An automated system combining safety signal detection and prioritization adapted to healthcare databases

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Disclosure

• I conducted this work during my PhD for which I was granted by the French Ministry for Higher Education and Research

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  – ANSM had no role concerning collection, analysis, and interpretation of the data; writing study reports and scientific articles
  – The results publication represents the views of the authors and does not necessarily represent the opinion of ANSM

• I have no conflict of interest directly relevant to the content presented
Introduction

- Actual post-marketing drug safety monitoring systems are based on spontaneous reporting data
  - They are limited in the identification of adverse events not evocative of a drug causation
    - E.g. myocardial infarction (rofecoxib, rosiglitazone)

- New tools using data from healthcare databases have recently been developed
  - Focused essentially on signal detection or signal validation
  - Signal prioritization have been neglected
Introduction

• Signal prioritization is the step following the detection
  – Detection needs to be sensitive to avoid missing a real drug safety issue
  – Detection leads thus to identify thousands of safety signals
    - Plausible and unknown
    - Plausible but already known
    - Implausible
    +
    ++
    +++

• Signal prioritization is thus crucial to help stakeholders handle these thousands of detected safety signals to make the relevant regulatory actions
Objectives

• To develop and to assess an automated system combining safety signal detection and prioritization
  – Adapted to healthcare databases
  – Adapted for the surveillance of drugs used in chronic diseases

• Plan
  – Study #1 – Development of the system: detection
  – Study #2 – Development of the system: prioritization
  – Study #3 – Assessment of the performance of the system
  – Study #4 – Concordance of prioritization: system vs. stakeholders
Study #1
Development of the system: detection
Study #1 – Introduction

• Background
  – Numerous methods for safety signal detection developed
  – Works conducted notably by International initiatives (ex. OMOP)
    • Systematic investigation of the best configuration
    • Assessment on empirical and simulated data
  – No consensus about the method to use

• Objective
  – To identify the most appropriate method for the safety signal
detection adapted to healthcare databases
Study #1 – Methods

• Literature review
  − Search strategy
    • PubMed and Scopus
    • Select articles related to International initiatives (e.g. OMOP)
    • Systematic screening of references
      − « snowballing » and « reverse snowballing » approaches

• Selection of the most appropriate method
  − Pre-selection based on statistical performance (AUC)
  − Final selection based on pragmatic criteria
    • Dedicated for screening any drug/AE pair
    • Understanding of its principle
    • Providing of a risk estimation
Study #1 – Results

- 15 methods classified in 7 groups

Pharmacoepidemiological study design
- Cohort
- Case/control
- Case-crossover
- Self-controlled cases series
- Self-controlled cohort

Sequence symmetry analysis

Temporal Association Rule
- MUTARA/HUNT
- IC-TPD
- Fuzzy logic

Sequential statistical testing
- MaxSPRT
- CSSP

Supervised machine learning
- Tree-based scan statistic

Disproportionality analysis
- PRR. ROR. MGPS. BCPNN
- LGPS-LEOPARD
Study #1 – Results

- **PRR. ROR. MGPS. BCPNN**
  - AUC = 0.63 / 0.53 / 0.60 / 0.55

- **LGPS-LEOPARD**
  - AUC = 0.58 / 0.59

- **Cohort**
  - AUC = 0.68 / 0.54 / 0.61

- **Case/control**
  - AUC = 0.61 / 0.59 / 0.61

- **Case crossover**
  - AUC = 0.61

- **Self-controlled case series**
  - AUC = 0.57 / 0.71 / 0.67

- **Self-controlled cohort**
  - AUC = 0.53 / 0.81 / 0.77

- **Sequence symmetry analysis**
  - Se = 0.67, Sp = 0.93, VPP = 0.77, VPN = 0.87

- **MUTARA/HUNT**
  - AUC = 0.60

- **IC-TPD**
  - AUC = 0.65 / 0.75 / 0.67 / 0.57

- **Fuzzy logic**
  - –

- **MasXPRT**
  - AUC = 0.23

- **CSSP**
  - AUC = 0.38

- **Supervised machine learning**
  - AUC = 0.81 / 0.86

- **Tree-based scan statistic**
  - –
Study #1 – Results

PRR. ROR. MGPS. BCPNN
AUC = 0.63 / 0.53 / 0.60 / 0.55

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Supervised machine learning
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Study #1 – Results

<table>
<thead>
<tr>
<th>Pragmatic criteria for distinguishing the methods for signal detection</th>
<th>Self-controlled designs*</th>
<th>Sequence symmetry analysis</th>
<th>Supervised machine learning</th>
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<tbody>
<tr>
<td>1. Dedicated for screening any drug/AE pair</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2. Understanding of its principle</td>
<td>+</td>
<td>+</td>
<td>−</td>
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<td>3. Providing of a risk estimation</td>
<td>+</td>
<td>+</td>
<td>−</td>
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</table>

*Include self-controlled case series and self-controlled cohort
# Study #1 – Results

## Pragmatic criteria for distinguishing the methods for signal detection

<table>
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*Include self-controlled case series and self-controlled cohort
Study #1 – Conclusion

• The sequence symmetry analysis (SSA)
  – Considers, for each drug/event pair and for each person,
    • 1st drug dispensing and 1st event occurrence
    • Only if they occur after a given run-in period (e.g. 12 months)
  – Computes the ratio of the number of persons, observed during the study period, experiencing
    • Sequence Drug→Event vs. sequence Event→Drug
    • Considering a given time period (e.g. 12 months)
  – Adjusts this ratio on trends of drug use and outcome occurrence
    • Adjusted sequence ratio (ASR)
    • Interpretation: equivalent to an incidence rate ratio
Study #1 – Conclusion

• Strengths of the SSA
  – Principle easy to understand and provides risk estimates
  – Dedicated for screening any drug/event pair in longitudinal data
  – Controlling for numerous confounding factors
    • Time-constant confounding factors
    • Biases related to the trends of drug use or event occurrence

• Limitations of the SSA
  – Sensitive to protopathic and indication biases
    • Concerned every method for signal detection in healthcare data
    • Biases to control +++ in the signal prioritization process
  – Sensitive to events affecting the probability to receive the drug
    • But, this does not impact the sensitivity of detection
Study #2
Development of the system: prioritization
Study #2 – Prioritization

• Background
  – Complex and multifactorial process
    • Clinical
    • Epidemiological
    • Pharmacological
    • Regulatory
  – Essential for handling the thousands of the detected signals
  – Pharmacovigilance systems have implemented
    • Concepts or frameworks for standardizing the prioritization process
    • Automated algorithms for the signal prioritization
      – Adapted to spontaneous reporting data

• Objective
  – To develop an automated algorithm for the signal prioritization
Study #2 – Methods

• Literature review
  – Search strategy
    • PubMed and Scopus
    • Articles related to “signal” AND “prioritization”, “filter”, or “triage”
    • Systematic screening of references
      – « snowballing » and « reverse snowballing » approaches

• Selection of the strategies
  – Essential criteria to use
    • Criteria adaptable to healthcare data
    • Supplementary criteria dedicated to healthcare data

• Selection of (semi-) automated algorithms
  – Combination of the criteria
  – Presentation of the results
Study #2 – Results

• 14 strategies for signal prioritization identified

• Inspired from the ‘SNIP’ concept of Waller et al. (1999)*
  – Strength of the signal
  – Novelty of the signal
  – clinical Importance (or Impact) of the signal
  – Potential for preventive measures

• Consensus on
  – « Strength », « Novelty », « Impact » are essentials
  – « Prevention » abandoned or replaced by other regulatory considerations

## Study #2 – Results

- Main criteria retrieved

<table>
<thead>
<tr>
<th>Strength of the signal</th>
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<th>Others criteria</th>
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<td>Seriousness of cases reported</td>
<td>Measures for prevention</td>
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<td>Biological plausibility</td>
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<td>Interest of stakeholders for the signal</td>
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<td>Information in favor of a causal link (e.g. positive rechallenge)</td>
<td>Increasing of reporting rate</td>
<td>Frail populations (e.g. children, pregnant women)</td>
<td>Risk perception in the population</td>
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<tr>
<td></td>
<td></td>
<td>Prevalence of drug use</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Estimated number of cases in excess</td>
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## Study #2 – Results

- **Main criteria retrieved**
  - Adaptable to healthcare data

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Study #2 – Results

• Criteria specific to healthcare data
  – Criteria related to the use of drugs
    • Incidence of use
    • Trends of incidence of use
  – Criteria related to the limitations of the signal detection
    • Event not related to drug indications (control for protopathic bias)
  – Criteria related to the risk estimates
    • Lower limit of the 95% confidence interval (95%CI)
    • Precision of the risk estimate
  – Criteria related to economical aspect
    • Cost of the event for the insurances
### Study #2 – Results

- 8 (semi-) automated algorithms for signal prioritization

<table>
<thead>
<tr>
<th>Criteria based on</th>
<th>Impact Analysis*</th>
<th>RPPS*</th>
<th>UMC triage*</th>
<th>VigiRank*</th>
<th>PS-SP</th>
<th>Lab MADA</th>
<th>Thai MADA*</th>
<th>EU-ADR</th>
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<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Other</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Criteria processing               |                   |       |             |           |       |          |            |        |
| Categorization                    | X                |       | X           | X         |       | X        | X          | X      |
| Normalization                     |                   |       |             |           |       |          |            |        |

| Output presentation               |                   |       |             |           |       |          |            |        |
| Grouping by level of priority     | X                |       | X           | X         |       | X        | X          | X      |
| Ranking by decreasing order of value of priority |                   |       |             |           |       |          |            |        |

*developed by regulatory authorities
Study #2 – Results

- 8 (semi-) automated algorithms for signal prioritization

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| Criteria processing                        |                  |       |             |           |       |          |            |        |
| Categorization                             | x                |       |             |           | x     |          |            | x      |
| Normalization                              |                  |       |             |           |       |          |            |        |

| Output presentation                        |                  |       |             |           |       |          |            |        |
| Grouping by level of priority              | x                |       |             |           | x     |          |            | x      |
| Ranking by decreasing order of value of priority | x    | x     |             |           | x     |          |            |        |

*developed by regulatory authorities
Study #2 – Conclusion

• Criteria to consider
  – Strength of the signal
  – Novelty of the signal
  – Impact of the signal
  – Other : patterns of drug use

• Categorization of the criteria
  – Allows to combine criteria of different nature
  – Weighting of the criteria

• Signals grouped by levels of priority
  – Appear more consistent with stakeholders expectations
Study #2 – Conclusion

- Longitudinal–SNIP (L–SNIP) algorithm
  - 14 criteria: categorized and weighted from 1 to 4
  - L–SNIP score: weighted sum of the criteria
  - Signal prioritization results
    - “prioritized” if L–SNIP score in top 10%
    - “not prioritized” otherwise

<table>
<thead>
<tr>
<th>Strength of the signal</th>
<th>Novelty of the signal</th>
<th>Impact of the signal</th>
<th>Patterns of drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk estimate</td>
<td>Signal not mention in SPC</td>
<td>Potential number of attributable cases</td>
<td>Event not related to drug indications</td>
</tr>
<tr>
<td>Lower limit of the 95%CI</td>
<td>Drug seniority</td>
<td>Cost of hosp. for the event</td>
<td>Drug use in vulnerable pop. (1): children</td>
</tr>
<tr>
<td>Precision of risk estimate</td>
<td>Increasing in risk over time</td>
<td>1</td>
<td>Drug use in vulnerable pop. (1): childbearing women</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Prevalence of drug use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Incidence of drug use</td>
</tr>
<tr>
<td></td>
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<td>1</td>
<td>Increasing of the incidence of drug use over time</td>
</tr>
</tbody>
</table>
Study #3

Assessment of the performance of the developed system
Study #3 – Performance

• Objective
  - To assess the performance of the system combining safety signal detection and prioritization from healthcare databases

• Pilot study applied on Type 2 diabetes
  - Frequent chronic disease in the population
    - New risk identified = major impact in terms of public health
  - Treatments have greatly changed for a decade
    - New drugs marketed in 2008
    - Withdrawal or restriction of use of glitazones for safety reasons
      - Bladder cancer, heart failure
Study #3 – Methods

• Data source
  – Echantillon Généraliste des Bénéficiaires (EGB) claims database
    • 1/97th sample of the population covered by the French national health insurance system
    • Representative in terms of age, sex, geographic location, and care consumption
  – EGB includes comprehensive and anonymous data
    • Outpatient drug dispensing (coded with ATC classification)
    • Hospitalization diagnoses (coded with ICD-10 classification)

• Study population
  – Persons included in EGB at least 1 year between 2005 and 2015
Study #3 – Methods

• Drug exposure definition
  – Dispensing as surrogate for drug exposure
  – Noninsulin glucose-lowering drugs (NIGLDs) identified at ATC level 5
  – Selection of the 1\textsuperscript{st} dispensing if it occurred $\geq 1$ year of follow-up

• Event definition
  – Hospitalization diagnoses as surrogates for adverse events
  – Selection of ICD-10 codes corresponding to MedDRA\textsuperscript{®} important medical events (IME)
    • Alignment of ICD-10 codes with those included in the MedDRA\textsuperscript{®} IME terms list using the Unified Medical Language System tool
  – Selection of the 1\textsuperscript{st} occurrence if it occurred $\geq 1$ year of follow-up
Study #3 – Methods

• Signal detection
  − Sequence Symmetry Analysis
  − Quarter analyses between 2008-2015 for each NIGLD/IME pair
    • ≥1 exposed case observed during the quarter of analysis
    • ≥3 exposed cases observed in the population
  − 95%CI computed using the bootstrap method (500 replications)
  − Signal detected if the lower limit of the 95%CI > 1

• Signal prioritization
  − L–SNIP algorithm
    • Signal prioritized if L–SNIP score in the top 10%
    • Signal not considered as priority otherwise
Study #3 – Methods

• Reference dataset
  – NIGLD/IME pairs with sufficient power to detect a relative risk of 2 based on the drug and event prevalence in the EGB
    • Positive controls: associations listed in SPCs
    • Negative controls
      – Random selection among all the other associations
      – Ratio of 3 negative controls for 1 positive control

• Performance assessment
  – Se, Sp, PPV, and NPV
  – Performance for signal prioritization
    • Selection of positive controls including in SPCs after 2008
    • Ability of the system to identify them before the mention in SPCs
Study #3 – Methods

• Analysis of prioritized signals
  – Development of a R Shiny App to analyze the detected and/or prioritized signals
Study #3 – Results

Introduction

1 – Detection

2 – Prioritization

3 – Performance

4 – Concordance

Conclusion
## Study #3 – Results

- **Performance for signal detection**
  - Reference set: 15 positive controls and 45 negative controls

<table>
<thead>
<tr>
<th></th>
<th>Positive controls</th>
<th>Negative controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detected</strong></td>
<td>7</td>
<td>14</td>
<td>PPV = $7/(7+14) = 33%$</td>
</tr>
<tr>
<td><strong>Not detected</strong></td>
<td>8</td>
<td>31</td>
<td>NPV = $31/(31+8) = 80%$</td>
</tr>
<tr>
<td></td>
<td>Se = $7/(7+8) = 47%$</td>
<td>Sp = $31/(31+14) = 69%$</td>
<td></td>
</tr>
</tbody>
</table>

Introduction

1. Detection
2. Prioritization
3. Performance
4. Concordance

Conclusion
Study #3 – Results

• Performance for signal prioritization
  – Positive controls limited to 3 associations
  – Added value of the prioritization of the signals detected
    • Se, Sp, and NPV similar
    • 7-fold increase of the PPV with the prioritization

<table>
<thead>
<tr>
<th></th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
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<tbody>
<tr>
<td>Detection + L–SNIP</td>
<td>33%</td>
<td>100%</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>Detection</td>
<td>33%</td>
<td>100%</td>
<td>14%</td>
<td>95%</td>
</tr>
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</table>
Study #3 – Results

- A relevant safety signal identified with the gliptins and the risk of venous thromboembolic events

*Association prioritized at least once*
Study #3 – Conclusion

• Performance for signal detection promising
  – Similar to that observed in other studies using SSA

• The use of the L–SNIP algorithm for the signal prioritization
  – Makes the identification of relevant signals easier
  – Performance needs to be confirmed in a larger reference set
    • Based on only 3 positive controls

• The developed system highlighted a new drug safety issue
  – Gliptins and risk of venous thromboembolism
  – Potentially major impact in terms of public health
Study #4:
Concordance of the signal prioritization: system vs. stakeholders
Study #4 – Concordance

• Background
  − The developed system needs to match with the stakeholders’ point of view
    • In the perspective of a future use for the routine surveillance of the safety of drugs
  − The prioritization is the crucial aspect
  − The L–SNIP algorithm could be subject to discussion
    • Criteria retained, weighting

• Objective
  − To assess the concordance of the signal prioritization from the L–SNIP algorithm with that of the stakeholders
Study #4 – Methods

• Target population
  − Persons with decision-making power
    • Health professionals with expertise mission for the Public Agencies
    • Managers in Public Agencies
    • Managers in pharmaceutical companies
  − Persons with ability to influence the decision-making
    • Managers in patient organizations
    • Journalists
Study #4 – Methods

• Questionnaire-based survey
  – Available online
    • To guarantee anonymity
    • Available during 3 months
    • E-mail reminder every 2 weeks
  – Data collection
    • Social information (position, diploma, etc.)
    • Appraisal of
      – The use of an automated prioritization as decision support
      – The criteria proposed for the signal prioritization
    • Signal prioritization exercise considering 10 fictive detected signals
Study #4 – Methods

• Prioritization exercise
  – 10 fictive signals related to long-term treatments
  – Based on some criteria included in the L–SNIP algorithm
    • Risk estimate
    • Prevalence and Incidence of drug use
    • Year of marketing
    • Mean cost of hospitalization for the adverse event
    • Number of potential attributable cases
    • Knowledge of the association
  – Prioritization according 3 levels of priority: High, Moderate, Weak
Study #4 – Methods

• Assessment of concordance of prioritization
  – Prioritization from the surveyed
    • Selection of the modal response among those collected
  – Prioritization from L–SNIP algorithm
    • L–SNIP scores compared to those obtained in Study #3
    • Classification modified to match with that proposed in the exercise
      – High if L–SNIP score in Top 1-10%
      – Moderate if L–SNIP score in Top 11-50%
      – Weak if L–SNIP score in Top 51-100%
  – Concordance measured with Kendall’s concordance coefficient $\tau$
Study #4 – Results

- 32 respondents among ~150 persons solicited

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<thead>
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<th>Actual or former organization</th>
<th>N (%)</th>
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<tr>
<td>Hospital</td>
<td>26 (81.3)</td>
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<tr>
<td>Public Agencies</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Pharmaceutical companies</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Media</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>Patients organizations</td>
<td>1 (3.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Main diploma</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.D.</td>
<td>14 (43.8)</td>
</tr>
<tr>
<td>Pharm.D.</td>
<td>9 (28.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific skills</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td>16 (50.0)</td>
</tr>
<tr>
<td>Epidemiology / pharmacoepidemiology</td>
<td>9 (28.1)</td>
</tr>
</tbody>
</table>
Study #4 – Results

• 20 (62.5%) favorable to an automated signal prioritization

• Appraisal of criteria proposed for signal prioritization

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No, not at all</th>
<th>Rather no</th>
<th>Rather yes</th>
<th>Yes definitely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk estimate</td>
<td>1</td>
<td>0</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Number of potential attributable cases</td>
<td>1</td>
<td>1</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Prevalence of drug use</td>
<td>1</td>
<td>6</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Incidence of drug use</td>
<td>1</td>
<td>4</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Knowledge of the association</td>
<td>1</td>
<td>3</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Year of marketing</td>
<td>5</td>
<td>10</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Mean cost of hospitalization for the event</td>
<td>11</td>
<td>14</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>
## Study #4 – Results

- Concordance of signal prioritization

<table>
<thead>
<tr>
<th>Fictive case</th>
<th>Drug indication</th>
<th>Adverse event</th>
<th>Prioritization stakeholders</th>
<th>Prioritization L–SNIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Type 2 diabetes</td>
<td>Cognitive disorders</td>
<td>5 High 22 Moderate 5 Weak</td>
<td>Weak</td>
</tr>
<tr>
<td>2</td>
<td>Type 2 diabetes</td>
<td>Crohn's disease</td>
<td>17 Moderate 11 Weak 4 Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Type 2 diabetes</td>
<td>Crohn's disease</td>
<td>17 Moderate 10 Weak 5 Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Prevention of VTE</td>
<td>Orthostatic hypotension</td>
<td>4 Moderate 15 Weak 13 Weak</td>
<td>Weak</td>
</tr>
<tr>
<td>5</td>
<td>Prevention of AMI</td>
<td>Migraine</td>
<td>8 Moderate 13 Weak 11 Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>6</td>
<td>Serious sleep disorder</td>
<td>Femoral neck fracture</td>
<td>15 Moderate 13 Weak 4 High</td>
<td>High</td>
</tr>
<tr>
<td>7</td>
<td>Epilepsy</td>
<td>Ventricular tachycardia</td>
<td>14 Moderate 15 Weak 3 Moderate</td>
<td>Moderate</td>
</tr>
<tr>
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<td>Schizophrenia</td>
<td>Anorexia</td>
<td>9 Moderate 15 Weak 8 Weak</td>
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<tr>
<td>9</td>
<td>Oral contraceptive</td>
<td>Iron deficiency anemia</td>
<td>3 Moderate 18 Weak 11 Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>10</td>
<td>Asthma</td>
<td>Sleep disorder</td>
<td>3 Moderate 15 Weak 14 Weak</td>
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### Study #4 – Results

- **Concordance of signal prioritization**

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Kendall’s concordance coefficient, $\tau = 59\%$
Study #4 – Conclusion

• L–SNIP algorithm could have a role of decision support among stakeholders
  – Signal prioritization globally concordant with that of the stakeholders
  – Criteria included in the L–SNIP algorithm judged favorably
    • Excepted for the cost of hospitalization for the event
      – Other medico-economic criterion to consider?

• Main limitation
  – Small sample with potential non-representativeness
Conclusion & perspectives
Conclusion

• The developed automated system of safety signal detection and prioritization in healthcare databases was based on the best evidence from the scientific literature

• The assessment of the developed system
  – Good performance from reference dataset assessment
  – Able to highlight a relevant safety signal (need to confirm)
  – Prioritization concordant with that of stakeholders

• Main perspectives
  – Improving the system by reducing biases in signal detection
  – Adapting the system for the identification of long-term drug adverse events