Cost-effectiveness Of Apixaban Compared To Warfarin, Dabigatran and Rivaroxaban For The Prevention Of Stroke In Nonvalvular Atrial Fibrillation: Results For High-Risk Patient Subgroups Based On The ARISTOPHANES Real-World Evidence Study

EE88

Chloe Spalding[1], Bethany Mountford[1], Sofie Czarnota-Bojarski[1], Thomas Strakosch[1], Rupesh Subash[2]

[1]FIECON, London, United Kingdom; [2] Pfizer Ltd, Tadworth, United Kingdom

Introduction

- Atrial fibrillation (AF) is the most prevalent heart arrhythmia in the UK, with an estimated general population prevalence of ~3%, rising to >8% ages 75+.[1,2]
- Prior to 2012, standard management of stroke and systemic embolism (SE) within the AF population was warfarin. Since 2012, a range of direct-acting oral anticoagulants (DOACs) have been recommended by the National Institute for Health and Care Excellence (NICE) as alternatives.
- Compared to other anticoagulants, apixaban was identified with the highest probability of being the most cost-effective first-line treatment for (non-valvular AF) NVAF patients.[3] However, there is limited cost-effectiveness evaluation of anticoagulants in high-risk NVAF subpopulations.
- ARISTOPHANES is a large real-world evidence (RWE) study which evaluated comparative rates of stroke/SE and bleeding across various subgroups among NVAF patients newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin utilising US data sources from 2013-2015.[4]
  - ARISTOPHANES is inclusive of an overall population and 10 key high-risk subgroups (cancer, diabetes, frailty, high risk of gastrointestinal [GI] bleed, multimorbidity, obesity, polypharmacy, prior bleed, elderly and stage 3-5 chronic kidney disease [CKD]).[4-14]

Objective

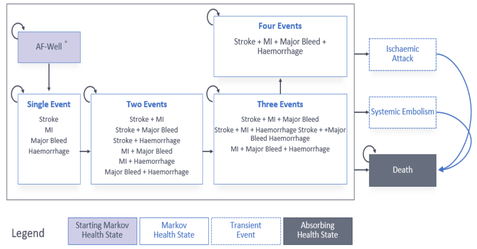
- This analysis utilised the ARISTOPHANES study to assess the real-world cost-effectiveness (CE) of apixaban compared to warfarin, dabigatran and rivaroxaban from a UK National Health Service (NHS) perspective over the lifetime in key high-risk NVAF subgroups.

Methods

Model structure

- A discrete time Markov multistate model based on the methodology of Lopez-Lopez et al.[15] and Sterne et al.[3] was developed and adapted to the UK NHS setting (**Figure 1**).

Figure 1. Model schematic



*AF well are newly diagnosed NVAF patients who have not experienced any of the model defined events.
Abbreviations: AF, atrial fibrillation; HS, health state; ICH, intracranial hemorrhage; MB, major bleed; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischemic attack

Model structure (cont.)

- NVAF was represented by 17 health states: AF well, four event health states (stroke, major bleed [MB], myocardial infarction [MI], and intracranial haemorrhage [ICH]), 11 multiple event combination health states and death (absorbing state).
  - Transient ischemic attack (TIA) and SE were modelled as transient event states that incurred one-time costs and utility decrements.
- A 3-month cycle length is adopted in line with published literature.
- A lifetime time-horizon with a maximum age of 100 years was considered.

Model inputs and outputs

- Effectiveness/safety inputs, population characteristics (age and sex distributions) and baseline event risks were based on the ARISTOPHANES RWE main and subgroup analyses.[5-14]
  - Where data were not available in the ARISTOPHANES studies, data from Sterne et al.[3] were used.
- Event history was considered through non-treatment specific hazard ratios (HRs).[15]
- Acute event costs,[17,18] annual maintenance costs,[15,17,18] treatment acquisition costs,[19] and monitoring costs.[20,21], were reported in 2020 GBP. Quality of life inputs for events presented in **Figure 1** were also sourced from the literature. [22-26]
  - Costs and quality-adjusted life years (QALYs) were discounted at 3.5%.[27]
- Multiple lines of therapy were considered based on event-driven discontinuation:[3,15]
  - For patients on warfarin first-line treatment, the only second-line intervention available was assumed to be no treatment.
  - For patients on a DOAC first-line treatment, second-line and third-line treatment were assumed to be warfarin and no treatment, respectively.
- Mortality rates (inclusive of all-cause mortality [ACM] and general population mortality) were applied cyclically, accounting for both treatment-specific event HRs and the UK ONS life tables.[16]
- Probabilistic sensitivity analyses (PSAs) were based on 1,000 iterations, and one-way sensitivity analyses (OWSAs) were based on confidence intervals estimated from published standard errors where available or assumed to be equal to 10% of the mean otherwise.
- Results within this poster can be interpreted through a willingness-to-pay (WTP) threshold of £30,000/QALY.

Results

Base case

- Apixaban was cost-effective (increased incremental costs and increased incremental QALYs) in the ARISTOPHANES main analysis population (£2,098/QALY) and dominant (reduced incremental costs and increased incremental QALYs) across all other high-risk subgroups versus warfarin (**Table 1**).
- Apixaban was dominant versus dabigatran and rivaroxaban in the main ARISTOPHANES population and across all high-risk subgroups.

Table 1. Deterministic and probabilistic results

Population	Type of analysis		Warfarin	Dabigatran (150mg bd)	Rivaroxaban (20mg od)
			Treatment arm – Apixaban (5mg bd)		
ARISTOPHANES overall population	Deterministic	ICER	CE (£2,098/QALY)	Dominant	Dominant
	Probabilistic	ICER	CE (£1,871/QALY)	Dominant	Dominant
		Probability (%) of being CE*	100%	71%	92%
Cancer	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	92%	59%	67%
Diabetes	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	Probability (%) of being CE*	Dominant	Dominant	Dominant
		ICER	91%	63%	63%
Frailty	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	100%	74%	93%
High risk of GI bleed	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	91%	62%	67%
Multimorbidity	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	97%	70%	72%
Obesity	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	89%	78%	64%
Polypharmacy	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	94%	72%	69%
Prior bleed	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	93%	70%	65%
Elderly	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	100%	89%	95%
Stage 3-5 CKD	Deterministic	ICER	Dominant	Dominant	Dominant
	Probabilistic	ICER	Dominant	Dominant	Dominant
		Probability (%) of being CE*	93%	60%	61%

Table 1 shows the deterministic and probabilistic cost-effectiveness results of apixaban versus warfarin and other DOACs. When apixaban is associated with increased incremental costs and increased incremental QALYs versus the comparator, apixaban is cost-effective (based on a £30,000 WTP threshold). When apixaban is associated with reduced incremental costs and increased incremental QALYs versus the comparator, apixaban is dominant. *As per 1,000 iterations of the cost-effectiveness model run probabilistically at a £30,000 WTP threshold.
Abbreviations: ACM, all-cause mortality; CE, cost-effective; CKD, chronic kidney disease; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; MB, major bleed; MI, myocardial infarction; NMB, net monetary benefit; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; WTP, willingness-to-pay.

Sensitivity analyses

- Probabilistic trends were consistent with the deterministic results for each subgroup (**Table 1**).
- The top three key drivers from the deterministic OWSA results for the ARISTOPHANES main population and all subgroups are presented in **Table 2**.
  - The net monetary benefit (NMB) remained positive in the majority of the inputs tested.

Limitations

- The ARISTOPHANES safety and effectiveness inputs informing this analysis are not derived from a UK population but rather in a population pooled from the US Centers for Medicare and Medicaid Services Medicare data and 4 commercial claims databases in the United States'.
- Due to the unavailability of head-to-head data in the ARISTOPHANES study for apixaban versus edoxaban (resulting from a lack of sample size), this analysis was limited in its ability to present this comparison.

Table 2. Results for deterministic OWSA

Population	Warfarin (lower, upper NMB)	Dabigatran (lower, upper NMB)	Rivaroxaban (lower, upper NMB)
ARISTOPHANES main analysis	1. Baseline age (£7,600, £27,457) 2. ACM, no treatment* (£20,409, £26,594) 3. ACM, apixaban* (£22,279, £25,811)	1. TIA, dabigatran* (£5,749, £11,996) 2. ACM, dabigatran* (£4,624, £10,630) 3. Baseline age (£2,832, £8,804)	1. Baseline age (£5,299, £16,971) 2. TIA, rivaroxaban* (£13,496, £18,138) 3. ACM, apixaban* (£13,218, £16,750)
Cancer	1. ACM, apixaban* (-£366, £32,086) 2. Baseline age (£4,027, £17,311) 3. ACM, no treatment* (£10,870, £18,120)	1. ACM, apixaban* (-£9,680, £22,772) 2. ACM, dabigatran* (-£10,261, £20,284) 3. Stroke, dabigatran* (£1,519, £12,492)	1. ACM, apixaban* (-£7,866, £24,587) 2. ACM, rivaroxaban* (-£9,165, £23,095) 3. ICH, apixaban* (£3,521, £10,447)
Diabetes	1. ACM, apixaban* (-£3,035, £31,663) 2. Baseline age (£2,484, £15,609) 3. ACM, no treatment* (£9,417, £15,946)	1. ACM, apixaban* (-£11,038, £23,659) 2. ACM, dabigatran* (-£12,377, £20,831) 3. Stroke, dabigatran* (£3,032, £7,894)	1. ACM, rivaroxaban* (-£13,748, £22,333) 2. ACM, apixaban* (-£11,025, £23,673) 3. Baseline age (£1,648, £6,055)
Frailty	1. Baseline age (£993, ££24,805) 2. Stroke, no treatment* (£17,599, £23,617) 3. ACM, no treatment* (£18,185, £22,249)	1. Baseline age (£1,112, £10,280) 2. Stoke, dabigatran* (£5,487, £11,456) 3. TIA, dabigatran* (£6,753 £11,351)	1. Baseline age (£1,592, £18,736) 2. TIA, rivaroxaban* (£14,142, £17,427) 3. ACM, apixaban* (£13,747, £16,611)
High risk of GI bleed	1. ACM, apixaban* (-£4,876, £31,248) 2. Baseline age (£1,597, £14,595) 3. ACM, no treatment * (£8,553, £14,753)	1. ACM, apixaban* (-£12,467, £23,657) 2. ACM, dabigatran* (-£14,022, £21,204) 3. Baseline age (£1,309, £5,524)	1. ACM, rivaroxaban* (-£12,889, £23,994) 2. ACM, apixaban* (-£10,666, £25,459) 3. Baseline age (£1,827, £7,930)
Multimorbidity	1. ACM, apixaban* (£4,791, £32,176) 2. Baseline age (£2,651, £20,474) 3. Stroke, no treatment* (£13,962, £22,752)	1. ACM, apixaban* -£4,422, £22,964) 2. ACM, dabigatran* (-£3,784, £20,635) 3. Baseline age (£2,082, £9,873)	1. ACM, apixaban* (-£5,146, £22,239) 2. ACM, rivaroxaban* (-£5,312, £21,021) 3. Baseline age (£1,764, £9,107)
Obesity	1. ACM, apixaban* (-£4,664, £34,603) 2. Baseline age (£4,898, £16,199) 3. ACM, no treatment* (£8,660, £16,561)	1. ACM, apixaban* (-£6,062, £33,205) 2. ACM, dabigatran* (-£5,677, £27,425) 3. Stroke, dabigatran* (£7,699, £17,722)	1. ACM, rivaroxaban* (-£15,067, £24,778) 2. ACM, apixaban* (-£11,780, £27,487) 3. Baseline age (£2,926, £7,426)
Polypharmacy	1. ACM, apixaban* (-£2,117, £33,241) 2. Baseline age (£2,245, £17,536) 3. ACM, no treatment* (£10,494, £17,247)	1. ACM, apixaban* (-£8,791, £26,567) 2. ACM, dabigatran* (-£9,407, £23,031) 3. Baseline age (£2,289, £9,304)	1. ACM, apixaban* (-£9,326, £26,032) 2. ACM, rivaroxaban* (-£11,223, £23,946) 3. Baseline age (£2,014, £8,855)
Prior bleed	1. ACM, apixaban* (£224, £24,546) 2. Baseline age (£1,152, £13,972) 3. Stroke, no treatment (£9,209, £15,373)	1. ACM, apixaban* (-£4,169, £20,153) 2. ACM, dabigatran* (-£3,314, £18,159) 3. Baseline age (£1,710, £8,726)	1. ACM, rivaroxaban* (-£7,233, £17,394) 2. ACM, apixaban* (-£6,580, £17,741) 3. Baseline age (£1,190, £5,993)
Elderly	1. Baseline age (£6,009, £28,254) 2. Stroke, no treatment* (£18,315, £23,028) 3. ACM, apixaban* (£18,382, £22,130)	1. Baseline age (£4,962, £20,333) 2. ACM, dabigatran* (£11,216, £17,535) 3. Stroke, dabigatran* (£12,081, £17,518)	1. Baseline age (£5,673, £23,106) 2. ACM, apixaban* (£14,613, £18,361) 3. TIA, rivaroxaban* (£15,639, £18,841)
Stage 3-5 CKD	1. ACM, apixaban* (-£2,715, £37,290) 2. ACM, no treatment* (£11,613, £18,536) 3. Baseline age (£11,853, £18,194)	1. ACM, apixaban* (-£13,217, £26,789) 2. ACM, dabigatran* (-£15,146, £22,763) 3. Stroke, dabigatran* (£2,406, £9,450)	1. ACM, rivaroxaban* (-£17,947, £24,586) 2. ACM, apixaban* (-£13,517, £26,488) 3. ICH, apixaban* (£1,311, £7,434)

*Event rate HRs for impact of treatment
Abbreviations: ACM, all-cause mortality; CKD, chronic kidney disease; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; MI, myocardial infarction; NMB – net-monetary benefit; OWSA – one-way sensitivity analysis; TIA – transient ischemic attack.

Conclusions

- Across all high-risk subgroups assessed in the ARISTOPHANES RWE study, apixaban dominated in all subgroups compared to warfarin, dabigatran and rivaroxaban.
- Sensitivity analyses demonstrated robustness of the base-case results for each subgroup.

References

[1] Davis RC, et al. Europace 2012. 14: 1553–9.
[2] Adderley NJ, et al. Heart 2018.
[3] Sterne JA, et al. Health Technol Assess 2017. 21: 1–386.
[4] Patel MR, et al. N Engl J Med 2011. 365: 883–91.
[5] Lip GYH, et al. Stroke 2010. 49: 2933–2944.
[6] Deitelzweig S, et al. JACC: CardioOncology 2021. 3: 411–424.
[7] Lip GYH, et al. Mayo Clinic Proceedings 2020. 95: 929–943.
[8] Lip GYH, et al. J Intern Med 2021. 289: 42–52.
[9] Lip GYH, et al. JAMA Netw Open 2021.
[10] Deitelzweig S, et al. Adv Ther 2021. 38: 3166–3184.
[11] Deitelzweig S, et al. JCM 2020. 9: 1633.
[12] Lip GYH, et al. Euro Heart J Cardiovasc Pharmacother 2021. 7: 405–414.
[13] Lip GYH, et al. J Thromb Thrombolysis 2022. 54: 33–46.
[14] Deitelzweig S, et al. J American Geriatrics Society 2019. 67: 1662–1671.
[15] Lopez-Lopez JA, et al. Bmj 2017. 359: j5058.
[16] Office for National Statistics. National life tables, UK: 2018 to 2020.
[17] Luengo-Fernandez R, et al. Int J Stroke 2013. 8: 308–14.
[18] Department of Health and Social Care. Policy paper: NHS reference costs 2013 to 2014.
[19] NHS England and Wales. NHS Business Services Authority NPS. Electronic Drug Tariff. 2018.
[20] Spackman EBJ. Evidence Review Group Report. 2011.
[21] Curtis L & Burns. Personal Social Services Research Unit, University of Kent, Canterbury. 2017.
[22] Robinson A, et al. J Health Serv Res Policy 2001. 6: 92–8.
[23] Lacey EA & Walters SJ. J Epidemiol Community Health 2003. 57: 622–7.
[24] Lenert LA & Soetikno RM. J Am Med Inform Assoc 1997. 4: 49–56.
[25] Department of Health and Social Care. Policy paper: NHS reference costs 2012 to 2013. 2018.
[26] Berg J, et al. Qual Life Res 2010. 19: 381–90.
[27] Kind P al. UK population norms for EQ-5D.
[28] NICE health technology evaluations: the manual 2022.

Disclosures

This study was sponsored by the Bristol-Myers Squibb-Pfizer Alliance. CS, BM, TS, and SCB are employed by FIECON, a paid consultant to the Bristol-Myers Squibb-Pfizer Alliance in connection with the development of this study. RS is an employee and shareholder of Pfizer.

Poster Presented at: ISPOR 2024, Atlanta, GA, US (May 5-8, 2024)