Population-level Estimation #3: Association of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on COVID incidence and complications

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Background

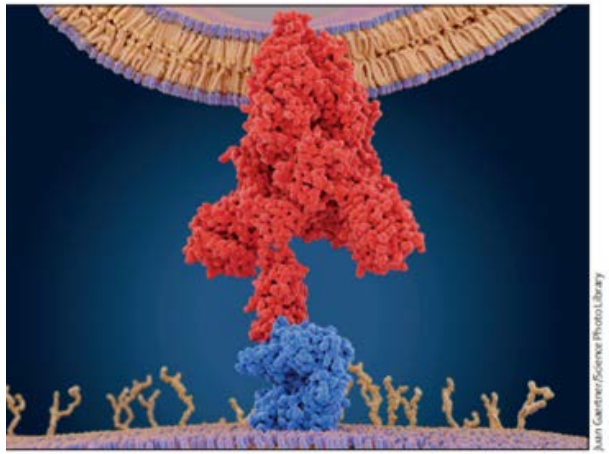
Authors	COVID Patients	Location	Key Content
Guan et al	1099	China	24% HTN in severe disease (vs 13%)
Zhou	191	China	HTN Univariate OR 3.1 (1.6-6.0) for death
Wang et al	138	China	HTN admissions 31%, HTN ICU 58%
Wu et al	201	China	HTN admissions 19%, HTN ARDS 27%

- People with hypertension (HTN) have worse COVID-19 outcomes
- Speculation that ACE/ARBs taken for HTN may be detrimental
  - Coronaviruses interact with RAS ACE-2 receptor, allowing them to enter the cell
  - ACE & ARBs upregulate ACE-2 receptors (limited data)
  - RAS ACE-2 expressed in lung, kidney, heart, GI tract
- Speculation that ARBs may be protective
  - Prevent the angiotensin I receptor from being stimulated
  - Regulate ACE-2 and reduce angiotensin production by ACE and increase production of the vasodilator angiotensin(1-7)

Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?

The most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with novel coronavirus disease

inhibitors and ARBs, which results in an upregulation of ACE2.[5] ACE2 can also be increased by thiazolidinediones and ibuprofen. These data suggest that ACE2 expression is increased in diabetes and treatment with ACE inhibitors and ARBs increases ACE2 expression. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesise that diabetes and hypertension treatment with



Fang et. Al. Lancet Resp Medicine 11 March 2020

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EMA advises continued use of medicines for hypertension, heart or kidney disease during COVID-19 pandemic

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Press release 27/03/2020

EMA is aware of recent media reports and publications which question whether some medicines, for instance angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs, or sartan medicines), could worsen coronavirus disease (COVID-19). ACE inhibitors and ARBs are most commonly used for treating patients with high blood pressure, heart failure or kidney disease.

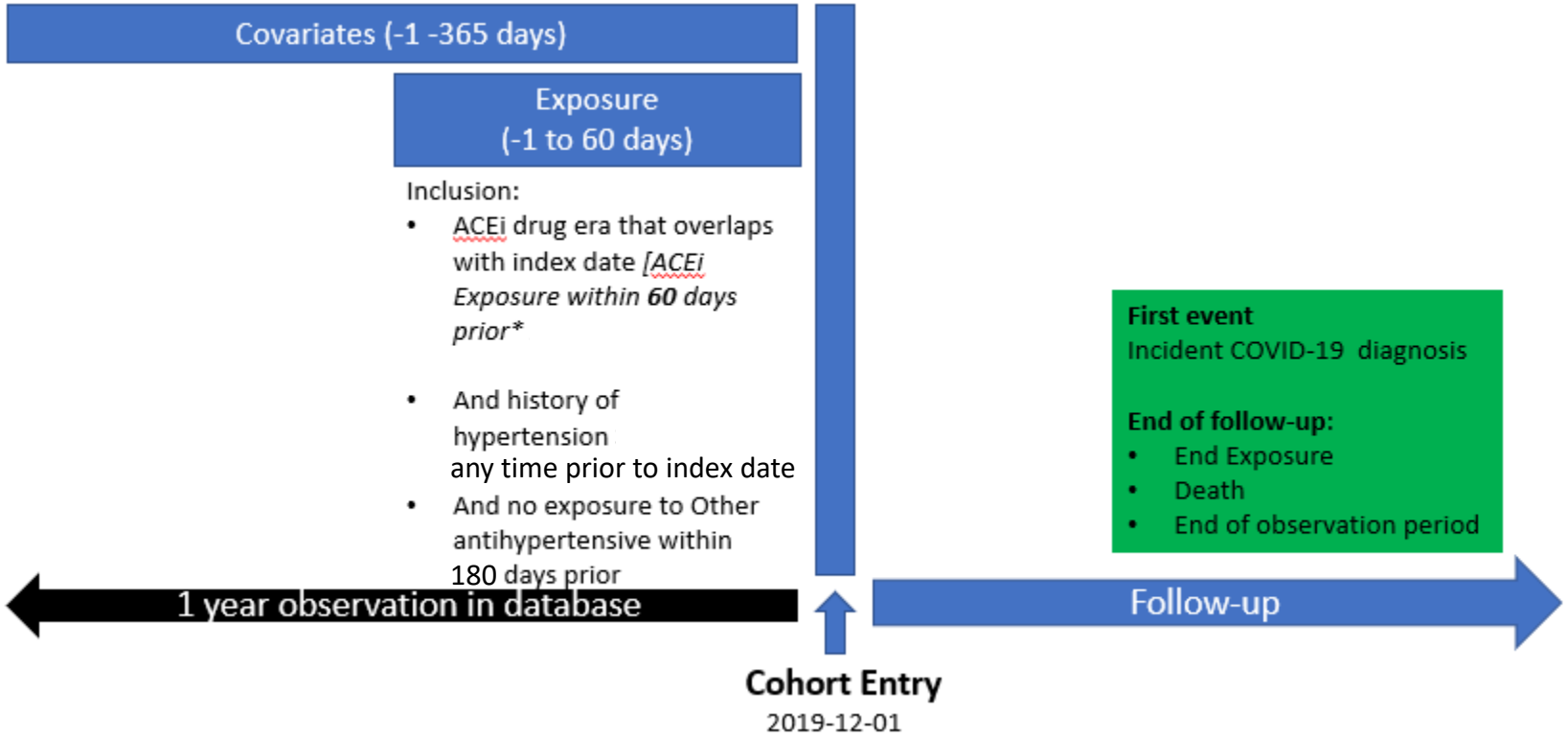
https://www.ema.europa.eu/en/news/ema-advises-continued-use-medicines-hypertension-heart-kidney-disease-during-covid-19-pandemic

Clinical Hypotheses

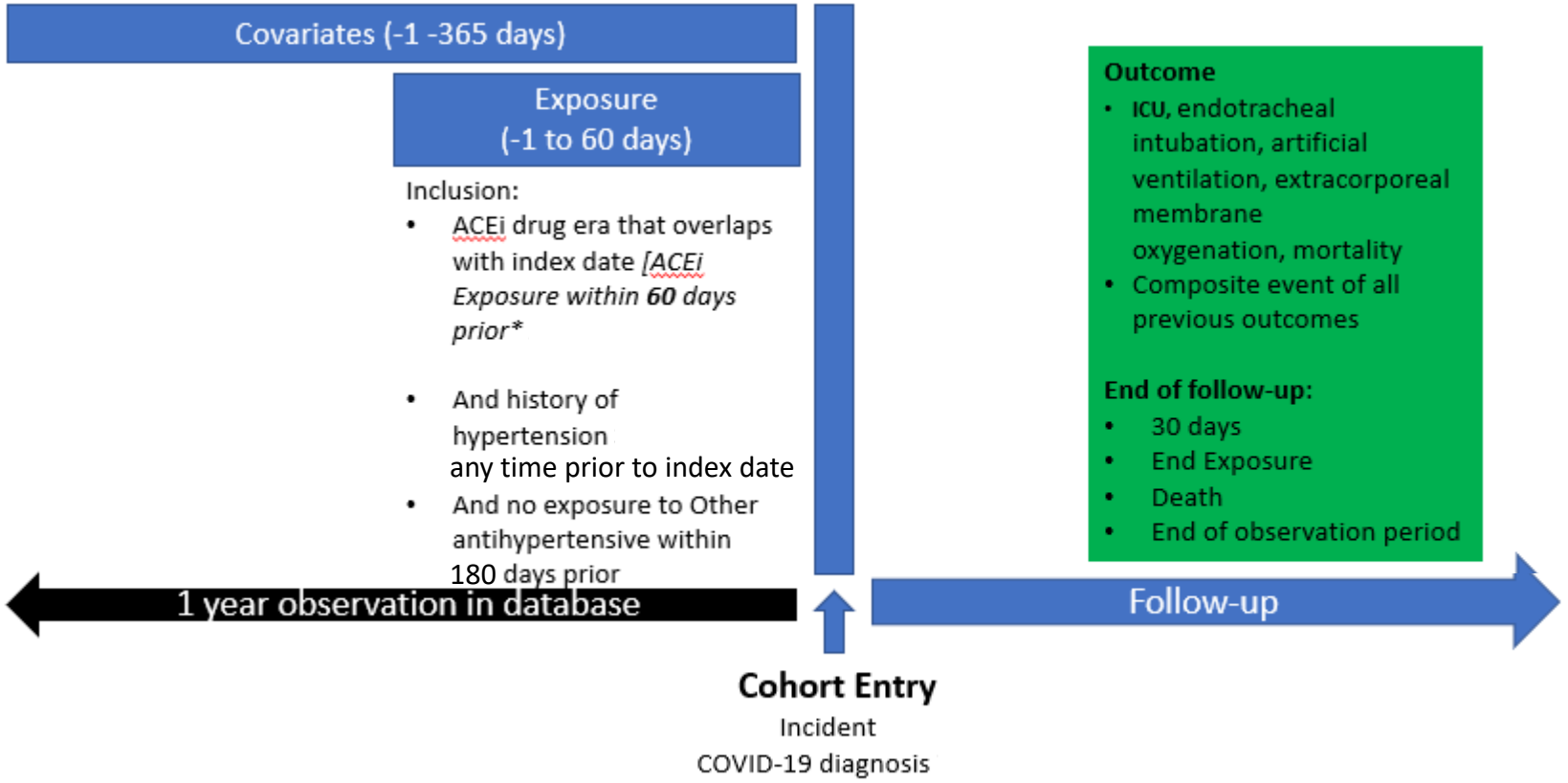
1. Prevalent ACE or ARB use is associated with a difference in risk of COVID-19 infection relative to an active comparator in hypertensive patients

2. Prevalent ACE or ARB use in COVID-19+ patients is associated with a difference in risk of intensive outcomes relative to an active comparator in hypertensive patients

Protocol for Hypothesis 1

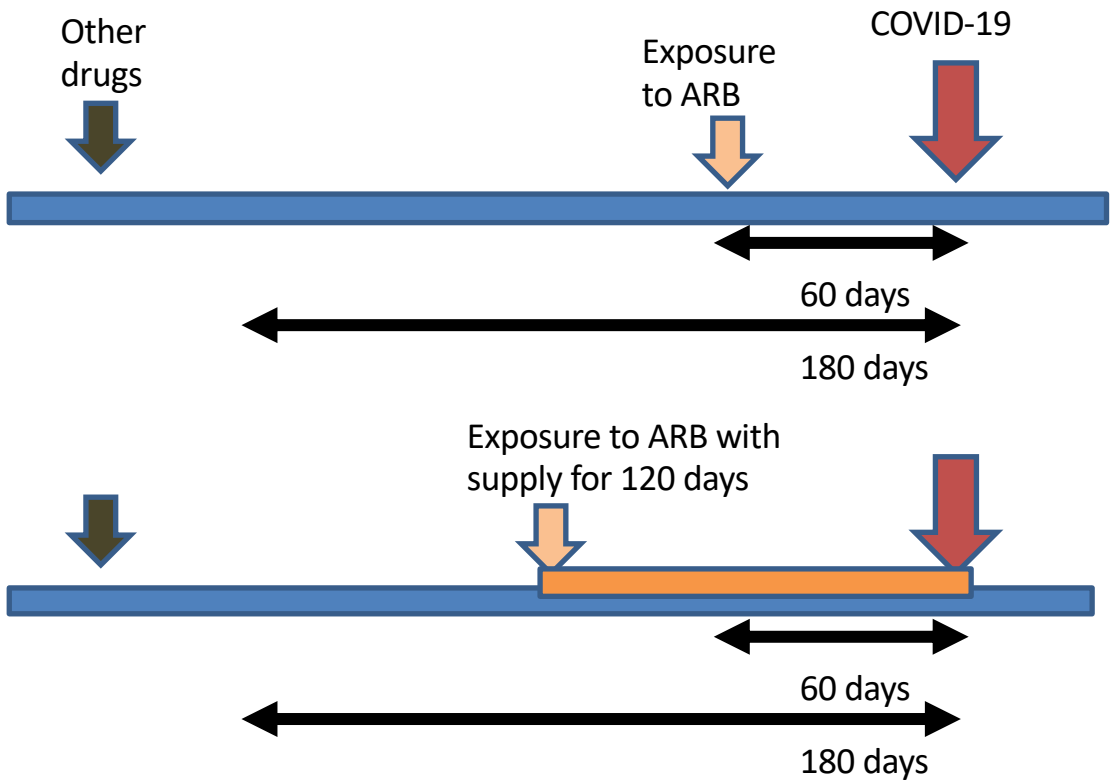


Protocol for Hypothesis 2



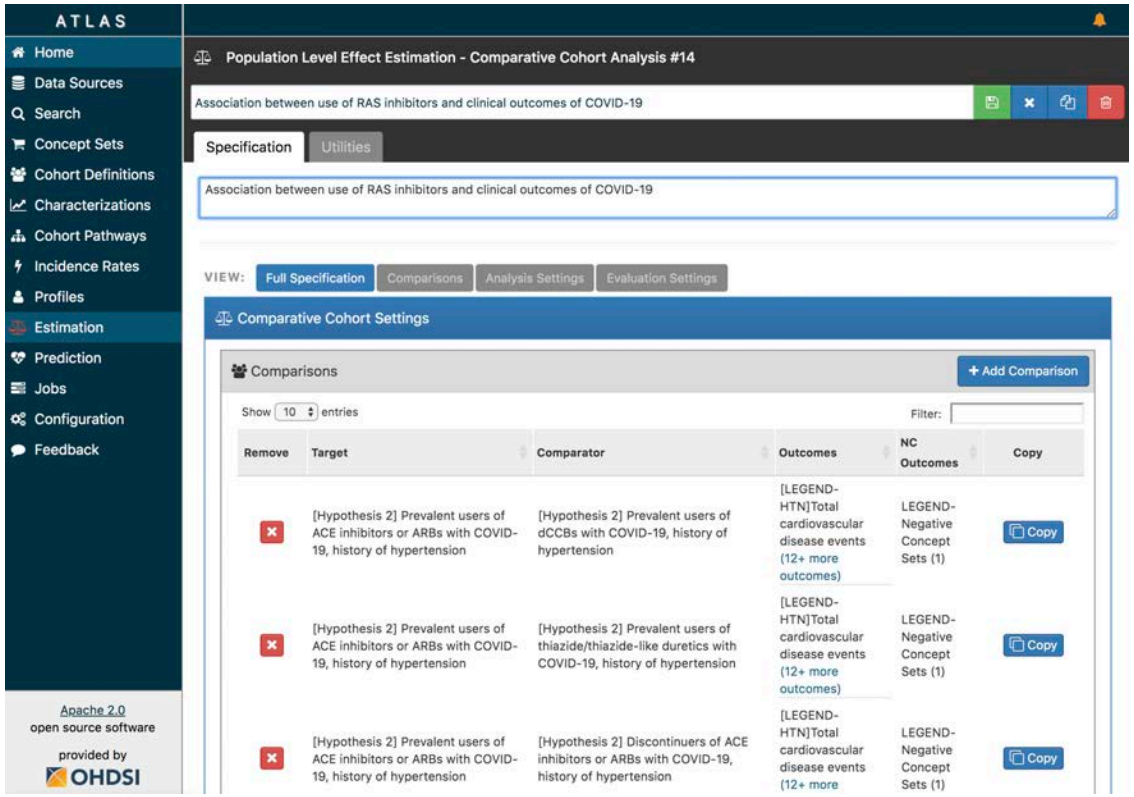
Drug Exposure Specification

Prevalent users of ARBs, with COVID-19, history of hypertension



http://atlas-covid19.ohdsi.org/#/cohortdefinition/268

Specification



Comparisons:

- ACE vs CCB
- ACE vs THZ
- ARB vs CCB
- ARB vs THZ
- RAS vs Discontinued RAS
- ACE vs ARB
- RAS vs CCB
- RAS vs THZ

Outcomes:

- ICU Care
- Ventilation
- ECMO
- All-cause mortality
- MI, HF, Stroke, CV death
- AKI
- LEGEND negative controls

Design:

- Logistic regression outcome (30/60/90 days) (cohort 2)
- PS matched / stratified (including age, gender, month)
- Potential for large-scale PS with larger cohorts

Results

- HIRA: study executes and preliminary results (coming in next presentation)
- Columbia University Medical Center/NYP
  - Successfully ran the main cohort of HTN, recent ACE, no other anti-HTN drugs, sufficient lookback => about 20 patients
  - Analysis using SQL showed we can increase patient numbers using less recent ACE (note we have 30d prescriptions with 5 refills = 180d)
  - Do not have hospital disposition yet, but have inferred ICU, for example, via medications given
  - (Do have a subpopulation on hydroxychloroquine)

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Apologies if your name is not here; let Marc know – he haphazardly compiled this list

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