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.

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

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

<table>
<thead>
<tr>
<th>Design variant</th>
<th>Case-control</th>
<th>Self-controlled case series</th>
<th>Case-population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk window</td>
<td>All occurrences / first occurrence</td>
<td>All occurrences / first occurrence</td>
<td>All occurrences / first occurrence</td>
</tr>
<tr>
<td>Lag periods</td>
<td>0/6/12/18/24 days</td>
<td>0/6/12/18/24 days</td>
<td>0/6/12/18/24 days</td>
</tr>
<tr>
<td>Controls matched per case (age and gender)</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Age included into the model</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>All dispensed drugs included into the model (multiple drug use)</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

- Performance of each design variant was assessed based on the area under the receiving operating 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.

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 SSCS 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.

References

[3] Calibration process reduced the number of false positives but increased the number of false negatives.

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