Renin-angiotensin system blockers and susceptibility to COVID-19: an international open science cohort study

Marc A Suchard, MD PhD, on behalf of the ICARIUS team
Background and Call for Evidence

- People with hypertension (HTN) have worse COVID-19 outcomes
- Speculation that ACEi/ARBs taken for HTN may be detrimental
  - Coronaviruses interact with RAS ACE-2 receptor, allowing them to enter the cell
- Speculation that ARBs may be protective
  - Prevent the angiotensin I receptor from being stimulated

<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% overall)</td>
</tr>
<tr>
<td>Zhou et al</td>
<td>191</td>
<td>China</td>
<td>HTN Univariate OR 3.1 (1.6-6.0) for death</td>
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</tbody>
</table>
1. Prevalent ACEi or ARB use is associated with a difference in risk of COVID-19 infection relative to an active comparator in hypertensive patients.

2. Prevalent ACEi 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.
   - This work is still in progress and will not be included in this presentation.
<table>
<thead>
<tr>
<th>Data sources</th>
<th>Country / sample size</th>
<th>Data elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information Systems for Research in Primary Care (SIDIAP) database</td>
<td>Spain ≈ 6 million</td>
<td><strong>GP EHR linked to hosp admits</strong>&lt;br&gt;Dx, Rx, labs, demographics, COVID-19 tests/Dx</td>
</tr>
<tr>
<td>US Department of Veterans Affairs (VA) database</td>
<td>U.S. ≈ 12 million</td>
<td><strong>Linked administrative claims</strong>&lt;br&gt;Dx, Rx, labs, lifestyle, sociodemographics, COVID-19 tests/Dx</td>
</tr>
<tr>
<td>Columbia University Irving Medical Center data warehouse (CUIMC)*</td>
<td>U.S. (NYC) ≈ 6 million</td>
<td><strong>Health-system EHR</strong>&lt;br&gt;Dx, Rx, labs, demographics, COVID-19 tests/Dx,</td>
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</tbody>
</table>

* Analyses implemented in CUIMC did not pass a priori diagnostic assessments. Thus, this presentation includes only limited description of those analyses and findings.
1000s of hours of dedication

Team SIDIAP
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- Maria Aragon
- Sergio Fernandez-Bertolin
- Andrea Pistillo

Team VA
- Scott DuVall
- Aize Cao
- Kristine Lynch
- Michael Matheny
Study Schematic

Eligibility
- Prior database enrollment ≥180 days
- No observed history of the outcome Any time prior to 0 days
- ≥1 hypertension Dx Any time prior to 0 days

Exposure
- No observed Rx for any other antihypertensive
- monotherapy analysis only -180 to 0 days

Adjustment
- Covariate assessment: conditions, drugs, procedures, measurements, devices, and observations Any time prior to 0 days
- -180 to 0 days
- -30 to 0 days

Outcomes
- Censoring: Rx discontinuation, data disenrollment, death, outcome (below)
- 1) COVID-19 diagnosis
- 2) COVID-19 hospitalization
- 3) Hospitalization with pneumonia
- 4) Hospitalization with pneumonia, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), sepsis

Follow-up +1 to end of data availability

Recently observed Rx for target or comparator drug
- last target drug Rx observed between 11/1/19 and 1/31/20

* It is not possible for patients to meet criteria to enter both target and comparator cohorts
Statistical Methods

• Large-scale propensity-score (PS) models selected using a data-driven regularized regression approach

• Balanced covariates using two PS approaches:
  – 1:N variable-ratio PS-matching
  – PS stratification using 5 quintiles

• Estimated hazard ratios (HRs) using cox proportional hazards models
  – Conditioned on PS strata or matching unit

• Empirical calibration using up to 123 negative controls
  – Negative control outcomes identified using a data-rich algorithm
  – Calibrated each HR estimate and 95% CI using the empirical null distributions

• These analyses do not statistically account for multiple testing
## Patient and event counts

<table>
<thead>
<tr>
<th></th>
<th>SIDIAP (Spain)</th>
<th></th>
<th>VA (U.S.)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Events</td>
<td>Patients</td>
<td>Events</td>
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<tr>
<td></td>
<td>T</td>
<td>C</td>
<td>T</td>
<td>C</td>
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<tr>
<td>ACE/ARB vs CCB/THZ</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>37,796</td>
<td>14,003</td>
<td>500</td>
<td>184</td>
</tr>
<tr>
<td>Combo therapy</td>
<td>45,239</td>
<td>19,007</td>
<td>627</td>
<td>250</td>
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<tr>
<td>ACE vs CCB/THZ</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>30,787</td>
<td>14,003</td>
<td>398</td>
<td>184</td>
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<tr>
<td>Combo therapy</td>
<td>36,323</td>
<td>29,239</td>
<td>485</td>
<td>399</td>
</tr>
<tr>
<td>ARB vs. CCB/THZ</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>6,753</td>
<td>14,003</td>
<td>95</td>
<td>184</td>
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<tr>
<td>Combo therapy</td>
<td>9,194</td>
<td>39,427</td>
<td>137</td>
<td>519</td>
</tr>
<tr>
<td>ACE vs. ARB</td>
<td></td>
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<td>95</td>
</tr>
<tr>
<td>Combo therapy</td>
<td>56,465</td>
<td>19,148</td>
<td>758</td>
<td>283</td>
</tr>
</tbody>
</table>

|                      |              |         |           |         |
|                      | T            | C       | T         | C       |
| ACE/ARB vs CCB/THZ   | 320,450       | 229,063 | 145       | 183     |
| ACE vs CCB/THZ       | 656,274       | 443,061 | 345       | 335     |
| ARB vs. CCB/THZ      | 457,557       | 639,500 | 218       | 494     |
| ACE vs. ARB          | 235,348       | 229,063 | 96        | 183     |
|                      | 457,557       | 639,500 | 218       | 494     |
|                      | 201,503       | 854,224 | 127       | 574     |
|                      | 235,348       | 82,872  | 96        | 46      |
|                      | 865,931       | 395,156 | 441       | 282     |
Baseline covariate balance: ACE/ARB vs. CCB/THZ monotherapy

- Baseline differences in diabetes, CKD, heart disease, heart failure, AF
- PS-methods capably balanced baseline covariates, except for PS-stratification in the CUIMC cohort
Calibrated HRs: ACE/ARB vs. CCB/THZ
Calibrated HRs: ACE vs. ARB
Key Limitations

• Defining drug exposure using “prevalent” not “new” use
  – We may adjust for mediators on the causal pathway between exposure and outcome
  – COVID-19 unlikely to have affected decision to initiate one drug versus another
  – Depletion of susceptible is likely minimal
  – Biological mechanisms relating to ACE2 expression may require chronic exposure

• Defining COVID-19 using diagnostic codes and positive test results underestimates the number of true cases
  – May vary by data partner, depending on local-area testing strategies
  – Analyses of COVID-19 hospitalization outcome produced concordant results
Conclusions

• These findings support regulatory and clinical society guidance not to modify ACE/ARB treatment on the basis of COVID-19 risk

• Marginal differences observed between ACEs and ARBs do not warrant class switching to reduce COVID-19 susceptibility
Acknowledgments

Contributors to this work

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Links to additional documentation

• Open-source OHDSI CohortMethod R package:
  – https://ohdsi.github.io/CohortMethod/

• Pre-specified ICARIUS protocol and start-to-finish open and executable source code
  – https://github.com/ohdsi-studies/Covid19Icarius

• Interactive web application presenting study diagnostics and results for all study effects
  – https://data.ohdsi.org/IcariusSusceptibility

• Pre-print manuscript, publicly posted to MedRxiv:
  – https://www.medrxiv.org/content/10.1101/2020.06.11.20125849v1