Benefit-risk profile of dabigatran compared with vitamin-K antagonists in elderly patients with non-valvular atrial fibrillation: results from a cohort study in the French nationwide claims database

Y. Cottin[1], P. Blin[2], J. Bénichou[3,4], C. Dureau-Pournin[2], A. Abouelfath[2], R. Lassalle[2], C. Droz-Perroteau[2], P. Mismetti[5], N. Moore[2,4]

[1]CHU, Dijon, France – [2]Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France – [3]CHU, Rouen, France – [4]INSERM U1219, Bordeaux, France – [5]CHU, Saint-Etienne, France

Purpose

- Direct oral anticoagulants (DOAC), dabigatran, rivaroxaban, 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 in the elderly are still uncertain.
- The purpose of this analysis was to compare in real-life setting in a whole country database, the one-year risk of major events in new elderly users of dabigatran or VKA for NVAF.
- For patients aged 80 years or more, the recommended dose for dabigatran is 110mg twice daily due to the higher risk for bleeding in this population.

Methods

Study design

Cohort study in the SNDS nationwide French claims database including all new users of dabigatran or VKA for NVAF aged ≥ 80 years in 2013, with three-year history and one-year follow-up 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;
- 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 valvular disease history and nor other probable indication (three-year database history).

Outcomes: during anticoagulant exposure period (on treatment)

- Clinical events: hospital admission with main diagnosis of clinically relevant bleeding (CRB), major bleeding, stroke and systemic embolism (SSE) and acute coronary syndrome (ACS);
- Death (all-cause);
- Composite criterion: first event among CRB, SSE, ACS 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 (hdPS)* (± 0.05).
- Cumulative incidence of outcomes using Kaplan-Meier estimate (death, composite) or cumulative incidence function (other outcomes).
- Hazard ratios (HR) [95% confidence interval] of outcomes during first prescribed anticoagulant exposure, using Cox proportional hazard risk (death, composite) or Fine and Gray models (other outcomes).

*Probability to be treated by dabigatran versus VKA using a logistic regression model with 500 variables including gender, age, stroke risk factors, bleeding risk factors

Declaration of interest: This study was funded by an unrestricted grant from Boehringer Ingelheim France. It was designed, conducted, and analysed independently by the Bordeaux PharmacoEpi of the Bordeaux University. It was overseen by independent experts.

Results

Populations

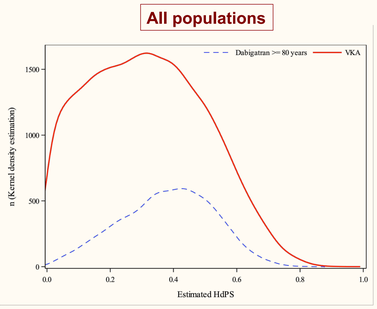
- Of 371,539 new users of dabigatran, rivaroxaban or VKA in 2013 in France:
  - **9,257** patients aged ≥ 80 years were treated with dabigatran,
  - **44,653** with VKA for NVAF.
- For dabigatran *versus* VKA, **8,569 patients were matched per treatment group** (93% of dabigatran group).
- Patient characteristics and hdPS distribution showed differences between treatment groups, and were normalized after matching (**Table 1, Figure 1**). After matching, standardized differences were < 10% for all variables, even ≤ 2% for most variables (**Figure 2**).

Table 1. Main patients characteristics in all NVAF populations

	Dabigatran ≥ 80 years n = 9,257		VKA n = 44,653	
Male, n (%)	3794	(41.0)	22868	(51.2)
Age at index date (in years), mean (± SD)	85.1	(3.9)	77.9	(11.1)
Age at index date (in categories), n (%)				
< 80 years	0	(0.0)	21296	(47.7)
≥ 80 years	9257	(100.0)	23357	(52.3)
Stroke risk factors[1] (score), n (%)				
Congestive heart failure	2151	(23.2)	13721	(30.7)
Hypertension	4451	(48.1)	23822	(53.3)
Age ≥ 75 years	9257	(100.0)	30164	(67.6)
Diabetes mellitus	1692	(18.3)	11707	(26.2)
Stroke or transient ischemic attack (TIA) history	1383	(14.9)	6708	(15.0)
Vascular disease history	1313	(14.2)	9664	(21.6)
Age 65-74 years	0	(0.0)	8712	(19.5)
Women	5463	(59.0)	21785	(48.8)
CHA_2DS_2-VASc score ≥ 2, n (%)	9257	(100.0)	39964	(89.5)
Bleeding risk factors[1] (score), n (%)				
Hypertension	4451	(48.1)	23822	(53.3)
Abnormal renal function	498	(5.4)	7408	(16.6)
Abnormal liver function	95	(1.0)	1373	(3.1)
Stroke history	1163	(12.6)	5828	(13.1)
Bleeding history	214	(2.3)	1411	(3.2)
Age > 65 years	9257	(100.0)	38130	(85.4)
Medication usage predisposing to bleeding	5439	(58.8)	28864	(64.6)
HAS-BLED score > 3, n (%)	852	(9.2)	6687	(15.0)

[1] *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*

All populations



Matched populations

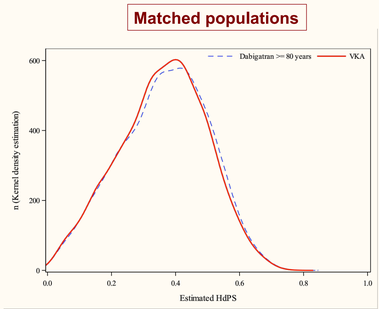
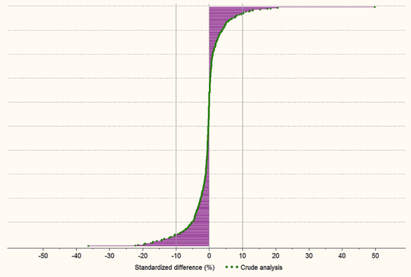


Figure 1. hdPS distribution in all and matched populations: dabigatran ≥ 80 years versus VKA

All populations



Matched populations

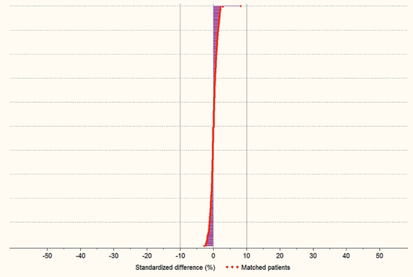


Figure 2. Standardized differences for all and matched populations: dabigatran ≥ 80 years versus VKA

One-year cumulative incidence of outcomes

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

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

	Dabigatran ≥ 80 years n = 8,569		VKA n = 8,569	
	n event	% [95%CI]	n event	% [95%CI]
Clinically relevant bleeding (CRB)	**229**	**3.7 [3.2; 4.2]**	**340**	**5.2 [4.7; 5.8]**
Major bleeding	119	2.0 [1.6; 2.4]	190	3.0 [2.6; 3.4]
Stroke and systemic embolism (SSE)	**114**	**2.1 [1.7; 2.5]**	**170**	**2.6 [2.2; 3.0]**
Acute coronary syndrome (ACS)	**91**	**1.6 [1.3; 1.9]**	**102**	**1.5 [1.2; 1.9]**
Death (all-cause)	**494**	**8.7 [7.9; 9.5]**	**674**	**10.6 [9.8; 11.4]**
Composite criterion (CRB, SSE, ACS, death)	**849**	**14.3 [13.4; 15.3]**	**1130**	**17.1 [16.2; 18.1]**

Benefit-risk of dabigatran ≥ 80 years *versus* VKA

- There were significant lower risk with dabigatran for clinically relevant bleeding, stroke and systemic embolism, death, composite, major bleeding, and no difference for acute coronary syndrome **(Figure 3)**.
- Results were similar for all patients with gender, age, and hdPS adjustment.

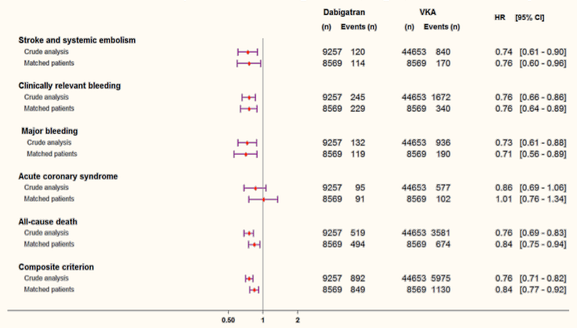


Figure 3. Hazard ratios and 95% CI of outcomes: dabigatran ≥ 80 years versus VKA

Conclusions

- Different dabigatran and VKA prescription patterns in the elderly patients, but same population characteristics after hdPS matching.
- Analysis of this nationwide cohort study of more than 50,000 new anticoagulant users for NVAF aged ≥ 80 years shows a significantly better benefit-risk profile for dabigatran *versus* VKA in elderly patients with 16% fewer major outcomes of clinically relevant bleedings, stroke and systemic embolism or death.

European Society of Cardiology Congress, August 25-29, 2018, Munich, Germany