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Benefit-risk and medical costs of rivaroxaban 15mg *versus* vitamin K antagonists from a French nationwide cohort of 220,000 patients with non-valvular atrial fibrillation

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Background

- Rivaroxaban (Xarelto®), dabigatran (Pradaxa®), and apixaban (Eliquis®), direct oral anticoagulants (DOAC), had better benefit-risk than vitamin K antagonists (VKA) for non-valvular atrial fibrillation (NVAF) in clinical trials.
- Real-life benefits and risks of DOAC remain uncertain.
- The low dosage of rivaroxaban (15mg) is recommended in this indication for patients with moderate or severe renal failure but not if renal clearance is below 15 ml/min.

Disclosure statement

This study was supported by an unconditional grant from Bayer AG. It was designed, conducted, and analysed independently by the Bordeaux PharmacoEpi of the Bordeaux University. It was overseen by independent experts.

Objectives

The aim of this study was to compare the benefit-risk and medical costs of rivaroxaban 15mg *versus* VKA for NVAF in real-life setting.

Methods

Study design

Cohort study in the SNDS nationwide French claims database including all new users of anticoagulant for NVAF in 2013 or 2014, with three-year history and one-year follow-up in the database (except for patients died).

Data source

The SNDS database contains individual pseudonymised information on:

- Gender, date of birth, area of residence, date of death;
- Long-term disease (LTD) registration with associated ICD-10 codes for full insurance coverage (with start and end dates);
- Outpatient reimbursed healthcare expenditures with codes, cost, date of event and date of prescription, prescriber and professional caregiver information;
- 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, cost coding system (diagnosis-related group [DRG] and stay-related group [SRG]).

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 (on treatment)

- Clinical events: hospital admission with main diagnosis of
  - Stroke and systemic embolism (SE)
  - Major bleeding*
  - Clinically relevant bleeding* (CRB)
  - Acute coronary syndrome (ACS)
- Death (all-cause)
- Composite criterion: first event among stroke and SE, major bleeding 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).
- Hazard ratios (HR) of outcomes during first prescribed anticoagulant exposure using Cox proportional hazard risk (death, composite) or Fine and Gray models (other outcomes).
- Medical costs estimated in euros (€) according to the collective perspective for the same period using mean costs of SRG for hospitalisations and amounts paid by patients for outpatient healthcare resources.

* With primary, linked or associated diagnosis for haemorrhagic stroke

** 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 220,011 new users of rivaroxaban, dabigatran, or VKA for NVAF in 2013-2014, 24,585 patients were treated with rivaroxaban 15mg and 108,666 with VKA.
- Patient characteristics showed differences between groups, and were normalized after matching (Table 1).
- For rivaroxaban 15mg *versus* VKA, 23,314 patients were matched per arm.

Table 1. Main patient characteristics in all and matched NVAF populations: rivaroxaban 15mg versus VKA

	All patients*		Matched patients		Standardized difference (%) Rivaroxaban 15mg *versus* VKA		
	Rivaroxaban 15mg n = 24,529	VKA n = 108,639	Rivaroxaban 15mg n = 23,314	VKA n = 23,314	Crude	Adjusted	Matched
Male, %	47.2	51.9	47.5	47.5	9.4	-0.7	0.0
Age (in years), mean (± SD)	79.8 (9.4)	78.4 (11.0)	80.1 (8.7)	80.1 (8.7)	14.2	-0.5	0.0
Risk factors, %							
Hypertension	45.2	55.7	45.9	45.9	-21.0	0.4	-0.1
Diabetes mellitus	21.1	27.0	21.4	21.8	-13.7	0.1	-0.9
Vascular disease history	16.5	23.0	16.8	17.1	-16.3	1.0	-0.8
Congestive heart failure	22.7	35.5	23.4	23.1	-28.3	0.2	0.8
Stroke or TIA history	10.9	14.9	11.2	11.4	-11.9	3.3	-0.5
Abnormal renal function	6.8	18.0	7.0	7.1	-34.6	-0.4	-0.4
Abnormal liver function	1.6	3.3	1.6	1.6	-10.6	-0.9	0.2
CHA_2DS_2-VASc score ≥ 2	92.3	90.7	92.9	92.9			
HAS-BLED score ≥ 3	36.2	47.8	37.0	36.8			

* Number of patients after hdPS trimming for groups comparison (exclusion of patients with extreme hdPS values)

Results

Benefit-risk and medical costs of rivaroxaban 15mg *versus* VKA

- There was no difference between risk with rivaroxaban 15mg and VKA for stroke and SE, a significant lower risk with rivaroxaban 15mg for major bleeding, death, composite, CRB, and at the significant threshold for ACS (Figure 1).
- The mean medical cost per patient followed during drug exposure was €8,288 for patients treated with rivaroxaban 15mg and €9,979 for those with VKA (Table 2, Figure 2):
  - The mean cost per patient was higher with rivaroxaban 15mg compared to VKA for AF drugs (€687 *vs* €95);
  - The mean cost per patient was lower with rivaroxaban 15mg for the majority of healthcare resources including lab tests (€196 *vs* €465), transport (€214 *vs* €284), nursing acts (€668 *vs* 968€), medical visits (€850 *vs* €954), specific hospitalisations (€891 *vs* €1,062), and other cardiovascular hospitalisations (€1,247 *vs* €1,826).

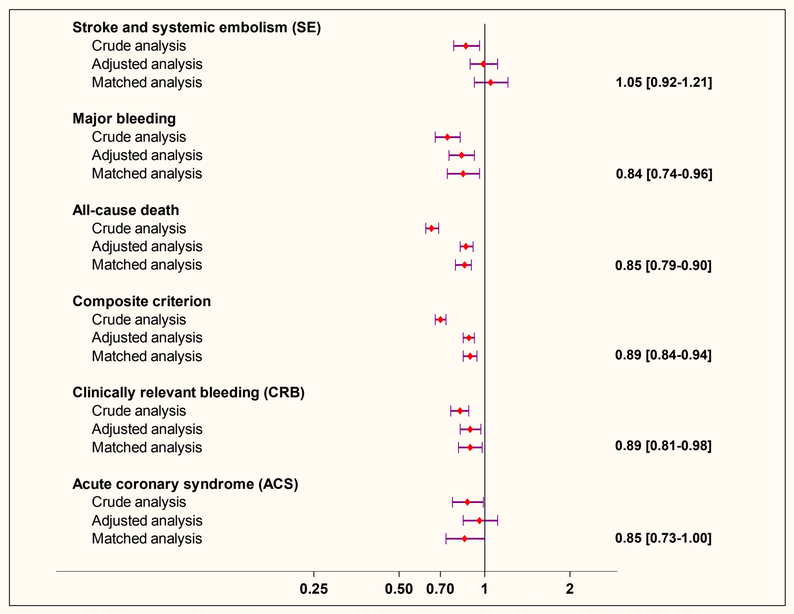

Figure 1. Rivaroxaban 15mg versus VKA: Hazard ratios and 95% CI of outcomes

Table 2. Costs of specific atrial fibrillation and general healthcare resources according to the collective perspective during drug exposure period in rivaroxaban 15mg and VKA matched NVAF populations

	Rivaroxaban 15mg n = 23,314		VKA n = 23,314	
	Mean (± SD)	[p25%; p75%]	Mean (± SD)	[p25%; p75%]
Total medical specific cost (in €) per patient	**1800.3 (2945.0)**	**[482.5; 1509.4]**	**1740.6 (3226.8)**	**[419.3; 1388.6]**
Specific hospitalisations[1]	890.7 (2883.6)	[0.0; 0.0]	1062.0 (3143.5)	[0.0; 0.0]
Atrial fibrillation drugs[2]	686.9 (409.8)	[239.3; 1032.4]	94.8 (64.3)	[42.4; 137.4]
Specific medical consultations and visits[3]	165.3 (155.7)	[55.0; 230.0]	211.7 (186.2)	[92.0; 280.6]
Specific lab tests[4]	55.5 (109.8)	[8.6; 55.3]	369.3 (353.8)	[161.5; 472.5]
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[5]	1.8 (33.7)	[0.0; 0.0]	2.8 (39.7)	[0.0; 0.0]
Total medical cost (in €) per patient	**8287.8 (8980.4)**	**[2453.6; 11164.7]**	**9978.6 (10593.9)**	**[2792.4;13430.9]**
Other non-cardiovascular hospitalisations	1841.6 (4513.3)	[0.0; 1363.5]	2253.3 (4979.8)	[0.0; 2482.8]
Other cardiovascular hospitalisations	1247.3 (3893.3)	[0.0; 0.0]	1825.9 (5360.2)	[0.0; 0.0]
Cardiovascular/antidiabetic drugs	949.3 (630.0)	[340.4; 1354.0]	436.5 (394.3)	[171.4; 575.8]
Specific hospitalisations	890.7 (2883.6)	[0.0; 0.0]	1062.0 (3143.5)	[0.0; 0.0]
Medical consultations, visits and technical acts	850.2 (1127.7)	[238.0; 1044.6]	953.5 (1168.1)	[325.6; 1150.1]
Nursing acts	667.8 (2236.1)	[0.0; 123.9]	968.4 (2430.9)	[39.4; 514.8]
Non-cardiovascular/non-antidiabetic drugs	524.9 (1442.0)	[76.7; 576.0]	643.9 (1907.1)	[120.8; 651.4]
Products and services	401.3 (1010.9)	[0.0; 261.9]	503.9 (1217.5)	[0.0; 402.7]
Physiotherapy acts	216.0 (615.9)	[0.0; 116.1]	250.7 (646.2)	[0.0; 188.2]
Transport	213.7 (703.8)	[0.0; 193.1]	283.9 (815.5)	[0.0; 275.9]
Other medical healthcare resources	197.8 (560.6)	[0.0; 91.3]	215.8 (592.3)	[0.0; 128.4]
Lab tests	196.0 (296.6)	[46.7; 246.3]	465.0 (384.6)	[234.6; 594.3]
Public hospital external consultations and acts (MCO)	107.4 (219.7)	[0.0; 131.6]	135.3 (248.3)	[0.0; 179.5]
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation	1.8 (33.7)	[0.0; 0.0]	2.8 (39.7)	[0.0; 0.0]
Total allowances (in €) per patient	**1.9 (59.1)**	**[0.0; 0.0]**	**1.6 (42.0)**	**[0.0; 0.0]**
Assistances, pensions and disability allowances	1.8 (59.1)	[0.0; 0.0]	1.6 (42.0)	[0.0; 0.0]
Sick leaves and daily allowances	0.0 (0.7)	[0.0; 0.0]	0.0 (0.3)	[0.0; 0.0]

[1]hospital-discharge summary with a primary diagnosis of atrial fibrillation (AF), clinically relevant bleeding, stroke and SE, and ACS including related transport; [2]DOAC/VKA, amiodarone/drodenarone, beta-blockers alone if no amiodarone/drodenarone and antiarrhythmics; [3]consultations and visits linked to prescription of AF drugs or specific lab tests including related transport; [4]INR, hemostasis, coagulation, creatinine, urea, ALAT and ASAT tests including related transport and related nursing acts plus majoration and travel allowances; [5]stays occurring during 1-year of follow-up and within 7 days after hospital discharge for outcome specific hospitalisation

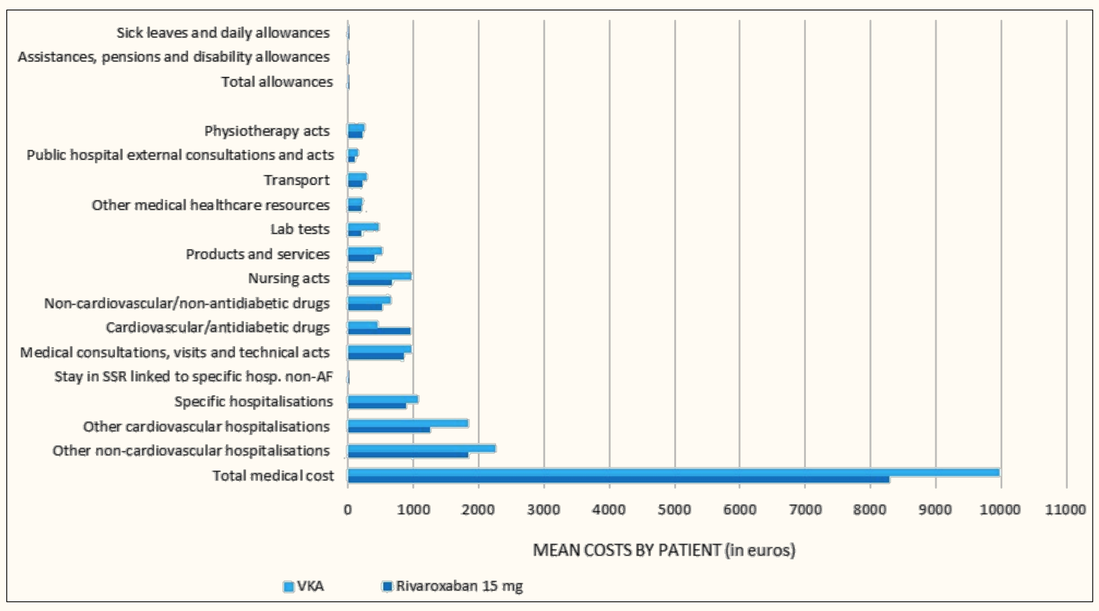

Figure 2. General healthcare resource costs according to the collective perspective during drug exposure period in rivaroxaban 15mg and VKA matched NVAF populations

Conclusions

- **Different rivaroxaban 15mg and VKA prescription patterns, but similar populations after matching.**
- **Rivaroxaban 15mg for NVAF is cost-saving compared to VKA with a better benefit-risk in real-life setting and a 17% lower medical cost for the French collective perspective.**