

Cost Effectiveness of Apixaban (Eliquis[®]) for the Prevention of Stroke and Systemic Embolism in People with Non-Valvular Atrial Fibrillation



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Background

1. In April 2013 Bristol-Myers Squibb Pharmaceuticals and Pfizer Healthcare Ireland submitted an economic evaluation on the cost effectiveness of apixaban (Eliquis®) for the prevention of stroke and systemic embolism (SE) in people with non-valvular atrial fibrillation (NVAf). The evaluation is presented from the perspective of the Health Services Executive. The basecase analysis pertains to the General Medical Services (GMS) population. Cost effectiveness on the Drug Payment Scheme (DPS) was investigated in a scenario analysis.
2. The basecase compared apixaban with warfarin (WfN), in people for whom vitamin K antagonists (VKAs) are suitable, using direct head-to-head evidence. ARISTOTLE was a double-blind, trial in which 18,201 Af patients were randomly assigned (1:1) to apixaban 5 mg BD or WfN (target INR 2-3) ^[1]. The mean CHADS₂ score was 2.1. The median duration of follow-up was 1.8 years.

The primary outcome was the occurrence of stroke or SE in the intention-to-treat (ITT) population. The rates of the primary outcome were 1.27%/year and 1.60%/year in the apixaban and WfN groups respectively (hazard ratio (HR) = 0.79; 95% CI, 0.66-0.95; p<0.001 for noninferiority; p=0.01 for superiority). The rates of major bleeding were 2.13%/ year and 3.09%/year for the apixaban and WfN groups respectively (HR= 0.69; 95%CI, 0.60-0.80; p<0.001). The rates of death from any cause were 3.52%/year and 3.94%/year, respectively (HR= 0.89; 95% CI, 0.80-0.99; p=0.047). The rates of hemorrhagic stroke were 0.24%/year in the apixaban group and 0.47%/year in the WfN group (HR= 0.51; 95% CI, 0.35-0.75; p<0.001), and the respective rates of ischemic or uncertain type of stroke were 0.97%/year and 1.05%/year respectively (HR=0.92; 95% CI, 0.74-1.13; p=0.42) ^[1].

3. In people for whom VKAs are unsuitable the comparator was aspirin. AVERROES was a double-blind superiority trial in which 15,599 Af patients who were at increased risk for stroke and for whom VKA therapy was unsuitable

were randomly assigned 1:1 to receive apixaban (5 mg BD) or aspirin (81-324 mg OD) ^[2]. The mean CHAD₂ scores in the apixaban and aspirin groups were 2.0±1.1 and 2.1±1.1 respectively. The median follow up period was 1.5 years. The primary outcome was the occurrence of stroke or SE in the ITT population.

There were 51 primary outcome events (1.6%/year) in the apixaban cohort and 113 (3.7%/year) in the aspirin cohort (HR = 0.45; 95% CI, 0.32-0.62; p<0.001). The corresponding rates of ischemic stroke were 1.1%/year and 3.0%/year respectively (HR=0.37; 95% CI, 0.25-0.55; p<0.001). The rates of death were 3.5%/ year and 4.4%/year in the apixaban and aspirin groups respectively (HR=0.79; 95% CI, 0.62-1.02; p= 0.07). There were no significant differences in the rates of major bleeding at 1.4%/year (apixaban) and 1.2%/year (aspirin) (HR=1.13; 95% CI, 0.74-1.75; p = 0.57) or intracranial hemorrhage (ICH) (0.4%/year vs. 0.4%/year; HR= 0.85; 95%CI, 0.38-1.90: p=0.69) ^[2].

4. No head-to-head data is available for apixaban compared with the other novel oral anticoagulants (NOACs). The efficacy of apixaban, in the VKA-suitable populations, was compared to dabigatran etexilate (DBG) and rivaroxaban indirectly using a network meta-analysis (NMA). The ARISTOTLE ^[1], RE-LY ^[3] and ROCKET-AF ^[4] studies were used to provide data for the NMA.

There were no statistically significant differences between the three drugs for the primary efficacy outcome (stroke and SE) and for the other efficacy outcomes. Apixaban was associated with a statistically significant reduction in myocardial infarction (MI) compared with DBG 150 mg and 110 mg. Apixaban had a statistically significant lower incidence of all bleeding outcomes compared with rivaroxaban. Apixaban had a statistically significant lower incidence of Major Bleeding, Other Major Bleeding, Gastro-Intestinal (GI) Bleeding, and 'Any Bleeding' compared with DBG 150 mg. Apixaban had a statistically significant lower incidence of 'Any Bleeding' compared with DBG 110 mg.

5. The cost effectiveness of apixaban was assessed using a comprehensive Markov model. The model predicts that the incremental cost effectiveness ratios (ICERs) of apixaban vs. WFN (the standard of care in VKA suitable patients) will be

€11,087/QALY and €16,533/QALY in the GMS and the DPS populations respectively. The model also predicts that the drug is cost effective compared to DBG and rivaroxaban in the VKA suitable population and to aspirin in the VKA unsuitable population.

According to the model, at a threshold of €45,000/QALY, apixaban will have the highest probability of being cost effective in both the VKA suitable (vs. WFN, rivaroxaban and DBG) and VKA unsuitable (vs. aspirin) populations under the GMS scheme.

We note the following caveats to this cost-effectiveness evaluation:

- There are differences in the baseline characteristics of the trial populations used in the NMA. Thus we believe that the true cost effectiveness of apixaban relative to the other NOACs cannot be established at this time.
- The model assumes that strokes, SE, MI, bleeding and cardiovascular hospitalisation will continue at the rates seen in the AVERROES ^[2], ARRISTOTLE ^[1], ROCKET-AF ^[4] and RE-LY ^[3] trials. This will introduce uncertainty. However we note that this approach is conventional and has been used in similar economic evaluations
- Similar to the other NOACs, there is no antidote to apixaban. The economic evaluation assumes that the cost of treating a bleed associated with WFN is the same as treating a bleed associated with a NOAC. If a bleed associated with apixaban was more expensive, the ICER (apixaban vs. warfarin) would increase.
- Health Related Quality of Life (HRQoL) data were not collected in the apixaban clinical trials. As such, all health state utilities were derived from the published literature. Values were obtained from disparate sources pertaining to different populations and different jurisdictions. Therefore the utility values in the model give rise to uncertainty. The review team believe, however, that the utility values used in the submission are reasonable estimates and concur with values used in

previous submissions.

- The ICER increases to over €45,000/QALY when the model time horizon is decreased to 2 years.
 - Subgroup analysis indicated that the model results are robust to a change in the median Centre Time in Therapeutic range (cTTR). The number of patients used to inform this analysis is relatively small. Further, the effect of changing the mean cTTR was not investigated.
 - The basecase analysis assumes that the opportunity costs associated with INR monitoring in substituted patients will be realised to the HSE. The NCPE set the INR monitoring cost was zero. This allows the cost effectiveness of apixaban to be investigated in the instance that the economic costs associated with INR monitoring in substituted patients, are not released from the anticoagulation services. The ICER (vs. WFN) reached €23,669/QALY in the GMS cohort.
6. The company Budget Impact (BI) model predicts that the 5 year cumulative cost of apixaban treatment will be about €12,609,670 and that the 5 year cumulative incremental BI will be approximately €1,286,626. The NCPE believe that this is an underestimate; we estimate a 5 year apixaban treatment cost which may reach about €24,700,000 and a 5 year cumulative incremental BI which may reach about €21,000,000.
 7. Population Expected Value of Perfect Information (PEVPI) estimates at €45,000/QALY are negligible.
 8. We conclude that apixaban can be considered cost effective for the prevention of stroke and SE in people with NVAf, at a threshold of €45,000/QALY, under standard decision rules.

References

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