Effectiveness and safety of standard and reduced doses of dabigatran versus rivaroxaban in non-valvular atrial fibrillation: a cohort study in the SNDS French nationwide claims database

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Disclosure statement

- Study funded by an unrestricted grant from Boehringer Ingelheim France
- Similar study funded by an unrestricted grant from Bayer Pharma AG
- Requested by the HAS, the French HTA agency
- Registered in EMA EUPAS n°13017
  - Supervised by an independent scientific committee
  - Designed, conducted and analysed independently by the Bordeaux PharmacoEpi platform of Bordeaux University

Background

- Better benefit-risk of dabigatran and rivaroxaban than VKA for stroke prevention in non-valvular atrial fibrillation (NVAF), but no randomized trial compared dabigatran versus rivaroxaban
- **Standard doses:** Dabigatran 150mg / rivaroxaban 20mg
- **Reduced doses** (Europe)
  - **Dabigatran 110mg:** recommended for older patients (≥ 80 years), or 75-80 years when thromboembolism risk low and bleeding risk high, patients with moderate renal impairment or high risk of bleeding
  - **Rivaroxaban 15mg:** recommended for patients with moderate renal impairment and with caution in patients with severe renal impairment

Objectives

- To compare **2-year risk** of major benefit-risk outcomes
- Between **new users** of dabigatran and rivaroxaban for NVAF
  - Standard doses
  - Reduced doses
- During drug exposure, i.e. "**on treatment**"

Method (1)

- **Cohort study**
  - All new users of dabigatran or rivaroxaban in 2013 (3-year history, as well as no other DOAC or VKA)
  - for NVAF*
  - Identified and followed for two years in the SNDS** database

* **NVAF:** Patients with chronic disease registration for full reimbursement 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)

- **high-dimensional Propensity Scores (hdPS*)**
  - **Dabigatran versus rivaroxaban (standard or reduced doses)**
  - Including individual stroke and bleeding risk factors (from CHA_2DS_2-VASc & HAS-BLED scores), COPD, cardioversion or catheter-based ablation, first prescriber speciality, hospital and non-hospital costs during the year and the month before index date, and 500 variables from 4 dimensions (chronic disease registration, hospitalisation diagnoses, drugs, other healthcare reimbursed) using Bross Algorithm
- **1:1 matched patient** on gender, age, date of first anticoagulant dispensing, and hdPS for the main analysis
  - **Standardized difference**** < 10% indicates a negligible difference between the 2 groups

* Open source from http://drugepi.org,

** Austin, Stat Med. 2009

Statistical analysis (2)

- **Dabigatran versus rivaroxaban according to the dose**
  - **Crude analysis** with all patients
  - **hsPS adjusted analysis** with all patients
  - Analysis of **matched patients** (Main analysis)

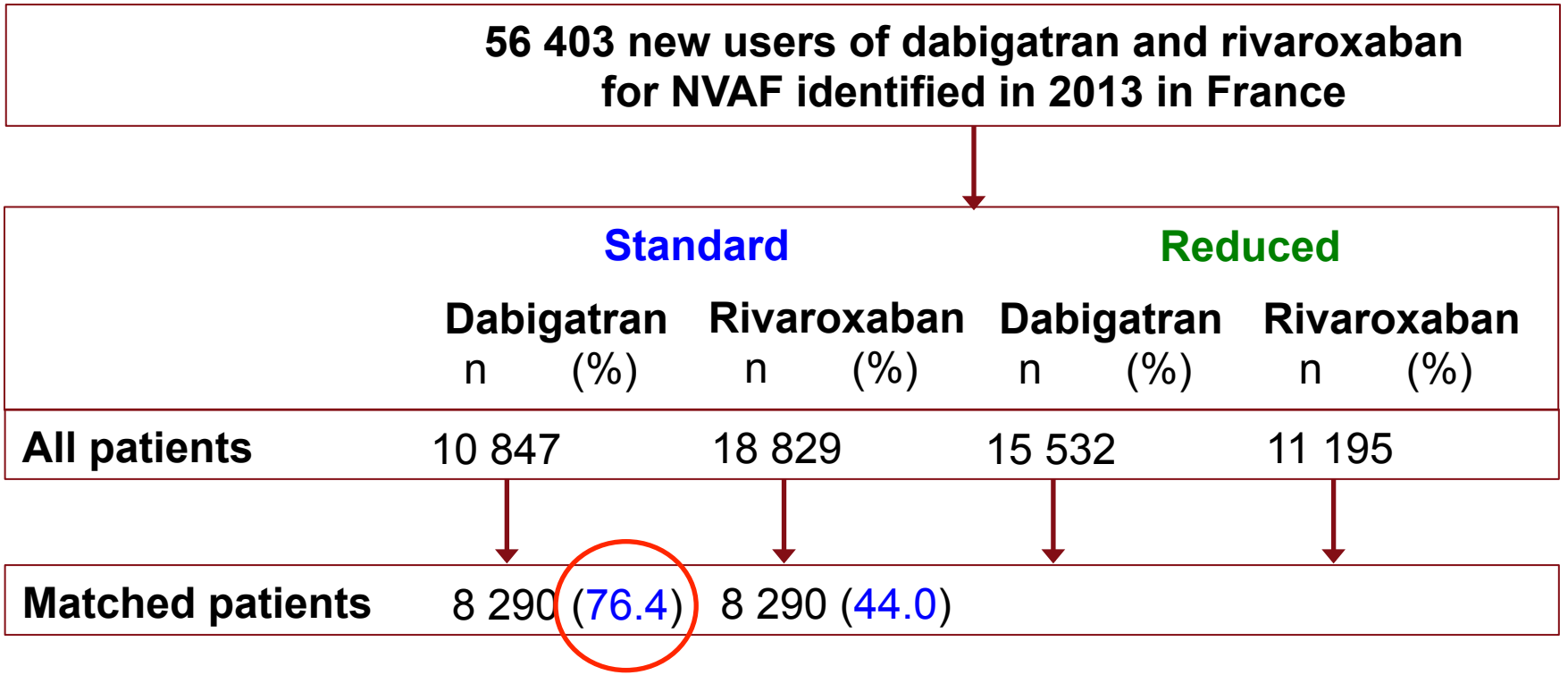
- **Cox proportional hazard risk model** for death & composite criterion
- **Fine and Gray model** for clinical outcomes (death as competing risk)

Populations

56 403 new users of dabigatran and rivaroxaban for NVAF identified in 2013 in France

	Standard (52.6%)				Reduced (47.4%)			
	Dabigatran		Rivaroxaban		Dabigatran		Rivaroxaban	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients	10 847		18 829		15 532		11 195	

Populations



Populations

56 403 new users of dabigatran and rivaroxaban for NVAF identified in 2013 in France

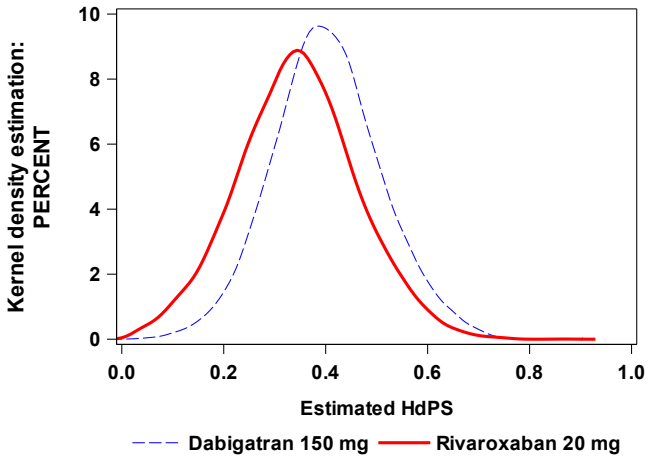
	Standard				Reduced			
	Dabigatran		Rivaroxaban		Dabigatran		Rivaroxaban	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients	10 847		18 829		15 532		11 195	
Matched patients	8 290	(76.4)	8 290	(44.0)	7 639	(49.2)	7 639	(68.2)

hdPS distributions

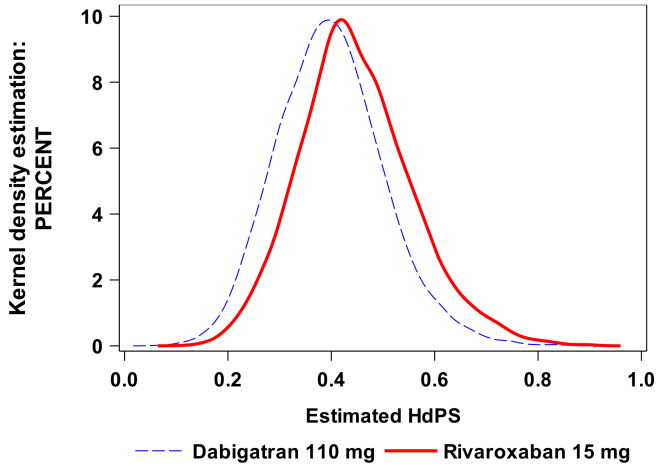
Dabigatran versus rivaroxaban

All patients

Standard doses



Reduced doses



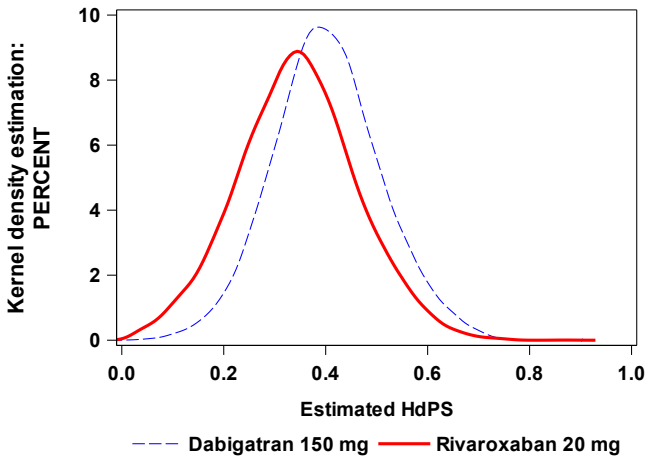
hdPS distributions

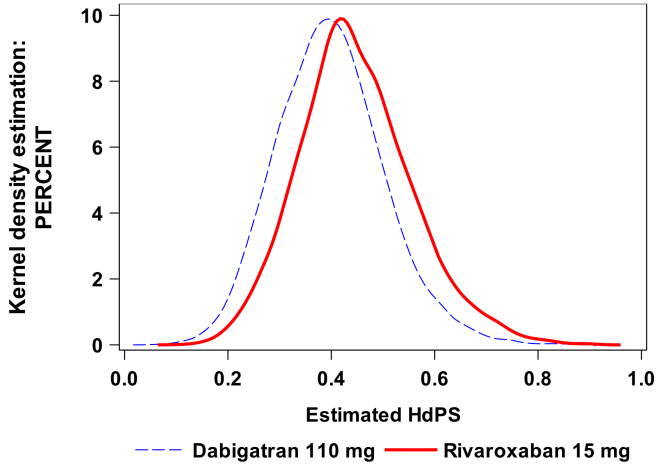
Dabigatran versus rivaroxaban

Standard doses

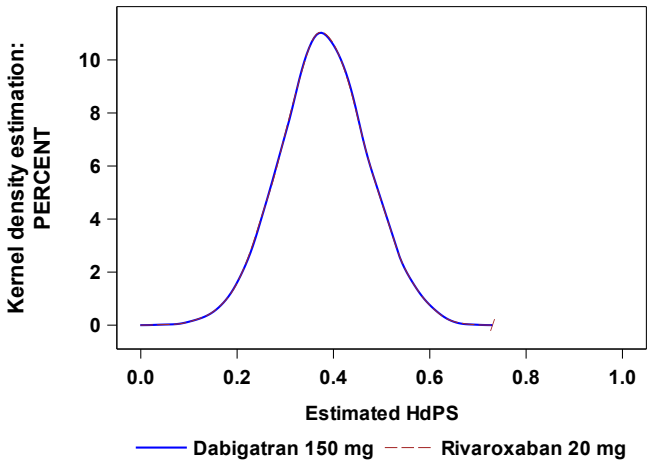
Reduced doses

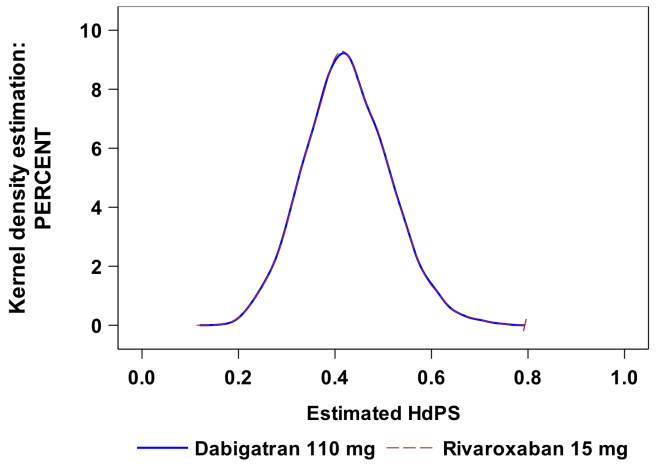
All patients





Matched patients





Patient characteristics

Standard dose	All patients		Standardized difference (%)
	Dabigatran n = 10,847	Rivaroxaban n = 18,829	Crude
Male, %	68.3	62.7	-11.9
Age, mean (± SD)	65.3 (10.2)	69.0 (11.1)	-34.7
Risk factors, %			
- Hypertension	31.0	33.0	-4.3
- Diabetes mellitus	19.9	19.8	0.4
- Vascular disease history	11.1	11.0	0.5
- Congestive heart failure	8.9	11.1	-7.4
- Stroke or TIA history	8.4	9.2	-2.6
- Abnormal renal function	1.3	2.1	-3.7
- Abnormal liver function	1.2	1.2	0.1
- CHA_2DS_2-VASc score ≥ 2	57.1	67.4	-21.5
- HAS-BLED score ≥ 3	15.7	20.0	-11.4

Patient characteristics

Standard dose	All patients		Matched patients		Standardized difference (%)	
	Dabigatran n = 10,847	Rivaroxaban n = 18,829	Dabigatran n = 8,290	Rivaroxaban n = 8,290	Crude	Matched
Male, %	68.3	62.7	69.7	69.7	-11.9	**0.0**
Age, mean (± SD)	65.3 (10.2)	69.0 (11.1)	66.9 (8.8)	66.9 (8.8)	-34.7	**0.0**
Risk factors, %						
- Hypertension	31.0	33.0	29.0	29.4	-4.3	**-1.0**
- Diabetes mellitus	19.9	19.8	19.3	19.6	0.4	**-0.9**
- Vascular disease history	11.1	11.0	9.8	9.8	0.5	**0.2**
- Congestive heart failure	8.9	11.1	8.9	8.9	-7.4	**0.0**
- Stroke or TIA history	8.4	9.2	7.9	7.8	-2.6	**0.4**
- Abnormal renal function	1.3	2.1	1.2	1.1	-3.7	**0.3**
- Abnormal liver function	1.2	1.2	0.9	1.1	0.1	**-0.6**
- CHA_2DS_2-VASc score ≥ 2	57.1	67.4	59.3	58.5	-21.5	**-1.6**
- HAS-BLED score ≥ 3	15.7	20.0	15.4	15.8	-11.4	**1.0**

Patient characteristics

Reduced dose	All patients		Matched patients		Standardized difference (%)	
	Dabigatran n = 15,532	Rivaroxaban n = 11,195	Dabigatran n = 7,639	Rivaroxaban n = 7,639	Crude	Matched
Male, %	48.5	46.6	46.4	46.4	-4.0	**0.0**
Age, mean (± SD)	78.5 (9.5)	79.9 (9.3)	80.4 (7.5)	80.4 (7.6)	-15.0	**0.0**
Risk factors, %						
- Hypertension	45.3	44.2	43.1	44.0	2.1	**-1.9**
- Diabetes mellitus	20.5	20.3	82.0	82.0	0.4	**0.0**
- Vascular disease history	19.6	20.5	18.4	19.4	-2.1	**-2.6**
- Congestive heart failure	14.4	16.1	14.0	14.9	-4.5	**-2.5**
- Stroke or TIA history	13.3	11.2	11.2	11.5	6.2	**-1.1**
- Abnormal renal function	4.6	6.9	4.9	5.0	-9.8	**-0.6**
- Abnormal liver function	1.6	1.6	1.5	1.5	0.0	**0.2**
- CHA_2DS_2-VASc score ≥ 2	92.3	91.0	94.0	93.9	-4.9	**-0.5**
- HAS-BLED score ≥ 3	35.2	33.9	34.8	33.2	-2.8	**-3.2**

Patient characteristics

Reduced dose	All patients		Matched patients		Standardized difference (%)	
	Dabigatran n = 15,532	Rivaroxaban n = 11,195	Dabigatran n = 7,639	Rivaroxaban n = 7,639	Crude	Matched
Male, %	48.5	46.6	46.4	46.4	-4.0	**0.0**
Age, mean (± SD)	78.5 (9.5)	79.9 (9.3)	80.4 (7.5)	80.4 (7.6)	-15.0	**0.0**
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- Congestive heart failure	14.4	16.1	14.0	14.9	-4.5	**-2.5**
- Stroke or TIA history	13.3	11.2	11.2	11.5	6.2	**-1.1**
- Abnormal renal function	4.6	6.9	4.9	5.0	-9.8	**-0.6**
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- Hypertension	31.0	33.0	29.0	29.4	-4.3	**-1.0**
- Diabetes mellitus	19.9	19.8	19.3	19.6	0.4	**-0.9**
- Vascular disease history	11.1	11.0	9.8	9.8	0.5	**0.2**
- Congestive heart failure	8.9	11.1	8.9	8.9	-7.4	**0.0**
- Stroke or TIA history	8.4	9.2	7.9	7.8	-2.6	**0.4**
- Abnormal renal function	1.3	2.1	1.2	1.1	-3.7	**0.3**
- Abnormal liver function	1.2	1.2	0.9	1.1	0.1	**-0.6**
- CHA_2DS_2-VASc score ≥ 2	57.1	67.4	59.3	58.5	-21.5	**-1.6**
- HAS-BLED score ≥ 3	15.7	20.0	15.4	15.8	-11.4	**1.0**

Standardized differences

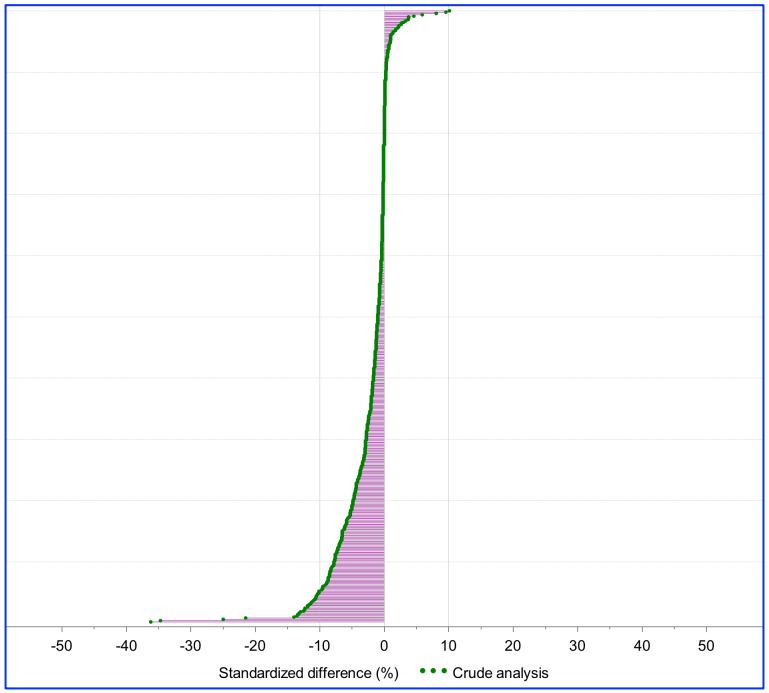
for 500 variables independent from hdPS selection

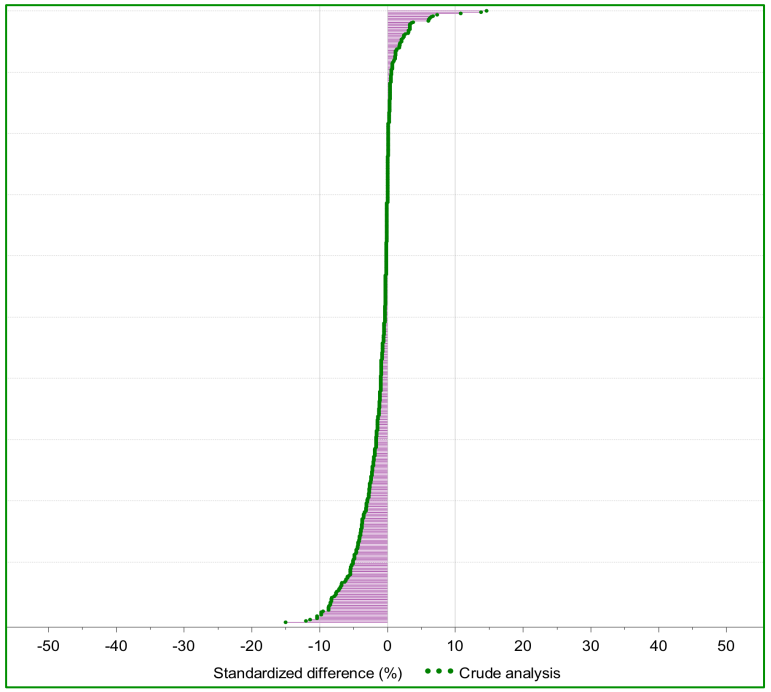
Dabigatran versus rivaroxaban

Standard doses

Reduced doses

All patients





Standardized differences

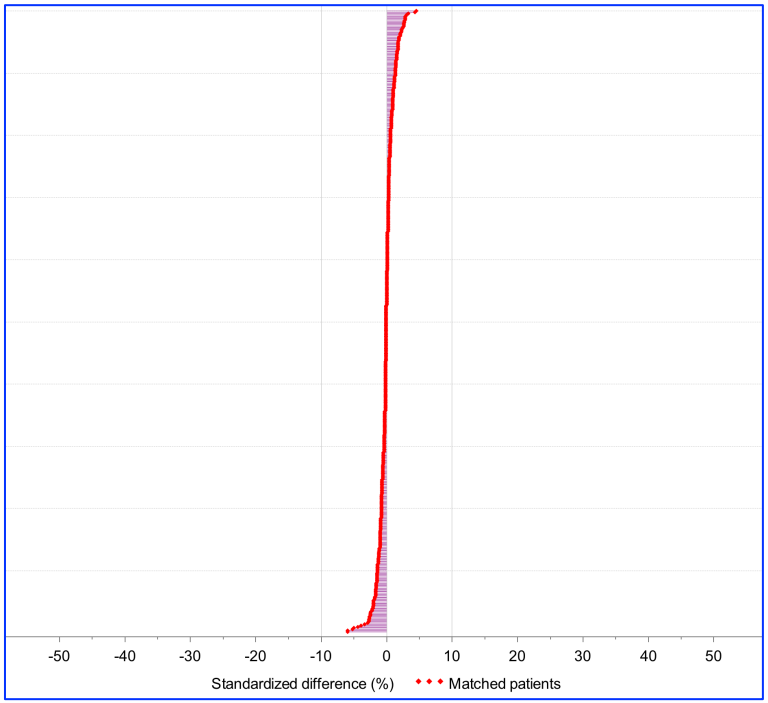
for 500 variables independent from hdPS selection

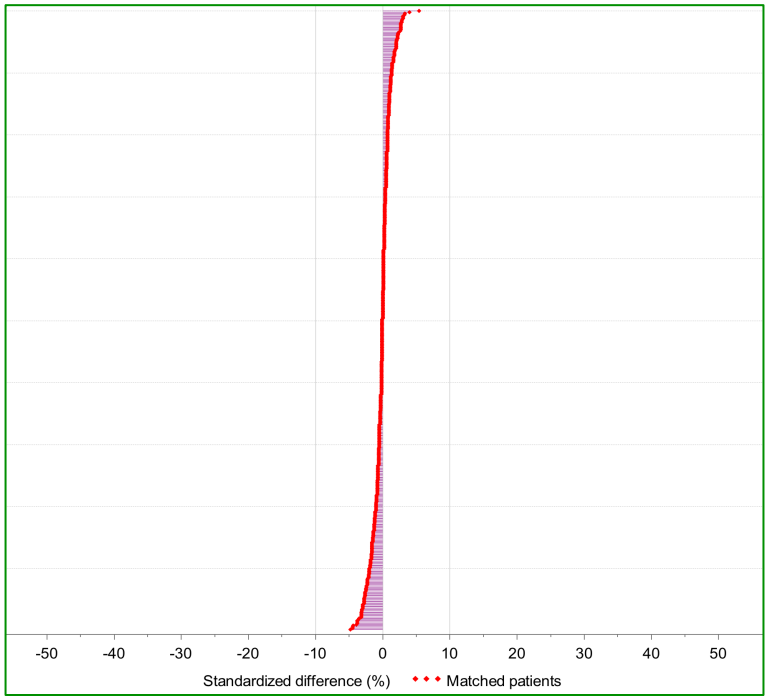
Dabigatran versus rivaroxaban

Standard doses

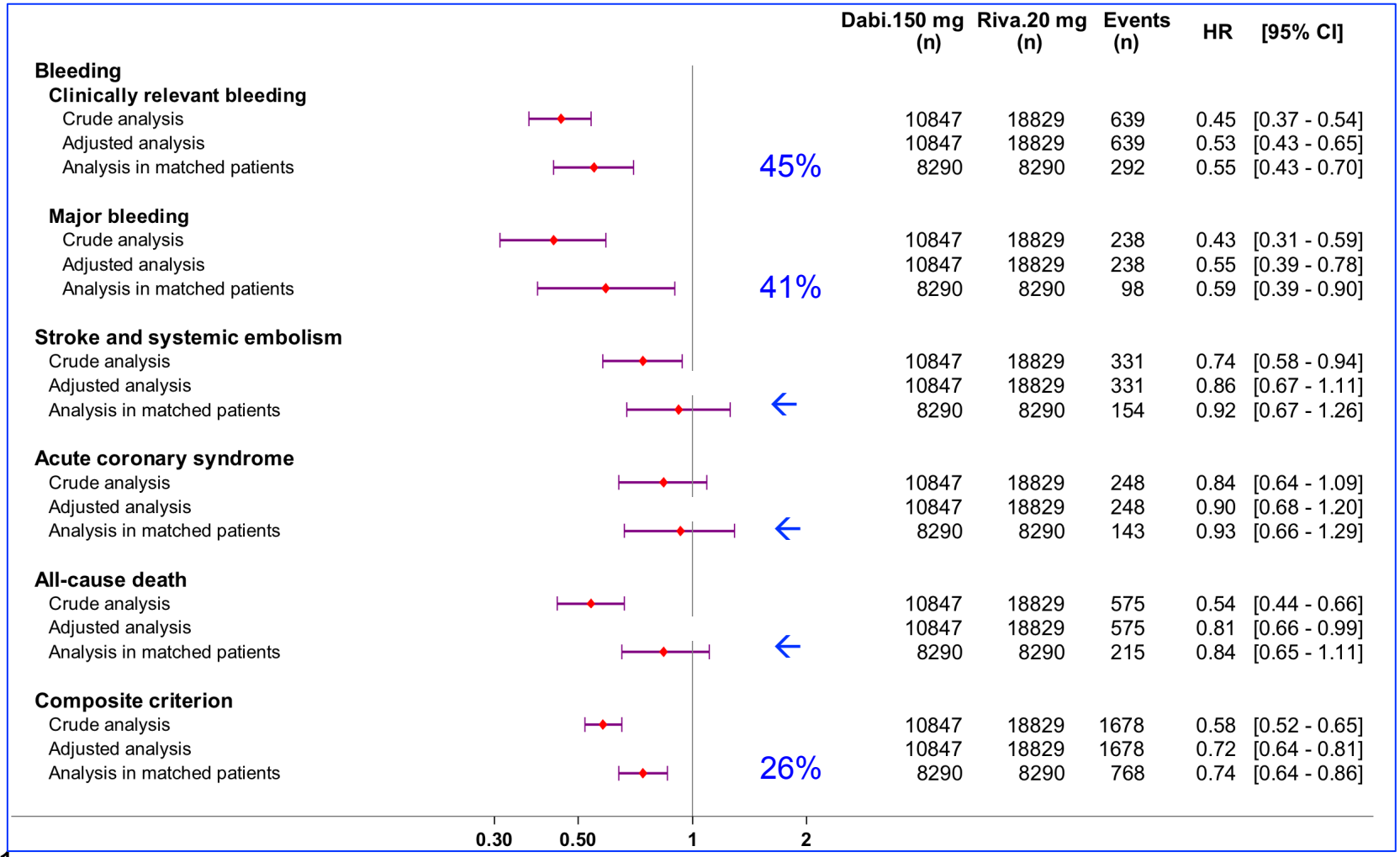
Reduced doses

Matched patients

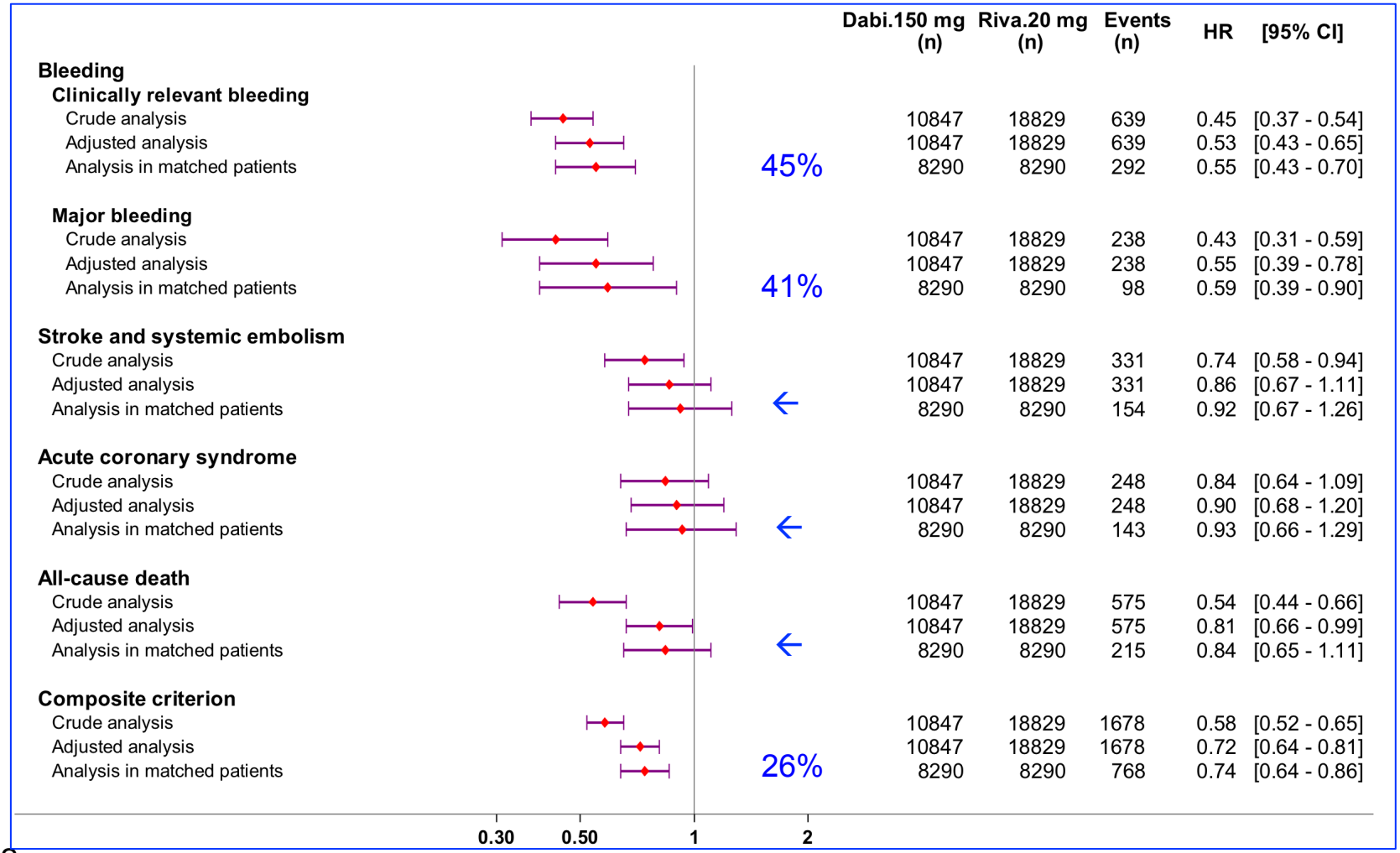




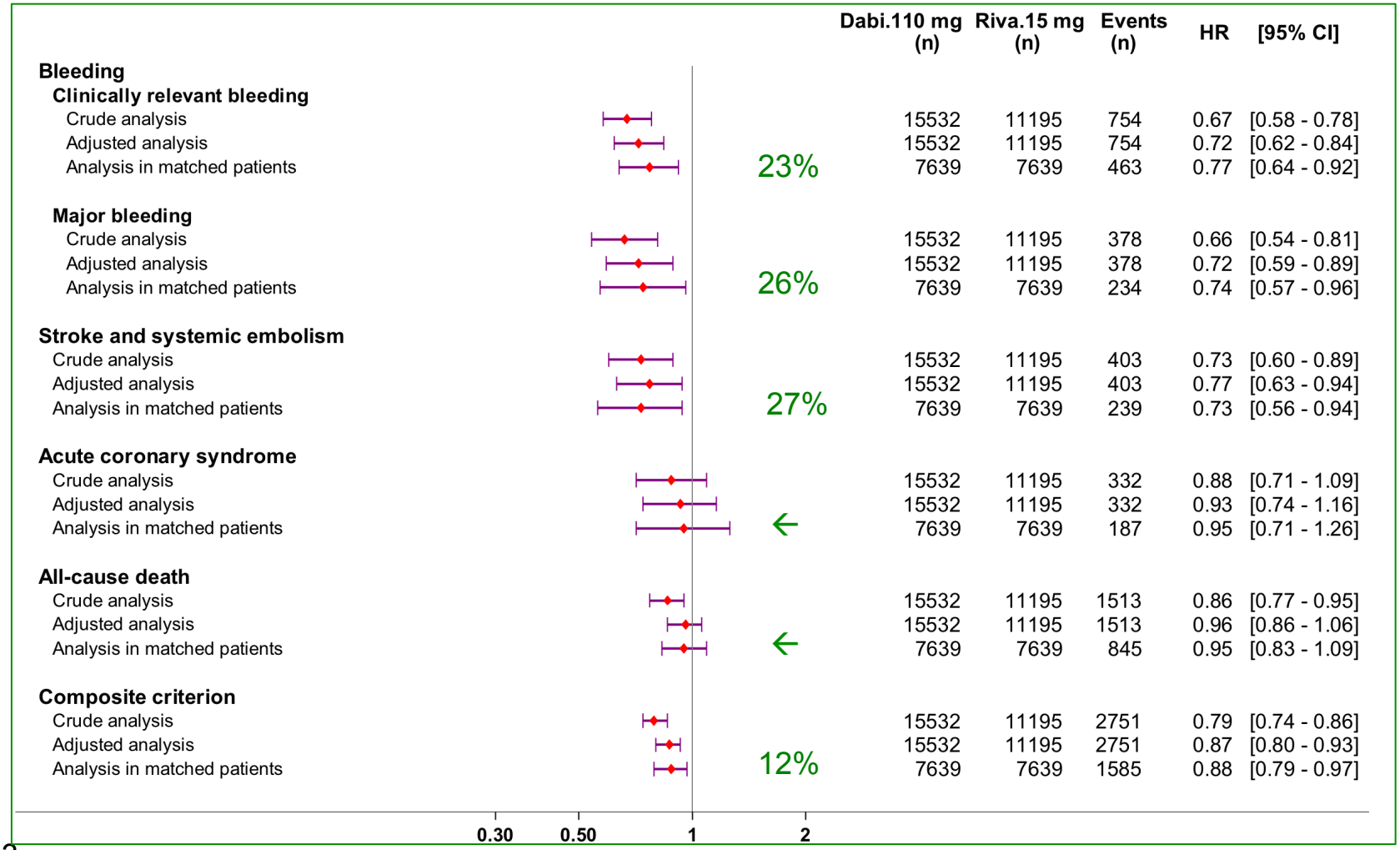
Benefit-risk standard doses



Benefit-risk standard doses



Benefit-risk reduced doses



Discussion

- Claims database with little clinical information to validate diagnoses, but high Predictive Positive Value published for ACS* and stroke** in the 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

Conclusions

This nationwide cohort study of new dabigatran or rivaroxaban users for NVAF shows:

- Some differences of prescription patterns between dabigatran and rivaroxaban according to doses in France
- No difference of effectiveness between two DOAC standard dose but a safer bleeding risk for dabigatran
- Better effectiveness and bleeding risk of dabigatran than rivaroxaban for reduced dose
- An overall benefit-risk profile in favour of dabigatran for both doses
- When compared within similar patients in hdPS matched groups, as well as for all patients and adjusted analysis

* Accepted for publication in Clinical Pharmacology & Therapeutics

Thank you for your attention

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