Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

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

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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

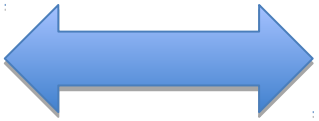
- A vs. B (et vs.C)
- Dans la même indication

- Identification de l'indication/choix des produits
- identification des produits/choix indication
- identification des patients similaires

Etudes de performances comparatives

Indication

Produits

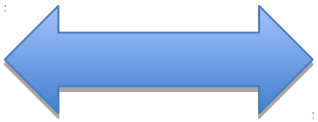
A  B

appariement hdPS

Etudes de performances comparatives

Produits

Indication

A  B

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

hdPS

ticagrelor ⟷ prasugrel

SPACE-AA

- Performance comparées chez les patients traités par antiagrégant plaquettaire (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

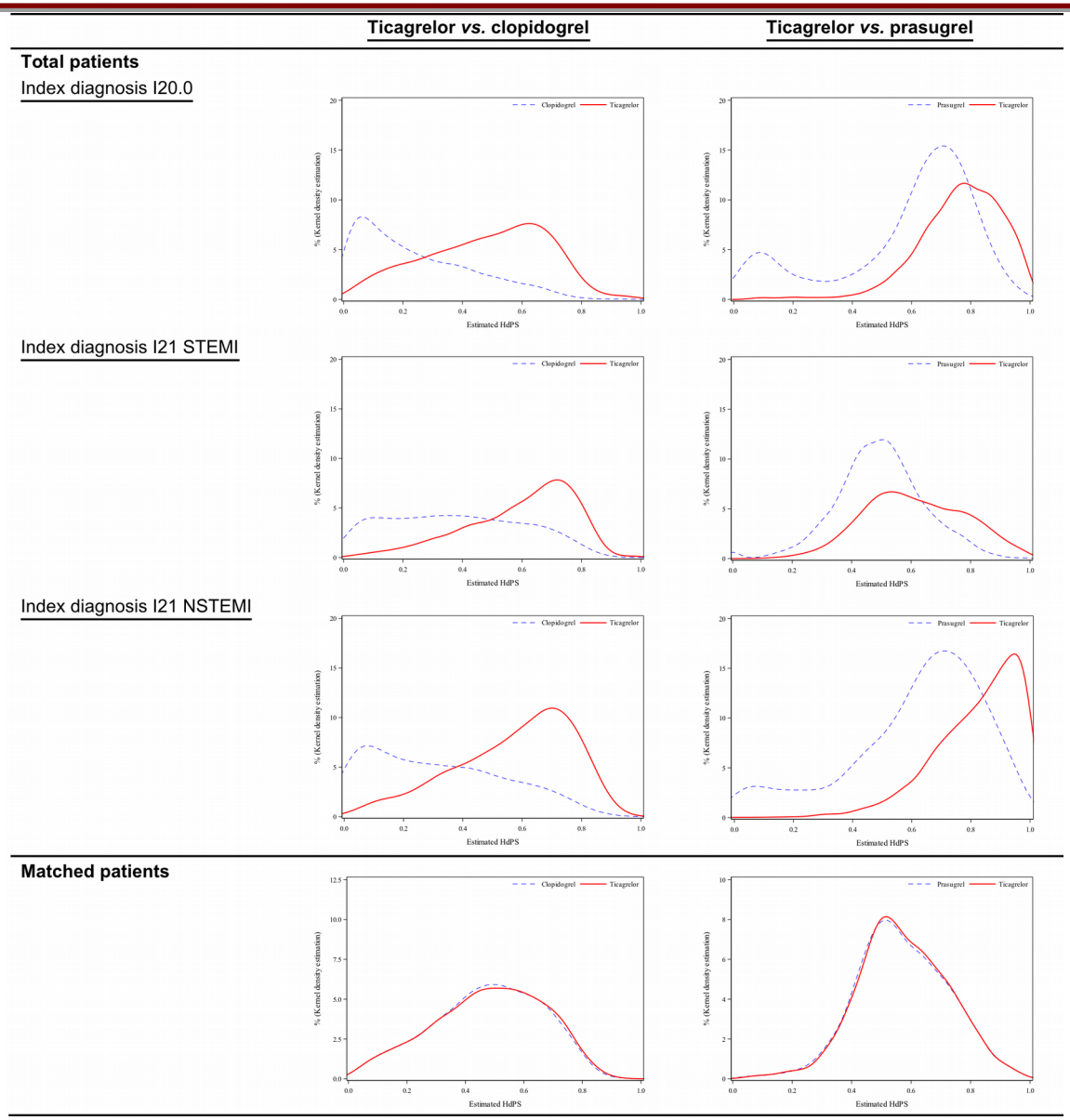
Résultats : Populations

	Population n
Selection criteria	**76 844**
- First hospitalisation with I20.0 or I21 primary diagnosis - Between 1st 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 SNIIRAM 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 (± ASA)	**19 796**
- Ticagrelor (± ASA)	**13 916**
- Prasugrel (± 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 (± 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

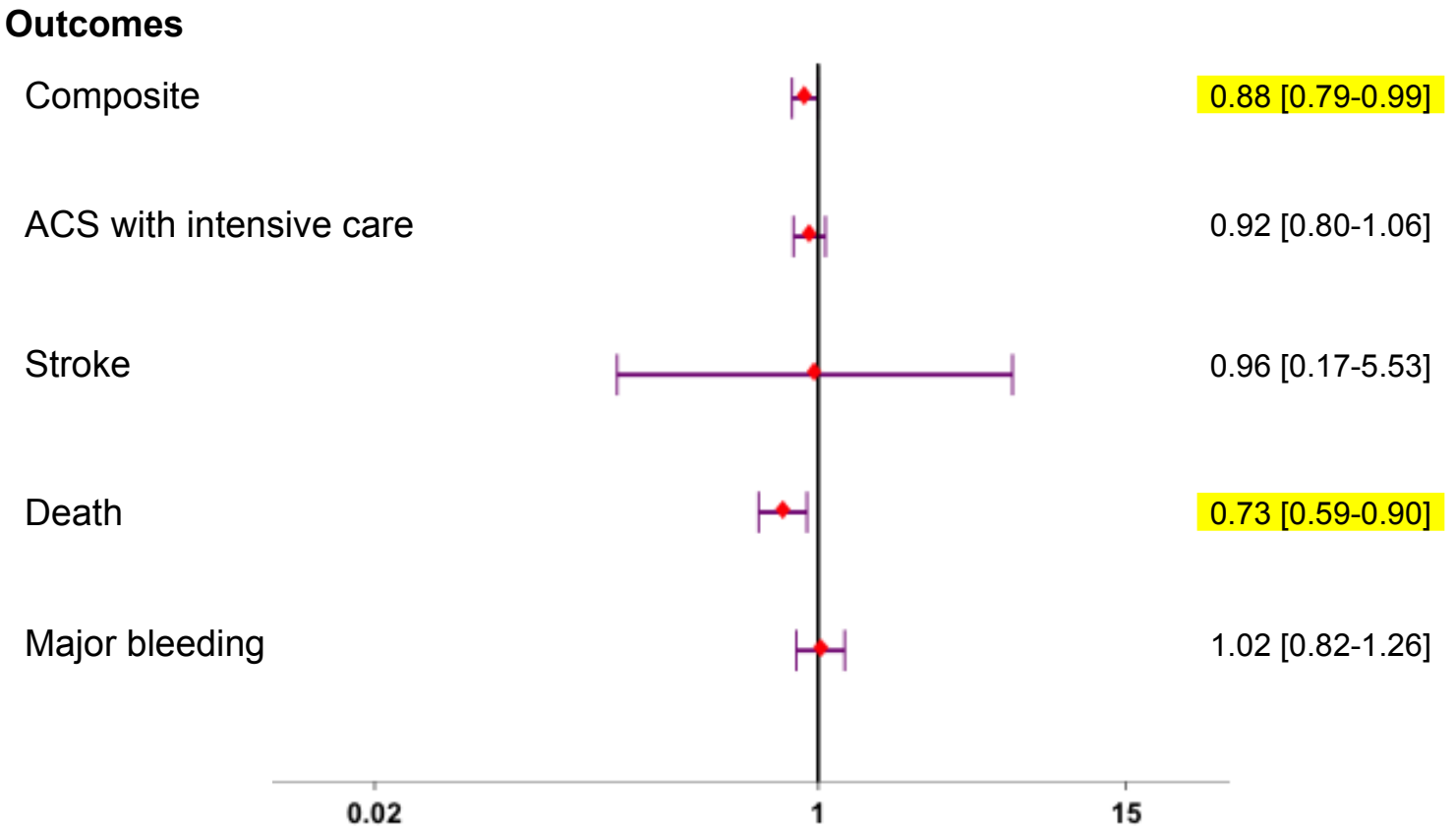
* Standardized difference

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

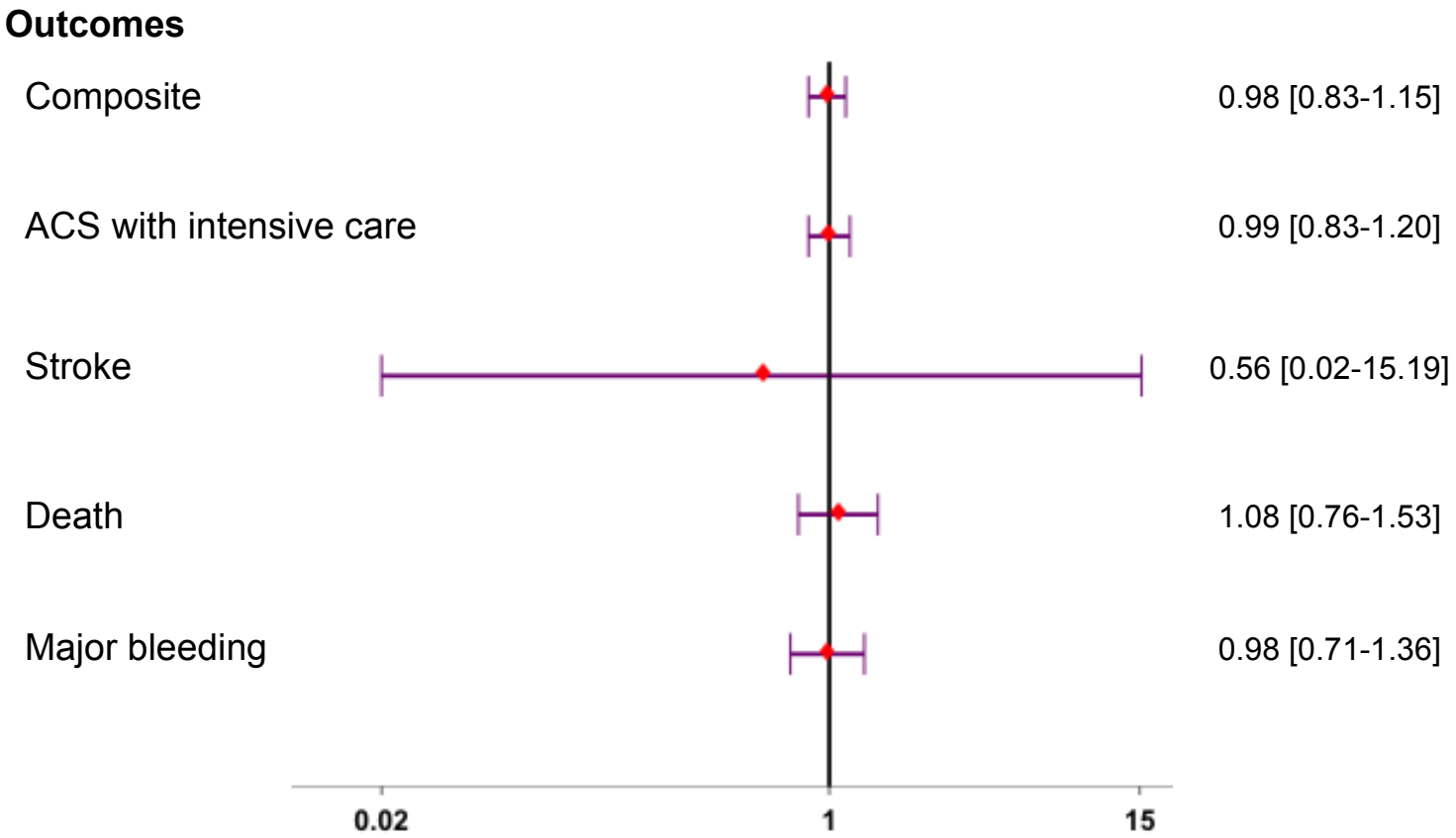


Hazard ratios with 95% CI, ticagrelor vs. clopidogrel in matched populations

- Différence en faveur du ticagrelor par rapport au clopidogrel

Efficacité et sécurité du ticagrelor

Ticagrelor *versus* prasugrel



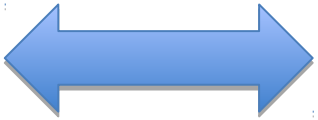
Hazard ratios with 95% CI, ticagrelor vs. prasugrel in matched populations

- Pas de différence entre ticagrelor et prasugrel

ENGEL

Dispensation d'anticoagulant

Fibrillation auriculaire non valvulaire

dabigatran  AVK

hdPS

rivaroxaban  AVK

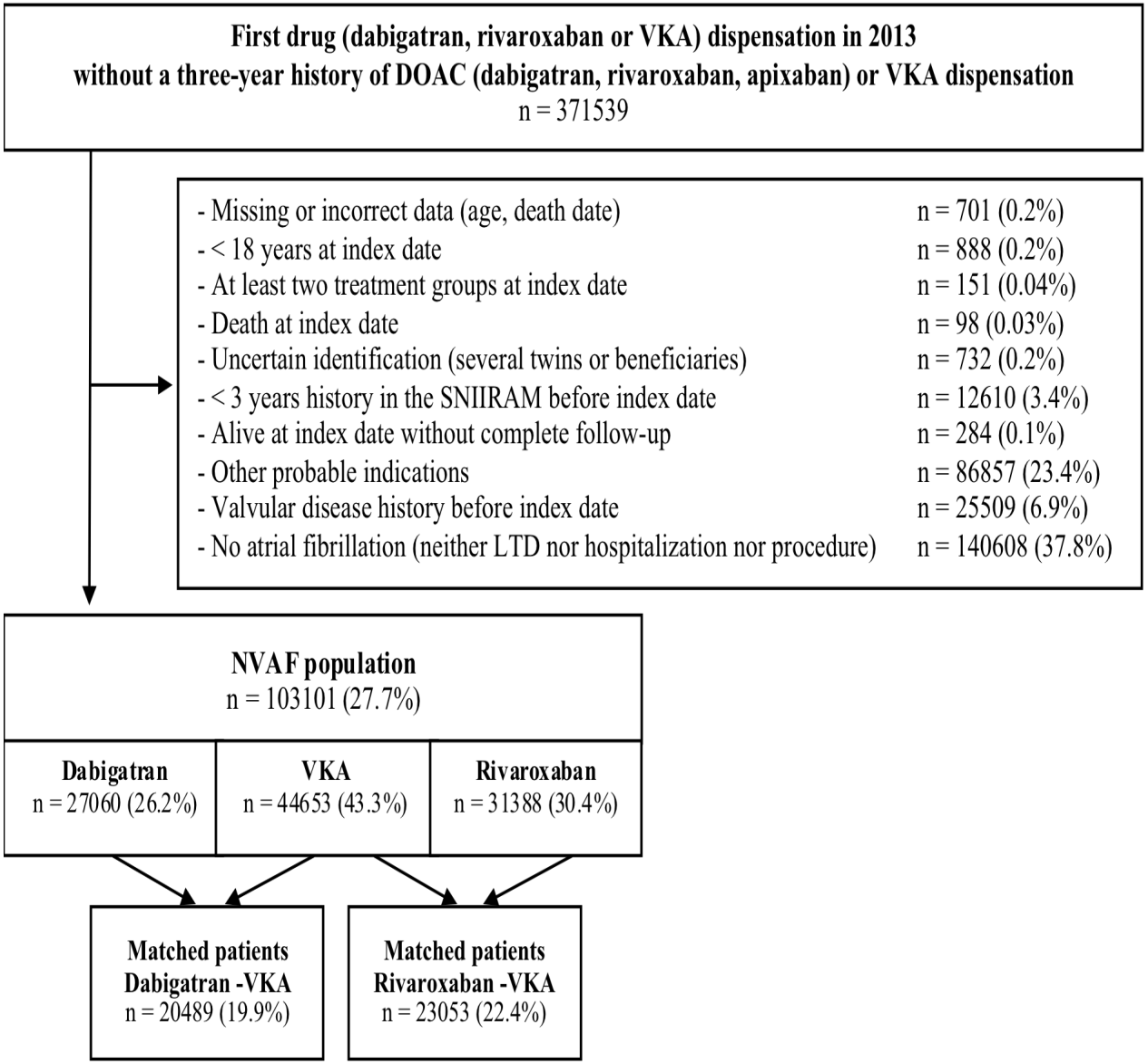
ENGEL 2

- 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



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)
CHA_2DS_2-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

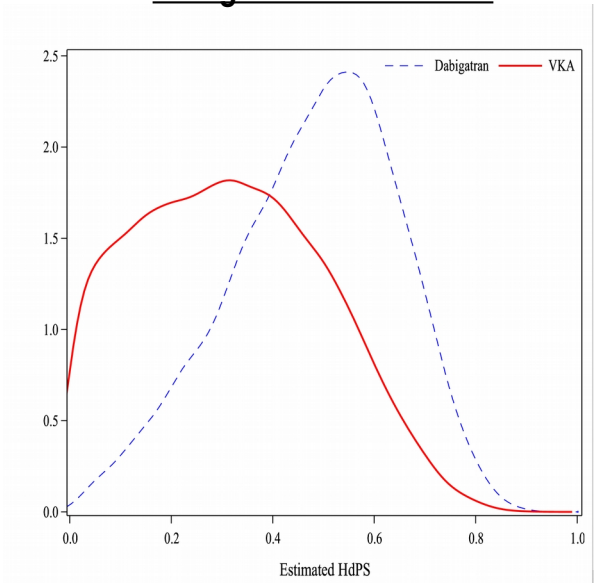
	Dabigatran n = 15903 PY[1]	**Rivaroxaban n = 19681 PY[1]**	**VKA n = 27242 PY[1]**
Clinically relevant **bleeding** (CRB)	2.7 [2.4; 2.9]	4.0 [3.7; 4.3]	6.1 [5.9; 6.4]
Haemorrhagic **stroke**	0.2 [0.1; 0.2]	0.5 [0.4; 0.6]	0.8 [0.7; 0.9]
Gastro-intestinal bleeding	1.3 [1.2; 1.5]	1.5 [1.3; 1.7]	1.9 [1.7; 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]

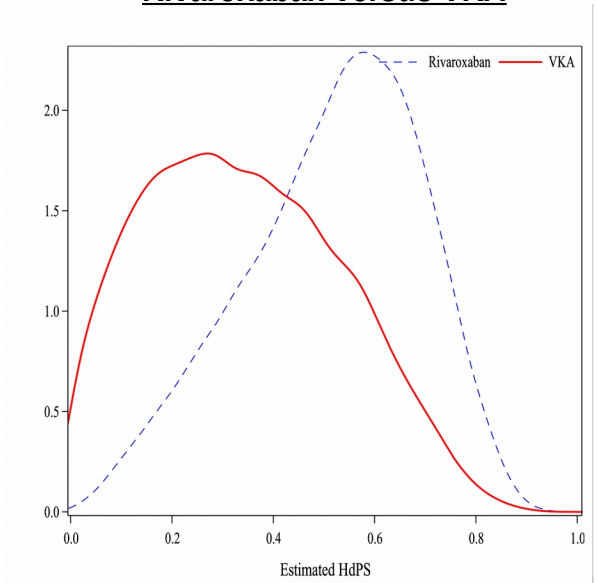
HdPS distribution

Dabigatran versus VKA

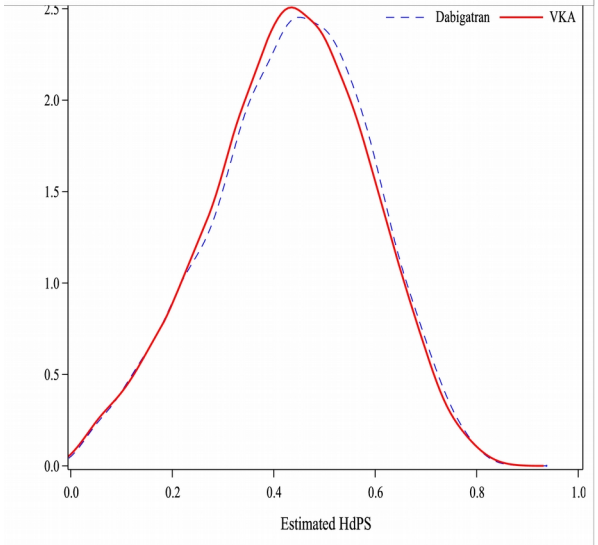
Rivaroxaban versus VKA

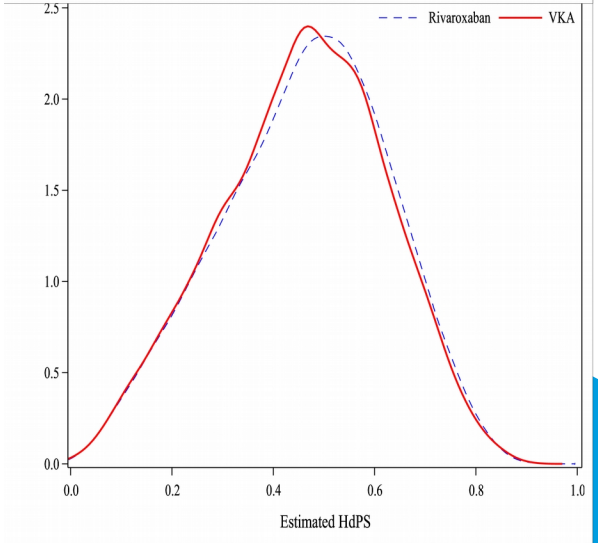
All patients



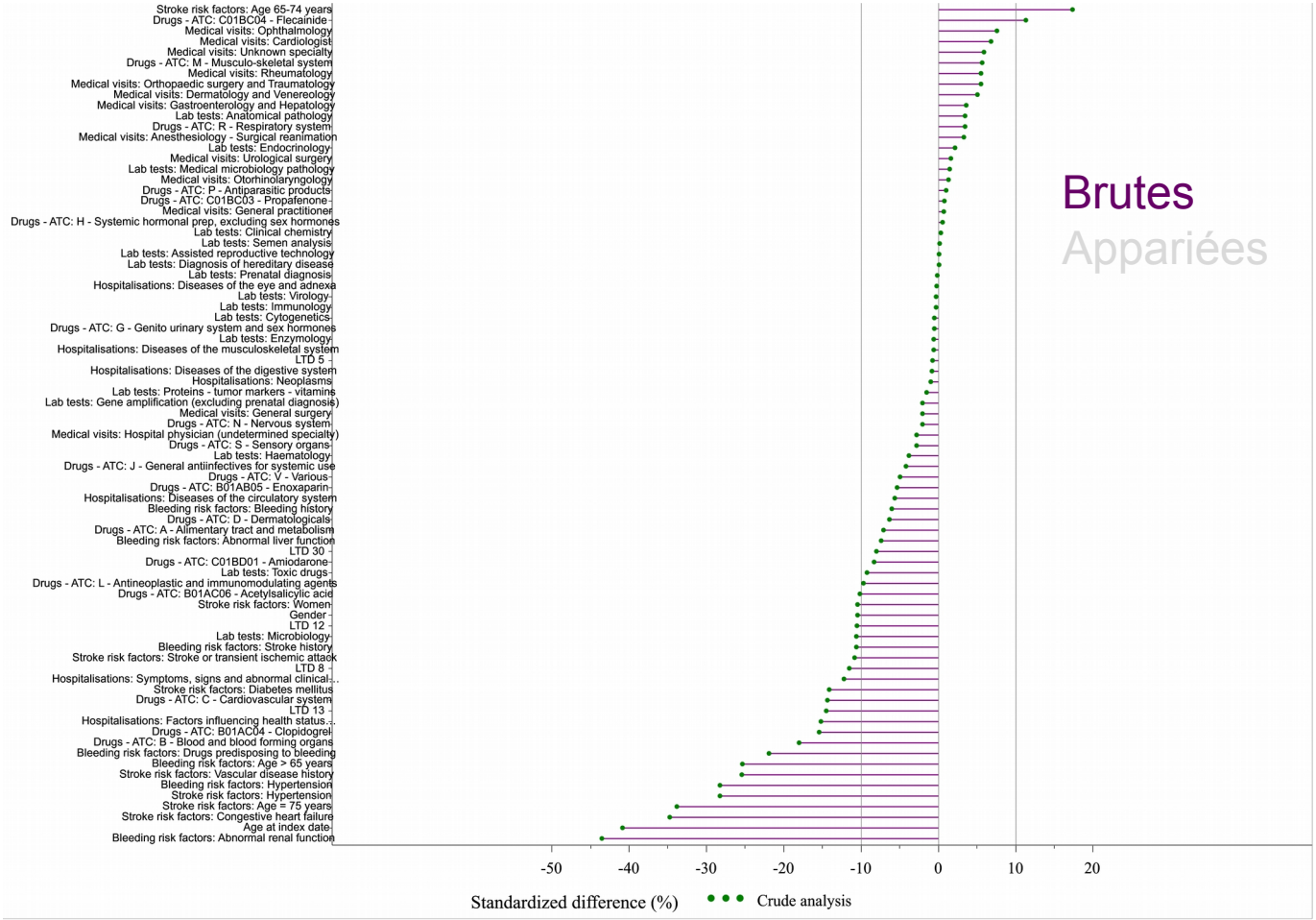


Matched patients

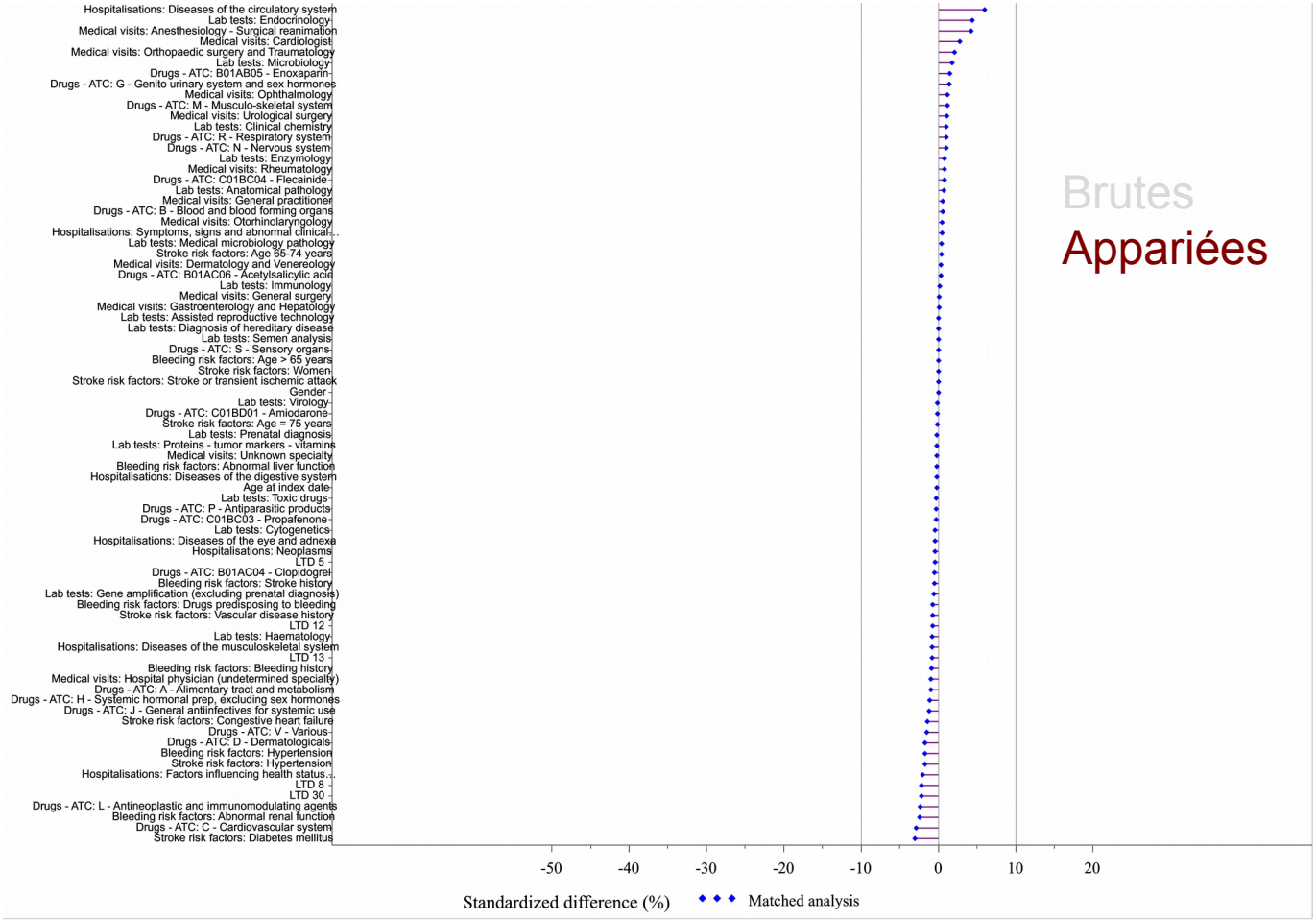




Différences standardisées



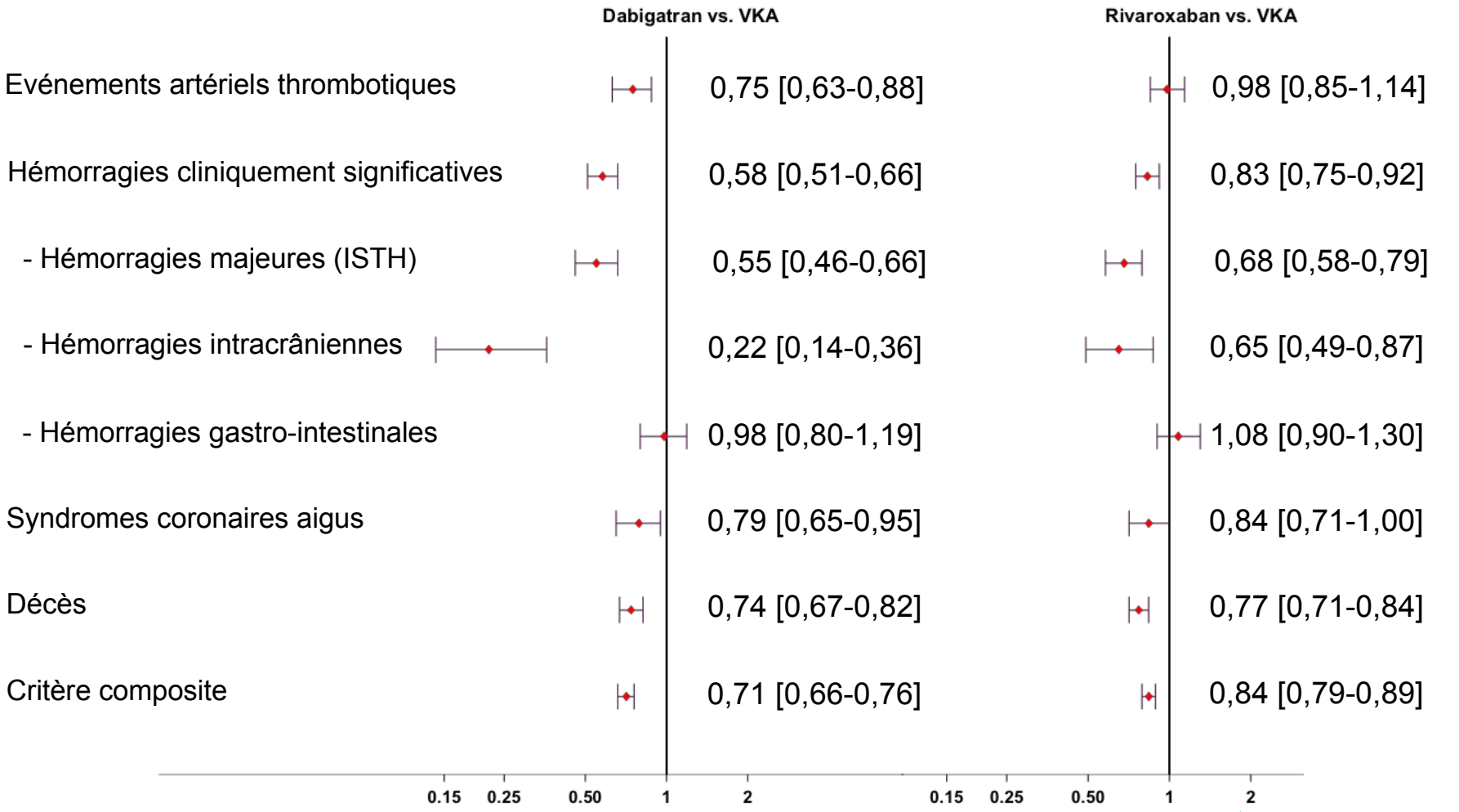
Différences standardisées



Caractéristiques des patients
population appariée

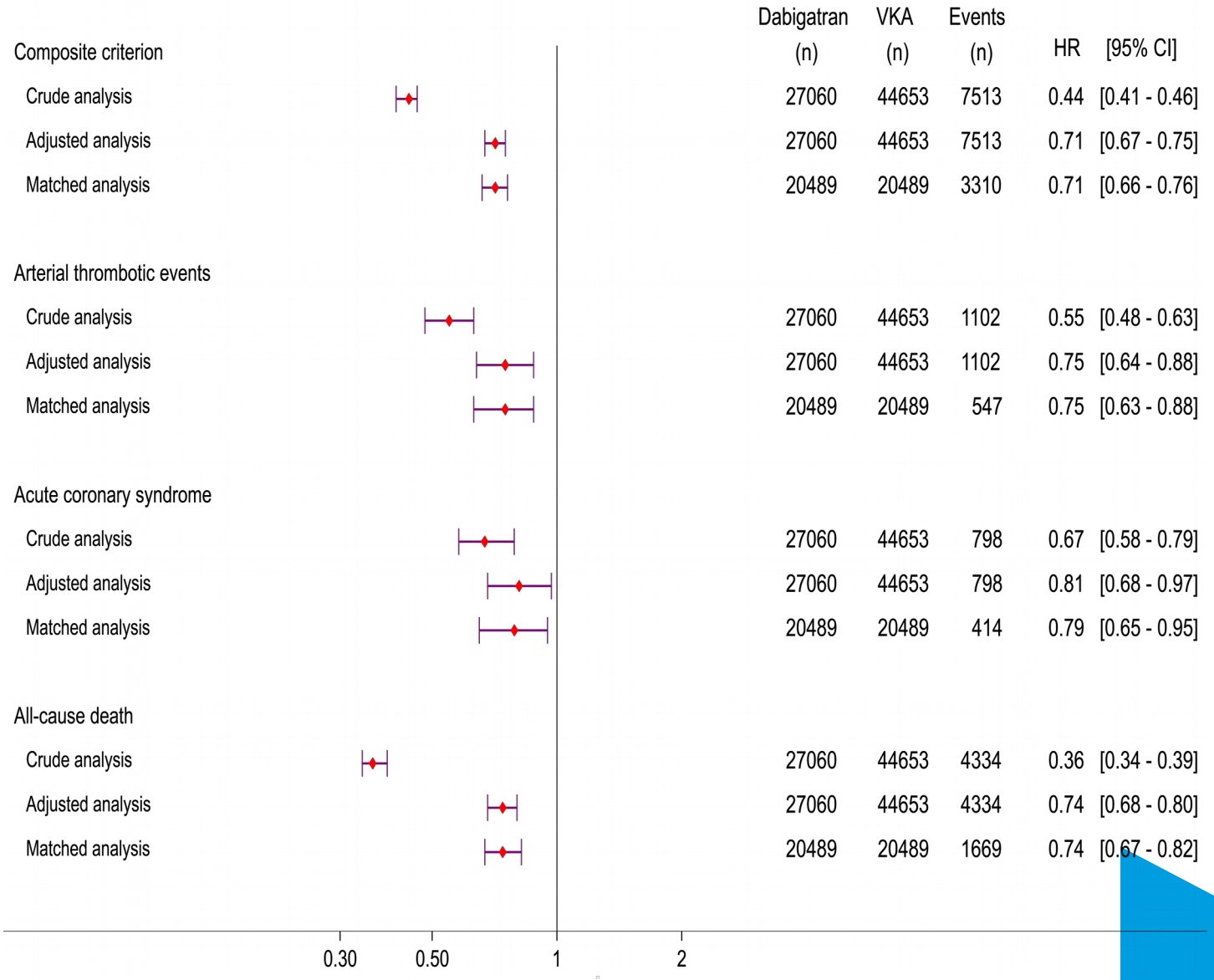
	Dabigatran n = 20489	**VKA n = 20489**	**Rivaroxaban n = 23053**	**VKA n = 23053**
Male, n (%)	11164 (54.5)	11164 (54.5)	12557 (54.5)	12557 (54.5)
Age	75.3 (10.7)	75.4 (10.7)	75.6 (10.7)	75.6 (10.7)
CHA_2DS_2-VASc				
0	1192 (5.8)	1183 (5.8)	1237 (5.4)	1268 (5.5)
1	2255 (11.0)	2196 (10.7)	2522 (10.9)	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



Hazard ratios with 95% CI, dabigatran vs. VKA and rivaroxaban vs. VKA in matched populations

Dabigatran *versus* VKA



Etudes de sécurité comparative

Evenement d'intérêt

Expositions

Cas-population

Cas-témoin

Cas propre témoin

EPIHAM

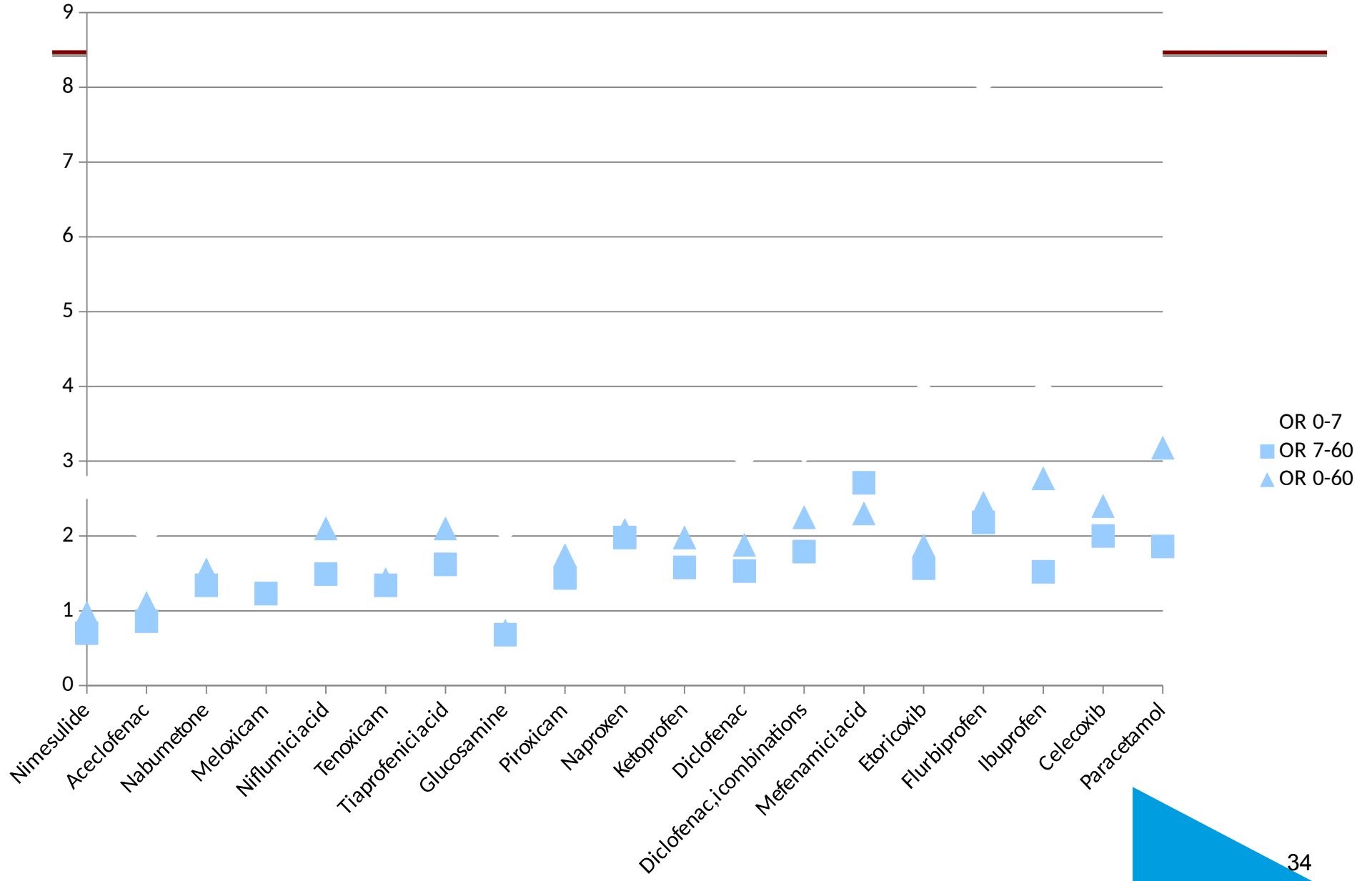
- Selection sur l'événement:
  - hépatite aigue hospitalisée
  - non virale, non alcoolique, etc...
- expositions préalables
  - 0-60 jours
  - 0-7 jours(biais protopathique)
  - 7-60 jours

EPIHAM

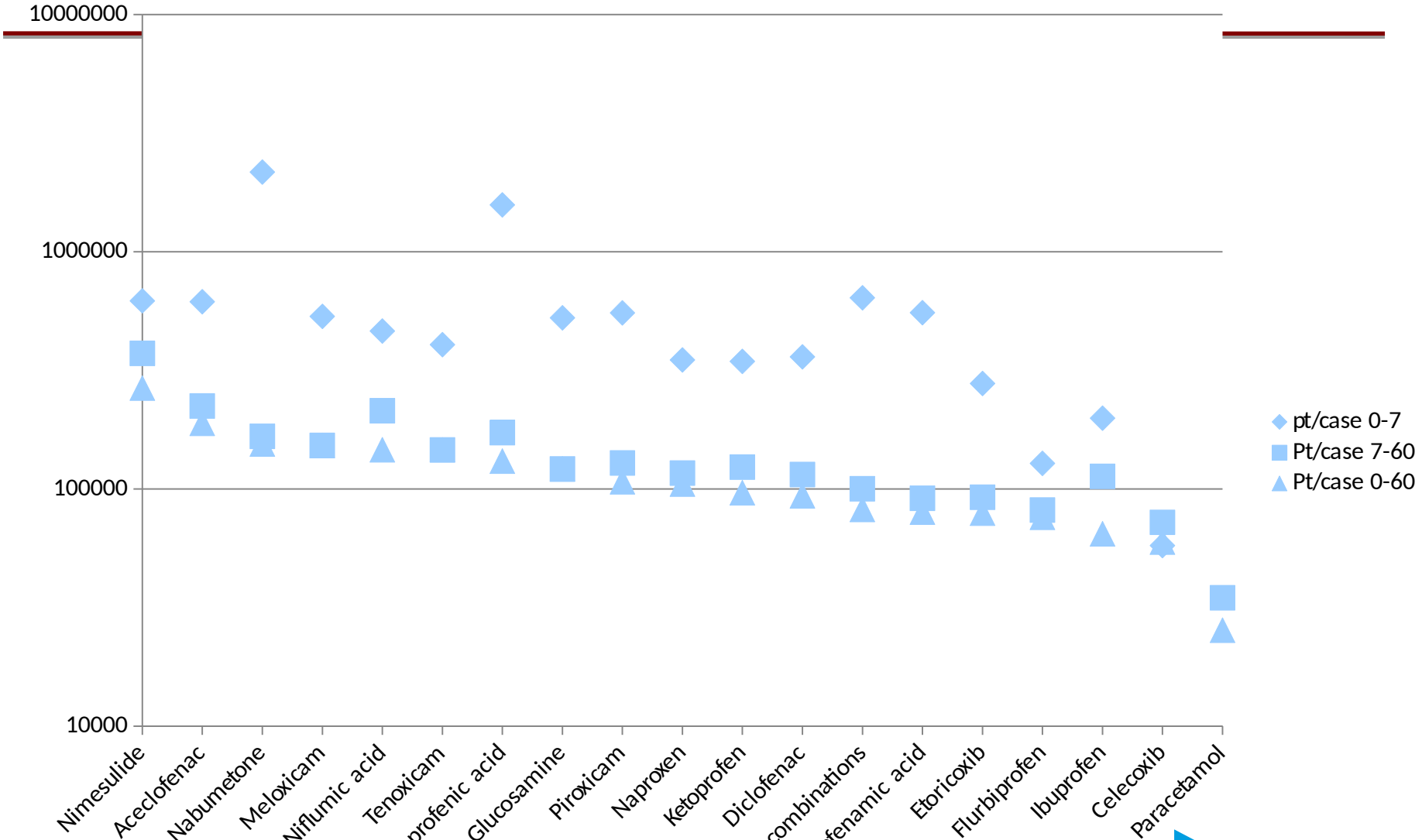
- In SNIIRAM: cases
- In EGB: controls, population
- 1/1/2010 - 31/12/2014

- Analysis
  - case-population
  - case-control
  - case-crossover

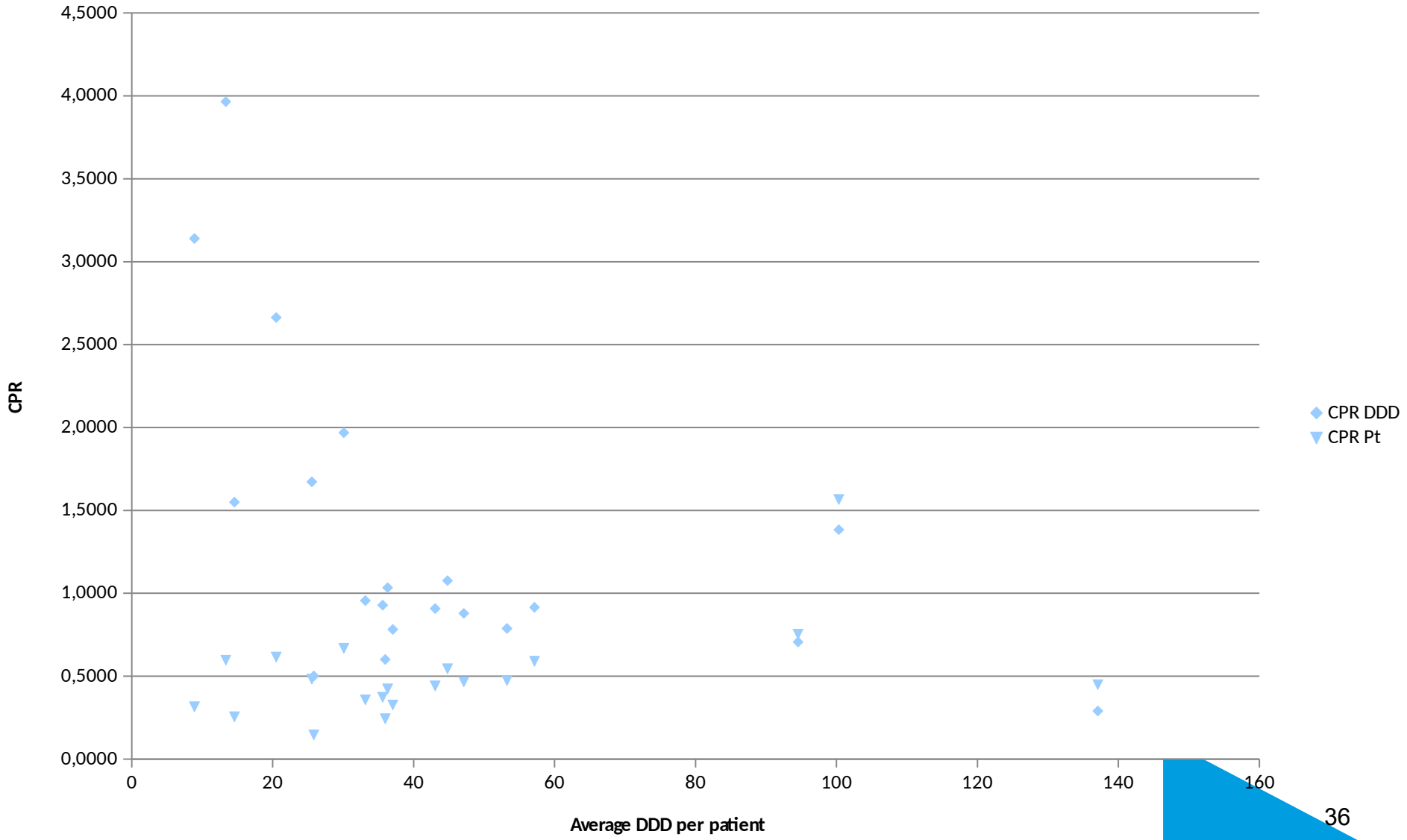
case-control Odds Ratios



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

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