Evaluation empirique d'approches pharmaco-épidémiologiques pour l'identification de médicaments associés à l'hémorragie digestive haute dans la base de données du Système National des Données de Santé

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Lien d'intérêts

- Basé sur le projet Alcapone
- Financé par la DGOS (PREPS, 14-0635)
- Supervisé par un comité scientifique international indépendent
- Respect du code de l'ENCePP (EMA EUPAS 13031)

Contexte

- Hémorragies digestives hautes (UGIB)
  - 36 à 172 cas pour 100 000 personnes / an
  - Décès dans 10% des cas
  - Souvent liées aux médicaments
- Système National des Données de Santé (SNDS)
  - Fort potentiel pour l'évaluation du médicament
  - Encore peu/pas utilisé pour la génération de signaux de pharmacovigilance

Objectifs

Identifier l’approche et le design optimal pour la détection et l’évaluation des médicaments associés à la survenue d’UGIB dans le SNDS

Population

- Classification Internationale des Maladies, 10e ed.
  - Ulcère gastrique, duodénal, peptique ou gastro jéjunal, avec hémorragie
  - Gastrite hémorragique aigue
  - Hématémèse
  - Méléna
- Données extraites du SNDS sur 2009 - 2014

Exposition

- 58 médicaments témoins positifs et négatifs

ATC code	International nonproprietary name	Source reference set	Type of control
A01AB09	MICONAZOLE	OMOP	Negative
A02BX02	SUCRALFATE	OMOP	Negative
A04AD01	SCOPOLAMINE	OMOP	Negative
A06AD11	LACTULOSE	OMOP	Negative
A10BF01	ACARBOSE	OMOP	Negative
A10BG02	ROSIGLITAZONE	OMOP	Negative
A10BG03	PIOGLITAZONE	OMOP	Negative
A10BH01	SITAGLIPTINE	OMOP	Negative
A11CA01	RETINOL (VIT A)	OMOP	Negative
M01AB01	INDOMETACINE	OMOP	Positive
M01AB02	SULINDAC	OMOP	Positive
M01AB08	ETODOLAC	OMOP	Positive
M01AC01	PIROXICAM	OMOP	Positive
M01AC06	MELOXICAM	OMOP	Positive
M01AE01	IBUPROFENE	OMOP	Positive
M01AE02	NAPROXENE	OMOP	Positive
M01AE03	KETOPROFENE	OMOP	Positive

Approches évaluées

- 3 approches déclinées en 196 variantes

	Approaches		
	Self-controlled case series	**Case-control**	**Case-population**
Settings	**Outcomes to include:** *All occurrences / First occurrence* **Risk window:** *30 days following dispensing / Overall period covered by dispensing* **Pre-exposure window:** *0 day / 7 days / 30 days* **Age included into the model:** *Yes / No* **Seasonality included into the model:** *Yes / No* **Adjustment for multiple drug use (all dispensed drugs included into the model except the one of interest)** *Yes /No*	**Outcomes to include:** *All occurrences / First occurrence* **Risk window:** *7 days / 30 days / 60 days* **Lag periods:** *0 day / 7 days / 15 days* **Controls matched per cases (on age and gender):** *Up to 2 / Up to 10*	**Outcomes to include:** *All occurrences / First occurrence* **Risk window:** *7 days / 30 days / 60 days* **Lag periods:** *0 day / 7 days / 15 days* **Approach** *Count data (per-user) / person-time* **Extrapolation of the aggregated data from SNDS* sample:** *Raw (no stratification) / Stratified on age and gender* **Measure of association** *Case-population Ratio / predicter Relative Risk*

Design approach	Analysis_ID	Outcomes to include	Naïve period	Risk window	Pre-exposure window	Include age into the model	Include seasonality into the model	Adjusting for multiple drugs
SCCS	2001	All occurrences	182d	30d from dispensing first day	30d	No	No	No
SCCS	2002	All occurrences	182d	30d from dispensing first day	30d	No	No	Yes
SCCS	2003	All occurrences	182d	30d from dispensing first day	30d	No	Yes	No
SCCS	2004	All occurrences	182d	30d from dispensing first day	30d	No	Yes	Yes
SCCS	2005	All occurrences	182d	30d from dispensing first day	30d	Yes	No	No
SCCS	2006	All occurrences	182d	30d from dispensing first day	30d	Yes	No	Yes
SCCS	2007	All occurrences	182d	30d from dispensing first day	30d	Yes	Yes	No
SCCS	2008	All occurrences	182d	30d from dispensing first day	30d	Yes	Yes	Yes
SCCS	2009	All occurrences	182d	30d from dispensing first day	7d	No	No	No
SCCS	2010	All occurrences	182d	30d from dispensing first day	7d	No	No	Yes
SCCS	2011	All occurrences	182d	30d from dispensing first day	7d	No	Yes	No
SCCS	2012	All occurrences	182d	30d from dispensing first day	7d	No	Yes	Yes
SCCS	2013	All occurrences	182d	30d from dispensing first day	7d	Yes	No	No
SCCS	2014	All occurrences	182d	30d from dispensing first day	7d	Yes	No	Yes
SCCS	2015	All occurrences	182d	30d from dispensing first day	7d	Yes	Yes	No
SCCS	2016	All occurrences	182d	30d from dispensing first day	7d	Yes	Yes	Yes
SCCS	2017	All occurrences	182d	30d from dispensing first day	No	No	No	No
SCCS	2018	All occurrences	182d	30d from dispensing first day	No	No	No	Yes
SCCS	2019	All occurrences	182d	30d from dispensing first day	No	No	Yes	No
SCCS	2020	All occurrences	182d	30d from dispensing first day	No	No	Yes	Yes
SCCS	2021	All occurrences	182d	30d from dispensing first day	No	Yes	No	No
SCCS	2022	All occurrences	182d	30d from dispensing first day	No	Yes	No	Yes
SCCS	2023	All occurrences	182d	30d from dispensing first day	No	Yes	Yes	No
SCCS	2024	All occurrences	182d	30d from dispensing first day	No	Yes	Yes	Yes
SCCS	2025	All occurrences	182d	Period of dispensing	30d	No	No	No
SCCS	2026	All occurrences	182d	Period of dispensing	30d	No	No	Yes
SCCS	2027	All occurrences	182d	Period of dispensing	30d	No	Yes	No
SCCS	2028	All occurrences	182d	Period of dispensing	30d	No	Yes	Yes
SCCS	2029	All occurrences	182d	Period of dispensing	30d	Yes	No	No
SCCS	2030	All occurrences	182d	Period of dispensing	30d	Yes	No	Yes
SCCS	2031	All occurrences	182d	Period of dispensing	30d	Yes	Yes	No
SCCS	2032	All occurrences	182d	Period of dispensing	30d	Yes	Yes	Yes
SCCS	2033	All occurrences	182d	Period of dispensing	7d	No	No	No
SCCS	2034	All occurrences	182d	Period of dispensing	7d	No	No	Yes
SCCS	2035	All occurrences	182d	Period of dispensing	7d	No	Yes	No
SCCS	2036	All occurrences	182d	Period of dispensing	7d	No	Yes	Yes
SCCS	2037	All occurrences	182d	Period of dispensing	7d	Yes	No	No

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Thurin, NH, Lassalle, R, Schuemie, M, et al. Empirical assessment of case-based methods for drug safety alert identification in the French National Healthcare System database (SNDS): Methodology of the ALCAPONE project. Pharmacoepidemiol Drug Saf. 2020; 1– 8. https://doi.org/10.1002/pds.4983

Méthodes d'évaluation

- Variantes évaluées selon
  - Aire sous la courbe ROC *(AUC)*
  - Erreur quadratique moyenne *(MSE)*

$$MSE = mean\left[[\log(RR_{est}) - \log(RR_{true})]^2\right]$$

- Paramètres avec un impact sur le pouvoir discriminant des variantes (AUC) identifiés via modèle de régression logistique

Effectifs

- Evénements n = 156 057
- Patients n = 139 172

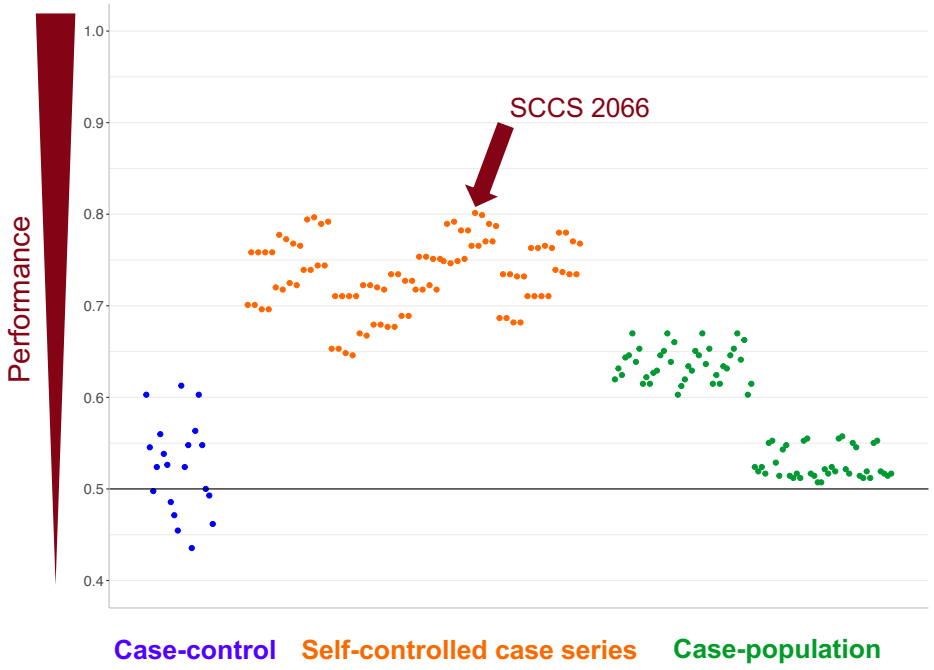
Performances générales

Aire sous la courbe ROC

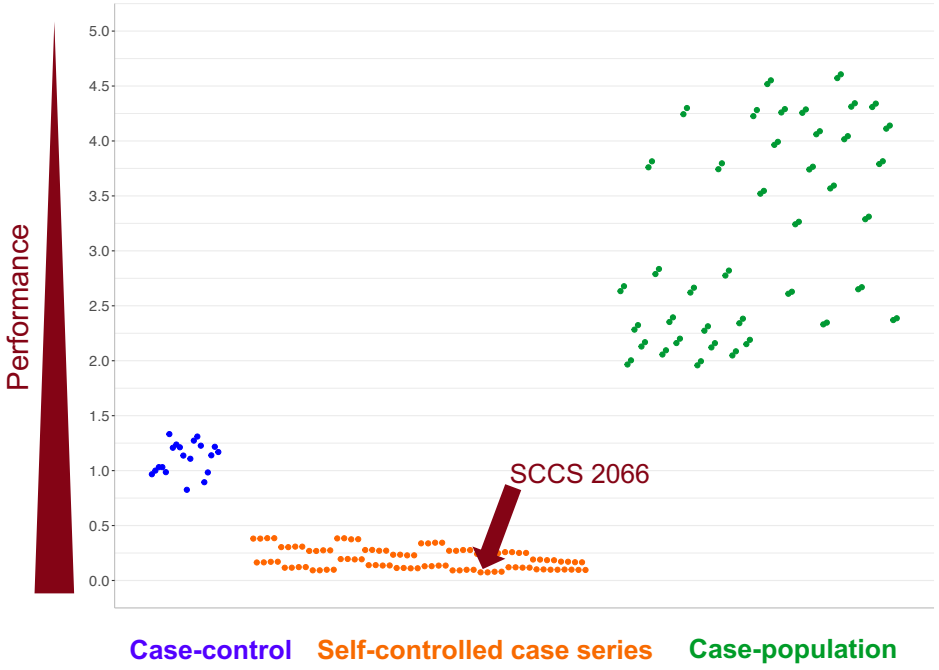
Erreur quadratique moyenne

Performances générales

Aire sous la courbe ROC



Erreur quadratique moyenne



Variante optimale

- SCCS 2066
  - Paramètres
    - Occurrence considered: first
    - Risk window: first 30 days after dispensing
    - Adjusted on multiple drugs
  - AUC = 0.801
  - MSE = 0.074

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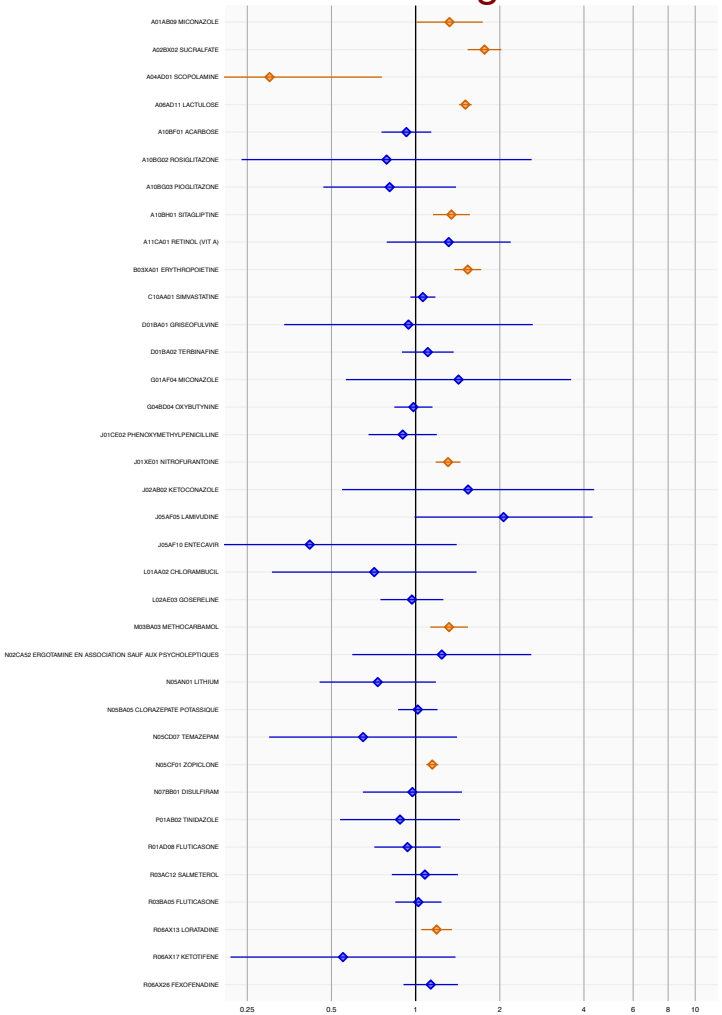
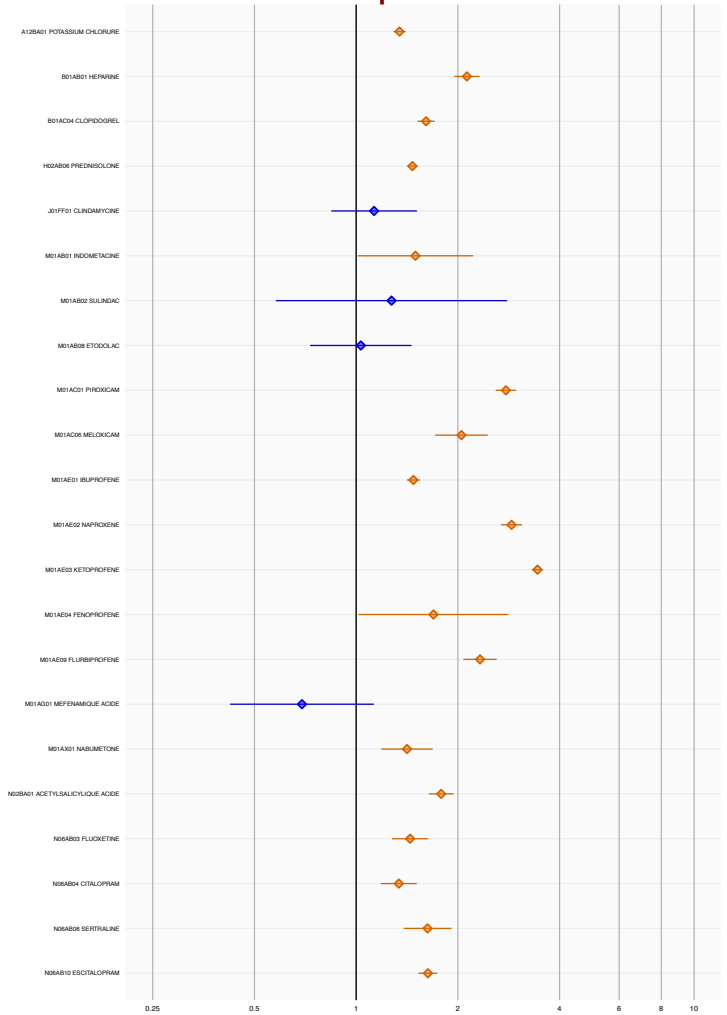
	Variants with low AUC n=59	Variants with high AUC n=37	High *vs.* Low AUC OR [IC à 95%]	*p*	AUC of the univariate model
Age				0.838	0.51
No	30 (50.8)	18 (48.6)	1		
Yes	29 (49.2)	19 (51.4)	1.09 [0.48 - 2.48]		
Seasonality				0.838	0.51
No	30 (50.8)	18 (48.6)	1		
Yes	29 (49.2)	19 (51.4)	1.09 [0.48 - 2.48]		
Outcome				0.009	0.64
All occurrences	36 (61.0)	12 (32.4)	1		
First occurrence	23 (39.0)	25 (67.6)	3.17 [1.34 - 7.50]		
Multiple drugs				<0.001	0.8
No	43 (72.9)	5 (13.5)	1		
Yes	16 (27.1)	32 (86.5)	15.58 [5.30 - 45.77]		
Pre-Exposure Window				0.140	0.62
No	16 (27.1)	16 (43.2)	1		
7 days	19 (32.2)	13 (35.1)	0.69 [0.26 - 1.86]		
30 days	24 (40.7)	8 (21.6)	0.35 [0.12 - 0.99]		
Risk window				<0.001	0.73
Period of dispensing	40 (67.8)	8 (21.6)	1		
30 days from dispensing first day	19 (32.2)	29 (78.4)	7.21 [2.80 - 18.54]		

SCCS 2066

Témoins négatifs

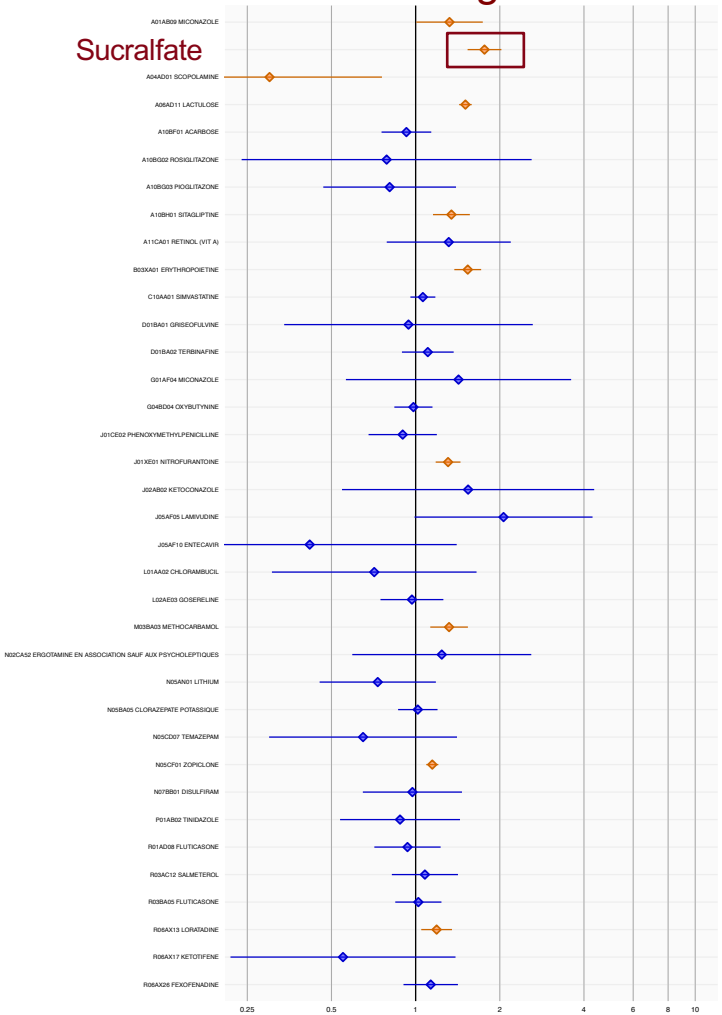


Témoins positifs

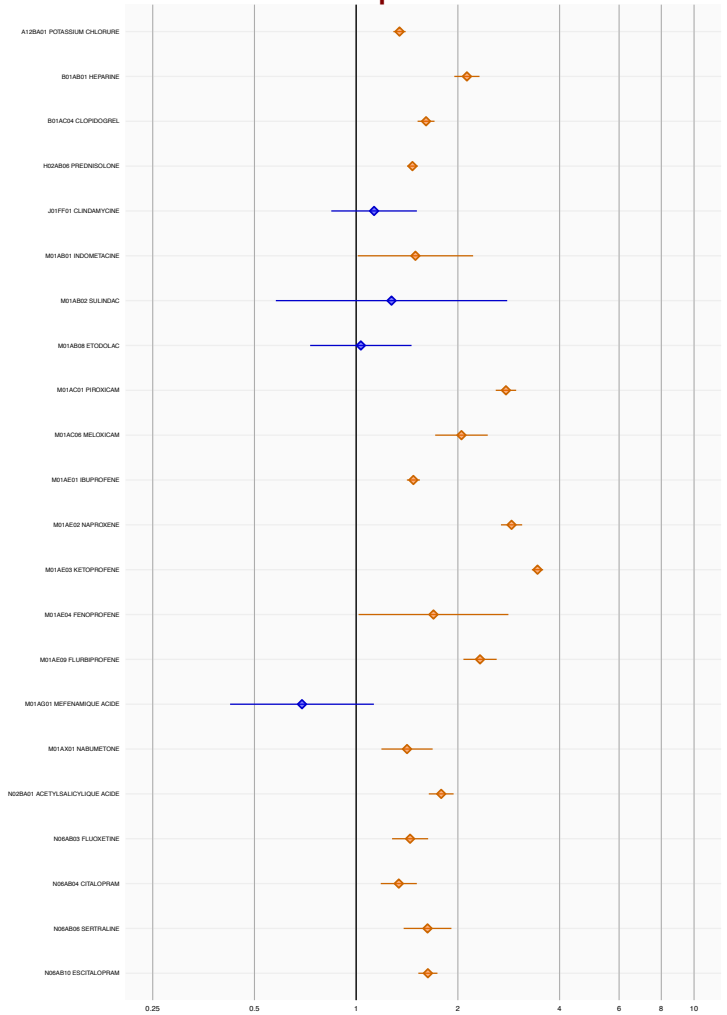


SCCS 2066

Témoins négatifs

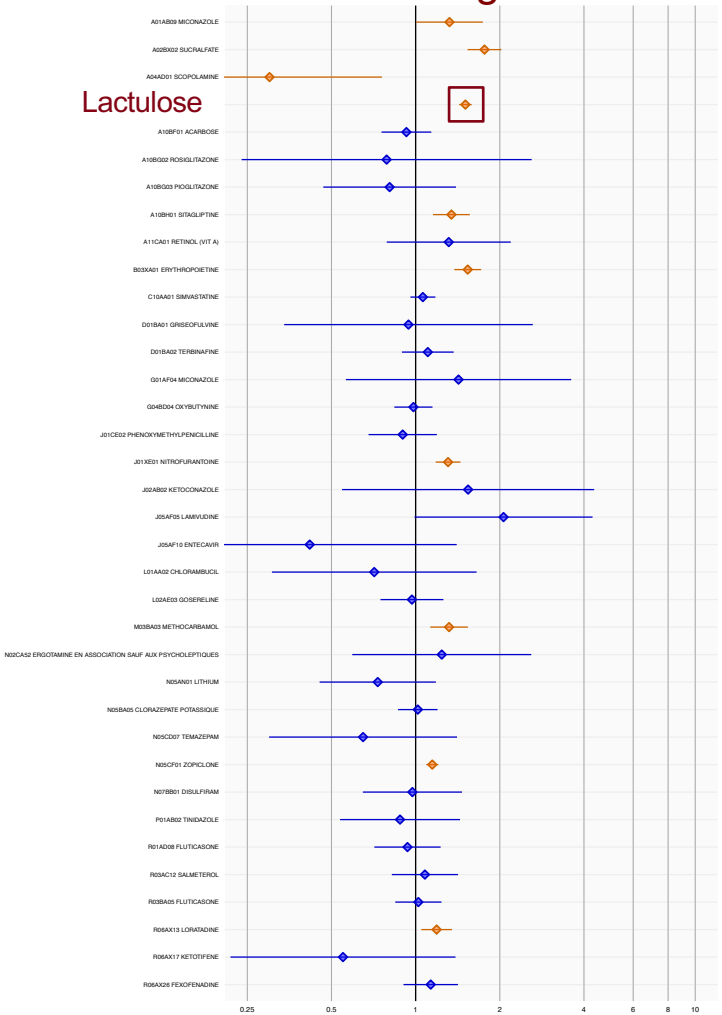


Témoins positifs

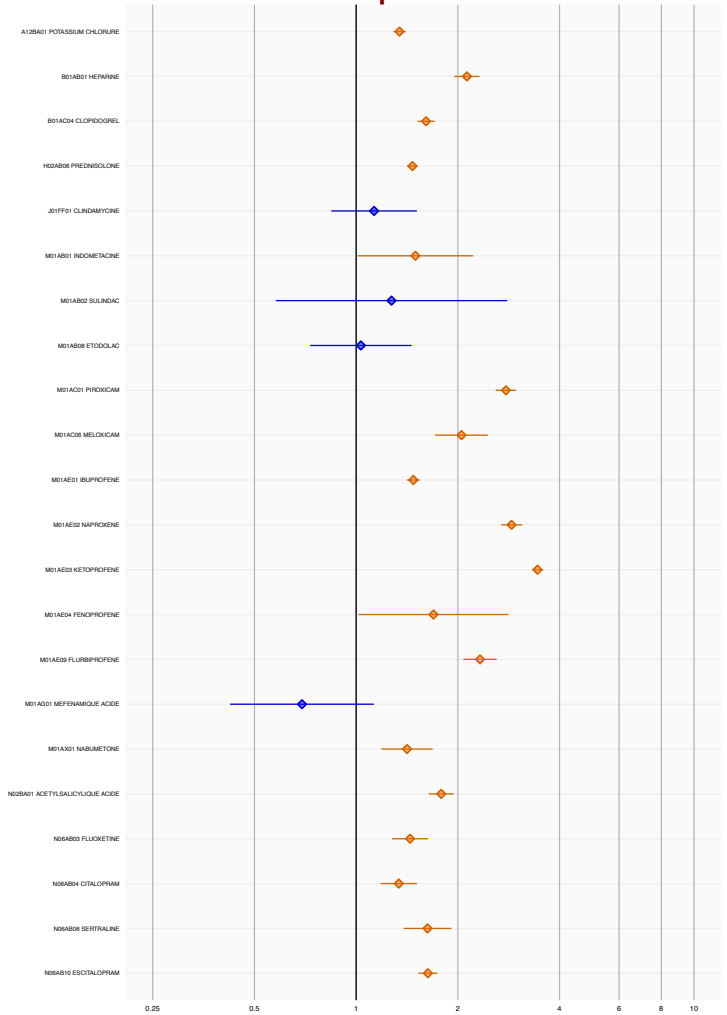


SCCS 2066

Témoins négatifs

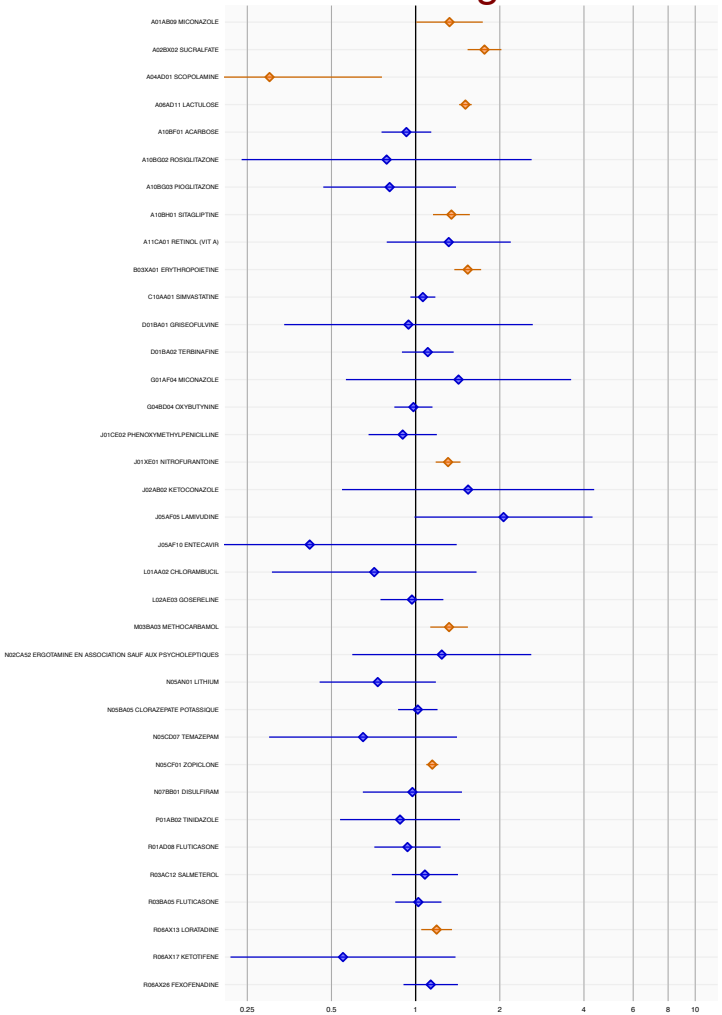


Témoins positifs



SCCS 2066

Témoins négatifs



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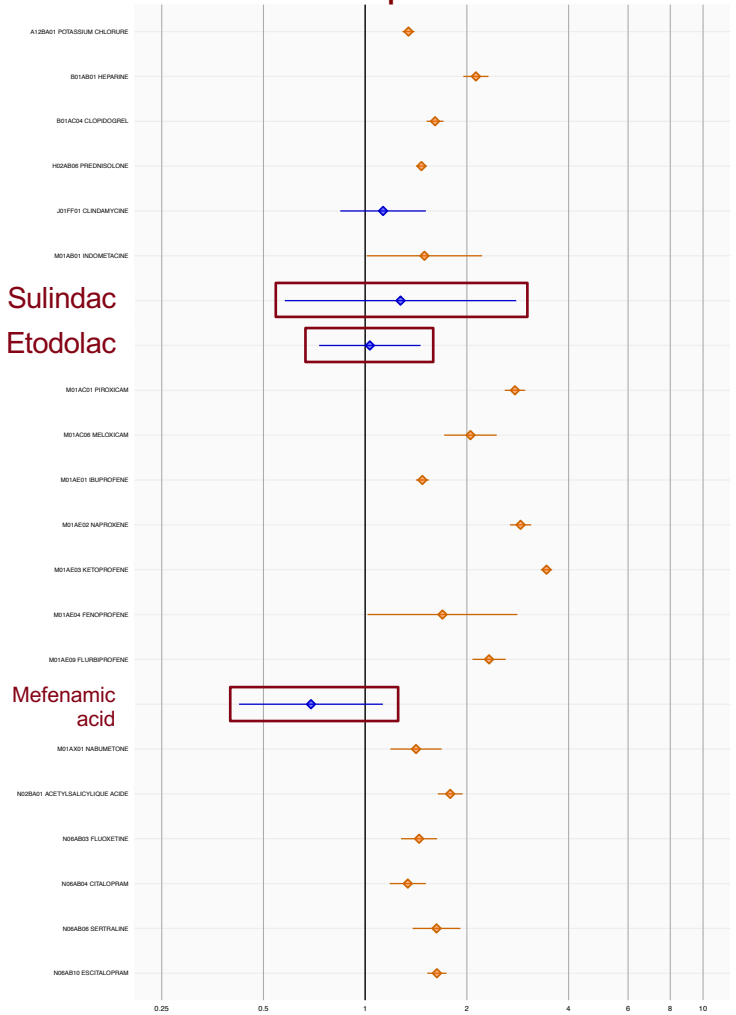

Conclusion

- SCCS = meilleures performances pour l'identification de médicaments associés à UGIB dans le SNDS
  - Paramètres à considérer
    - Ajustement sur l'utilisation des autres médicaments
    - Fenêtre de risque = 30 premiers jours d'exposition
  - Faibles biais résiduels
  - Biais protopathique / Biais d'indication
- Fort potentiel pour la génération d'alertes de pharmacovigilance avec une estimation de la magnitude de l'effet

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