Effectiveness and safety of standard and reduced doses of dabigatran compared to rivaroxaban in non-valvular atrial fibrillation: Long-term results from a cohort in the French nationwide claims database SNDS

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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.
- This analysis aimed to estimate the real-life comparative benefit-risk of standard (dabigatran 150mg versus rivaroxaban 20mg) and reduced doses (dabigatran 110mg versus rivaroxaban 15mg) on major events over 3 years of follow-up.

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

The 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

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, 110mg, rivaroxaban 20mg or 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 which were 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 2**).

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

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.
- There was a significant lower risk with dabigatran 110mg for CRB, major bleeding and the composite criterion, and no difference for SSE, ACS, and death (**Figure 3**).

Tables and Figures

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

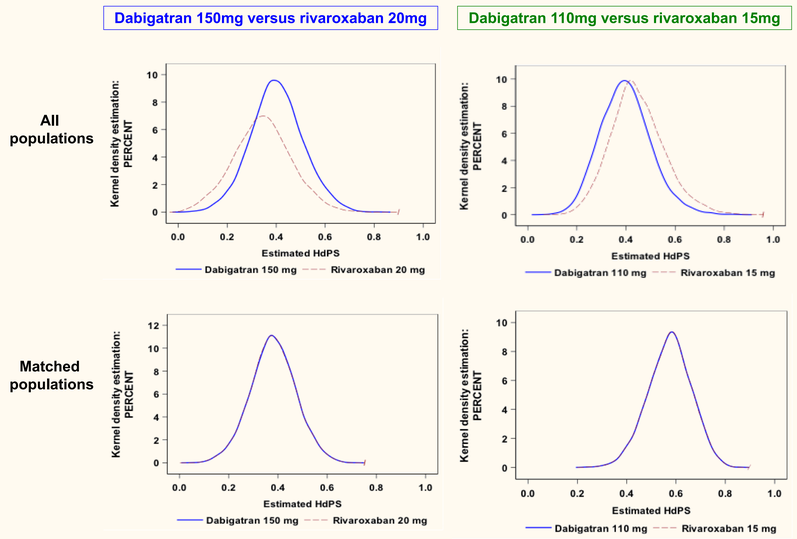

Figure 1. hdPS distribution in all and matched populations: dabigatran 150mg versus rivaroxaban 20mg, dabigatran 110mg versus rivaroxaban 15mg

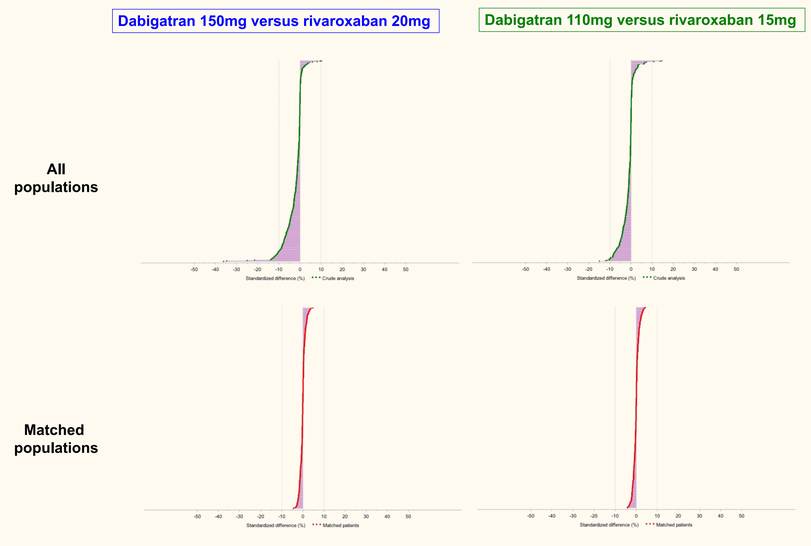

Figure 2. Standardized differences for all and matched populations: dabigatran 150mg versus rivaroxaban 20mg, dabigatran 110 mg versus rivaroxaban 15mg

Table 2. Three-year cumulative incidence of outcomes during the drug exposure period for matched NVAF populations

	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]**

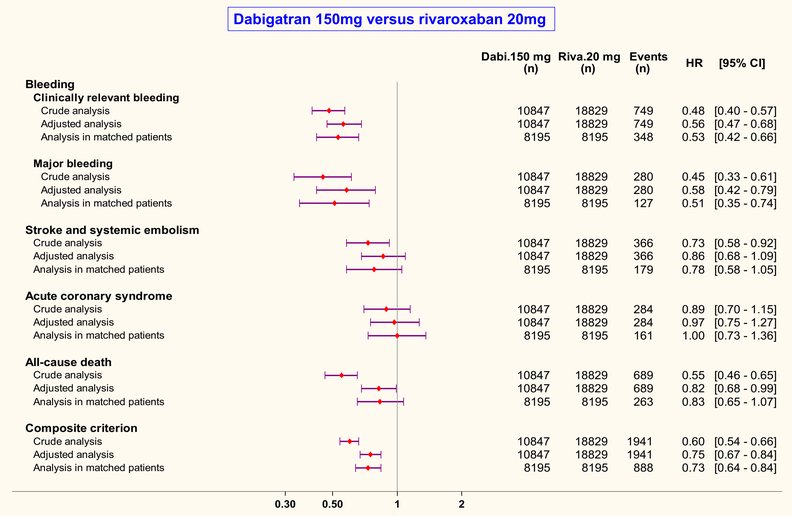

Figure 3. Hazard ratios and 95% CI of outcomes: dabigatran 150mg versus rivaroxaban 20mg, dabigatran 110 mg versus rivaroxaban 15mg

Conclusions

This real-life nationwide study with three-year follow-up shows :

- No significant difference of effectiveness between the two drugs for standard and reduced doses
- A lower bleeding risk of dabigatran at either dose
- Similar results to those of the 2-year of follow-up and other observational studies with an overall benefit-risk profile in favour of dabigatran for both doses

Disclosure of 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.

ACC 69th Annual Scientific Session, March 28-30 March, 2020, Chicago, USA