



Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

Bordeaux
BPE
PharmacoEpi

Utilisation des bases de données de l'assurance maladie pour l'évaluation des performances comparatives des médicaments commercialisés : l'expérience de Bordeaux PharmacoEpi



Pr Nicholas Moore

BORDEAUX PHARMACOEPI

Plateforme de recherche en pharmaco-épidémiologie
Service de Pharmacologie médicale, INSERM CIC1401

université
de BORDEAUX

CHU
Hôpitaux de
Bordeaux

Instituts
thématisques

Inserm
Institut national
de la santé et de la recherche médicale

Adera

Bases de données

- SNIIRAM
 - 66 M personnes
 - remboursements + PMSI + Décès
 - accès « lent »
- EGB : échantillon 1/97
 - 700 000 personnes
 - accès « rapide »

Typologies d'études

- **entrée par la pathologie**
 - validation des diagnostics
 - épidémiologie des maladies
 - populations cibles
 - parcours de soins
 - génération d'alertes

Typologies d'études

- **Partant du traitement**
 - description de l'utilisation
 - quantification du risque
 - performances comparatives

Etudes de performances comparatives

- Validation d'essais cliniques
 - généralisabilité du RCT?
 - retrouve-t'on en vraie vie le résultat du RCT?
- produits non comparés avant AMM
 - produits récents

Etudes de performances comparatives

- A vs. B (et vs.C)
- Dans la même indication
- Identification de l'indication/choix des produits
- identification des produits/choix indication
- identification des patients similaires

Etudes de performances comparatives

Indication



Produits



A B
appariement hdPS

Etudes de performances comparatives

Produits



Indication



appariement hdPS

Deux exemples

- **identification par la pathologie**
 - performances comparatives : **SPACE-AA**
- **identification par la prescription**
 - performances comparatives : **ENGEL**

SPACE-AA

Syndrome coronaire aigü



Antiagrégants plaquettaires

ticagrelor



clopidogrel

ticagrelor



prasugrel

SPACE-AA

- Performance comparées chez les patients traités par antiagrégant plaquetttaire (AAP) après hospitalisation :
 - sélection syndrome coronaire aigu (SCA) + passage en unité de soins intensifs (USI) dans le SNIIRAM
 - identification patients traités par ticagrelor (T), clopidogrel (C) ou prasugrel (P)
 - suivis 1 an
- Evénements cliniques
 - Critères d'**efficacité** :
 - Composite incluant SCA avec passage en USI, AVC, décès
 - Chaque événement du composite
 - Critère de **sécurité** : hémorragies majeures
- Populations appariées sur score de propension haute dimension
 - T vs. C; T vs. P

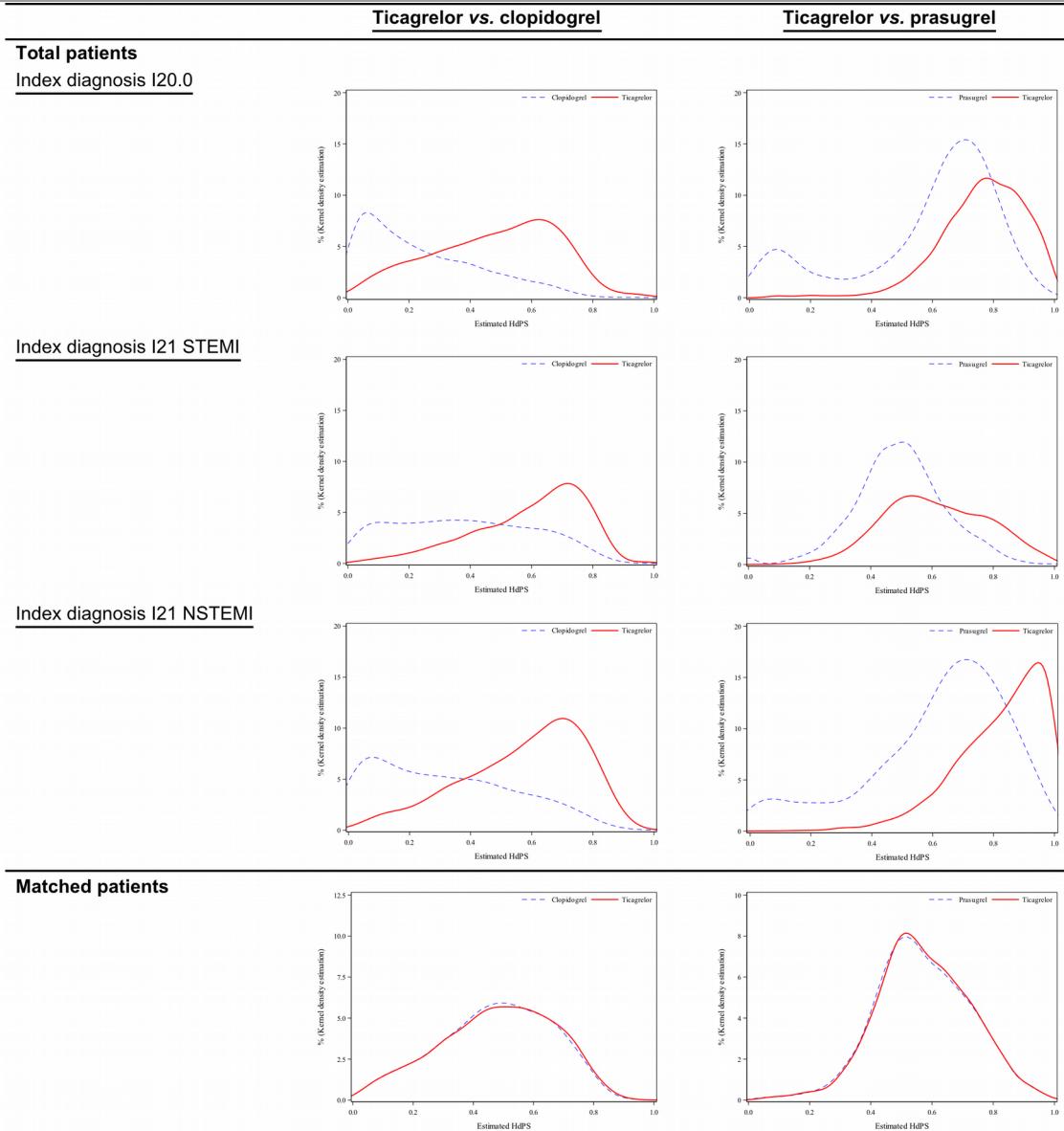
Résultats : Populations

	Population n
Selection criteria	76 844
- First hospitalisation with I20.0 or I21 primary diagnosis	
- Between 1 st January 2013 and 31 December 2013	
- Without history of ACS (I20.0, I21-24) in the 30 days before	
- In a teaching/regional hospital, other public or private hospital	
- With at least one day in an intensive care unit	
Exclusion criteria	22 747
- Index hospitalisation duration = 0 day and alive at discharge	748
- Uncertain identification (several twins or beneficiaries)	68
- Less than 18 years at index date	6
- Less than 365 days of history in SNIRRAM before index date	2 095
- Death during index hospitalisation	3 911
- Alive at discharge and without any reimbursed healthcare in the 365 days after index date	1 888
- Rehabilitation centre in the 30 days after index date	14 031
Study Population	54 097
- Clopidogrel (\pm ASA)	19 796
- Ticagrelor (\pm ASA)	13 916
- Prasugrel (\pm ASA)	8 242
- ASA alone	7 068
- No APA (no dispensation within 30 days after discharge)	5 026
- Others: other APA or association of several APA (\pm ASA)	49
Matched populations	
Ticagrelor versus clopidogrel (per group)	9 224
Ticagrelor versus prasugrel (per group)	6 752

Caractéristiques des populations population totale

	Clopidogrel n = 19796	Prasugrel n = 8242	Ticagrelor n = 13916
Gender male, n (%)	13374 (67.6)	7059 (85.6)	10605 (76.2)
Mean age at index ACS hospitalisation (in years) (± SD)	71.5 (13.1)	58.1 (10.0)	63.4 (12.7)
Primary diagnosis of the index ACS hospitalisation, n (%)			
Unstable angina	8135 (41.1)	1538 (18.7)	3767 (27.1)
STEMI	8237 (41.6)	5969 (72.4)	7642 (54.9)
NSTEMI	3424 (17.3)	735 (8.9)	2507 (18.0)
Procedures performed during index ACS hospitalisation, n (%)			
Percutaneous coronary intervention	13908 (70.3)	7743 (93.9)	12364 (88.8)
Coronary artery bypass graft	153 (0.8)	3 (0.0)	18 (0.1)
Charlson comorbidity index (in categories), n (%)			
[0-1]	560 (2.8)	244 (3.0)	510 (3.7)
[2-3]	3155 (15.9)	3368 (40.9)	4354 (31.3)
[4-5]	5422 (27.4)	2916 (35.4)	4767 (34.3)
[6-7]	5675 (28.7)	1272 (15.4)	2882 (20.7)
>7	4984 (25.2)	442 (5.4)	1403 (10.1)
≥ 1 cardiac risk factors in the previous year, n (%)			
Diabetes mellitus	5371 (27.1)	1705 (20.7)	2808 (20.2)
Hypertension	5561 (28.1)	944 (11.5)	1969 (14.1)
Coronary artery disease	4371 (22.1)	898 (10.9)	1714 (12.3)
Congestive heart failure	1581 (8.0)	153 (1.9)	365 (2.6)
Peripheral arterial disease	1672 (8.4)	238 (2.9)	518 (3.7)
Acute coronary syndrome	2178 (11.0)	441 (5.4)	928 (6.7)
Ischemic or undefined stroke	688 (3.5)	58 (0.7)	200 (1.4)
Major bleeding	551 (2.8)	84 (1.0)	161 (1.2)

Distribution des hdPS



Caractéristiques des populations populations appariées

	Clopidogrel n = 9224	Ticagrelor n = 9224	SD*	Prasugrel n = 6752	Ticagrelor n = 6752	SD*
Gender male, n (%)	6776 (73.5)	6776 (73.5)	0.0	5732 (84.9)	5732 (84.9)	0.0
Mean age at index ACS hospitalisation (in years) (± SD)	66.5 (12.4)	66.5 (12.4)	0.0	58.5 (10.0)	58.4 (10.0)	0.0
Primary diagnosis of the index ACS hospitalisation, n (%)						
Unstable angina	2894 (31.4)	2894 (31.4)	0.0	1246 (18.5)	1246 (18.5)	0.0
STEMI	4730 (51.3)	4730 (51.3)	0.0	4917 (72.8)	4917 (72.8)	0.0
NSTEMI	1600 (17.3)	1600 (17.3)	0.0	589 (8.7)	589 (8.7)	0.0
Procedures during index ACS hospitalisation, n (%)						
Percutaneous coronary intervention	7810 (84.7)	7793 (84.5)	-0.5	6365 (94.3)	6382 (94.5)	1.1
Coronary artery bypass graft	19 (0.2)	14 (0.2)	-	1 (0.0)	0 (0.0)	-
Charlson comorbidity index (in categories), n (%)						
[0-1]	314 (3.4)	325 (3.5)	0.7	218 (3.2)	198 (2.9)	-1.7
[2-3]	2202 (23.9)	2315 (25.1)	2.8	2805 (41.5)	2729 (40.4)	-2.3
[4-5]	3170 (34.4)	3014 (32.7)	-3.6	2337 (34.6)	2604 (38.6)	8.2
[6-7]	2275 (24.7)	2302 (25.0)	0.7	1030 (15.3)	971 (14.4)	-2.5
>7	1263 (13.7)	1278 (13.7)	0.2	362 (5.4)	250 (3.7)	-8.0
≥1 cardiac risk factors in the previous year, n (%)						
Diabetes mellitus	2071 (22.5)	2002 (21.7)	-1.8	1303 (19.3)	1183 (17.5)	-4.6
Hypertension	1654 (17.9)	1583 (17.2)	-2.0	683 (10.1)	602 (8.9)	-4.1
Coronary artery disease	1253 (13.6)	1284 (13.9)	1.0	578 (8.6)	604 (8.9)	1.4
Congestive heart failure	315 (3.4)	300 (3.3)	-0.9	103 (1.5)	100 (1.5)	-0.4
Peripheral arterial disease	422 (4.6)	431 (4.7)	0.5	178 (2.6)	184 (2.7)	0.6
Acute coronary syndrome	652 (7.1)	669 (7.3)	0.7	262 (3.9)	300 (4.4)	2.8
Ischemic or undefined stroke	192 (2.1)	158 (1.7)	-2.7	46 (0.7)	62 (0.9)	-
Major bleeding	142 (1.5)	130 (1.4)	-1.1	62 (0.9)	61 (0.9)	-1.1

* Standardized difference

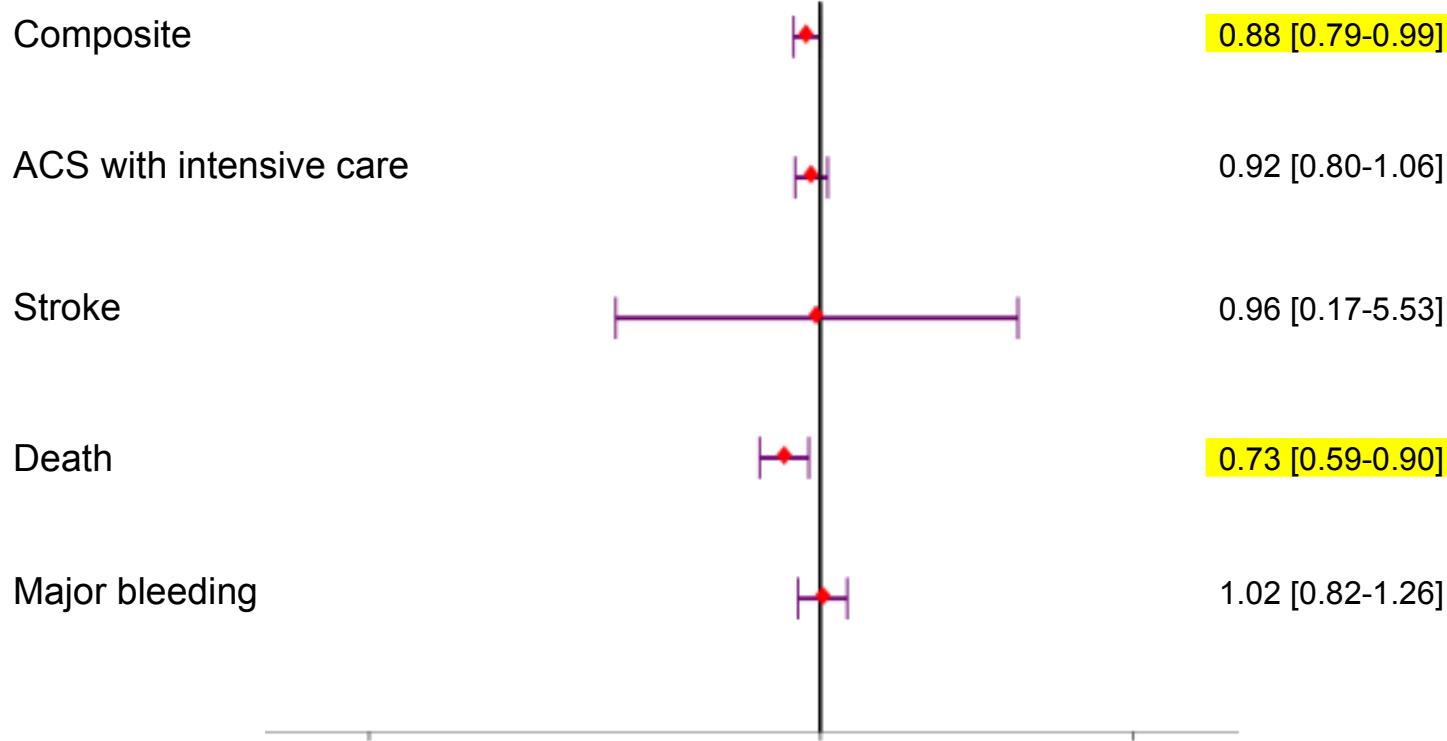
Incidence cumulée à 1 an des événements durant l'exposition au traitement AAP

	Ticagrelor vs. clopidogrel n=9224 per group				Ticagrelor vs. prasugrel n=6752 per group			
	Events, n		Cumulative incidence (%)		Events, n		Cumulative incidence (%)	
	T	C	T	C	T	P	T	P
Composite	551	658	7.2	8.2	294	306	5.0	5.1
ACS with ICU	376	432	4.9	5.4	221	226	3.8	3.8
Stroke	41	46	0.6	0.6	14	26	0.2	0.4
Death	150	217	2.1	2.8	64	61	1.1	1.0
Major bleeding	170	163	2.2	2.2	73	76	1.3	1.3

Efficacité et sécurité du ticagrelor

Ticagrelor versus clopidogrel

Outcomes



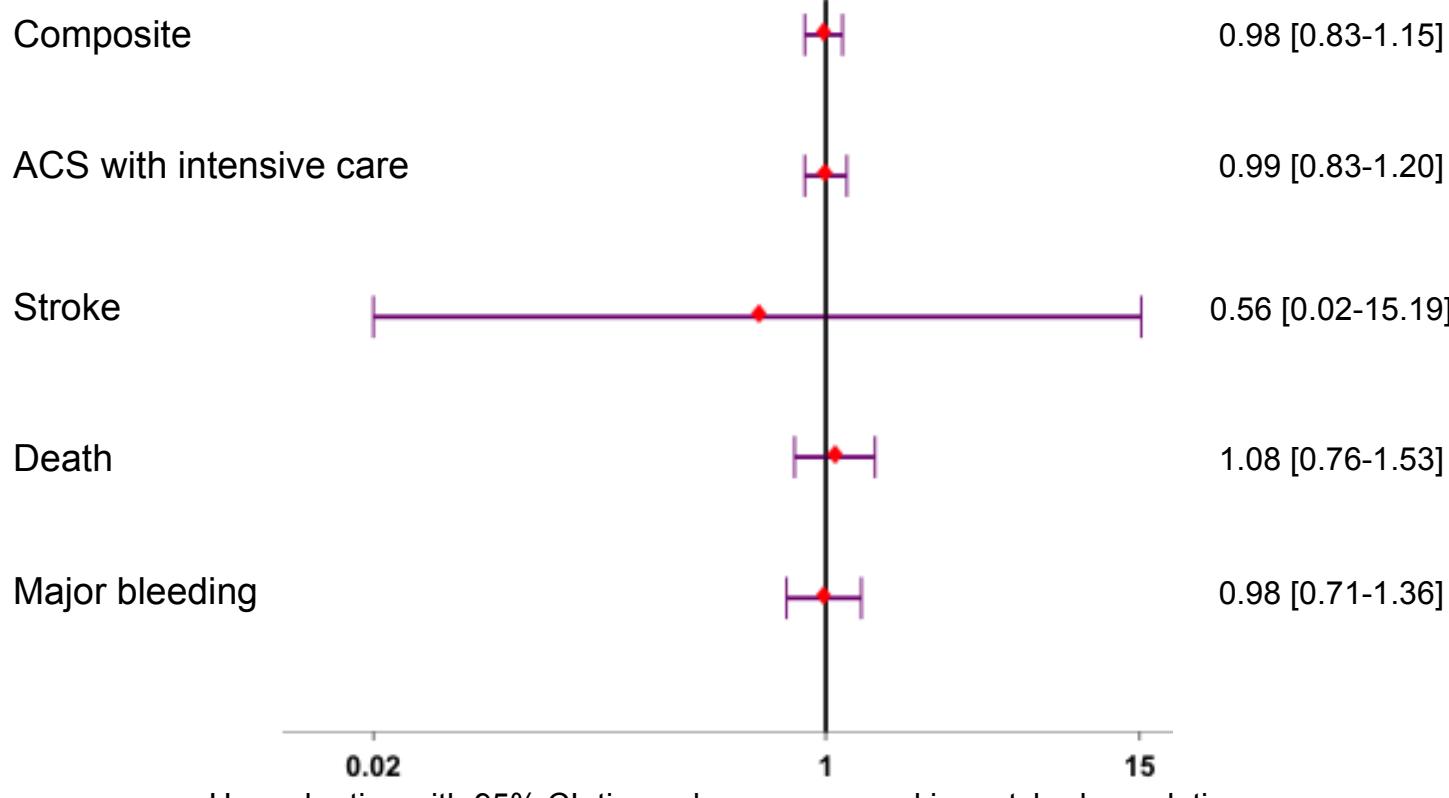
Hazard ratios with 95% CI, ticagrelor vs. clopidogrel in matched populations

⬆️ Différence en faveur du ticagrelor par rapport au clopidogrel

Efficacité et sécurité du ticagrelor

Ticagrelor versus prasugrel

Outcomes



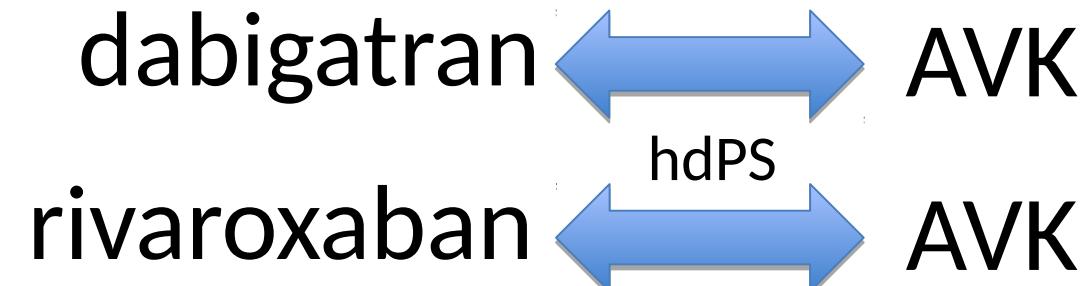
■ Pas de différence entre ticagrelor et prasugrel

ENGEL

Dispensation d'anticoagulant



Fibrillation auriculaire non valvulaire



ENGEL 2

- Performance comparées de deux anticoagulants directs (DOAC), *versus* AVK
- Sélection sur première dispensation d'anticoagulant
 - patients avec FA non valvulaire
 - « New user design »
- Cohorte de patients identifiés dans le SNIIRAM
 - initiant un traitement par Dabigatran, Rivaroxaban, ou AVK en 2013 avec 3 ans d'historique et suivi jusqu'à fin 2016

Critères d'évaluation

- Hospital admissions for
 - Bleeding: Clinically Relevant Bleeding (CRB)
 - major bleeding, GI bleeding, intracerebral hemorrhage,...
 - Arterial Thrombotic Events (ATE) incl. stroke
 - Acute Coronary Syndrome (ACS)
- Death (all-cause)
- Composite criterion (CRB, ATE, ACS or death)

Populations

First drug (dabigatran, rivaroxaban or VKA) dispensation in 2013
without a three-year history of DOAC (dabigatran, rivaroxaban, apixaban) or VKA dispensation
n = 371539

- Missing or incorrect data (age, death date)	n = 701 (0.2%)
- < 18 years at index date	n = 888 (0.2%)
- At least two treatment groups at index date	n = 151 (0.04%)
- Death at index date	n = 98 (0.03%)
- Uncertain identification (several twins or beneficiaries)	n = 732 (0.2%)
- < 3 years history in the SNIIRAM before index date	n = 12610 (3.4%)
- Alive at index date without complete follow-up	n = 284 (0.1%)
- Other probable indications	n = 86857 (23.4%)
- Valvular disease history before index date	n = 25509 (6.9%)
- No atrial fibrillation (neither LTD nor hospitalization nor procedure)	n = 140608 (37.8%)

NVAF population
n = 103101 (27.7%)

Dabigatran
n = 27060 (26.2%)

VKA
n = 44653 (43.3%)

Rivaroxaban
n = 31388 (30.4%)

Matched patients
Dabigatran -VKA
n = 20489 (19.9%)

Matched patients
Rivaroxaban -VKA
n = 23053 (22.4%)

Caractéristiques des patients population totale

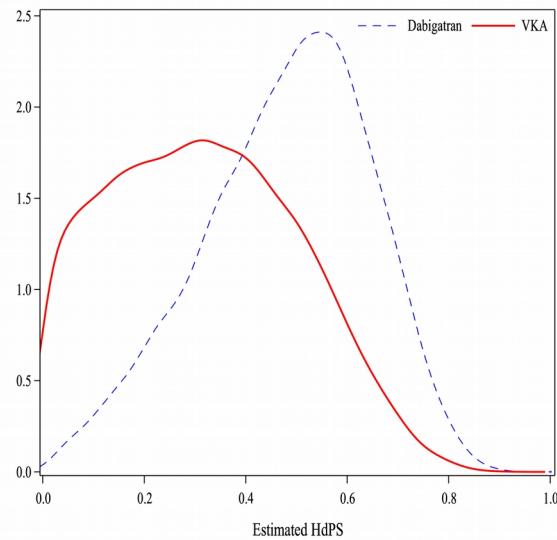
	Dabigatran n = 27060	Rivaroxaban n = 31388	VKA n = 44653
Male, n (%)	15253 (56.4)	17653 (56.2)	22868 (51.2)
Age at index date (SD)	73.2 (11.8)	73.2 (11.8)	77.9 (11.1)
CHA₂DS₂-VASc score			
0	2381 (8.8)	2667 (8.5)	1518 (3.4)
1	3750 (13.9)	4520 (14.4)	3171 (7.1)
≥ 2	20929 (77.3)	24201 (77.1)	39964 (89.5)
HAS-BLED score			
0	2703 (10.0)	2965 (9.4)	1318 (3.0)
1	7536 (27.8)	8828 (28.1)	7776 (17.4)
2	9649 (35.7)	11432 (36.4)	15473 (34.7)
3	5594 (20.7)	6319 (20.1)	13399 (30.0)
> 3	1578 (5.8)	1844 (5.9)	6687 (15.0)
Low-dose use* (%)	57.4	35.7	N/A

Incidence cumulée à 1 an des événements population totale

	Dabigatran n = 15903 PY ¹	Rivaroxaban n = 19681 PY ¹	VKA n = 27242 PY ¹
Clinically relevant bleeding (CRB)	2.7 [2.4; 2.9]	4.0 [3.7; 4.3]	6.1 [5.9; 6.4]
Haemorrhagic stroke	0.2 [0.1; 0.2]	0.5 [0.4; 0.6]	0.8 [0.7; 0.9]
Gastro-intestinal bleeding	1.3 [1.2; 1.5]	1.5 [1.3; 1.7]	1.9 [1.7; 2.1]
Major bleeding	1.3 [1.1; 1.4]	1.8 [1.6; 1.9]	3.4 [3.2; 3.7]
Arterial thrombotic events (ATE)	1.6 [1.4; 1.8]	2.1 [1.9; 2.3]	3.1 [2.9; 3.3]
Acute coronary syndrome (ACS)	1.4 [1.2; 1.6]	1.5 [1.3; 1.7]	2.1 [1.9; 2.3]
Death (all-cause)	4.7 [4.4; 5.1]	5.1 [4.8; 5.4]	13.1 [12.7; 13.5]
Composite criterion (death, CRB, ATE, ACS)	9.7 [9.2; 10.1]	11.8 [11.4; 12.3]	21.9 [21.4; 22.4]

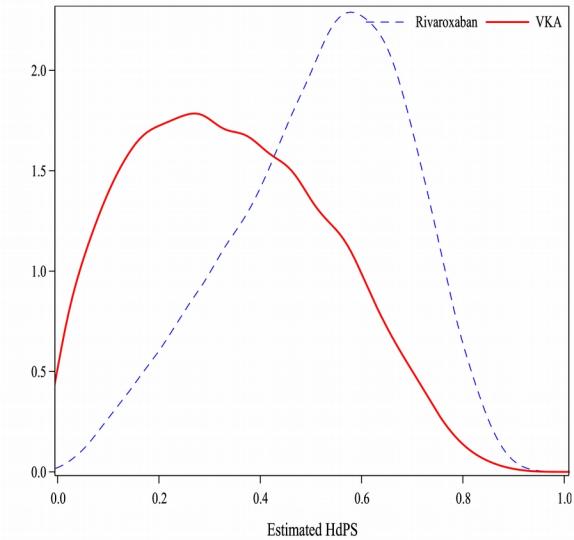
HdPS distribution

Dabigatran versus VKA

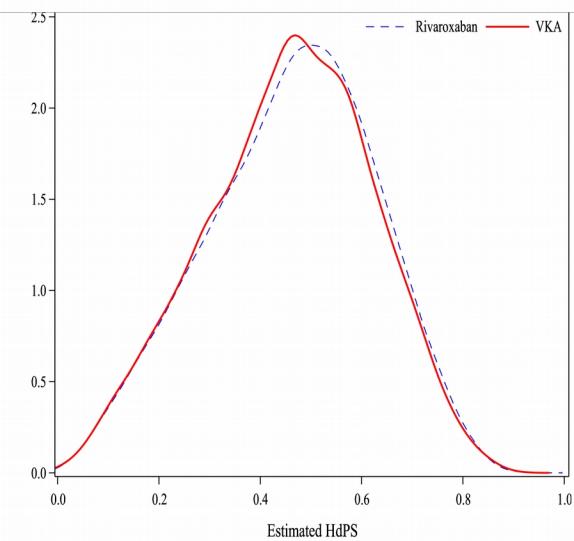
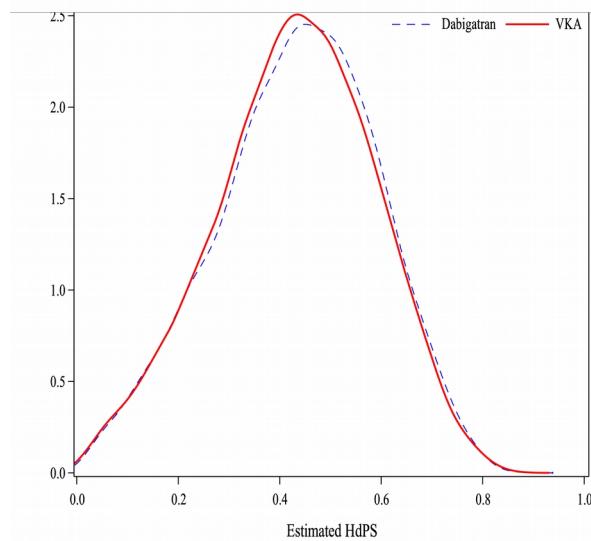


All patients

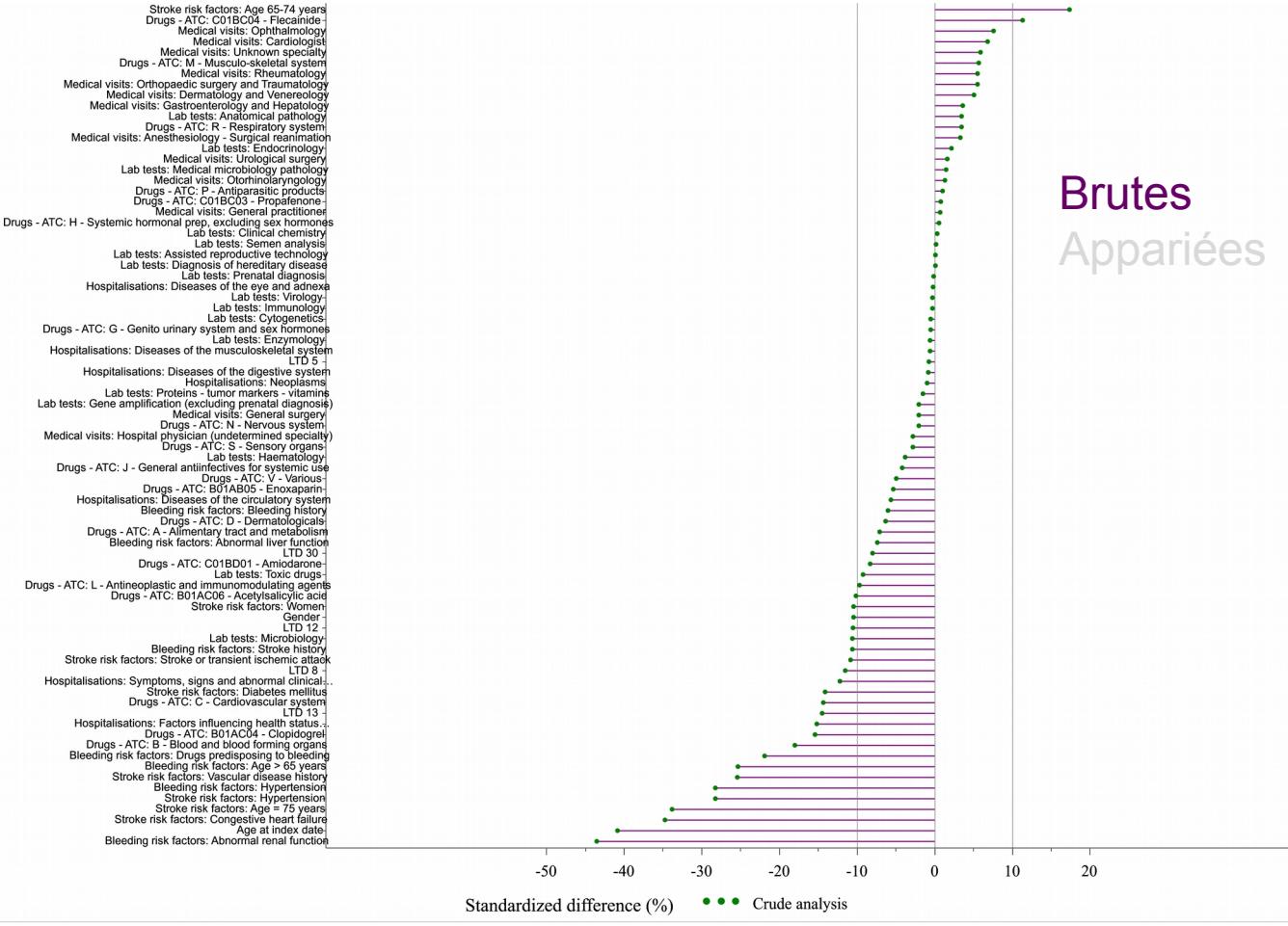
Rivaroxaban versus VKA



Matched patients

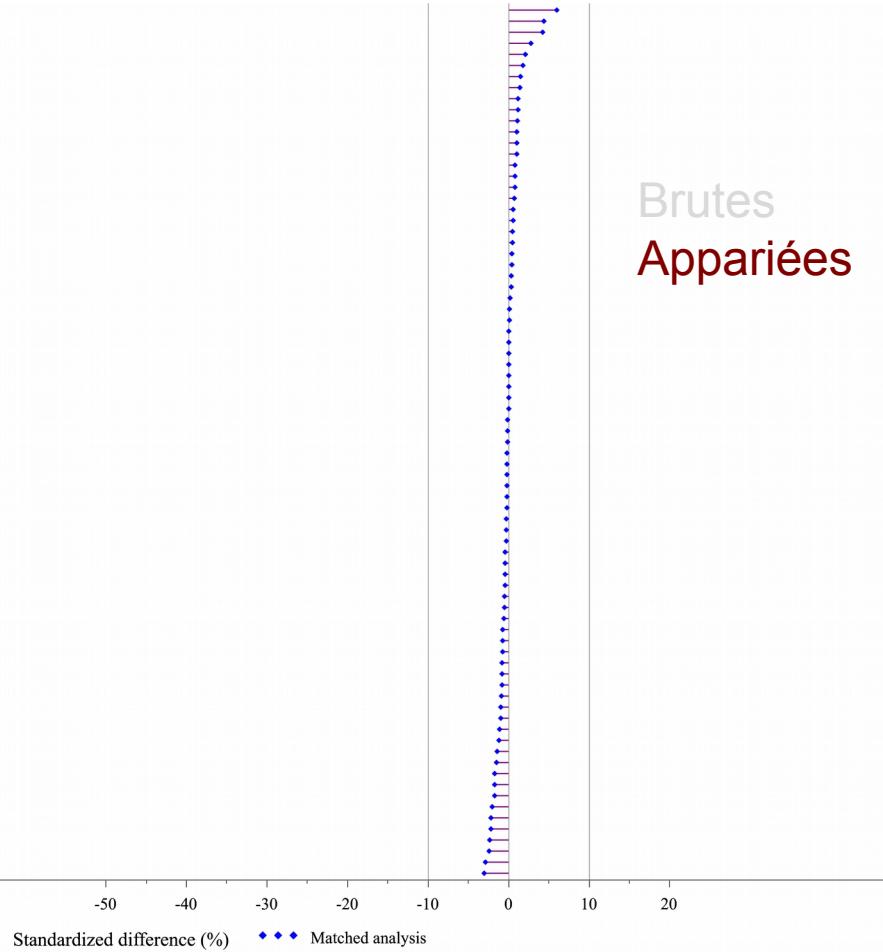


Différences standardisées



Différences standardisées

Hospitalisations: Diseases of the circulatory system
 Lab tests: Endocrinology
 Medical visits: Anesthesiology - Surgical reanimation
 Medical visits: Cardiology
 Medical visits: Orthopaedic and Traumatology
 Lab tests: Microbiology
 Drugs - ATC: G - Genito urinary system and sex hormones
 Drugs - ATC: M - Musculo-skeletal system
 Medical visits: Urological surgery
 Lab tests: Clinical chemistry
 Drugs - ATC: R - Respiratory system
 Drugs - ATC: S - Senses organs
 Lab tests: Enzymology
 Medical visits: Rheumatology
 Drugs - ATC: C01BC04 - Flecainide-
 Lab tests: Allergology
 Medical visit: General practitioner
 Drugs - ATC: B - Blood and blood forming organs
 Medical visits: Orthinolaryngology
 Hospitalisations: Symptoms, signs and abnormal clinical-..
 Lab tests: Biochemistry, endocrinology
 Stroke risk factors: Age 65-74 years
 Medical visits: Dermatology and Venereology
 Drugs - ATC: B01AC06 - Acetylsalicylic acid
 Medical visits: General surgery
 Medical visits: Gastroenterology and Hepatology
 Lab tests: Assisted reproductive technology
 Lab tests: Diagnosis of hereditary disease
 Drugs - ATC: S - Senses organs and anesthe-
 Bleeding risk factors: Age > 65 years
 Stroke risk factors: Women
 Stroke risk factors: Stroke or transient ischemic attack
 Other
 Lab tests: Virology
 Drugs - ATC: C01BD01 - Amiodarone
 Stroke risk factors: Age = 75 years
 Lab tests: Biochemistry, endocrinology
 Lab tests: Protein - tumor markers - vitamins
 Medical visits: Unknown specialty
 Bleeding risk factors: Abnormal liver function
 Hospitalisations: Diseases of the digestive system
 Lab tests: Toxic drugs
 Drugs - ATC: P - Antiparasitic products
 Drugs - ATC: C01BC03 - Propafenone
 Lab tests: Cytogenetics
 Hospitalisations: Diseases of the eye and ear
 Hospitalisations: Neoplasms
 LTD 5 -
 Drugs - ATC: B01AC04 - Clopidogrel
 Bleeding risk factors: Bleeding history
 Lab tests: Gene amplification (excluding prostate diagnosis)
 Bleeding risk factors: Drugs predisposing to bleeding
 Stroke risk factors: Vascular disease history
 LTD 12 -
 Lab tests: Haemostasis
 Hospitalisations: Diseases of the musculoskeletal system
 LTD 13 -
 Bleeding risk factors: Bleeding history
 Medical visits: Hospital physician (undetermined specialty)
 Drugs - ATC: A - Alimentary tract and metabolism
 Drugs - ATC: H - Systemic hormonal prep, excluding sex hormones
 Drugs - ATC: J - General antinefectives for systemic use
 Stroke risk factors: Congestive heart failure
 LTD 19 -
 Drugs - ATC: D - Dermatologicals
 Bleeding risk factors: Hypertension
 Stroke risk factors: Hypertension
 Hospitalisations: Factors influencing health status..
 LTD 30 -
 Drugs - ATC: L - Antineoplastic and immunomodulating agents
 Bleeding risk factors: Abnormal renal function
 Drugs - ATC: C - Cardiovascular system
 Stroke risk factors: Diabetes mellitus

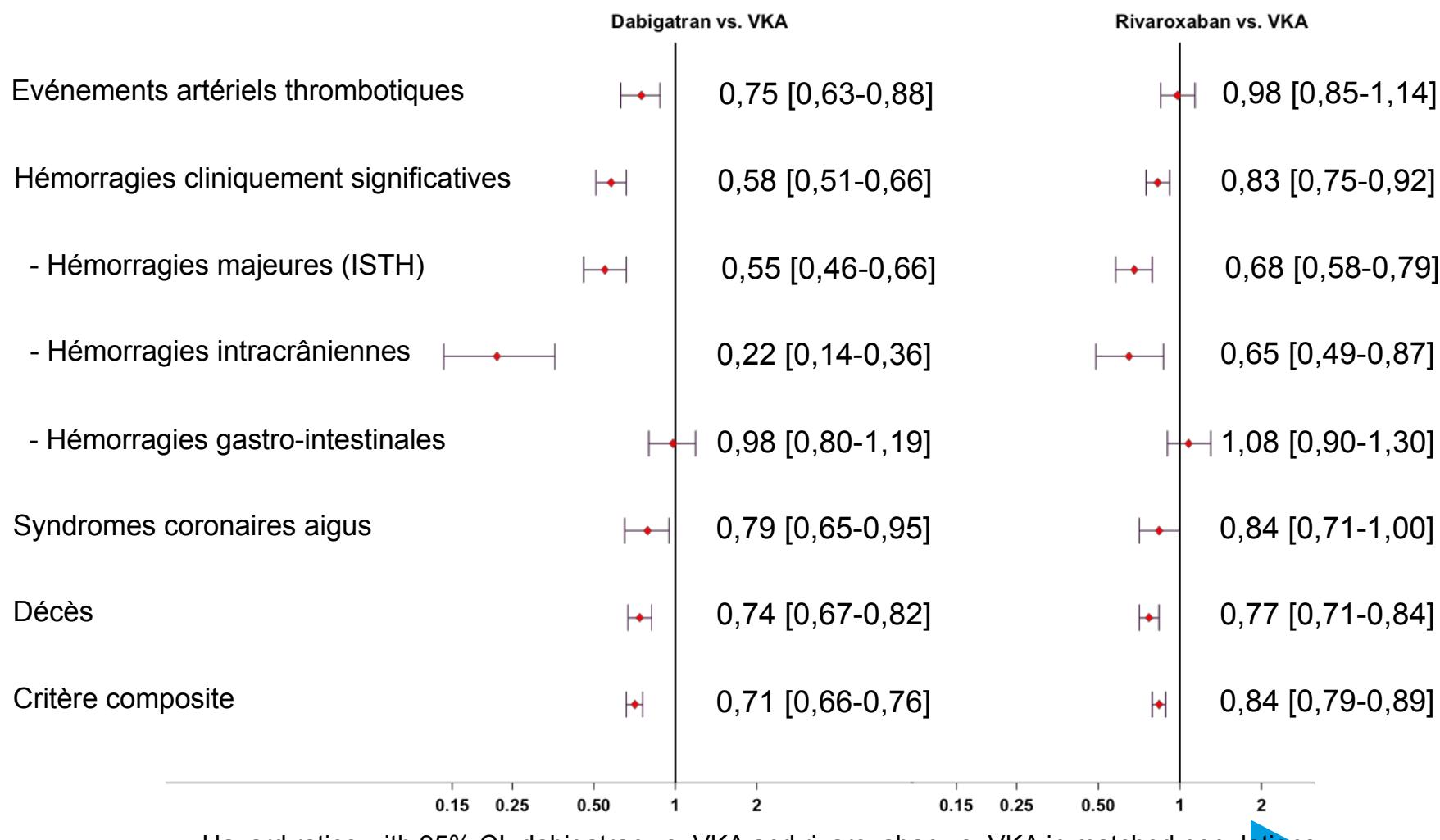


Caractéristiques des patients population appariée

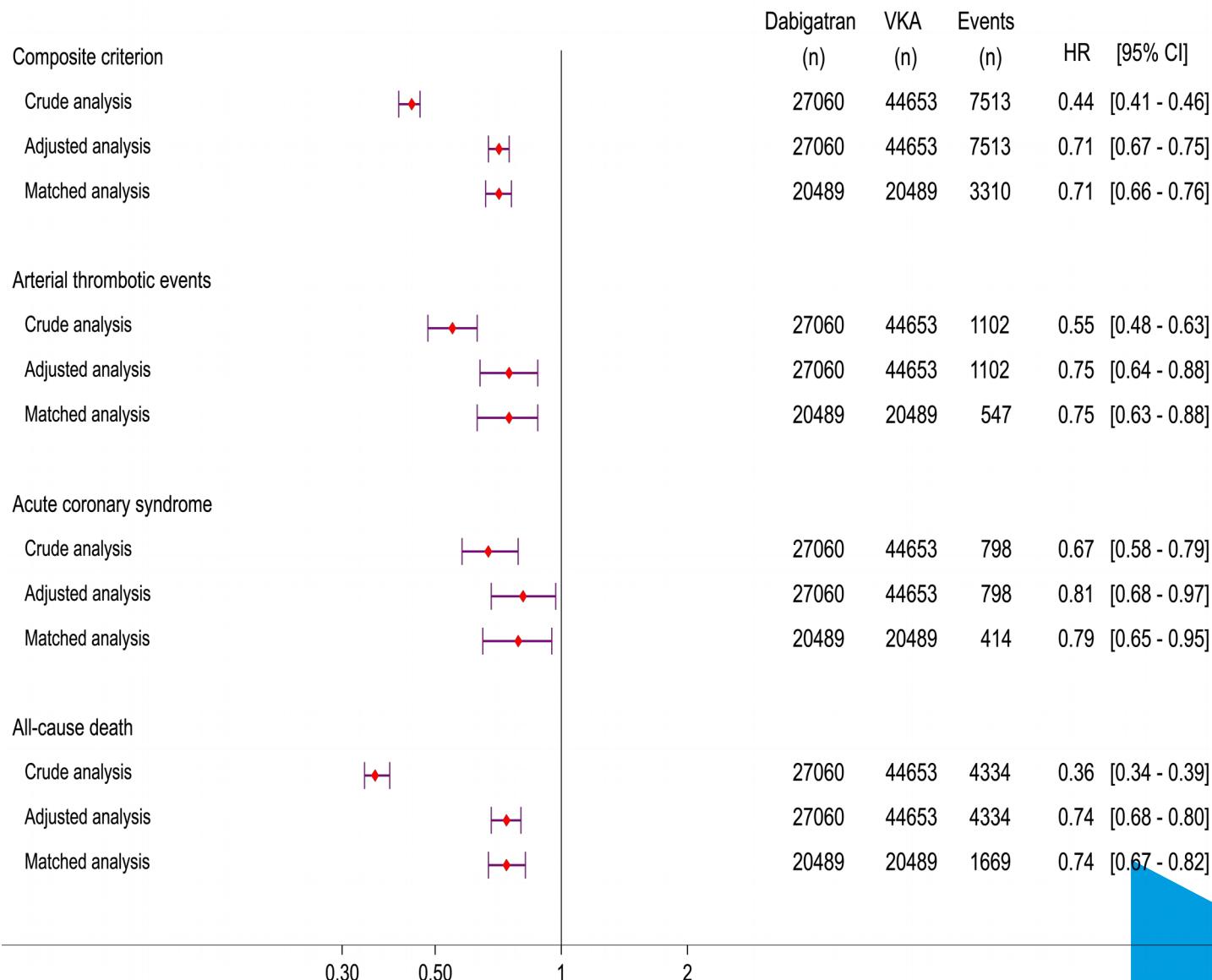
	Dabigatran n = 20489	VKA n = 20489	Rivaroxaban n = 23053	VKA n = 23053
Male, n (%)	11164 (54.5)	11164 (54.5)	12557 (54.5)	12557 (54.5)
Age	75.3 (10.7)	75.4 (10.7)	75.6 (10.7)	75.6 (10.7)
CHA₂DS₂-VASc				
0	1192 (5.8)	1183 (5.8)	1237 (5.4)	1268 (5.5)
1	2255 (11.0)	2196 (10.7)	2522 (10.9)	2451 (10.6)
≥ 2	17042 (83.2)	17110 (83.5)	19294 (83.7)	19334 (83.9)
HAS-BLED				
0	1251 (6.1)	1079 (5.3)	1330 (5.8)	1093 (4.7)
1	5078 (24.8)	4968 (24.2)	5579 (24.2)	5543 (24.0)
2	7714 (37.6)	7980 (38.9)	8931 (38.7)	9047 (39.2)
3	4960 (24.2)	4999 (24.4)	5457 (23.7)	5671 (24.6)
> 3	1486 (7.3)	1463 (7.1)	1756 (7.6)	1699 (7.4)

Bénéfice-risque AOD versus AVK

Population appariée



Dabigatran versus VKA



Etudes de sécurité comparative

Evenement d'intérêt



Expositions

Cas-population

Cas-témoin

Cas propre témoin

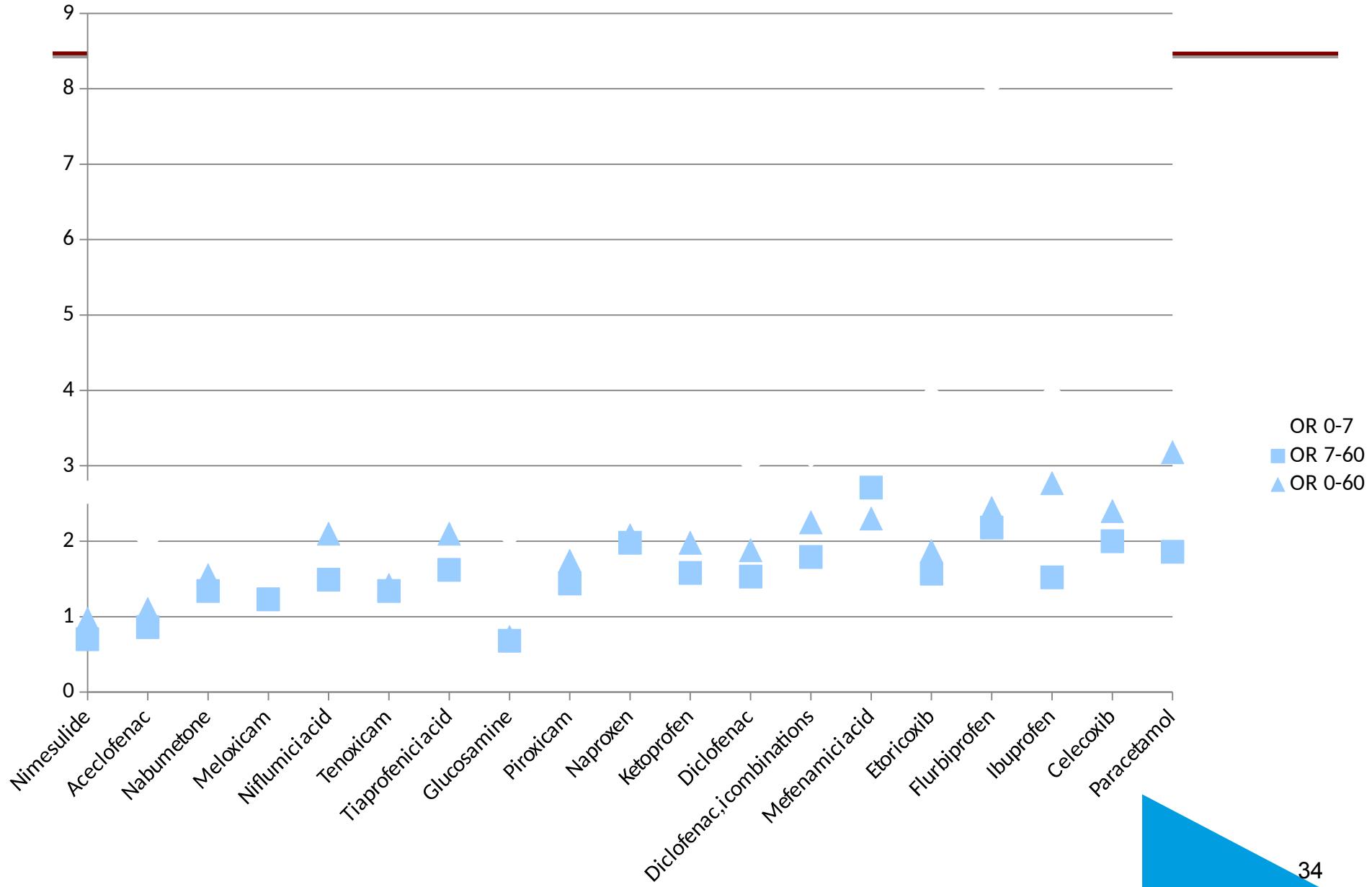
EPIHAM

- Selection sur l'événement:
 - hépatite aigue hospitalisée
 - non virale, non alcoolique, etc...
- expositions préalables
 - 0-60 jours
 - 0-7 jours(biais protopathique)
 - 7-60 jours

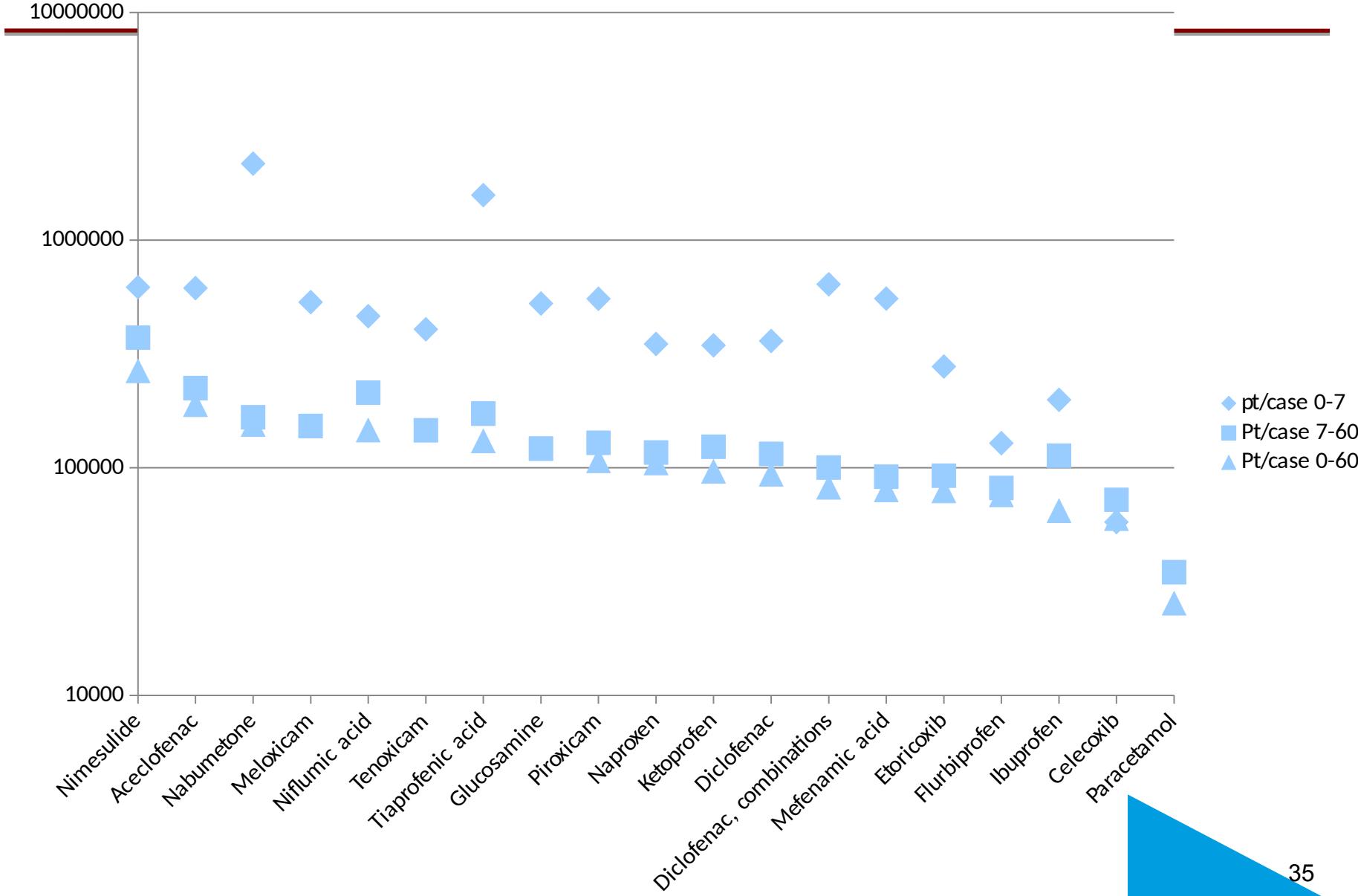
EPIHAM

- In SNIIRAM: cases
- In EGB: controls, population
- 1/1/2010 - 31/12/2014
- Analysis
 - case-population
 - case-control
 - case-crossover

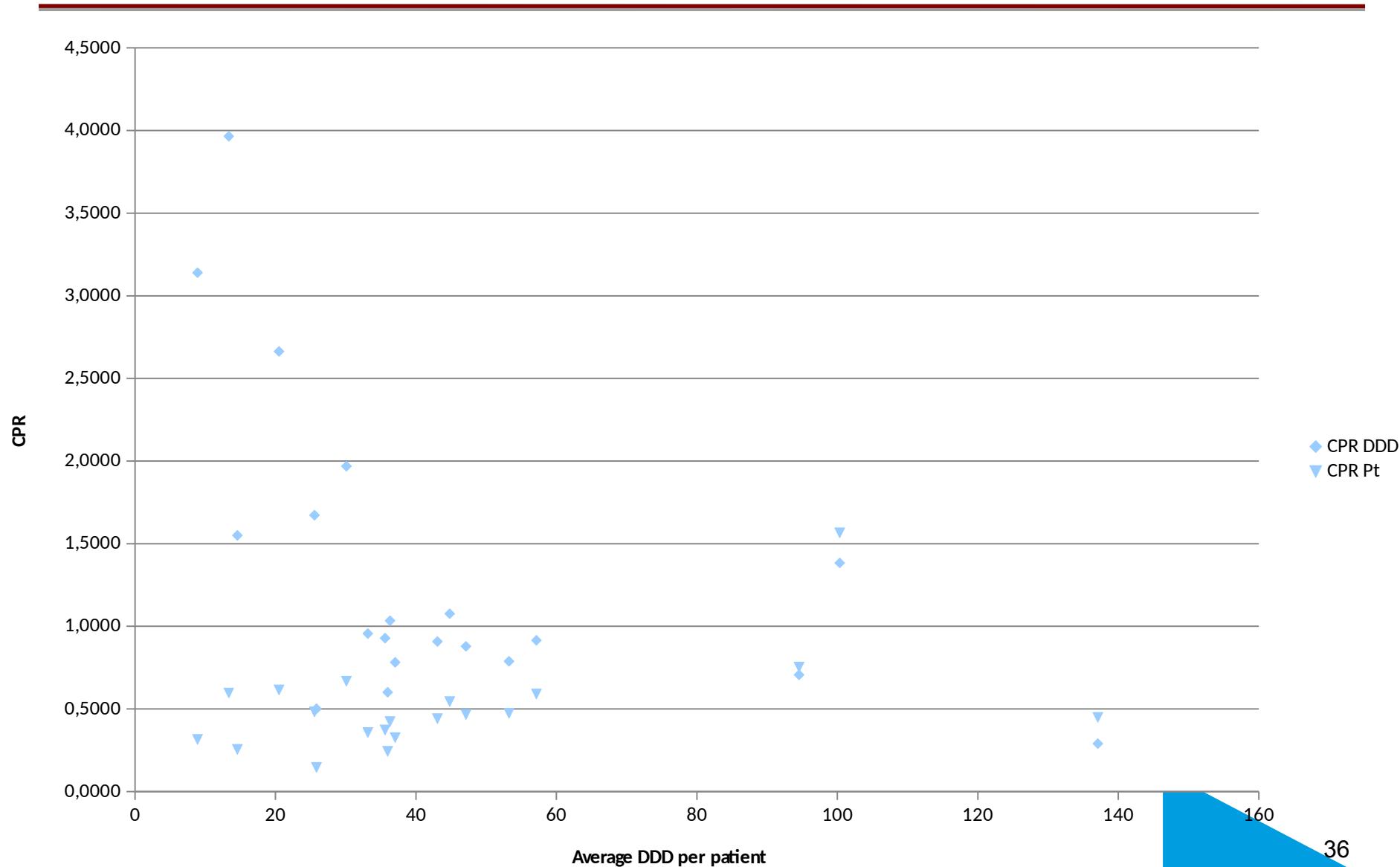
case-control Odds Ratios



Cas-Pop Number of patients/case

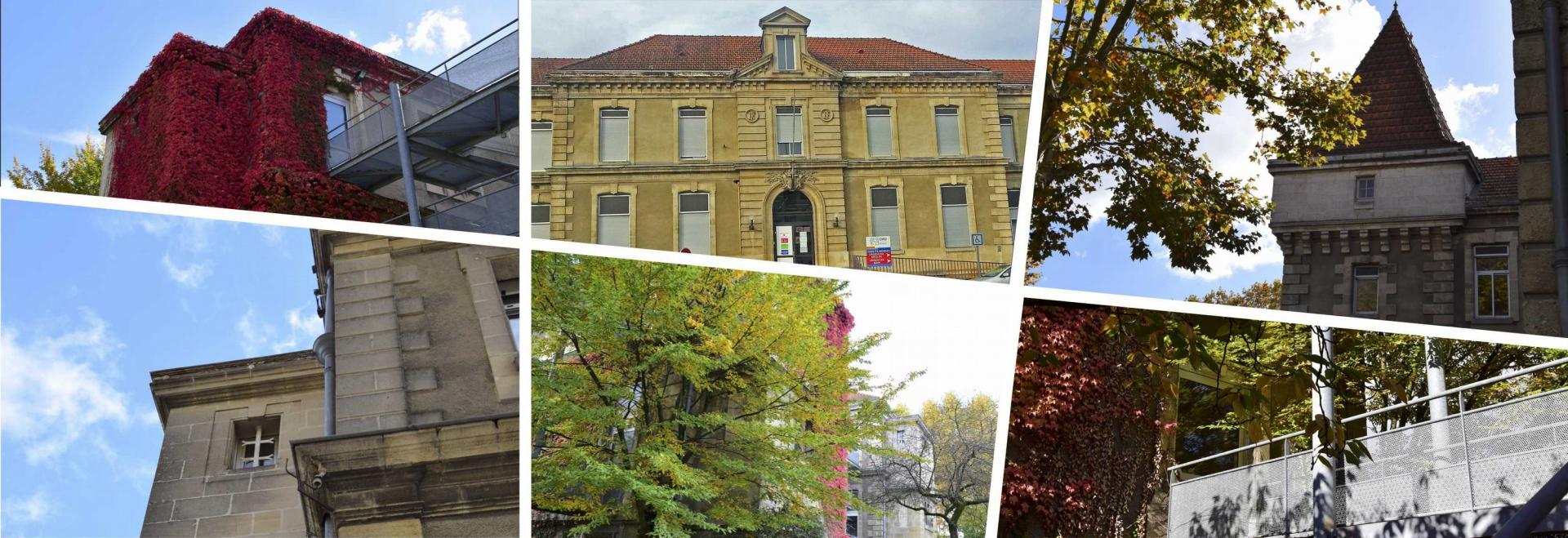


CPR per DDD vs per Pt: 7-60



Conclusion

- des données superbes
- une puissance inégalée
- mais nécessite un peu de maîtrise
 - des données
 - de l'analyse



Merci pour votre attention



Nicholas.moore@u-bordeaux.fr, <http://www.pharmacoepi.eu>

Bordeaux PharmacoEpi

Plateforme de recherche en Pharmaco-épidémiologie

Service de Pharmacologie médicale, 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