Background

- **Dabigatran** and **rivaroxaban** showed a better benefit-risk than vitamin-K antagonists (VKA) for stroke prevention in non-valvar atrial fibrillation (NVAF); but no randomized trial has compared dabigatran to rivaroxaban.

- However, our previous results and other studies conducted in real-life settings found similar or better results with dabigatran at either dose than rivaroxaban after 1 or 2 years of follow-up.

- **Dabigatran 150mg** and **rivaroxaban 20mg** are the standard doses. Dabigatran 110mg is a reduced dose indicated in patients with moderate renal impairment, a higher risk of bleeding or in older patients, whereas rivaroxaban 15mg is just recommended for patients with moderate renal impairment.

**Objectives**

To estimate the comparative effectiveness and safety of standard and reduced doses of dabigatran versus rivaroxaban over a 3-year follow-up in real-life setting.

**Methods**

- **Study design**
  - Cohort studies in the SINDS (Système National des Données de Santé) nationwide French claims database including all new users of dabigatran (150mg or 110mg), or rivaroxaban 20mg or 15mg for NVAF in 2013, with three-year history and three-year follow-up in the database (except for patients who did not survive).

- **Data source**
  - SINDS database contains individual pseudonymised information from 66 million persons on:
    - **Gender**, date of birth, area of residence, date of death;
    - Long-term disease registration with associated ICD-10 codes for full insurance coverage (with start and end dates);
    - Outpatient reimbursed healthcare expenditures: visits, medical procedures, lab tests, drugs, …
    - Hospital discharge summaries with ICD-10 codes for diagnosis (primary, linked and associated diagnoses) for all private and public medical, obstetric and surgery hospitalisations, with the date and duration of hospitalisation, medical procedures.

- **NVAF population**
  - Patients with long-term disease registration, hospitalisation or procedure for atrial fibrillation without valvular disease history, and nor other probable indication using three-year database history.

- **Outcomes**: during anticoagulant exposure period (on treatment)
  - **Clinical events**: hospital admission with main diagnosis of clinically relevant bleeding (CRB), major bleeding, stroke and systemic embolism (SSE), and acute coronary syndrome (ACS);
  - **Death** (all-causes);
  - **Composite criterion**: first event among CRB, SSE, ACS, or death.

- **Data analysis**
  - 1:1 matched analysis on gender, age (± 1 year), date of the first drug dispensing (± 14 days), and high-dimensional propensity score (hPS)**¹**(± 0.01)
  - Cumulative incidence of outcomes using Kaplan-Meier estimate (death, composite) or cumulative incidence function (other outcomes).
  - **Hazard ratios (HR)** [95% confidence interval (CI)] of outcomes during first prescribed anticoagulant exposure, using Cox proportional hazard risk (death, composite) or Fine and Gray models (other outcomes) for crude, adjusted and matched patient analyses.

**Results**

- **Populations**
  - Of 371,539 new users of dabigatran, rivaroxaban or VKA in 2013 in France, 10,847, 15,522, 18,829 and 11,195 were treated for NVAF with dabigatran 150mg, dabigatran 110mg, rivaroxaban 20mg or rivaroxaban 15mg, respectively.
  - For standard doses comparison, 8,195 patients were matched per arm (76% of dabigatran 110mg group and 44% of rivaroxaban 20mg group).
  - For reduced doses comparison, 7,651 patients were matched per arm (49% of dabigatran 110mg group and 68% of rivaroxaban 15mg group).
  - **Patient characteristics** and hPS distribution showed differences between groups dramatically reduced after matching (Table 1, Figure 1). For both comparisons, after matching, standardized differences were < 5% for all variables, even < 2% for most variables (Figure 1).

**Conclusion**

This real-life nationwide study with three-year follow-up shows:
- **No significant difference of effectiveness between the 2 drugs for standard and reduced doses**
- A **lower bleeding risk of dabigatran at either dose**
- **Similar results** to those after two years of follow-up and other observational studies with an overall benefit-risk profile in favour of dabigatran for both doses.

**Declaration of Interest Statement**

This study was funded by an unrestricted grant from Boehringer Ingelheim France. It was designed, conducted, and analysed independently by the Bordeaux PharmacoEpi of the Bordeaux University. It was overseen by independent experts.