# Clinical and economic implications of using non-vitamin k antagonist oral anticoagulants for non-valvular atrial fibrillation using available evidence from real-world experience

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**Key findings:** Despite the cost for drug acquisition remained higher for DOACs compared to VKAs, among available DOACs, ***apixaban could represent a valuable option improving both effectiveness and sustainability of treatment for non-valvular atrial fibrillation in daily clinical practice***.

## The Problem

In addition to the large amount of randomized clinical trials (RCTs) evaluating the effects of vitamin K antagonist (VKAs) versus the non-vitamin K antagonist oral anticoagulants (DOACs), nowadays a relatively high number of real-world studies has also became available. In real-world, patients are outside the highly controlled environment of RCTs and this may drive to discrepancy with results obtained from RCTs. This gap is relevant both for a proper ascertainment of the treatment effect and also for evaluating its health-economic impact. Therefore, **the aim of the present study is to understand clinical and economic implications of DOACs versus VKAs using available real-world evidence (RWE)**.

## Methods

Using a systematic literature review and considering the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement method real-world studies published between 2009 and 2019 and comparing the use of apixaban, dabigatran, rivaroxaban and edoxaban and versus VKAs (e.g. warfarin) in patients with non-valvular atrial fibrillation were searched on Pubmed and Scopus. **Incidence of stroke/systemic embolism (SE), major bleeding (MB), intracranial hemorrhage (ICH) and all-cause of death** were extracted from studies satisfying pre-specified inclusion criteria. After combining results from selected studies using a network meta-analysis relying on a Bayesian approach, these data were used as input for a **cost-effectiveness analysis** considering a lifetime horizon and the Italian National Health System (INHS) perspective. The analysis was based on a previously developed Markov model.

**Direct costs of the oral anticoagulant therapy, monitoring costs and costs of events** were considered in the analysis. For the different treatment options, costs related to the oral anticoagulant therapy were estimated multiplying daily dosage times unit costs of the product considering ex-factory prices from the National Italian Gazette. Costs related to the incidence of events were estimated considering reimbursement associated with the hospitalization for the management of each event according to official national charges set by the Italian Ministry of Health. Costs related to post-stroke rehabilitation and monitoring costs associated to VKAs treatment were derived from previously published data. All costs were expressed in Euros and updated to 2018, all costs and outcomes in the model were discounted at 3.5% annum.

## Key Results

About 30 studies were included in the meta-analysis; of note, no studies related to edoxaban were included in the analysis. Results from the meta-analysis performed showed that all DOACs resulted in a significantly reduced risk of stroke/SE and mortality. Compared to VKA, dabigratan reduced the risk of MB by about 30% while apixaban implied about 40% reduction for the risk both MB and ICH, thus resulting in incremental QALYs and LYs gained. As compared to VKA, rivaroxaban did not produce significant beneficial effect with respect to the risk of experiencing MB.

Among all the DOACs considered, apixaban resulted the treatment option with lower overall costs; moreover, also when compared to VKA, higher acquisition costs for apixaban were offset by savings related to better disease management and additional costs for monitoring required with VKA.

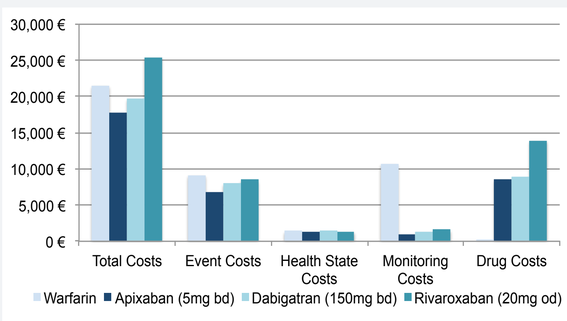
In details, for overall costs**, apixaban induced savings when compared to other treatments (VKAs or other DOACs); QALYs and LYs were higher for apixaban when compared to warfarin and rivaroxaban, while dabigratan and apixaban showed similar results in terms of effectiveness.**

## Additional Considerations

***Impact of the treatment on the risk of events according to data from RWE***

| | HR (95% CI) |
|---|---|
| *Stroke/SE* | |
| Apixaban vs Warfarin | **0.815 (0.664-0.991)** |
| Dabigratan vs Warfarin | **0.874 (0.696-1.083)** |
| Rivaroxaban vs Warfarin | **0.836 (0.706-0.983)** |
| *Major Bleeding* | |
| Apixaban vs Warfarin | **0.573 (0.497-0.657)** |
| Dabigratan vs Warfarin | **0.727 (0.613-0.856)** |
| Rivaroxaban vs Warfarin | 1.048 (0.925-1.183) |
| *Intracranial hemorrage* | |
| Apixaban vs Warfarin | **0.610 (0.381-0.926)** |
| Dabigratan vs Warfarin | 0.491 (0.193-1.037) |
| Rivaroxaban vs Warfarin | 0.703 (0.450-1.049) |

***Details of the cost-effectiveness evaluation***




**Total costs per patient and costs related to different cost items according to the treatment arm over a lifetime perspective (30 years).**

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