Benefit-risk profile of dabigatran 150mg *versus* vitamin-K antagonists in patients with non-valvular atrial fibrillation: Results from a matched cohort study in the French nationwide claims database

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Abstract

Background: The RE-LY trial compared dabigatran 150mg or 110mg to vitamin-K antagonists (VKA) for stroke prevention in patients with non-valvular atrial fibrillation (NVAF); dabigatran 150mg was associated with lower rates of stroke and systemic embolism, but similar rates of major bleeding compared to VKA. **Objectives:** To test the reproducibility of these findings in real life in countrywide French claims data. **Methods:** Cohorts of new users of dabigatran 150mg or VKA for NVAF in 2013 were identified and followed-up for one year in the SNDS 66 million persons nationwide French claims database. Dabigatran and VKA patients were 1:1 matched on gender, age, date of the first drug dispensing, and high-dimensional propensity scores (hdPS) including CHA_2DS_2-VASc and HAS-BLED risk factors. Hazard ratios (HR) [95% confidence interval] were estimated during first prescribed anticoagulant exposure, using Cox proportional hazards risk or Fine and Gray models. **Results:** Of 103,101 new anticoagulant users for NVAF in 2013, 27,060 used dabigatran of whom 10,847 dabigatran 150mg (40%); 44,653 used VKA; 8,389 dabigatran 150mg and VKA users were matched per arm. Mean age was 67 years, 67% male, about 65% with CHA_2DS_2-VASc score equal to or above 2; fewer than 5% had HAS-BLED scores above 3. One-year cumulative incidences of arterial thrombotic events with dabigatran 150mg or VKA were respectively 1.3% and 1.7% (HR 0.76 [0.56-1.04]), 0.9% and 1.6% for acute coronary syndromes (0.58 [0.42-0.81]). The event rates for clinically relevant bleedings were respectively 1.4% and 3.4% (HR: 0.42 [95%CI: 0.33-0.54]), for death 1.4% and 3.1% (0.46 [0.35-0.59]), and 4.7% and 8.9% for the composite criterion of all events above (0.52 [0.45-0.60]). Results were similar with hdPS adjusted analyses of all patients. **Conclusions:** In this nationwide real life study, the results of the RE-LY trial were partially reproduced, in that dabigatran was associated with slightly lower arterial thrombotic event rates, but significantly fewer clinically relevant bleeding or death. Overall there were 48% fewer major outcomes with dabigatran 150mg than with VKA, confirming the overall clinical benefit found in the RE-LY trial.

Disclosure statement

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.

Background

- The RE-LY trial compared dabigatran 150mg or 110mg to vitamin-K antagonists (VKA) for stroke prevention in patients with non-valvular atrial fibrillation (NVAF).
- Dabigatran 150mg was associated with lower rates of stroke and systemic embolism, but similar rates of major bleeding compared to VKA.

Objectives

- To test the reproducibility of these findings in real life in countrywide French claims data.

Methods

Study design

Cohort study in the SDNS nationwide French claims database including all new users of dabigatran 150mg or VKA for NVAF 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);
- 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, 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 150mg versus VKA using a logistic regression model with 500 variables including gender, age, stroke risk factors, bleeding risk factors.*

Results

Populations

- Of 371,539 new users of dabigatran, rivaroxaban or VKA in 2013 in France, **10,847** and **44,653** were treated for NVAF with dabigatran 150mg and VKA, respectively.
- For dabigatran 150mg *versus* VKA**, 8,389 patients were matched per treatment group** (77% of dabigatran 150mg 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 < 5% for all variables even ≤ 2% for most variables (**Figure 2**).

Table 1. Main patients characteristics in all NVAF populations

	Dabigatran 150mg n = 10,847		VKA n = 44,653	
Male, n (%)	7409	(68.3)	22868	(51.2)
Mean age at the index date, years (± SD)	65.3	(10.2)	77.9	(11.1)
Stroke risk factors[1] (score), n (%)				
Congestive heart failure	1207	(11.1)	13721	(30.7)
Hypertension	3361	(31.0)	23822	(53.3)
Age ≥ 75 years	1919	(17.7)	30164	(67.6)
Diabetes mellitus	2160	(19.9)	11707	(26.2)
Stroke or transient ischemic attack (TIA) history	913	(8.4)	6708	(15.0)
Vascular disease history	962	(8.9)	9664	(21.6)
Age 65-74 years	4406	(40.6)	8712	(19.5)
Women	3438	(31.7)	21785	(48.8)
CHA_2DS_2-VASc score ≥ 2 , n (%)	6190	(57.1)	39964	(89.5)
Bleeding risk factors[1] (score), n (%)				
Hypertension	3361	(31.0)	23822	(53.3)
Abnormal renal function	142	(1.3)	7408	(16.6)
Abnormal liver function	132	(1.2)	1373	(3.1)
Stroke history	769	(7.1)	5828	(13.1)
Bleeding history	125	(1.2)	1411	(3.2)
Age > 65 years	5844	(53.9)	38130	(85.4)
Medication usage predisposing to bleeding	5248	(48.4)	28864	(64.6)
HAS BLED score > 3, n (%)	289	(2.7)	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*

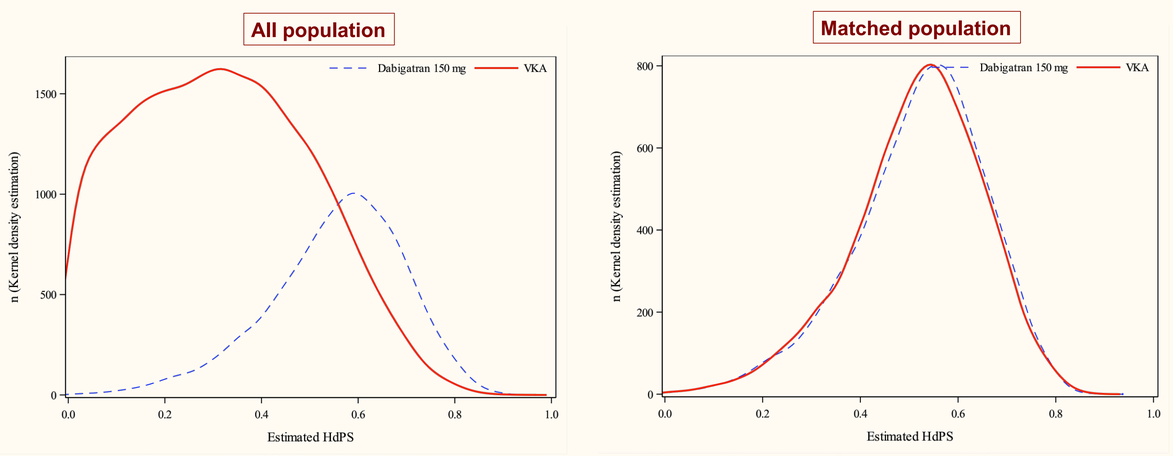

Figure 1. hdPS distribution in all and matched populations: dabigatran 150mg versus VKA

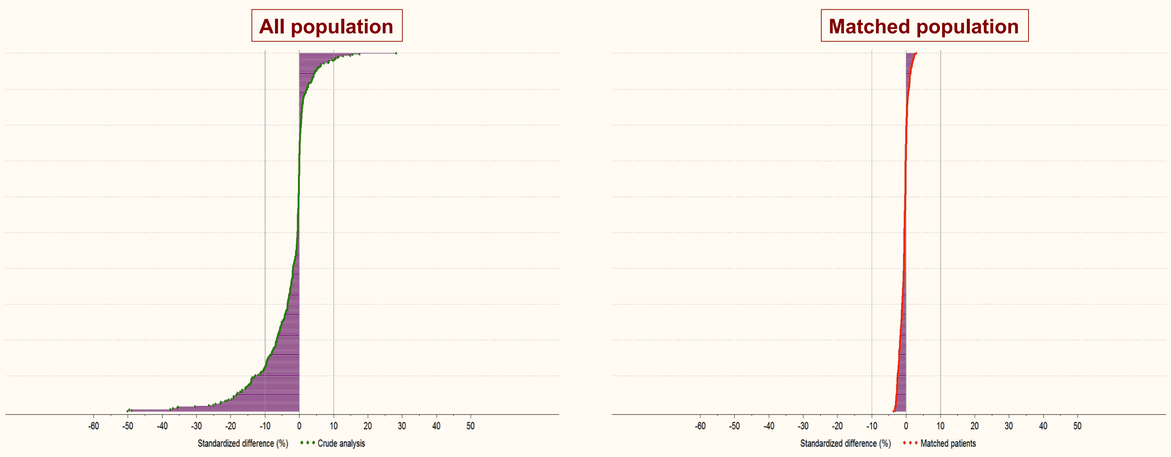

Figure 2. Standardized differences for all and matched populations: dabigatran 150mg versus VKA

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 150mg n = 8,389		VKA n = 8,389	
	n event	% [95%CI]	n event	% [95%CI]
Clinically relevant bleeding (CRB)	**87**	**1.4 [1.1; 1.8]**	**203**	**3.4 [2.9; 3.9]**
Major bleeding	29	0.5 [0.3; 0.7]	95	1.6 [1.3; 1.9]
Stroke and systemic embolism (SSE)	**74**	**1.3 [1.0; 1.6]**	**94**	**1.7 [1.3; 2.0]**
Acute coronary syndrome (ACS)	**56**	**0.9 [0.7; 1.2]**	**95**	**1.6 [1.3; 2.0]**
Death (all-cause)	**84**	**1.4 [1.1; 1.7]**	**179**	**3.1 [2.7; 3.7]**
Composite criterion (CRB, SSE, ACS, death)	**285**	**4.7 [4.2; 5.3]**	**527**	**8.9 [8.1; 9.7]**

Benefit-risk of dabigatran 150mg *versus* VKA

- There was a significant lower risk with dabigatran 150mg for clinically relevant bleeding, acute coronary syndrome, death, composite, major bleeding, and no significant difference for stroke and systemic embolism **(Figure 3)**.
- Results were similar for all patients with gender, age, and hdPS adjustment.

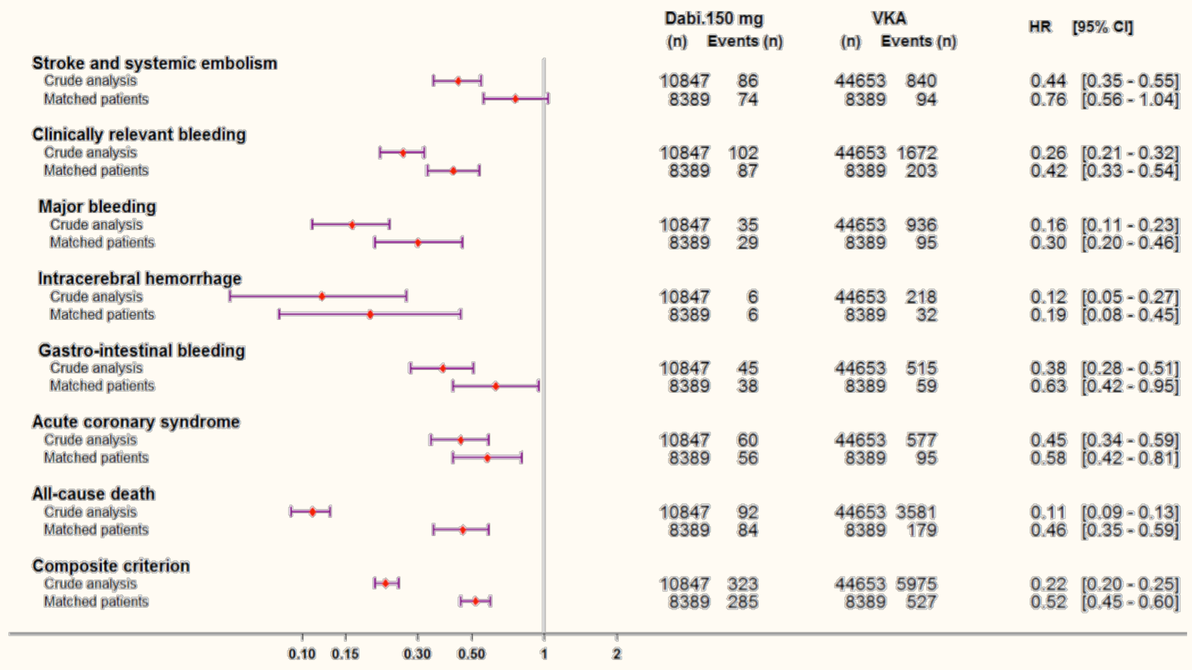

Figure 3. Hazard ratios and 95% CI of outcomes: dabigatran 150mg versus VKA

Conclusions

- Different dabigatran 150mg and VKA prescription patterns, but same population characteristics after hdPS matching.
- Dabigatran 150mg was associated with slightly lower stroke and systemic embolism rates, but significantly fewer bleeds (clinically relevant, major, intracerebral, and gastro-intestinal bleedings), death, and acute coronary syndrome.
- Overall there were 48% fewer major outcomes with dabigatran 150mg than with VKA, confirming the overall clinical benefit found in the RE-LY trial.

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