Result of the ALCAPONE project: Identification of the best design for the assessment of drugs associated with upper gastrointestinal bleeding in the French National Healthcare System database (SNDS)

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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.

➔ **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.

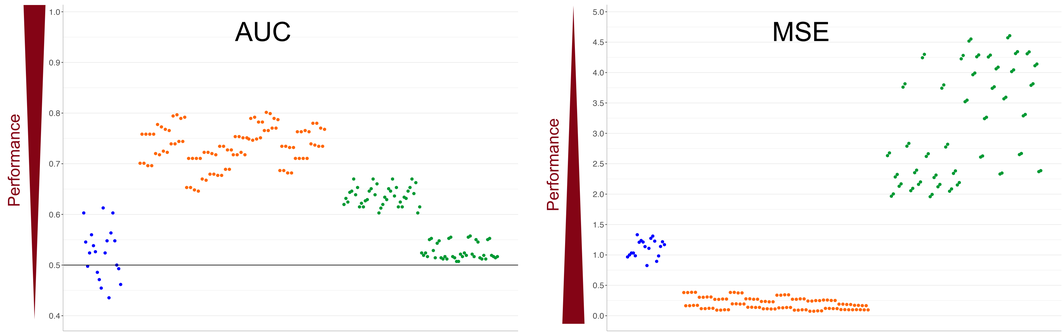


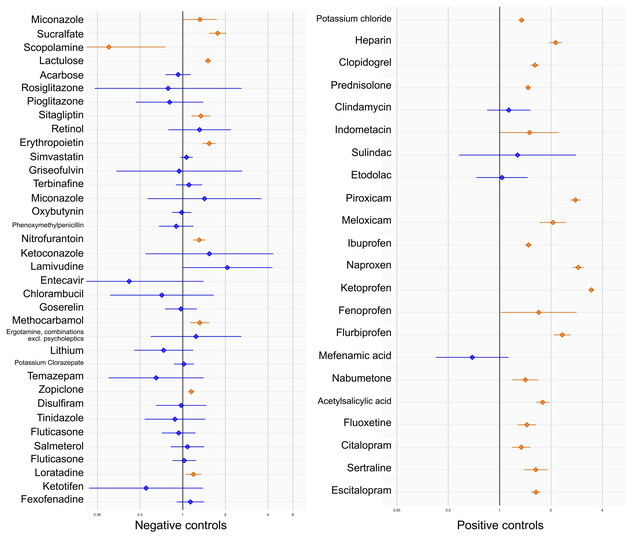
***Figure 1**. Area under the receiver operating characteristics curve (AUC) and mean square error (MSE) for the assessed variants in the 1/10th sampled population*

***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*

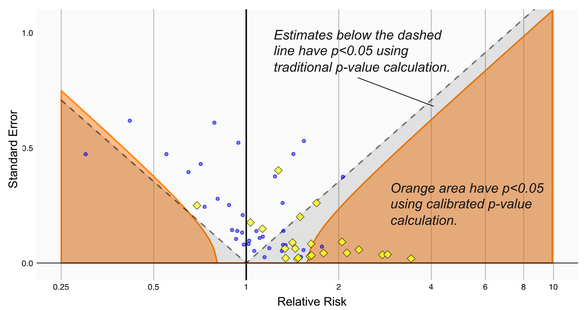
	Variants with low AUC n=59	Variants with high AUC n=37	High *vs.* Low AUC OR [IC à 95%]	*p*	AUC of the univariate model
Age				0.8375	0.51
Not included	30 (50.8)	18 (48.6)	1		
Included	29 (49.2)	19 (51.4)	1.09 [0.48 - 2.48]		
Seasonality				0.8375	0.51
Not included	30 (50.8)	18 (48.6)	1		
Included	29 (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.**

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