Background and Research Question

• Previous OHDSI work has shown that incidence estimates are quite sensitive to a range of factors, including age, sex, calendar time, indexing event, and database.

• Some drugs can be indicated to target multiple diseases — ex, SGLT2 inhibitors for both Type II diabetes and in left heart failure.

• It is possible that the incidence of different health outcomes could differ by indication; if that is the case, then what is the extent of the variation?
Method (The Big Picture)

• Calculate incidence rates for various health outcomes across 12 different drug classes, stratified by indication
• Compare incidence rates for outcomes across the different indications
• Additionally stratify results by age and sex
Method (The Details)

- Analysis was conducted in October 2023 on 13 databases
- Study Design:
  - Target cohorts: First occurrence of drug exposure
  - Outcome cohorts: 73 different outcomes (defined in the OHDSI phenotype library)
  - Time at risk: 1 day to 365 day after cohort start (Intent to treat)
  - Stratifications: Age and gender

\[
\text{Incidence Rate} = \frac{\text{# persons in the target cohort who have new outcome occurrence during the time-at-risk}}{\text{person-time-at-risk for persons in the target cohort with time at risk}}
\]
### Method

**Target cohorts:**

12 Drug classes, nested by indication

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Blockers</td>
<td>1) hypertension, 2) heart failure, 3) acute myocardial infarction</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1) Urinary tract infection, 2) pneumonia</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>1) Hypertension</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>1) Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>1) Urinary tract infection, 2) pneumonia</td>
</tr>
<tr>
<td>GLP-1 antagonists</td>
<td>1) Type 2 diabetes mellitus, 2) obesity</td>
</tr>
<tr>
<td>IL-23 Inhibitors</td>
<td>1) Psoriasis</td>
</tr>
<tr>
<td>JAK inhibitors</td>
<td>1) Rheumatoid arthritis, 2) Ulcerative colitis</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>1) Type 2 diabetes mellitus, 2) heart failure</td>
</tr>
<tr>
<td>Thiazide Diuretics</td>
<td>1) Hypertension</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>1) Urinary tract infection, 2) pneumonia</td>
</tr>
<tr>
<td>TNF-alpha inhibitors</td>
<td>1) Rheumatoid arthritis, 2) Psoriatic Arthritis, 3) Crohns disease, 4) Ulcerative colitis, 5) Psoriasis</td>
</tr>
</tbody>
</table>
Method

Outcomes Cohort examples (73 total)

**Cardiovascular**
- 3 and 4-point major adverse cardiovascular event (MACE) outcomes
- Cardiac death
- Torsades de Pointes
- Hospitalization with heart failure events

**Neurologic**
- Stroke
- Headache
- Guillen-Barre Syndrome (GBS)

**Gastrointestinal**
- Abdominal Pain
- Acute Liver Injury
- Diarrhea
- GI Bleed
Analysis

- Random effect meta-analysis of incidence rates across the 13 databases
- For drug classes with >1 indication: Fixed-effect moderators model to evaluate whether incidence rates differed across indications
  - For outcomes where incidence rates by indication were significantly different ($p < 0.05$), we found the standard deviation of the effect estimates
- R `metafor` package (`rma`)
Results

• 77,631 total incidence rates calculated
• 8 different drug classes had at least 2 indications

<table>
<thead>
<tr>
<th>Drug class</th>
<th># of Indications</th>
<th>Differing incidence rates across indications (F statistic p val &lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Blockers</td>
<td>3</td>
<td>61/73 (83.5%)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>2</td>
<td>51/73 (69.9%)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>2</td>
<td>63/73 (86.3%)</td>
</tr>
<tr>
<td>GLP-1 antagonists</td>
<td>2</td>
<td>3/73 (4.1%)</td>
</tr>
<tr>
<td>JAK inhibitors</td>
<td>2</td>
<td>15/73 (20.5%)</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>2</td>
<td>55/73 (75.3%)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>2</td>
<td>68/73 (93.1%)</td>
</tr>
<tr>
<td>TNF-alpha inhibitors</td>
<td>5</td>
<td>26/73 (35.6%)</td>
</tr>
</tbody>
</table>
Zooming in on Beta Blockers...

Incidence Rate by Beta Blocker Indication and Data Source

Data Source
- Epic Legacy CUMC MERGE
- France DA
- IBM CCAE
- IBM MCD
- IBM MDCR
- LPD Belgium
- LPD Italy
- LPDAU
- Optum EHR
- OPTUM Extended SES
- PharMetrics
- STARR

Drug Indication
Log Incidence Rate

Incidence Rate by Beta Blocker Indication and Data Source

Data Source
- Epic Legacy CUMC MERGE
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Drug Indication

Zooming in on Beta Blockers...
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- **3 Highest SD (rates are different between indications):**
  - Hospitalization with heart failure (SD = 4.17)
  - 4-point MACE (4)
  - Total CV disease events (4)

- **3 Lowest SD (rates are similar across indications):**
  - Gout (SD = 0.35)
  - Bone Fracture (SD = 0.58)
  - Cough (SD = 0.59)
What about stratifying by sex?
What about stratifying by age?

Incidence Rate by Beta Blocker Indication and Data Source, stratified by Age

Data Source
- Epic Legacy CUMC MERGE
- France DA
- IBM COAE
- IBM MDCD
- IBM MDCR
- LPD Belgium
- LPD Italy
- Optum EHR
- OPTUM Extended SES
- PharMetrics
- STAHR
Key Takeaways & Next Steps

• Meta-analyzed incidence rates for beta blockers were sensitive to stratifications by indications
  – They are preserved even when we stratify by age and gender

• Trimethoprim was most sensitive to stratification by indication, and GLP-1 least sensitive

• For some health outcomes, it may be important to nest exposures within the different indications