COVID-19: Implications for Pharmacists: Round 2, What's New?

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UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

COLORADO PHARMACISTS SOCIETY

Objectives

- Describe the relationship between NSAIDs and COVID-19
- Summarize the cardiovascular implications of hydroxychloroquine use
- Review the role of azithromycin in treatment of COVID-19
- List the actions the Colorado Pharmacists Society has taken during the COVID-19 crisis.

Disclaimer

New data is created and distributed hourly. It is very possible that information presented today will already be outdated by the end of this webinar.

Slides last updated 4/1/2020

Questions to be answered…

1. How big of a problem is QT prolongation with hydroxychloroquine?
2. Does azithromycin offer additional benefit when combined with an antimalarial?
3. Should we tell people to only use acetaminophen if they a fever suspected to be COVID-19?
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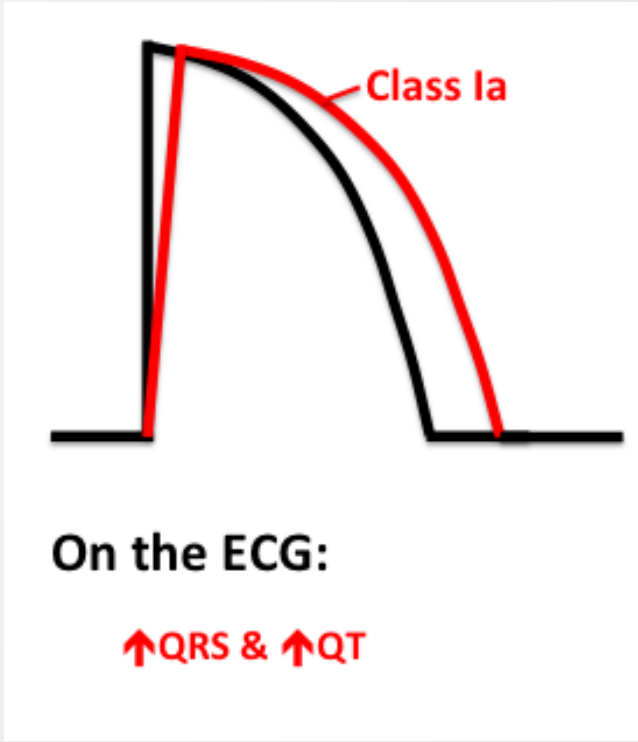
Hydroxychloroquine & Cardiac Conduction

- Hydroxychloroquine similar to quinine (class Ia antiarrhythmic)

- Pharmacology implications
  - Inhibition of sodium channels
  - Inhibition of potassium (hERG) channels
  - Hypokalemia from intracellular shifting can contribute to dysrhythmias



Ideal data

- QTc data before and after hydroxychloroquine 200 mg, 400 mg, and 600 mg
  - Healthy patients
  - Patients with cardiovascular diseases
  - Patients taking additional QT prolonging medications – especially azithromycin

Long QT and Hydroxychloroquine; A Poorly Recognized Problem In Rheumatology Patients

- 2013 American College of Rheumatology abstract
- N=19, 16 female, 3 male
  - CV history: hypertension (n=7), obesity (n=5), ischemic heart disease (n=4), deep vein thromboses (n=3) and cerebral vascular accidents (n=3)
- Dose: 200 mg (n=4), 400 mg (n=15) per day

	Baseline, mean (range)	6 mo after HCQ, mean (range)
QTc, msec	424 (377-584)	449 (387-620)
Long QTc, n	4	8

Assessment of the Relationship Between Dose, Drugs, and QTc

- Descriptive data from cohort of patients with lupus
- ECGs on admission and six hours later
- QTc interval determined using Bazett's formula

	Normal QTc, n=103	Prolonged QTc, 47
Age	34 ± 84	36 ± 54
Hydroxychloroquine, n (%)	60 (58)	39 (83)
Mean HCQ dose, msec	283	333

Shiraz E-Med J. 2020 ; 21(2):e83710. doi: 10.5812/semj.83710.

Tisdale Risk Score for Drug-Induced QT

Points	Risk Factors
1	Age ≥68 years, female sex, loop diuretic
2	Serum K+ ≤3.5 mEq/L, admission QTc ≥450 msec, acute myocardial infarction
3	≥2 QTc-prolonging drugs, sepsis, heart failure, one QTc-prolonging drug
21	Maximum Risk Score

Risk level points
Low risk ≤ 6
Moderate risk 7-10
High risk ≥ 11

Suggested contraindications: Baseline QTc > 500 msec, or
Tisdale risk ≥ 11 without ECG monitoring

Tisdale JE et al. Circ Cardiovasc Qual Outcomes. 2013;6:479-487.

Hydroxychloroquine Cardiology Summary

- Prolongs QT similar to class I antiarrhythmic
- QT prolongation is dose related
- Small cohort showed mean QTc increase of 25 msec
  - Doses of 200 and 400 mg daily

- Consider
  - Continuous ECG monitoring for patients with baseline QT of > 500 msec or Tisdale score ≥ 11
  - Hydroxychloroquine in multiple doses instead of daily dosing

Guidance:
ACC COVID-19
Mayo COVID-19 QTc

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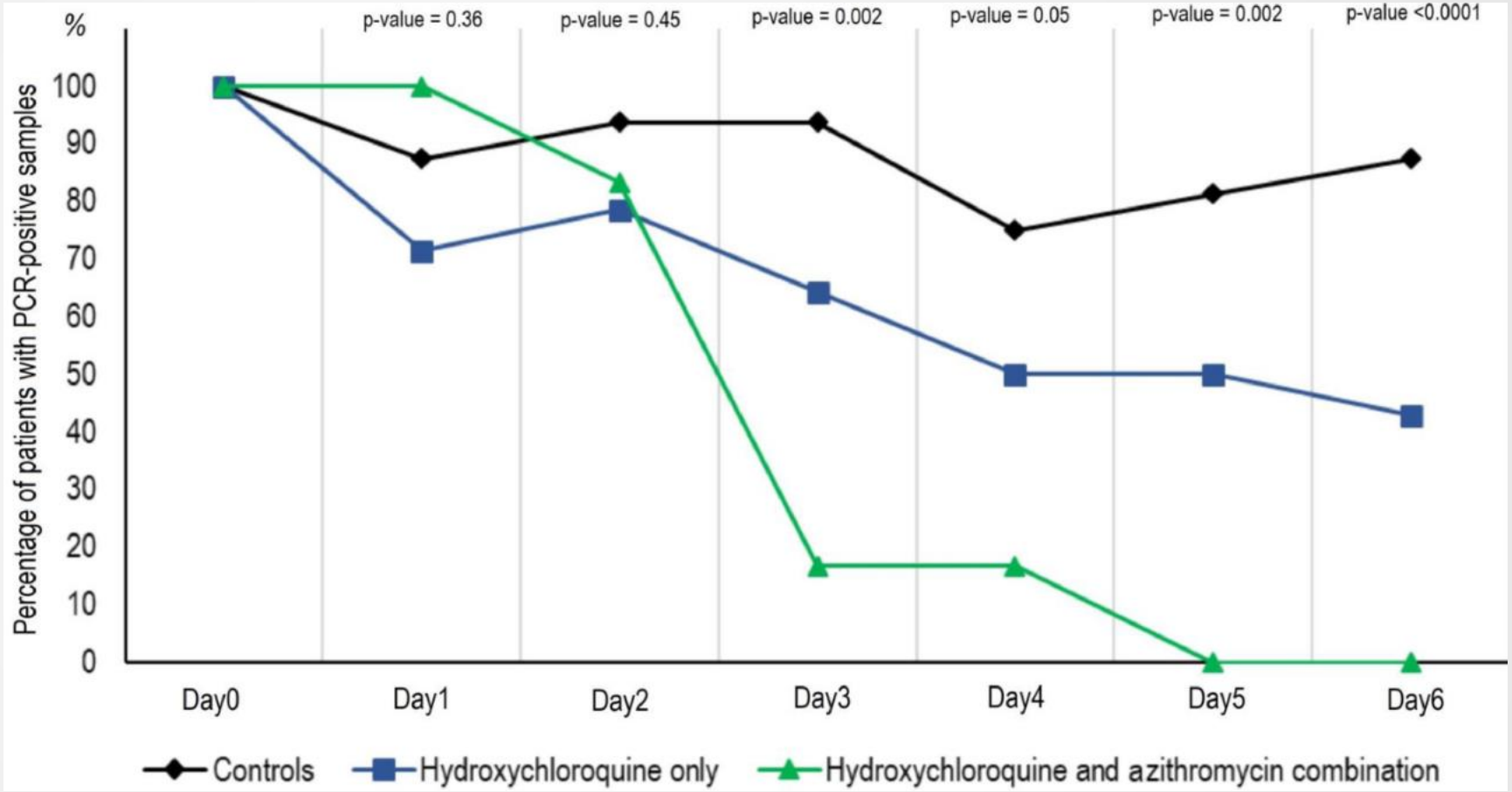
Gautret P, et al. #1, Open label trial

- HCQ, n=14
- HCQ + azith, n=6
- Controls, n=16 (outside hospital)

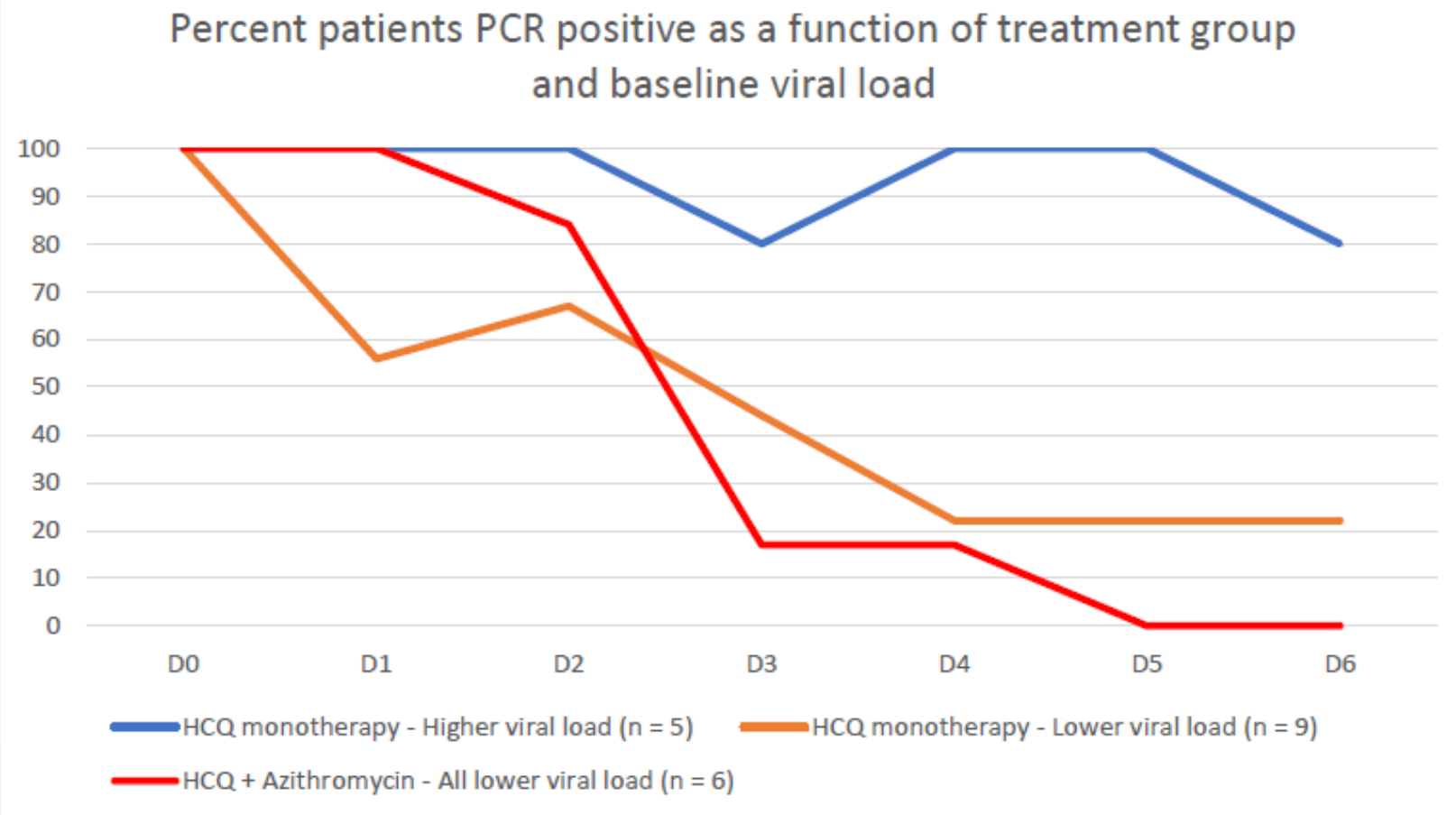
- N=6 HCQ lost to follow-up
  - 1 died
  - 3 transferred to ICU



Gautret et al. Int J Antimicrob Agents. 2020;105949.

Gautret P, et al. Open label – Deep Dive

- Contagion Live article: *COVID-19 Treatment: Updates March 19-24, 2020*
- Erin McCreary, PharmD, BCIDP
- Jason Pogue, PharmD, BCIDP



Gautret P, et al. #2,

Not yet peer reviewed

- Treatment
  - HCQ 200 mg PO TID x 10 days + azith 500 mg, 250 mg daily x 5 total days
  - PLUS ceftriaxone 1 g daily if PNA or moderate-severe illness

  - ECG at baseline and 2 days after treatment
  - Treatment dc'd if QTc > 500 msec (Bazett's formula)
  - Concurrent QT prolonging medications discontinued

Gautret P, et al. #2,

Not yet peer reviewed

- Symptom onset to treatment = 5 days
- Treatment started on day 0 = 49, 1 = 26

- Outcome
  - Favorable outcome (discharged) = 65/80 (81%)
  - Transferred to ICU = 3/80 (4%), 2 improved, 1 died

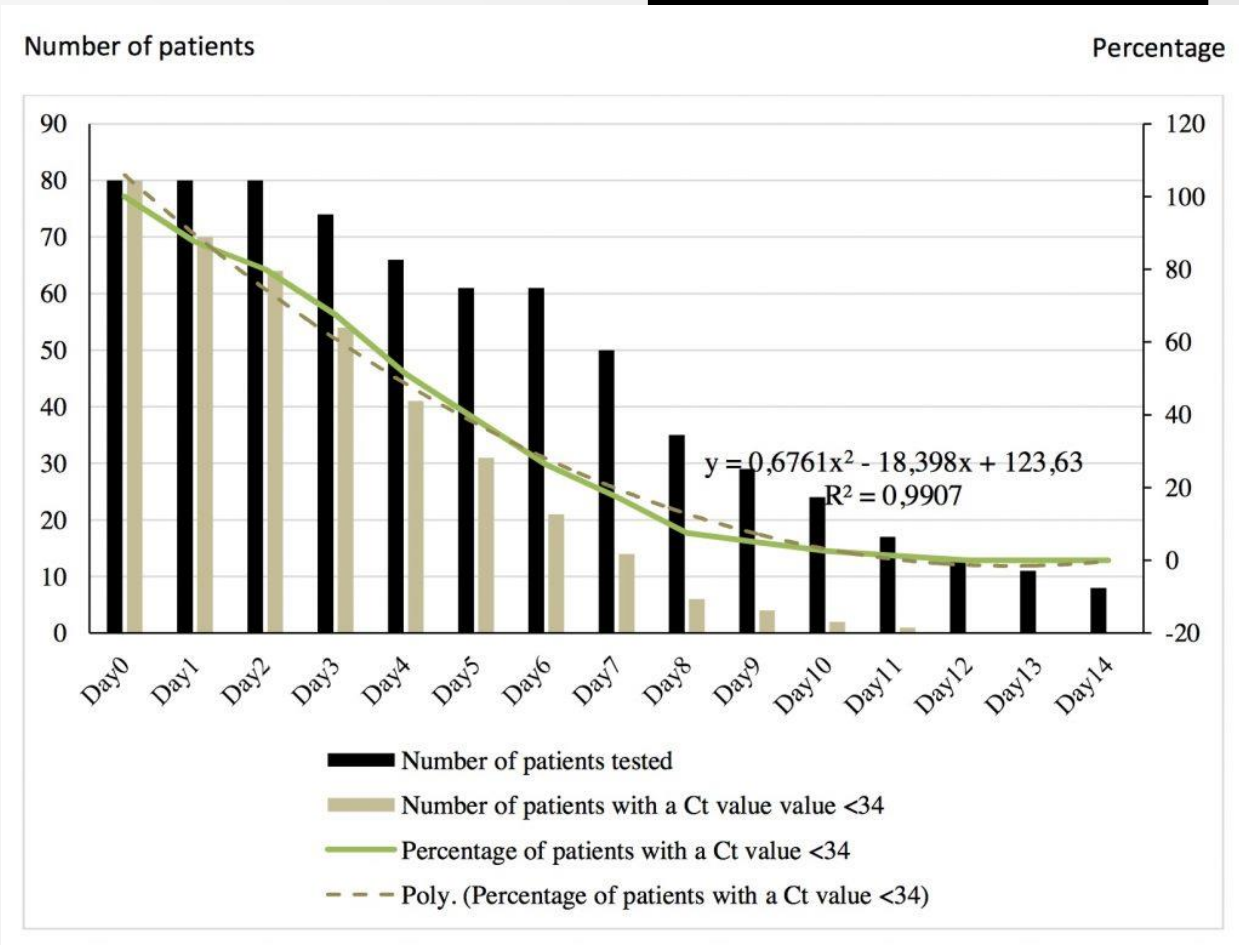
- NO QT DATA REPORTED

Gautret P, et al. #2,

Not yet peer reviewed

- Day 0 to 1: 10 pts are negative?!? (10 of 49)
- Day 1 to 2: only 6 pts more
- Day 3 – 5 pts have left the study (supposed to have 6 days of follow-up to be included)

- Lacking viral load data
- Control data



Andrew Morris @ASPphysician · Mar 28

So in our totally useless followup study, mostly very low-risk pts (92%)—of whom only 14% had a fever—were coerced into experimental treatment in our hospital with HCQ/**azithromycin**. Thankfully, their virus cleared so I can keep pushing this non-evidence. mediterranee-infection.c
content/upl...

Clinical and microbiological effect of a combination of hydroxychloroquine

azithromycin in 80 COVID-19 patients with at least a six-day follow up: an

observational study

Running title: Hydroxychloroquine-Azithromycin and COVID-19

Philippe Gautret[1,2,6], Jean-Christophe Lagier[1,3,5], Philippe Parola[1,2], Van Thuan

Line Meddeb[1], Jacques Sevestre[1], Morgane Mailhe[1], Barbara Doudier[1], Camille

Sophie Amrane[1], Piseth Seng[1], Marie Hocquart[1], Julie Finance[5], Vera Esteves V

Tissot Dupont[1,3], Stéphane Honoré[6,7], Andreas Stein[1,3], Matthieu Million[1,3], Phil

2 3 46

Vasilios Athans @AthansID · Mar 28

Live look at new HCQ/**azithromycin** studies being published.

12 104 400

Chen et al. HCQ RCT

Not yet peer reviewed

- Chen et al. RCT, Wuhan, China, mild illness, otherwise healthy
- HCQ 200 mg BID x 5 days vs. standard of care

	HCQ, n=31	Control, n=31
Age, years ± SD	44 ± 16	45 ± 15
Adverse effects, n (%)	2 (7)	0 (0)
Clinical improvement, n (%)	25 (81)	17 (55)
Exacerbation, n (%)	2 (7)	9 (29)
Progressed to severe, n (%)	0 (0)	4 (13)

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Why all the concern?

- March 14, 2020:
  - French health officials suggested adverse events with NSAID use in patients with COVID-19; recommended acetaminophen instead
- March 18, 2020:
  - The European Medicines Agency response:
    - Currently "no scientific evidence" that NSAIDs, such as ibuprofen, could worsen coronavirus disease
    - When starting treatment for fever or pain in COVID-19, patients and healthcare professionals should consider all available treatment options including paracetamol and NSAIDs

https://www.medscape.com/viewarticle/926940?nlid=134635_4822&src=WNL_mdplsfeat_200324_mscpedit_phar&uac=39775MJ&spon=30&impID=2323218&faf=1

World Health Organization (WHO)
@WHO

Q: Could #ibuprofen worsen disease for people with #COVID19?

A: Based on currently available information, WHO does not recommend against the use of of ibuprofen.

https://twitter.com/WHO/status/1240409217997189128

FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19

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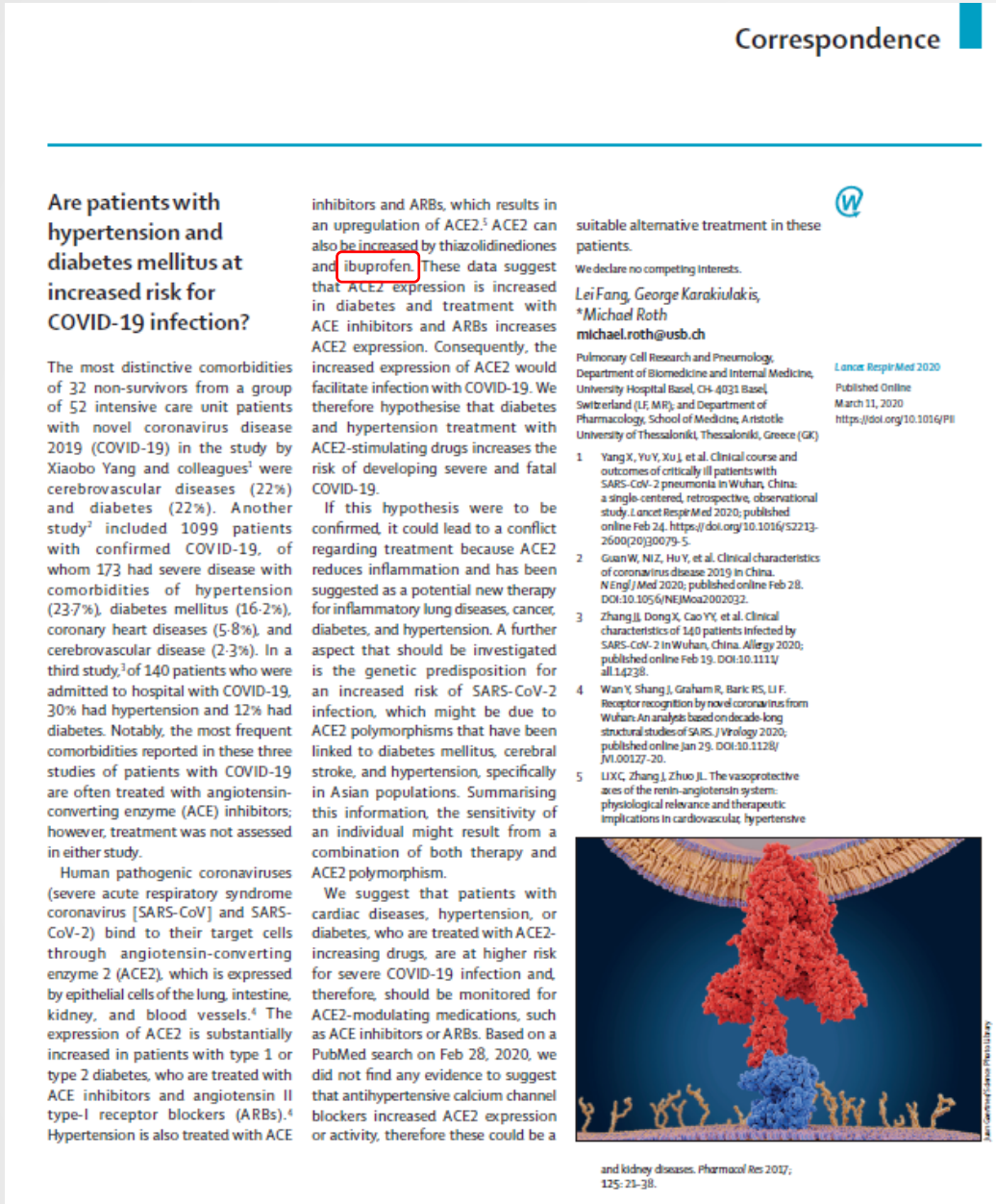
[3/19/2020] FDA is aware of news reports stating the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, could worsen coronavirus disease (COVID-19). These news reports followed a March 11, 2020 letter in The Lancet medical journal, which hypothesized that an enzyme (a molecule that aids a biochemical reaction in the body) is increased by NSAIDs and could aggravate COVID-19 symptoms.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19



Correspondence

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 2019 (COVID-19) in the study by Xiaobo Yang and colleagues[1] were cerebrovascular diseases (22%) and diabetes (22%). Another study[2] included 1099 patients with confirmed COVID-19, of whom 173 had severe disease with comorbidities of hypertension (23·7%), diabetes mellitus (16·2%), coronary heart diseases (5·8%), and cerebrovascular disease (2·3%). In a third study,[3] of 140 patients who were admitted to hospital with COVID-19, 30% had hypertension and 12% had diabetes. Notably, the most frequent comorbidities reported in these three studies of patients with COVID-19 are often treated with angiotensin-converting enzyme (ACE) inhibitors; however, treatment was not assessed in either study.

Human pathogenic coronaviruses (severe acute respiratory syndrome coronavirus [SARS-CoV] and SARS-CoV-2) bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.[4] The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs).[4] Hypertension is also treated with ACE 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 ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19.

If this hypothesis were to be confirmed, it could lead to a conflict regarding treatment because ACE2 reduces inflammation and has been suggested as a potential new therapy for inflammatory lung diseases, cancer, diabetes, and hypertension. A further aspect that should be investigated is the genetic predisposition for an increased risk of SARS-CoV-2 infection, which might be due to ACE2 polymorphisms that have been linked to diabetes mellitus, cerebral stroke, and hypertension, specifically in Asian populations. Summarising this information, the sensitivity of an individual might result from a combination of both therapy and ACE2 polymorphism.

We suggest that patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection and, therefore, should be monitored for ACE2-modulating medications, such as ACE inhibitors or ARBs. Based on a PubMed search on Feb 28, 2020, we did not find any evidence to suggest that antihypertensive calcium channel blockers increased ACE2 expression or activity, therefore these could be a suitable alternative treatment in these patients.

We declare no competing interests.

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Lancet Respir Med 2020
Published Online
March 11, 2020
https://doi.org/10.1016/PII

1 Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; published online Feb 24. https://doi.org/10.1016/S2213-2600(20)30079-5.

2 Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; published online Feb 28. DOI:10.1056/NEJMoa2002032.

3 Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. *Allergy* 2020; published online Feb 19. DOI:10.1111/all.14238.

4 Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *J Virology* 2020; published online Jan 29. DOI:10.1128/JVI.00127-20.

5 Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. *Pharmacol Res* 2017; 125: 21–38.

- Hypertension, diabetes, CVD identified as common comorbidities in COVID-19
- SARS-CoV-2 binds to ACE2
- ACE2 increases in diabetes patients treated with ACEi or ARB
- ACE2 expression increased by ibuprofen and may facilitate COVID-19

Fang L, et al. Published online March 11, 2020 https://doi.org/10.1016/S2213-2600(20)30116-8

Bottom Line: NSAIDs and COVID-19

- FDA Advisory:
  - Not aware of scientific evidence connecting NSAID use with worsening COVID-19 symptoms
  - NSAID label already warns that “the pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections”
  - Other options such as acetaminophen are reasonable to use, patients should consult a healthcare professional
- **Use typical NSAID precautions (e.g., nephrotoxicity, bleeding), nothing different just because of COVID-19**

https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19

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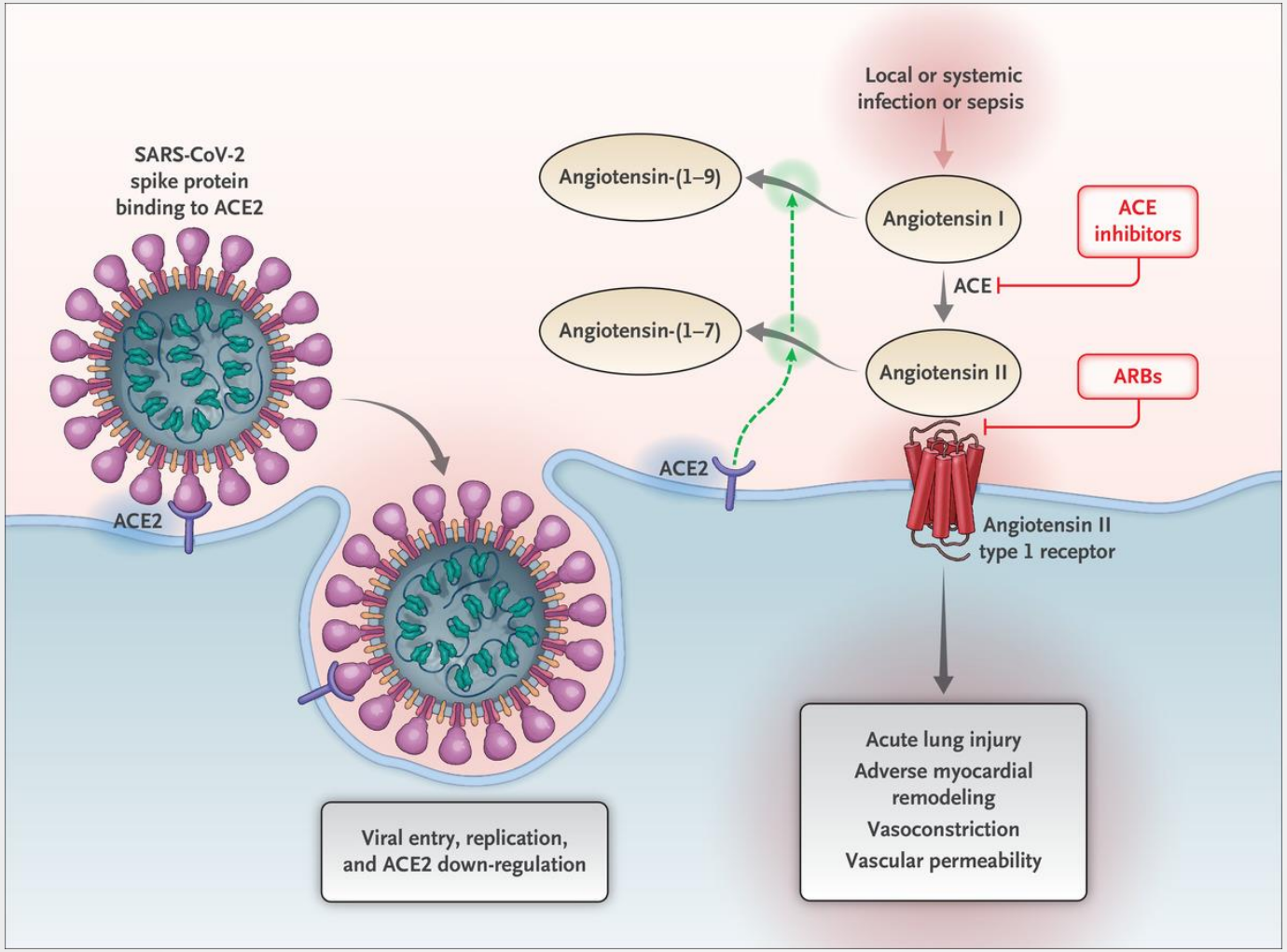
SARS-CoV-2 and the RAAS are Related!



M Vaduganathan et al. N Engl J Med 2020.
DOI: 10.1056/NEJMsr2005760

Random Facts and Confusion

- ACEi or ARB therapy can upregulate ACE2 expression in animal models
- ACEi or ARB therapy might increase SARS-CoV-2 attachment and COVID-19
- Observational data show that COVID-19 patients with CVD/risk factors have worse outcomes
- Retrospective review of elderly COVID-19 patients:
  - significantly decreased risk of severe infection with ARB therapy
- Small study from China showed ACEi or ARB not associated with increased morbidity and mortality!

No quality clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using an ACEi or ARB

Ferrario CM, et al. Circulation 2005;111(20):2605-2610.
Guo T, et al. JAMA Cardiol: March 27, 2020 [Epub ahead of print] doi 10.1001/jamacardio.2020.1017.
Liu Y, et al. doi: https://doi.org/10.1101/2020.03.20.20039586.
Peng YD, et al. Chinese J Cardiovasc Dis 2020;48. doi: 10.3760 / cma.j.cn112148-20200220-00105.

Expert Opinions: ACEi/ARB and COVID-19

Society	Update
European Society of Hypertension	March 12, 2020
European Society of Cardiology Council on Hypertension	March 13, 2020
Hypertension Canada	March 13, 2020
Canadian Cardiovascular Society	March 15, 2020
The Renal Association, United Kingdom	March 15, 2020
International Society of Hypertension	March 16, 2020
American College of Physicians	March 16, 2020
Spanish Society of Hypertension	March 16, 2020
American Heart Association/Heart Failure Society of America/American College of Cardiology	March 17, 2020
European Renal Association/European Dialysis and Transplant Association	March 17, 2020
American Society of Pediatric Nephrology	March 17, 2020
High Blood Pressure Research Council of Australia	March 18, 2020
Australian Diabetes Society	March 29, 2020

All either recommend or strongly encourage continuing ACEi or ARB therapy

http://www.nephjc.com/news/covidace2

Bottom Line: ACEi/ARB and COVID-19

- ACE2 is the functional receptor to SARS-CoV-2
- Preclinical studies suggest ACEi/ARB therapy may increase ACE2 expression
- Insufficient data to determine if findings translate to humans
- Clinical trials are under way to further assess risks
- **Abrupt withdrawal of ACEi/ARB therapy in high CV risk patients may result in instability and adverse outcomes**
- **Continue ACEi or ARB therapy in other-wise stable patients**

M Vaduganathan et al. N Engl J Med 2020.
DOI: 10.1056/NEJMsr2005760

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What is CPS doing?

- Many asks granted from the governor's office
  - Remote practice without prior authorization
  - Delayed technician certification deadline
  - Allowing pharmacists and techs in other states to temporarily practice in CO to meet staffing needs if necessary
- Waiving all signature requirements (granted by b CMS)

What is CPS doing?

- Requesting broader authority for pharmacists
  - Treatment of mild ailments
  - Therapeutic substitution for drug shortages
- Working with hospital groups to try to ensure access to sedative medications for ventilated patients
- Representing the pharmacy profession in larger healthcare discussions
- Assisting the Department of Public Health (CDPHE)

What about PPE?

- Collecting and sharing information about best practices
- Facemasks prioritized for:
  - Essential surgeries/procedures
  - Close contact with a potentially infectious patient
- PPE should be used for immunizations
  - Influenza and pneumococcal vaccines strongly recommended due to increased risk of secondary infections

Community Pharmacy Best Practices

- eRx's only
- No patient signatures (CMS has waived Part D plan signatures)
- Staff handling money/credit cards should wear gloves
- Process as credit vs. debit transactions to avoid PIN pad use
- Clean credit card machine keypads between customers
- Physical barriers (plexiglass or clear plastic)
- Drive-thru, delivery, or curb-side pick up whenever possible

We need to hear from you

- We can only advocate for issues we are made aware of
- Our avenues – other professional associations (local and national), CDPHE, legislators, governor's office, etc.
- Call or email
  - Emily Zadvorny, Executive Director (emily.zadvorny@cuanschutz.edu; 303-818-9045)
  - Gina Moore, President (gina.moore@cuanshutz.edu; 720-939-6586)

Favorite COVID-19 Resources

- Society of Infectious Diseases Pharmacists
  - https://www.sidp.org/
  - YouTube channel
- ASHP
  - Continuously updated “Assessment of Evidence for COVID-19-Related Treatments”
- Contagion Live
  - https://www.contagionlive.com/
- COVID-19 and ACE2 and Hypertension
  - http://www.nephjc.com/news/covidace2

Continuing Education

How to claim credit (pharmacists & pharmacy technicians)

1. Navigate to **UCDenver.edu/pharmacy/continuingeducation**
2. Select **Online CE**
3. Select Today's Webinar

Questions: sop.continuingeducation@cuanschutz.edu

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