Benefit-risk profile of dabigatran 110mg *versus* vitamin-K antagonists in patients with non-valvular atrial fibrillation: a cohort study in the French nationwide claims database

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Abstract

Background: The RE-LY trial compared dabigatran 150 mg or 110 mg to vitamin-K antagonists (VKA) for stroke prevention in patients with non-valvular atrial fibrillation (NVAF); dabigatran 110 mg was associated with similar rates of stroke and systemic embolism, but lower 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 110 mg 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 110 mg 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, 15,532 of whom used dabigatran 110 mg (57%), 44,653 with VKA; 14,442 were matched per arm. Mean age was 79 years, 49% male, 91% with CHA_2DS_2-VASc score equal to or below 2 and 8% with HAS-BLED score above 3. One-year cumulative incidence of clinically relevant bleedings was respectively 2.9% and 4.7% for matched dabigatran 110 mg and VKA patients (HR: 0.62 [95%CI: 0.54-0.72]), 1.6% and 2.3% for arterial thrombotic events (0.69 [0.56-0.84]), 1.5% and 1.6% for acute coronary syndromes (0.93 [0.74-1.15]), 6.2% and 7.6% for death (0.84 [0.76-0.94]), 11.0% and 14.3% for the composite criterion of all events above (0.77 [0.72-0.84]). Results were similar for all patients with hdPS adjusted analyses. **Conclusions:** In this nationwide real life study, dabigatran 110 mg was associated with lower arterial thrombotic event rates, and significantly fewer clinically relevant bleeding or death. Overall there were 23% fewer major outcomes with dabigatran 110 mg than with VKA, improving the clinical benefits 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 110mg was associated with similar rates of stroke and systemic embolism, but lower 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 110mg 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 110mg 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, **15,532** and **44,653** were treated for NVAF with dabigatran 110mg and VKA, respectively.
- For dabigatran 110mg *versus* VKA, **14,442 patients were matched per treatment group** (93% of dabigatran 110mg 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 110mg n = 15,532		VKA n = 44,653	
Male, n (%)	7539	(48.5)	22868	(51.2)
Mean age at the index date, years (± SD)	78.5	(9.5)	77.9	(11.1)
Stroke risk factors[1] (score), n (%)				
Congestive heart failure	3048	(19.6)	13721	(30.7)
Hypertension	7030	(45.3)	23822	(53.3)
Age ≥ 75 years	11468	(73.8)	30164	(67.6)
Diabetes mellitus	3179	(20.5)	11707	(26.2)
Stroke or transient ischemic attack (TIA) history	2059	(13.3)	6708	(15.0)
Vascular disease history	2243	(14.4)	9664	(21.6)
Age 65-74 years	2732	(17.6)	8712	(19.5)
Women	7993	(51.5)	21785	(48.8)
CHA_2DS_2-VASc score ≥ 2, n (%)	14130	(91.0)	39964	(89.5)
Bleeding risk factors[1] (score), n (%)				
Hypertension	7030	(45.3)	23822	(53.3)
Abnormal renal function	711	(4.6)	7408	(16.6)
Abnormal liver function	250	(1.6)	1373	(3.1)
Stroke history	1761	(13.1)	5828	(13.1)
Bleeding history	1411	(11.3)	1411	(3.2)
Age > 65 years	13993	(90.1)	38130	(85.4)
Medication usage predisposing to bleeding	8978	(57.8)	28864	(64.6)
HAS BLED score > 3, n (%)	1234	(7.9)	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

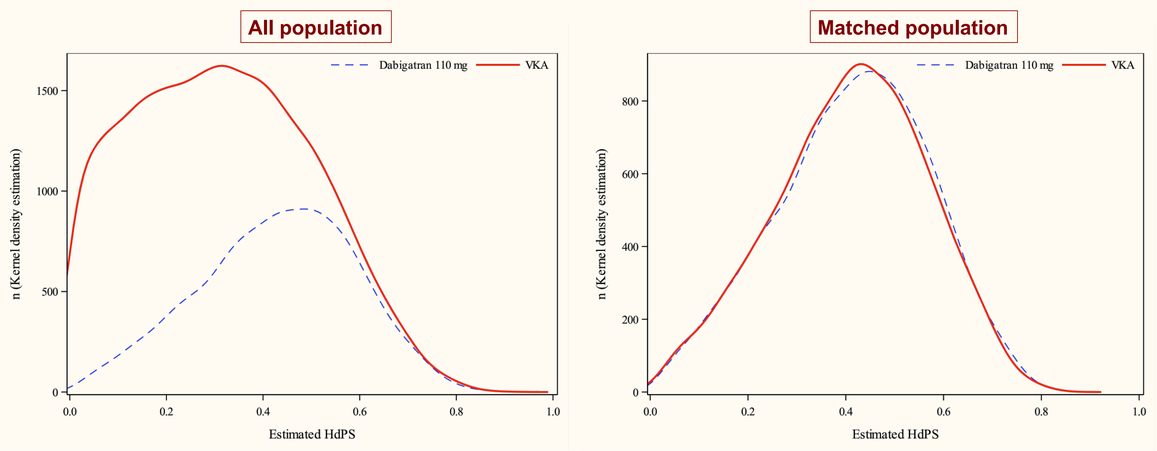

Figure 1. hdPS distribution in all and matched populations: dabigatran 110mg versus VKA

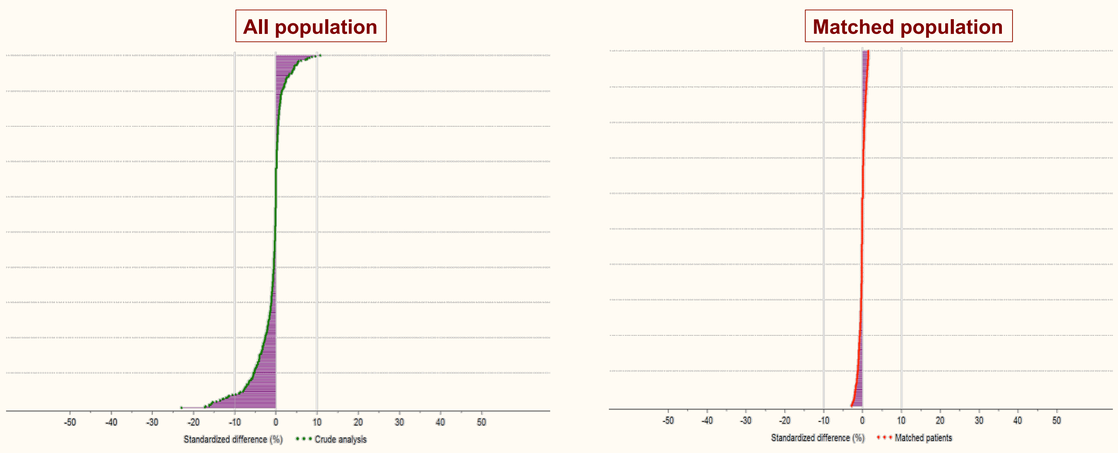

Figure 2. Standardized differences for all and matched populations: dabigatran 110mg versus VKA

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 110mg n = 14,442		VKA n = 14,442	
	n event	% [95%CI]	n event	% [95%CI]
Clinically relevant bleeding (CRB)	**298**	**2.9 [2.5; 3.2]**	**517**	**4.7 [4.3; 5.1]**
Major bleeding	151	1.5 [1.2; 1.7]	264	2.4 [2.2; 2.8]
Stroke and systemic embolism (SSE)	**155**	**1.6 [1.4; 1.9]**	**245**	**2.3 [2.0; 2.6]**
Acute coronary syndrome (ACS)	**149**	**1.5 [1.2; 1.7]**	**176**	**1.6 [1.4; 1.9]**
Death (all-cause)	**606**	**6.2 [5.7; 6.7]**	**792**	**7.6 [7.1; 8.2]**
Composite criterion (CRB, SSE, ACS, death)	**1109**	**11.0 [10.3; 11.6]**	**1544**	**14.3 [13.6; 15.0]**

Benefit-risk of dabigatran 110mg *versus* VKA

- There was a significant lower risk with dabigatran 110mg for clinically relevant bleeding, stroke and systemic embolism, death, composite, major bleeding, and no significant difference for acute coronary syndrome **(Figure 3)**.
- Results were similar for all patients with gender, age, and hdPS adjustment.

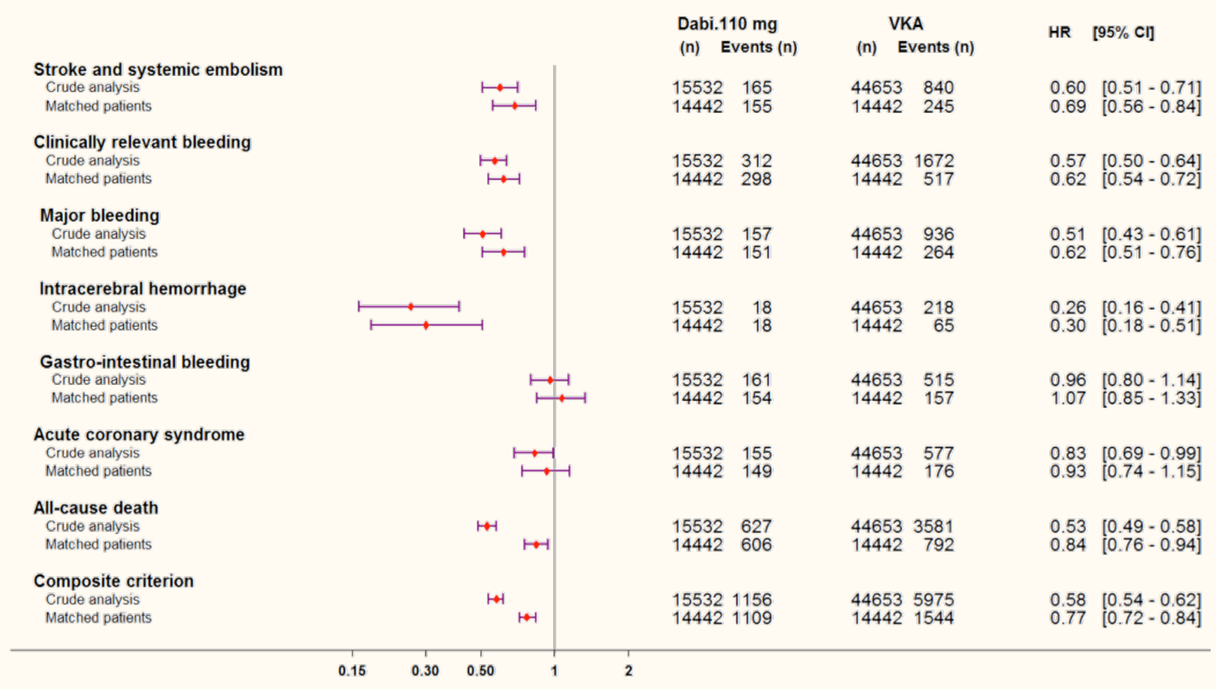

Figure 3. Hazard ratios and 95% CI of outcomes: dabigatran 110mg versus VKA

Conclusions

- Different dabigatran 110mg and VKA prescription patterns, but same population characteristics after hdPS matching.
- In this nationwide real life study, dabigatran 110mg was associated with lower stroke and systemic embolism event rates, and significantly fewer bleeds (clinically relevant, major, and intracerebral bleedings), and death.
- Overall there were 23% fewer major outcomes with dabigatran 110mg than with VKA, improving the clinical benefits found in the RE-LY trial.

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