Empirical assessment of case-based methods for identification of drugs associated with upper gastrointestinal bleeding in the French National Healthcare System database (SNDS)

Nicolas H Thurin[1,2], Régis Lassalle[1], Martijn Schuemie[3, 4], Marine Pénichon[1], Joshua J. Gagne[5], Jeremy A. Rassen[5], Jacques Benichou[7, 8], Alain Weill[9], Patrick Blin[1], Nicholas Moore[1, 2], Cécile Droz-Perroteau[1]

[1]Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France; [2]INSERM U1219, France; [3]Epidemiology Analytics, Janssen Research and Development, Titusville, NJ, USA [4]OHDSI, New York, NY, USA; [5]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [5]Aetion, Inc., New York, NY, USA; [7]Department of Biostatistics and Clinical Research, Rouen University Hospital Rouen, France ; [8]INSERM U1018; [9]Caisse Nationale de l'Assurance Maladie, Paris, France

Background

- **Upper gastrointestinal bleeding (UGIB)** is a serious medical emergency leading to death in about 10% of cases.
- **The French Nationwide Healthcare System database (SNDS)** covers the overall French population from birth to death (66.6 million people). It includes individual pseudonymised information on all reimbursed healthcare expenditures, including drugs, and hospital discharges summaries.

Objectives

- Drug safety alert generation associated with UGIB may be achieved through the application of empirically validated and calibrated case-based methods in the SNDS.
- The present work aims to identify the optimum design and settings for the identification of drugs associated with UGIB in the SNDS.

Methods

- **156 057 UGIB cases** were extracted from SNDS over 2009-2014.
- **Reference set adapted to the French market** was constructed with
  - Positive controls: drugs with a known association with UGIB
  - Negative controls: drugs with no known association with UGIB
  - Controls with a minimal detectable relative risk ≤1.30 in the relevant population were deemed detectable and kept.
- **96 SCCS, 20 CC and 80 CP variants** were used to measure association between drug controls and UGIB in a 1/10th sample of the population (**Table 1**).

Table 1. Description of design variants

	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* **All dispensed drugs included into the model (multiple drug use):** *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:** *Raw (no stratification) / Stratified on age and gender* **Measure of association** *Case-population Ratio / predicter Relative Risk*

- **Performance** of each design variants was assessed based on the **area under the receiving operator curve** (AUC), the **mean square error** (MSE).
- **Parameters that had major impact on results of the best performing approach were identified through logistic regression:**
  - Dependent variable = probability that a variant had an AUC >70th percentile of the AUC distributions of the variants.
  - Independent covariates = parameters that were varied in the variant.
- The **variant with the best AUC and MSE was applied to the full unsampled UGIB population.**
- An empirical null distribution was derived from negative control estimates based on how often $p < 0.05$ while the null hypothesis was true, and used to calibrate p-value to take into account systematic and random error.

Results

- SCCS globally showed better performances than CC and CP with higher AUCs and lower MSEs (**Figure 1**).
- Univariate regressions showed that high AUCs were achieved with SCCS using the first occurrence of the outcome, multiple drug adjustment and a 30-day fixed risk window starting at exposure (**Table 2**).
- The best performing design variant in the 1/10th sampled population considered the first occurrence of the outcome, a 30-day risk window, and only adjusted on multiple drug use.

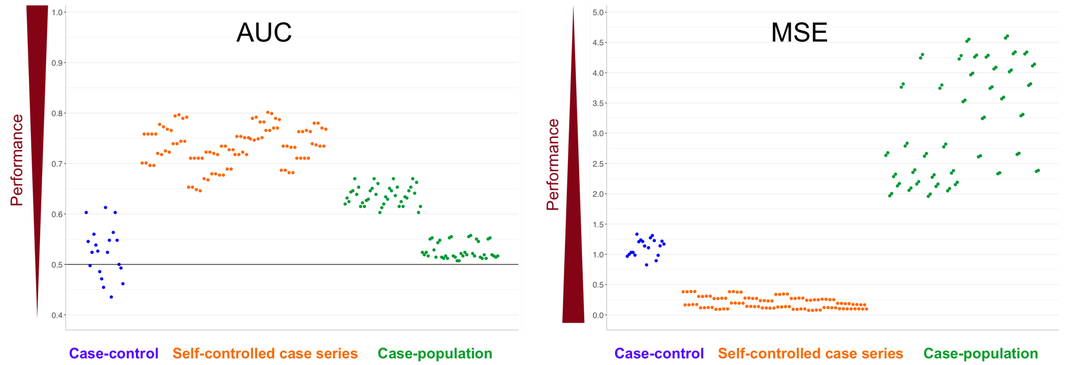


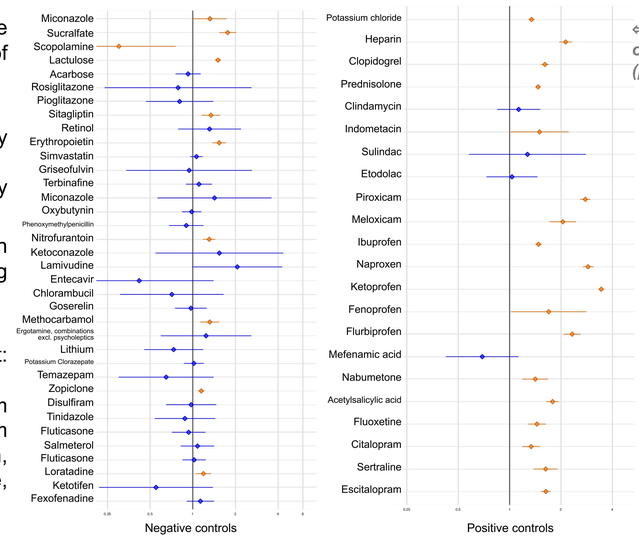
Figure 1. Area under the receiver operating characteristics curve (AUC) and mean square error (MSE) for the assessed variants in the 1/10th sampled population

Table 2. Univariate logistic regression analysis of self-controlled case series parameters influencing on the area under the receiver operating characteristics curve (AUC) in the 1/10th sampled population

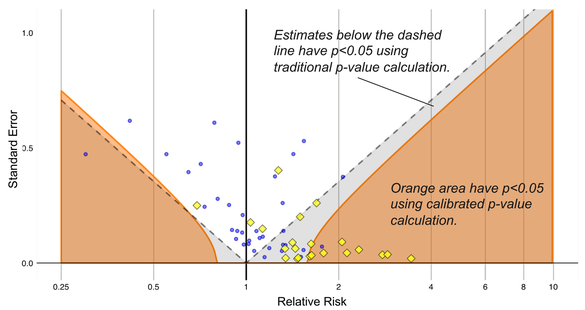
	Variants with low AUC n=59	Variants with high AUC n=37	High *vs.* Low AUC OR [IC à 95%]	*p*	AUC of the univariate model
Age				0.8375	0.51
Not included	30 (50.8)	18 (48.6)	1		
Included	29 (49.2)	19 (51.4)	1.09 [0.48 - 2.48]		
Seasonality				0.8375	0.51
Not included	30 (50.8)	18 (48.6)	1		
Included	29 (49.2)	19 (51.4)	1.09 [0.48 - 2.48]		
Outcome				**0.0087**	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 drug use				**<0.0001**	0.80
Not included	43 (72.9)	5 (13.5)	1		
Included	16 (27.1)	32 (86.5)	15.58 [5.30 - 45.77]		
Pre-Exposure Window				0.1404	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				**<0.0001**	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]		

AUC = area under the receiver operating characteristics curve; A high AUC was defined as an AUC≥0.75

- The optimum design variant in the unsampled population led to an AUC of 0.84 and a MSE of 0.14.
- **Figure 2** shows that:
  - 10 negative controls were significantly associated with UGIB;
  - 4 positive controls were not significantly associated with UGIB.
- Derived empirical null distribution (supposed gaussian) had the following parameters: μ =0.12; σ =0.17.
- Calibrating p-values (**Figure 3**)
  - 2 negative controls were still significant: sucralfate and scopolamine;
  - 9 positive controls moved from significant to non-significant: potassium chloride, prednisolone, indomethacin, ibuprofen, fenoprofen, nabumetone, fluoxetine, citalopram, sertraline.



⇐ *Figure 2. Point estimates of negative and positive controls for the optimum design variant. Estimates that are significantly different from 1 ($p < 0.05$) are marked in orange, others are marked in blue.*



⇑ *Figure 3. Point estimates from the best performing variant Blue dots indicate negative controls. Yellow diamonds indicates positive controls.*

Conclusions

- **SCCS considering the first outcome occurrence, adjusting for multiple drugs and using a 30-day risk window showed the best performances for drug-related UGIB assessment in the SNDS.**
- **Low systematic error seems to affect SCCS but protopathic bias and confounding by indication remained unaddressed issues.**
- **Calibration process reduced the number of false positives but increased the number of false negatives.**
- **ALCAPONE showed that SCCS with optimum settings has the potential to generate accurate UGIB-related drug safety alerts from SNDS, including hypotheses on its possible population impact.**

ICPE All Access- September 17-18, 2020,

www.bordeauxpharmacoepi.eu
@BxPharmacoEpi