



Benefit-risk of rivaroxaban 20 or 15mg compared to vitamin-K antagonists in patients with non-valvular atrial fibrillation: a cohort study in the French nationwide claims database

P. Blin¹, C. Dureau-Pournin¹, M-A. Bernard¹, R. Lassalle¹, L. Fauchier², F. Sacher³, J. Dallongeville⁴, C. Droz-Perroteau¹, **N. Moore**^{1,5}



¹Bordeaux PharmacoeEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France - ²Hôpital Trousseau, Chambray-lès-Tours, France - ³IHU LIRYC/CHU, Pessac, France - ⁴Institut Pasteur, INSERM U1167, Lille, France - ⁵INSERM U1219, Bordeaux, France



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Disclosure statement

- Study funded by an unrestricted grant from Bayer AG
- EMA EUPAS registry n°14567
- Designed, conducted and analysed independently by the Bordeaux PharmacoSpi platform of Bordeaux University
- Supervised by a scientific committee who received expert fees from Bayer AG

Background

- In clinical trials, direct oral anticoagulants (DOAC: rivaroxaban, dabigatran, and apixaban) had better benefit-risk than vitamin-K antagonists (VKA) for non-valvular atrial fibrillation (NVAf)
- Real-life benefits and risks remain uncertain
- Request from the French health authorities for a study about benefit-risk generalization in real-life setting

Objectives

- To compare **1-year risk** of outcomes
 - **Effectiveness**: stroke and systemic embolism (SSE), acute coronary syndrome (ACS), death
 - **Safety**: bleeding (major and clinically relevant bleedings)
- Between **new rivaroxaban or VKA users for NVAF**
 - Rivaroxaban 20mg vs VKA
 - Rivaroxaban 15mg vs VKA
- **Rivaroxaban 20mg**: standard dose
Rivaroxaban 15mg: dose recommended for patients with moderate or severe renal failure (if renal clearance ≥ 15 ml/min)

Method (1)

- **Cohort study**
 - In the 66 Million persons French nationwide claims database (SNDS, *Système National des Données de Santé*)
 - New users of rivaroxaban 20mg, 15mg or VKA for NVAf in 2013-2014
 - With 3-year history and 1-year follow-up
- **NVAf population**
 - Patients with long-term disease registration, hospitalisation or procedure for atrial fibrillation without rheumatic valve disease or valve replacement, and nor other probable indication (3-year history)

Method (2)

- **Outcomes (on treatment)**
 - Hospital admission (primary diagnosis) for:
 - ✓ Stroke and systemic embolism (SSE)
 - ✓ Major bleeding*
 - ✓ Clinically relevant bleeding*
 - ✓ Acute coronary syndrome (ACS)
 - Death (all-cause)
 - Composite criterion: 1st event among SSE, major bleeding, or death

* Primary, linked, or associated diagnosis for haemorrhagic stroke

Method (3)

- **Statistical analysis**
 - **1:1 matched analysis** on gender, age, date of first anticoagulant dispensing, and logit of high-dimensional propensity score (hdPS), including stroke and bleeding risk factors, and 500 variables from 4 dimensions
 - **1-year cumulative incidence of outcomes** using Kaplan-Meier estimate (death, composite) or cumulative incidence function (other outcomes)
 - **Comparison of risk** using Cox proportional hazard risk model (death, composite) or Fine and Gray model (other outcomes)

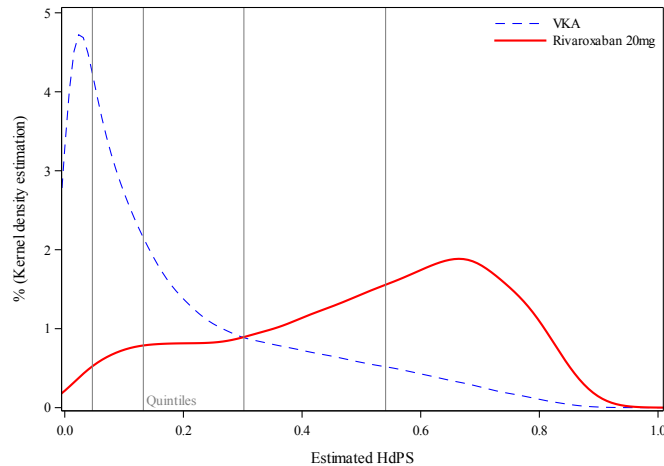
Results: Populations

- **178,402** new users of rivaroxaban or VKA for NVAf in 2013-2014 in France
 - 42,531 rivaroxaban 20mg
 - 24,585 rivaroxaban 15mg
 - 108,666 VKA
- **Matched populations**
 - 31,171 per arm for rivaroxaban 20mg vs VKA (73% of rivaroxaban 20mg group)
 - 23,314 per arm for rivaroxaban 15mg vs VKA (95% of rivaroxaban 15mg group)

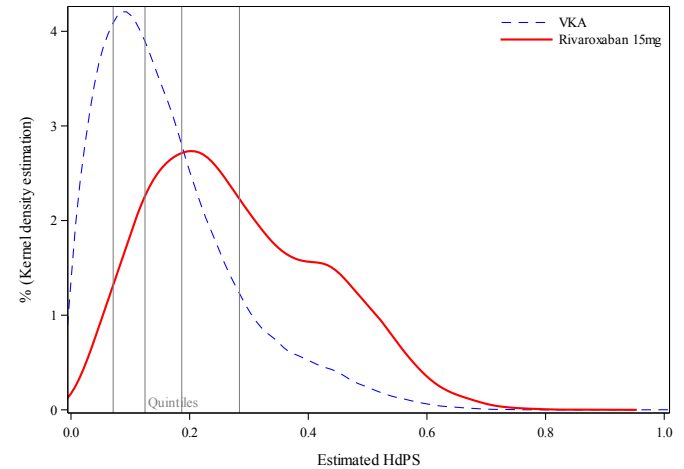
hdPS distributions

All
patients

Rivaroxaban 20mg vs VKA



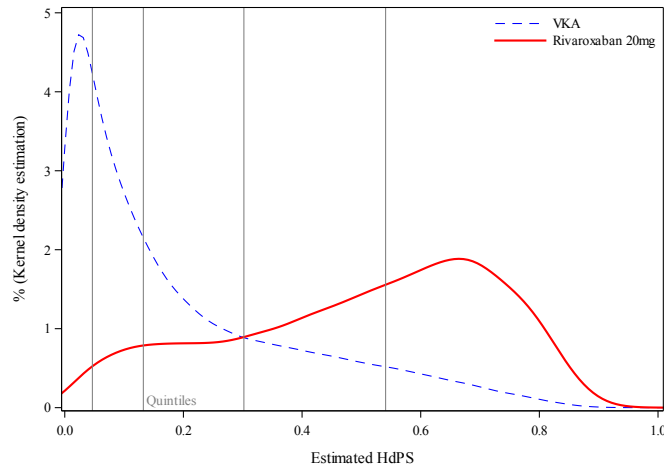
Rivaroxaban 15mg vs VKA



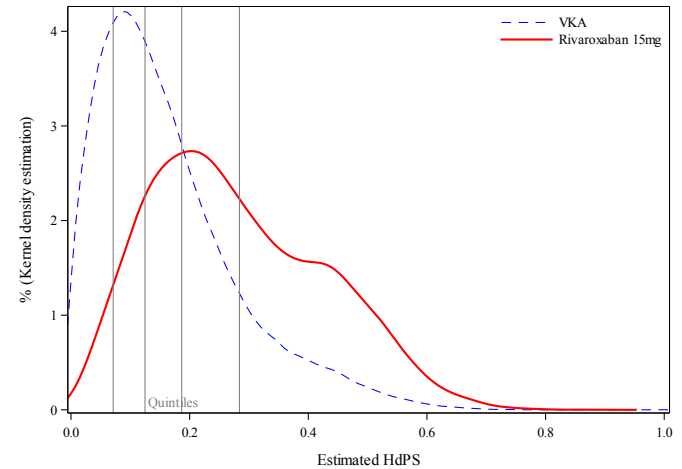
hdPS distributions

**All
patients**

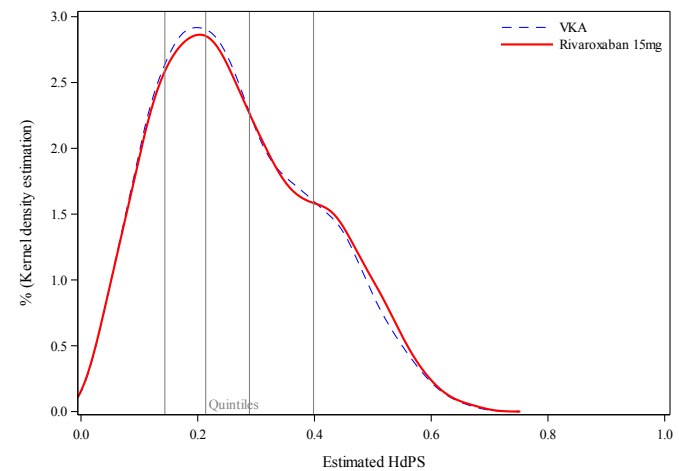
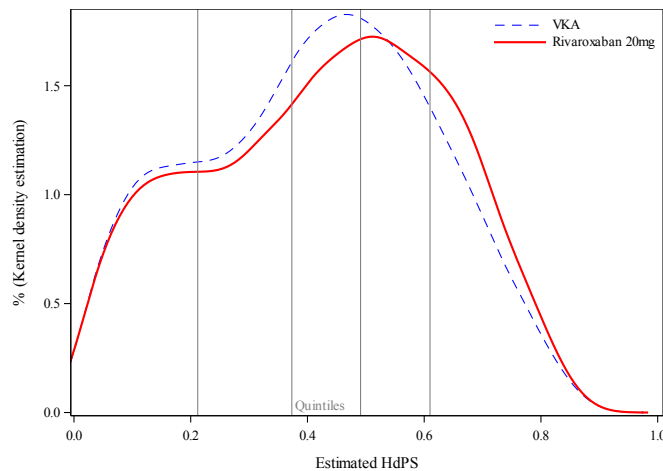
Rivaroxaban 20mg vs VKA



Rivaroxaban 15mg vs VKA



**Matched
patients**



Patient characteristics (20 mg)

	All patients		Standardized difference (%)
	Rivaroxaban 20mg* n = 42,480	VKA* n = 108,656	Crude
Male, %	64.4	51.9	25.6
Age, mean (± SD)	68.6 (11.1)	78.4 (11.0)	-88.2
Risk factors, %			
Hypertension	33.6	55.7	-45.4
Diabetes mellitus	20.5	27.0	-15.3
Congestive heart failure	12.4	35.5	-56.0
Vascular disease history	10.9	23.0	-32.6
Stroke or TIA history	8.8	14.9	-19.1
Abnormal renal function	2.1	18.0	-54.8
Abnormal liver function	1.4	3.2	-12.6
CHA ₂ DS ₂ -VASc score ≥ 2	66.2	90.7	-
HAS-BLED score ≥ 3	20.3	47.8	-

*Number of patients after hdPS trimming for groups comparison (exclusion of patients with extreme hdPS values)

Patient characteristics (20 mg)

	All patients		Matched patients		Standardized difference (%)	
	Rivaroxaban 20mg n = 42,480	VKA n = 108,656	Rivaroxaban 20mg n = 31,171	VKA n = 31,171	Crude	Matched
Male, %	64.4	51.9	62.0	62.0	25.6	0.0
Age, mean (± SD)	68.6 (11.1)	78.4 (11.0)	71.2 (10.0)	71.2 (10.0)	-88.2	-0.2
Risk factors, %						
Hypertension	33.6	55.7	38.2	39.6	-45.4	-2.9
Diabetes mellitus	20.5	27.0	22.5	23.4	-15.3	-2.1
Congestive heart failure	12.4	35.5	15.6	15.9	-56.0	-0.8
Vascular disease history	10.9	23.0	13.1	13.8	-32.6	-2.0
Stroke or TIA history	8.8	14.9	10.7	11.3	-19.1	-2.0
Abnormal renal function	2.1	18.0	2.7	3.3	-54.8	-3.6
Abnormal liver function	1.4	3.2	1.7	1.8	-12.6	-0.8
CHA ₂ DS ₂ -VASc score ≥ 2	66.2	90.7	75.6	76.2	-	-
HAS-BLED score ≥ 3	20.3	47.8	25.6	26.8	-	-

Patient characteristics (15 mg)

	All patients		Matched patients		Standardized difference (%)	
	Rivaroxaban 15mg* n = 24,529	VKA* n = 108,639	Rivaroxaban 15mg n = 23,314	VKA n = 23,314	Crude	Matched
Male, %	47.2	51.9	47.5	47.5	9.4	0.0
Age, mean (± SD)	79.8 (9.4)	78.4 (11.0)	80.1 (8.7)	80.1 (8.7)	14.2	0.0
Risk factors, %						
Hypertension	45.2	55.7	45.9	45.9	-21.0	-0.1
Diabetes mellitus	21.1	27.0	21.4	21.8	-13.7	-0.9
Congestive heart failure	22.7	35.5	23.4	23.1	-28.3	0.8
Vascular disease history	16.5	23.0	16.8	17.1	-16.3	-0.8
Stroke or TIA history	10.9	14.9	11.2	11.4	-11.9	-0.5
Abnormal renal function	6.8	18.0	7.0	7.1	-34.6	-0.4
Abnormal liver function	1.6	3.3	1.6	1.6	-10.6	0.2
CHA ₂ DS ₂ -VASc score ≥ 2	92.3	90.7	92.9	92.9	-	-
HAS-BLED score ≥ 3	36.2	47.8	37.0	36.8	-	-

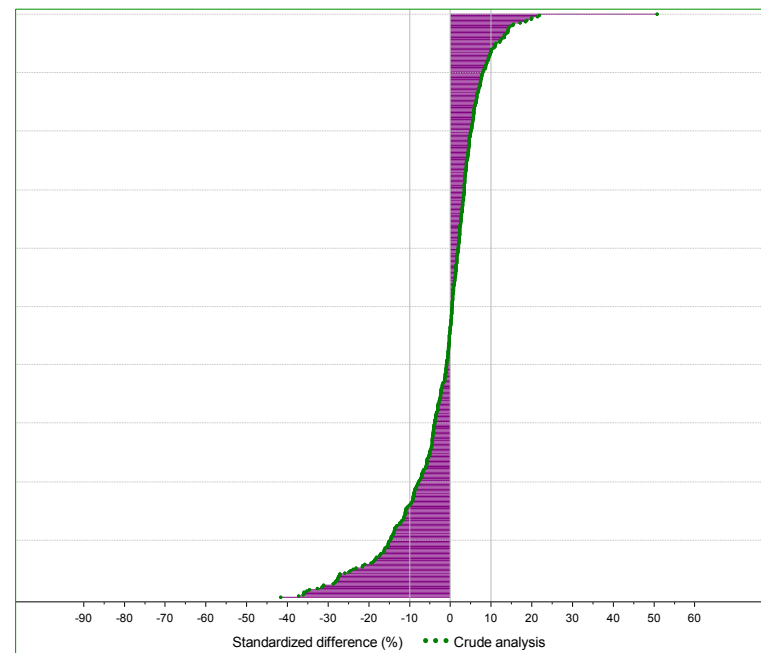
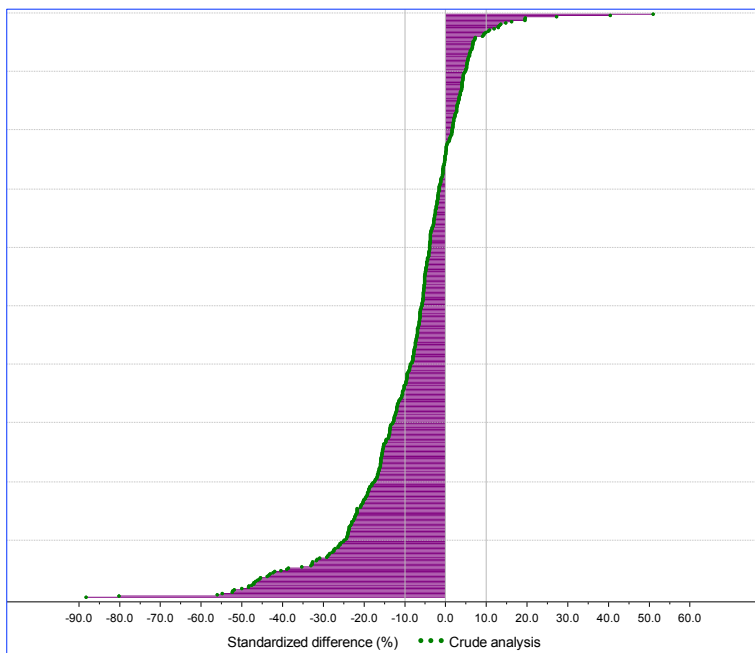
*Number of patients after hdPS trimming for groups comparison (exclusion of patients with extreme hdPS values)

Standardized differences (481 variables)

Rivaroxaban 20mg vs VKA

Rivaroxaban 15mg vs VKA

All
patients

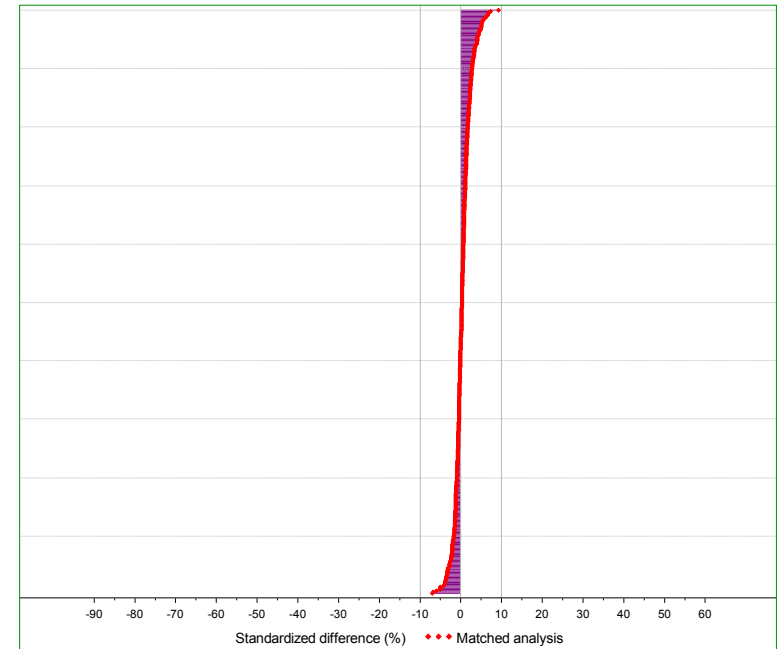
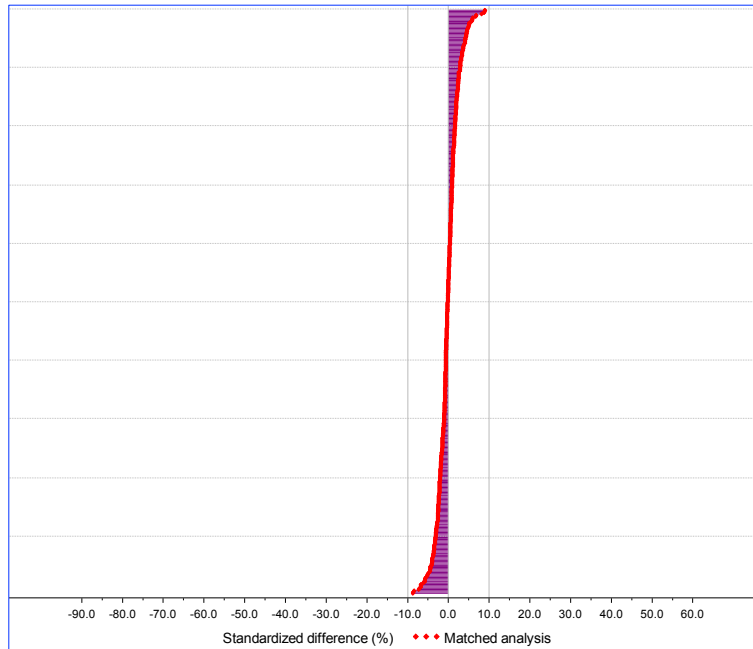


Standardized differences (481 variables)

Rivaroxaban 20mg vs VKA

Rivaroxaban 15mg vs VKA

Matched
patients



1-year cumulative incidence (20 mg)

	Rivaroxaban 20mg n = 31,171 % [95%CI]	VKA n = 31,171 % [95%CI]	
SSE	1.5 [1.4; 1.7]	1.9 [1.8; 2.1]	
Major bleeding	1.5 [1.4; 1.7]	2.2 [2.1; 2.4]	
Clinically relevant bleeding	3.3 [3.1; 3.6]	4.0 [3.7; 4.2]	
Death	3.9 [3.7; 4.2]	5.8 [5.5; 6.1]	
Composite criterion*	6.3 [6.0; 6.6]	8.9 [8.5; 9.2]	
ACS	1.2 [1.0; 1.3]	1.4 [1.3; 1.6]	

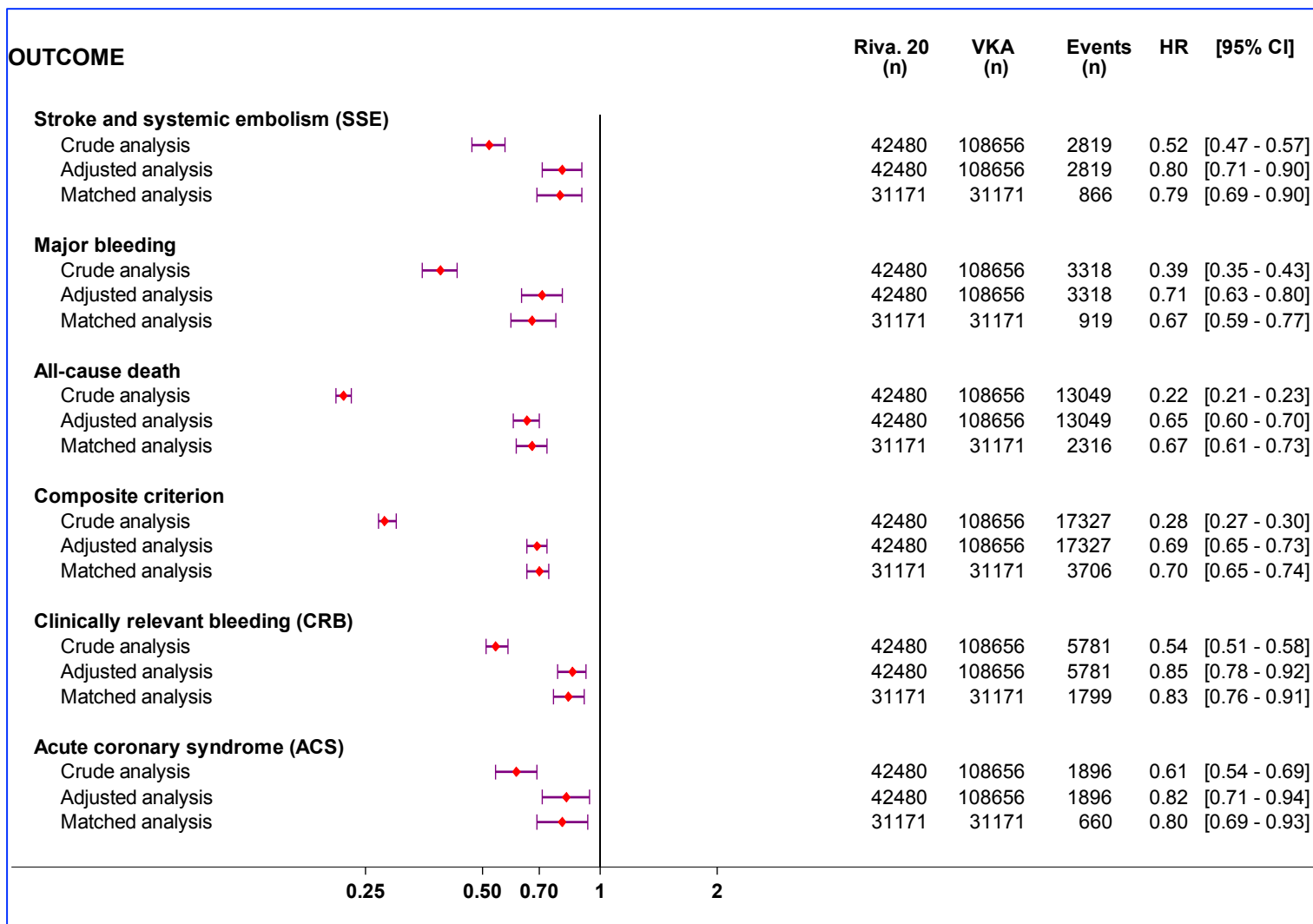
*SSE, major bleeding, or death

1-year cumulative incidence(15 mg)

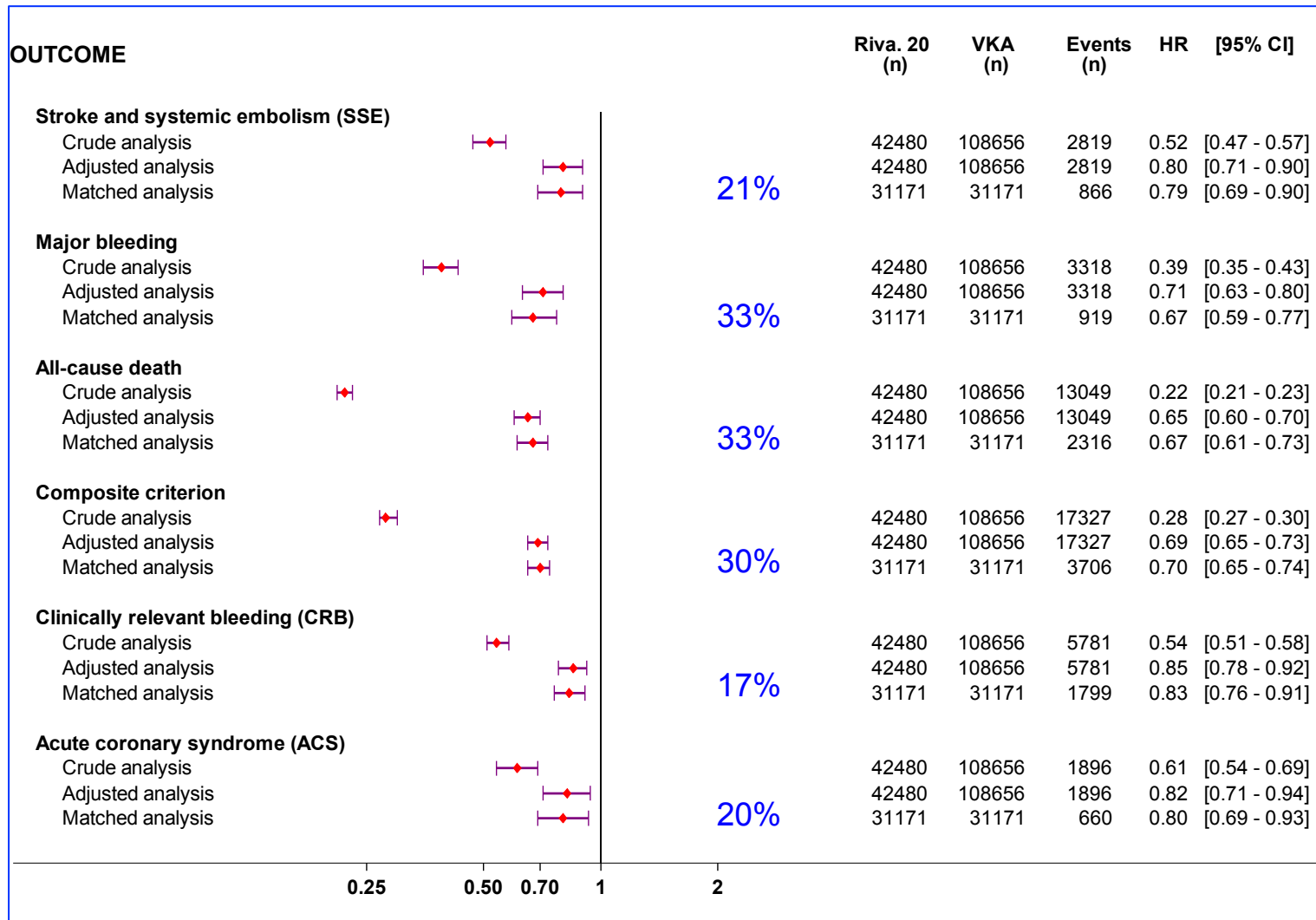
	Rivaroxaban 20mg n = 31,171	VKA n = 31,171	Rivaroxaban 15mg n = 23,314	VKA n = 23,314
	% [95%CI]	% [95%CI]	% [95%CI]	% [95%CI]
SSE	1.5 [1.4; 1.7]	1.9 [1.8; 2.1]	2.3 [2.0; 2.5]	2.1 [1.9; 2.3]
Major bleeding	1.5 [1.4; 1.7]	2.2 [2.1; 2.4]	2.4 [2.2; 2.6]	2.9 [2.6; 3.1]
Clinically relevant bleeding	3.3 [3.1; 3.6]	4.0 [3.7; 4.2]	4.4 [4.1; 4.7]	4.9 [4.6; 5.3]
Death	3.9 [3.7; 4.2]	5.8 [5.5; 6.1]	9.1 [8.6; 9.5]	10.8 [10.3; 11.2]
Composite criterion*	6.3 [6.0; 6.6]	8.9 [8.5; 9.2]	12.5 [12.0; 13.0]	14.0 [13.5; 14.5]
ACS	1.2 [1.0; 1.3]	1.4 [1.3; 1.6]	1.5 [1.3; 1.7]	1.7 [1.6; 1.9]

*SSE, major bleeding, or death

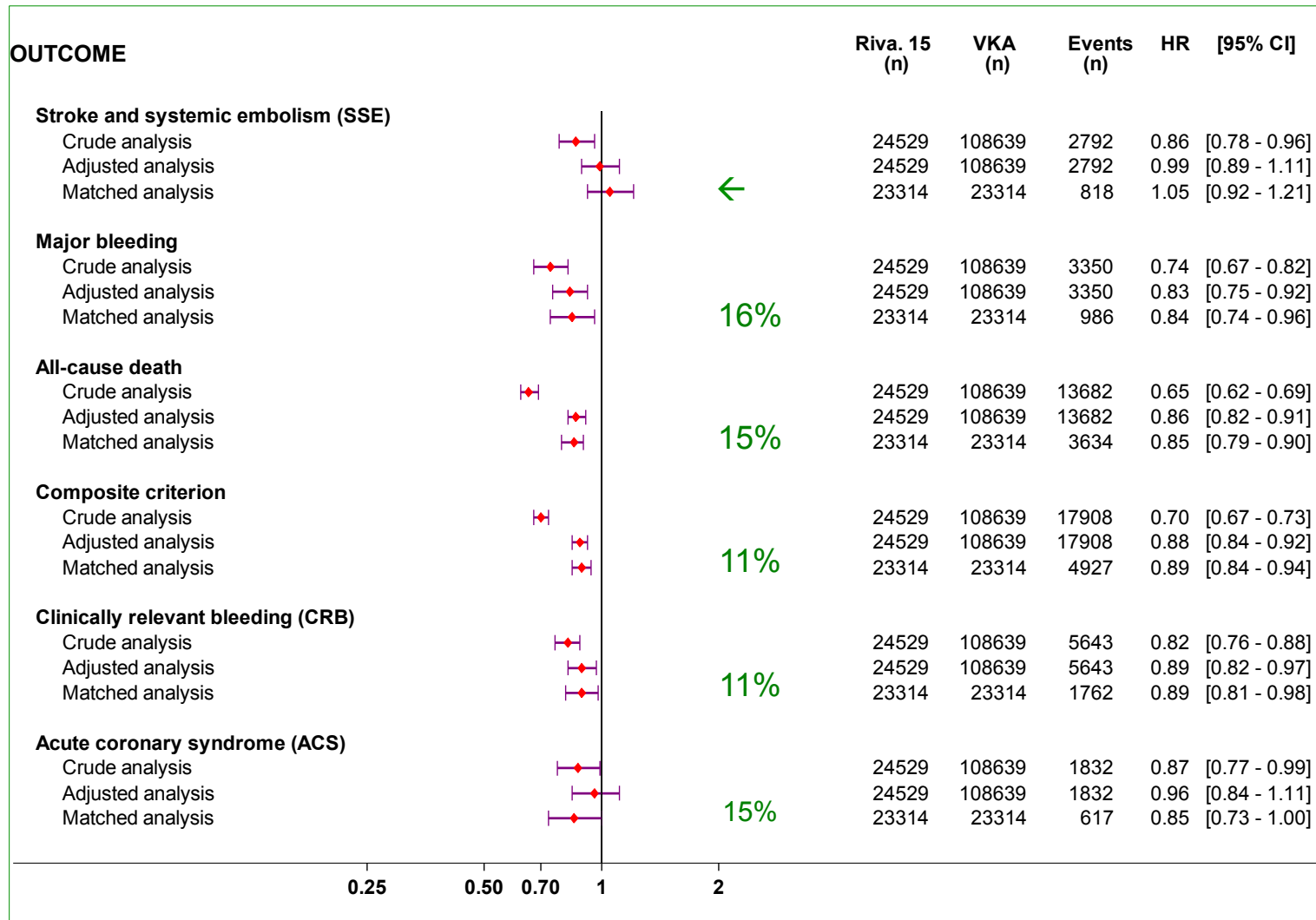
Benefit-risk rivaroxaban vs VKA



Benefit-risk rivaroxaban 20 vs VKA



Benefit-risk rivaroxaban 15 vs VKA



Discussion / Conclusion

This nationwide cohort study of new rivaroxaban or VKA users for NVAf shows:

- Different rivaroxaban 20 or 15mg and VKA prescription patterns in France
- A significantly overall better benefit-risk in real-life of rivaroxaban 20 or 15mg compared to VKA
- When compared within similar patients in hdPS matched groups, as well as for all patients and adjusted analysis



Thank you

nicholas.moore@u-bordeaux.fr



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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