National Essential Medicines List Pharmacoeconomics and Budget impact analysis Adult Hospital Level Component: Cardiovascular conditions

Date: 11 December 2015
Medication: Rivaroxaban
Indication: Stroke prevention in atrial fibrillation

1 INTRODUCTION

A motivation was received for rivaroxaban to be added to the EML for the following conditions;

- Post hip and knee surgery prophylaxis
- Treatment of DVT and pulmonary embolism
- Stroke prevention in treatment of non-valvular atrial fibrillation

The evaluation considered rivaroxaban as it was the NOAC that was presented for review by the EML. There is another NOAC currently available on the market, dabigatran, which also has clinical evidence for use in AF and other conditions. However, the EML elected to review rivaroxaban because it is a once daily dosing and does not require differential dosing dependent on age. Dabigatran is a twice daily dose and recommends 150mg in patients under 80 years of age, with a 110mg dose of patients over 80 years.

This report deals with the pharmacoeconomics and budget impact analysis for the use of rivaroxaban compared to warfarin in the prevention of stroke in patients with non-valvular atrial fibrillation (AF)

2 PHARMACOECONOMICS MODEL - METHODS

A simple markov model was developed. The health states selected for the model were; well (ie well with atrial fibrillation), stroke, intracranial haemorrhage, gastrointestinal bleed (major bleed), death. The basecase of the model ran for a 10 year time horizon. The age of patients entering the model was 75 years – this was based on the age of entry for the ROCKET trial.

A discount rate of 5% was selected for both cost and clinical inputs.

The only incremental medicine cost was that of the rivaroxaban vs warfarin+INR – ie all treatments for atrial fibrillation remained the same.

Only one event could happen to a patient in the duration of the model – for example if they had a stroke in year 2, the model did not allow for a GI bleed in year 3

A more sophisticated model is probably required to better analyse the concurrent nature of long term consequences, however, it is unclear whether this would materially impact the outcome.

3 CLINICAL INPUTS

The clinical input variables for the cost-effectiveness analysis were obtained from a number of sources. The main effect size variables were taken from the ROCKET-AF trial (Patel MR 2011). These inputs were also used in the published health economic studies.

In order to determine a transition probability (assuming a 1-year cycle period) for the health economics model, an annual event rate is required rather than a total event rate over the duration of the trial. Therefore the event rate per year as reported in the ROCKET trial was used (see table below).

Baseline Event Risk and Relative Treatment Efficacy
All patients were as per the demographics of the ROCKET trial ie 75 years or older

Outcome	**Base-case (% per year)**	**Range (CI of HR)**	**P value**
Stroke or Systemic Embolism (ITT)			
Warfarin	2.40%		Combined CHADS2 Scores
Rivaroxaban	2.10%	0.75-1.03	
ROCKET showed p<0.001 for non-inferiority and p=0.12 for superiority			
Using Safety, as-treated population			
Warfarin	2.20%		
Rivaroxaban	1.70%	0.65-0.95	p<0.001 non-inferiority, p=0.02 superiority
Uisng Per Protocol, as treated population			
Warfarin	2.20%		
Rivaroxaban	1.70%	0.66-0.96	p<0.001 non-inferiority
Intracranial Haemorrhage			
Warfarin	0.70%		
Rivaroxaban	0.50%	0.47-0.93	p=0.02
Major GI Haemorrhage			
Warfarin	2.20%		
Rivaroxaban	3.20%	1.04-1.41	p<0.001
Mortality			
Warfarin	2.20%		
Rivaroxaban	1.90%	0.7-1.02	p=0.07

Table 1. Effect size used in model based on ROCKET trial data

The utilities used to calculate the QALYs were obtained from 2 cost-effectiveness analyses. It was assumed that the utility value applied to the cycle (ie 1 year) in which the event occurred. Thereafter the utility returned to that of the Well state (ie well with AF).

Health State		*Utilities*
Well with AF		0.98
Ischaemic stroke		0.39
Ischaemic stroke disability		0.75
Post ischaemic stroke no disability		0.95
Haemorragic stroke		0.39
Haem stroke disability		0.75
Post haem stroke no disability		0.95
Major bleed		0.96
Dead		0.00

Table 2. Utility values for events and health states

4 COST INPUTS

The medicine costs were based on 2015 data. The price of warfarin was determined from the current contract price and the price of the rivaroxaban was obtained from the Single Exit Price database (ie a private sector price). The impact of varying the price of rivaroxaban was analysed in the sensitivity analysis.

The total annual medicine cost of treating a patient is shown below;

	per month	**per annum**
Rivaroxaban 20mg	700.26	8403.08
Warfarin	8.76	105.08
Warfarin+INR	49.67	596.00

Table 3. Annual medicine cost of treating for prevention of stroke

It was assumed that, on average, patients had 12 INRs per annum at a cost of R40.91 per test. In the event of lack of warfarin control, it is likely that patients would have more than 12 INRs in the year and therefore a sensitivity analysis was carried out to assess the impact of up to 36 INRs per annum.

The event costs were adapted from private sector data. These costs need further confirmation as they are currently estimates. Variance in the costs of each event was analyzed in the sensitivity analysis

Event Costs pa	*Rands*
Mortality Cost	1000
Ischaemic Stroke event cost	55000
Post-Isc stroke disability costs	17000
Intracranial Haemorragic stroke event cost	55000
Post-Haem stroke disability costs	17000
Major bleed disability costs	17000
Major bleed cost	25000
No major bleed cost	360
No disability costs	360

Table 4. Estimated costs per event per annum

5 MODEL RESULTS

The base case incremental cost-effectiveness ratio for the model was **R609 890/QALY.**

A sensitivity analysis was carried out to determine which parameters had the most impact on the ICER result. The sensitivity analysis included varying costs, clinical event rates as well as discount rate or time horizon. The Tornado diagram below indicates that the model was most sensitive to a variation in time horizon from 1 to 10 years. When the stroke event rates for warfarin and rivaroxaban were equivalent (ie assuming non-inferiority), the ICER increased to above R1.1million/QALY. Gastrointestinal bleeds (major) also showed some sensitivity both in utility variation as well as to changes in the event rate of GI bleeds for warfarin.

The model was insensitive to discounting as well as changes in number of INR tests carried out per annum ranging from only 4 to 36 pa. Changes in ICH costs and utility did not have much impact on the sensitivity of the model.

The only parameter which shifted the ICER range in any way below an ICER of R400 000/QALY was the cost of rivaroxaban. However, even at a rivaroxaban price discount of 80%, the ICER was R303 284/QALY.

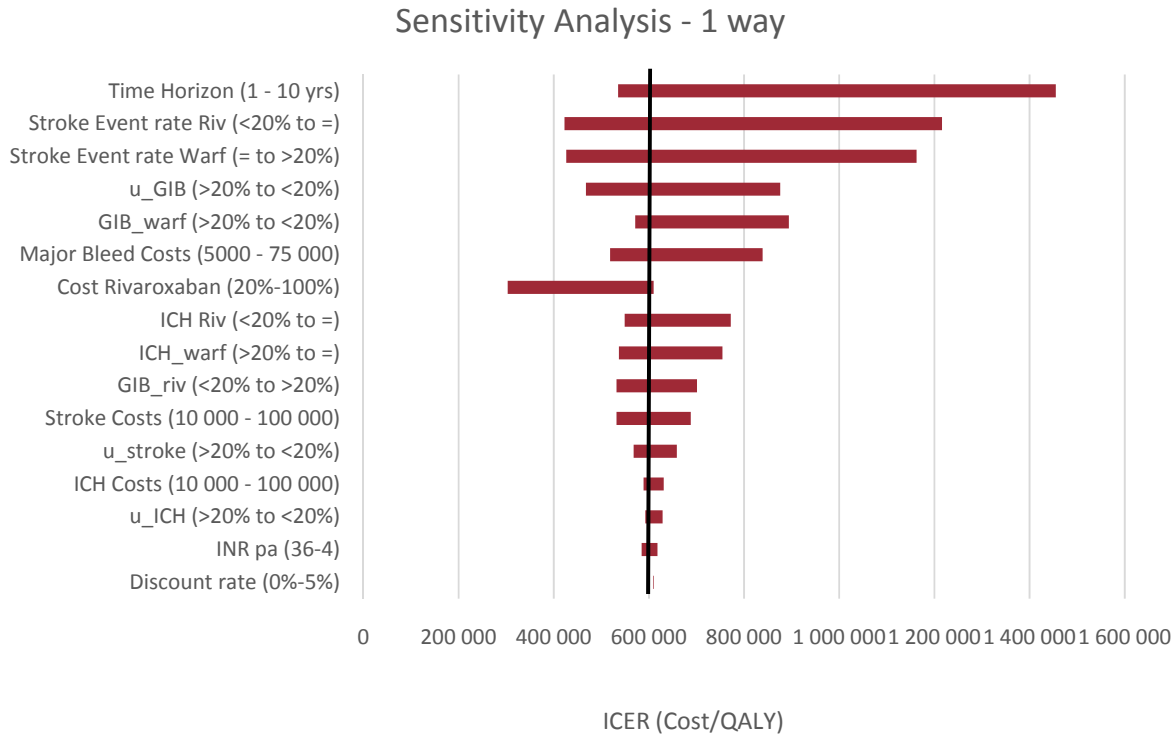

Figure 1. Tornado diagram of one-way Sensitivity Analysis

This model does not take into account multiple simultaneous variations in parameters (ie probabilistic sensitivity analysis).

5.1 PUBLISHED COST-EFFECTIVENESS STUDIES

The cost-effectiveness of the NOACs has been carried out in a number of settings and countries. 2 systematic reviews of cost-effectiveness analyses of the NOACs have been published recently (Zheng Y 2014, Ferreira J 2015) as well as a review of the methodologies and results of the NOAC cost-effectiveness studies(Singh SM 2015).

The table below shows the different rivaroxaban studies and the cost-effectiveness model outcomes from these studies

Study	ICER	Setting	Comment
Harrington, 2013	US$ 11 150/QALY	USA	Cost effective in 14.9% of simulations
Lee et al, 2012	US$27 498/QALY	USA	Price of rivaroxaban USD6.8
Kleintjens, 2013	EUR 8809/QALY	Belgium	Threshold EUR 35 000/QALY
Coyle et al, 2013	CAD 55 757/QALY	Canada	Cost-effective in 2.1% of simulations
Kansal, 2012	CAD 22 475/QALY	Canada	Threshold CAD 30 000/QALY

Table 5. Summary of published cost-effectiveness outcomes

A meta-analysis of the data by Ferreira et al showed that the mean ICER for rivaroxaban was EUR 17 960±12 005/QALYs which was deemed to be cost effective at a willingness to pay (WTP) threshold of EUR 30 000/QALY.

In the Zheng et al study, a meta-analysis of the data was used to create a new model which showed an ICER of £7203/QALY. At a cost-effectiveness threshold of £20 000/QALY this was considered to be cost-effective. However, this model also showed that dabigatran was more cost-effective than either rivaroxaban or apixaban compared to warfarin and, in fact, was shown to be dominant (ie costs less and has better clinical outcomes)

There are a number of uncertainties in the published cost-effectiveness studies and in the analysis carried out here.

The uncertainties related to the clinical trial data include the following;

- Duration of treatment and follow-up; the average duration of follow-up in the trials is around 2 years and therefore the trial-based clinical data is obtained from this information. However, AF is a lifelong condition and therefore treatment is likely to continue on a long-term basis. The clinical outcomes beyond 2 years are uncertain and based on assumption and extrapolations
- Wafarin control (TTR) – generally poorer warfarin control in the public sector in SA than in the trials
- Baseline stroke or haemorrhage risk in SA population
- Age of patients – average age in the trials is around 71-73 years. In SA, the average age of AF patients is similar in the private sector but unclear in the public sector.
- Management of bleeding – treatment patterns and cost

6 BUDGET IMPACT ANALYSIS

For the budget impact analysis (BIA), an excel spreadsheet model was developed to take into consideration the following factors; total AF population, patients on warfarin, uptake of rivaroxaban, cost of INR testings, change in effect size of intracranial haemorrhage and major bleeds. The BIA was based on a total population of 45 244 189 million people (Day C 2014). This excluded the approximately 8 million people covered under medical insurance in the private healthcare sector.

The prevalence of AF in males (565/100 000) and females (366/100 000) was derived from the Global AF Study [ref]. The proportion of patients with non-valvular AF was determined from two studies to give a lower limit of 56% (Soweto Heart study) and upper limit of 73% (Jardine et al, SAMJ). In the Jardine et al AF Survey in South Africa, the proportion of patients on warfarin was around 75%.

	No of Patients
Total AF patients	421 585
AF Males	255 946
AF Females	165 638
Pts with non-valvular AF	236 087
Growth rate in patients with AF	2%
Uptake of rivaroxaban	20%

Table 6. Estimated prevalence data for non-valvular AF

The costs of treating AF with either warfarin+INR vs rivaroxaban were not inflation adjusted per annum (assuming prices remained static), however a 2% growth rate in the number of AF patients was included. An uptake of around 20% in utilization of patients taking rivaroxaban was used in the model. This may vary considerably and it is likely this is an over-estimate in the first year, however may be surpassed in subsequent years once rivaroxaban utilization is established. It is expected that use of rivaroxaban, as with warfarin, is ongoing chronic lifelong treatment. Based on these figures, the incremental budget impact analysis for 2015 would be around R277 million.

		2015	**2016**	**2017**	**2018**	**2019**
Pts on Warfarin - all		177 538	181 089	184 711	188 405	192 173
Pts on Rivaroxaban		35 508	36 218	36 942	37 681	38 435
Cost wafarin+INR - all		105 813 372	107 929 640	110 088 233	112 289 997	114 535 797
Cost wafarin+INR - new		84 650 698	86 343 712	88 070 586	89 831 998	91 628 638
Cost rivaroxaban		298 373 130	304 340 593	310 427 404	316 635 952	322 968 672
Total Cost new		383 023 828	390 684 304	398 497 991	406 467 950	414 597 309
Incremental cost		**277 210 455**	**282 754 665**	**288 409 758**	**294 177 953**	**300 061 512**

7 CONCLUSION

Although numerous published cost-effectiveness analyses suggest that rivaroxaban is cost-effective in a long-term setting, there is still considerably uncertainty around the long-term outcomes and clinical benefits in a mixed population, real-world setting.

In this model, the only variable that could be changed sufficiently to reach an incremental cost-effectiveness ratio (ICER) of below R300 000/QALY was to reduce the price of rivaroxaban by 80%. A more sophisticated model (with probabilistic sensitivity analysis and more health states) may have the outcome of reducing the ICER but at the current model outcome of R600 000/QALY it is unlikely to reduce the ICER to a point which could be considered cost-effective in the public health setting.

Furthermore, the budget impact needs to be considered. The prevalence figures for non-valvular AF in the public sector are simply estimates and it is challenging to predict what the actual budget impact is likely to be. This will be very dependent on uptake and utilization.

Other factors need to be considered;

- How to define warfarin failure or true warfarin intolerance in order to be eligible for NOACs
- The baseline risk of patients in the current healthcare setting compared to the clinical trial setting
- How to improve warfarin control and monitoring as an alternative strategy

8 REFERENCES

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