Effectiveness and safety of reduced dose rivaroxaban compared to vitamin K antagonists in patients at high risk of bleeding

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Introduction

- In our previous analyses performed in this national database, direct oral anticoagulants (DOAC), dabigatran and rivaroxaban had an effectiveness on stroke and systemic embolism (SSE) prevention in atrial fibrillation similar to vitamin K antagonists (VKA), but greater safety, with less major bleeding (MB) especially intracranial hemorrhage [1, 2]. However, it is not know how these results vary according to the value of the CHA_2DS_2-VASc and the HAS-BLED scores in particular for rivaroxaban.
- The reduced dose of DOAC is expected to reduce the occurrence of bleeding in patients at high risk of bleeding, but without altering the effectiveness of the drug on the prevention of SSE.

Objective

- To compare the 2-year risk of SSE and MB in new users of reduced dose rivaroxaban versus VKA for non valvular atrial fibrillation (NVAF) in real-life setting according to the CHA_2DS_2-VASc and HAS-BLED scores.

Methods

Study design

Cohort study in the SNDS (*Système National des Données de Santé*) nationwide French claims database including all new users of dabigatran, rivaroxaban or VKA for NVAF in 2013, with three-year prior history and two-year follow-up or until death in the database.

Data source

The SNDS database contains individual pseudonymised information from 66 million persons on:

- Gender, date of birth, area of residence, date of death;
- Chronic disease registration (*affection de longue durée*, ALD) 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 chronic disease registration, hospitalisation or procedure for atrial fibrillation without rheumatic valve disease or valve replacement, and no other probable indication using three-year database history.

Outcomes: during anticoagulant exposure period (on treatment)

For this re-analysis, studied clinical outcomes were the followings:

- Stroke and systemic embolism, defined as a hospital admission with one of the following main diagnosis of ischemic or undefined stroke and other systemic arterial embolism or surgical procedure for systemic arterial embolism;
- Major bleeding, defined as a hospital admission with one of the following main diagnosis of haemorrhagic stroke (linked or associated diagnosis also considered), other critical organ or site bleeding and other bleeding with a transfusion during hospital stay, or resulting in death.

Data analysis

- 1:1 matched analysis on gender, age (± 1 year), date of the first drug dispensing (± 14 days), and logit of high-dimensional propensity score (hdPS)* (± 0.2 SD);
- 2-year cumulative incidence of outcomes using cumulative incidence function;
- Hazard ratios (HR) [95% confidence interval (CI)] of outcomes during first prescribed anticoagulant exposure using Fine and Gray model.

*Probability to be treated by rivaroxaban 15mg *versus* VKA using a logistic regression model with 500 variables including gender, age, stroke risk factors, bleeding risk factors, hospital and non-hospital costs

Results

Populations

- Of 387,788 incident anticoagulant users in 2013 in France, 118,048 had NVAF; 53,252 were treated with VKA and 12,800 with rivaroxaban 15mg.
- For rivaroxaban 15mg versus VKA:
  - 12,018 patients were matched per arm (94% of rivaroxaban group);
  - About 800, 2,000, 3,300, and 6,000 patients for CHA_2DS_2-VASc score 0-1, 2, 3, ≥ 4, respectively;
  - About 2,600, 8,200 and 1,200 patients for HAS-BLED score 0-1, 2-3, >3, respectively.
- Patient characteristics and hdPS distribution showed differences between groups, and were normalized after matching (**Table 1, Figure 1**).
  After matching, standardized differences were <15% for all variables, even ≤5% for most variables (**Figure 2**).

Table 1. Baseline patient characteristics in matched NVAF populations

	Rivaroxaban 15mg n = 12,018	VKA n = 12,018
Male, %	47.3	47.3
Age, mean (± SD)	80.4 (8.6)	80.4 (8.6)
Risk factors, %		
Hypertension	47.1	47.9
Diabetes mellitus	21.7	21.9
Congestive heart failure	24.8	24.6
Vascular disease history	17.7	18.0
Stroke or transient ischemic attack history	11.5	11.9
Abnormal renal function	8.0	8.6
Abnormal liver function	1.6	1.7
CHA_2DS_2-VASc score		
0-1	6.8	6.5
2	16.1	15.6
3	27.5	27.4
≥4	49.6	50.5
HAS-BLED score		
0-1	21.9	20.3
2-3	68.3	69.8
>3	9.8	9.9

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[1] Blin P, et al. Effectiveness and Safety of Rivaroxaban 15 or 20 mg Versus Vitamin K Antagonists in Nonvalvular Atrial Fibrillation. Stroke. 2019 Sep;50(9):2469-2476. doi: 10.1161/STROKEAHA.119.025824. Epub 2019 Aug 8.

[2] Blin P, et al. Effectiveness and safety of 110 or 150 mg dabigatran vs. vitamin K antagonists in nonvalvular atrial fibrillation. Br J Clin Pharmacol. 2019 Feb;85(2):432-441. doi: 10.1111/bcp.13815. Epub 2018 Dec 16.

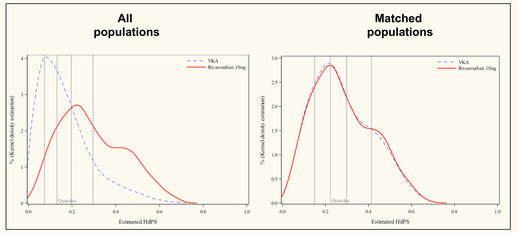

Figure 1. hdPS distribution in all and matched populations

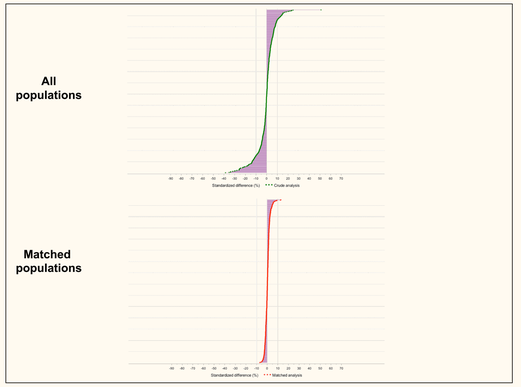

Figure 2. Standardized differences for all and matched populations

The two-year cumulative incidences of SSE and MB

according to the stroke and bleeding risk scores for matched patients are presented in **Tables 2 and 3**. The outcomes incidence increased with the value of the CHA_2DS_2-VASc or HAS-BLED scores for the two treatment groups.

Benefit-risk of rivaroxaban 15mg versus VKA

- For SSE, no statistical difference of rivaroxaban compared to VKA whatever the CHA_2DS_2-VASc score (**Table 2**);
- For MB, a significant lower risk with rivaroxaban 15mg, with a gradient from 0.56 to 1.14 for HAS-BLED scores >3 to 0-1 (**Table 3**).

Table 2. Two-year cumulative incidence and HR of stroke and systemic embolism according to the CHA_2DS_2-VASc score during the drug exposure period for matched NVAF populations

SSE	Rivaroxaban 15mg			VKA			Rivaroxaban 15mg versus VKA
	Size (n)	Event (n)	Cumulative incidence (%) [95% CI]	Size (n)	Event (n)	Cumulative incidence (%) [95% CI]	HR [95% CI]
All matched patients	12018	298	3.7 [3.3; 4.1]	12018	286	3.2 [2.9; 3.6]	1.14 [0.97; 1.34]
CHA_2DS_2-VASc score							
0-1	815	12	2.3 [1.2; 3.9]	785	8	1.5 [0.7; 2.9]	1.49 [0.61; 3.65]
2	1936	27	2.0 [1.4; 2.9]	1869	29	1.9 [1.3; 2.7]	0.95 [0.56; 1.60]
3	3301	65	2.8 [2.2; 3.6]	3293	64	2.7 [2.1; 3.4]	1.12 [0.79; 1.58]
≥4	5966	194	4.9 [4.2; 5.6]	6071	185	4.1 [3.6; 4.8]	1.19 [0.97; 1.45]

Table 3. Two-year cumulative incidence and HR of major bleeding according to the HAS-BLED score during the drug exposure period for matched NVAF populations

MB	Rivaroxaban 15mg			VKA			Rivaroxaban 15mg versus VKA
	Size (n)	Event (n)	Cumulative incidence (%) [95% CI]	Size (n)	Event (n)	Cumulative incidence (%) [95% CI]	HR [95% CI]
All matched patients	12018	299	3.7 [3.3; 4.1]	12018	406	4.6 [4.2; 5.1]	0.80 [0.69; 0.93]
HAS-BLED score							
0-1	2634	51	3.1 [2.3; 4.0]	2444	45	2.7 [2.0; 3.6]	1.14 [0.76; 1.70]
2-3	8209	216	3.8 [3.3; 4.3]	8386	295	4.8 [4.3; 5.4]	0.81 [0.68; 0.97]
>3	1175	32	4.0 [2.8; 5.6]	1188	66	7.2 [5.6; 9.0]	0.56 [0.37; 0.86]

Conclusions

- Different rivaroxaban 15mg and VKA prescription patterns, but similar population characteristics after hdPS matching.
- Increasing risk scores for stroke and systemic embolism and major bleeding are associated with increasing incidence of events.
- No better effectiveness of reduced dose rivaroxaban compared to VKA.
- Clear benefit of reduced dose rivaroxaban on bleeding in the higher-risk groups with HAS-BLED scores ≥2.

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