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

Daniel Morales
University of Dundee
Background

- 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)

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

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

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.

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

Covariates (-1 to 365 days)

Exposure (-1 to 60 days)

- Inclusion:
  - ACEI drug era that overlaps with index date
  - Exposure within 60 days prior
  - And history of hypertension any time prior to index date
  - And no exposure to Other antihypertensive within 180 days prior

First event:
- Incident COVID-19 diagnosis

End of follow-up:
- End Exposure
- Death
- End of observation period

1 year observation in database

Follow-up

Cohort Entry
2019-12-01
Protocol for Hypothesis 2

Covariates (-1 to 365 days)

Exposure (-1 to 60 days)

Inclusion:
- ACEI drug era that overlaps with index date [ACEI Exposure within 60 days prior*]
- And history of hypertension any time prior to index date
- And no exposure to Other antihypertensive within 180 days prior

1 year observation in database

Follow-up

Outcome
- ICU, endotracheal intubation, artificial ventilation, extracorporeal membrane oxygenation, mortality
- Composite event of all previous outcomes

End of follow-up:
- 30 days
- End Exposure
- Death
- End of observation period

Cohort Entry
Incident
COVID-19 diagnosis
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

Outcomes:
- ICU Care
- Ventilation
- ECMO
- All-cause mortality

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

LEGEND negative controls
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)
Acknowledgments

Key participants:

- Kees van Bochove
- Mitchell Conover
- George Hripcsak
- Christophe Lambert
- Michael Matheny
- Daniel Morales
- Fredrik Nyberg
- Nicole Pratt
- Daniel Prieto Alhambra
- Marc Suchard
- Cynthia Sung
- Seng Chan You

Partial funding provided through NIH U19 AI135995 and R01 LM006910

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