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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.

Objectives

- Drug safely 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).

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.

Conclusions

- 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, naproxen, fluoxetine, citalopram, sertraline.
- SCCS considering the first outcome occurrence, adjusting for multiple UGIB-related 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.

Table 1. Description of design variants

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Case-control</th>
<th>Case-population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-controlled case series</td>
<td>All occurrences / First occurrence</td>
<td>All occurrences / First occurrence</td>
</tr>
<tr>
<td>Risk window: 30 days following / Overall period covered by dispensing</td>
<td>0 day / 7 days / 30 days</td>
<td>0 day / 7 days / 30 days</td>
</tr>
<tr>
<td>Pre-exposure window: 0 day / 7 days / 30 days</td>
<td>Age included into the model: Yes / No</td>
<td>Age included into the model: Yes / No</td>
</tr>
<tr>
<td>Seasonality included into the model: Yes / No</td>
<td>All dispensed drugs included into the model (multiple drug use): Yes / No</td>
<td></td>
</tr>
<tr>
<td>All dispensed drugs included into the model: Yes / No</td>
<td>Parameters that had major impact on results of the best performing approach were identified through logistic regression:</td>
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</tr>
</tbody>
</table>
| 1. Dependent variable = probability that a variant had an AUC >70th percentile of the AUC distributions of the variants. | | Dependence of 
| 2. Independent covariates = parameters that were varied in the variant. | | Handels / predictors |
| The variant with the best AUC and MSE was applied to the full unsampled UGIB population. | | Calibration approach for multiple drug use: The AUC of the aggregated data, extrapolation of the aggregated data, and measure of association. |
| 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 calculate p-value to take into account systematic and random error. | | |