PCV29

## OBJECTIVE

Cost-effectiveness assessment of rivaroxaban and acetylsalicylic acid versus acetylsalicylic acid in the treatment of coronary or peripheral artery disease

## ANALYSIS

Cost-utility, cost-effectiveness, net monetary benefit and value of information analysis applying trial and Finnish real world evidence

## KNOWLEDGE GAINED

Adding rivaroxaban to acetylsalicylic acid was cost-effective and modelled to save €8,791 per patient with the most plausible assumed willingness-to-pay

## KEY MESSAGE

Full health economic evaluation demonstrated the value of rivaroxaban, which is currently reimbursed in Finland

# Cost-effectiveness of Coronary and Peripheral Artery Disease Treatments


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## BACKGROUND

15–20% of individuals with coronary (CAD) or peripheral artery disease (PAD) on routine treatment experience cardiovascular events (CVE) at 3–4 years. [1]

Acetylsalicylic acid 100 mg daily (ASA100) has long been the mainstay antithrombotic treatment for the CAD/PAD. [2,3]

Recently, rivaroxaban 2.5 mg + ASA100 (RIV2.5+ASA100) has demonstrated its clinical value in a large COMPASS trial for stable CAD or symptomatic PAD populations at risk of CVE (CAD/PAD). [4]

## OBJECTIVE

Using Patients-Intervention-Comparators-Outcomes-Setting-Time-Effects-Perspective-Sensitivity analyses (PICOSTEPS) reporting setting, [5,6] we evaluated the cost-effectiveness of RIV2.5+ASA100 in the prevention of CVEs among Finns with CAD/PAD. (Table 1)

**Table 1.** Health economic evaluation (HEE) in PICOSTEPS [5,6] framework.

| COMPONENT | CONTENT |
|---|---|
| **P:Patients** | Finns with stable coronary (CAD) or symptomatic peripheral artery disease (PAD) and at risk of cardiovascular events (CVE) (CAD/PAD).<br>**CAD/PAD:** age 68.2 years, SD 7.9 years, N 27,395, 78.0% males.<br>**Respective subgroups:** CAD (68.3, 7.8, 24,824, 79.7%), PAD (67.8, 8.5, 7,470, 71.8%), CAD and PAD (68.1, 8.2, 4,906, 77.1%), CAD with heart failure (HF, 65.5, 9.0, 5,714, 77.3%), CAD with chronic kidney disease (CKD) (71.4, 7.3, 5,561, 70.8%). |
| **I: Intervention** | Lifelong rivaroxaban 2.5 mg (RIV2.5) + acetylsalicylic acid 100 mg (ASA100) |
| **C: Comparator** | Lifelong ASA100 |
| **O: Outcomes** | **Primary:** Deterministic incremental cost-effectiveness ratio (ICER) defined as additional costs (euros)/quality-adjusted life-years (QALY) gained.<br>**Secondary:** ICER defined as cost/life-years gained (LYG). Total and disaggregated costs and QALYs.<br>**Tertiary:** Probabilistic ICER, incremental net monetary benefits, cost-effectiveness acceptability frontier and expected value of perfect information |
| **S: Setting** | CAD/PAD in Finland. Incremental cost-effectiveness analysis based on Markov model with event-free health (EFH), main (MCVE), other CVEs (OCVE) and mortality (Figure 1) |
| **T: Time** | Lifetime horizon (max age 100 years), 2019 base year with year 2019 expected drug and other costs, three months modelling cycle. 3% discounting/annum |
| **E: Effects** | ASA100 transition probabilities for MCVE, OCVE and CV-adjusted Finnish general population mortality, hazard ratios (HR) for RIV2.5+ASA100, EQ-5D-3L health-related quality of life (HRQoL) from the COMPASS trial adjusted to Finland, and Finnish real-world evidence (RWE) of resource use and costs |
| **P: Perspective** | Finnish public payer perspective, i.e. patient co-payments of health services, travellingand indirect costs (absenteeism, presenteeism, sickness allowances, pensions, education, unemployment, household chores, taxes, other income transfers) are ignored |
| **S: Sensitivity analyses** | Scenario analyses including<br>• **Patients:** The subgroups of patients<br>• **Time:** Time horizon: 15 years; discounting: 0%, 5%; cost year: 2020, 2021<br>• **Effects:**<br>– Event and death transition probabilities with zero probability after the first event imputed (EFH state figures); and zero event probabilities from EFH state to a second event and zero probabilities for death imputed (0.00001)<br>– Discontinuation rate of 0.029/3-month cycle for RIV2.5 applied for the first four years and the treatment costs for patients discontinuing RIV2.5+ASA100 modelled as equal to ASA100 treatment costs<br>– The RIV2.5 discontinuation rate used for the full model duration and the transition and event probabilities and treatment costs after discontinuing RIV2.5+ASA100 modelled to be equal to ASA100<br>– All statistically insignificant HRs set to 1.00<br>– The most recent MCVE cost applied for MCVEs<br>– Additive MCVE costs applied for MCVEs<br>– HRQoL based on the most recent MCVE<br>– Multiplicativity of MCVE HRQoL<br>– HRQoL from ATLAS with age-adjustment<br>– HRQoL from literature<br>Deterministic sensitivity analysis<br>Probabilistic sensitivity analysis distributions<br>• Patients: Beta gender; Normal baseline age; LogNormal age-dependent CVE risk and age-dependent CV-death risk<br>• Intervention: LogNormal CVE HRs and CV-death HRs<br>• Comparator: Beta EFH, MCVE risks, OCVE risks, mortalities and proportion of IS deaths among stroke patients; LogNormal OCVE durations<br>• Effects: Gamma for costs; Beta for HRQoL values and disutilities |

## METHODS

Myocardial infarction (MI), ischaemic stroke (IS), intracerebral haemorrhage (ICH), acute limb ischaemia (ALI), amputations, major extracranial bleed (MB) and various CVE-related reasons of death were modelled in a Markov model examining a cohort of stable CAD or symptomatic PAD patients at risk of CVE. (Figure 1)

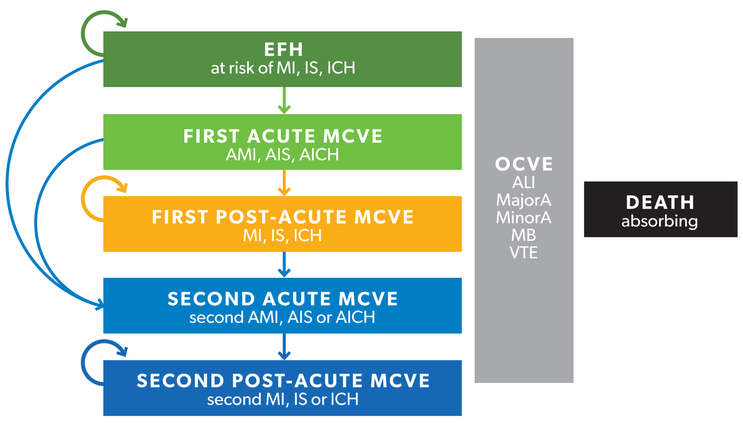


**Figure 1.** Simplified presentation of Markov model.
Legend: OCVE or death may happen from any state. EFH, event-free health; MCVE, major cardiovascular event; MI, myocardial infarction; IS, ischaemic stroke; ICH, intracerebral bleed; AMI, acute MI; AIS, acute IS; AICH, acute ICH; OCVE, other cardiovascular event; ALI, acute limb ischaemia; MajorA, major amputation; MinorA, minor amputation; MB, major extracranial bleed; VTE, venous thromboembolism.

Relative effects of **intervention** (RIV2.5+ASA100) were based on COMPASS trial. In addition to the non-fatal and fatal CVEs, **effects** also covered Finnish non-CVE background mortality, Finnish quality of life and Finnish direct costs from public payer **perspective**. (Table 1)

Primary **outcome** was 3%/year discounted incremental cost-effectiveness ratio (ICER), defined as cost (2019 euros) per quality-adjusted life-year (QALY) gained in Finnish
**setting** over life**time** horizon:

$$ICER_{RIV2.5+ASA100} = \frac{(Costs_{RIV2.5+ASA100} - Costs_{ASA100})}{(Health\ outcome_{RIV2.5+ASA100} - Health\ outcome_{ASA100})}.$$

Disaggregated costs and QALYs, costs per life-year gained (LYG) and ischemic stroke avoided, net monetary benefit (NMB, with purchasing power adjusted most plausible willingness-to-pay from the United Kingdom [7]), expected value of perfect information (EVPI), cost-effectiveness table and acceptability frontier were examined as other outcomes. Probabilistic and deterministic **sensitivity analyses** were conducted. (Table 1)

## RESULTS

In the modelled comparison to ASA100 over lifetime horizon, RIV2.5+ASA100 resulted to deterministic discounted 0.404 QALYs gained, 0.474 LYGs, additional cost of €3,241, and an ICER of €8,031/QALY. (Table 2)

**Table 2.** Deterministic and probabilistic discounted outcomes per patient.

| DETERMINISTIC | RIV2.5+ASA100 | ASA100 | INCREMENTAL |
|---|---|---|---|
| **Costs (€)** | 41,788 | 38,547 | 3,241 |
| Drugs | 11,929 | 403 | 11,525 |
| Medical care | 19,846 | 24,411 | -4,565 |
| Acute non-fatal CV | 1,520 | 1,985 | -465 |
| Mortality | 1,089 | 1,332 | -243 |
| Events | 7,404 | 10,415 | -3,011 |
| **QALYs** | 10.333 | 9.929 | 0.404 |
| ICER (€/QALY gained) | | | 8,031 |
| **LYs** | 12.995 | 12.521 | 0.474 |
| ICER (€/LYG) | | | 6,834 |
| **PROBABILISTIC** | **QALYS** | **COSTS** | **ICER** |
| **Mean incremental** | 0.420 | 1,811 | 4,313 |
| **SD incremental** | 0.203 | 4,796 | 12,045 |
| **Median incremental** | 0.405 | 2,899 | 11,304 |
| **Percentile, 2.5%** | 0.107 | -12,176 | 597 |
| **Percentile, 97.5%** | 0.899 | 7,730 | 39,421 |

Legend: RIV2.5, rivaroxaban 2.5 mg; ASA100, acetylsalicylic acid 100 mg; deterministic, based on the mean values; CV, cardiovascular; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; LY, life year; LYG, life year gained; CV, cardiovascular; SD, standard deviation; VTE, venous thromboembolism; probabilistic, based on the modelled distributions.

The probabilistic ICER was €4,313/QALY (EVPI €1,829/patient). RIV2.5+ASA100 had positive NMB of €8,791/patient, EVPI of €88/patient and 91% probability of cost-effectiveness with the most plausible willingness-to-pay gained adapted from the United Kingdom and converted to the Finnish setting using purchasing power parities. (Figures 2 and 3)

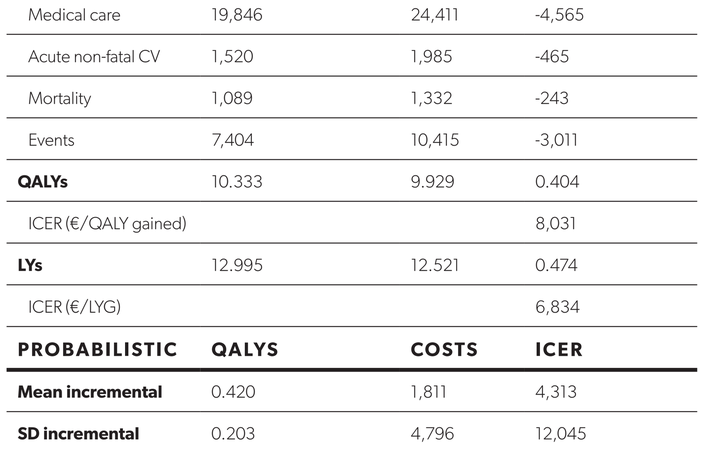


**Figure 2.** Cost-effectiveness plane for the discounted base case results.
Legend: RIV2.5, rivaroxaban 2.5 mg; ASA100, acetylsalicylic acid 100 mg; Q, quartile; QALY, quality-adjusted life year.

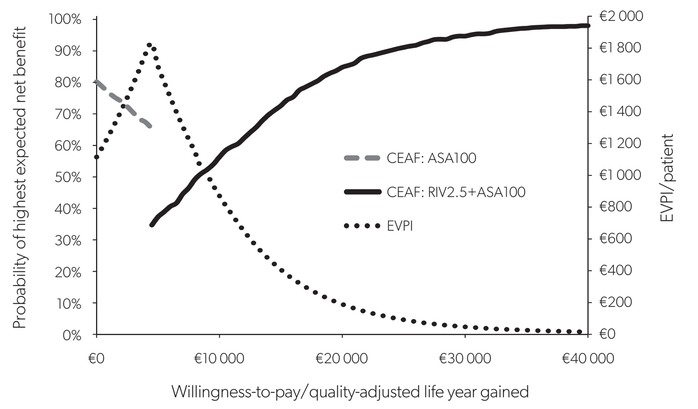


**Figure 3.** Cost-effectiveness acceptability frontier (CEAF) and expected value of perfect information (EVPI) per patient for the discounted base case results.
Legend: RIV2.5, rivaroxaban 2.5mg; ASA100, acetylsalicylic acid 100mg.

The primary result was conservative and robust for RIV2.5+ASA100. All scenario and deterministic sensitivity analysis results for RIV2.5+ASA100 versus ASA100 were clearly below the most plausible assumed willingness-to-pay threshold. In the one-way deterministic sensitivity analyses, the hazard ratios of minor amputation, IS, major amputation, MI and ICH had the biggest impact on the ICER. (Figure 4)

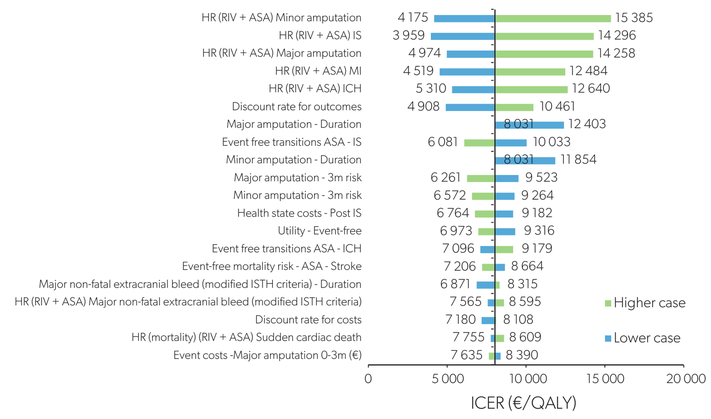


**Figure 4.** Tornado diagram for the most influential drivers of deterministic sensitivity analysis, discounted.
Legend: HR, hazard ratio; RIV, rivaroxaban 2.5mg; ASA, acetylsalicylic acid 100mg; IS, ischaemic stroke; ICH, intracerebral haemorrhage.

### AMONG THE SUBGROUPS:

- Lower than the base case ICER was modelled for the patients with PAD (€779/QALY), CAD and heart failure (€4,933/QALY) or CAD and PAD together (€6,605/QALY).
- Higher ICER was modelled for the patients with CAD and chronic kidney disease (€9,290/QALY) or CAD alone (€11,993/QALY).

### AMONG THE SCENARIO ANALYSES:

- 15 years modelling scenario increased average discounted ICER to €18,192/QALY for RIV2.5+ASA100 versus ASA100.
- The undiscounted ICER was lower (€4,708/QALY) and the 5% discounted ICER was higher (€10,562/QALY).
- Year 2020 as the base year resulted to a lower discounted average primary outcome of €7,221/QALY, and base year 2021 further decreased the primary outcome to €6,901/QALY.
- The imputation of zero probabilities decreased the modelled average ICER a little to €7,930/QALY for RIV2.5+ASA100 versus ASA100.
- The discontinuation applied for the first four years resulted to the modelled cost-savings of €478 (i.e., dominance of RIV2.5+ASA100) and constant discontinuation applied for the full model duration resulted to a low ICER of €1,007/QALY.
- The ICER increased when including only significant HRs (€20,780/QALY) or when using the most recent CVE costs in the case of multiple CVEs (€8,683/QALY).
- When the multiple MCVE costs were modelled to be additive, RIV2.5+ASA100 dominated ASA100 with the average cost savings of €65.
- The ICER increased a little when HRQoL was based on the most recent MCVE (€8,056/QALY) or ATLAS study (€8,057/QALY) and decreased more when multiplicative HRQoL for MCVEs (€7,320/QALY) or HRQoL based on the literature (€6,986/QALY) was modelled.

## CONCLUSION

Adding rivaroxaban 2.5mg to ASA 100mg was cost-effective in the modelled comparisons among stable CAD or symptomatic PAD patients at risk of CVE. Rivaroxaban 2.5mg is reimbursed for prevention of atherothrombotic events for high-risk CAD or PAD patients.


### FUNDING

The financial supporter (Bayer Oy, Espoo, Finland) participated to identification, design, conduct and reporting of the study.


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MAC-XAR-FI-0005-1/10-2019



ISPOR Europe 2019, Copenhagen, 5th November 2019.