NICE National Institute for Health and Care Excellence

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

Lead team presentation

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Company: Bayer

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Key issues (clinical effectiveness)

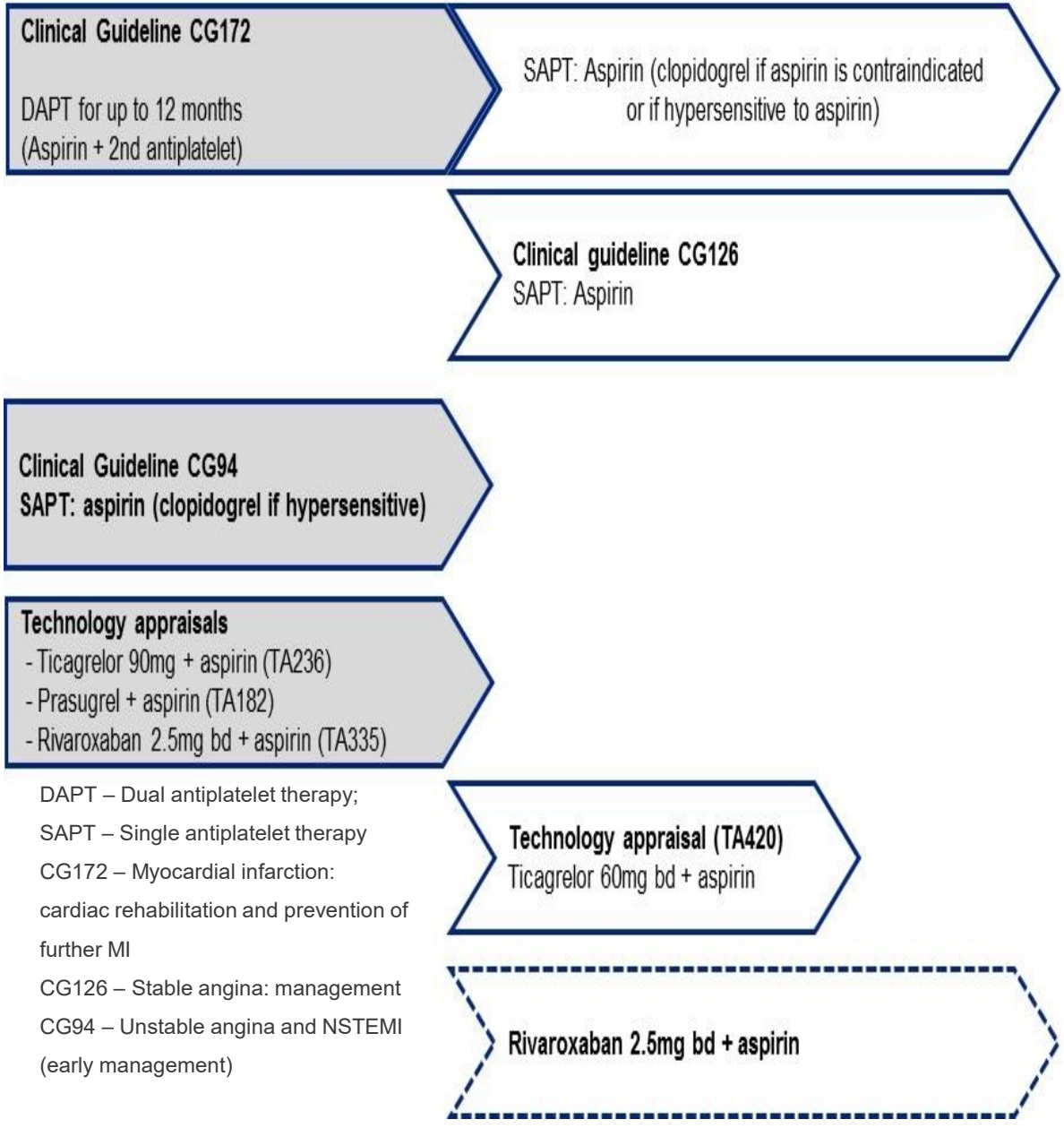
- Who would be considered for this treatment if it were available?
- Are the three subgroups proposed by the company clinically relevant and reasonable?
- What is the committee's view of the risks and benefits of this treatment and the relative effects in the proposed subgroups?
- Is aspirin the 'key' comparator?
- Given that people with symptomatic PAD are included in the marketing authorisation for rivaroxaban, can clopidogrel be excluded as a comparator for the overall COMPASS population (that is, adults with coronary artery disease (CAD) or peripheral artery disease (PAD) at high risk of ischaemic events)?
- How important is ticagrelor plus aspirin as a comparator given the MA for ticagrelor is limited to 3 years post MI? Should it be compared with a subset of the COMPASS population given that only 5% of the COMPASS trial population with coronary artery disease had had an MI within the prior year?

[redacted]

Coronary and peripheral artery disease

- Coronary artery disease (CAD) is the most common type of cardiovascular disease and involves atherosclerotic plaque the coronary arteries potentially leading to angina and myocardial infarction
- CAD affects approximately 1.8 million people in England and is the most common cause of death in England (with 53,668 deaths in 2016)
- Peripheral arterial disease (PAD) is also a common condition, in which a build-up of atheromatous deposits in the arteries restricts blood supply to the limbs
- The risk of ischemic events is determined by patient history and extent of atheroma. People with heart failure, diabetes, poor renal function or diffuse atherosclerosis affecting several areas such as both coronary and peripheral arteries have the greatest risk of further events. Other factors that increase risk are increasing age, BMI and smoking
- Lifestyle changes such as increased exercise, cessation of smoking, dietary changes, and weight loss form initial management of CAD.
- Despite widespread use of aspirin in both the acute and secondary setting, the risk of CV death, MI, and stroke remains high.

Management of CAD and position of rivaroxaban + aspirin in the treatment pathway



DAPT – Dual antiplatelet therapy;
SAPT – Single antiplatelet therapy
CG172 – Myocardial infarction: cardiac rehabilitation and prevention of further MI
CG126 – Stable angina: management
CG94 – Unstable angina and NSTEMI (early management)

CG172 *(Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease)* recommends dual antiplatelet therapy for all people who have had an acute myocardial infarction (MI)

CG126 *(Stable angina: management)* and **CG172** recommend maintenance with long-term aspirin 75mg daily for secondary prevention of cardiovascular events

TA420 Ticagrelor (with aspirin) is recommended for preventing atherothrombotic events in people with a history of MI at high risk of a further event

Treatment choice based on balancing the risks of an increase in bleeding against the reduction in ischaemic events associated with combined anti-platelet therapy

Management of PAD

- NICE Clinical Guideline 147 (peripheral arterial disease: diagnosis and management) recommends lifestyle changes such as smoking cessation, diet/weight management and exercise are first steps for managing PAD
- Lipid lowering drugs (statins) are recommended for primary and secondary prevention of cardiovascular disease
- Antiplatelet agents such as aspirin, clopidogrel, and aspirin plus dipyridamole have been shown to reduce major cardiovascular events in people with symptomatic PAD.
- Technology Appraisal guidance 210 recommends clopidogrel as an option to prevent occlusive vascular events for people who have PAD or multi-vascular disease.

NOTE: Clinical and cost effectiveness results for the comparison of rivaroxaban + aspirin with clopidogrel not presented by the company as they are not seeking a recommendation for the PAD only population.

[redacted]

Patient and carer perspectives

- Patients diagnosed with PAD or CAD are concerned about risk of heart attack or stroke. These health issues can be challenging to manage and require the patient, family or carer to consider making significant adjustments to their lifestyle, diet and exercise in order to reduce risk along with taking medications long term to prevent recurrences and worsening of the disease
- Patients rely on clinicians to present the best options for prevention and treatment
- Patients need to understand why they are being prescribed dual therapy and how the different drugs work. This can assist with drug compliance
- Increased bleeding risk will need to be discussed appropriately with patients to ensure the risks and benefits of the treatment are fully explained
- Rivaroxaban as an anticoagulant does not need regular monitoring which is an advantage of the treatment

Rivaroxaban (Xarelto, Bayer)

Marketing authorisation	Rivaroxaban, co-administered with aspirin, has a marketing authorisation “for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events”.
Administration	Oral. Rivaroxaban 2.5 mg twice daily in combination with daily dose of aspirin 75-100mg
List price	56 tablets for £50.40. The treatment period is indefinite.

[redacted]

Decision problem

	NICE scope		Company submission
Population	Adults with CAD/PAD, excluding people with atrial fibrillation, at high risk of ischaemic events		Only results for people with stable CAD at high risk of ischaemic events provided.
Intervention	Rivaroxaban 2.5mg bd + aspirin		As per scope
Comparator	**People with CAD:** - aspirin - aspirin + ticagrelor	**People with PAD:** - aspirin - clopidogrel	Results presented for comparison of rivaroxaban against aspirin and ticagrelor 60mg + aspirin. No results presented for comparison with clopidogrel
Outcomes	• non-fatal myocardial infarction • non-fatal stroke • bleeding events • mortality • adverse events • health-related quality of life.		As per scope
Subgroups	Where the evidence allows, the following subgroups will be considered: • People with CAD who also have poor renal function (PRF) • People with CAD who also have PAD • People who have had a previous MI • People who have had multiple MI's		• People with CAD and poor renal function (CAD+PRF) • People with CAD and PAD (CAD+PAD) • People with CAD and heart failure (CAD+HF)- not specified in scope but represent people at high risk of thrombotic events who stand to benefit from treatment with rivaroxaban + aspirin. rivaroxaban + aspirin is not anticipated to be used to treat patients defined solely by prior MI's

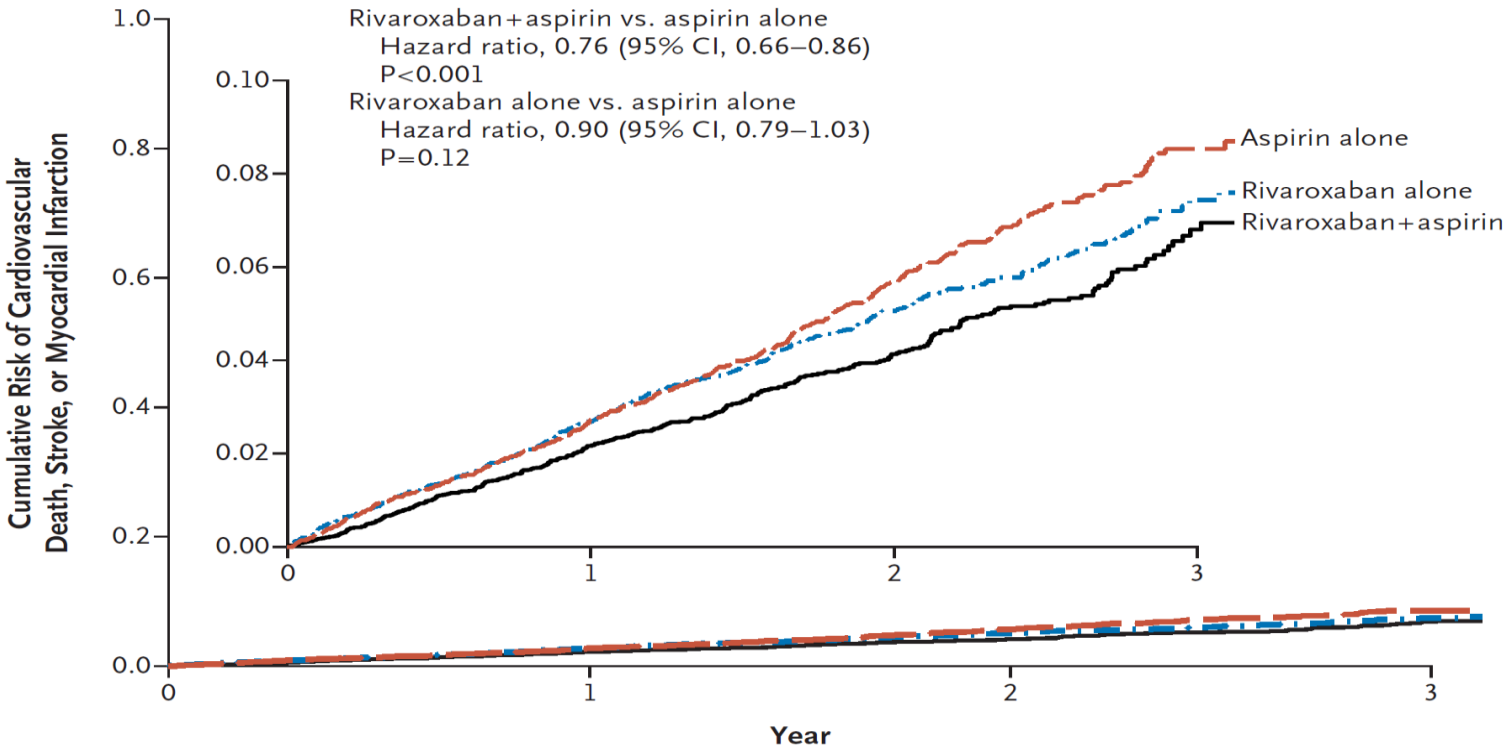
Summary of clinical effectiveness evidence for rivaroxaban

Clinical trial	COMPASS, randomised controlled trial comparing rivaroxaban 2.5 mg + aspirin 100 mg (n=9152) with aspirin 100 mg (n= 9126)
Trial population	People with CAD and/or PAD at high risk of ischaemic events. Patients did not have an indication for dual antiplatelet therapy or full dose anticoagulation (e.g. atrial fibrillation), nor have high bleeding risk that would contraindicate long-term anticoagulant therapy
Trial location	602 international study sites in 33 countries from Europe (including 14 sites in the UK recruiting 541 patients), Middle East, Africa, North and South America, Australia and Asia
Trial key results	**For both the overall trial population and subgroups:** • Statistically significant reduction in risk of primary efficacy outcome (composite of cardiovascular death, stroke or MI) in the rivaroxaban + aspirin arm compared with aspirin • Major bleeding events (primary safety outcome) occurred more often the rivaroxaban + aspirin arm than aspirin only arm
Comparison with ticagrelor+ aspirin	Indirect treatment comparison between COMPASS and PEGASUS trials could only be performed for the overall COMPASS population , CAD +PAD subgroup and CAD+ PRF subgroup. No data from PEGASUS from the CAD+HF subgroup was available
Key result	No statistically significant differences

COMPASS primary efficacy outcome: composite of cardiovascular death, stroke or MI

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	Crude incidence n (%)	N=9152	N=9126	0.76 (0.66-0.86)	<0.001
		379 (**4.1**)	496 (**5.4**)		
CAD+PAD	Crude incidence n (%)	n=1656	n=1641	0.67 (0.52-0.87)	0.003
		94 (**5.7**)	138 (**8.4**)		
CAD+HF	Crude incidence n (%)	n=1909	n=1912	0.68 (0.53-0.87)	0.002
		105 (**5.5**)	151 (**7.9**)		
CAD+PRF	Crude incidence n (%)	n=1824	n=1873	0.73 (0.57-0.92)	0.007
		119 (**6.5**)	165 (**8.8**)		

Overall COMPASS trial population Kaplan-Meier curves of primary efficacy outcome (composite of composite of CV death, stroke, or MI)



No. at Risk				
Aspirin alone	9126	7808	3860	669
Rivaroxaban alone	9117	7824	3862	670
Rivaroxaban+aspirin	9152	7904	3912	658

[redacted]

Source: Figure 4 of company submission

COMPASS primary safety outcome: major bleeding (composite outcome, modified ISTH criteria)

Population	Outcome: Major bleeding (composite outcome)	Rivaroxaban 2.5mg bd + aspirin 100mg od	Aspirin 100mg od	Rivaroxaban 2.5mg bd + aspirin 100mg vs. aspirin 100mg	
				HR (95% CI)	P value
ITT	Crude incidence n (%)	N=9152	N=9126	1.70 (1.40-2.05)	<0.001
		288 (**3.1**)	170 (**1.9**)		
CAD+PAD	Crude incidence n (%)	N=1656	N=1641	1.43 (0.93-2.19)	0.10
		52 (**3.1**)	36 (**2.2**)		
CAD+HF	Crude incidence n (%)	N=1909	N=1912	1.35 (0.87-2.07)	0.18
		49 (**2.6**)	36 (**1.9**)		
CAD+PRF	Crude incidence n (%)	N=1824	N=1873	1.41 (1.00-2.00)	0.05
		75 (**4.1**)	55 (**2.9**)		

Clinical expert opinion

- Registry and trial data demonstrate that people with CAD and PAD are at risk of adverse CV events despite the application of guideline recommended secondary prevention.
- Clinical expert opinion differs regarding the absolute clinical benefit of rivaroxaban + aspirin. One expert notes that rivaroxaban+ aspirin significantly reduces cardiovascular death/MI/ stroke and adverse limb events, with a large impact on stroke reduction. Another expert states that there is negligible benefit for people with CAD although there may potentially be a larger benefit for people with PAD.
- This difference of opinion is also seen for bleeding risk. One expert notes that the bleeding risks of rivaroxaban + aspirin mainly manifest in the first year of treatment, whereas the benefits continue to accrue over time and are of similar risk magnitude to those seen with dual antiplatelet therapy. However, another expert considers that bleeding risk is high, has been underestimated in the trial and can lead to significant morbidity and even permanent disability. Management of bleeding events related to rivaroxaban as well as associated costs and training need to be considered
- One expert opinion is that rivaroxaban + aspirin is the only antithrombotic secondary prevention therapy to reduce cardiovascular and all cause mortality. Findings supportive of a "step change" to improve outcomes among patients with vascular disease and markers of vascular risk

Issue 1: Should the focus be on the whole population or 'high risk' subgroups? (1)

Background	Expert comments
• Company is seeking recommendation for 3 subpopulations that represent people at higher risk of ischaemic events: 1) CAD+ HF 2)CAD+ PAD and 3) CAD + PRF • If subgroups are appropriate, should treatment effects be based on the hazard ratios for the whole population, or the different groups	• Reasonable to limit the use of rivaroxaban to subgroups of people at high risk, however as there is no between group heterogeneity in treatment effects, the overall population treatment effects should be applied • To ensure consistency in approach and to reduce uncertainty in results introduced by small and underpowered subgroups, treatment with rivaroxaban should not be restricted to the 3 high risk subgroups • Other groups that are of high thrombotic risk include people with previous MI / stroke, multi-vessel coronary disease and diabetes would be excluded. People with risk factors other than the 3 subgroups were included in COMPASS and showed similar treatment benefits

[redacted]

Issue 1: Should the focus be on the whole population or 'high risk' subgroups? (2)

Company comments	ERG comments
• Rationale for subgroups based on clinical feedback. Most patients who would be considered for treatment would be captured within these subpopulations. • Analyses using HRs from the overall COMPASS population (instead of subgroup specific HRs) presented. Analyses showed using a fixed HR does not produce ICER's in excess of £20,000 per QALY gained	• fixed HRs only used for the rivaroxaban + aspirin arm in the updated analyses provided. For the ticagrelor + aspirin arm, HRs for the three respective subgroups of the PEGASUS trial are used. The ERG considers that fixed HRs should also be used for the ticagrelor + aspirin arm (i.e. the HR for the whole PEGASUS trial population) for consistency. Analyses using fixed HRs for rivaroxaban + aspirin (COMPASS trial) and the ticagrelor + aspirin arm (PEGASUS trial) show that these changes only alter the results for ticagrelor + aspirin.

Question: should treatment effects be based on the hazard ratios for the whole population ?

[redacted]

Issue 2: clopidogrel as a comparator for people with PAD

Background	Expert comments
• Comparison with clopidogrel for people with combined CAD/PAD, or the overall COMPASS population not presented. Clopidogrel listed in NICE scope as a comparator for people with PAD • The ERG note that clopidogrel is used to treat people with stable CAD and PAD	• Expert 1: It should be included as a comparator for the overall COMPASS analysis as it is frequently used in this population. • Expert 2: clopidogrel is only recommended in CAD for people who cannot tolerate aspirin. People intolerant of aspirin were not eligible for COMPASS, therefore it is not a relevant comparator for COMPASS population. • Clopidogrel is not often used long-term for patients with CAD only but in the CAD+PAD subgroup, it is an obvious comparator.
	Company comments
	• Clopidogrel is only recommended if aspirin is contraindicated. Rivaroxaban cannot be added to aspirin if the patient has a contraindication or hypersensitivity, therefore it is only an option where rivaroxaban is not • In the acute setting, people with CAD may be treated with clopidogrel and aspirin. Rivaroxaban + aspirin not expected to be used in the acute setting, therefore clopidogrel is not valid comparator in the long-term

Question: can clopidogrel be excluded as a comparator for the overall COMPASS population?

Issue 3: comparison with ticagrelor + aspirin in people with history of MI (1)

Background	Expert comments
• Indirect treatment comparison(ITC) comparing rivaroxaban + aspirin with ticagrelor + aspirin used data from COMPASS and PEGASUS • COMPASS and PEGASUS trials had different proportions of people with a myocardial infarction (MI): ➢ Proportion of people with prior MI 100% in PEGASUS, 62% in COMPASS ➢ Time since an MI was 1-3 years in PEGASUS, but any time in the last 20 years in COMPASS ➢ Different bleeding criteria used in the 2 trials: modified ISTH in COMPASS and TIMI in PEGASUS • ERG scenario analysis comparing rivaroxaban + aspirin with ticagrelor + aspirin for people with a prior MI gave lower ICER than the company base case	• Expert 1: limiting COMPASS population to people with a history of MI to align with PEGASUS population would help reduce heterogeneity • Expert 2 :100% of patients in PEGASUS had an MI in the previous 1-3 years and had received treatment with either ticagrelor or clopidogrel + aspirin. Patients with an indication for dual antiplatelet therapy were not eligible for inclusion in COMPASS: • rivaroxaban +aspirin is not an alternative to dual anti-platelet therapy in the acute setting after an MI • The PEGASUS population was not naive to dual anti-platelet therapy. People with bleeding complications during the 1st year after MI would not have been eligible for inclusion in trial. In contrast, the COMPASS population was on maintenance treatment with aspirin and the baseline bleeding risk would be higher in this population • Modified ISTH criteria to classify bleeding risk is more sensitive than the TIMI and neither used in clinical practice

Issue 3: comparison with ticagrelor + aspirin in people with history of MI (2)

Company comments

- History of MI is an insufficient reason alone for addition of rivaroxaban to ongoing treatment with aspirin:
  - absence/presence of MI was not effect-modifying for the primary outcome of COMPASS
  - requirement for a recent MI is a restriction in the marketing authorisation for ticagrelor. Rivaroxaban does not have this restriction
  - using MI subgroup-specific HRs conflicts with the preference for fixed (whole trial population) HRs for subgroup analyses (as discussed in Issue 1)
  - subgroup analysis would be post-hoc and would involve subdividing the COMPASS population twice to a subset of patients who had a previous MI and restricted to MI in the last three years. Uncertainty in results would increase rather than decreasing
- Results using HRs specific to the CAD + recent MI population and using fixed HRs from the overall COMPASS population show that ICERs for rivaroxaban + aspirin remained below £20,000 per QALY gained for subgroup of people with previous MI
- No evidence that the different bleeding classification criteria used in COMPASS and PEGASUS (modified ISTH and TIMI, respectively) would affect respective HRs versus aspirin. Important as HRs used in the economic model.

ERG critique

- Subgroup analysis restricting COMPASS population would be post-hoc analyses that subdivide the population twice increasing uncertainty in results.

Question: Would limiting the COMPASS trial population to people with a history of MI to align with the PEGASUS trial population increase uncertainty in the results?

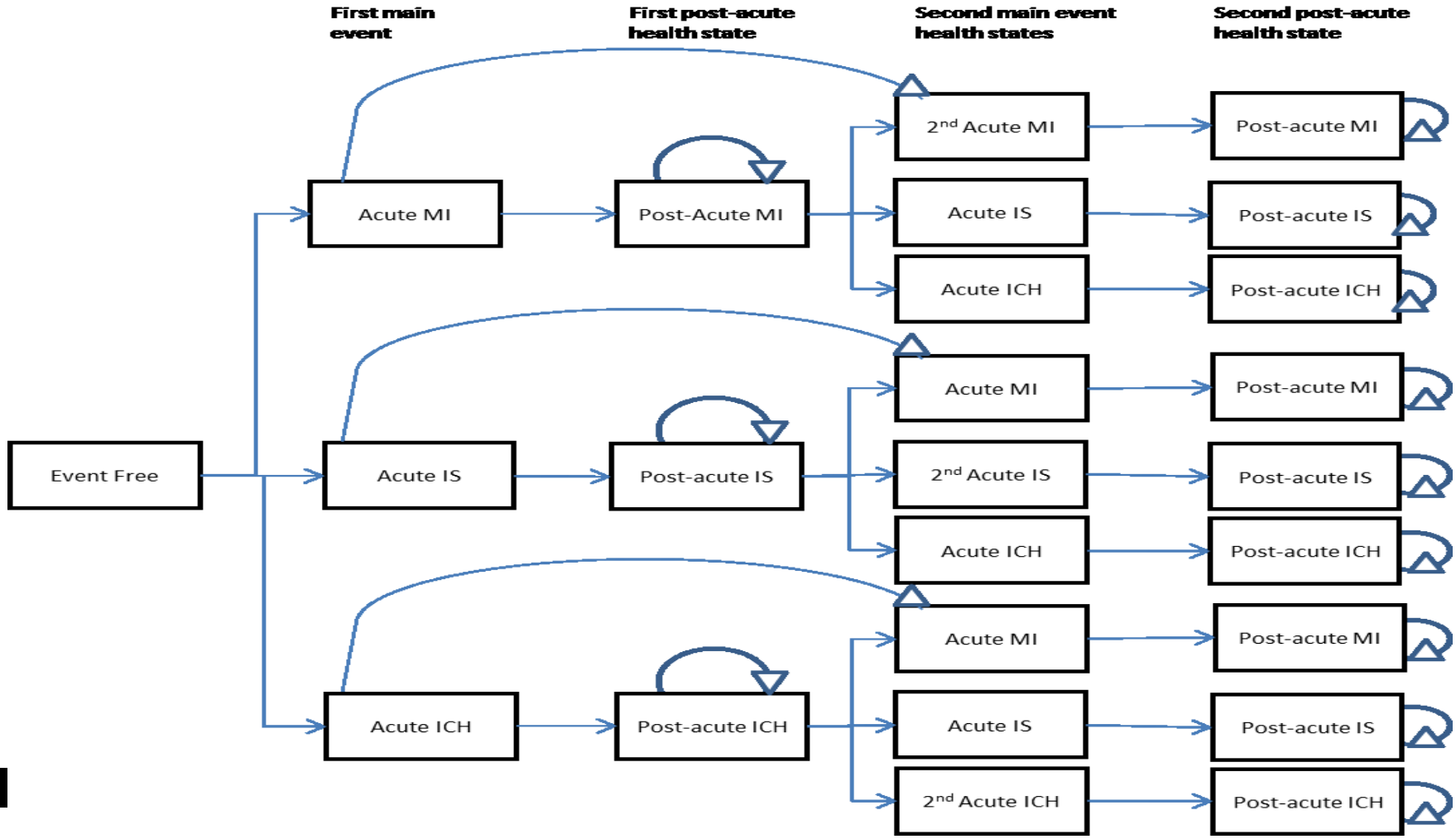
Key issues (cost effectiveness)

- Are the subgroup populations proposed by the company sufficiently clinically distinct such that the relative treatment effect of rivaroxaban + aspirin compared to aspirin would be different from the ITT population?
- For the comparison of rivaroxaban + aspirin with ticagrelor + aspirin, should the subgroup of patients with a history of MI by used from the COMPASS trial population to align with the PEGASUS trial population?
- In order to appropriately capture the uncertainty around the composite outcome of “all CV deaths”, should it be varied in sensitivity analysis simultaneously or by varying each component of CV death individually??

[redacted]

Summary of cost effectiveness evidence (1)

- Company model structure: Markov model with 26 health states. 5 main event health states: 1) event-free, 2) non-fatal MI, 3) ischaemic stroke (IS), 4) intracranial haemorrhage (ICH), 5) death. Main states (MI, IS, ICH) sub-divided into acute event (0-3 months after acute event) or post-event (3+ months after acute event) as well as health states for a second acute event.



Summary of cost effectiveness evidence (2)

- **Population**
  - As per NICE scope and proposed marketing authorisation
  - Characteristics obtained from COMPASS for overall population and subgroups
  - Mean age=68.3 years; 78% male
- **Intervention**
  - Rivaroxaban 2.5mg bd + aspirin 75mg od compared against aspirin 75mg od
  - Rivaroxaban 2.5mg bd + aspirin 75mg compared against ticagrelor 60mg bd + aspirin 75mg
- **Comparators**
  - Aspirin
    - Cost and clinical outcomes from COMPASS
  - Ticagrelor +aspirin
    - Clinical outcomes using data from PEGASUS (as previously used in TA420)
    - Data from ITC of COMPASS and PEGASUS not used directly to inform the economic model. Instead, respective COMPASS and PEGASUS trial-based HRs (compared to aspirin) were used
  - Clopidogrel
    - NICE scope specifies clopidogrel as a comparator in people with PAD, however, the company does not report cost-effectiveness analyses for this comparator and subgroups

[redacted]

Summary of cost effectiveness results- overall COMPASS population (1)

Updated base case after technical engagement incorporates transition probabilities from the REACH registry, all ERG preferences, correction of coding error and uses subgroup specific HRs

Base case incremental cost-effectiveness results– COMPASS population

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER vs baseline (£/QALY)	ICER inc (£/QALY)
Aspirin monotherapy	**12942**	**11.14**	**8.31**					
Ticagrelor + aspirin	14631	11.25	8.39	1689	0.10	0.08	20,833	Extendedly dominated
Rivaroxaban + aspirin	16863	11.50	8.59	2232	0.25	0.20	14,185	

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Cost effectiveness – based on subgroup-specific HR from COMPASS population

Technologies	Total costs	Total LY	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER vs baseline (£/QALY)	ICER inc (£/QALY)
Base case incremental cost-effectiveness results – CAD + PAD population								
Aspirin monotherapy	**13854**	**9.94**	**7.05**					
Ticagrelor + aspirin	15656	10.29	7.31	1802	0.35	0.26	6,930	
Rivaroxaban + aspirin	17191	10.54	7.48	1535	0.25	0.18	7,624	8,639
Base case incremental cost-effectiveness results – CAD + HF population								
Aspirin monotherapy	**11785**	**10.01**	**7.62**					
Ticagrelor + aspirin	13521	10.18	7.75	1735	0.17	0.14	12,756	Ext dom
Rivaroxaban + aspirin	16120	10.91	8.31	2599	0.73	0.56	6,270	
Base case incremental cost-effectiveness results – CAD + PRF population								
Aspirin monotherapy	**11769**	**8.86**	**6.62**					
Ticagrelor + aspirin	13276	8.95	6.70	1507	0.09	0.07	20,788	Ext dom
Rivaroxaban + aspirin	14785	9.34	6.99	1508	0.39	0.29	8,215	

Cost effectiveness – subgroups based on HR from overall COMPASS population

Technologies	Total costs	Total LY	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER vs baseline (£/QALY)	ICER inc (£/QALY)
Base case incremental cost-effectiveness results – CAD + PAD population								
Aspirin monotherapy	**13976**	**10.02**	**7.10**					
Ticagrelor + aspirin	15774	10.37	7.36	1797	0.35	0.26	6,966	
Rivaroxaban + aspirin	17382	10.48	7.44	1609	0.11	0.08	10,054	19,923
Base case incremental cost-effectiveness results – CAD + HF population								
Aspirin monotherapy	**11801**	**10.03**	**7.63**					
Ticagrelor + aspirin	13535	10.20	7.76	1734	0.17	0.14	12,808	Ext dom
Rivaroxaban + aspirin	15952	10.62	8.09	2417	0.42	0.32	9,105	
Base case incremental cost-effectiveness results – CAD + PRF population								
Aspirin monotherapy	**11793**	**8.88**	**6.64**					
Ticagrelor + aspirin	13297	8.97	6.71	1504	0.09	0.07	21,094	Ext dom
Rivaroxaban + aspirin	15080	9.30	6.96	1783	0.33	0.25	10,216	

NOTE: results above incorporate fixed HRs for the rivaroxaban + aspirin arm only. Analyses using fixed HRs for rivaroxaban + aspirin (COMPASS trial) and ticagrelor + aspirin arm (PEGASUS trial) show that using fixed HRs only alter the results for ticagrelor + aspirin

Issue 5: Underestimation of impact of CV death on ICER

Background	Company comments
• Mortality outcome, CV death is stratified by 1) death due to MI, 2) stroke, 3) CV procedure, 4) sudden cardiac death, 5) 'other CV death' and 6) 'all CV death'. However, HR estimates from COMPASS are for "all CV death" and the same HR is assumed for all stratified death events in the model as for "all CV death". In sensitivity analyses, the company has varied each of these mortality HRs separately. As each death rate only has a fraction of the CV deaths, the effect of varying the HRs individually in the DSA and PSA is small. • Company's DSA underestimates impact of varying the stratified mortality outcome of 'CV death'. This has the largest effect on the ICER in ERG scenario analyses • ERG considers better approach is to set all CV mortality HRs to vary together, rather than independently.	• ERG approach assumes each component is independent of the others. In contrast, varying all the components together assumes that they are perfectly correlated. Neither approach is entirely realistic. Therefore, ERG approach could even overestimate uncertainty. • Scenario analysis by ERG should be viewed as a worst-case view of uncertainty around all CV death

Question: should varying the HRs for "all CV deaths" as in the COMPASS trial rather than varying the individual components of CV death represent a worst case scenario for uncertainty or be a standard approach?

[redacted]

Key issues (clinical effectiveness)

- Who would be considered for this treatment if it were available?
- Are the three subgroups proposed by the company clinically relevant and reasonable?
- What is the committee's view of the risks and benefits of this treatment and the relative effects in the proposed subgroups?
- Is aspirin the 'key' comparator?
- Given that people with symptomatic PAD are included in the marketing authorisation for rivaroxaban, can clopidogrel be excluded as a comparator for the overall COMPASS population (that is, adults with coronary artery disease (CAD) or peripheral artery disease (PAD) at high risk of ischaemic events)?
- How important is ticagrelor plus aspirin as a comparator given the MA for ticagrelor is limited to 3 years post MI? Should it be compared with a subset of the COMPASS population even though given that only 5% of the COMPASS trial population with coronary artery disease had had an MI within the prior year?

Key issues (cost effectiveness)

- Are the subgroup populations proposed by the company sufficiently clinically distinct such that the relative treatment effect of rivaroxaban + aspirin compared to aspirin would be expected to be different from the ITT population?
- For the comparison of rivaroxaban + aspirin with ticagrelor + aspirin, should the subgroup of patients with a history of MI by used from the COMPASS trial population to align with the PEGASUS trial population?
- In order to appropriately capture the uncertainty around the composite outcome of “all CV deaths”, should it be varied in sensitivity analysis simultaneously or by varying each component of CV death individually?? population the results?

[redacted]