Exposure models based on the Waiting Time Distribution.

To be exposed or not – is that the question?

Henrik Støvring

stovring@ph.au.dk

Joint work with Anton Pottegård & Jesper Hallas

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**Conflict of interest statement**

- Henrik Støvring
  - None relevant, but has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers and from Astra Zeneca, Pfizer, and AbbVie.

- Anton Pottegård
  - None

- Jesper Hallas
  - None relevant, but has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers and from Nycomed, Astellas, Pfizer, Novartis, Astra Zeneca, Menarini, Leo Pharmaceuticals, and Ferring.
Overview

• Reverse parametric waiting time distribution – a primer
  • Concept
  • Fundamental feature of the WTD: Two-component mixture
  • Covariates
  • Estimation of treatment probability

• Using probability of treatment as exposure covariate
  • Application: Upper gastrointestinal bleeding and NSAID treatment
  • Magnitude and precision of estimated association

• Future directions and perspectives
Reverse parametric waiting time distribution – a primer
Construction of Reverse Waiting Time Distribution
Reverse WTD

- **Answers the questions:** What is the distribution of time from the last prescription in an interval to the end of the interval?
- **Does not require subsequent follow-up to estimate prevalence**
Reverse WTD with covariates

- **Warfarin**: Package size clearly impacts the reverse WTD
Reverse WTD with covariates – Warfarin

- Joint analysis – with number of pills as covariate
- Log-normal BRD
- Estimates on exponentiated scale
- 95% CI in parantheses

<table>
<thead>
<tr>
<th>Number of pills</th>
<th>Odds ratio / odds (prevalence fraction)</th>
<th>Median ratio / Median (days)</th>
<th>σ ratio / σ (log-time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>200</td>
<td>1.66 (1.37; 2.01)</td>
<td>1.46 (1.38; 1.55)</td>
<td>0.86 (0.77; 0.96)</td>
</tr>
<tr>
<td>300+</td>
<td>1.49 (0.98; 2.25)</td>
<td>2.05 (1.88; 2.25)</td>
<td>0.75 (0.61; 0.93)</td>
</tr>
<tr>
<td>Reference</td>
<td>3.61 (3.40; 3.84)</td>
<td>54.3 (52.9; 55.8)</td>
<td>0.51 (0.49; 0.53)</td>
</tr>
</tbody>
</table>

- Odds in reference group corresponds to 78.3% prevalent users
- Median for 200 pills: \(54.3 \text{ days} \times 1.46 = 79.3 \text{ days}\)
Reverse WTD with covariates – Warfarin

- Joint analysis – with number of pills as covariate
- Adjusted for
  - Sex
  - Age continuous (centered at age 50 years)
  - Interaction of sex and age

<table>
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<th>Number of pills</th>
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<td>1.69 (1.39; 2.05)</td>
<td>1.54 (1.46; 1.63)</td>
<td>0.85 (0.76; 0.94)</td>
</tr>
<tr>
<td>300+</td>
<td>1.54 (1.01; 2.25)</td>
<td>2.21 (2.02; 2.42)</td>
<td>0.77 (0.65; 0.92)</td>
</tr>
<tr>
<td>Reference (male, 50 years, 100 pills)</td>
<td>3.02 (2.55; 3.62)</td>
<td>39.7 (36.6; 43.1)</td>
<td>0.54 (0.46; 0.64)</td>
</tr>
</tbody>
</table>
Estimated Inter-Arrival Distributions - Warfarin

Median: 54.3 days

Median: 79.3 days
Estimation of 80$^{th}$ percentile of IAD from the FRD

The percentile $\tau_{80\%}$ can be found from as the time $t$, which satisfies

$$M \cdot g(t) = (100\% - 80\%)$$
Estimate probability of still being treated

Example: If a patient has had 118 days after previous redemption without a new redemption, then there is a 20% chance the patient is still treated.
Using probability of treatment as exposure covariate
Background

- Use of NSAIDs is a known risk factor for Upper Gastro-Intestinal Bleeding (UGIB)
- Data from Funen with all hospitalizations with UGIB diagnoses in 1995-2006 and all redemptions of NSAIDs
- Matched case-control study (1:10) with matching on age and sex
- Other covariates
  - Other relevant drugs
  - Previous hospital diagnoses (UGIB, peptic ulcer, COPD, diabetes, CVD, ...)
  - Smoking and alcohol related prescriptions and diagnoses

- Standard analysis: Exposed if an NSAID was redeemed less than 30 days before the index date (Or 60... Or 90... Or 120...)
- Generally assumed: Better classification of exposure status yields higher association (OR)
Methods

• We propose the following algorithm:
  1. Estimate reverse WTD based on NSAID prescriptions in last year before index date for controls
  2. Based on last NSAID prescription redeemed before the index date, we estimate the probability that the subject is exposed to NSAID
  3. If a subject has no NSAID prescription in last year before index date -> defined as unexposed with respect to NSAID
• We estimated the reverse WTD with a Log-Normal BRD and with and without covariates
• Covariates considered:
  age, sex, quantity dispensed (in DDD), use of ibuprofen, use of PPI, diagnosis of rheumatoid arthritis, psoriasis arthritis or spondylarthritis, use of methotrexate or systemic corticosteroids
• Estimated association between UGIB hospitalization and NSAID use with logistic regression
# Results

- Conventional methods

<table>
<thead>
<tr>
<th>Exposure definition</th>
<th>Exposure probability, cases</th>
<th>Exposure probability, controls</th>
<th>Crude OR (95% confidence interval)</th>
<th>Adjusted OR #) (95% confidence interval)</th>
<th>Upper/lower confidence limit ratio for adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichotomous exposure</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Fixed window</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>30 days</td>
<td>45.0%</td>
<td>10.8%</td>
<td>7.06 (6.17 - 8.06)</td>
<td>5.17 (2.40 - 11.11)</td>
<td>4.62</td>
</tr>
<tr>
<td>60 days</td>
<td>52.4%</td>
<td>16.3%</td>
<td>5.78 (5.16 - 6.47)</td>
<td>5.13 (2.75 - 9.55)</td>
<td>3.47</td>
</tr>
<tr>
<td>90 days</td>
<td>55.3%</td>
<td>20.3%</td>
<td>4.96 (4.46 - 5.51)</td>
<td>4.73 (2.72 - 8.23)</td>
<td>3.02</td>
</tr>
<tr>
<td>120 days</td>
<td>56.5%</td>
<td>22.9%</td>
<td>4.44 (4.01 - 4.91)</td>
<td>3.64 (2.14 - 6.18)</td>
<td>2.89</td>
</tr>
</tbody>
</table>

# Adjusted for

(1) current use of the following drugs: vitamin K antagonists, aspirin, other antiplatelet drugs, dipyridamol, beta-blockers, selective serotonin reuptake inhibitors, systemic corticosteroids, proton pump inhibitors, H2 receptor antagonists, statins, nitrates, pironolactone, calcium antagonists, and bisphosphonates; (2) any history of the following events: previous UGIb, Helicobacter pylori eradication, peptic ulcer, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, heart failure, stroke, hypertension, inflammatory bowel disease, malignant disease, and renal failure; and (3) prescription or diagnosis markers of smoking or excessive alcohol consumption.

Current drug use definition: redeeming a prescription within less than 120 days before the index date.
## Results

- **WTD based method – probability of being exposed**

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<th>Exposure probability, controls</th>
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<tr>
<td>Continuous treatment probability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple model</td>
<td>0.057 (&lt;0.001 - 0.915) *)</td>
<td>&lt;0.001 (&lt;0.001 - 0.027) *)</td>
<td>6.77 (6.16 - 7.45)</td>
<td>4.75 (3.88 - 5.83)</td>
<td>1.50</td>
</tr>
<tr>
<td>Full multivariable model</td>
<td>0.037 (&lt;0.001 - 0.903) *)</td>
<td>&lt;0.001 (&lt;0.001 - 0.014) *)</td>
<td>6.99 (6.35 - 7.69)</td>
<td>4.37 (3.62 - 5.28)</td>
<td>1.46</td>
</tr>
<tr>
<td>Reduced multivariable model</td>
<td>0.038 (&lt;0.001 - 0.895) *)</td>
<td>&lt;0.001 (&lt;0.001 - 0.014) *)</td>
<td>6.98 (6.34 - 7.68)</td>
<td>4.46 (3.69 - 5.39)</td>
<td>1.46</td>
</tr>
</tbody>
</table>

*) Median and interquartile range for ever-users of NSAIDs
**Understanding the conventional methods**

Probability of being treated as estimated by reverse WTD

a: median (IQR)  b: 95\textsuperscript{th} (90\textsuperscript{th}; 99\textsuperscript{th}) percentile

<table>
<thead>
<tr>
<th>Continuous Treatment Probability, Simple Model</th>
<th>Exposed\textsuperscript{a}</th>
<th>Unexposed\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed window</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>0.985 (0.926-0.999)</td>
<td>0.350 (0.062-0.760)</td>
</tr>
<tr>
<td>60 d</td>
<td>0.915 (0.732-0.995)</td>
<td>0.125 (0.015-0.394)</td>
</tr>
<tr>
<td>90 d</td>
<td>0.829 (0.509-0.985)</td>
<td>0.043 (0.005-0.203)</td>
</tr>
<tr>
<td>120 d</td>
<td>0.760 (0.367-0.980)</td>
<td>0.020 (0.003-0.104)</td>
</tr>
<tr>
<td><strong>Fixed daily intake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 DDD/d</td>
<td>0.985 (0.904-1.000)</td>
<td>0.475 (0.095-0.953)</td>
</tr>
<tr>
<td>1.0 DDD/d</td>
<td>0.968 (0.802-0.999)</td>
<td>0.310 (0.045-0.892)</td>
</tr>
<tr>
<td>0.5 DDD/d</td>
<td>0.904 (0.621-0.995)</td>
<td>0.128 (0.014-0.732)</td>
</tr>
<tr>
<td>0.2 DDD/d</td>
<td>0.746 (0.303-0.975)</td>
<td>0.029 (0.003-0.394)</td>
</tr>
</tbody>
</table>
Conclusions

• Treatment probability as exposure
  • Improved precision
  • Strong associations
  • Meaningful agreement with conventional methods
  • Intuitively appealing – avoids binary classification

• Limitations
  • Discards information on uncertainty from WTD estimation in the subsequent logistic regression
  • No simulation studies have examined the properties of the method (what is actually the true value we are aiming at?)
Thank you for your attention – questions welcome!
References

References (cont’d)


• Zhao Y. Parametric inference from window censored renewal process data. 2006. Available at: https://etd.ohiolink.edu/rws_etd/document/get/osu1164678679/inline.