The COVID Infodemic: Stepping Back to Move Forward

Presenters and Panelists:
Dr. Roxana Mehran MD
Dr. Michelle Kittleson MD
Dr. Harlan Krumholz MD

Moderated by Dr. Katie Berlacher MD
Infodemic:

“An excessive amount of information concerning a problem such that the solution is made more difficult”
We are battling TWO Diseases:

COVID 19

Infodemic

Credit: CDC / Science Photo Library

Credit: Getty images
The COVID Infodemic: Stepping Back to Move Forward
Critical Appraisal of Studies

Roxana Mehran, MD, FACC, FAHA, MScAi, FESC
Mount Sinai Professor Of Cardiovascular Clinical Research and Outcomes
Professor of Medicine (Cardiology), and Population Health Science and Policy
Director of Interventional Cardiovascular Research and Clinical Trials,
Icahn School of Medicine at Mount Sinai,
New York, NY, USA

@Drroxmehran
<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant/Advisory/Speaking Engagements</td>
<td>Abbott Laboratories (to institution), Abiomed (spouse), Boston Scientific, Idorsia Pharmaceuticals Ltd. (no fee), Janssen, Medscape, Medtelligence (Janssen Scientific Affairs), Roivant Sciences Inc, Sanofi, Siemens Medical Solutions, Regeneron Pharmaceuticals (no fee), Spectranetics/Philips/Volcano Corp (to institution), The Medicines Company (spouse)</td>
</tr>
<tr>
<td>Research Funding to Institution</td>
<td>Abbott Laboratories, Abiomed, Applied Therapeutics, AstraZeneca, Bayer, Beth Israel Deaconess, BMS, CERC, Chiesi, Concept Medical, CSL Behring, DSI, Medtronic, Novartis, OrbusNeich</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>Bristol-Myers Squibb (to institute), Medtelligence (Janssen Scientific Affairs), Merck (spouse)</td>
</tr>
<tr>
<td>Equity, &lt;1%</td>
<td>Claret Medical, Elixir Medical</td>
</tr>
<tr>
<td>DSMB membership paid to the institution</td>
<td>Watermark Research Partners</td>
</tr>
<tr>
<td>Associate Editor</td>
<td>ACC, AMA</td>
</tr>
</tbody>
</table>
The statistical results of a study (by themselves) do not communicate much meaning. Statistical results must be interpreted in context of study design and execution.
6 Key Points for Interpreting Clinical Research

1. Credibility and accuracy of results
2. Precision of the estimate of effects
3. Magnitude of effects and importance
4. Meaning of the results and study conclusions
5. Generalizability of the results (e.g., included population)
6. Implication of the results in clinical practice and future research
Concerns related to:

- Quality of the peer review process
- Quality of the data
Hydroxychloroquine Use in COVID-19

As of May 23rd

225 Studies found for: hydroxychloroquine OR chloroquine | COVID
Also searched for SARS-CoV-2, Plaquenil, and Alexoquine. See Search Details

17 result(s) found for: covid AND hydroxychloroquine. Displaying page 1 of 1.

24 trials have been registered

How Reliable Are These Studies?
Hydroxychloroquine Presented as Potential Treatment

Prescriptions of antimalarial drugs soared
Number of prescriptions for chloroquine and hydroxychloroquine

Time when first reports supported HCQ use in COVID-19

Data from US insurance claims, hospital prescriptions excluded
Source: IPM.ai, a subsidiary of Swoop
Two trials came out in late March supporting the use of HCQ in COVID-19 patients...

1. Journal Pre-proof

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret, Jean-Christophe Lagier, Philippe Parola, Yan Thuan Hoang, Line Meddeb, Morgane Mailhe, Barbara Doudier, Johan Courjon, Valérie Giordanengo, Vera Esteves Vicira, Hervé Tissot Duport, Stéphane Honoré, Philippe Colson, Eric Chabrière, Bernard La Scola, Jean-Marc Rolain, Philippe Brouqui, Didier Raoult

2. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial

Zhaowei Chen¹, Jijia Hu¹, Zongwei Zhang¹, Shan Jiang², Shoumeng Han³, Dandan Yan⁴, Ruhong Zhuang⁵, Ben Hu⁶ and Zhan Zhang⁷,*
1. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial (Gautret et al.)

36 Patients Included:
- 20 patients received HCQ 600 mg/day + azithromycin 500 mg on day 1 followed by 250 mg/day for 4 days
- 16 patients as control group (control group was not pre-specified in protocol)

Limitations and sources of bias
- Drug-related adverse events were not reported.
- Time of outcome assessment changed from “Days 1, 4, 7, and 14” in the protocol to “presence and absence of virus on Day-6 post-inclusion” in the analysis (not pre-specified).
- Viral clearance was assessed with a single rather than repeated measurements. In some patients, virus tests were negative at one time-point, but subsequently became positive, raising doubts on the arbitrary choice of a single measurement for the assessment of viral clearance.
2. Efficacy of Hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial (Chen et al.)

62 Patients Included:
- 31 patients received standard treatment
- 31 patients received standard treatment + HCQ 200 mg BID

Limitations and sources of bias
- The study exclusion criteria mentioned in the publication were not pre-specified (possible selection bias).
- Standard treatment included “antiviral/antibacterial agents, and immunoglobulin with or without corticosteroids.” Neither the antiviral/antibacterial agents nor the proportions of individuals on these treatments were reported.
- The adequacy of the randomization process could not be assessed as baseline characteristics were not reported in the manuscript.
- The blinding process throughout the trial was unclear.
Mean cough duration (days) was 2.0±0.2 vs. 3.1±1.5 while mean fever duration (days) was of 2.2±0.4 vs. 3.2±1.3 in the HCQ-treatment vs standard-treatment groups, respectively. For both cough and fever, the standard deviations in the two groups are strikingly different. Therefore, comparisons by t-tests (parametric) may have been inappropriate.

- No multivariable adjustment was performed for treatment effect estimates.
2. Efficacy of Hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial (Chen et al.)

CONSORT Checklist

The manuscript is still in preprint version, yet it has been already cited over 60 times!
Key Messages From These Two Trials

- Methodological discrepancies between protocols and subsequent publications
- Unclear study design and lack of pre-specified methodology (e.g., inadequate randomization, unclear blinding process, etc).
- Major methodological flaws in statistical analysis
Largest observational study published to date on the effects of hydroxychloroquine +/- macrolide in 96,032 hospitalized patients

- **Primary outcome**: In-hospital mortality; occurrence of de-novo sustained or non-sustained ventricular tachycardia or ventricular fibrillation.
- **Multivariable Cox hazard model** was used to control for confounding variables, including age, sex, ethnicity, comorbidities, other medications, and COVID-19 severity.
- Sensitivity analyses using **propensity score matching** confirmed the observed results.
▪ Mortality rates ranged from 16% to 24% in the HCQ-treated groups (+/- macrolide) compared with 10% in control group.

▪ Incidence of repetitive ventricular arrhythmias ranged from 4.3% to 8.1% in patients treated with HCQ, compared with 0.3% in the control group (p<0.0001).

*Increased risk of in-hospital deaths due to higher incidence of drug-induced ventricular arrhythmias?*
The relationship between death and ventricular tachycardia was not studied and causes of deaths (i.e. arrhythmic vs non-arrhythmic) were not adjudicated.

The number of deaths in the treatment groups was much greater than the number of patients who had ventricular arrhythmias.

**How Should We Interpret these Findings?**

Funck-Brentano et al., The Lancet, 2020
1. Addition of a macrolide to HCQ did not carry an increased risk of death, whereas it would be expected that the combination of two QTc-prolonging drugs would increase their pro-arrhythmic potential.

2. The HRs for death were similar in men and women, despite women having a higher risk for drug-induced QTc prolongation and drug-induced torsade de pointes than men.

Study results do not suggest that the increased risk of death with HCQ was due to a pro-arrhythmic mechanism.

Despite limitations inherent to the observational nature of this study, authors provided results from a well-designed and methodologically sound study on the effects of hydroxychloroquine, with or without a macrolide, in a very large sample of hospitalized patients with COVID-19.
SOLIDARITY Trial

- Aged at least 18 years
- Hospitalized
- SARS-CoV-2 infection
- No drug contraindication

All patients will receive standard of care

Randomization

- No Additional Treatment
- Lopinavir + Ritonavir
- Lopinavir + Ritonavir + INF-β

Outcomes

Need for ventilation or intensive care, time-to-discharge, and death.

Over 400 hospitals in 35 countries are actively recruiting patients and nearly 3500 patients have been enrolled from 17 countries.
COVID-19 Hub

- Aged at least 18 years
- Hospitalized
- SARS-CoV-2 infection
- No drug contraindication

All patients will receive standard of care

Randomization

- No Additional Treatment
- Lopinavir-Ritonavir
- Hydroxychloroquine
- Interferon 1β
- Low-dose Corticosteroids

28 Days
In-hospital death, discharge, and need for ventilation.
Key Take-home Messages

1. Determine if the study population and the measured outcomes are relevant to the research question.

2. Evaluate the study design by looking at deviations from the study protocol.

3. Look for potential sources of bias and interpret the results accordingly.
4. Interpret study results by assessing if data were properly analyzed and that methods and results are adequately reported.

5. Correlate results with clinical implications.
Thank You!
The COVID Infodemic: Stepping Back to Move Forward
The ACEI/ARB Story

Michelle M. Kittleson MD PhD
Professor of Medicine
Smidt Heart Institute, Cedars-Sinai
@MKittlesonMD
The Case

• A 65-year old man with EF 40% due to hypertensive cardiomyopathy calls your office for advice. He feels well with NYHA Class II symptoms.

• Medications: lisinopril 40 mg QD, carvedilol 25 mg BID, spironolactone 25 mg QD, and furosemide 20 mg QD.

• He has heard on the news that patients who take ACEI or ARB are at risk for severe COVID-19. **He wants to know: should he stop taking lisinopril?**
Observations

Hypertension more common in patients who have severe disease or die from COVID
RAAS inhibitors upregulate ACE2 expression - ACE2 is the co-receptor for SARS-CoV-2 entry into cells
Hypertension is often treated with RAAS inhibitors

Limitations

Studies did not control for age, comorbidities
... in animal models. ... unclear in humans.
But not in China: 30-40% pts with HTN treated; 25-30% of those with RAAS inhibitors

Adapted from Rush CJ et al. Eur Heart Journal 2018; 39: 3418.
Patients don’t read manuscripts or guidelines

Daily Mail UK, March 13, 2020  87K shares

Medicines taken by 6.6million people with high blood pressure and diabetes could raise the risk of deadly coronavirus symptoms, scientists claim

- ACE inhibitors and angiotensin receptor blockers may lead to worse illness

Daily Mail UK, May 2, 2020  1.3K shares

Common blood pressure pills DO NOT make coronavirus worse: Tablets taken by 6.6million Britons make 'no difference to whether you get infected', three major studies find

- ACE inhibitors and angiotensin receptor blockers do not lead to worse illness
## What Do We Know?

<table>
<thead>
<tr>
<th>Study</th>
<th>Question</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>Do ACEI/ARB affect COVID-19 infection or disease severity?</td>
<td>ACEI/ARB → no impact on COVID-19 infection or disease severity</td>
</tr>
<tr>
<td>Mancia et al. NEJM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>Do ACEI/ARB affect COVID-19 severity in hosp patients w/HTN?</td>
<td>ACEI/ARB → no impact on COVID-19 in-hospital severity or mortality</td>
</tr>
<tr>
<td>Li et al. JAMA Card</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mehra et al. NEJM</td>
<td></td>
<td>ACEI → decr mortality</td>
</tr>
<tr>
<td>America</td>
<td>Do ACEI/ARB affect COVID-19 hospitalization or mortality in pts w/HTN?</td>
<td>ACEI/ARB → no diff in hosp/mortality except ACEI → decr hosp in Medicare (older) group</td>
</tr>
<tr>
<td>Khera et al. MedRxiv</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Do ACEI/ARB affect COVID-19 infection or disease severity?

- **Who?** Population of Lombardy, Italy
  - 6272 SARS-CoV2 cases
  - 30759 controls matched for age, sex, location

- **Exposure?** ACEI/ARB prescriptions

- **Outcome?** COVID-19 infection, critical/fatal dz
  - No difference in risk of COVID-19 infection *after adjustment*
  - No difference in risk of severe COVID-19 disease

---

**Can we trust the results?**

- **GOOD NEWS**
  - Unselected, large population → generalizable
  - Were pts really taking ACEI/ARB? → 3 diff criteria: any rx in 2019, at least 3 rx in 2019, at least 1 rx in last quarter of 2019
  - Adjusted for CV, respiratory, kidney disease
  - Used pre-specified endpoints

- **BAD NEWS**
  - Case-control design, not propensity matched cohorts

Do ACEI/ARB affect COVID-19 severity in hosp patients w/HTN?

- **Who?** Pts w/HTN hospitalized with COVID-19
  - 362 pts from 1 hospital in China
- **Exposure?** ACEI/ARB on admission and continued during hospitalization
- **Outcome?** Severe illness, death
  - No difference in severe disease
  - No difference in death

**Can we trust the results?**

- **BAD NEWS**
  - Single center in China → not generalizable
  - Unclear reliability of ACEI/ARB designation
  - ACEI and ARB lumped together- might dilute disparate effects

Do ACEI/ARB impact in-hospital COVID-19 mortality?

- **Who?** Pts hosp w/COVID-19
  - 8910 pts at 169 hospitals

- **Exposure?** ACEI/ARB at admission

- **Outcome?** In-hospital death
  - Adjusted for age, race, CV dz, DM, COPD, smoking, HTN, hyperlipidemia, immunocomp state

---

**Can we trust the results?**

- **GOOD NEWS**
  - Large multicenter → generalizable
  - Adjusted for comorbid conditions

- **BAD NEWS**
  - Unclear reliability of ACEI/ARB designation
  - Comparators were not limited to those w/HTN

Do ACEI/ARB affect COVID-19 hospitalization or mortality in pts w/HTN?

- **Who?** HTN pts w/SARS-CoV-2
  - HTN: ICD codes/pharmacy claims
  - 2263 with SARS-CoV-2 positive test
  - 7933 hosp w/COVID-19
  - Propensity-matched cohorts without COVID-19

- **Exposure?** ACEI/ARB by pharmacy claims

- **Outcome?** Hosp/Mortality
  - Adjusted for age, sex, race, DM, MI, CKD, each of the comorbidities included in the Charlson Comorbidity Index

---

**Can we trust the results?**

- **GOOD NEWS**
  - Large multicenter → generalizable
  - Same chronic illness (HTN) → equally likely to seek care/hospitalization
  - Reliable databases for diagnoses, outcomes
  - Propensity-matching

- **BAD NEWS**
  - It’s still hypothesis-generating. . .
### What Do We Need? Randomized Controlled Trials!

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04355429</td>
<td>COVID-19, on O2</td>
<td>Captopril nebulization</td>
<td>Ventilator-free survival</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT04345406</td>
<td>COVID-19</td>
<td>Captopril or enalapril</td>
<td>Virologic cure</td>
</tr>
<tr>
<td>Egypt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT04311177</td>
<td>SARS-CoV-2 infection</td>
<td>Losartan 10 days</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Minnesota</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT04312009</td>
<td>COVID-19, on O2</td>
<td>Losartan</td>
<td>PaPO2/FiO2 at 7 days</td>
</tr>
<tr>
<td>Minnesota</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEEDED</strong></td>
<td>SARS-CoV-2 infection</td>
<td>Prophylactic ACE inhibitor</td>
<td>Hospitalization/mortality</td>
</tr>
</tbody>
</table>
The Case: What do you tell your patient?

- A 65-year-old man with EF 40%, due to hypertensive cardiomyopathy, calls your office for advice. He feels well with NYHA Class II symptoms.

- Medications: lisinopril 40 mg QD, carvedilol 25 mg BID, spironolactone 25 mg QD, and furosemide 20 mg QD.

- He has heard on the news that patients who take ACEI or ARB are at risk for severe COVID-19.

He wants to know: should he stop taking lisinopril?

With all our patients, we will have to ask ourselves a new question: What is the best approach to treating their disease, and how does our fear of COVID-19 affect our shared risk–benefit calculus? We must do our best to chart a course in the face of uncertainty as the pandemic spreads.

Key Takeaway Points

• Clinical decisions cannot be based on plausible pathophysiology
  • Pathophysiology suggests ACEI/ARB good or bad in COVID-19

• Observational studies are hypothesis-generating
  • Uniformity of findings is reassuring: ACEI/ARB ≠ harm
  • Observed benefit from ACEI = rationale for clinical trial not change in practice

• In the absence of randomized controlled trials, stick with best possible established evidence over observation
  • Don’t just do something, stand there
Beware of false knowledge; it is more dangerous than ignorance.

-George Bernard Shaw

The road to bad outcomes is paved with wishful thinking.

--Anonymous
Panel Discussion

• Dr. Harlan Krumholz

• Dr. Michelle Kittleson

• Dr. Roxana Mehran
Questions?

Thank You!!