Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

Second additional report

BMJ Technology Assessment Group

Evidence Review Group (ERG) second additional report for Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

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Additional analyses carried out by the ERG

In response to additional questions from the Appraisal Committee for this Single Technology Appraisal (STA), the ERG has carried out additional analyses of:

1. The licensed indication for rivaroxaban compared with the population of ROCKET-AF;
2. The effect of using the North America subgroup as a surrogate for good International Normalised Ratio (INR) control in ROCKET-AF;
3. The clinical and cost-effectiveness of rivaroxaban compared with dabigatran 110mg and 150mg for the composite outcome of ischaemic stroke and systemic embolism;
4. The average annual anticoagulation monitoring cost assumed in the manufacturer's model.

1. The licensed indication for rivaroxaban compared with the population of ROCKET-AF

The ERG notes that the manufacturer's European licence for use in atrial fibrillation is for the "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack". In the manufacturer's submission[1] the manufacturer reported that this equates to a $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke history [double]) score of ≥1, which the ERG notes is the population specified in the final scope issued by NICE[2] for this STA.

The ERG notes that the majority of the population of the key trial, ROCKET-AF,[3] that provides clinical effectiveness data for rivaroxaban for this STA has a $CHADS_2$ score ≥3 (87% of the total intention-to-treat [ITT] population). The ERG considers that the population of ROCKET-AF represents a generally high-risk population compared with the final scope issued by NICE. The ERG notes that there is limited clinical evidence regarding the efficacy of rivaroxaban in the moderate risk AF population (defined as $CHADS_2$ score 1–2), and is unsure whether the results of ROCKET-AF can be generalised to this population. A breakdown of the $CHADS_2$ score distribution of patients in ROCKET-AF is presented in Table 1.

The ERG discusses the issues around the population of ROCKET-AF in sections 3.1 and 4.2.2 of the ERG report.[4]

Table 1. Baseline $CHADS_2$ scores for ROCKET-AF ITT population

$CHADS_2$,	**Rivaroxaban (n = 7,131)**		**Warfarin (n = 7,133)**		**Total (n = 14,264)**	
	n	%	n	%	n	%
1, n (%)	1	0.01	2	0.03	3	0.02
2, n (%)	925	12.97	934	13.09	1,859	13.03
3, n (%)	3,058	42.88	3,158	44.27	6,216	43.58
4, n (%)	2,092	29.34	1,999	28.02	4,091	28.68
5, n (%)	932	13.07	881	12.35	1,813	12.71
6, n (%)‡	123	1.72	159	2.23	282	1.98

‡ $p < 0.05$ for the between-group comparison.

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled).

2. The effect of using the North America subgroup as a surrogate for good INR control in ROCKET-AF

In their original submission[1], the manufacturer reports that the North America region subgroup had the highest overall INR control; [redacted] 58% for the overall ROCKET-AF population (Note: mean overall trial TTR 55%). The ERG thus considers that the most appropriate data to inform the question of the clinical effectiveness of rivaroxaban compared with warfarin in a population with good INR control are the ROCKET-AF trial data from the North America subgroup. These data are presented alongside the full trial data in Table 2.

Table 2. Results for North America subgroup versus whole trial data for ROCKET-AF (HR < 1 favours rivaroxaban; HR > 1 favours warfarin)

Outcomes	**Safety-on-treatment**		**Intention-to-treat**	
	North America HR‡ (95% CI)	**Full trial data HR‡ (95% CI)**	**North America HR‡ (95% CI)**	**Full trial data HR‡ (95% CI)**
Efficacy				
Primary efficacy endpoint	[redacted]	0.79* (0.65 to 0.95)	[redacted]	0.88 (0.75 to 1.03)
Stroke	[redacted]	0.85 (0.7 to 1.03)	[redacted]	[redacted]
• Primary ischaemic stroke	[redacted]	0.94 (0.75 to 1.17)	[redacted]	[redacted]
• Primary haemorrhagic stroke	[redacted]	0.59* (0.37 to 0.93)	[redacted]	[redacted]
Non-CNS systemic embolism	[redacted]	0.23* (0.09 to 0.61)	[redacted]	[redacted]

Outcomes	Safety-on-treatment		Intention-to-treat	
	North America HR‡ (95% CI)	Full trial data HR‡ (95% CI)	North America HR‡ (95% CI)	Full trial data HR‡ (95% CI)
Myocardial infarction	[redacted]	0.81 (0.63 to 1.06)	[redacted]	[redacted]
Vascular death	[redacted]	0.89 (0.73 to 1.10)	[redacted]	[redacted]
All-cause mortality	[redacted]	0.85 (0.7 to 1.02)	[redacted]	0.92 (0.82 to 1.03)
Safety				
Principal safety endpoint (a)	[redacted]	1.03 (0.96 to 1.11)	[redacted]	[redacted]
Major bleeding	[redacted]	1.04 (0.9 to 1.2)	[redacted]	[redacted]
Non-major clinically relevant bleeding	[redacted]	1.04 (0.96 to 1.13)	[redacted]	[redacted]
Gastro-intestinal major bleed	[redacted]	[redacted]	[redacted]	[redacted]

‡ HRs are for rivaroxaban versus warfarin.

*p < 0.05

[redacted]

[redacted]

[redacted]The ERG acknowledges that the manufacturer does not draw any conclusions based on any of the subgroup results, and that the subgroups were not powered at the start of the trial to detect statistically significant differences in treatment effect.[redacted]

3. The clinical and cost-effectiveness of rivaroxaban compared with dabigatran 110mg or 150mg for the composite outcome of ischaemic stroke and systemic embolism

The ERG has conducted an exploratory analysis to assess the impact of combining the outcome data for ischaemic stroke and systemic embolism. Analysing this new composite outcome using the ERG's NMA (presented in the ERG report[4]), provides further information on the clinical efficacy of rivaroxaban versus dabigatran 110mg and dabigatran 150mg (Table 3). The ERG feels it important to highlight that this comparison may potentially be confounded by double counting of events for people who suffered both an ischaemic stroke and a systemic embolism, and thus the results should be interpreted with caution. The ERG would also like to highlight that the primary composite outcomes for both ROCKET-AF[3] and RE-LY[5] (the trials informing rivaroxaban and dabigatran in the network, respectively) included the composite of stroke (ischaemic and haemorrhagic) and systemic embolism, and due to the inclusion of haemorrhagic stroke these data could not be used for this comparison.

Table 3. Results from the NMA conducted by the ERG for the comparison of rivaroxaban with dabigatran (OR <1 favours rivaroxaban; OR >1 favours dabigatran)

Outcome	Dabigatran 110mg		Dabigatran 150mg	
	Mean OR	95% CrI	Mean OR	95% CrI
Ischaemic stroke	0.82	0.59 to 1.11	1.20	0.84 to 1.66
Systemic embolism	0.36*	0.09 to 0.95	0.42	0.10 to 1.11
Composite of ischaemic stroke and systemic embolism	0.78	0.57 to 1.05	1.12	0.80 to 1.53

*Statistically significant at the 5% level.

Abbreviations used in table: 95% CrI, 95% Credible Interval; OR, odds ratio.

The results of the comparison of rivaroxaban with dabigatran for the composite outcome of ischaemic stroke and systemic embolism are similar to the results for the corresponding comparison in ischaemic stroke alone. For the composite outcome of ischaemic stroke and systemic embolism, the ERG's exploratory analyses suggest that rivaroxaban is more effective at reducing the composite of ischaemic stroke and systemic embolism events compared with dabigatran 110mg but not when compared with dabigatran 150mg. However, neither result reaches statistical significance (see Table 3).

4. The average annual anticoagulation monitoring cost assumed in the manufacturer's model

In the updated model, the manufacturer has assumed an annual anticoagulation cost of £[redacted]. This includes initial and subsequent visits in primary or secondary care and patient transport costs. It also takes account of whether or not patients are warfarin naive or experienced. All costs are taken from NHS unit costs where available and resource use is based on the manufacturer's survey commissioned in support of the submission. For further details, please see section 5.3.9 of the original ERG report.[4]

5. References

1 Bayer Plc. *Submission to National Institute for Health and Clinical Excellence (NICE), Single Technology Appraisal (STA) of Rivaroxaban (Xarelto®) for the Prevention of Stroke in Atrial Fibrillation*. August 2011.

2 National Institute for Health and Clinical Excellence. *Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation: final scope*. NICE, 2011. http://www.nice.org.uk/nicemedia/live/13308/55112/55112.pdf (accessed February 2012).

3 Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91.

4 Edwards SJ, Hamilton V, Nherera L, Trevor N, Barton S. *Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation: A Single Technology Appraisal*. BMJ-TAG, London, 2011.

5 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.