



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
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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

	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

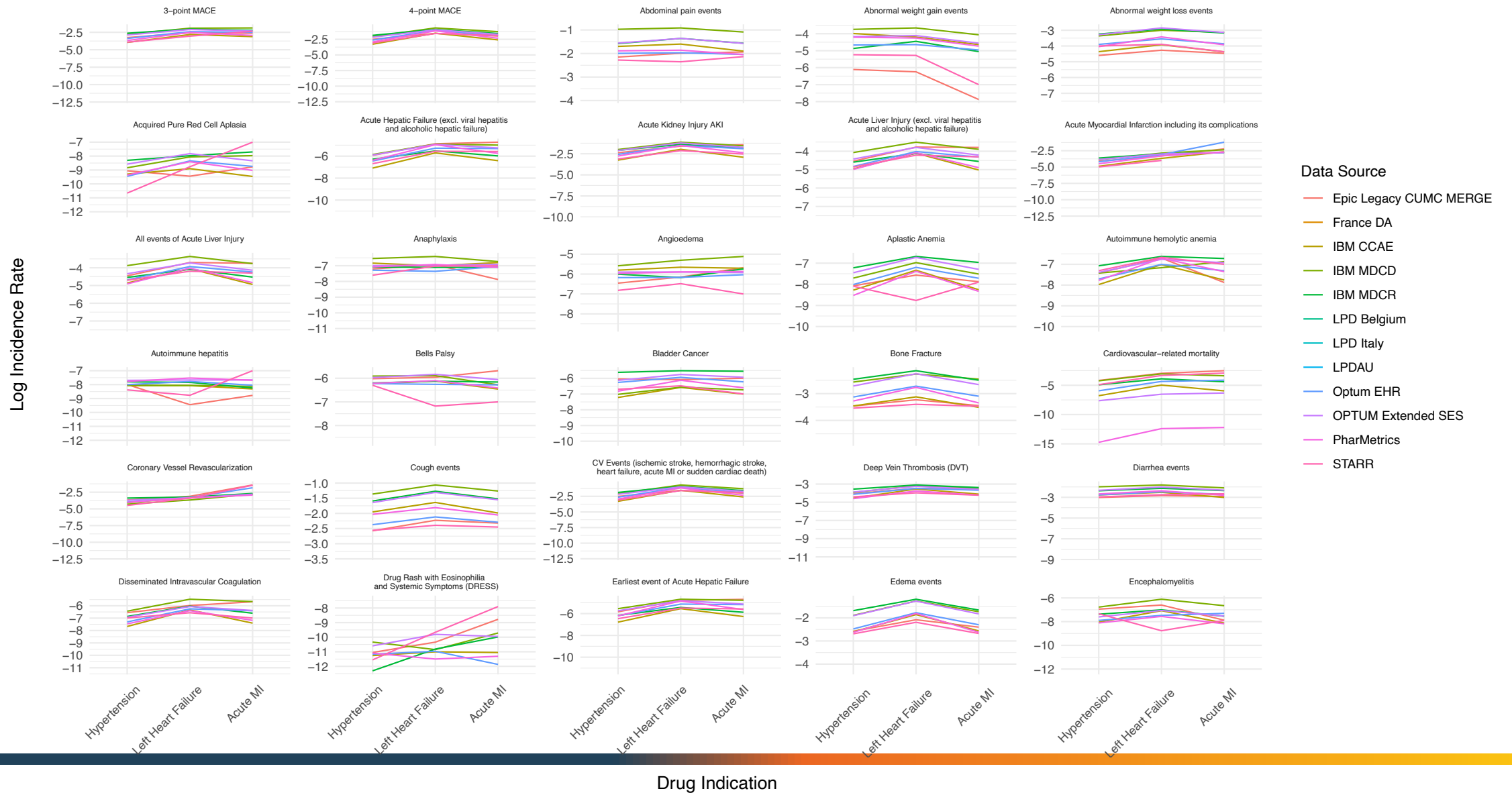
- 77,631 total incidence rates calculated
- 8 different drug classes had at least 2 indications

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...

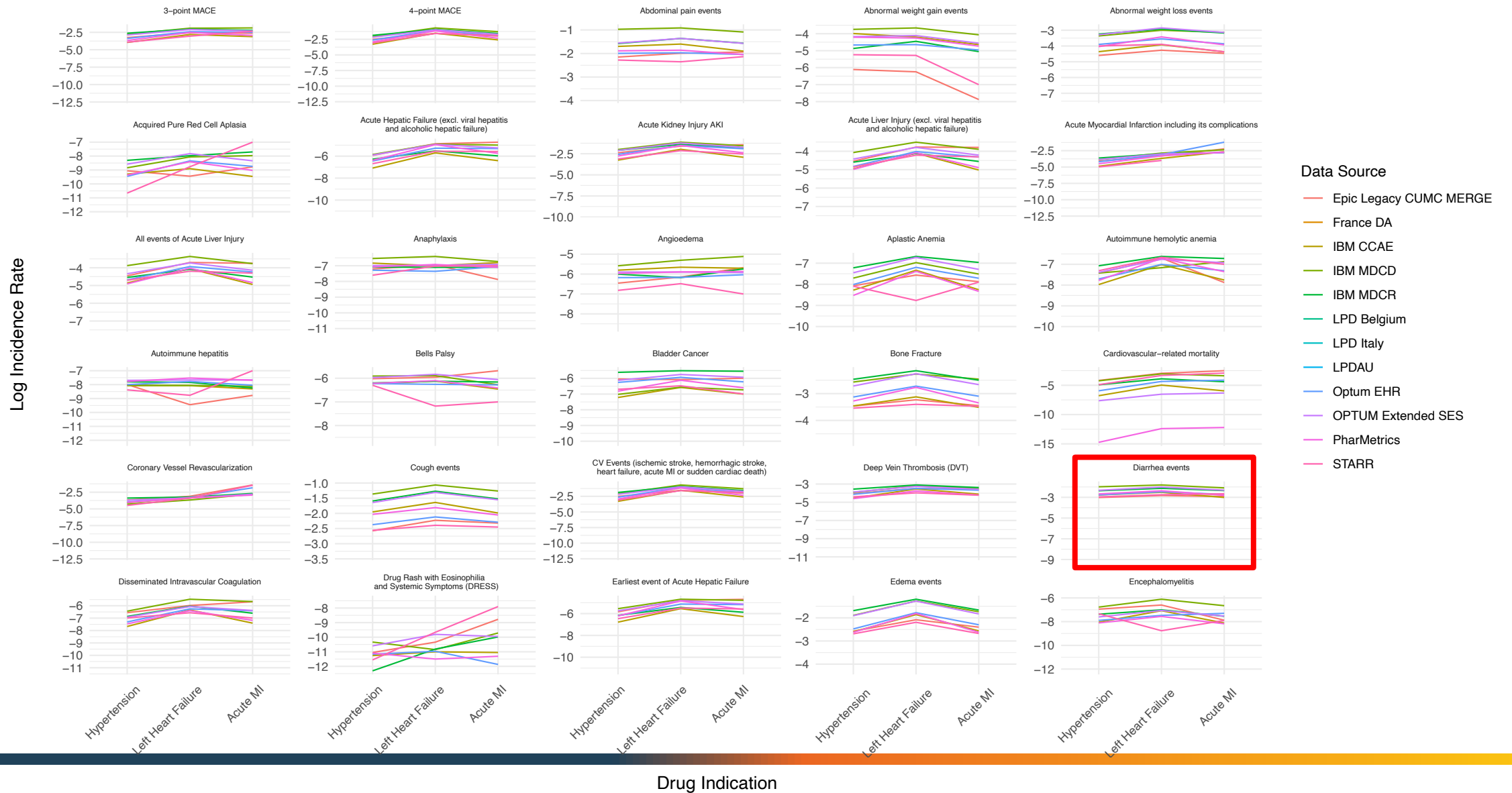
Incidence Rate by Beta Blocker Indication and Data Source





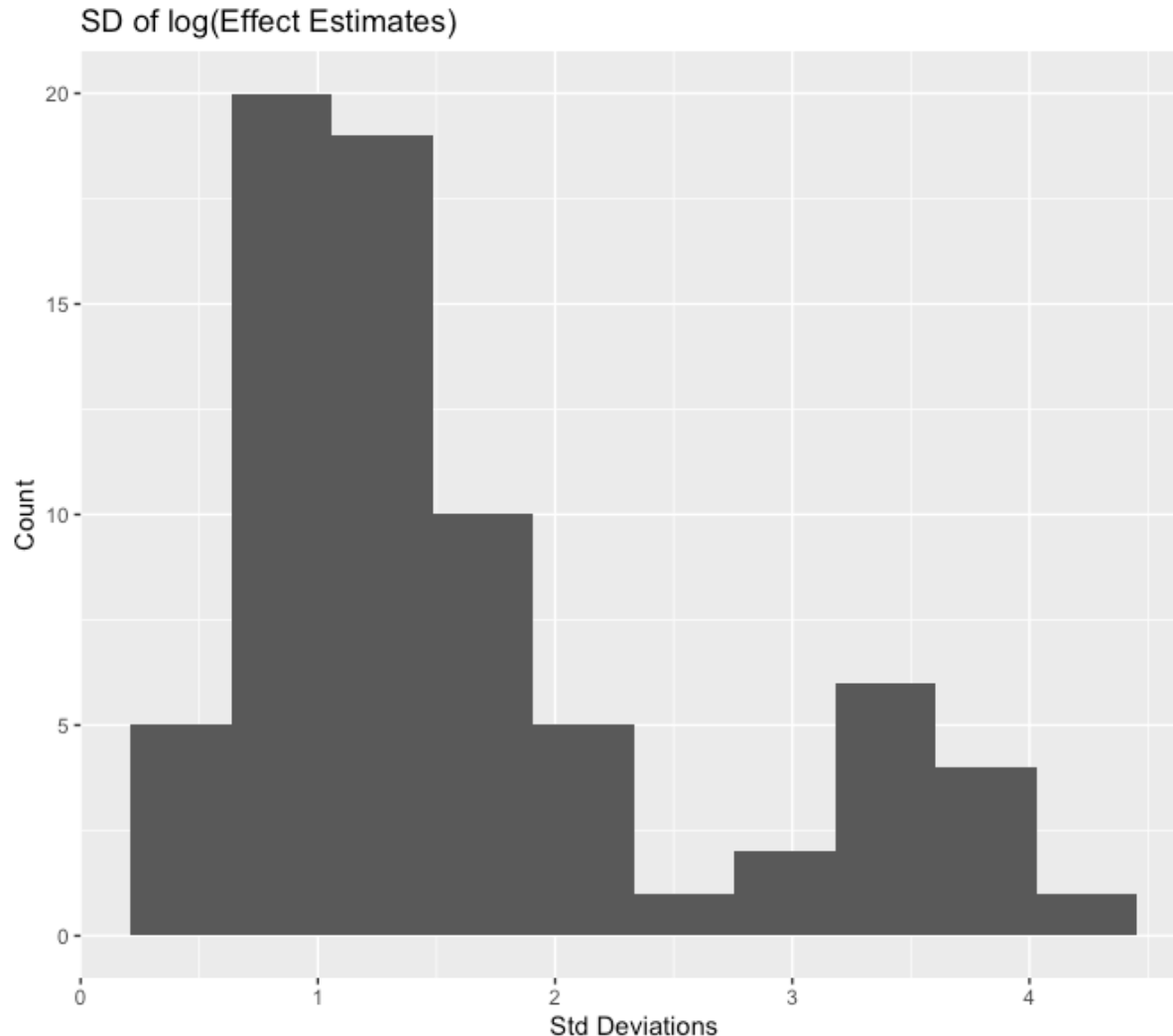
Zooming in on Beta Blockers...

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Zooming in on Beta Blockers...

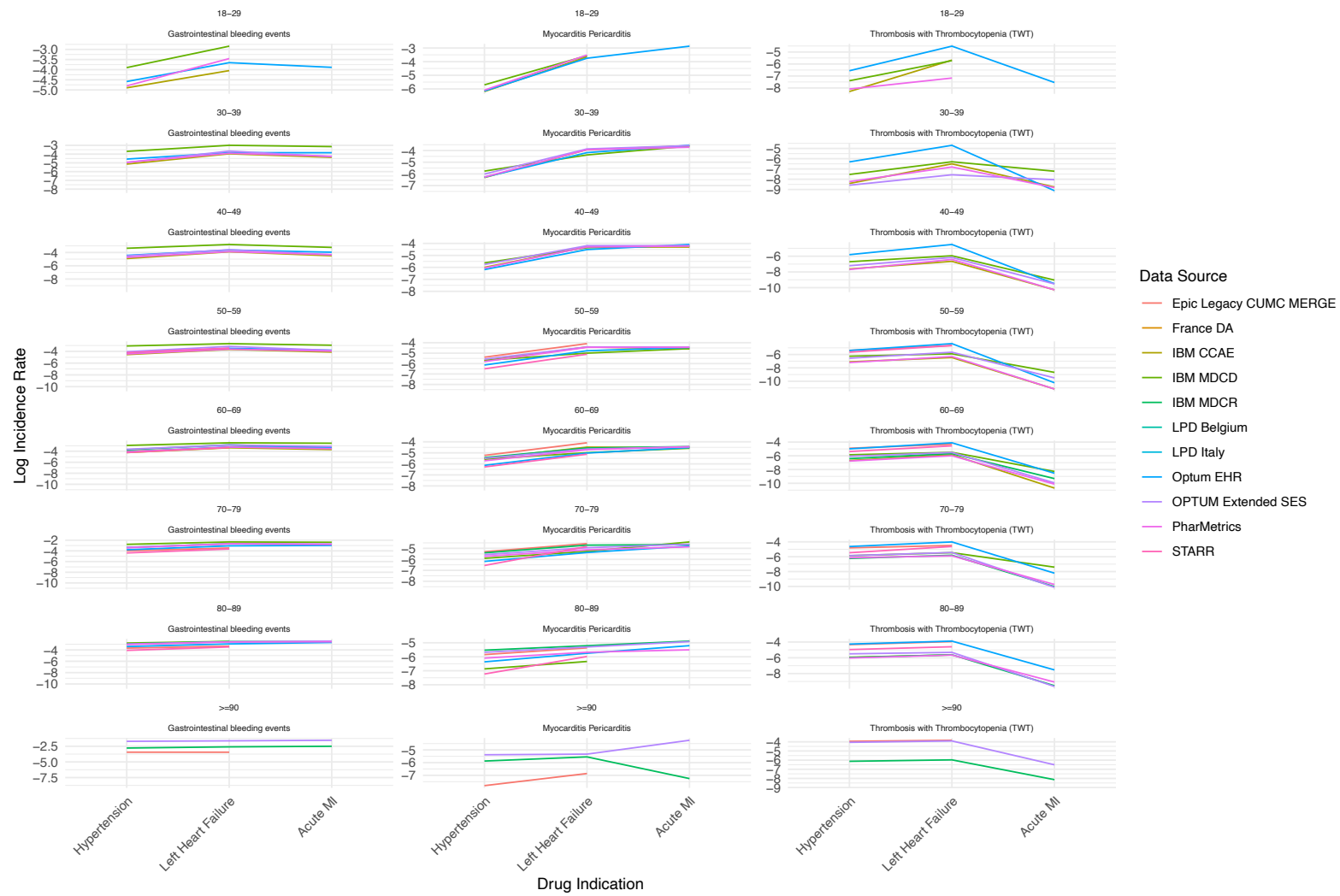


- 3 Highest SD (rates are different between indications):
 - Hospitalization with heart failure (SD = 4.17)
 - 4-point MACE (4)
 - Total CV disease events (4)
- 3 Lowest SD (rates are similar across indications):
 - Gout (SD = 0.35)
 - Bone Fracture (SD = 0.58)
 - Cough (SD = 0.59)



What about stratifying by 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