Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

Alert generation using the case-population approach in the French claims databases: ALCAPONE

N. Thurin[1,2,3], R. Lassalle[1], P. Blin[1], M. Pénichon[1], M. Schuemie[4], J.J. Gagne[5], J. Rassen[6], J. Benichou[7,2], A. Weill[8], C. Droz-Perroteau[1], N. Moore[1,2,3]

[1]Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France – [2]INSERM U1219, Bordeaux, France – [3]CHU de Bordeaux, Bordeaux, France – [4]Janssen Research & Development, Observational Health Data Sciences and Informatics (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 – [6]Aetion, Inc., New York, NY, USA – [7]CHU de Rouen, INSERM U1219, Rouen, France – [8]Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés, Paris, France

Abstract

Background: France has a nationwide healthcare insurance system database – the SNIIRAM (*Système national d'information inter-régimes de l'Assurance maladie*) – that covers about 99% of the French population. A 1/97th sample – the EGB (*Echantillon généraliste de bénéficiaires*) – is also available. SNIIRAM has not been tested for drug safety alert generation. **Objectives**: To present the methodology and assess the feasibility of the ALCAPONE project. **Methods**: ALCAPONE is based on historical data from the SNIIRAM, and the OMOP reference set which, consists of 4 main outcomes - Acute Liver Injury (ALI), Myocardial Infarction (MI), Acute Kidney Injury (KI), and Upper Gastrointestinal Bleeding (UGIB) – and 165 positive and 235 negative drug controls. ALCAPONE consists of 3 main stages: (i) selection of detectable positive and negative controls (*ie.* with a minimum detectable relative risk ≤ 1.25) through the realization of a feasibility study in the EGB; (ii) detection of the selected controls *via* 3 case-based designs: case-population approach (CP), case-control design (CC) and self-controlled case series (SCCS), including several variants (number of controls, risk window, adjustment strategy, *etc.*); and (iii) comparison of design performance using area under the ROC curve. Cases were identified between 01/01/2009 and 12/31/2014 according to hospitalization primary diagnoses. A narrow and a broad definition have been developed for each outcome. For each design and outcome, the accuracy of the measures of association will be used to calibrate the methods. **Results**: The feasibility study is currently ongoing. Based on the broad outcome definitions, 40 ALI, 6,334 MI, 758 KI and 1,771 UGIB have been identified in the EGB, versus 33 ALI, 3,202 MI, 94 KI and 1,390 UGIB for the narrow one. In respect of the reference set, 120 positive and 126 negative drug controls are present in the EGB. Power calculations are in process to determine which controls will have enough power to be investigated through the 80 CP, 40 CC and 336 SCCS variants. **Conclusions**: This project will identify and calibrate the best design to investigate ALI, MI, KI and UGIB in the SNIIRAM, thus enabling the generation and validation of drug safety alerts.

Conflict of Interest Statement

This study is supported by an unconditional grant from the French Ministry of Health (PREPS, 2014, 14-0635), and supervised by an independent expert Scientific Committee. It was designed, conducted, and analyzed independently by the Bordeaux PharmacoEpi Platform, CIC Bordeaux CIC1401 of the Bordeaux University. This study was registered with the European Medicine agency's EUPAS registry (www.encepp.eu), under study number 13031, and carries the ENCePP Study seal.

Background

- **The SNIIRAM[1]** is the French nationwide healthcare insurance system database covering 99% of the French population. It has not ben tested for drug safety signal generationa
- **The EGB[2]** is a 1/97th SNIIRAM sample
- **ALCAPONE** (Alert generation using the case-population approach in the French claims databases) is a project aiming to:
  - ✓ Develop on SNIIRAM the **case-population approach for drug safety signal generation**
  - ✓ **Compare the performances** of this approach with the case-control design and self-controlled case series ones, according to the Observational Medical Outcome Partnership (OMOP) methodology

[1] *Système national d'information inter-régimes de l'Assurance maladie* – [2] *Echantillon généraliste de bénéficiaires*

Objectives

- **To present the methodology** of the ALCAPONE project.
- **To assess the feasibility** of the project through preliminary results from the EGB database.

Methods

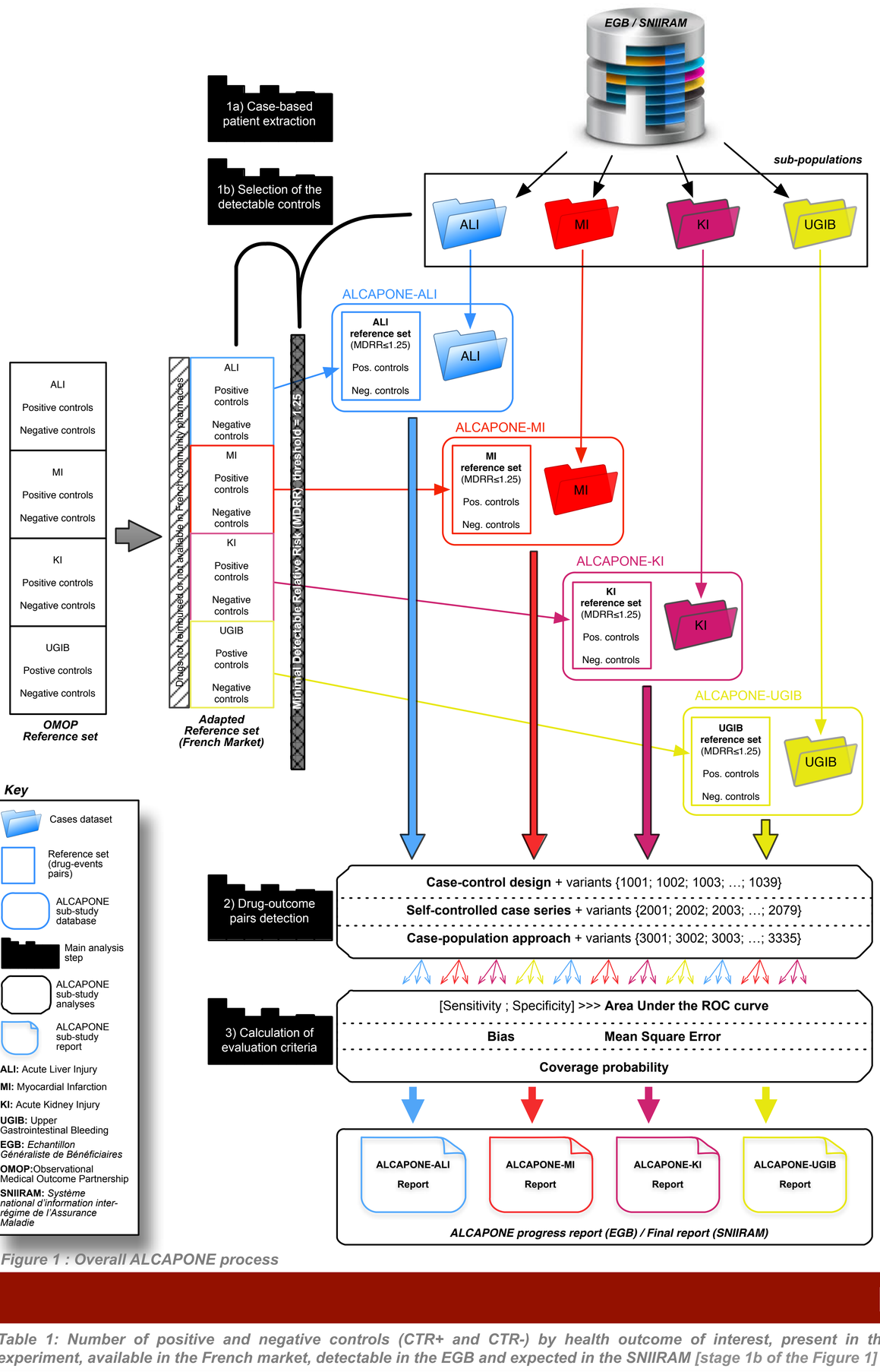

Figure 1 : Overall ALCAPONE process

• Study design

- ✓ **OMOP reference set**
  - 4 health outcomes of interest
    - Acute liver injury (ALI)
    - Acute kidney injury (KI)
    - Myocardial infarction (MI)
    - Upper gastrointestinal bleeding (UGIB)
  - Drug controls
    - Positive controls (CTR+) = have been associated with the outcome of interest (RR>1)
    - Negative controls (CTR-) = have not been associated with the outcome of interest (RR≈1)
- ✓ **Historical data**
  - From the **EGB** (feasibility study) and from the **SNIIRAM** (final study)
  - Case-based extractions between 01/01/2009 and 12/31/2014

• Project stages

1. Case-based patients extraction and selection of the detectable drug controls

- Extraction (from EGB or SNIIRAM) of 4 sub-populations : ALI, MI, KI, UGIB
  - According to a narrow definition
  - According to a broad definition.
- Selection of the drugs available and reimbursed in the French community pharmacies among the ones of the OMOP Reference set .
- Calculation of the minimum detectable relative risk (MDRR) with α = 0,05 and 1-β = 0,80 of each drug-outcome pair. $MDRR = \left[1 + \frac{z_\alpha - z_{1-\beta}}{2\sqrt{patients\ exposed}}\right]^2$
- Elimination of the controls with MDRR > 1,25.

➔ Generation of 4 sub-study databases composed of the cases extracted for a health outcome of interest and the corresponding reference containing the detectable drug controls.

2. Drug-outcome pairs detection

- Generation of a measure of association for each drug-outcome pair
  - *Via* 3 study designs: (1) case-control, (2) self-controlled case series and (3) case-population
  - Each study design is repeated according to different settings *e.g.*:
    - Case-control: number of controls per case, matching strategy…
    - Self-controlled case series: adjustment strategy, pre-exposure window…
    - Case-population exposure window, exclusion period…
  - Each setting of a design is considered as a variant.

➔ Generation of one measure of association by drug-outcome pair and design variant.

3. Comparison of design and design variants performances

- Discriminating power
  - Detected CTR+ et CTR- ➔ Specificity & Sensitivity ➔ Area under the ROC curve
- Accuracy of the measure of association (for CTR- only)
  - $MSE = mean[[\log(RR_{est}) - \log(RR_{true})]^2]$
  - $Bias = mean[\log(RR_{est}) - \log(RR_{true})]$
  - Coverage probability: frequency over replications that the confidence interval contains the true value.

➔ Selection of the best design variant for each health outcome of interest.

➔ Calibration of the selected design variant based on the CTR-.

Results

Table 1: Number of positive and negative controls (CTR+ and CTR-) by health outcome of interest, present in the OMOP experiment, available in the French market, detectable in the EGB and expected in the SNIIRAM [stage 1b of the Figure 1]

		OMOP Experiment[1]			French market	EGB (1/97th SNIIRAM sample)		SNIIRAM	
		OMOP Reference set	Number of detectable controls[2]		Reference set	Number of detectable controls[2]		Expected number of detectable controls[2]	
			Narrow definition	Broad definition		Narrow definition	Broad definition	Narrow definition	Broad definition
ALI	CTR+	81	57	63	56	0	0	15	18
	CTR-	37	32	32	19	0	0	1	2
MI	CTR+	36	26	33	26	3	5	23	23
	CTR-	66	37	46	37	1	5	29	31
KI	CTR+	24	19	-	19	0	3	11	18
	CTR-	64	34	-	32	0	0	5	16
UGIB	CTR+	24	24	22	19	5	7	18	19
	CTR-	66	53	49	38	1	1	30	31

[1] Results from the MarketScan Commercial Claims and Encounters database [2] Drug controls with MDRR≤1.25

- The left part of Table 1 shows the number of controls with MDRR≤1.25 in a database of the OMOP experiment. The right side displays the results of the feasibility study and its extrapolation to the SNIIRAM. Table 2 presents the number of outcomes extracted from the EGB.

***Example of Table 1. reading**: Among the 81 positive controls of the ALI OMOP Reference set, only 56 are available on the French market. The number of exposed cases in the EGB is not enough to detect an association ≤1.25 whatever the definition. By extrapolation, the SNIIRAM would be powerful enough to detect an association ≤1.25 for 15 of the 56 positive controls and 1 of the 19 negative ones (narrow definition).*

Table 2: Outcomes included in the ALCAPONE project and corresponding number of patients by health outcome of interest definition in the EGB; Expected number for SNIIRAM [stage 1a of the Figure 1]

		ALI		MI		KI		UGIB	
		Narrow Def.	Broad Def.	Narrow Def.	Broad Def.	Narrow Def.	Broad Def.	Narrow Def.	Broad Def.
EGB (observed)	n (outcomes)	33	40	3202	6334	94	93	1390	1771
	n (patients)	32	40	2757	4962	758	712	1213	1522
SNIIRAM (expected)	n (outcomes)	3960	4800	384240	760080	11280	11160	166800	212520
	n (patients)	3840	4800	330840	595440	90960	85440	145560	182640

- The low number of detectable controls in ALI and KI could result from the small size of the extraction and the random error: to be considered as detectable in the SNIIRAM, only 2 exposed cases are required in the EGB.

Conclusion

- The feasibility study shows that the EGB is not powerful enough, especially when the event and/or the exposition is rare. The SNIIRAM seems to have a sufficient size to implement the ALCAPONE process.
- The step 1b) "Selection of detectable controls" must be repeated after SNIIRAM extraction to confirm the number of detectable drug controls. If necessary, additional ones could be added to enhance the French market Reference set.
- The identification of the optimal design for a health outcome of interest will enable the generation and the validation of drug safety alerts.

Scan me to download ALCAPONE poster

33rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 26-30, 2017, Montréal, QC, Canada