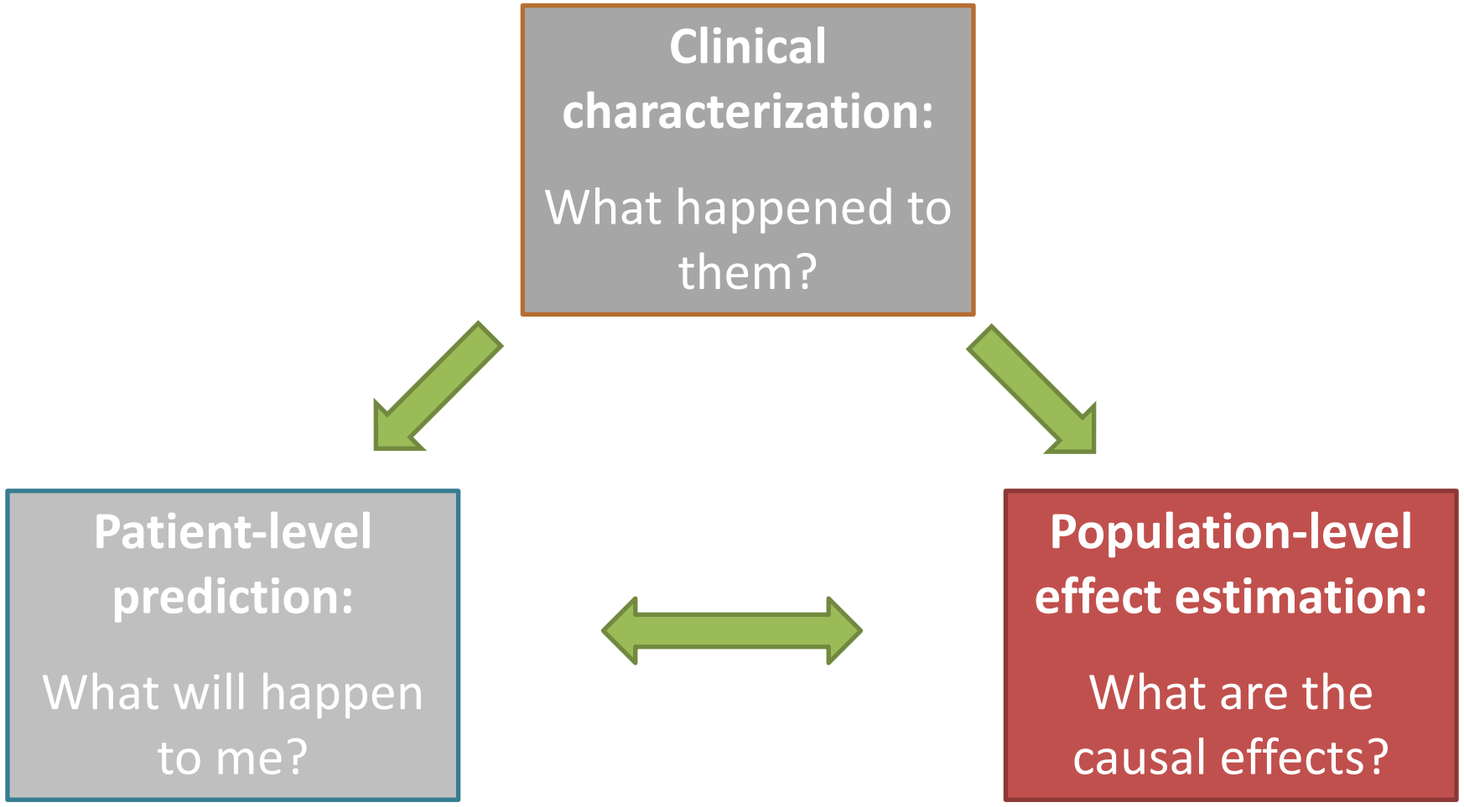
SARS-Cov-2 Large-scale Longitudinal Analyses on the comparative safety and effectiveness of treatments under evaluation for COVID-19 across an international observational data network:

The SCYLLA STUDY

Complementary evidence to inform the patient journey



Head-2-head comparisons - Rationale

- Guidelines (eg NIH) and clinicians have divided COVID-19 therapies into **Anti-viral**, and '**Adjunctive**' therapies

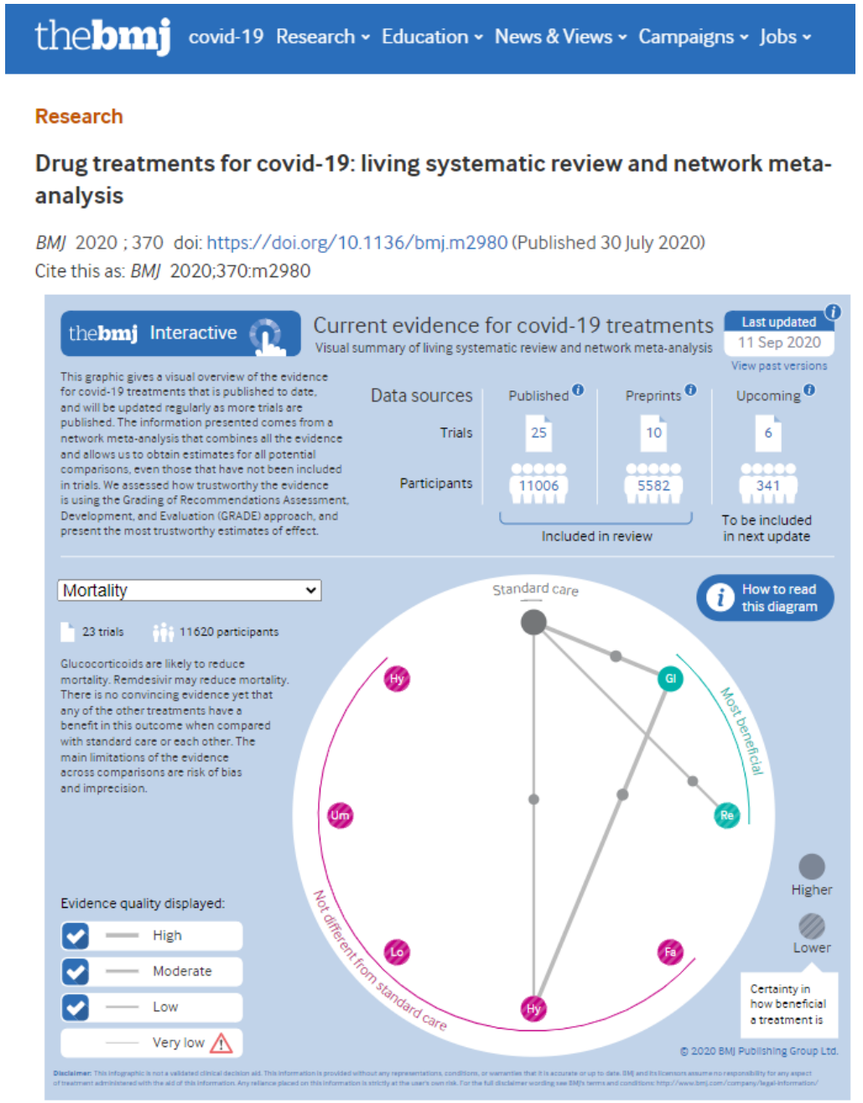
- The latter are divided further into:
  - Anti-thrombotics
  - Immune-based therapy
  - Antibiotics
  - Concomitant (antihypertensive, statin, antidiabetic, others)

Head-2-head comparisons – Rationale (2)

- Many trials ongoing
- Many already published
- Most in some ‘living’ meta-analysis of RCTs

- All study treatment/s vs placebo or ‘standard care’

- But …
  - Are all corticosteroids equally safe?
  - Are anticoagulants better than antithrombotics?
  - Are IL-inh safer than corticosteroids?
  - …

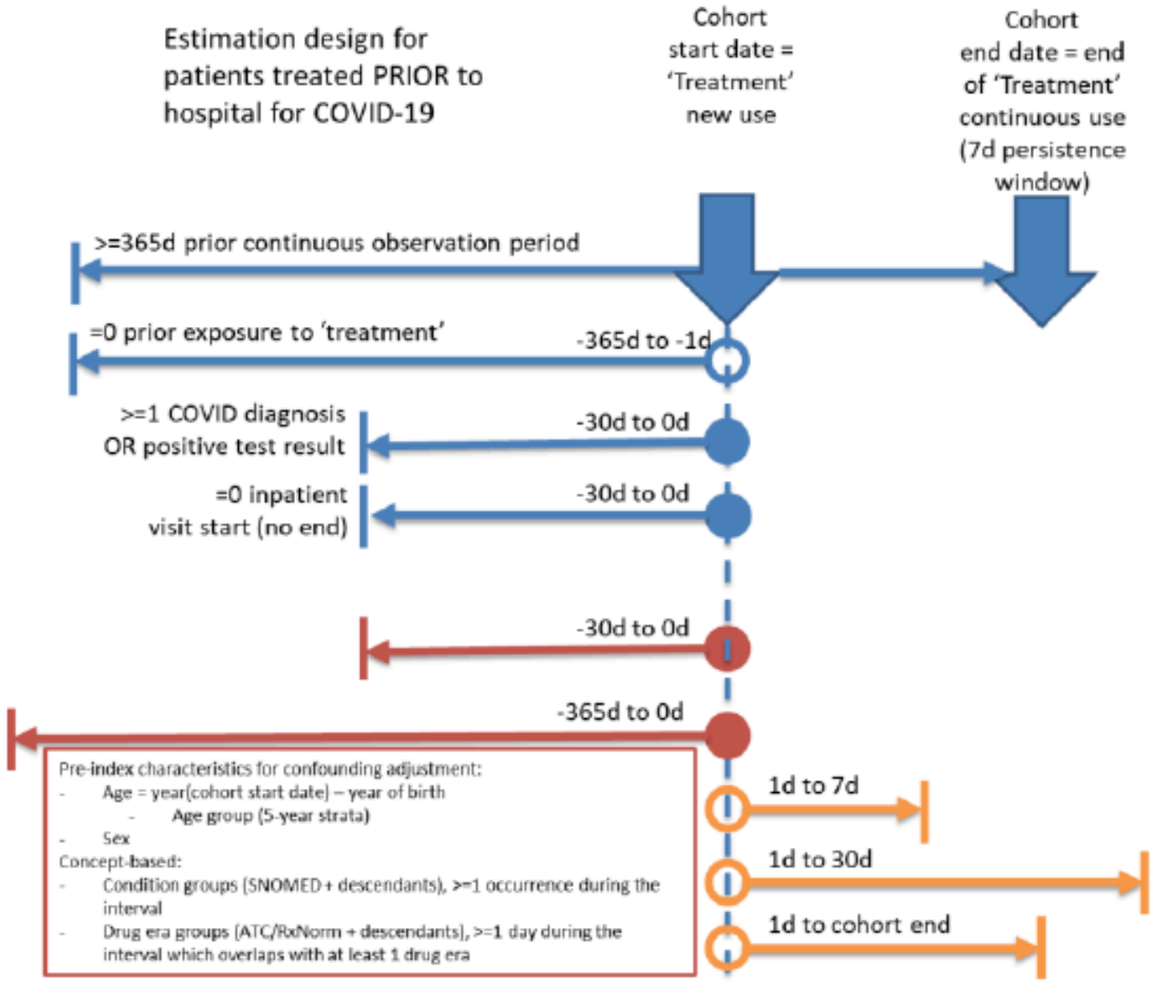


METHODS

Full protocol available at http://www.encepp.eu/encepp/viewResource.htm?id=37226

New user cohorts in Scylla - OUTPATIENT

To assess comparative effectiveness and safety among treatments administered after COVID positive testing and prior to hospitalization



'Treatment' Cohorts: (can be used as target AND comparator)

- Antivirals
- Immune-based therapies
- Antithrombotics
- Antibiotics
- Anti-hypertensives
- Anti-diabetics
- Statins
- Concomitant therapies

Outcomes:

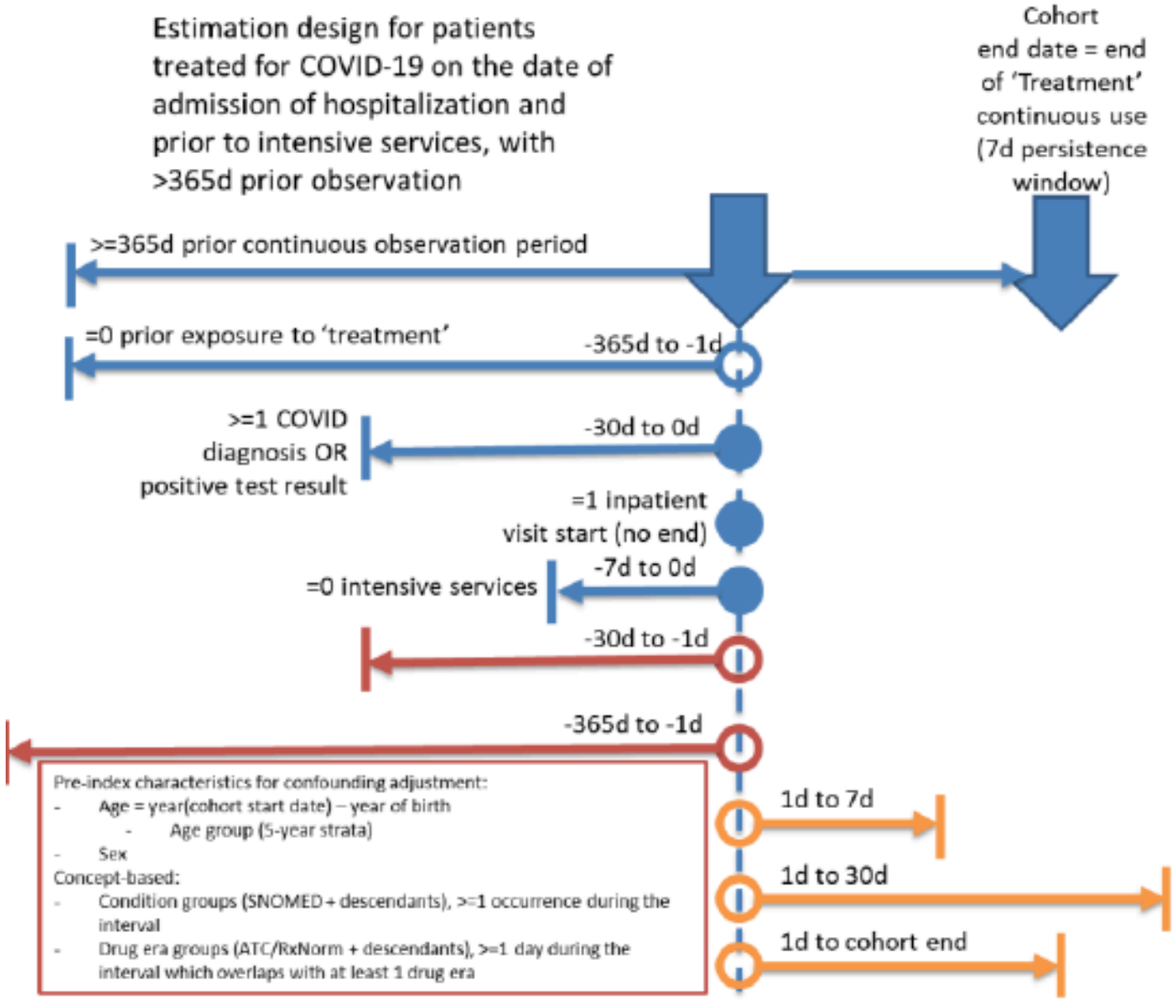
- Admission to Hospitalization
- Initiation of hospitalization intensive services (ventilation, tracheostomy, ECMO)
- Haemodialysis
- Death (all-cause mortality, cardiovascular-related mortality)
- Pneumonia
- Acute kidney injury
- Sepsis
- Venous thromboembolism (Pulmonary embolism, Deep Vein Thrombosis)
- Arrhythmia
- Haemorrhage
- Angina
- Asthma/COPD exacerbation
- Hepatic failure
- Acute pancreatitis
- Cardiovascular disease events (stroke, heart failure, acute myocardial infarction, sudden cardiac death)
- Transient ischemic attack
- Gastrointestinal bleeding

Analysis:

- Logistic regression (odds ratio on proportion having event in TAR)
- Cox PH (hazards ratio for time-to-event analysis)

New user cohorts in Scylla – INPATIENT (pre-ICU)

- To assess comparative effectiveness and safety among treatments administered on the date of admission of hospitalization and prior to intensive services



'Treatment' Cohorts: (can be used as target AND comparator)

- Antivirals
- Immune-based therapies
- Antithrombotics
- Antibiotics
- Anti-hypertensives
- Anti-diabetics
- Statins
- Concomitant therapies

Outcomes:

- Initiation of hospitalization intensive services (ventilation, tracheostomy, ECMO)
- Haemodialysis
- Discharge from Hospitalization (or Death)
- Death (all-cause mortality, cardiovascular-related mortality)
- Pneumonia
- Acute kidney injury
- Sepsis
- Venous thromboembolism (Pulmonary embolism, Deep Vein Thrombosis)
- Arrhythmia
- Haemorrhage
- Angina
- Asthma/COPD exacerbation
- Hepatic failure
- Acute pancreatitis
- Cardiovascular disease events (stroke, heart failure, acute myocardial infarction, sudden cardiac death)
- Transient ischemic attack
- Gastrointestinal bleeding

Analysis:

- Logistic regression (odds ratio on proportion having event in TAR)
- Cox PH (hazards ratio for time-to-event analysis)

DESIGN AND ANALYTICS

- New user, active comparator, cohort designs
- Large-scale propensity scores - *observed* confounding
- Negative control outcomes and empirical calibration – *unobserved* confounding

DESIGN AND ANALYTICS (2)

- Diagnostics

1. Power/sample size for each drug-outcome-setting
2. Propensity score models and overlap
3. Covariate imbalance <0.1 SD
4. Systematic error = negative control outcomes

RESULTS
Somewhat predictable challenges…

PS FITTING

- Instrumental variables ‘sneaking’ into our PS models. Eg ‘chemotherapy or iv administration’

- 2-step SOLUTION:
  1. Look at correlation between concepts and T/C cohorts
  2. Exclude those with a high correlation coefficient

DIAGNOSTICS FAILED FOR MANY T-C

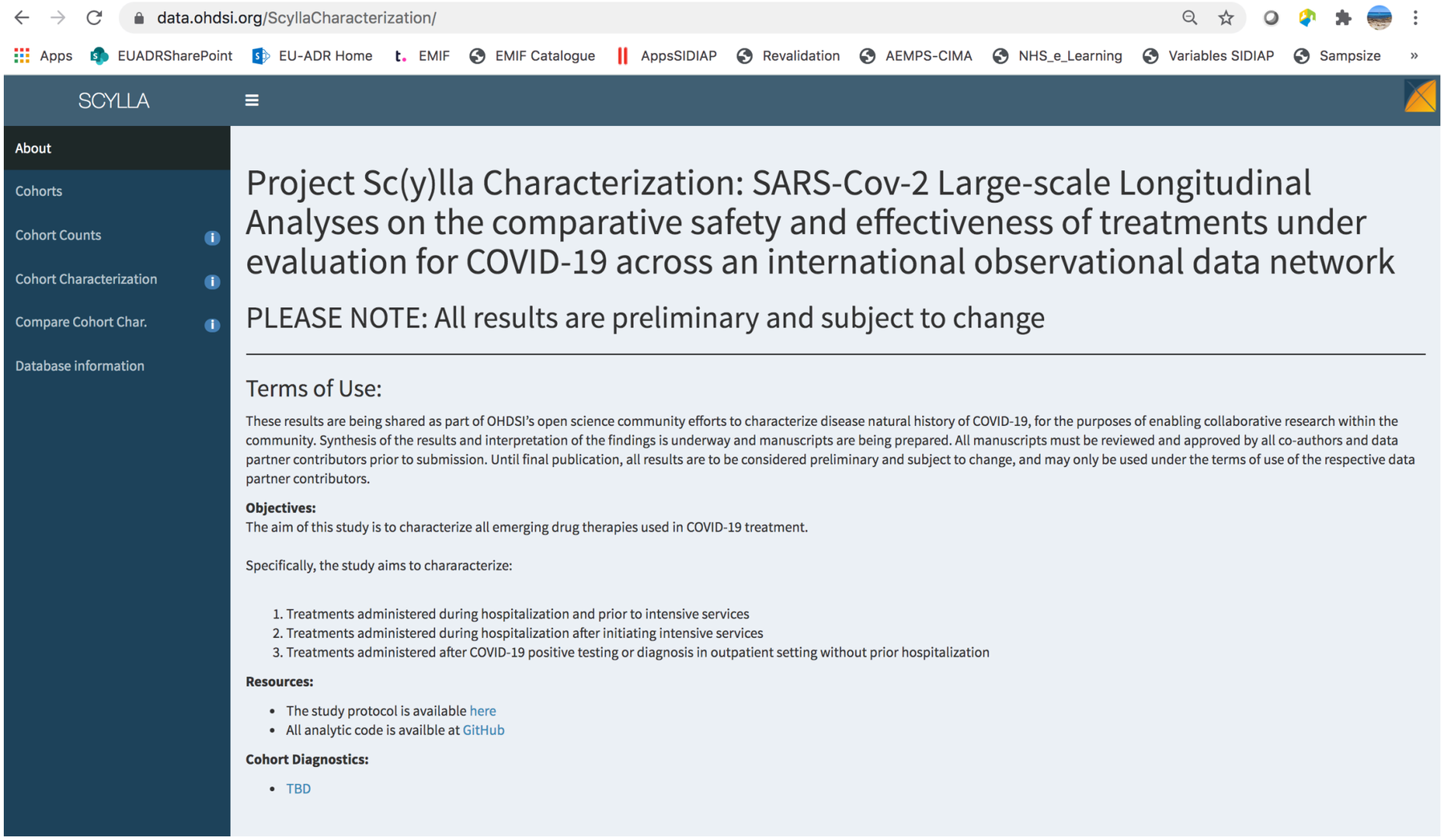
- Plethora of medicines used for COVID-19
- Relatively rarely find ‘clean’ new user cohorts

- OUTCOME:
  1. Mostly inpatient treatments pass diagnostics
  2. Only large cohorts make it to the analysis

SCYLLA Patient-level Drug User Characterisation

Preliminary findings – web app

data.ohdsi.org/ScyllaCharacterization/



Drug and setting-specific, across data source characterisation

Cohort Characterization

Compare Cohort Char.

Database information

Database

HM, IPCI, cdm_health_verity

Cohort (Target)

dexamethasone

subgroup (Target)

with Persons hospitalized w

Domain

Demographics

INPATIENT,

DEXAMTH

Show 25 entries

Search:

Covariate Name	CDM_OPTUM_EHR_COVID_v1239 (n = 222)	cdm_premier_covid_v1260 (n = 1,020)	HM (n = 216)
	CDM_OPTUM_EHR_COVID_v1239_pct	cdm_premier_covid_v1260_pct	HM_pct
age group: 00-04	<2.3%	2.6%	
age group: 05-09	<2.3%	<0.5%	
age group: 10-14	<2.3%	<0.5%	
age group: 15-19	<2.3%	0.8%	
age group: 20-24	2.7%	2.0%	
age group: 25-29	3.2%	4.2%	
age group: 30-34	5.0%	4.1%	
age group: 35-39	5.4%	4.7%	<2.3%
age group: 40-44	5.0%	5.4%	<2.3%
age group: 45-49	5.4%	6.9%	5.6%
age group: 50-54	6.8%	7.2%	5.1%
age group: 55-59	12.2%	9.4%	9.7%
age group: 60-64	9.0%	9.7%	8.8%
age group: 65-69	9.0%	9.9%	14.8%
age group: 70-74	12.2%	8.1%	13.9%
age group: 75-79	8.1%	8.0%	13.4%
age group: 80-84	4.5%	7.4%	9.7%
age group: 85-89	7.7%	6.6%	6.5%
age group: 90-94		2.3%	9.7%
age group: 95-99			<2.3%
gender = female	59.5%	49.5%	31.0%
gender = male	40.5%	50.5%	69.0%

Compare Cohort Char.

Database information

Database

CDM_OPTUM_EHR_COVID

Cohort (Target)

Hydroxychloroquine

subgroup (Target)

with Persons with a COVID-1

Cohort (Comparator)

Hydroxychloroquine + Azith

subgroup (Comparator)

with Persons with a COVID-1

Domain

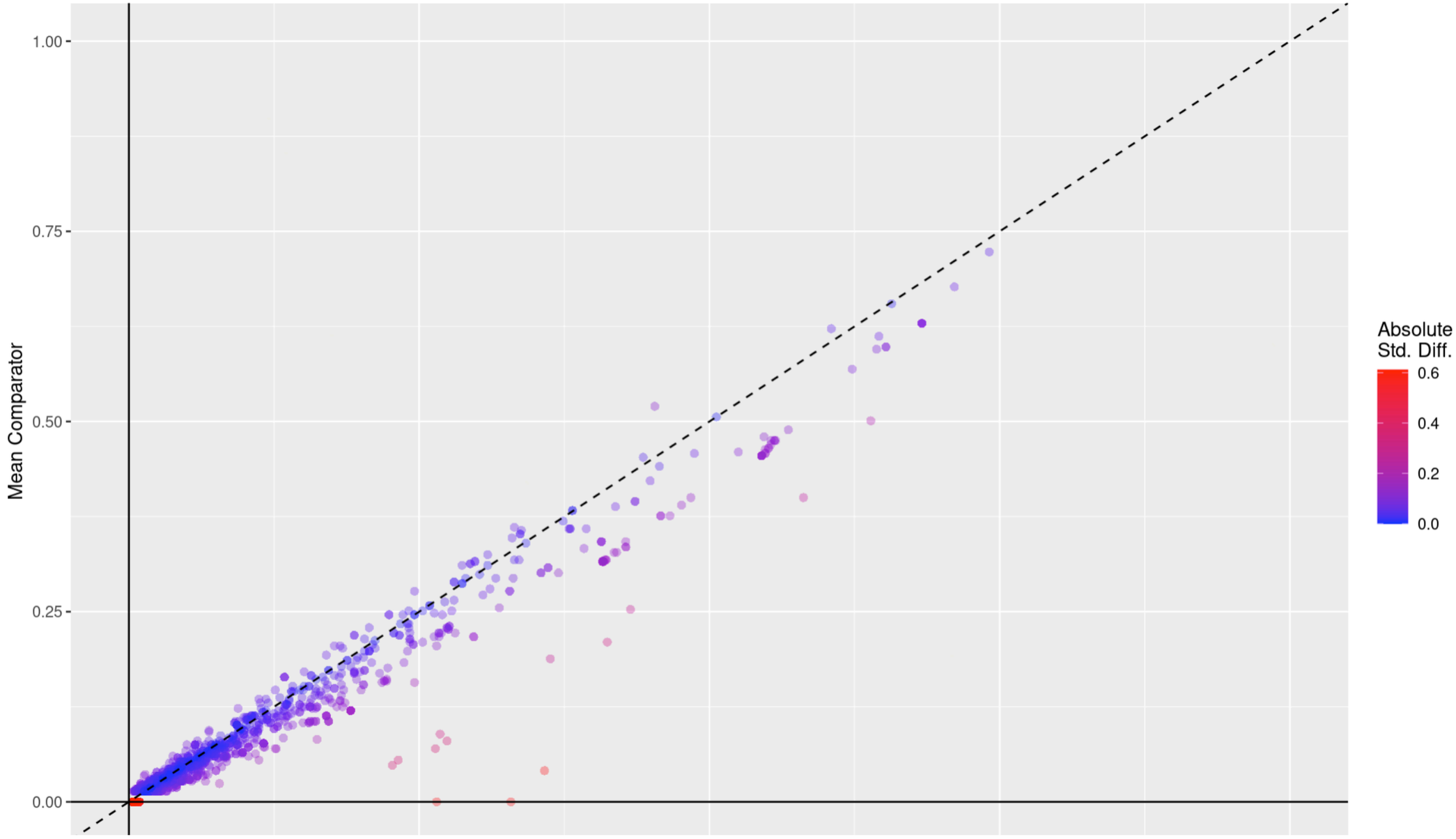
All

Time Window

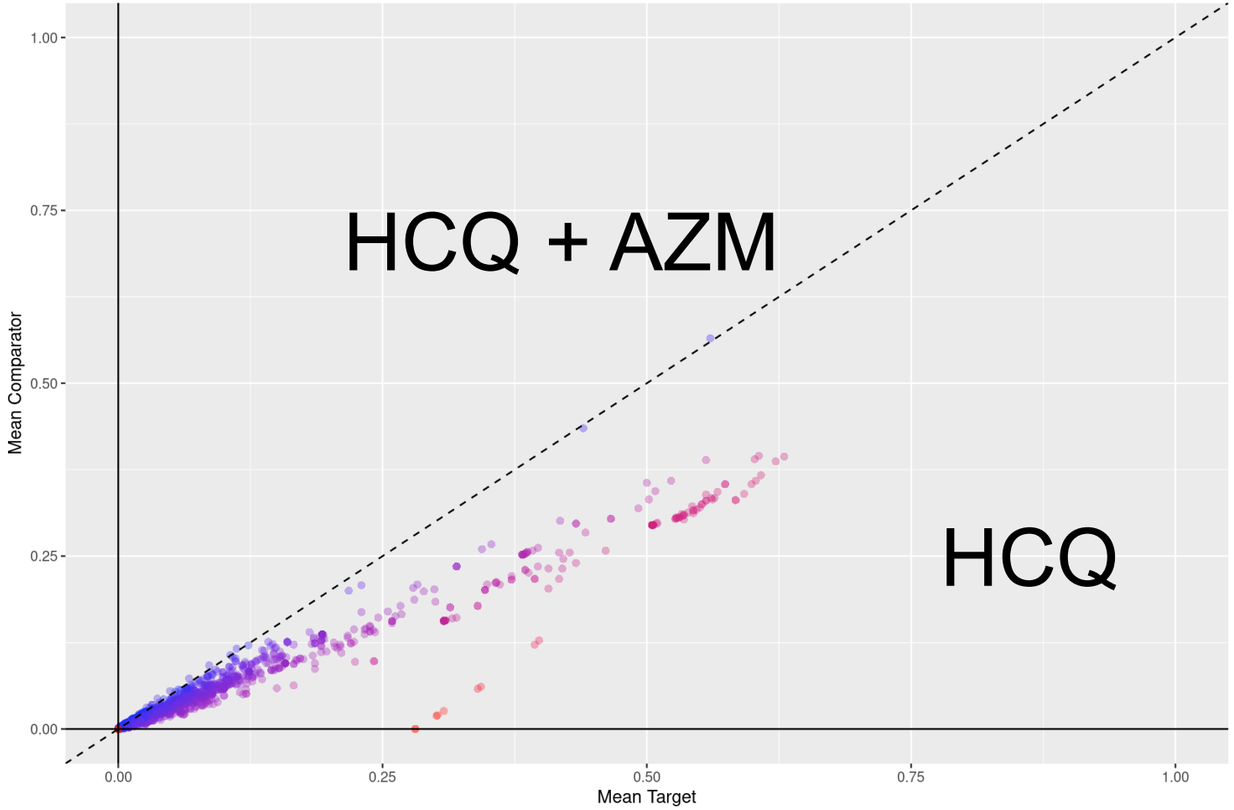
-365d to -1d, -30d to -1d

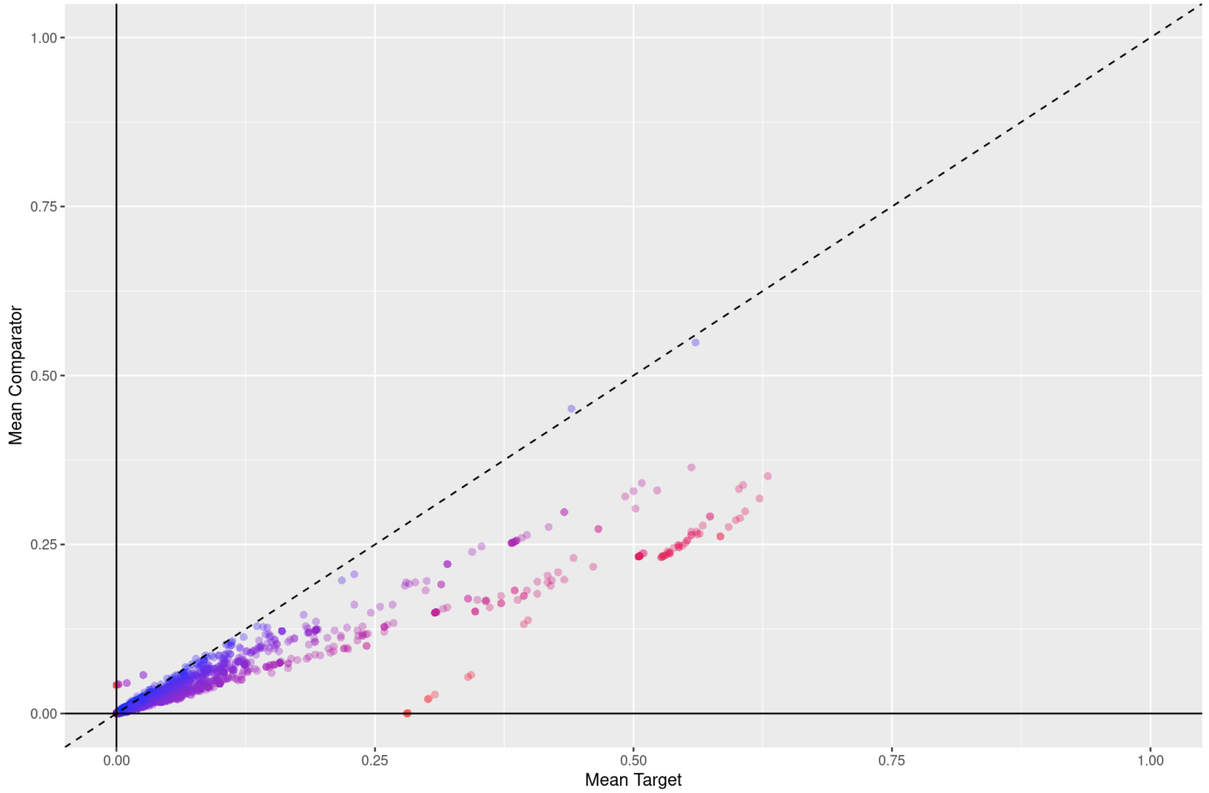
Table Plot

Compare Cohort Characterization

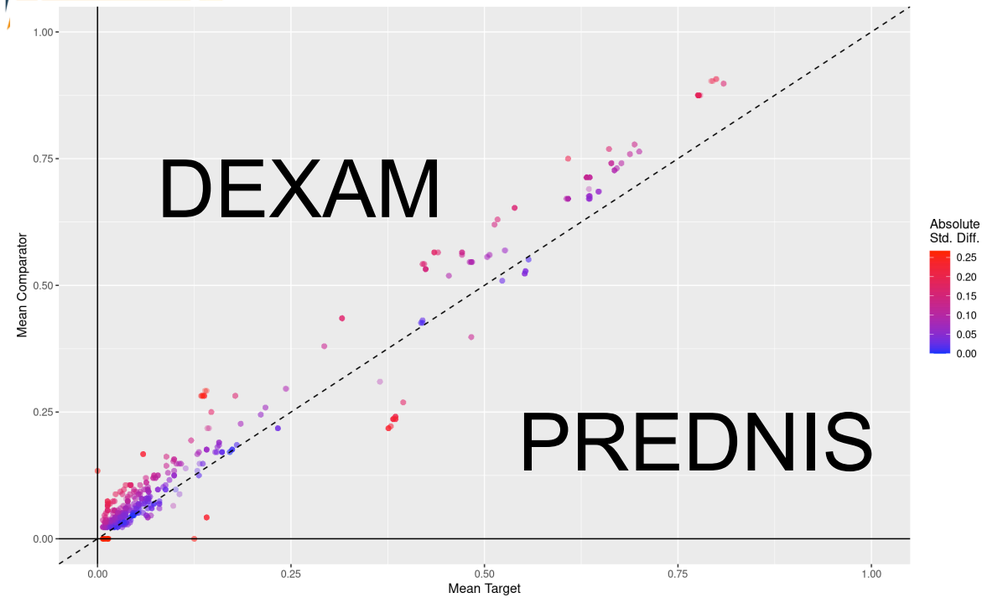


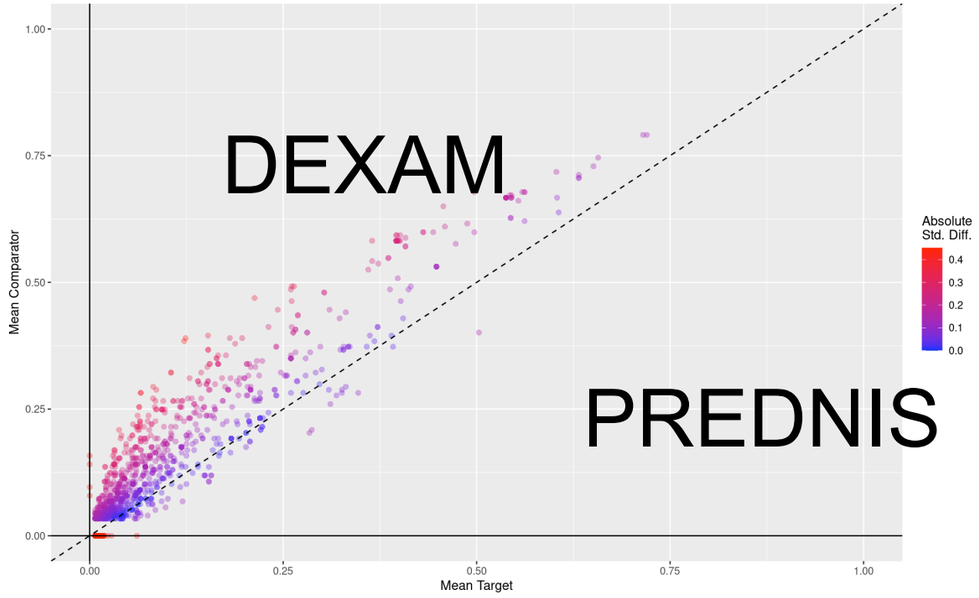
Eg Antivirals – Premier

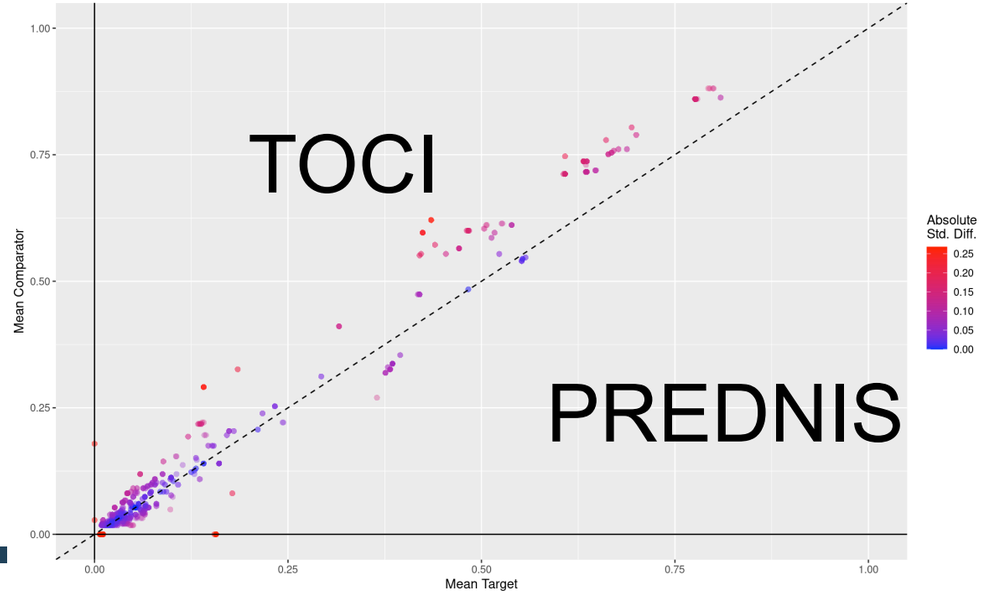


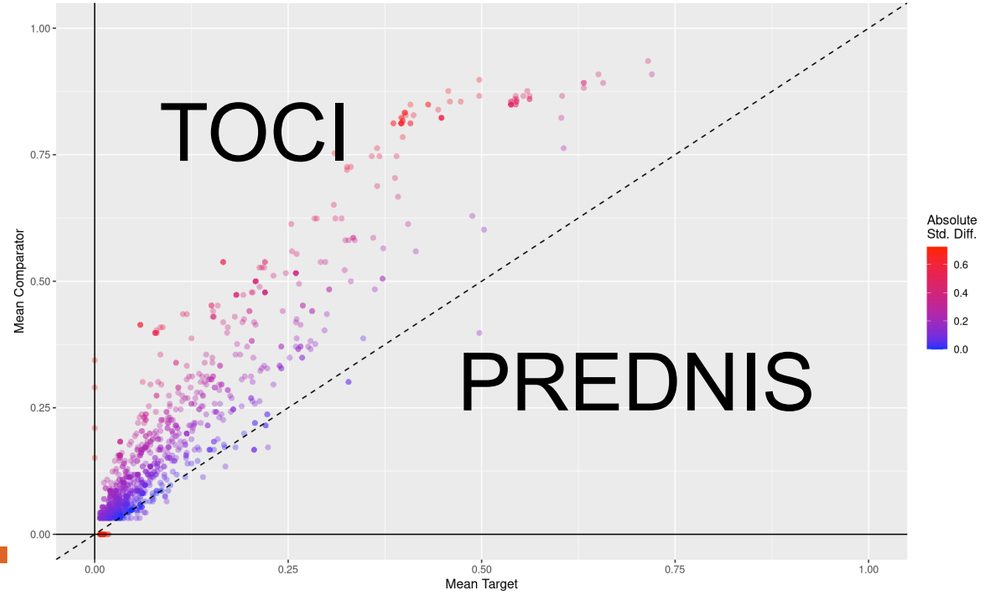


Immune-based therapies in HM (L) and Optum EHR (R)









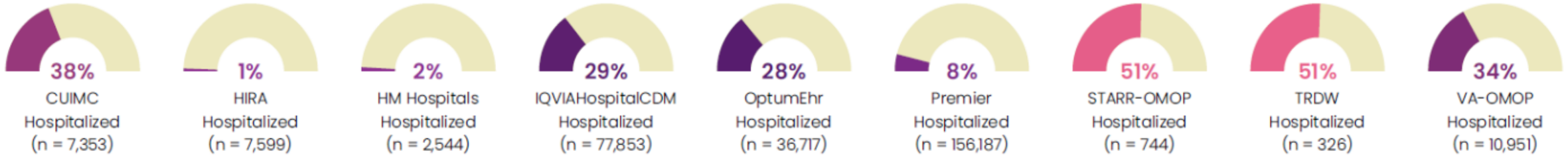
PRELIMINARY FINDINGS – Heparin vs Aspirin

A relevant clinical research question

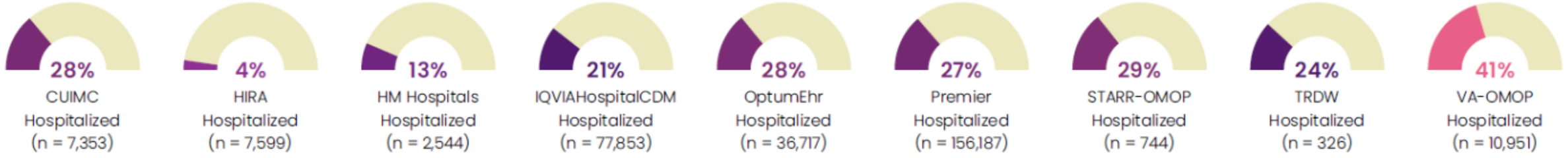
- Is anticoagulation worth it (beneficial, not too risky) in patients with COVID-19?

Public health impact?
% of heparin/AAS users in Charybdis

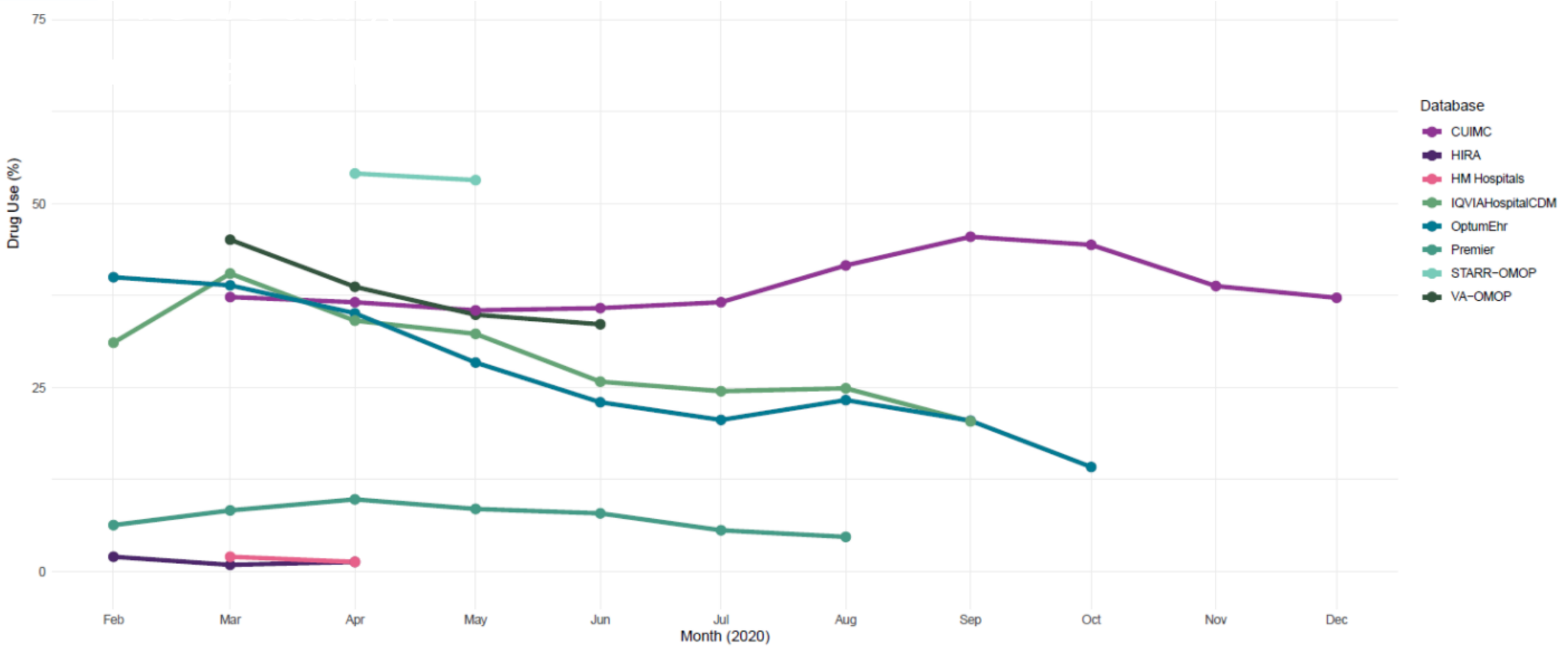
Heparin use in patients diagnosed or tested + for COVID



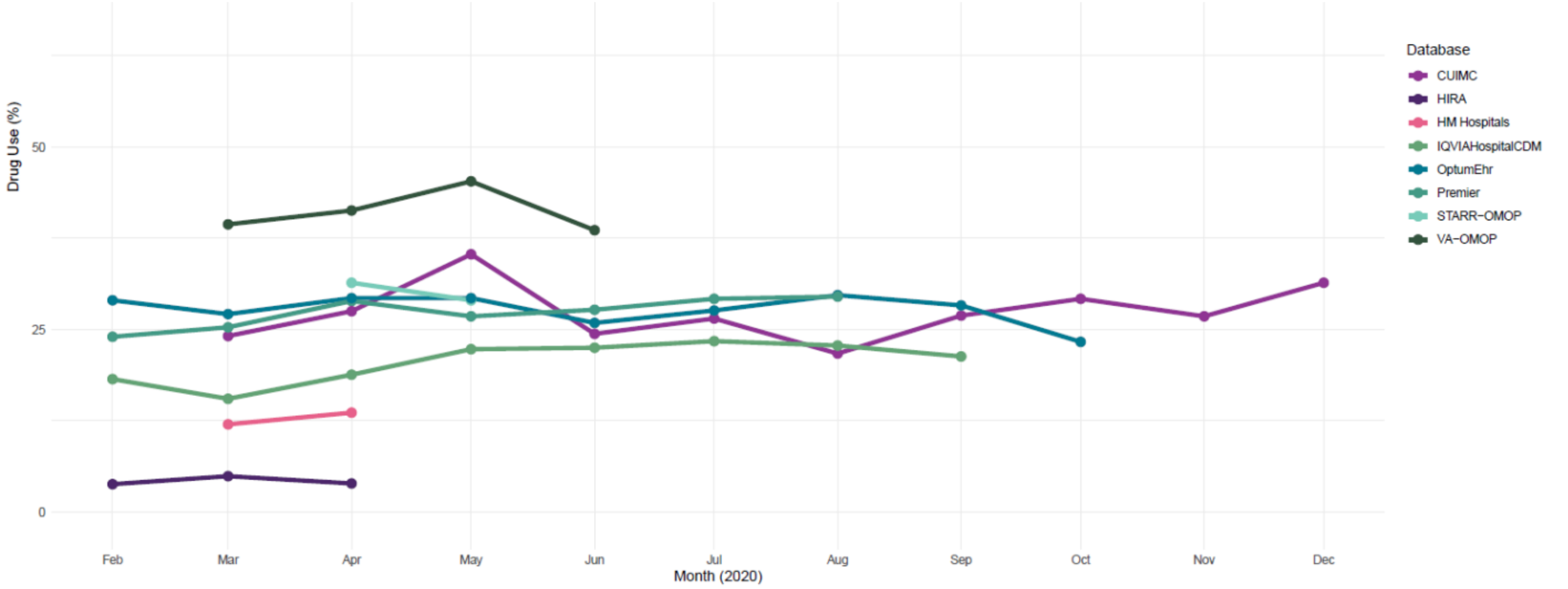
Aspirin use in patients diagnosed or tested + for COVID



Trends in % of heparin users



Trends in % of AAS users



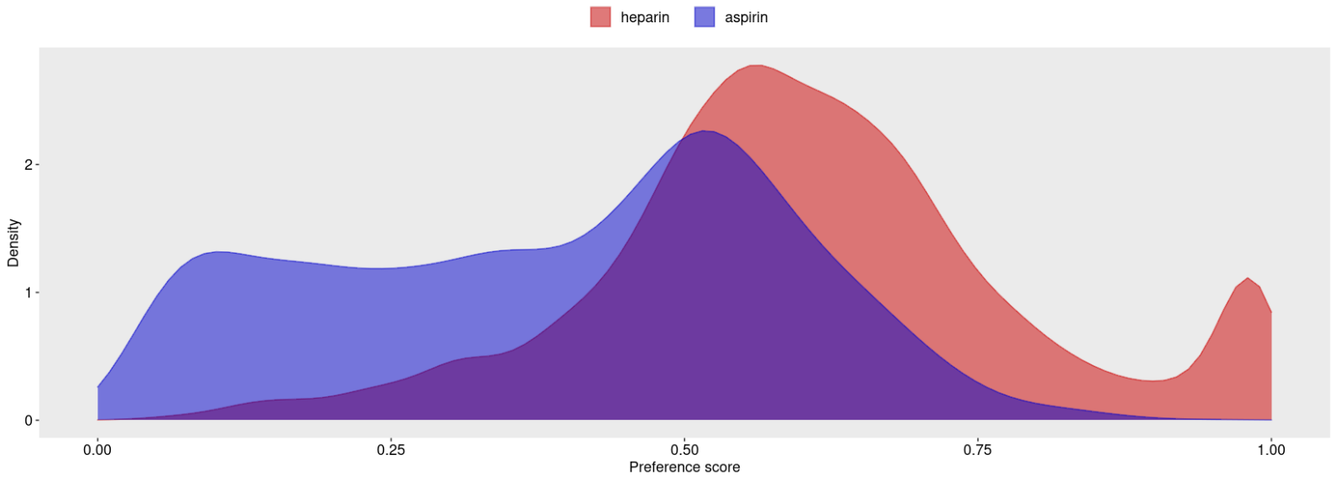
What's the evidence?

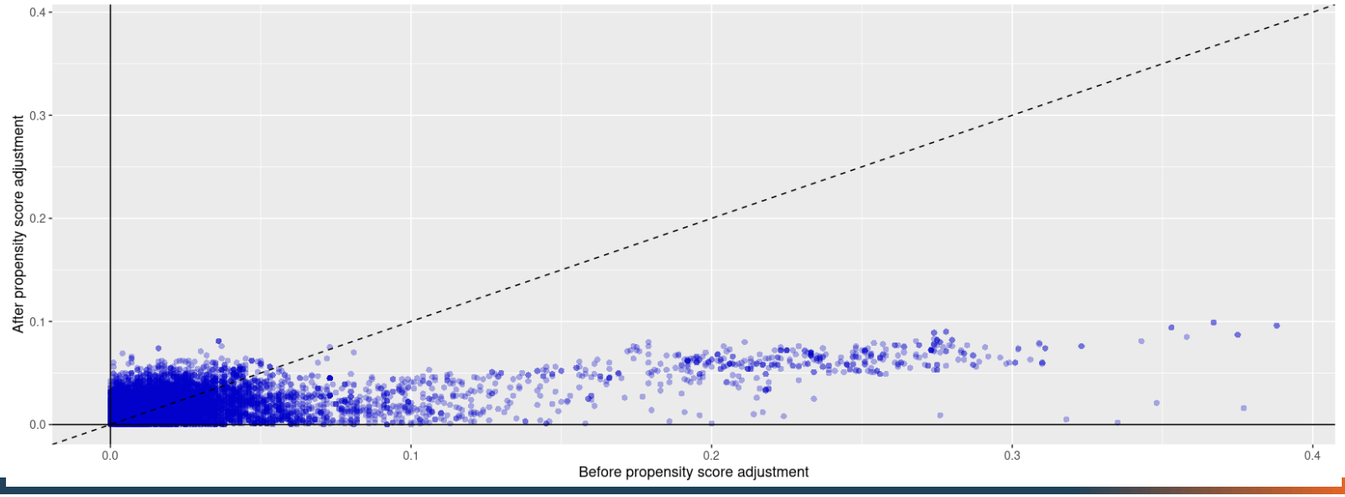
- Large multi-platform RCT ATTACC/REMAP-CAP/ACTIV-4a (still a preprint) suggests reduction in morbidity and mortality in COVID wards but not in ICU/severe patients

- An analysis of VA in BMJ suggests 30% reduction in mortality
- https://www.bmj.com/content/372/bmj.n311

- **Question** is: would platelet aggregation safer? And would it do the trick?

Scylla findings (to date) – Heparin vs Aspirin Diagnostics IQVIA Hospital CDM





- PS overlap -> PS matching to ‘common support’ area should enable ATT estimation

- No relevant (SMD>0.1) observable imbalance after PS matching

Scylla findings (to date) – Heparin vs Aspirin Outcomes - effectiveness

PRELIMINARY FINDINGS: Do not interpret as yet ☺

Rx initiation (index)	ARDS HR [95CI]	Total CVE HR [95CI]	ICU HR [95CI]	Death HR [95CI]	Discharge HR [95CI]
On admission	0.96 [0.87-1.06]	**0.75 [0.63-0.89]**	1.12 [0.97-1.29]	**1.28 [1.08-1.53]**	**0.89 [0.81-0.98]**
During admission	0.97 [0.89-1.05]	**0.77 [0.66-.0.89]**	**1.20 [1.06-1.36]**	**1.35 [1.15-1.58]**	**0.83 [0.76-0.90]**

Scylla findings (to date) – Heparin vs Aspirin
Outcomes - safety

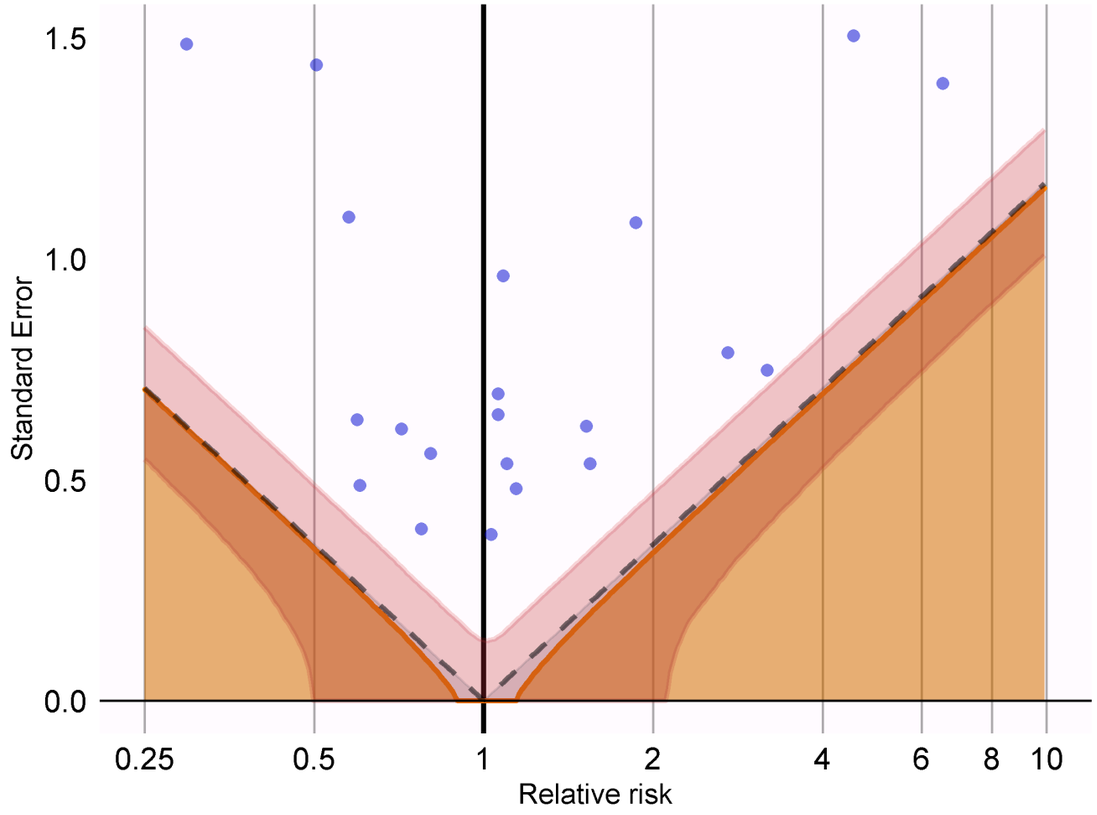
PRELIMINARY FINDINGS: Do not interpret as yet ☺

Rx initiation (index)	GI Bleed HR [95CI]	Haemorr Stroke HR [95CI]	AKI HR [95CI]	Liver failure HR [95CI]
On admission	1.09 [0.65-1.85]	2.24 [0.69-10.03]	**1.51 [1.32-1.73]**	0.92 [0.47-1.80]
During admission	1.09 [0.72-1.65]	1.38 [0.54-4.01]	**1.50 [1.34-1.68]**	1.43 [0.85-2.48]

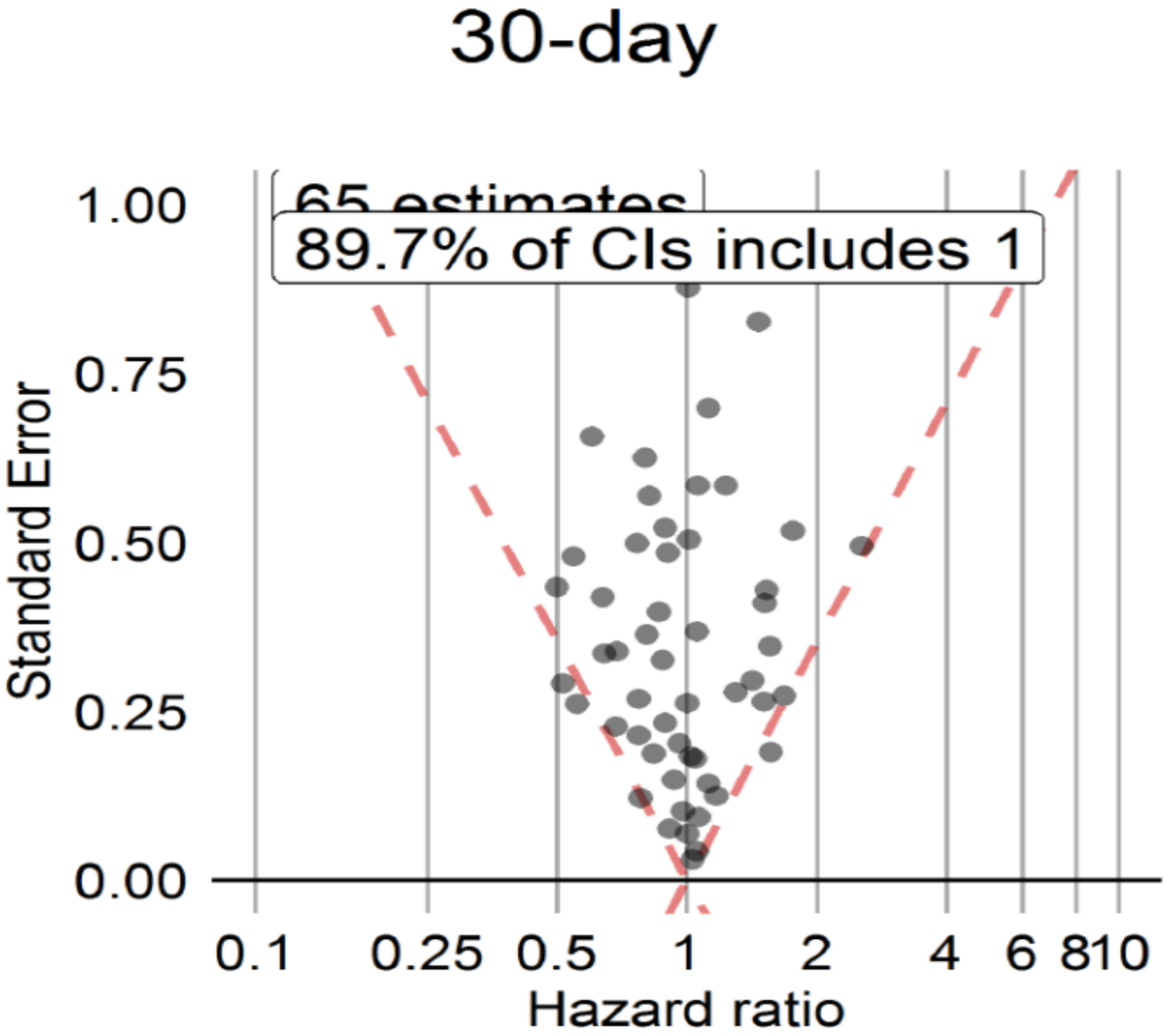
Scylla findings (to date) – Heparin vs Aspirin "Positive" and Neg Control Outcomes

PRELIMINARY FINDINGS: Do not interpret as yet ☺

Rx initiation (index)	Isch stroke HR [95CI]	Acute MI HR [95CI]	VTE HR [95CI]
Admission day	**0.59 [0.35-0.99]**	**0.61 [0.48-0.77]**	2.33 [1.70-3.22]
During admission	**0.36 [0.19-0.65]**	**0.73 [0.60-0.89]**	2.27 [1.72-3.05]



What do well powered NCO look like?



From Lane J et al. HCQ safety.

Lancet Rheum 2020

So what next?

1. Look into index date misclassification w VTE (luckily we are working on this as part of AESI rates work)
2. Look for additional/alternative negative control outcomes
3. Run the Scylla estimation package in additional databases (e-mail me prietoalhambra@ohdsi.org)
4. Wait for more data to accrue in the same data sources …

So what next?

1. Look into index date misclassification w VTE (luckily we are working on this as part of AESI rates work)
2. Look for additional/alternative negative control outcomes
3. Run the Scylla estimation package in additional databases (e-mail me prietoalhambra@ohdsi.org)
4. Wait for more data to accrue in the same data sources …
5. All of the above ☺

Questions?