



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

P. Blin¹, C. Dureau-Pournin¹, A. Abouelfath¹, R. Lassalle¹, J. Bénichou^{2,3},
Y. Cottin⁴, P. Mismetti⁵, C. Droz-Perroteau¹, N. Moore^{1,3}

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



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Disclosure statement

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 - Supervised by an independent scientific committee
 - Designed, conducted and analysed independently by the Bordeaux PharmacoeEpi platform of Bordeaux University

Background

- Better benefit-risk of dabigatran than VKA for stroke prevention in non-valvular atrial fibrillation (NVAf) from premarketing trials
- Only 16% of the randomized patients were ≥ 80 years while they represent a large part of the NVAf treated population
- Real-life benefit-risk in the elderly still uncertain
- In Europe, dabigatran 110mg twice daily is the recommended dose for patients ≥ 80 years

Objectives

- To compare 1-year risk of major benefit-risk outcomes between new users of dabigatran or VKA for NVAF in patients ≥ 80 years
- During drug exposure, i.e. “on treatment”

Method (1)

- **Cohort study**

- All new users of dabigatran or VKA for NVAF* in 2013
- ≥ 80 years old
- Identified and followed for one year in the SNDS** database

* **NVAF**: Patients with long-term disease registration or hospitalization diagnosis, or procedure for atrial fibrillation without valvular disease history, and no other probable indication (3-year history)

** **SNDS** (Système National des Données de Santé): the 66.6 Million person French nationwide claims database

Method (2)

- **Outcomes**

- Hospitalisation with primary diagnosis for
 - Clinically Relevant Bleeding (CRB)
 - Major bleeding
 - Stroke and Systemic Embolism (SSE)
 - Acute Coronary Syndrome (ACS)
- Death (all-cause)
- Composite criterion: CRB, SSE, ACS, or death (1st event)

Statistical analysis (1)

- **Dabigatran vs VKA high dimensional Propensity Score (hdPS*)**
 - including individual stroke and bleeding risk factors (from CHA₂DS₂-VASc & HAS-BLED scores), and 500 variables from 4 dimensions (Long Term Disease registration, hospitalisation diagnoses, drugs, other healthcare reimbursed)
 - **Dabigatran and VKA 1:1 matching** on gender, age, date of first anticoagulant dispensing, and hdPS (caliper ± 0.05)
 - **Standardized difference**** < 10% indicates a negligible difference between the 2 groups

* Open source from <http://drugapi.org>,

** Austin, Stat Med. 2009

Statistical analysis (2)

- **Cox proportional hazard risk model** for death & composite criterion,
- **Fine and Gray model** for clinical outcomes (death as competing risk)
 - **Crude analysis** with all patients
 - **1:1 matched analysis**

Populations

New users for NVAF	Dabigatran		VKA		ALL	
	n	(%)	n	(%)	n	(%)
In 2013 in France	27 060		44 653		71 713	

Populations

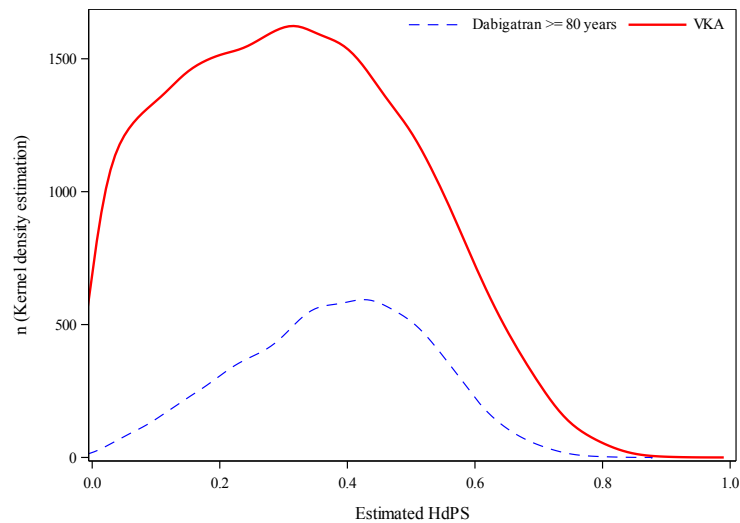
New users for NVAF	Dabigatran n (%)	VKA n (%)	ALL n (%)
In 2013 in France	27 060	44 653	71 713
≥ 80 years old	9 257 (34.2)	23 357 (52.3)	32 614 (45.5)

Populations

New users for NVAF	Dabigatran n (%)	VKA n (%)	ALL n (%)
In 2013 in France	27 060	44 653	71 713
≥ 80 years old	9 257	23 357	32 614
Matched	8 569 (92.6)	8 569 (36.7)	17 138 (52.5)

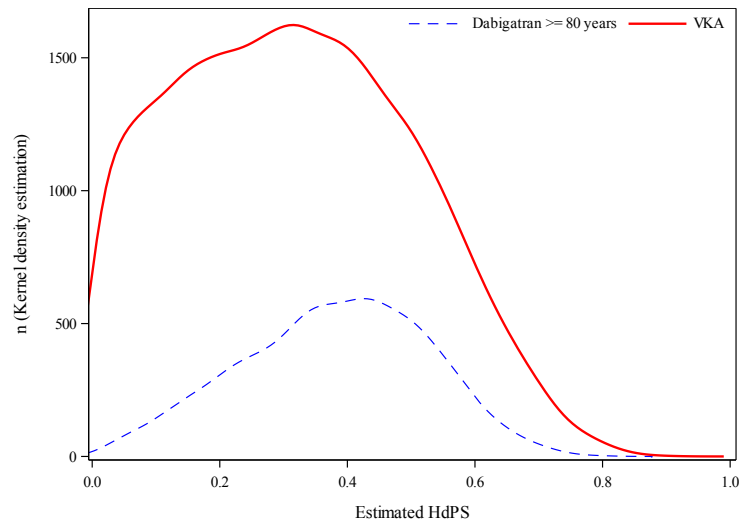
hdPS distributions

All patients

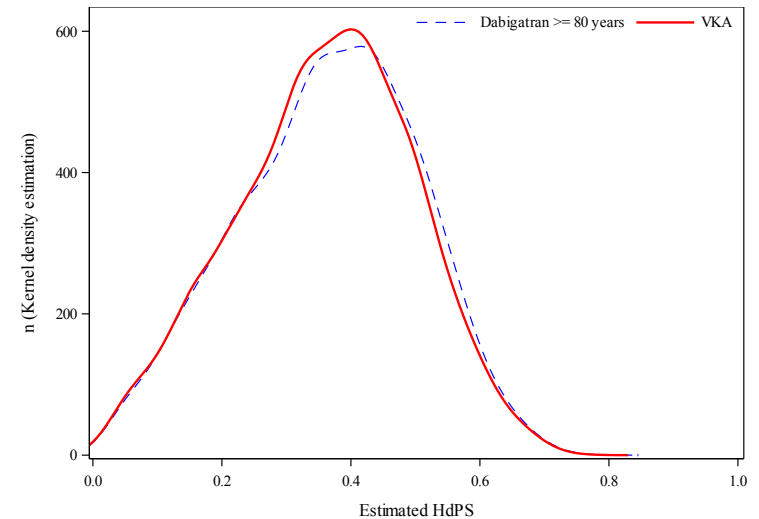


hdPS distributions

All patients



Matched patients



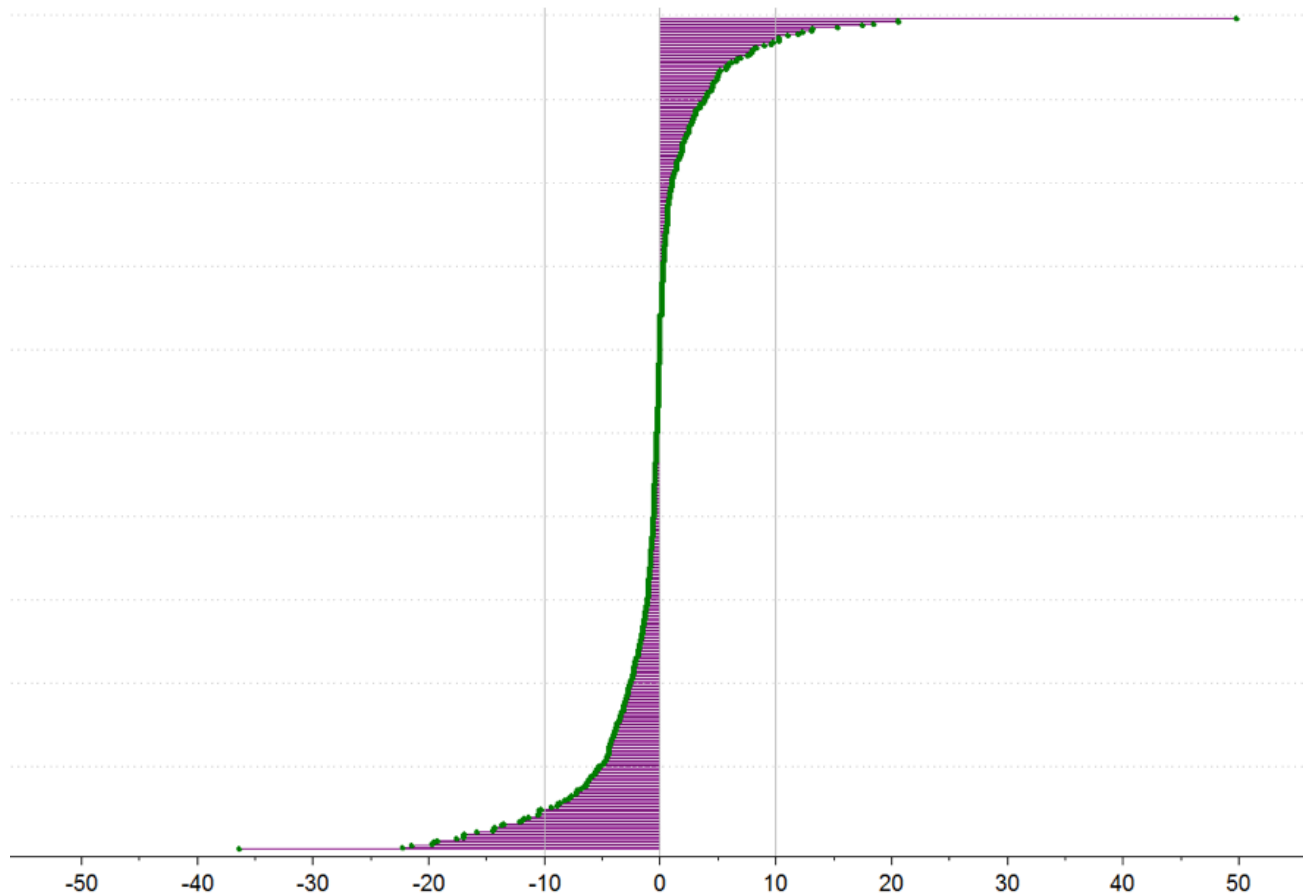
Matched patient characteristics

	Matched patients		Standardized difference (%)
	Dabigatran n = 8,569	VKA n = 8,569	
Male, %	40.5	40.5	0.0
Age, mean (± SD)	85.1 (3.9)	85.0 (4.0)	1.4
Risk factors, %			
- Hypertension	49.3	49.7	-1.0
- Diabetes mellitus	18.6	19.3	-1.8
- Congestive heart failure	24.4	25.1	-1.7
- Vascular disease history	14.8	12.2	1.8
- Stroke or TIA history	15.5	14.9	1.7
- Abnormal renal function	5.8	6.4	-2.8
- Abnormal liver function	1.1	0.9	0.9
- CHA ₂ DS ₂ -VASc score ≥ 2	100.0	100.0	
- HAS-BLED score ≥ 3	39.7	38.3	

Standardized differences

for 500 variables independent from hdPS selection

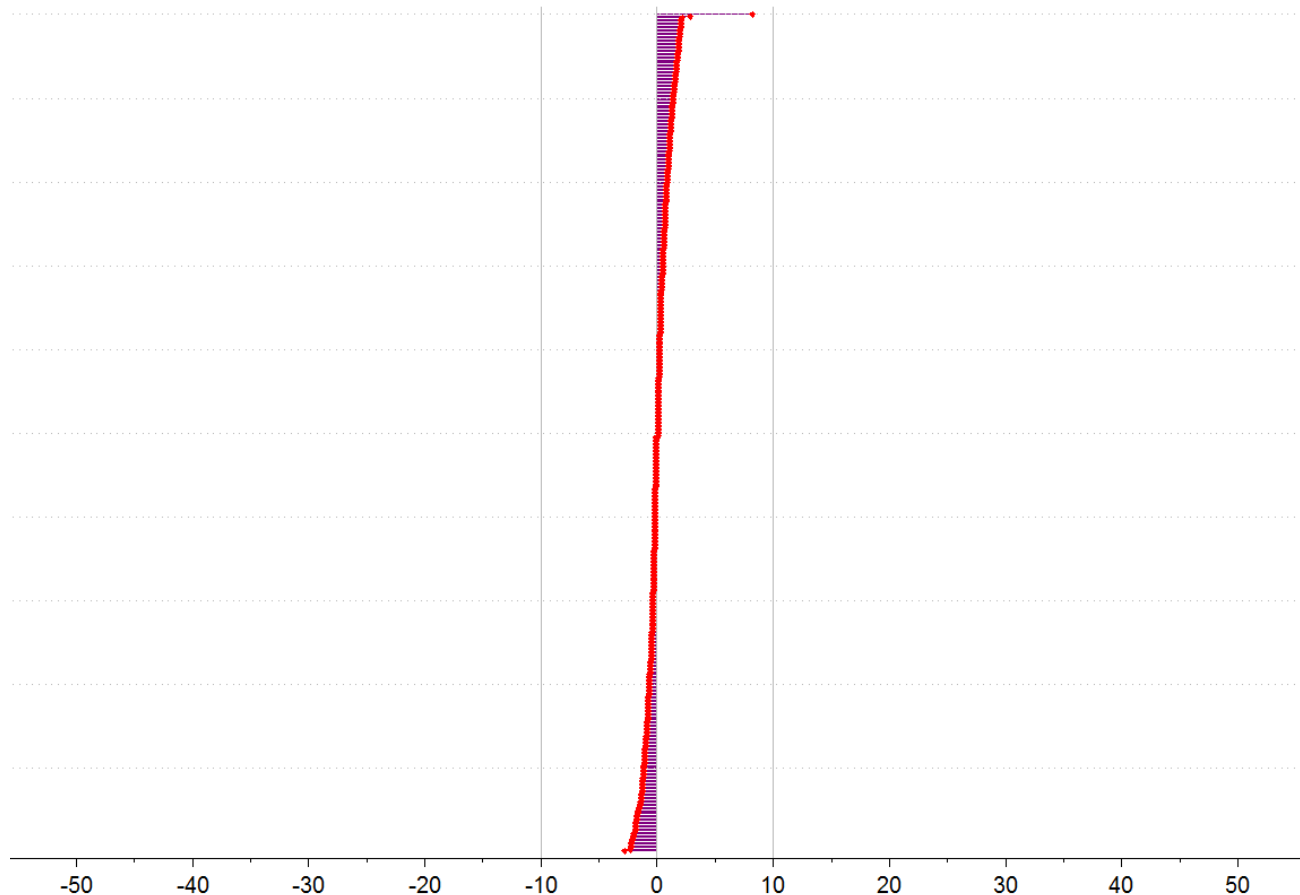
All patients



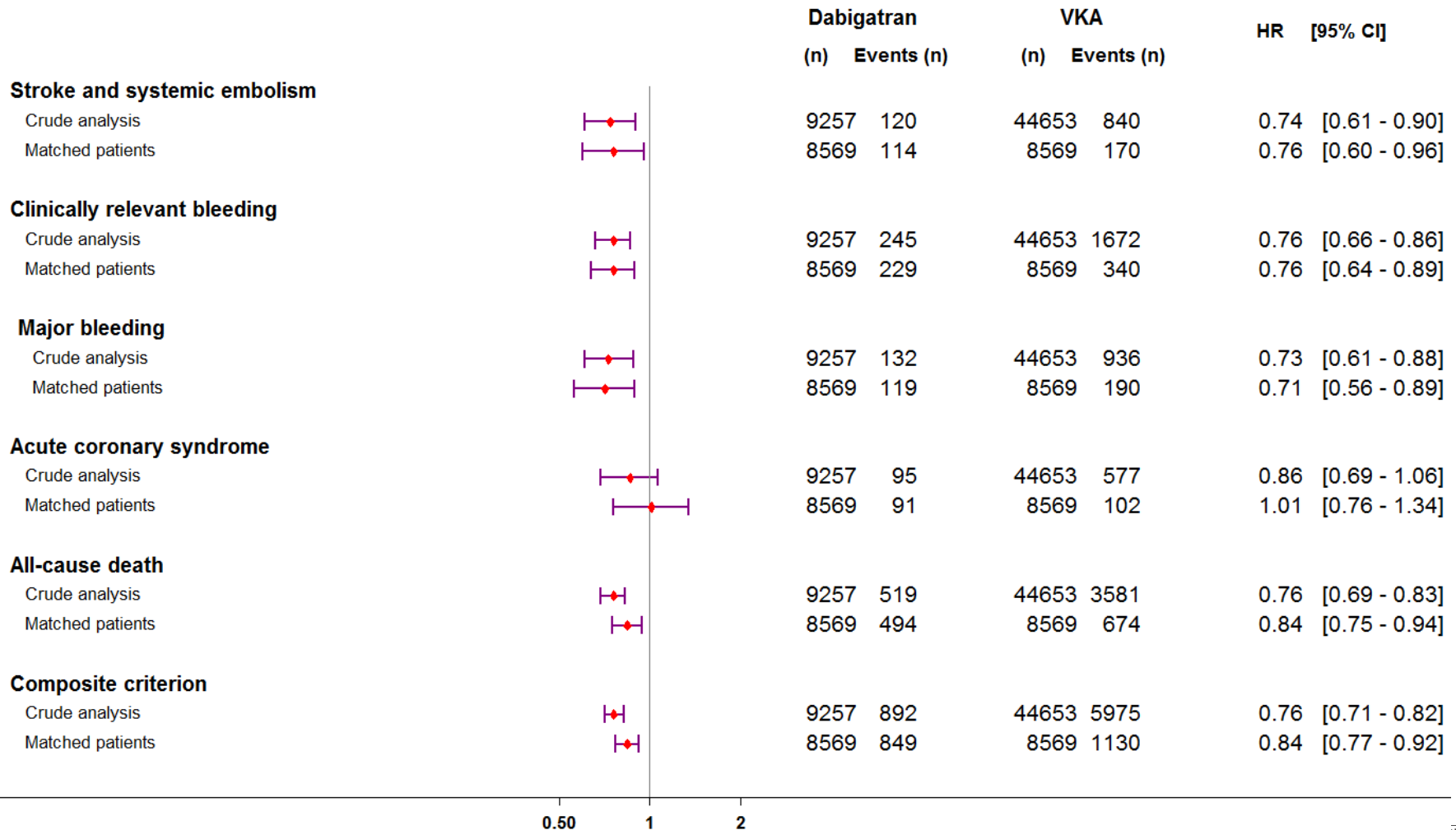
Standardized differences

for 500 variables independent from hdPS selection

Matched patients



Dabigatran vs VKA benefit-risk



Discussion

- Claims database with little clinical information to validate diagnoses, but high PPV published for ACS* and stroke** in SNDS database, and consistency between clinical events and death
- Not a randomized trial, and residual confounding cannot be excluded but probably very limited with standardized differences < 3% for 500 variables at inclusion, independently selected from hdPS algorithm; and collectively a good proxy for information not available in the database

* Bezin, Fund & Clin Pharmacol 2015, ** Giroud, Eur Neurol 2015

Conclusion

This nationwide cohort study shows that

1. Almost half of the NVAf new patients treated by an anticoagulant were ≥ 80 years
2. For these patients, dabigatran had 16% fewer major outcomes than VKA in real-life setting (i.e. CRB, SSE, ACS, or death)



Thank you

patrick.blin@u-bordeaux.fr



Bordeaux PharmacoeEpi - <http://www.pharmacoeEpi.eu>
Plateforme de recherche en Pharmacoe-épidémiologie

CIC Bordeaux CIC1401

INSERM - Université de BORDEAUX - CHU de Bordeaux - Adera

Bâtiment Le Tondu - case 41 - 146 rue Léo Saignat - 33076 Bordeaux Cedex

Acc. +33 (0)5 57 57 46 75 – Fax +33 (0)5 57 57 47 40