Direct oral anticoagulants in adults with non-valvular atrial fibrillation: Systematic review and network meta-analysis of real-world evidence

Rupesh Subash[1], Steven Lister[2], Christopher Lewis[1], Silva Rabar[3], Michael J. Hale[3], Amiee Kang[2], Carissa Dickerson[3]

[1]Pfizer Inc., Tadworth, UK; [2]Bristol Myers Squibb Pharmaceutical Ltd., Uxbridge, UK; [3]Health Economics and Outcomes Research Ltd., Cardiff, UK

#129084

Introduction

- Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately 3% of the general population.[1]
- AF is associated with a five-fold increase in the risk of stroke[2] and is linked to more severe stroke.[3]
- Vitamin K antagonists (VKAs) such as warfarin, and direct oral anticoagulants (DOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban are routinely prescribed to patients with non-valvular atrial fibrillation (NVAF) to reduce the risk of ischaemic stroke and systemic embolism (SE).[4]
- Meta-analyses of randomised controlled trials (RCTs) demonstrate that DOACs are at least equivalent to VKAs in terms of efficacy and safety,[5] however, whether analyses of real-world evidence (RWE) conclude the same is less clear.
- Whilst RCT evidence is the gold-standard for evidence-based medicine, outcomes reported in RWE may be more reflective of clinical practice and are important to consider alongside RCT evidence.
- Therefore, the purpose of this study was to compare the effectiveness and safety of DOACs compared with VKAs in patients with NVAF based on RWE.

Objective

The purpose of this study was to compare the effectiveness and safety of DOACs compared with VKAs in patients with NVAF based on RWE.

Methods

Systematic literature review (SLR)

- A systematic literature review (SLR) was initially conduced in January 2020 and updated in October 2021 using a protocol designed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) checklist.[6]
- Searches were conducted across the following electronic databases: Ovid MEDLINE® (including: MEDLINE:Publisher, In-Data-Review, In-Process and PubMed-not-MEDLINE records from the National Library of Medicine), Ovid Embase, and the Cochrane Database of Systematic Reviews (CDSR; via Ovid).
- The complete SLR included studies published from January 2013 through to October 2021.
- No language restrictions were applied in the search strategies, however only English language full-text studies were included in the SLR.
- Titles and abstracts identified by the search strategy were independently assessed for eligibility by two reviewers; any discrepancies were resolved by a third senior reviewer.
- Full texts of potentially eligible studies were retrieved and assessed against the Population-Intervention-Comparators-Outcomes-Study design (PICOS) eligibility criteria (Table 1).
- Following data extraction, kinning was undertaken to remove studies with overalppying datasets to avoid double counting.
- Risk of bias was assessed by the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool.[7]

Table 1. Systematic literature review eligibility criteria

PICOS	Inclusion criteria
Population	Adults with **NVAF** (studies of mixed populations enrolling ≥ 90% of patients with NVAF were included)
Intervention	**DOACs** (apixaban, dabigatran, edoxaban, rivarox-aban), at standard or mixed doses
Comparators	**VKAs** (including warfarin, phenprocoumon and acenocoumarol) or head-to-head comparisons with other DOACs
Outcomes	All-cause mortality, major bleeding, intracranial haemorrhage, stroke, systemic embolism, composite of all-cause stroke/systemic embolism
Study design	**Real-world studies** (e.g. prospective and retrospective cohort studies, cross-sectional studies, case-control studies, and pragmatic trials)

DOACs: direct oral anticoagulants; NVAF: non-valvular atrial fibrillation; VKAs: vitamin K antagonists

Network meta-analysis (NMA)

- All studies identified in the SLR were included in the NMA, except those with patient populations who were entirely treatment experienced, and those with patient subpopulations taking reduced doses of DOACs.
- The conduct and reporting of NMA adhered to best practice guidelines, including NICE Decision Support Unit,[8] the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[9,10] and PRISMA guidelines.[11]

Methods (continued)

Network meta-analysis (NMA) continued

- A Bayesian approach was used to estimate treatment effect posterior distributions using a generalised linear model framework.
- Posterior densities were estimated using Markov Chain Monte Carlo (MCMC) simulation, consisting of 4 chains, with 100,000 iterations after a burn-in of 50,000. Vague default prior distributions[12] were used which allowed the data to dominate.
- All data were analysed via log hazard ratios using a normal likelihood with identity link.
- Both fixed effects and random effects models were fitted. Deviance information criterion (DIC) was used to inform which model would be considered the best fitting, where lower DIC suggests a better fitting model. I^2 statistics were used to assess the amount of heterogeneity between the studies in each model. Convergence checks, trace density plots and Gelman-Rubin-Brooks plots, were carried out to ensure model convergence.
- The reference treatment for each network was chosen as VKA – the treatment to which most other treatments were directly connected.
- VKA was defined as a composite of unspecified VKA, warfarin, acenocoumarol and phenprocoumon.
- Where a study had three or more arms a standard error of the reference arm was required. Standard error was calculated using the standard error of the treatment arms and a correlation factor (0.5 for three arm trials).

Results

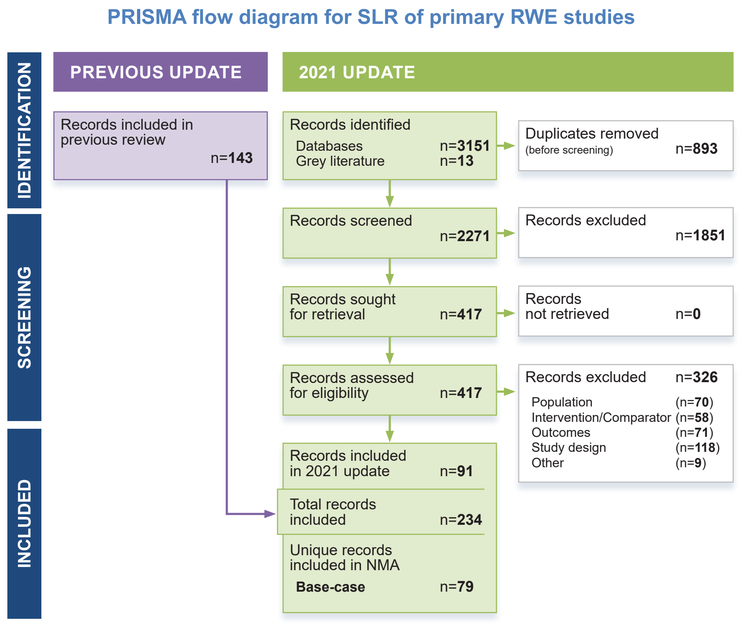
- Literature searches conducted in January 2020 identified 2,756 records after removal of duplicates (143 records included), and searches in October 2021 identified a further 3,164 records. In total, 234 studies met the inclusion criteria and were retained for data extraction, after kinning, 79 were included in the NMA.

Table 2. Summary of NMA outcomes (VKA as reference)

	Stroke/SE	Ischaemic stroke	Systemic embolism	Major bleeding	Intracranial haemorrhage	All-cause mortality
Apixaban	**0.72** (0.65 to 0.80)	**0.77** (0.62 to 0.97)	**0.51** (0.37 to 0.71)	**0.64** (0.60 to 0.68)	**0.60** (0.55 to 0.67)	**0.80** (0.74 to 0.86)
Dabigatran	**0.78** (0.70 to 0.86)	**0.87** (0.76 to 0.99)	**0.78** (0.59 to 1.06)	**0.73** (0.68 to 0.78)	**0.49** (0.44 to 0.54)	**0.73** (0.68 to 0.79)
Edoxaban	**0.76** (0.55 to 1.06)	**0.91** (0.81 to 1.02)	**0.49** (0.15 to 1.64)	**0.64** (0.55 to 0.74)	**0.57** (0.44 to 0.73)	**0.81** (0.60 to 1.09)
Rivaroxaban	**0.83** (0.75 to 0.92)	**0.91** (0.80 to 1.03)	**0.90** (0.65 to 1.16)	**0.96** (0.89 to 1.02)	**0.74** (0.67 to 0.82)	**0.89** (0.83 to 0.96)

All values are HR (95% CI)
Aqua shading denotates significantly better outcome vs VKA

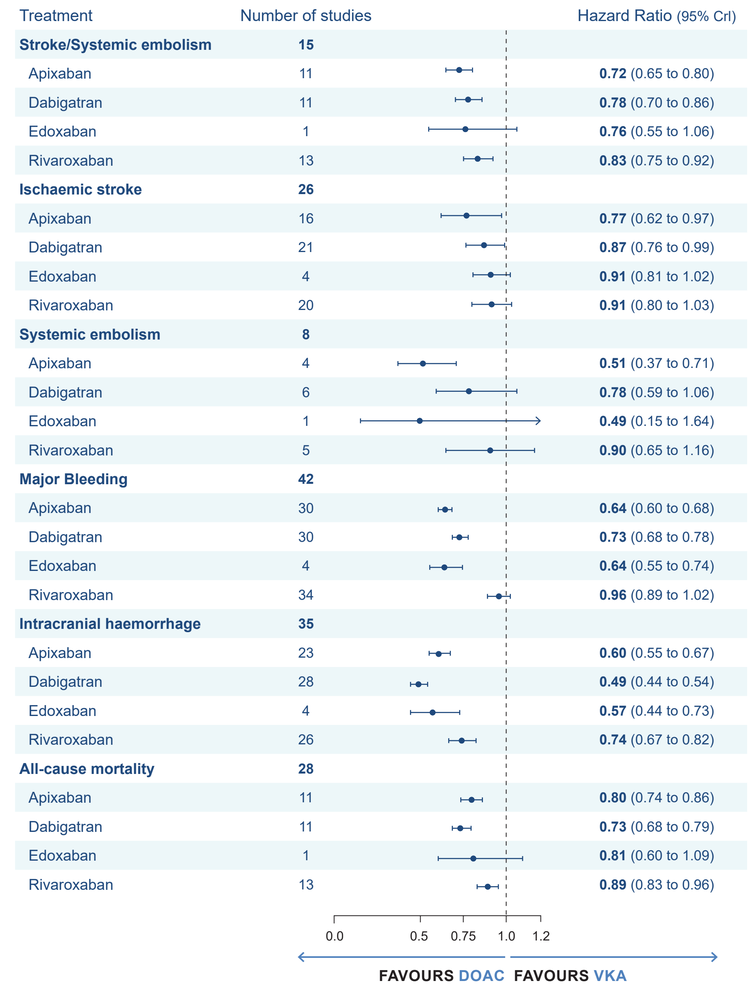
Figure 1. PRISMA flow diagram



- All DOACs (except edoxaban) were associated with reduced risk of stroke/SE (HRs: 0.72 to 0.83; Table 2; Figure 2).
- Apixaban and dabigatran were associated with reduced risk of ischaemic stroke (HRs: 0.77 and 0.87 respectively); apixaban was also associated with almost half the risk of systemic embolism (HR (95% CI): 0.51 (0.37 to 0.71)) compared with VKA.
- All DOACs (except rivaroxaban) were associated with reduced risk of major bleeding (HRs: 0.64 to 0.96), and all DOACs were linked to reduced risk of intracranial haemorrhage (HRs: 0.49 to 0.74) compared with VKA.
- All DOACs (except edoxaban) were associated with reduced risk of all-cause mortality. (HRs: 0.73 to 0.89).

Results (continued)

Figure 2. Forest plot of NMA outcomes



Limitations

- Outcomes for edoxaban should be interpreted with caution due to low study numbers.
- No distinction was made between treatment doses during analysis.

Conclusions

- In line with evidence from similar NMAs of RCTs, the results of this NMA of 79 real-world studies demonstrates that all DOACs are at least as effective as VKAs in terms of both effectiveness and safety.
- Apixaban was the only DOAC to demonstrate reduced risk across all outcomes evaluated compared with VKAs, however outcomes for some DOACs may be underpowered.

References

1. Adderley NJ, et al. Heart 2019;105(1):27-33.
2. Wolf PA, et al. Stroke 1991;22(8):983-989.
3. Pistoia F, et al. Cardiol Clin 2016;34(2):255-268.
4. Hindricks G, et al. Eur Heart J 2020;42(5):373-498
5. Lopez-Lopez JA, et al. BMJ 2017;359:j5058.
6. Moher D, et al. Syst Rev 2015;4(1):1. doi: 10.1186/2046-453-4-1.
7. Sterne JA, et al. BMJ 2016; 355:i4949.
8. Dias S, et al. NICE Decision Support Unit Technical Support Documents. London 2014
9. Hoaglin DC, et al. Value Health 2011;14(4):429-37
10. Jansen JP, et al. Value Health 2011;14(4):417-28
11. Page MJ, et al BMJ 2021;372:n71
12. van Valkenhoef G, et al. Res Synth Methods 2012;3(4):285-299

Disclosures

This study was sponsored by the Bristol Myers Squibb-Pfizer Alliance.

Rupesh Subash, Steven Lister, Christopher Lewis, and Amiee Kang are current or former employees of Pfizer Inc. or Bristol Myers Squibb. Silvia Rabar, Mike Hale, and Carissa Dickerson are current or former employees of Health Economics and Outcome Research Ltd., paid consultants to the Bristol Myers Squibb-Pfizer Alliance in connection with the development of this poster.

Poster presented at: ISPOR Europe 2023; November 12-15, 2023; Copenhagen, Denmark