > 2 events in total.
- Several transitions were not possible according to observed data in the COMPASS trial. For example, there were no possible ICH events after an MI or an IS. This is, arguably, unrealistic in real life.
- The base case presumably overestimated lifetime rivaroxaban costs by omitting treatment non-persistence and interruption.
- All these limitations are considered conservative assumptions (underestimating rivaroxaban benefit or overestimating rivaroxaban costs).

CONCLUSION

- 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.

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REFERENCE
1. Eikelboom JW et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017 Oct 5;377(14):1319-1330