Pharmacologie médicale

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Effectiveness and safety of the 15 mg dose of rivaroxaban compared with vitamin K antagonists in patients with atrial fibrillation: results from a cohort study in the nationwide French claims and hospitalization database

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Background

- Rivaroxaban (Xarelto®) had better benefit-risk than vitamin K antagonists (VKA) for non-valvular atrial fibrillation (NVAF) in clinical trials.
- Evidence on reduce dose regimens of direct oral anticoagulants (DOAC) from real-life clinical practice is scarce.
- Recent Danish analysis[a] found mixed results with higher mortality for patients treated with reduced dose of some DOAC.
- The low dosage of rivaroxaban (15 mg) is recommended in NVAF for patients with moderate or severe renal failure but not if renal clearance is below 15 ml/min.

Objectives

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

Methods

- **Study design**

  Cohort study in the SNDS (*Système National des Données de Santé*) 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 who did not survive).

- **Data source**

  The database contains individual pseudonymised information 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);

  ✓ Outpatient reimbursed healthcare expenditures with codes, 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, and medical procedures.

Methods

- **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 (SSE)
  - Major bleeding:
    - Haemorrhagic stroke*
    - Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular)
    - Other bleeding (gastro-intestinal (GI), urogenital and other bleeding) with a transfusion during hospitalisation stay, or resulting in death
  - Clinically relevant bleeding (CRB):
    - Haemorrhagic stroke*
    - Other critical organ or site bleeding
    - GI bleeding
    - Urogenital bleeding
    - Other bleeding
  - 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 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).

** Primary, linked or associated diagnosis*
*** Probability to be treated by rivaroxaban 15 mg 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 734,599 new users of rivaroxaban, dabigatran, or VKA in 2013 or 2014, 133,251 were treated with rivaroxaban 15 mg or VKA for NVAF: 24,585 with rivaroxaban 15 mg, and 108,666 with VKA.

  ✓ Patient characteristics showed differences between groups, and were normalized after matching (Table 1).

  ✓ For rivaroxaban 15 mg *versus* VKA, 23,314 patients were matched per arm (94.8% of rivaroxaban 15 mg group).

Table 1. Main patient characteristics in all and matched NVAF populations

	All patients*		Matched patients		Standardized difference (%) R 15 mg *versus* VKA		
	R 15 mg n = 24,529	VKA n = 108,639	R 15 mg 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)

- **One-year cumulative incidence of outcomes**

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

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

  ✓ There were significant lower risk with rivaroxaban 15 mg for major bleeding, death, composite, CRB, at the significant threshold for ACS, and no difference for stroke and SE (Figure 1).

Table 2. Cumulative incidence of outcomes (Kaplan-Meier or cumulative incidence function estimates) during the drug exposure period for matched NVAF populations

	R 15 mg n = 23,314		VKA n = 23,314	
	n event	% [95% CI]	n event	% [95% CI]
Stroke and systemic embolism (SSE)	399	2.3 [2.0; 2.5]	419	2.1 [1.9; 2.3]
Major bleeding (MB)	426	2.4 [2.2; 2.6]	560	2.9 [2.6; 3.1]
Clinically relevant bleeding (CRB)	787	4.4 [4.1; 4.7]	975	4.9 [4.6; 5.3]
Death (all-cause)	1565	9.1 [8.6; 9.5]	2069	10.8 [10.3; 11.2]
Composite criterion (SSE, MB, and death)	2189	12.5 [12.0; 13.0]	2738	14.0 [13.5; 14.5]
Acute coronary syndrome (ACS)	270	1.5 [1.3; 1.7]	347	1.7 [1.6; 1.9]

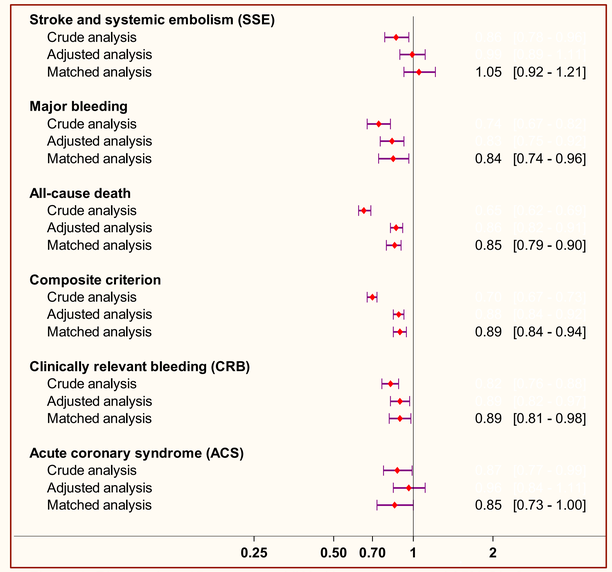

Figure 1. Rivaroxaban 15 mg versus VKA: Hazard ratios and 95% CI of outcomes

Conclusion

- **Different rivaroxaban 15 mg and VKA prescription patterns, but same population characteristics after hdPS matching.**
- **Rivaroxaban 15 mg associated with lower rates of bleeding and mortality compared with VKA, and similar rate of stroke and systemic embolism.**

Disclosure statement

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[a] *Gorst-Rasmussen A, Lip GY, Larsen TB. Rivaroxaban versus* warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in *Danish routine care. Pharmacoepidemiology Drug Saf. 2016 Nov;25(11):1236-1244.*