A cost outcomes analysis of apixaban versus rivaroxaban for the treatment of patients with non-valvular atrial fibrillation in the United States

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Introduction

- Direct-acting oral anticoagulants (DOACs), including apixaban and rivaroxaban, are recommended to reduce risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)[1]
- Whilst there are no head-to-head trials comparing efficacy and safety of DOACs against each other in patients with NVAF, real-world evidence (RWE) studies report differences in clinical effectiveness and safety[2,3]
- The ongoing loss of exclusivity (LOE) of branded DOACs in the US may result in decision makers favoring more affordable generic alternatives without considering the broader clinical and economic consequences

Objective

- To assess the clinical and cost implications of apixaban versus rivaroxaban for patients with NVAF from the US Medicare perspective, incorporating generic pricing assumptions to account for anticipated price erosions following LOE

Methods

- A cost outcomes model was added to a previously published Markov model **(Figure 1)**,[4] to evaluate the five-year clinical and cost impact of two scenarios (100% rivaroxaban [20 mg once-daily] or apixaban [5 mg twice-daily]) in newly-diagnosed patients with NVAF
- Baseline event probabilities were sourced from the Lopez-Lopez et al.[5] and Sterne et al.[6] network meta-analysis of randomized controlled trial data **(Table 1)**. Clinical event hazard ratios (HRs) were obtained from two alternative US-based retrospective RWE studies, Graham et al.[2] and Ray et al.[3]
- The model applied one-off acute event costs in the cycle of event occurrence (including fatal event costs), post-event maintenance costs to all cycles following a stroke, myocardial infarction (MI), or intracranial hemorrhage (ICH) event, and per-cycle treatment acquisition and monitoring costs while on therapy. US-specific inputs for acute event costs and long-term management costs were sourced from literature;[7-11] drug costs (maximum fair price [MFP]) and monitoring costs were sourced from Medicare databases.[12-13] All costs were inflated to 2025 USD. No discounting for costs and outcomes was applied in the model
- The model included 3-monthly cycles with a start date of January 2026. Based on forecasted LOE dates (rivaroxaban: January 2027 (cycle 4); apixaban: April 2028 (cycle 9)), generic pricing was set as 35% discount on brand price, assuming 55% uptake of the discounted price in the first cycle with generic entry (increasing by 2.5% per subsequent cycle)[4]
- Primary analysis included incremental costs (difference between rivaroxaban and apixaban) and clinical events (stroke, bleed, MI, ICH, systemic embolism [SE] and transient ischemic attack [TIA]) per 1,000 patients. A secondary analysis was performed using outcomes reported in the RWE studies[2,3] only (i.e., stroke, bleed, ICH, and SE)
- A deterministic sensitivity analysis (DSA) was undertaken (varying key model parameters independently by their 95% confidence interval [CI] or -/+ 20% of the base case value) to evaluate the influence of individual parameters on model outcomes

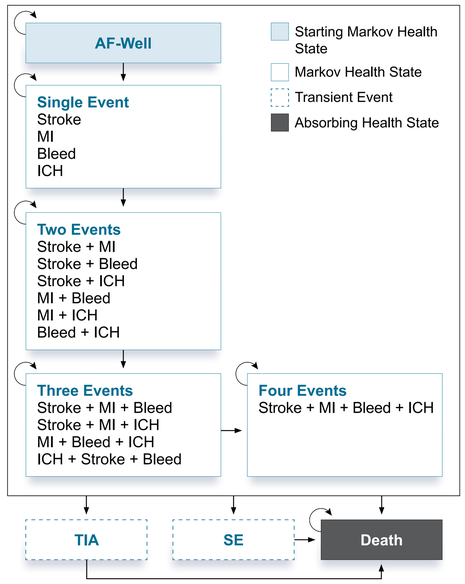
Results

- Treatment with apixaban was associated with 725, 468, 335, and 319 fewer overall clinical events over five years (cumulative per 1,000 patients) than rivaroxaban based on inputs from Graham et al.[2] (primary and secondary analysis) and Ray et al.[3] (primary and secondary analysis), respectively **(Figure 2)**
- Despite higher drug costs for apixaban due to earlier generic entry of rivaroxaban, treatment with apixaban was associated with cumulative total cost savings of $3,559,893, $2,565,845, $2,014,175, and $1,992,661 per 1,000 patients, based on inputs from Graham et al.[2] (primary and secondary analysis) and Ray et al.[3] (primary and secondary analysis), respectively **(Table 2)**
- Cost savings for apixaban were driven by a reduction in clinical events, namely bleeding events **(Figure 2, Table 2)**
- Based on the DSA, apixaban remained cost-saving versus rivaroxaban under all parameter changes (with the exception of changes in the annual baseline event probabilities for bleed in the Ray et al.[3] analysis (both primary and secondary))

Limitations

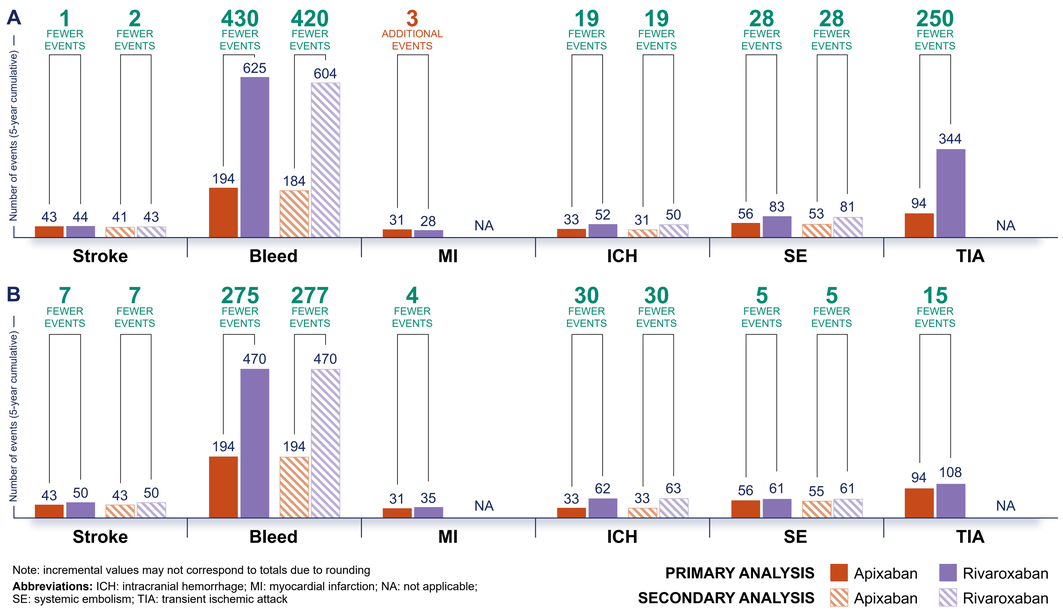
- No distinction was made between ischemic stroke severity
- Given the short time horizon, event rates were assumed to remain constant with age
- Maintenance costs for multiple event states utilize the maximum cost for constituent events, thus may underestimate total costs

Figure 1. Markov model schematic



Abbreviations: AF: atrial fibrillation; ICH: intracranial hemorrhage; MI: myocardial infarction; SE: systemic embolism; TIA: transient ischemic attack

Figure 2. Cumulative total clinical events for apixaban and rivaroxaban (and incremental for apixaban vs rivaroxaban) per 1,000 patients over five years based on event inputs from Graham et al.[2] (A) and Ray et al.[3] (B)



Note: incremental values may not correspond to totals due to rounding

Abbreviations: ICH: intracranial hemorrhage; MI: myocardial infarction; NA: not applicable; SE: systemic embolism; TIA: transient ischemic attack

Table 1. Clinical event inputs

	ANNUAL BASELINE EVENT PROBABILITIES MEAN (SE)		MEAN HR (SE)			
			Apixaban (5 mg bd)		Rivaroxaban (20 mg od)	
	Graham et al.[2]*	Ray et al.[3]^	Graham et al.[2]	Ray et al.[3]§	Graham et al.[2]	Ray et al.[3]
Stroke	**1.20%** (0.001)	**0.85%** (0.001)	**0.710** (0.059)	**1.000** (0.000)	**0.720** (0.051)	**1.120** (0.041)
Bleed‡	**6.60%** (0.025)	**3.42%** (0.016)	**0.510** (0.033)	**1.000** (0.000)	**1.380** (0.051)	**2.090** (0.043)
Myocardial infarction	**0.79%** (0.001)	**0.68%** (0.002)	**0.860** (0.115)	**1.000** (0.000)	**0.790** (0.102)	**1.120**† (0.041)
Intracranial hemorrhage	**0.94%** (0.003)	**0.51%** (0.002)	**0.540** (0.064)	**1.000** (0.000)	**0.650** (0.054)	**1.480** (0.102)
Systemic embolism	**1.70%** (0.009)	**1.11%** (0.012)	**0.650** (0.217)	**1.000** (0.000)	**0.950** (0.087)	**1.050** (0.181)
Transient ischemic attack	**2.50%** (0.021)	**1.86%** (0.067)	**0.740** (0.821)	**1.000** (0.000)	**2.680** (4.040)	**1.120**† (0.041)
All-cause mortality	**3.80%** (0.006)	**2.52%** (0.006)	**0.660** (0.036)	**1.000** (0.000)	**0.810** (0.033)	**1.060** (0.018)

*baseline probabilities with warfarin as reference[5,6]; ^baseline probabilities with apixiaban as reference (calculated using the baseline event probabilities for warfarin from Lopez-Lopez et al.[5] and Sterne et al.,[6] which were subsequently re-scaled by applying HRs for warfarin versus apixaban reported in the Graham et al.[2] publication); §assumption as baseline probabilities are for apixaban; †HR for "ischemic event"[3]; ‡baseline event probabilities used "clinically relevant bleed" from Lopez-Lopez et al.[5] and Sterne et al.[6]. Event risk was calculated using HRs for "major extracranial bleed" in Graham et al.[2] and "gastrointestinal bleeding" in Ray et al.[3]

Abbreviations: bd: twice-daily; HR: hazard ratio; od: once-daily; SE: standard error

Table 2. Cumulative incremental costs for apixaban vs rivaroxaban per 1,000 patients over five years

	PRIMARY ANALYSIS	SECONDARY ANALYSIS	PRIMARY ANALYSIS	SECONDARY ANALYSIS
	Graham et al.[2]	Graham et al.[2]	Ray et al.[3]	Ray et al.[3]
Total costs	**-$3,559,893**	**-$2,565,845**	**-$2,014,175**	**-$1,992,661**
Acute event costs	-$6,114,893	-$4,740,487	-$3,769,329	-$3,695,857
Long-term management costs	-$613,221	-$701,215	-$1,273,667	-$1,277,136
Monitoring costs	$16,845	$2,414	$5,305	$1,282
Drug costs	$3,151,375	$2,873,444	$3,023,516	$2,979,050
PPPM	-$67.81	-$47.88	-$37.65	-$36.18

Abbreviations: PPPM: per patient per month

Conclusions

- Apixaban was associated with fewer overall clinical events and lower cumulative costs despite later generic entry relative to rivaroxaban
- This dynamic pricing cost outcomes analysis indicates that short-term drug acquisition cost savings following generic entry may not translate into lower total costs over longer time horizons (i.e. five years) when future generic availability and downstream clinical events are considered

References

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