EFFECTIVENESS AND SAFETY OF STANDARD AND REDUCED DOSE RIVAROXABAN COMPARED TO VITAMIN K ANTAGONISTS IN PATIENTS AT HIGH RISK OF BLEEDING OR STROKE

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Introduction

- 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, the results correlation with the CHA_2DS_2-VASc and HAS-BLED scores is not known.

Objective

- To compare the 2-year risk of SSE and MB in new users of rivaroxaban 20mg (standard dose) or 15mg (reduced dose) 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 rivaroxaban or VKA for NVAF in 2013, with three-year 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;
  - 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;
  - 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 20mg or 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, 20,465 with rivaroxaban 20mg, and 12,800 with the 15mg.
- For **rivaroxaban 20mg versus VKA**:
  - 15,680 patients were matched per arm (77% of rivaroxaban 20mg group);
  - More than 3,500 patients per CHA_2DS_2-VASc score group;
  - About 5,700, 9,100 and 800 patients for HAS-BLED score 0-1, 2-3, >3, respectively.
- For **rivaroxaban 15mg versus VKA**:
  - 12,018 patients were matched per arm (94% of rivaroxaban 15mg 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.
- Main baseline patient characteristics for matched populations are presented in **Table 1**.

Table 1. Baseline patient characteristics in matched NVAF populations

	Rivaroxaban 20mg n = 15,680	VKA n = 15,680	Rivaroxaban 15mg n = 12,018	VKA n = 12,018
Male, %	61.9	61.9	47.3	47.3
Age, mean (± SD)	71.3 (10.1)	71.3 (10.1)	80.4 (8.6)	80.4 (8.6)
Risk factors, %				
Hypertension	38.2	39.3	47.1	47.9
Diabetes mellitus	22.8	23.6	21.7	21.9
Congestive heart failure	15.2	15.4	24.8	24.6
Vascular disease history	13.5	14.1	17.7	18.0
Stroke or transient ischemic attack history	11.0	11.3	11.5	11.9
Abnormal renal function	2.8	3.3	8.0	8.6
Abnormal liver function	1.5	1.6	1.6	1.7
CHA_2DS_2-VASc score				
0-1	24.1	24.1	6.8	6.5
2	24.2	23.0	16.1	15.6
3	23.2	23.0	27.5	27.4
≥ 4	28.4	29.9	49.6	50.5
HAS-BLED score				
0-1	36.5	34.8	21.9	20.3
2-3	58.2	60.0	68.3	69.8
> 3	5.2	5.1	9.8	9.9

- **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 all treatment groups.

Benefit-risk of rivaroxaban 20mg or 15mg versus VKA

- For SSE, no statistical difference of rivaroxaban compared to VKA at either dose and whatever the CHA_2DS_2-VASc score (**Tables 2 and 3**);
- For MB, a significant lower risk with rivaroxaban 20mg, and with a gradient for HAS-BLED from 0.59 to 0.89 for scores 0-1 to >3 HR; with rivaroxaban 15mg, and with a gradient for HAS-BLED from 0.56 to 1.14 for scores >3 to 0-1 HR (**Tables 2 and 3**).

Table 2. Two-year cumulative incidence and HR of SSE and MB according to CHA_2DS_2-VASc and HAS-BLED scores during the drug exposure period for matched NVAF populations: rivaroxaban 20mg versus VKA

Stroke and systemic embolism (SSE)	Rivaroxaban 20mg Size (n)	Rivaroxaban 20mg Event (n)	Rivaroxaban 20mg Cumulative incidence (%) [95% CI]	VKA Size (n)	VKA Event (n)	VKA Cumulative incidence (%) [95% CI]	Rivaroxaban 20mg versus VKA HR [95% CI]
All matched patients	15680	280	2.6 [2.3; 2.9]	15680	292	2.7 [2.4; 3.0]	0.99 [0.84; 1.16]
CHA_2DS_2-VASc score							
0-1	3782	38	1.4 [1.0; 2.0]	3781	38	1.7 [1.2; 2.3]	1.00 [0.64; 1.57]
2	3798	59	2.3 [1.7; 2.9]	3603	53	2.0 [1.5; 2.6]	1.07 [0.74; 1.56]
3	3643	57	2.2 [1.7; 2.9]	3604	65	2.4 [1.9; 3.1]	0.89 [0.63; 1.27]
≥ 4	4457	126	3.8 [3.2; 4.6]	4692	136	3.9 [3.3; 4.6]	1.02 [0.80; 1.31]

Major bleeding (MB)	Rivaroxaban 20mg Size (n)	Rivaroxaban 20mg Event (n)	Rivaroxaban 20mg Cumulative incidence (%) [95% CI]	VKA Size (n)	VKA Event (n)	VKA Cumulative incidence (%) [95% CI]	Rivaroxaban 20mg versus VKA HR [95% CI]
All matched patients	15680	250	2.4 [2.1; 2.7]	15680	372	3.5 [3.2; 3.9]	0.69 [0.59; 0.81]
HAS-BLED score							
0-1	5728	50	1.5 [1.1; 1.9]	5462	82	2.5 [2.0; 3.1]	0.59 [0.41; 0.83]
2-3	9132	168	2.6 [2.3; 3.1]	9414	253	3.8 [3.3; 4.3]	0.70 [0.58; 0.85]
>3	820	32	5.2 [3.6; 7.2]	804	37	6.1 [4.3; 8.2]	0.89 [0.55; 1.43]

Table 3. Two-year cumulative incidence and HR of SSE and MB according to CHA_2DS_2-VASc and HAS-BLED scores during the drug exposure period for matched NVAF populations: rivaroxaban 15mg versus VKA

SSE	Rivaroxaban 15mg Size (n)	Rivaroxaban 15mg Event (n)	Rivaroxaban 15mg Cumulative incidence (%) [95% CI]	VKA Size (n)	VKA Event (n)	VKA Cumulative incidence (%) [95% CI]	Rivaroxaban 15mg versus VKA 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]

MB	Rivaroxaban 15mg Size (n)	Rivaroxaban 15mg Event (n)	Rivaroxaban 15mg Cumulative incidence (%) [95% CI]	VKA Size (n)	VKA Event (n)	VKA Cumulative incidence (%) [95% CI]	Rivaroxaban 15mg versus VKA 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 20mg or 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 statistical difference in effectiveness of rivaroxaban compared to VKA at either dose.
- Clear benefit of rivaroxaban for safety, which increases with increasing risk in the high-risk of bleeding patients given reduced dose rivaroxaban.

Conflict of interest statement

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