National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Bayer	Bayer considers it appropriate to refer this topic for NICE appraisal.	Comment noted.
	British Society for Haematology and Royal College of Pathologists (BSH and RCPath)	Yes	Comment noted.
	Thrombosis UK	This is an important development in cardiovacular disease prevention. The population in the study were a well managed group which recived added benefit from the intervention compared to conventional care. The potential population that could receive the intervention is very large and direction to whether this whole group should be considered or if sub-population will gain	Comments noted Subgroups which may gain more benefit were identified during the

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		more benefit will need to be explored if the potential benefits of this intervention is to be recognised	scoping workshop and were included in the "other considerations" section of the scope.
Wording	Bayer	Bayer only intends to request a recommendation in the following subgroups: 1) Patients with coronary artery disease who also have heart failure 2) Patients with coronary artery disease who also have renal disease (eGFR <60ml/min) 3) Patients with coronary artery disease who also have peripheral artery disease Therefore we suggest the wording of the remit is changed to reflect these populations which are within the anticipated marketing authorisation. Our suggested alternative wording is: *To appraise the clinical and cost-effectiveness of rivaroxaban for the prevention of atherothrombotic events in the following subgroups of patients:* *1) Patients with coronary artery disease who also have heart failure* *2) Patients with coronary artery disease who also have renal disease (eGFR <60ml/min)* *3) Patients with coronary artery disease who also have peripheral artery disease*	
	BSH and RCPath	Yes	Comment noted.
	Thrombosis UK	The whole COMPASS population included people with carotid artery disease in the PAD population, this would normally be seen as a 'stroke' population. The proportion of the whole study population was relatively small but has not been included. Another study around the same time did not suggest benefit	Comment noted.

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		from rivaroxaban in ESUS (previously 'cryptogenic stroke') but the question there was different, as was the dose of rivaroxaban	
Timing Issues	Bayer	It is anticipated that rivaroxaban will gain a license in this indication in [confidential information removed]	Comment noted.
	BSH and RCPath	Coronary artery disease and peripheral vascular disease are two important disease conditions that affect many people with increasing age. Prevention of major cardiovascular events and complications in these patients is an important clinical need. However there are many therapies available for use in this situation.	Comment noted.
	Thrombosis UK	This is a substantial development and it is right that NICE consider this before licence to ensure it can be offered to appropriate patients as soon as possible	Comment noted.
Additional comments on the draft remit	Bayer	None	Response noted.
	BSH and RCPath	None	Response noted.
	Thrombosis UK	None	Response noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bayer	The initial description of PAD conveys occlusive pathology focused on the lower limbs. However, PAD encompasses atherosclerosis in other vascular extremities i.e. carotid, vertebral, mesenteric and renal arteries.	Comment noted. The background section has been amended to

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		The description of PAD might anatomically benefit from including the other spectrum of vascular beds that are affected.	read "…peripheral arterial disease (PAD) is caused by atherosclerosis in which narrowed arteries reduce blood flow to the limbs (PAD usually develops in the legs, but other arteries may be involved)."
	BSH and RCPath	Yes	Comment noted.
	Thrombosis UK	Acceptable	Comment noted.
The technology/ intervention	Bayer	No comment	Response noted.
	BSH and RCPath	Yes	Comment noted.
	Thrombosis UK	Yes	Comment noted.
Population	Bayer	It is Bayer's intention to request a recommendation in the following subgroups only: 1) Patients with coronary artery disease who also have heart failure 2) Patients with coronary artery disease who also have renal disease (eGFR <60ml/min) 3) Patients with coronary artery disease who also have peripheral artery disease	Comments noted Subgroups which may gain more benefit were identified during the scoping workshop and were included in the

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		Patients with CAD represent a diverse group of patients with different baseline risks of atherothrombotic events. The three subgroups above represent those patients at higher risk of events who stand to benefit most from therapy with rivaroxaban.	"other considerations" section of the scope.
	BSH and RCPath	Adult patients with stable coronary or peripheral artery disease with standard risk factors. Those patients high risk disease with additional risk factors like antiphospholipid syndrome and other autoimmune diseases. Conditions such as rheumatoid arthritis and lupus should not be included in this as these patients have more aggressive disease, behave differently to patients with standard risk factors and may need more intense treatment. Patients with high BMI/overweight patient should be considered separately.	Comments noted. Subgroups which may gain more benefit were identified during the scoping workshop and were included in the "other considerations" section of the scope.
	Thrombosis UK	See comments above around secondary stroke prevention in those with known carotid disease; the AF population should not be considered	Comment noted. Attendees at the scoping workshop agreed the AF population were not included in this population as they have a different treatment pathway to patients in this scope.
Comparators	Bayer	Bayer is requesting a recommendation in patients who have coronary artery disease in combination with other conditions which puts them at particularly high risk of future events. As such aspirin monotherapy is the main comparator. We agree that ticagrelor + aspirin is a comparator but it should	Comments noted. Attendees at the scoping workshop

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		be considered secondary to aspirin monotherapy. Ticagrelor + aspirin is restricted to patients with a history of MI for a maximum duration of three years since an event. As such it represents a comparator in a proportion of patients in the subgroups we are requesting and only for a relatively short period of time. Clopidogrel is not a comparator in patients with CAD.	agreed that aspirin monotherapy is the main comparator. Attendees at the scoping workshop agreed that clopidogrel is an appropriate comparator in patients with PAD.
	BSH and RCPath	Currently many patients on dual antiplatelet treatment Aspirin and clopidogrel, and Clopidogrel only group for CAD Naftidrofuryl does not need be considered as a comparator (as it is a vasodilator and not therapy to prevent occlusive events) Some patient may be on warfarin instead of dual antiplatelet treatment and also some high risk patients on aspirin and warfarin	Comments noted. Consultees agreed that naftidrofuryl was not an appropriate comparator so it has not been added to the scope. The majority of the attendees at the scoping workshop agreed that warfarin was not an appropriate comparator so it has not been added to the scope.
	Thrombosis UK	We note that TA 223 is included. This intervention is around symptom management in people with PAD, not prevention of disease progression or limb salvage as would not seem appropriate in this setting	Comment noted. Consultees agreed that TA223 was not related and it has been

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			removed from the scope.
Outcomes	Bayer	Bayer agrees with the suggested outcome measures.	Response noted.
	BSH and RCPath	It would be better to include incidence of venous thromboembolism as well	Comment noted. Attendees at the scoping workshop agreed that incidence of venous thromboembolism was not an appropriate comparator and should not be included in the scope.
	Thrombosis UK	Acceptable	Response noted.
Economic analysis	Bayer	No comment	Response noted.
	BSH and RCPath	Yes. The cost of reversal agents for Factor XA inhibitors has been included in the economic analysis	Comment noted.
	Thrombosis UK	Acceptable	Response noted.
Equality and Diversity	Bayer	Bayer is not aware of any issues relating to inequalities.	Comment noted.
	BSH and RCPath	No specific comments to add	Comment noted.

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	Thrombosis UK	It could be noted that aspirin resistance in the BME community has been stated to be as high as 20% and this intervention may assist in this subgroup. How this group was seen in the entire COMPASS population was not discussed in the paper but maybe worthy of consderation	Comment noted. NICE guidance will not make differential recommendations by race so this subgroup will not be considered separately.
Other considerations	Bayer	No additional issues have been identified	Response noted.
	BSH and RCPath	None	Response noted.
	Thrombosis UK	The entire COMPASS population would be a large intervention group if this intervention was to be adopted across all those documented with disease. There may be sub groups which will have a greater benefit for the cost of intervention and we would suggest that the cost effectiveness of the intervention for the whole CVD population should be considered but also attention to the three arterial beds (coronary artery, carotid artery and peripheral arteries) are also considered seperately as there may be more cost effetive groups for intervention while rivaroxaban is at its current costs which should be reviewed if there is cost reduction in the future	Comments noted Subgroups which may gain more benefit were identified during the scoping workshop and were included in the “other considerations” section of the scope.
Innovation	Bayer	Bayer considers rivaroxaban is innovative for the prevention of atherothrombotic events in patients with non-acute coronary artery disease. These patients continue to possess significant risk of further events. This risk can be significantly reduced with the addition of rivaroxaban.	Comment noted.

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	BSH and RCPath	Yes Among patients with stable atherosclerotic vascular disease, rivaroxaban plus aspirin would provide a better cardiovascular outcomes. Although, more major bleeding events can be expected from these patients compared to aspirin alone, the clinical studies have not shown increase incidence of life threatening bleeding	Comment noted.
	Thrombosis UK	Yes; the value of additional benefit from anticoagulation, previously warfarin, has been know for a while but at the cost of more bleeding and hence harm was too large. This intervention with a low dose Xa inhibitor has reduced always present risk of harm when modifying the coagulation systems of the body to a more acceptable level	Comment noted.
NICE Pathways	Bayer	**Where do you consider rivaroxaban will fit into the existing NICE pathways** • **Lower limb peripheral arterial disease (2018) NICE pathway,** • **Cardiovascular disease prevention (2017) NICE pathway,** • **Myocardial infarction: rehabilitation and preventing further cardiovascular disease (2017) NICE pathway?** Of the three pathways rivaroxaban will fit in the pathway of drug treatment for patients who have had an MI. Rivaroxaban already has a recommendation from NICE for ACS (TA335). If recommended in non-acute patients following this assessment rivaroxaban would bridge both the acute and non-acute MI settings.	Comments noted.

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		However, it will also be used in CAD patients who may not have a history of MI and a pathway specific to these patients is not listed above.	
	BSH and RCPath	None	Response noted.
	Thrombosis UK	None	Response noted.
Questions for consultation	Bayer	**What is the treatment pathway for patients with CAD? What other therapies would they be on at this stage? Would they continue on these as well as rivaroxaban?** The treatment pathway for patients with CAD is as recommended in NICE guidelines i.e. dual antiplatelet therapy during the acute phase reducing to single antiplatelet therapy (low dose aspirin) once the patient is no longer considered to be acute. Patients with CAD tend to be on a background of statins and blood pressure medication. These medications would be continued if rivaroxaban were to be added to existing therapy. **What is the treatment pathway for patients with PAD? What other therapies would they be on at this stage? Would they continue on these as well as rivaroxaban?** The treatment pathway for patients with PAD is as recommended in NICE guidelines. Background standard of care mirrors that of CAD patients (e.g. blood pressure and lipid-lowering medication).	Comments noted. See previous responses.

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		PAD pharmacological therapy is subdivided into peripheral vasodilators (e.g. naftidrofuryl oxalate) for alleviation of leg pain produced by intermittent claudication or therapy aimed at the prevention and or recurrence of occlusive vascular events. Background standard of care and peripheral vasodilators would be continued if rivaroxaban were to be added to existing therapy. **Have all relevant comparators for rivaroxaban been included in the scope?** No comparator treatments are missing from the existing scope. **Which treatments are considered to be established clinical practice in the NHS for preventing major cardiovascular events in people with coronary or peripheral artery disease?** Rivaroxaban will be used to reduce the risk of events in patients who are no longer considered to be an 'acute' patient. Established clinical practice in these patients to reduce thrombotic events is aspirin monotherapy. Ticagrelor + Aspirin is recommended by NICE for up to three years in patients who have had an MI. However its use in comparison to aspirin monotherapy is low. **Is aspirin in combination with warfarin a comparator for people with CAD and PAD?**	

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		Aspirin in combination with warfarin is not used in clinical practice in patients who have 'stable' disease. It is not a comparator for this appraisal. **Are treatments specifically for intermittent claudication (e.g. naftidrofuryl oxalate) a comparator for people with PAD?** These pharmacological treatments are distinctly licensed for the alleviation of leg pain produced by intermittent claudication (i.e. peripheral vasodilator therapy). They are used for control of such symptoms and are not indicated to reduce atherothrombotic events. They are not comparators for this appraisal. **Are there subgroups of people in whom rivaroxaban is expected to be more clinically effective and cost effective or other groups that should be examined separately?** The subgroups where rivaroxaban is expected to be more clinically effective and cost-effective are: • Patients with coronary artery disease who also have heart failure • Patients with coronary artery disease who also have renal disease (eGFR <60ml/min) • Patients with coronary artery disease who also have peripheral artery disease **Where do you consider rivaroxaban will fit into the existing NICE pathways**	

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		• **Lower limb peripheral arterial disease (2018) NICE pathway,** • **Cardiovascular disease prevention (2017) NICE pathway,** • **Myocardial infarction: rehabilitation and preventing further cardiovascular disease (2017) NICE pathway?** Of the three pathways rivaroxaban will fit in the pathway of drug treatment for patients who have had an MI. Rivaroxaban already has a recommendation from NICE for ACS (TA335). If recommended in non-acute patients following this assessment rivaroxaban would bridge both the acute and non-acute MI settings. However, it will also be used in CAD patients who may not have a history of MI and a pathway specific to these patients is not listed above.	
	BSH and RCPath	Following additional questions need be included in the consultation 1) Whether this alters the risk benefit balance for revascularisation procedures and how it can be integrated into the current therapy for people who have had them (CABG or stent)? 2) Should we consider those patients high risk disease with additional risk factors like antiphospholipid syndrome and other autoimmune and high BMI patients separately from this scope? 3) Naftidrofuryl does not need be considered as a comparator (as it is a vasodilator and not therapy to prevent occlusive events) 4) Incidence of VTE should be included as an outcome measure	Comments noted. See previous responses.
	Thrombosis UK	What is the treatment pathway for patients with CAD & PAD? What other therapies would they be on at this stage? Would they continue on these as well as rivaroxaban?	Comments noted. See previous responses.

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		-Yes the population study were receiving excellent secondary preventive therapy and this intervention achieved additional benefit Have all relevant comparators for rivaroxaban been included in the scope? Which treatments are considered to be established clinical practice in the NHS for preventing major cardiovascular events in people with coronary or peripheral artery disease? Is aspirin in combination with warfarin a comparator for people with CAD and PAD? -There are studies looking at the use of warfarin in those post MI and post cryptogenic stroke, however the complexities of warfarin have interfered with intervention and has never been widely adopted post MI and the bleeding rates were too high in the stroke population THIS IS NOT LOOKING AT ANTICOAGULATION IN THOSE WITH AF AND IT IS IMPORTANT THAT THIS POPULATION IS NOT INCLUDED Are treatments specifically for intermittent claudication (e.g. naftidrofuryl oxalate) a comparator for people with PAD? -As stated above this is inappropriately included Are there subgroups of people in whom rivaroxaban is expected to be more clinically effective and cost effective or other groups that should be examined separately? -As stated above, the three specific arterial beds should be considered as a whole and also seperately in cost analysis	

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		Do you consider rivaroxaban to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? -Yes	
Additional comments on the draft scope	Bayer	No additional comments	Response noted.
	BSH and RCPath		
	Thrombosis UK	No.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

TREND UK