Benefit-risk of rivaroxaban 20 or 15mg compared to vitamin-K antagonists in patients with non-valvular atrial fibrillation: a cohort study in French nationwide claims database

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Purpose

- Direct oral anticoagulants (DOAC), rivaroxaban, dabigatran, and apixaban had better benefit-risk than vitamin-K antagonists (VKA) for non-valvular atrial fibrillation (NVAF) in clinical trials, but real-life benefits and risks remain uncertain.
- Rivaroxaban 20mg is the standard dose and rivaroxaban 15mg, the dose recommended for patients with moderate or severe renal failure but not if renal clearance is below 15 ml/min.
- The purpose of this study was to compare the one-year risk of major events in new users of rivaroxaban 20mg and rivaroxaban 15mg versus VKA for NVAF 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 rivaroxaban 20mg, rivaroxaban 15mg or VKA for NVAF in 2013-2014, with three-year history and one-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);
- 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 rheumatic valve disease or valve replacement, 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 stroke and systemic embolism (SSE), major bleeding*, clinically relevant bleeding (CRB)* and acute coronary syndrome (ACS);
- Death (all-cause);
- Composite criterion: first event among SSE, major bleeding, or 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).
- 1-year cumulative incidence of outcomes was estimated 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).

*With primary, linked or associated diagnosis for haemorrhagic stroke
**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

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Results

Populations

- Of 734,599 new users of dabigatran, rivaroxaban or VKA in 2013-2014 in France, **42,531**, **24,585** and **108,666** were treated for NVAF with rivaroxaban 20mg,15mg or VKA, respectively.
- For rivaroxaban 20mg versus VKA and for rivaroxaban 15mg versus VKA, **31,171 and 23,314 patients were matched per arm**, respectively (73% of rivaroxaban 20mg group and 95% of rivaroxaban 15mg group).
- Patient characteristics and hdPS distribution showed differences between groups, and were normalized after matching (**Table 1, Figure 1**). For both comparisons, after matching, standardized differences were < 10% for all variables, even ≤ 5% for most variables (**Figure 2**).

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

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

- The risk of all outcomes was significantly lower with rivaroxaban 20mg.
- There was a significant lower risk with rivaroxaban 15mg for major bleeding, death, composite, clinically relevant bleeding, at the significant threshold for acute coronary syndrome, and no difference for stroke and systemic embolism (**Figure 3**).

Table 1. Main patients characteristics in all NVAF populations

	Rivaroxaban 20mg* n = 42,480		VKA* n = 108,656		Rivaroxaban 15mg* n = 24,529		VKA* n = 108,639	
Male, n (%)	27352	(64.4)	56349	(51.9)	11574	(47.2)	56350	(51.9)
Age at index date (in years), mean (± SD)	68.6	(11.1)	78.4	(11.0)	79.8	(9.4)	78.4	(11.0)
Stroke risk factors (score), n (%)**								
Congestive heart failure	5282	(12.4)	38534	(35.5)	5580	(22.7)	38533	(35.5)
Hypertension	14284	(33.6)	60473	(55.7)	11084	(45.2)	60462	(55.7)
Age ≥ 75 years	13678	(32.2)	75405	(69.4)	19172	(78.2)	75383	(69.4)
Diabetes mellitus	8713	(20.5)	29335	(27.0)	5186	(21.1)	29333	(27.0)
Stroke or transient ischemic attack (TIA) history	3735	(8.8)	16225	(14.9)	2683	(10.9)	16224	(14.9)
Vascular disease history	4645	(10.9)	24993	(23.0)	4051	(16.5)	24989	(23.0)
Age 65-74 years	15471	(36.4)	20359	(18.7)	3709	(15.1)	20357	(18.7)
Women	15128	(35.6)	52307	(48.1)	12955	(52.8)	52289	(48.1)
CHA_2DS_2-VASc score ≥ 2, n (%)	28110	(66.2)	98598	(90.7)	22648	(92.3)	98574	(90.7)
Bleeding risk factors (score), n (%)**								
Hypertension	14284	(33.6)	60473	(55.7)	11084	(45.2)	60462	(55.7)
Abnormal renal function	891	(2.1)	19538	(18.0)	1660	(6.8)	19538	(18.0)
Abnormal liver function	579	(1.4)	3531	(3.2)	397	(1.6)	3531	(3.3)
Stroke history	3107	(7.3)	14124	(13.0)	2240	(9.1)	14123	(13.0)
Bleeding history	647	(1.5)	3658	(3.4)	588	(2.4)	3657	(3.4)
Age > 65 years	27590	(64.9)	93976	(86.5)	22625	(92.2)	93952	(86.5)
Medication usage predisposing to bleeding	22611	(53.2)	72275	(66.5)	15249	(62.2)	72267	(66.5)
HAS-BLED score > 3, n (%)	1640	(3.9)	18020	(16.6)	2158	(8.8)	18019	(16.6)

*Number of patients after hdPS trimming for groups comparison (exclusion of patients with extreme hdPS values)
**Based on general characteristics of patients, long-term disease with full insurance coverage, as well as three-year history of hospital-discharge summary diagnosis, and drugs reimbursed

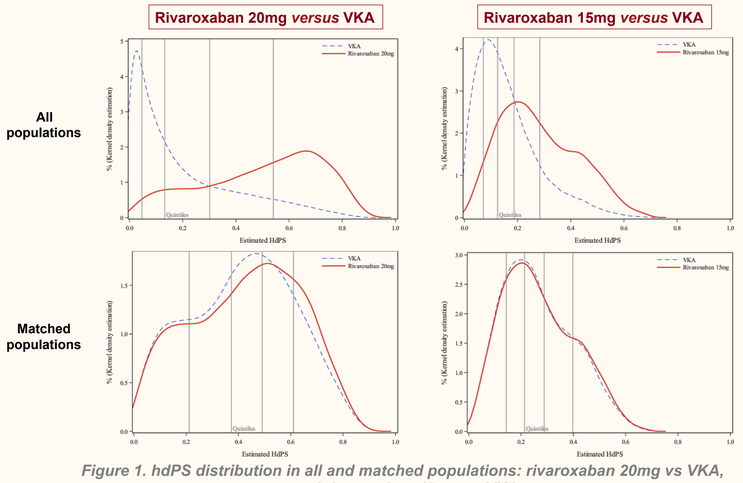

Figure 1. hdPS distribution in all and matched populations: rivaroxaban 20mg vs VKA, and rivaroxaban 15mg vs VKA

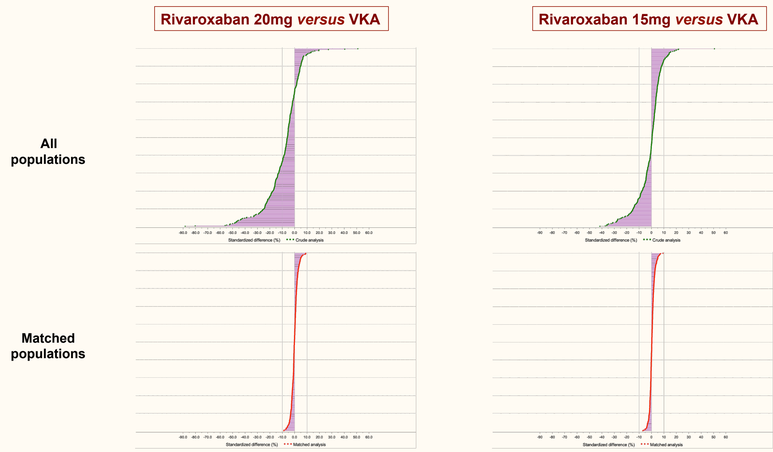

Figure 2. Standardized differences for all and matched populations: rivaroxaban 20mg versus VKA, and rivaroxaban 15mg versus VKA

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

	Rivaroxaban 20mg n = 31,171		VKA n = 31,171		Rivaroxaban 15mg n = 23,314		VKA n = 23,314	
	n event	% [95%CI]	n event	% [95%CI]	n event	% [95%CI]	n event	% [95%CI]
Stroke and systemic embolism (SSE)	**372**	**1.5 [1.4; 1.7]**	**494**	**1.9 [1.8; 2.1]**	**399**	**2.3 [2.0; 2.5]**	**419**	**2.1 [1.9; 2.3]**
Major bleeding	**359**	**1.5 [1.4; 1.7]**	**560**	**2.2 [2.1; 2.4]**	**426**	**2.4 [2.2; 2.6]**	**560**	**2.9 [2.6; 3.1]**
Clinically relevant bleeding (CRB)	798	3.3 [3.1; 3.6]	1001	4.0 [3.7; 4.2]	787	4.4 [4.1; 4.7]	975	4.9 [4.6; 5.3]
Death (all causes)	**902**	**3.9 [3.7; 4.2]**	**1414**	**5.8 [5.5; 6.1]**	**1565**	**9.1 [8.6; 9.5]**	**2069**	**10.8 [10.3; 11.2]**
Composite criterion (SSE, major bleeding, death)	**1489**	**6.3 [6.0; 6.6]**	**2217**	**8.9 [8.5; 9.2]**	**2189**	**12.5 [12.0; 13.0]**	**2738**	**14.0 [13.5; 14.5]**
Acute coronary syndrome (ACS)	**286**	**1.2 [1.0; 1.3]**	**374**	**1.4 [1.3; 1.6]**	**270**	**1.5 [1.3; 1.7]**	**347**	**1.7 [1.6; 1.9]**

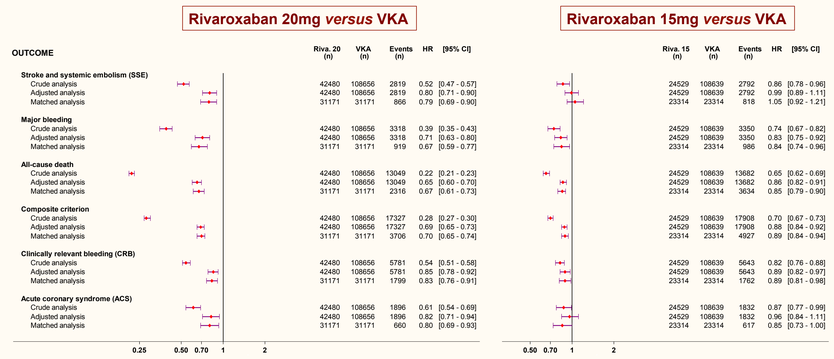

Figure 3. Hazard ratios and 95% CI of outcomes: rivaroxaban 20mg versus VKA, and rivaroxaban 15mg versus VKA

Conclusions

- Different rivaroxaban 20mg or 15mg and VKA prescription patterns, but similar population characteristics after hdPS matching.
- This nationwide cohort study of new anticoagulant users for NAVF shows a significantly overall better benefit-risk in real-life of rivaroxaban 20mg or 15mg compared to matched VKA.

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