Face-to-face 3-year comparative effectiveness and safety of dabigatran and rivaroxaban, standard and reduced doses, for nonvalvular atrial fibrillation: a cohort study in the French nationwide claims database

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Background

- Dabigatran and rivaroxaban showed a better benefit-risk than vitamin-K antagonists (VKA) for stroke prevention in non-valvular 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

Cohorts study in the SNDS (*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

SNDS 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-cause);
- 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 (hdPS)* (± 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.

*Probability to be treated by dabigatran 150mg versus rivaroxaban 20mg or dabigatran 110mg versus rivaroxaban 15mg using a logistic regression model with 500 variables including gender, age, stroke risk factors, bleeding risk factors

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.

Results

Populations

- Of 371,539 new users of dabigatran, rivaroxaban or VKA in 2013 in France, **10,847**, **15,532**, **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 150mg 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 hdPS 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**).

Table 1. Main patient characteristics in matched NVAF populations

	Standard dose		Reduced dose	
	Dabigatran n = 8,195	Rivaroxaban n = 8,195	Dabigatran n = 7,651	Rivaroxaban n = 7,651
Male, %	69.6	69.6	46.6	46.6
Age, mean (± SD)	66.9 (8.7)	66.9 (8.7)	80.5 (7.5)	80.5 (7.5)
Risk factors, %				
Hypertension	29.4	29.3	43.7	43.9
Diabetes mellitus	19.6	20.1	19.8	19.8
Vascular disease history	9.2	9.2	14.4	14.9
Congestive heart failure	9.8	9.7	18.7	20.0
Stroke or transient ischemic attack history	8.3	7.3	11.4	11.6
Abnormal renal function	1.2	1.1	4.8	4.8
Abnormal liver function	1.0	0.9	1.3	1.4
CHA_2DS_2-VASc score ≥ 2	58.6	59.3	94.1	94.1
HAS-BLED score ≥ 3	15.9	15.1	33.7	34.6

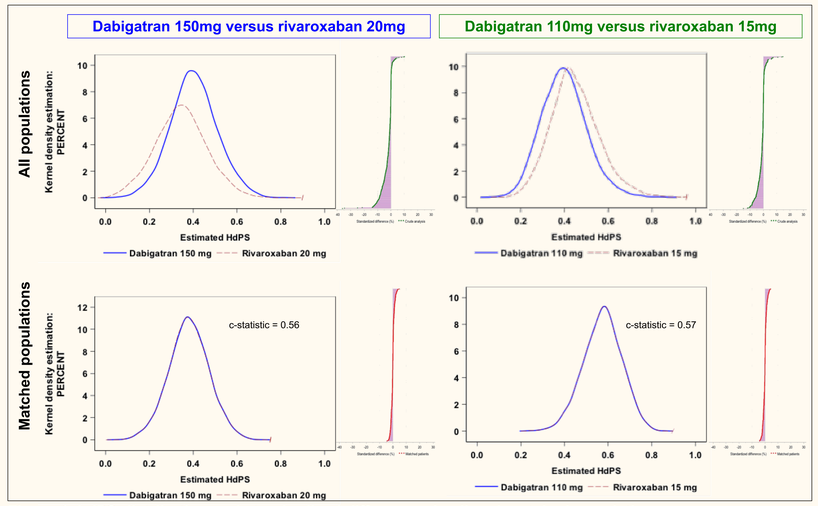

Figure 1. hdPS distribution and standardized differences in all and matched populations

- **The 3-year cumulative incidence of outcomes** for matched patients are presented in **Table 2**.

Table 2. 3-year cumulative incidence of outcomes for matched NVAF populations (on treatment)

	Standard dose				Reduced dose			
	Dabigatran n = 8,195		Rivaroxaban n = 8,195		Dabigatran n = 7,651		Rivaroxaban n = 7,651	
	n event	% [95%CI]	n event	% [95%CI]	n event	% [95%CI]	n event	% [95%CI]
Clinically relevant bleeding (CRB)	113	3.2 [2.6; 3.8]	235	5.5 [4.8; 6.3]	208	5.3 [4.5; 6.1]	319	7.8 [6.9; 8.7]
Major bleeding	40	1.2 [0.8; 1.7]	87	2.1 [1.6; 2.6]	97	2.3 [1.8; 2.8]	162	4.0 [3.4; 4.7]
Stroke and systemic embolism (SSE)	75	1.8 [1.4; 2.3]	104	2.4 [1.9; 2.9]	116	3.2 [2.6; 3.9]	156	3.8 [3.2; 4.5]
Acute coronary syndrome (ACS)	77	2.1 [1.6; 2.7]	84	1.9 [1.5; 2.3]	92	2.3 [1.8 ; 2.9]	115	2.6 [2.1; 3.2]
Death (all causes)	113	3.3 [2.7; 4.0]	150	3.8 [3.2; 4.5]	449	12.9 [11.7; 14.2]	532	13.9 [12.8; 15.2]
Composite criterion (CRB, SSE, ACS, death)	357	9.6 [8.5; 10.7]	531	12.2 [11.2; 13.3]	795	21.1 [19.6; 22.6]	1009	24.1 [22.7; 25.6]

Benefit-risk of dabigatran 150mg versus rivaroxaban 20mg and dabigatran 110mg versus rivaroxaban 15mg

- The risk of CRB, major bleeding and the composite criterion was significantly lower with dabigatran 150mg, and with no difference for SSE, ACS, and death.
- Similar results were found for reduced doses comparison (Figure 2).

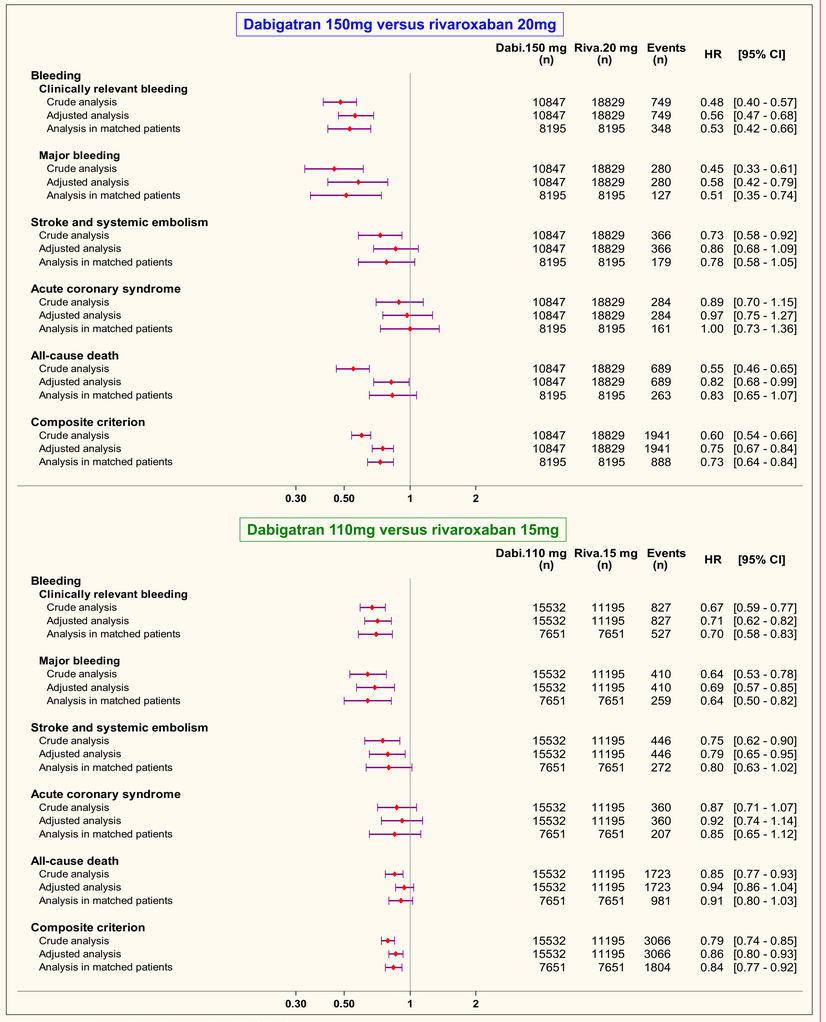

Figure 2. Hazard ratios and 95% CI of outcomes

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**

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