Direct Oral Anticoagulants and Incidence of Dementia in Patients with Nonvalvular Atrial Fibrillation

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1 Background

In patients with atrial fibrillation (AF), oral anticoagulation is essential for stroke prevention but may also prevent cognitive decline and dementia.

However, it remains unclear whether direct oral anticoagulants (DOACs) have similar effectiveness against dementia.

2 Objective

The primary objective was to compare the risk of dementia among AF patients initiating different DOACs, with head-to-head comparisons between apixaban, edoxaban and rivaroxaban.

3 Methods

Design
Head-to-head new-user cohort study comparing direct oral anticoagulants (DOACs) in patients newly diagnosed with nonvalvular atrial fibrillation (AF).

Data Source
Data were from the UK Clinical Practice Research Datalink (CPRD - Gold and Aurum databases), a large primary care database of electronic medical records representative of the UK population.

Study Population
We assembled a base cohort of patients aged ≥50 years newly diagnosed with nonvalvular atrial fibrillation (AF) between January 1, 2011, and June 30, 2023.

Within this base cohort, we formed three new-user cohorts for head-to-head comparisons:
- Apixaban vs Rivaroxaban (2013–2023)
- Edoxaban vs Rivaroxaban (2015–2023)
- Edoxaban vs Apixaban (2015–2023)

Cohort entry was defined as the date of the first DOAC prescription after AF diagnosis.

Follow-up began six months after cohort entry for latency considerations and ended at dementia diagnosis, treatment change/discontinuation, death, end of registration, or June 30, 2023, whichever came first.

Exposure
Exposure was defined using an as-treated approach. Patients were considered continuously exposed starting six months after their first DOAC prescription.

Censoring occurred at treatment discontinuation or switching to another oral anticoagulant, with a 6-month grace period for gaps between prescriptions.

Outcome
The primary outcome was the first recorded diagnosis of dementia, regardless of subtype (e.g., Alzheimer's disease, vascular, unspecified, or other).

Statistical Analysis
We used propensity score fine stratification weighting to control for confounding. For each comparison, we applied weighted Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals for incident dementia.

We conducted 6 subgroup analyses to explore effect modification and 5 sensitivity analyses to assess the robustness of our findings.

4 Results

The three cohorts included up to:
- 131,663 apixaban new users
- 48,405 edoxaban new users
- 70,038 rivaroxaban new users

After propensity score fine stratification weighting, covariates were well-balanced across all cohorts.

Across weighted cohorts:
- Mean age ranged from 74.7 to 77.9 years
- Female proportion ranged from 42.2% to 46.2%
- Median follow-up ranged from:
  - 746–759 days (apixaban)
  - 345–383 days (edoxaban)
  - 820–880 days (rivaroxaban)

Table 1. Adjusted Hazard Ratios for the Risk of Dementia, by Cohort

	Events	Person- Years	Adjusted Incidence Rate[a] (95% CI)	Adjusted HR[b] (95% CI)
Apixaban vs. Rivaroxaban				
Rivaroxaban	2,689	215,455	13.1 (12.6-13.6)	1.00 (Reference)
Apixaban	4,725	343,120	13.2 (12.9-13.6)	**1.01 (0.96-1.06)**
Edoxaban vs. Rivaroxaban				
Rivaroxaban	1,961	166,584	12.2 (11.6-12.7)	1.00 (Reference)
Edoxaban	1,019	74,784	12.7 (12.1-13.5)	**1.05 (0.96-1.16)**
Edoxaban vs. Apixaban				
Apixaban	4,509	330,263	13.5 (13.1-13.9)	1.00 (Reference)
Edoxaban	1,004	73,173	14.3 (13.6-15.1)	**1.06 (0.98-1.15)**

Abbreviations: CI=Confidence Interval, HR=Hazard Ratio
a. Incidence rates are expressed per 1,000 persons per year.
b. Adjusted for all covariates

Table 2. Forest Plot Summarizing Stratified Analyses of Dementia Risk in the Apixaban vs. Rivaroxaban Cohort

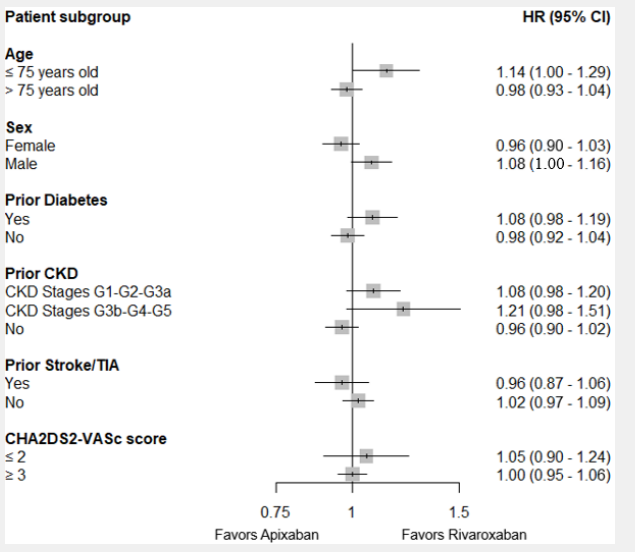
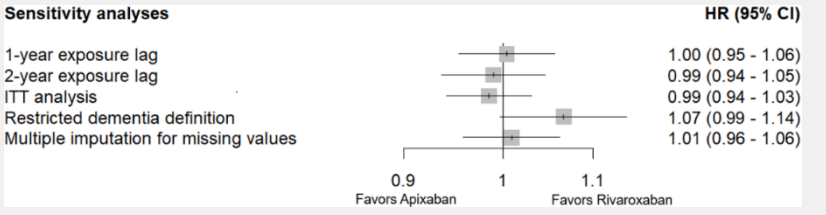


Table 3. Forest Plot Summarizing Sensitivity Analyses of Dementia Risk in the Apixaban vs. Rivaroxaban Cohort



5 Conclusion

In patients with AF, **no meaningful differences in dementia risk were observed across DOACs** in the primary analyses, suggesting that the choice of DOAC does not influence dementia risk.

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