Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

Effectiveness and safety of direct oral anticoagulants versus VKA

a cohort study of about 100,000 non-valvular atrial fibrillation patients from the nationwide French claims and hospitalisation database

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33rd ICPE, August 26-30, 2017, Montreal, Canada

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Adera

Conflicts of interest

- Study supported by an unconditional grant from Boehringer Ingelheim France
- EMA EUPAS registry n°13017
- Supervised by an independent scientific committee
- Conducted and analysed independently by the Bordeaux PharmacoEpi platform

Background

- European market authorizations for direct-acting oral anticoagulants (DOAC: dabigatran, edoxaban, rivaroxaban, apixaban)
- Premarketing trials found a better benefit-risk of DOAC than VKA for stroke prevention in non-valvular atrial fibrillation (NVAF)
- Request from HAS, the French health assessment technology (HTA) agency, for a study about benefit-risk generalization in real-life setting

Objectives

- **To compare 1-year risk of outcomes**
  - **Safety:** Clinically relevant bleeding (CRB) with subgroups (major bleeding, cerebral hemorrhage, GI bleeding)
  - **Effectiveness:** arterial thrombotic event (ATE)
  - Acute coronary syndrome (ACS) and death
- **Between new DOAC or VKA users for NVAF**
  - **dabigatran (D) versus VKA** during drug exposure
  - **rivaroxaban (R) versus VKA** during drug exposure

* Edoxaban and apixaban not yet marketed at the time of the study

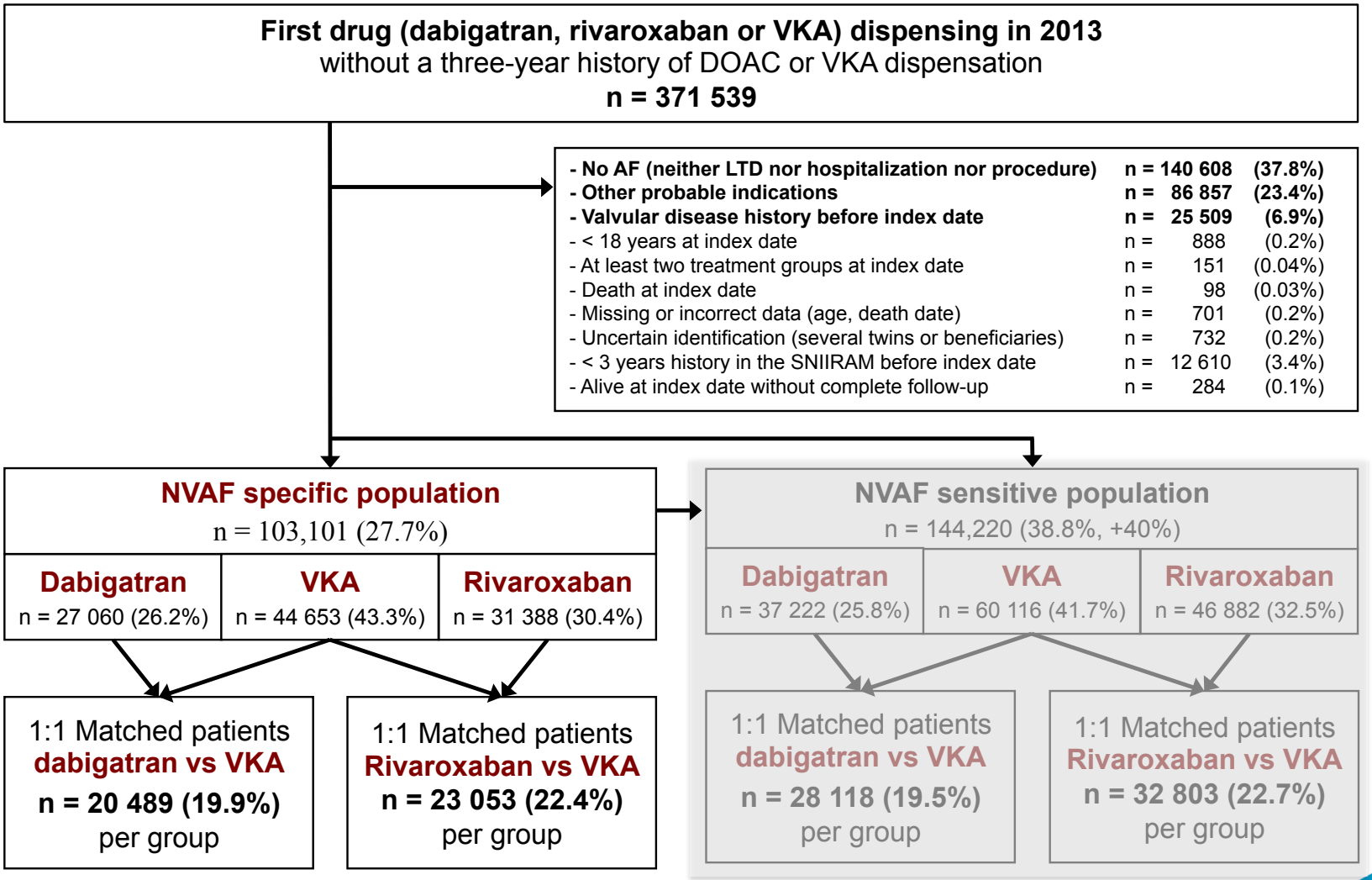
Methods (1)

- **Cohort study**
  - in the French nationwide claims database (SNIIRAM)
  - All news DOAC or VKA users for NVAF in 2013
  - With 1 year of follow-up and a 3-year database history
- **NVAF study populations**
  - **Specific:** hospitalization or long-term disease registration for AF (ICD-10 code I48) or AF procedure, without valvular disease history, and nor other probable indication
  - **Sensitive:** specific population plus probable NVAF using a disease score

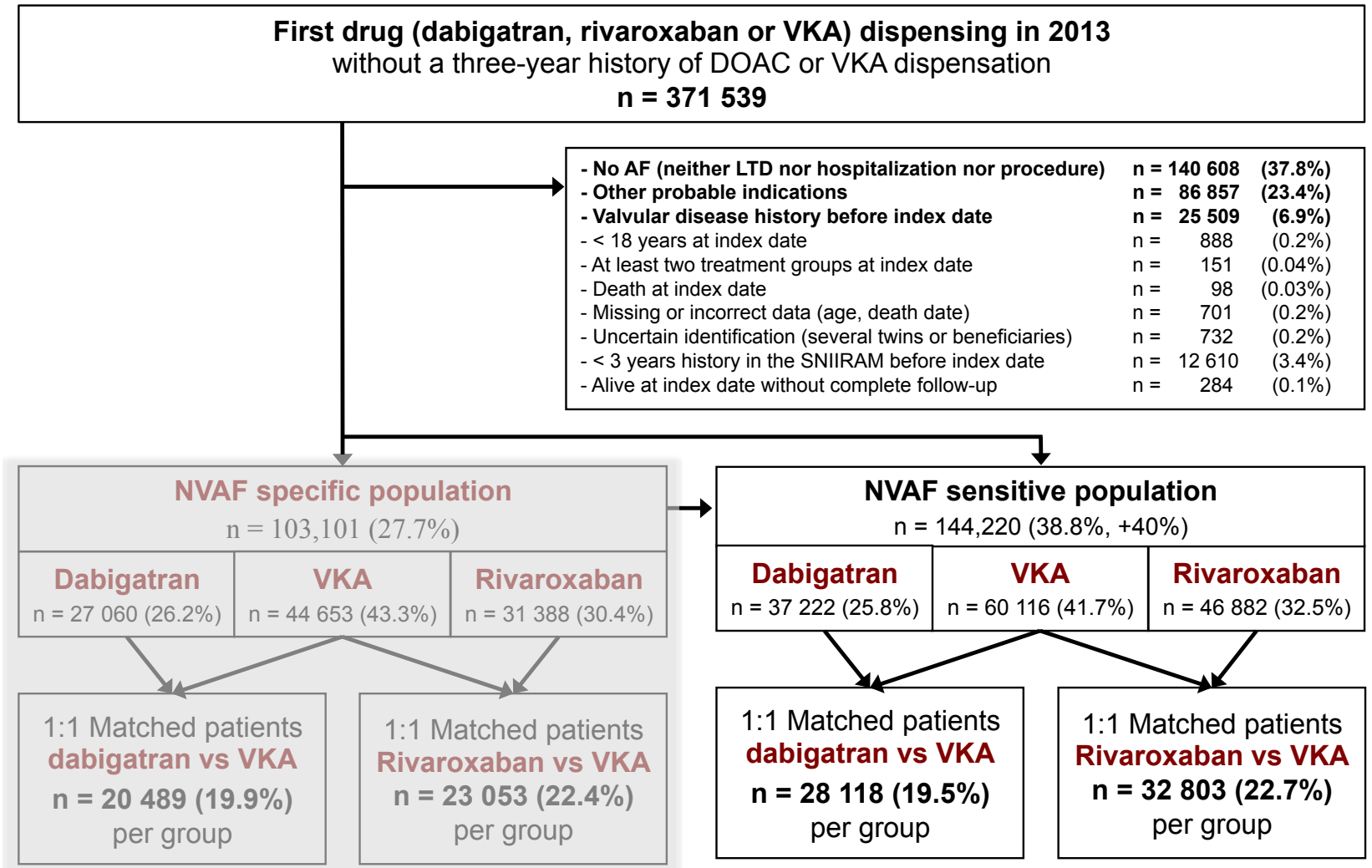
Methods (2)

- **Outcomes**
  - hospitalization with primary diagnosis of CRB, ATE, ACS
  - Death (all-cause)
  - Composite: CRB, ATE, ACS, and death
- **Data analysis**
  - **1:1 Matching** on gender, age, date of first drug dispensing and hdPS including AF stroke and bleeding risk factors, and 500 variables from 4 dimensions
  - **Statistics:** Cox proportional hazard risk model (death, composite) or Fine and Gray model (clinical events)
  - for matched patients, as well as for all patient with hdPS adjustment

Results: populations



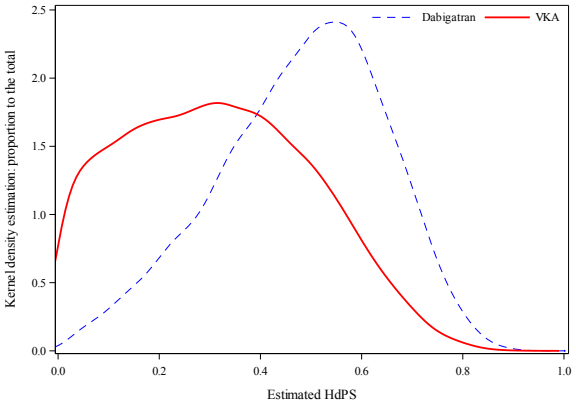
Results: populations



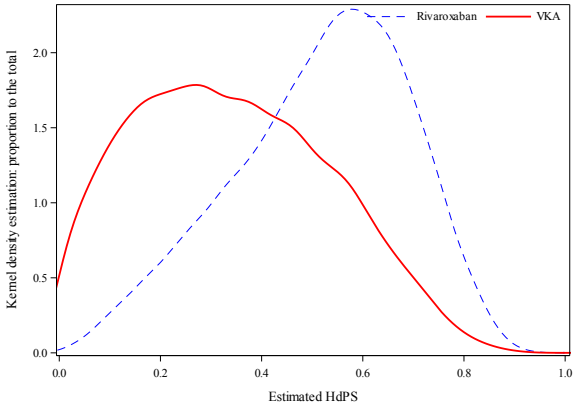
hdPS distributions

All patients

Dabigatran vs VKA



Rivaroxaban vs VKA

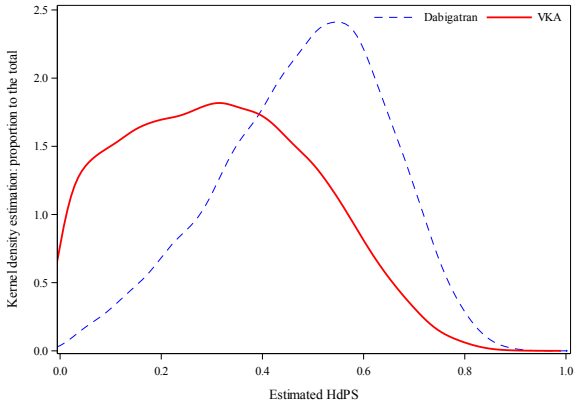


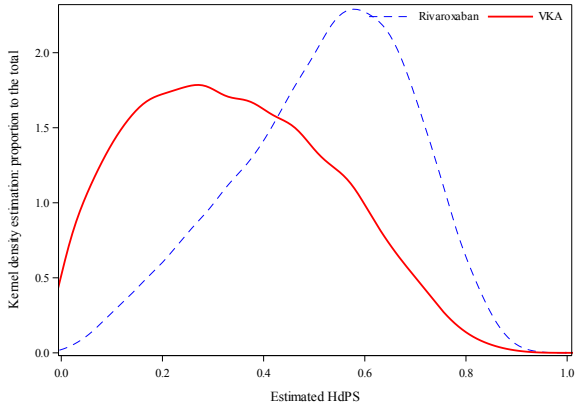
hdPS distributions

Dabigatran vs VKA

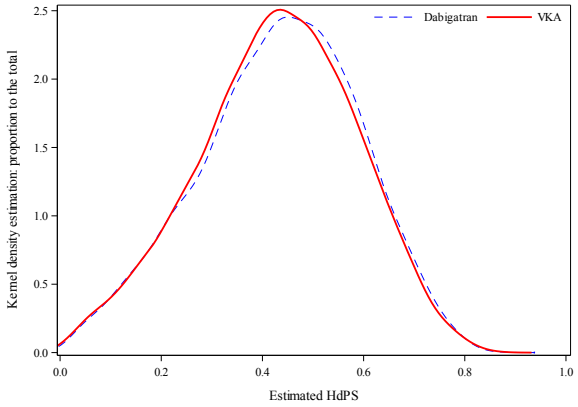
Rivaroxaban vs VKA

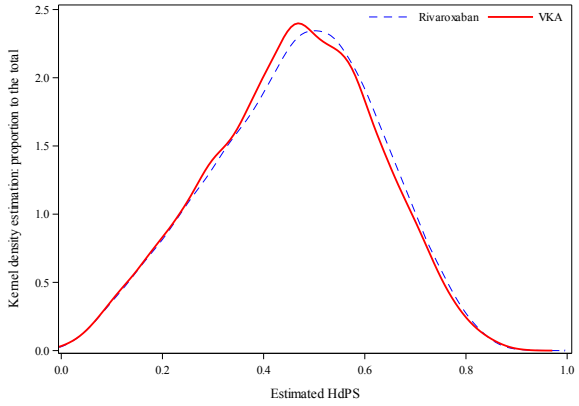
All patients





Matched patients





Patients' characteristics

	All patients		Standardized difference (%)
	Dabigatran n = 27 060	VKA n = 44 653	Crude
Male	56.4%	51.2%	-10.4
Age, mean (± SD)	73.2 (11.8)	77.9 (11.1)	-40.8
Risk factors			
- Hypertension	39.4%	53.3%	-28.2
- Diabetes mellitus	20.3%	26.2%	-14.1
- Vascular disease history	12.2%	21.6%	-25.4
- Congestive heart failure	16.2%	30.7%	-34.7
- Stroke or TIA history	11.4%	15.0%	-10.8
- Abnormal renal function	3.3%	16.6%	-43.5
- Abnormal liver function	1.5%	3.1%	-7.4
- CHA_2DS_2-VASc score ≥ 2	77.3%	89.5%	-33.1
- HAS-BLED score ≥ 3	26.5%	45.0%	-39.3

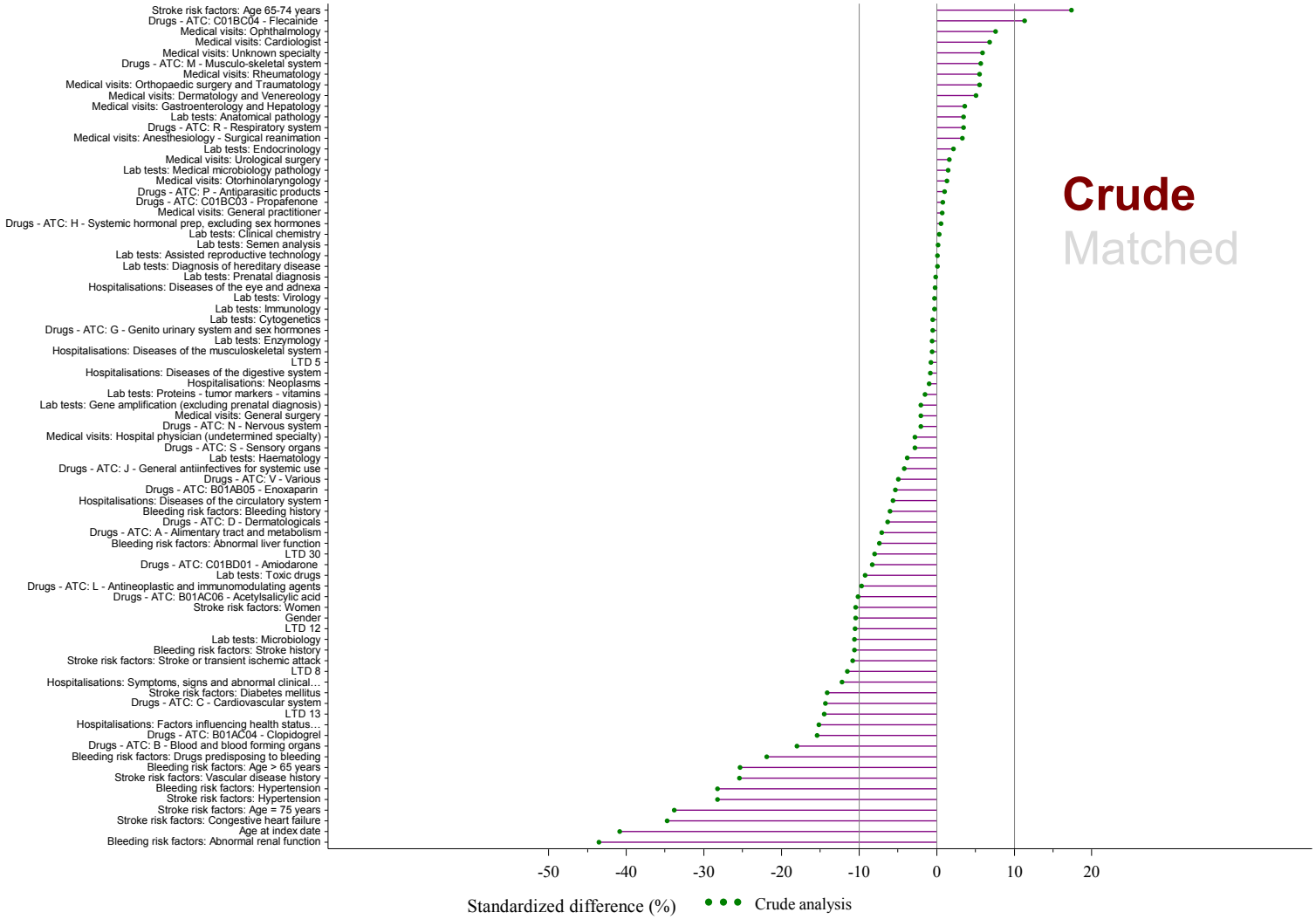
Patients' characteristics

	All patients		Matched patients		Standardized difference (%)		
	Dabigatran n = 27 060	VKA n = 44 653	Dabigatran n = 20 489	VKA n = 20 489	Crude	Adjusted	Matched
Male	56.4%	51.2%	54.5%	54.5%	-10.4	0.1	0.0
Age, mean (± SD)	73.2 (11.8)	77.9 (11.1)	75.3 (10.7)	75.4 (10.7)	-40.8	-1.3	-0.2
Risk factors							
- Hypertension	39.4%	53.3%	43.2%	44.0%	-28.2	0.3	-1.7
- Diabetes mellitus	20.3%	26.2%	21.7%	22.9%	-14.1	-0.4	-3.0
- Vascular disease history	12.2%	21.6%	14.2%	14.4%	-25.4	0.6	-0.7
- Congestive heart failure	16.2%	30.7%	19.3%	19.9%	-34.7	0.7	-1.4
- Stroke or TIA history	11.4%	15.0%	12.9%	12.9%	-10.8	2.0	0.0
- Abnormal renal function	3.3%	16.6%	4.3%	4.8%	-43.5	-1.6	-2.4
- Abnormal liver function	1.5%	3.1%	1.7%	1.8%	-7.4	0.0	-0.2
- CHA_2DS_2-VASc score ≥ 2	77.3%	89.5%	83.2%	83.5%	-33.1	4.9	-0.9
- HAS-BLED score ≥ 3	26.5%	45.0%	31.5%	31.5%	-39.3	3.8	-0.2

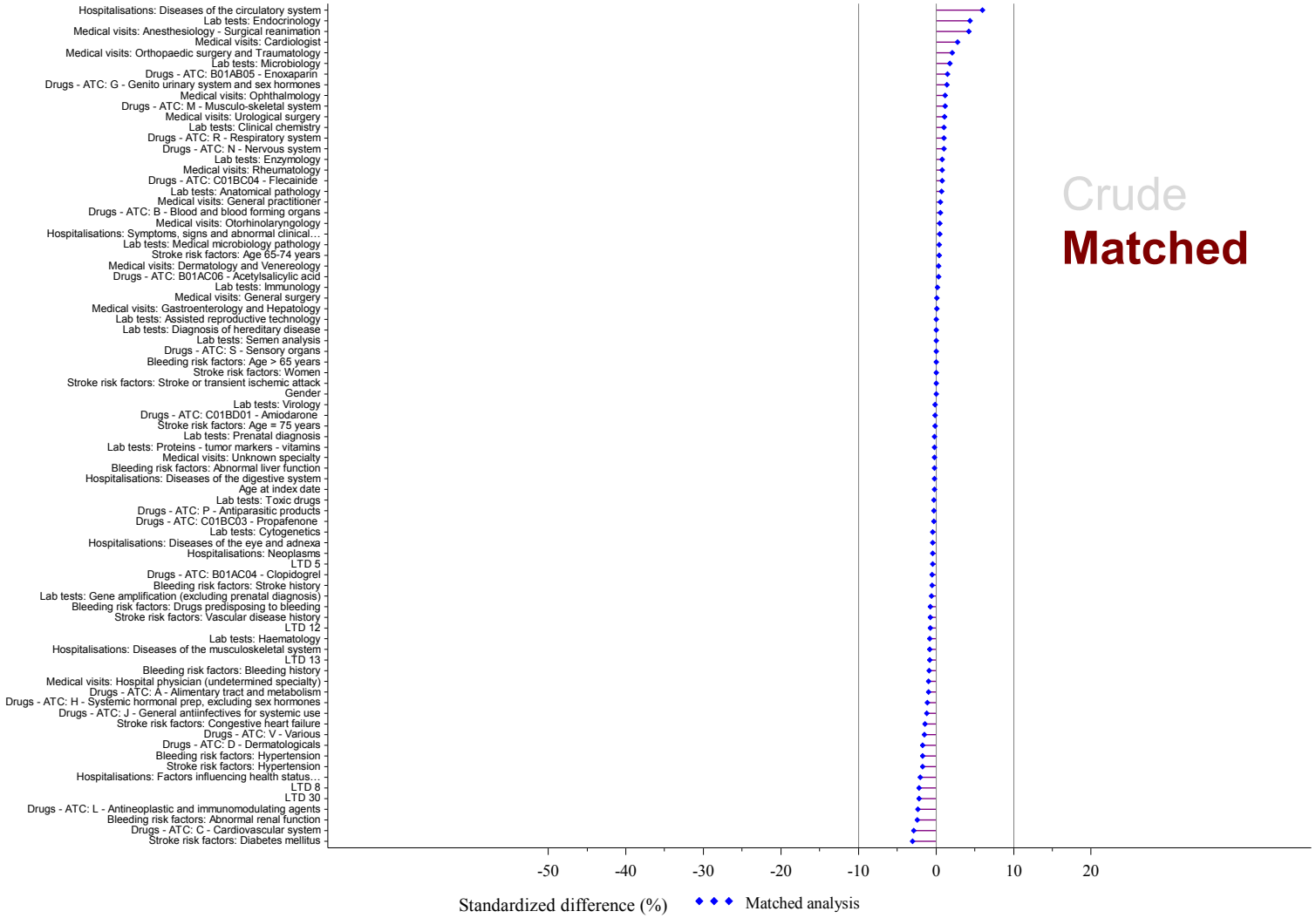
Patients' characteristics

	All patients		Matched patients		Standardized difference (%)		
	Rivaroxaban n = 31 388	VKA n = 44 653	Rivaroxaban n = 23 053	VKA n = 23 053	Crude	Adjusted	Matched
Male	56.2%	51.2%	54.5%	54.5%%	-10.1	0.2	0.0
Age, mean (± SD)	73.2 (11.8)	77.9 (11.1)	75.6 (10.7)	75.6 (10.7)	-40.5	-1.6	0.0
Risk factors							
- Hypertension	37.4%	53.3%	42.2%	43.1%	-32.4	0.9	-1.8
- Diabetes mellitus	20.0%	26.2%	21.7%	22.7%	-14.8	-0.1	-2.3
- Vascular disease history	13.0%	21.6%	15.2%	15.6%	-23.0	0.4	-1.0
- Congestive heart failure	14.7%	30.7%	18.3%	18.5%	-38.9	0.3	-0.5
- Stroke or TIA history	10.2%	15.0%	12.0%	12.3%	-14.7	1.1	-0.9
- Abnormal renal function	4.0%	16.6%	5.3%	5.7%	-41.2	-0.3	-1.9
- Abnormal liver function	1.4%	3.1%	1.7%	1.6%	-7.7	-0.2	0.4
- CHA_2DS_2-VASc score ≥ 2	77.1%	89.5%	83.7%	83.9%	-33.7	4.1	-0.5
- HAS-BLED score ≥ 3	26.0%	45,0%	31.3%	32.0%	40.5	2.7	-1.5

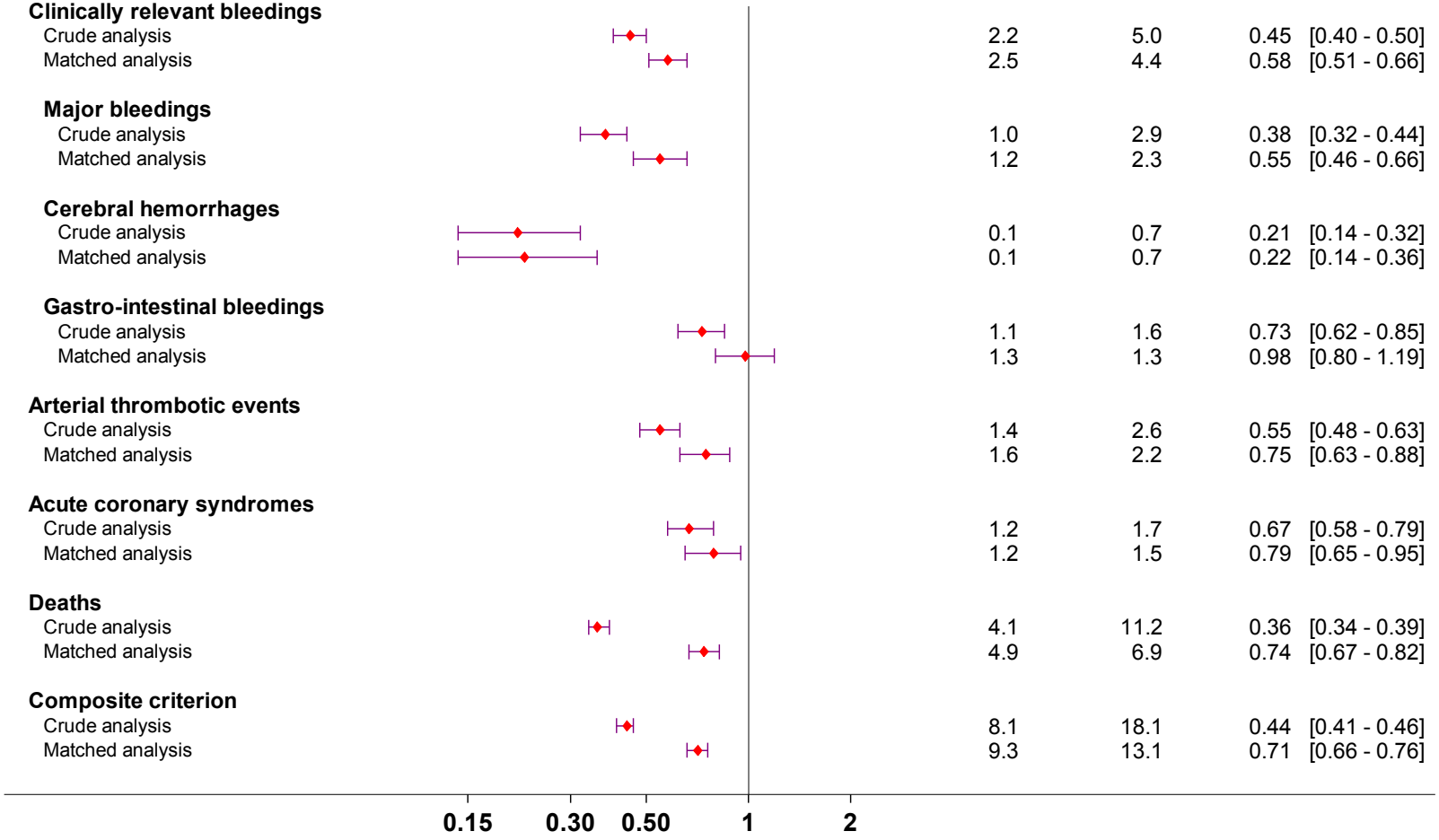
Standardized differences



Standardized differences

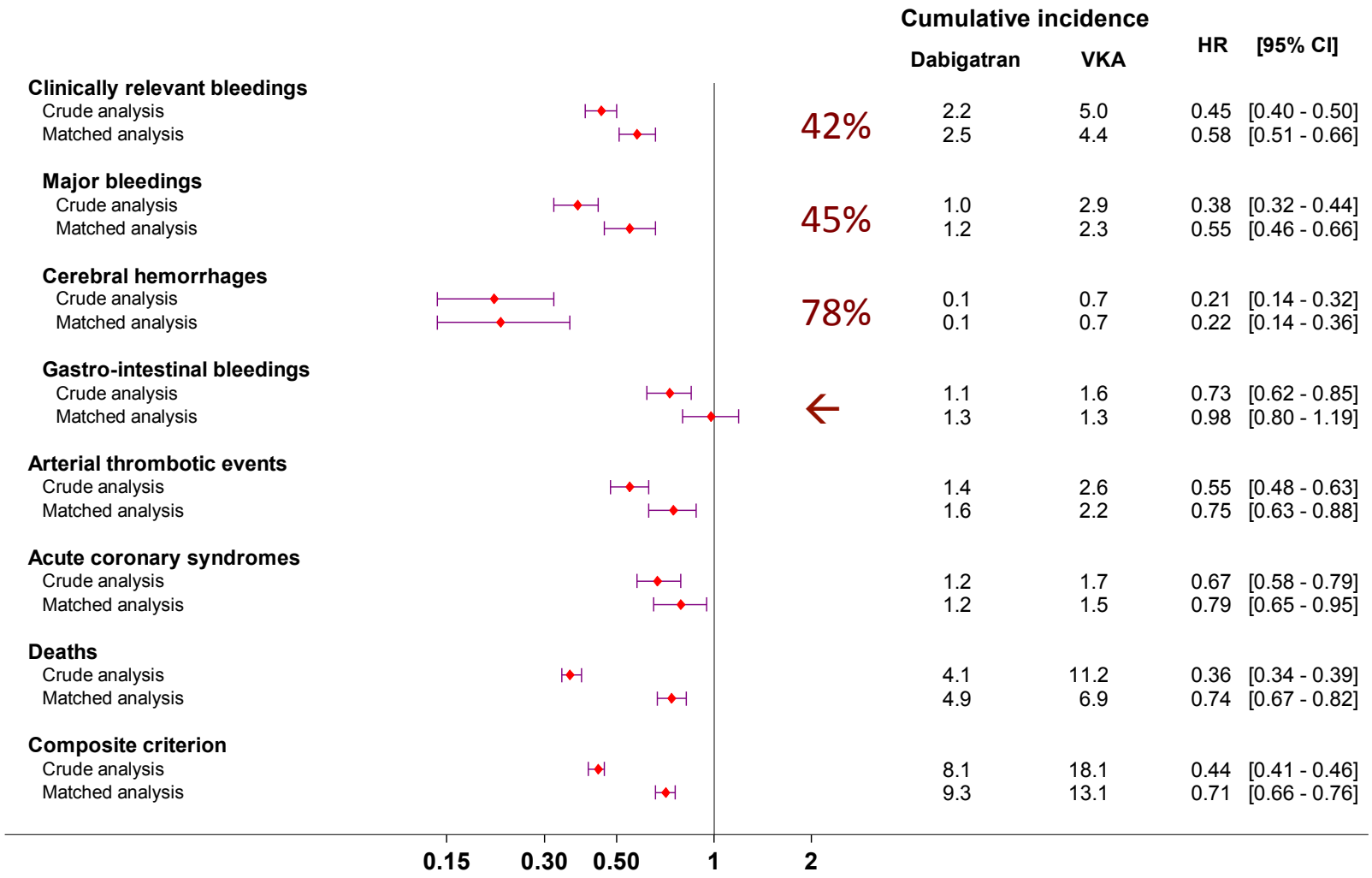


Benefit-risk DOAC versus VKA

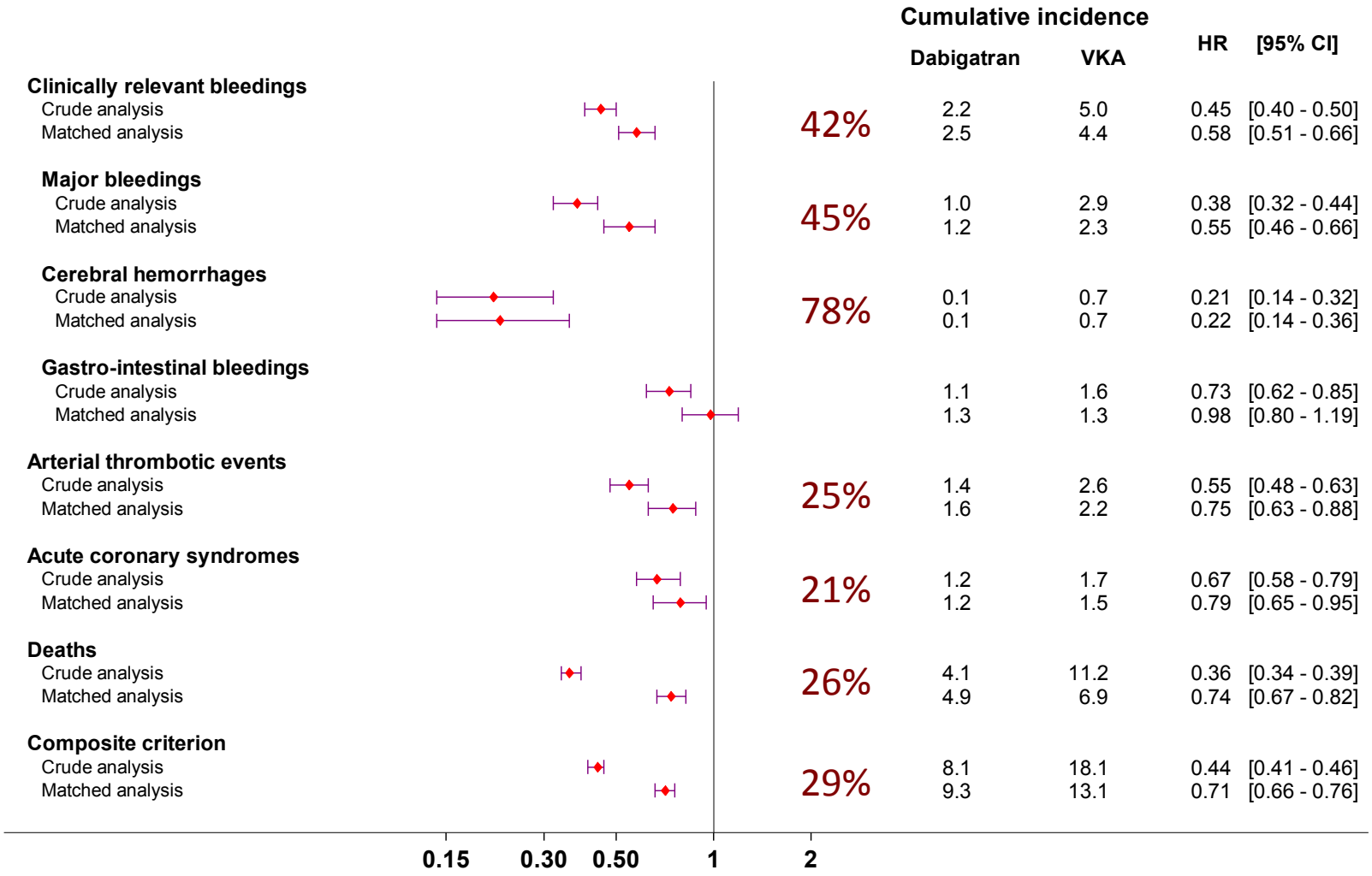


	Cumulative incidence		HR	[95% CI]
	Dabigatran	VKA		
Clinically relevant bleedings				
Crude analysis	2.2	5.0	0.45	[0.40 - 0.50]
Matched analysis	2.5	4.4	0.58	[0.51 - 0.66]
Major bleedings				
Crude analysis	1.0	2.9	0.38	[0.32 - 0.44]
Matched analysis	1.2	2.3	0.55	[0.46 - 0.66]
Cerebral hemorrhages				
Crude analysis	0.1	0.7	0.21	[0.14 - 0.32]
Matched analysis	0.1	0.7	0.22	[0.14 - 0.36]
Gastro-intestinal bleedings				
Crude analysis	1.1	1.6	0.73	[0.62 - 0.85]
Matched analysis	1.3	1.3	0.98	[0.80 - 1.19]
Arterial thrombotic events				
Crude analysis	1.4	2.6	0.55	[0.48 - 0.63]
Matched analysis	1.6	2.2	0.75	[0.63 - 0.88]
Acute coronary syndromes				
Crude analysis	1.2	1.7	0.67	[0.58 - 0.79]
Matched analysis	1.2	1.5	0.79	[0.65 - 0.95]
Deaths				
Crude analysis	4.1	11.2	0.36	[0.34 - 0.39]
Matched analysis	4.9	6.9	0.74	[0.67 - 0.82]
Composite criterion				
Crude analysis	8.1	18.1	0.44	[0.41 - 0.46]
Matched analysis	9.3	13.1	0.71	[0.66 - 0.76]

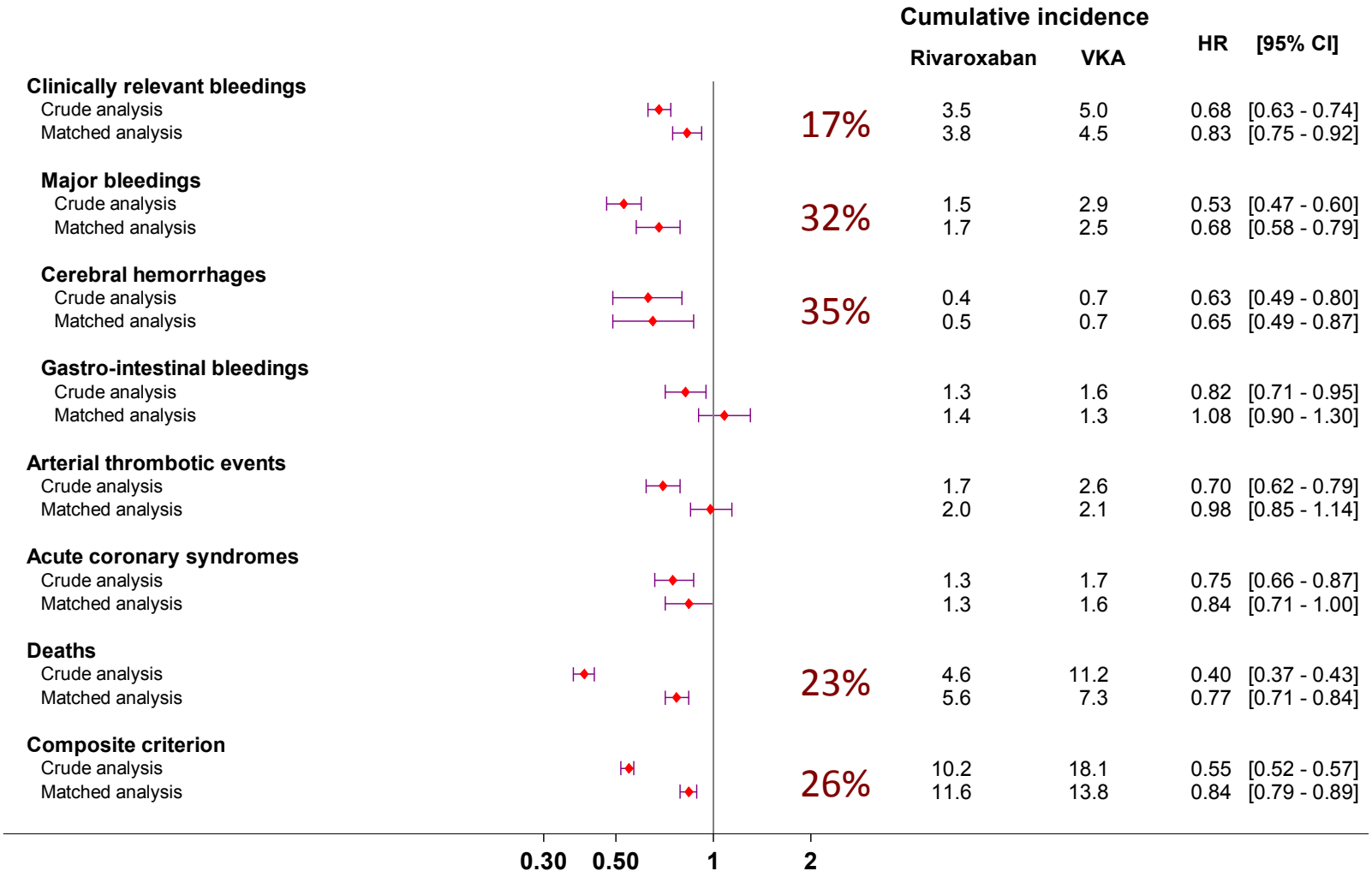
Benefit-risk DOAC versus VKA



Benefit-risk DOAC versus VKA



Benefit-risk DOAC versus VKA



Discussion

- **Strengths**
  - 1-year inclusion of all NVAF patients from nationwide claims database with high specificity of NVAF and outcomes diagnoses, and exhaustive outpatient drug exposure
  - Similar results for the sensitive population and hdPS adjusted analyses with all patients
- **Limits**
  - Inpatient anticoagulant information not available, but short period of time and high probability of same drugs before and/or after hospitalization
  - Lack of clinical and biological information (potential confounders), but hdPS 1:1 matching with a large set of variables, that work together as a proxy for potential confounders not available in the database, limiting the risk of residual confounding

Conclusion

This nationwide cohort study of first users of DOAC or VKA for NVAF shows:

- Different DOAC and VKA prescription patterns in France
- A better safety, death and composite criteria risk profile of both DOAC than VKA, and a better effectiveness profile of dabigatran than VKA, as used in France
- When compared within similar patients in hdPS matched groups, as well as for all patients and adjusted analyses.

Thank you for your attention

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