How Often: Results from the 2023 Global Symposium

OHDSI Community Call

July 2024

Agenda

- How Often Refresher (5 mins)
- Preliminary Results from the Global Symposium
  - How Often Azza (10 mins)
  - How Often George (10 mins)
  - How Often and Clinicaltrials.gov data (10 mins)
- Next steps (10 mins)

OHDSI's journey into incidence rates

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FAST TRACK

Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study

Xintong Li,[1] Anna Ostropolets,[2] Rupa Makadia,[3] Azza Shoaibi,[3] Gowtham Rao,[3] Anthony G Sena,[3,6] Eugenia Martinez-Hernandez,[4] Antonella Delmestri,[1] Katia Verhamme,[6,7] Peter R Rijnbeek,[6] Talita Duarte-Salles,[5] Marc A Suchard,[8,9] Patrick B Ryan,[2,3] George Hripcsak,[2] Daniel Prieto-Alhambra[1,6]

ABSTRACT

OBJECTIVE
To quantify the background incidence rates of 15 prespecified adverse events of special interest (AESIs) associated with covid-19 vaccines.

DESIGN
Multinational network cohort study.

SETTING
Electronic health records and health claims data from eight countries: Australia, France, Germany, Japan, the Netherlands, Spain, the United Kingdom, and the United States, mapped to a common data model.

PARTICIPANTS
126 661 070 people observed for at least 365 days before 1 January 2017, 2018, or 2019 from 13 databases.

MAIN OUTCOME MEASURES
Events of interests were 15 prespecified AESIs (non-haemorrhagic and haemorrhagic stroke, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, anaphylaxis, Bell's palsy, myocarditis or pericarditis, narcolepsy, appendicitis, immune thrombocytopenia, disseminated intravascular coagulation, encephalomyelitis

and database. Rates were pooled across databases using random effects meta-analyses and classified according to the frequency categories of the Council for International Organizations of Medical Sciences.

RESULTS
Background rates varied greatly between databases. Deep vein thrombosis ranged from 387 (95% confidence interval 370 to 404) per 100 000 person years in UK CPRD GOLD data to 1443 (1416 to 1470) per 100 000 person years in US IBM MarketScan Multi-State Medicaid data among women aged 65 to 74 years. Some AESIs increased with age. For example, myocardial infarction rates in men increased from 28 (27 to 29) per 100 000 person years among those aged 18-34 years to 1400 (1374 to 1427) per 100 000 person years in those older than 85 years in US Optum electronic health record data. Other AESIs were more common in young people. For example, rates of anaphylaxis among boys and men were 78 (75 to 80) per 100 000 person years in those aged 6-17 years and 8 (6 to 10) per 100 000 person years in those older than 85 years in Optum electronic health record data. Meta-analytic estimates of AESI rates were classified according to age and sex.

Contextualising adverse events of special interest to characterise the baseline incidence rates in 24 million patients with COVID-19 across 26 databases: a multinational retrospective cohort study

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OHDSI's journey into incidence rates

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Characterising th
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Factors Influencing Background Incidence Rate Calculation: Systematic Empirical Evaluation Across an International Network of Observational Databases

Anna Ostropolets[1†], Xintong Li[2†], Rupa Makadia[3], Gowtham Rao[3], Peter R. Rijnbeek[4], Talita Duarte-Salles[5], Anthony G. Sena[3,4], Azza Shaoibi[3], Marc A. Suchard[6,7], Patrick B. Ryan[1,3], Daniel Prieto-Alhambra[2] and George Hripcsak[1,8]*

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Objective: Background incidence rates are routinely used in safety studies to evaluate an association of an exposure and outcome. Systematic research on sensitivity of rates to the choice of the study parameters is lacking.

Materials and Methods: We used 12 data sources to systematically examine the influence of age, race, sex, database, time-at-risk, season and year, prior observation and clean window on incidence rates using 15 adverse events of special interest for COVID-19 vaccines as an example. For binary comparisons we calculated incidence rate ratios and performed random-effect meta-analysis.

Results: We observed a wide variation of background rates that goes well beyond age and database effects previously observed. While rates vary up to a factor of 1,000 across age groups, even after adjusting for age and sex, the study showed residual bias due to the other parameters. Rates were highly influenced by the choice of anchoring (e.g., health visit, vaccination, or arbitrary date) for the time-at-risk start. Anchoring on a healthcare encounter yielded higher incidence comparing to a random date, especially for short time-at-risk. Incidence rates were highly influenced by the choice of the database (varying by up to a factor of 100), clean window choice and time-at-risk duration, and less so by secular or seasonal trends.

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OHDSI Symposium October 2023

- How Often: Large scale characterization of incidence of outcomes following drug exposure
- Pre-Symposium
  - Draft protocol
  - Develop and evaluate phenotypes
  - Gathered research questions from OHDSI community
  - Release analysis package that has all the targets and outcomes of interest
- During Symposium (October 2023)
  - Execute How Often Analysis Package across OHDSI Network
  - Deploy viewer to allow for exploration of results
  - Collaborate on appropriate use of evidence
    - How to ensure reliability of results?
    - How to improve user interface to disseminate results?
    - What have we learned that can fill evidence gaps and improve decision making?
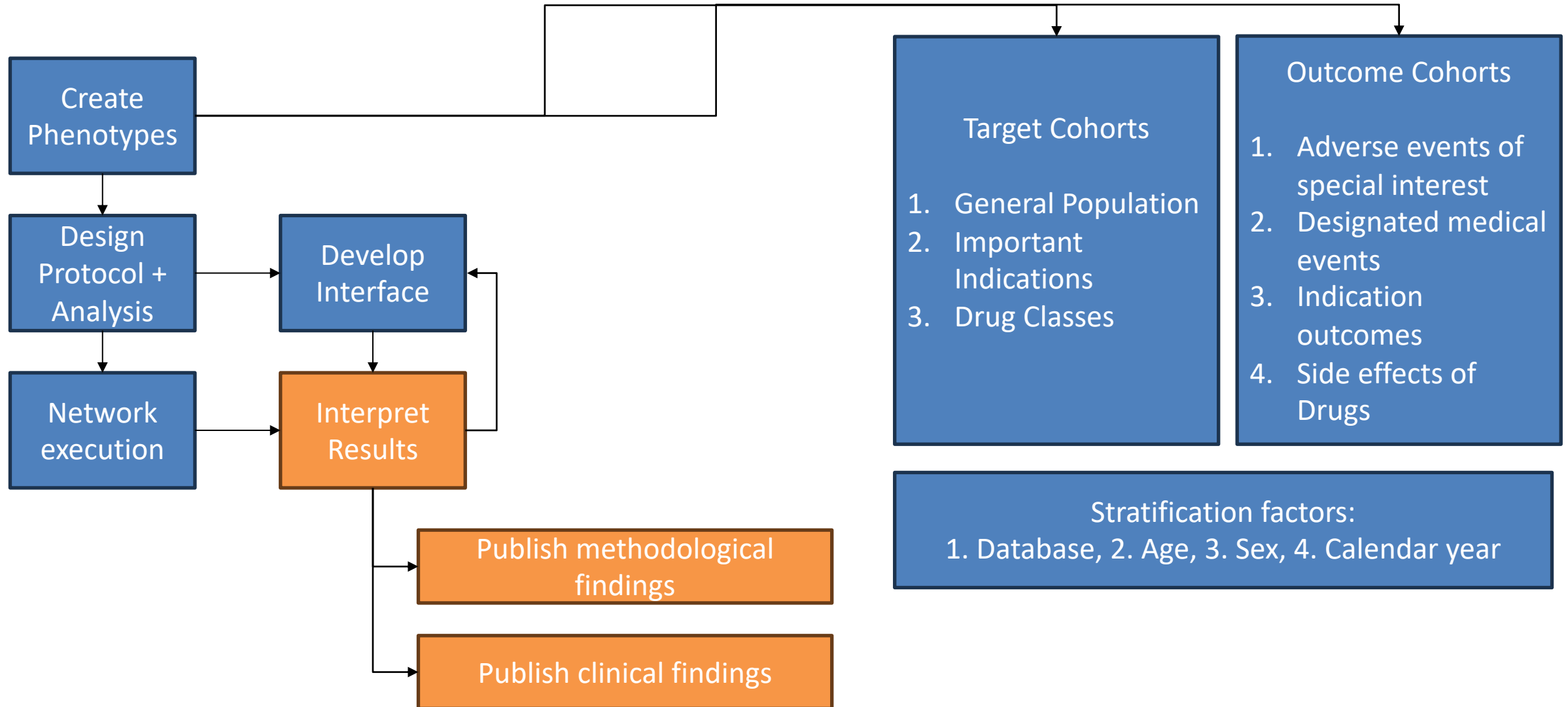
Preliminary Results

- 6 Different Studies
  - More than 20 different research questions

- 265 Different Phenotypes

- 16 databases

- 54 million Incidence Rates Generated!
  - Stratified by age, gender, index year, and database

All results are publicly available at https://results.ohdsi.org/

Preliminary Results

- All results are publicly available at https://results.ohdsi.org/

Results we will present today

- How Often Azza (Azza)
- How Often George (Cindy)
- How Often x Clinicaltrials.gov (Elise)

How Often Azza

How Often George

"Does Indication Matter?"

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

$$\text{Incidence Rate} = \frac{\text{\# persons in the target cohort who have new outcome occurance during the time–at–risk}}{\textbf{person–time–at–risk} \text{ for persons in the target cohort with time at risk}}$$

Method

Target cohorts:

12 Drug classes, nested by indication

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

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

Drug class	# of Indications	Differing incidence rates across indications (F statistic p val <0.05)
Beta Blockers	3	61/73 (83.5%)
Cephalosporins	2	51/73 (69.9%)
Fluoroquinolones	2	63/73 (86.3%)
GLP-1 antagonists	2	3/73 (4.1%)
JAK inhibitors	2	15/73 (20.5%)
SGLT2 Inhibitors	2	55/73 (75.3%)
Trimethoprim	2	68/73 (93.1%)
TNF-alpha inhibitors	5	26/73 (35.6%)

Zooming in on Beta Blockers...
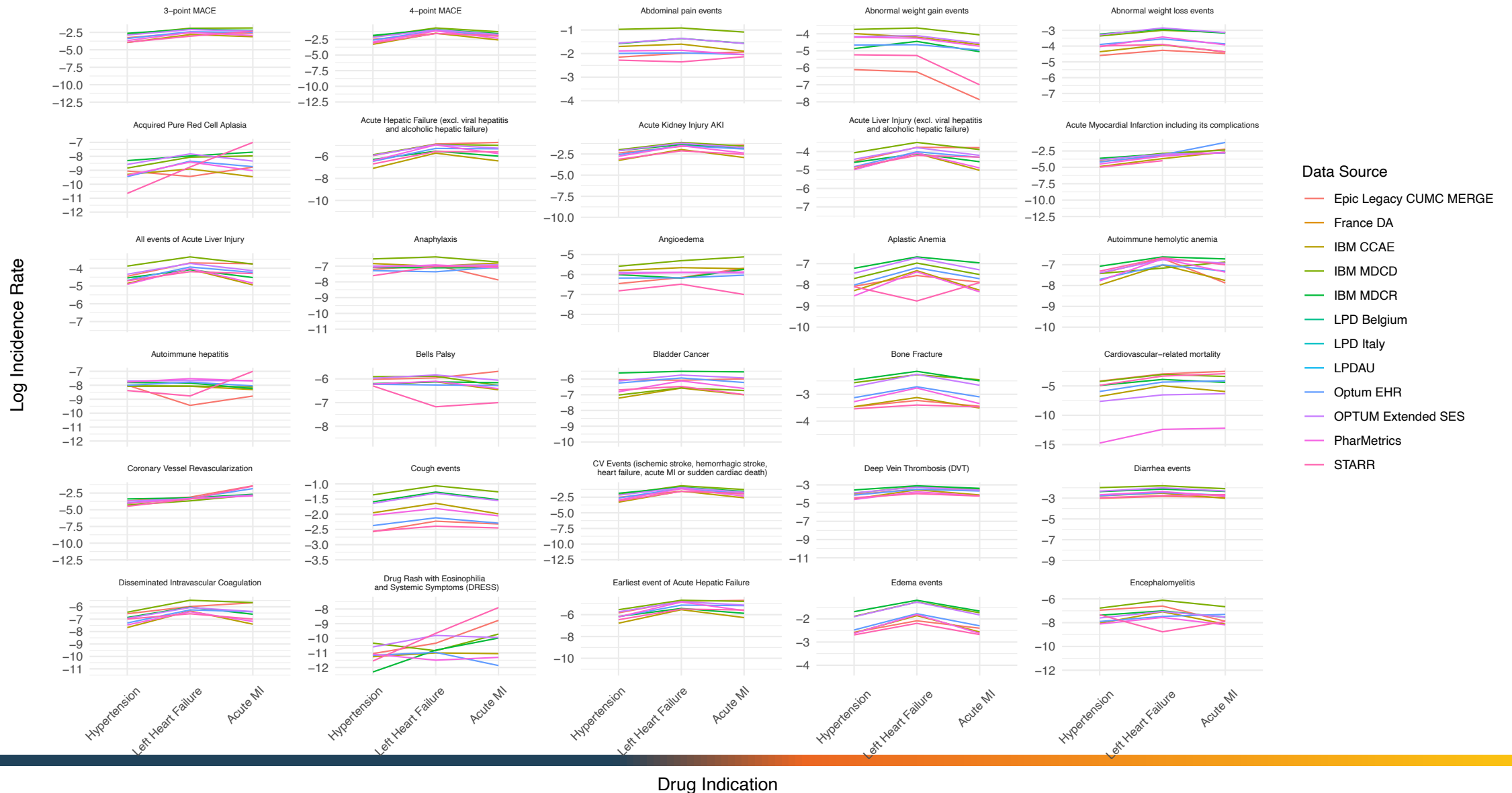
Incidence Rate by Beta Blocker Indication and Data Source
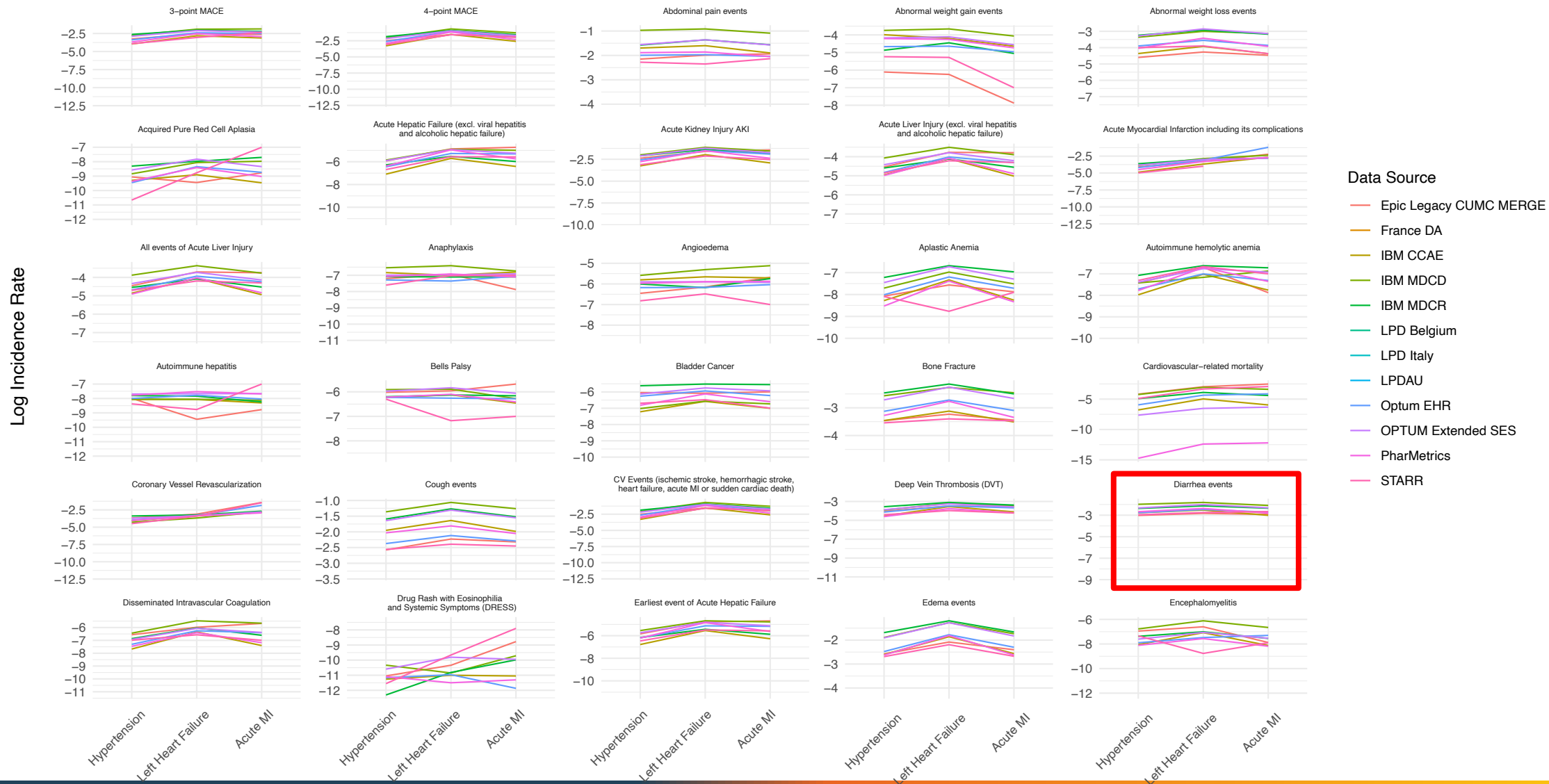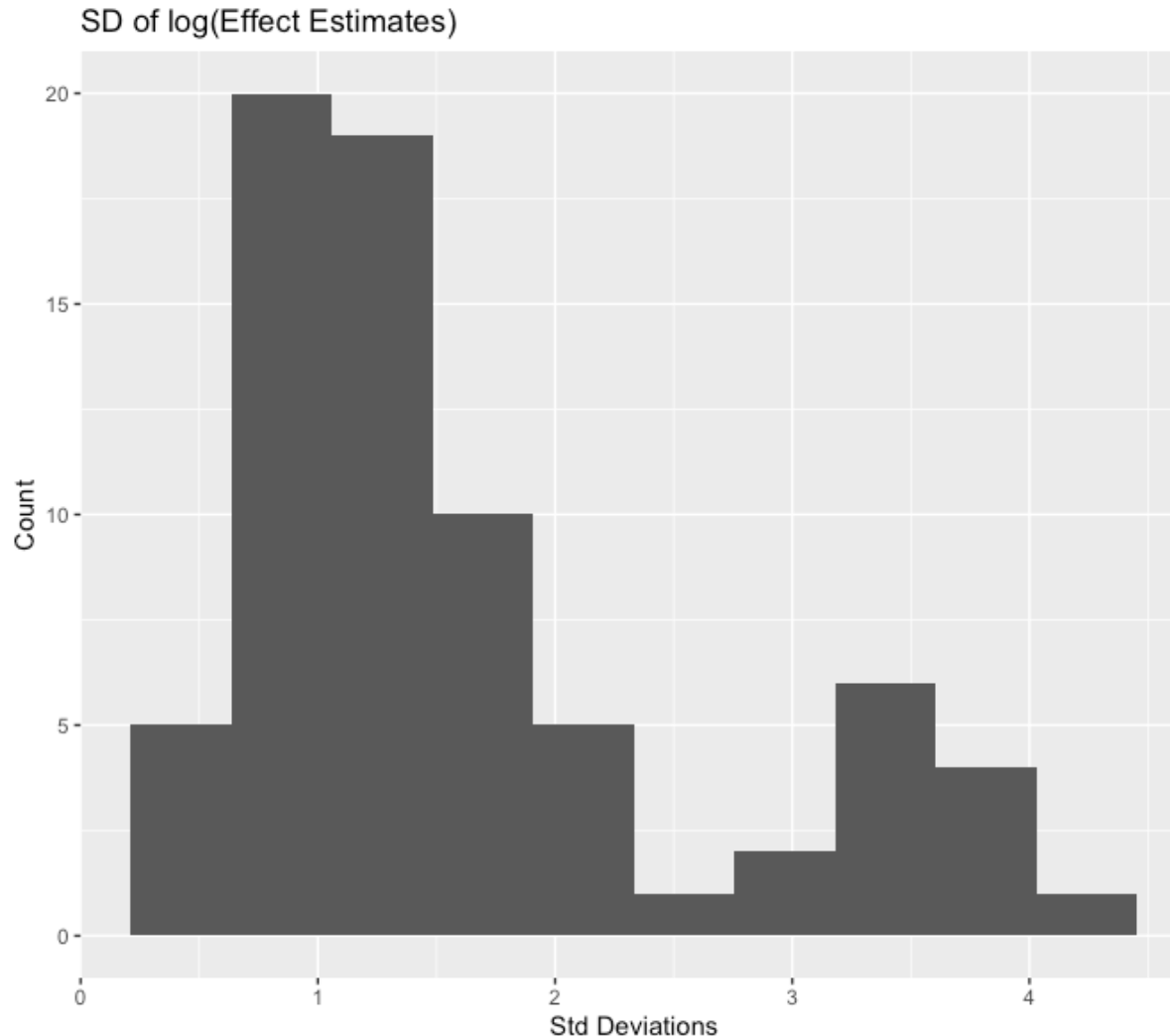
Zooming in on Beta Blockers...

Zooming in on Beta Blockers...

Incidence Rate by Beta Blocker Indication and Data Source

Log Incidence Rate

Drug Indication

Data Source
- Erac Legacy CUMC MERGE
- France DA
- IBM CCAE
- IBM MDCD
- IBM MDCR
- LPD France
- LPD Italy
- LPD AU
- Optum EHR
- Optum Extended SES
- PharMetrics
- STARR

Zooming in on Beta Blockers…

SD of log(Effect Estimates)

- 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)
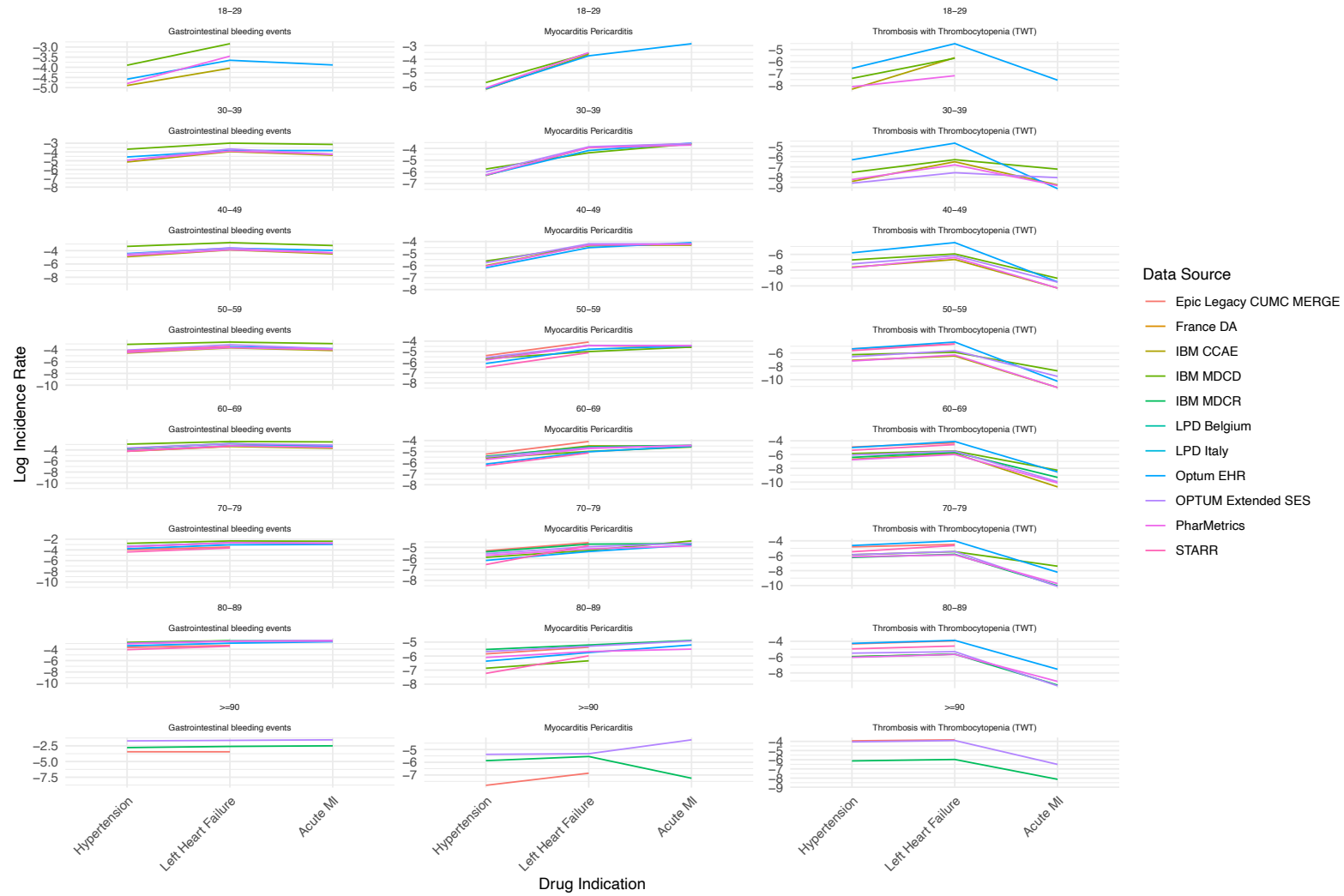
What about stratifying by sex?

Incidence Rate by Beta Blocker Indication and Data Source, Stratified By Gender
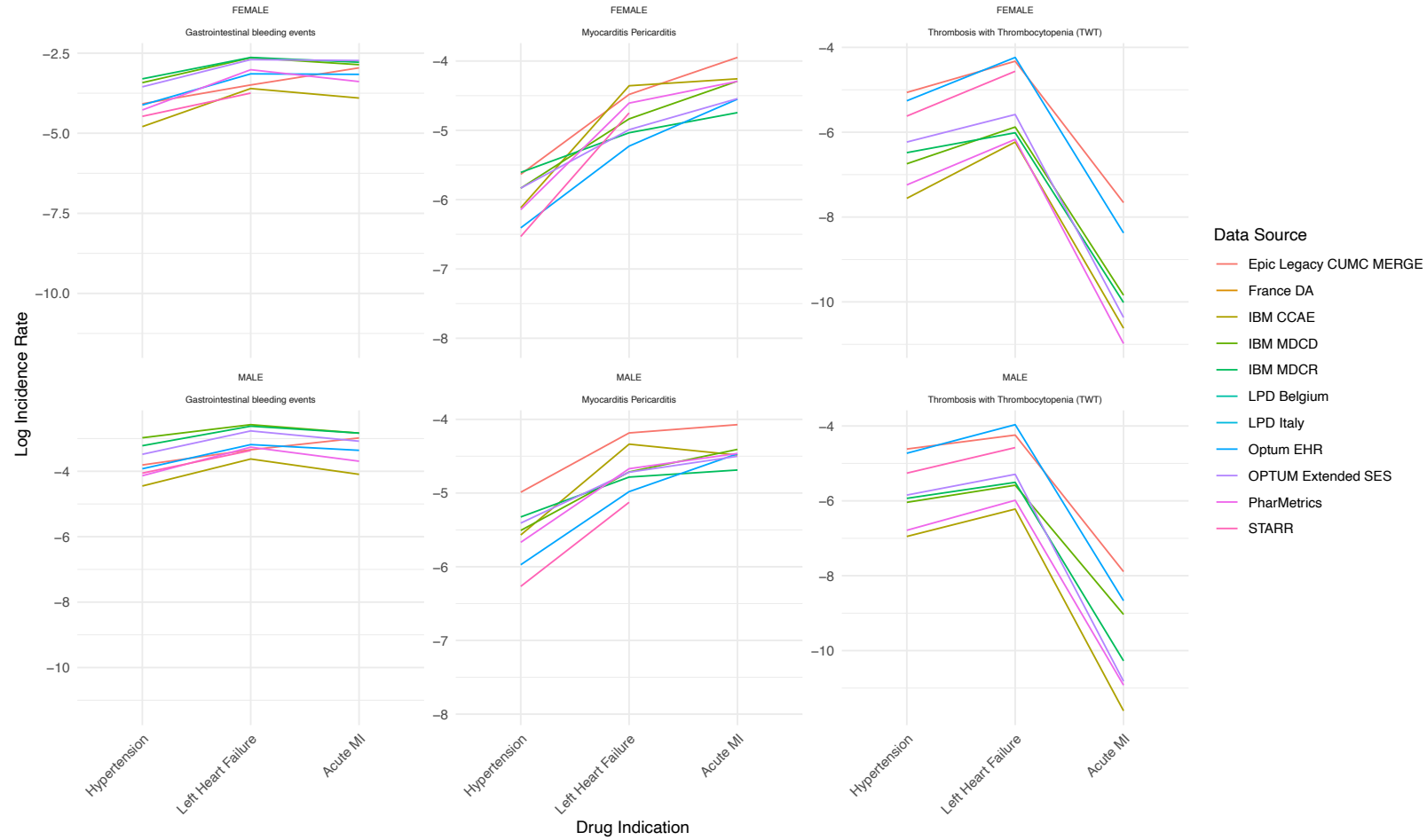
What about stratifying by age?

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

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