Two-year benefit-risk of standard and reduced doses of rivaroxaban versus vitamin-K antagonists in non-valvular atrial fibrillation: a cohort study in the French nationwide claims database

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Introduction

- 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 recommended dose for patients with moderate or severe renal impairment but not if renal clearance is below 15 ml/min.

Objective

- To compare the two-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 dabigatran, 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)

- 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).
- 2-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) for crude, adjusted and matched patient analyses.

*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 387,788 new users of dabigatran, rivaroxaban or VKA in 2013 in France, **20,465**, **12,800** and **53,252** were treated for NVAF with rivaroxaban 20mg, 15mg or VKA, respectively.
- For rivaroxaban 20mg versus VKA and for rivaroxaban 15mg versus VKA, **15,680 and 12,018 patients were matched per arm**, respectively (77% of rivaroxaban 20mg group and 94% 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 < 15% for all variables, even ≤ 5% for most variables (**Figure 2**).

Table 1. Main 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 ≥ 2	75.9	75.9	93.2	93.5
HAS-BLED score ≥ 3	25.7	26.5	38.5	39.4

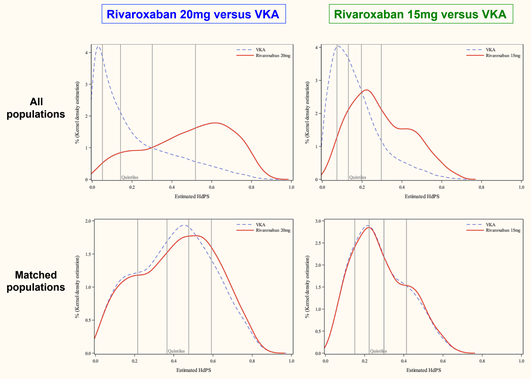

Figure 1. hdPS distribution in all and matched populations: rivaroxaban 20mg versus VKA, and rivaroxaban 15mg versus VKA

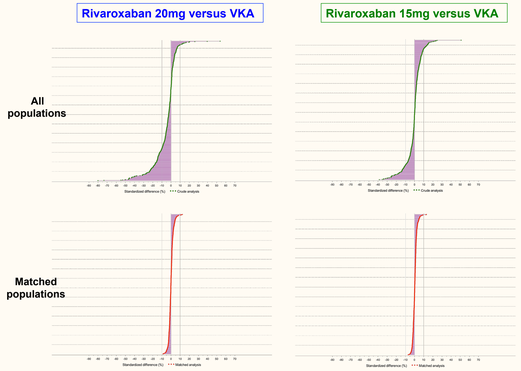

Figure 2. Standardized differences for all and matched populations: rivaroxaban 20mg versus VKA, and rivaroxaban 15mg versus VKA

The two-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, except for SSE for which there was no difference.
- There was a significant lower risk with rivaroxaban 15mg for major bleeding, death, composite, clinically relevant bleeding, and no difference for ACS and for SSE (**Figure 3**).

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

	Rivaroxaban 20mg n = 15,680		VKA n = 15,680		Rivaroxaban 15mg n = 12,018		VKA n = 12,018	
	n event	% [95%CI]	n event	% [95%CI]	n event	% [95%CI]	n event	% [95%CI]
Stroke and systemic embolism (SSE)	**280**	**2.6 [2.3; 2.9]**	**292**	**2.7 [2.4; 3.0]**	**298**	**3.7 [3.3; 4.1]**	**286**	**3.2 [2.9; 3.6]**
Major bleeding	**250**	**2.4 [2.1; 2.7]**	**372**	**3.5 [3.2; 3.9]**	**299**	**3.7 [3.3; 4.1]**	**406**	**4.6 [4.2; 5.1]**
Clinically relevant bleeding (CRB)	581	5.5 [5.0; 5.9]	685	6.4 [5.9; 6.9]	547	6.7 [6.2; 7.3]	677	7.6 [7.1; 8.2]
Death (all-cause)	**661**	**6.5 [6.0; 7.0]**	**1000**	**9.7 [9.1; 10.3]**	**1105**	**14.1 [13.3; 14.9]**	**1536**	**18.3 [17.5; 19.2]**
Composite criterion (SSE, major bleeding, death)	**1080**	**10.2 [9.6; 10.8]**	**1491**	**14.0 [13.3; 14.7]**	**1526**	**18.9 [18.0; 19.8]**	**1998**	**23.2 [22.3; 24.1]**
Acute coronary syndrome (ACS)	**180**	**1.6 [1.4; 1.9]**	**247**	**2.2 [1.9; 2.5]**	**194**	**2.4 [2.0; 2.7]**	**205**	**2.3 [2.0; 2.7]**

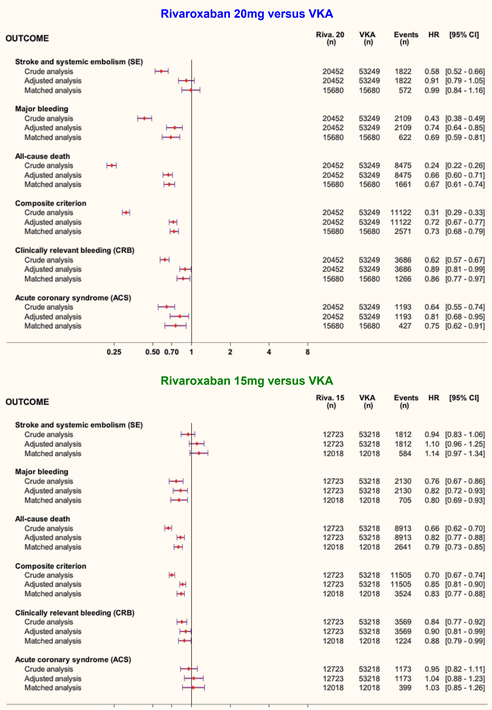

Figure 3. Hazard ratios and 95% CI of outcomes: rivaroxaban 20mg versus VKA, and rivaroxaban 15mg versus VKA

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 NVAF shows a significantly overall better long-term benefit-risk in real-life of rivaroxaban 20mg or 15mg compared to VKA.

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