An Update on ACEIs, ARBs & NSAIDs in Patients with COVID-19

A Review of Pertinent Drug Information for SARS-CoV-2

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Objective

- Review available evidence and organizational positions supporting use or discontinuation of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19.

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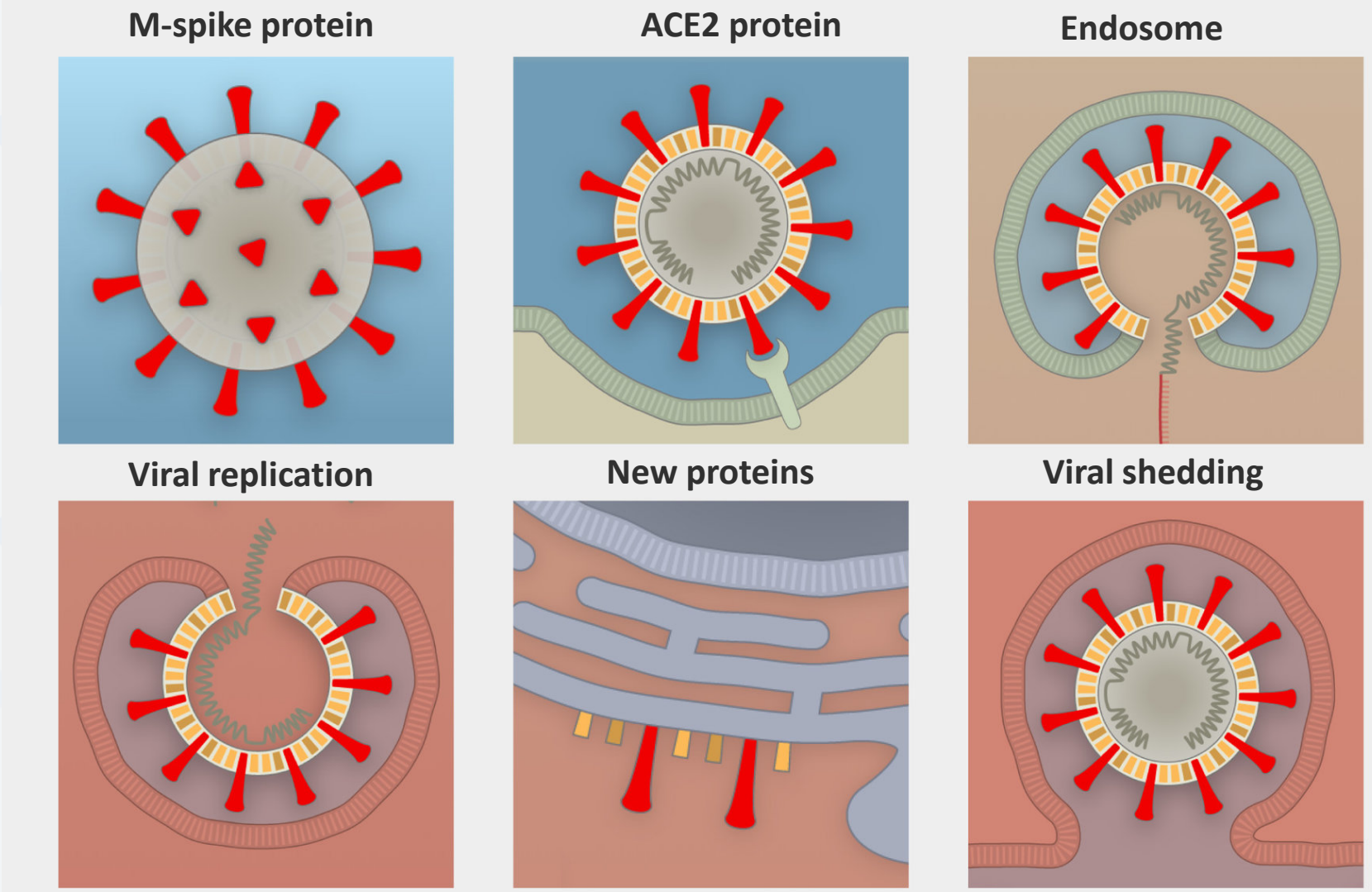
COVID-19

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19[1]
- ACE2 receptors are the human cell entry point for SARS-CoV-2[2,3]
  - ACE2 expressed near surface of human epithelial cells (e.g. lung)



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1.Guan WJ, et al. *N Engl J Med.* February 28, 2020 [epub ahead of print] doi: 10.1056/NEJMoa2002032
2. Lu R, et al. *Lancet.* 2020;395(10224):565–574.
3. Hoffmann M, et al. Cell. 2020;S0092-8674(20)30229-4.
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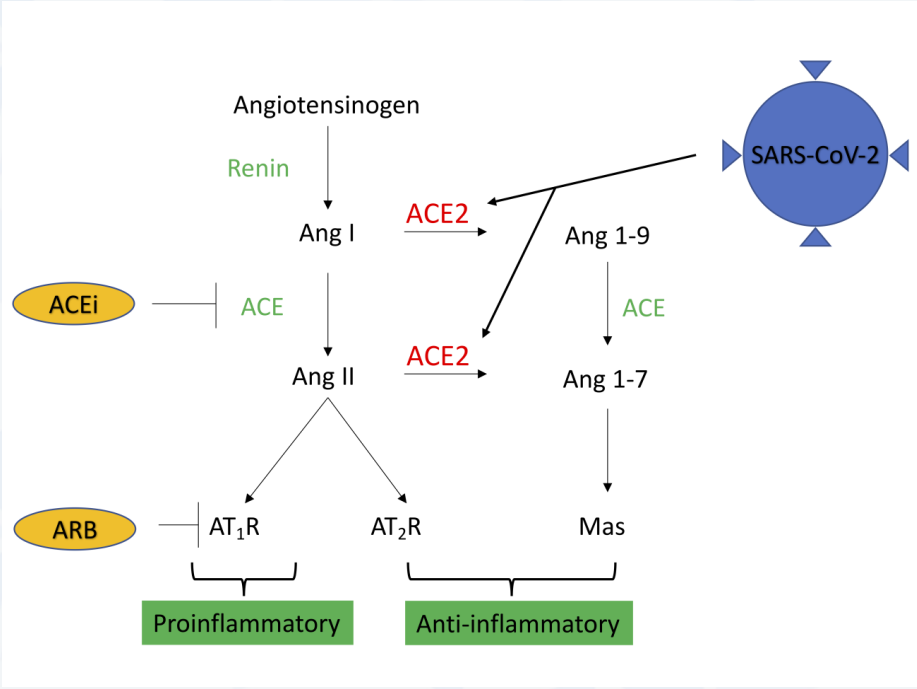
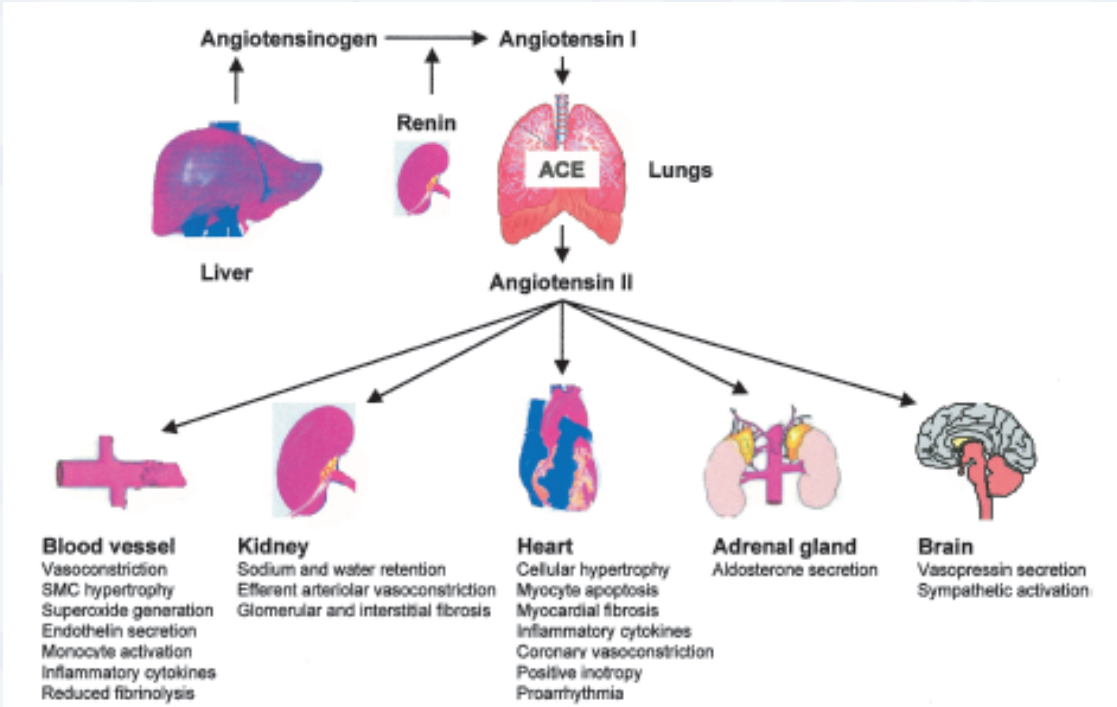
Renin-Angiotensin System (RAS)

- ACE converts Angiotensin (Ang) I to Ang II
- Ang II is a vasoactive peptide → systemic **vasoconstriction** and **aldosterone release**
  - Aldosterone = Na+ and water retention, ↑ BP
- *Downstream Ang II effects blocked by ACEIs and ARBs*
  - Also increase ACE2 expression
- ACE2 provides check against RAS
  - Catalyzes Ang I and Ang II
  - Ang I and Ang II degradation products promote vasodilation





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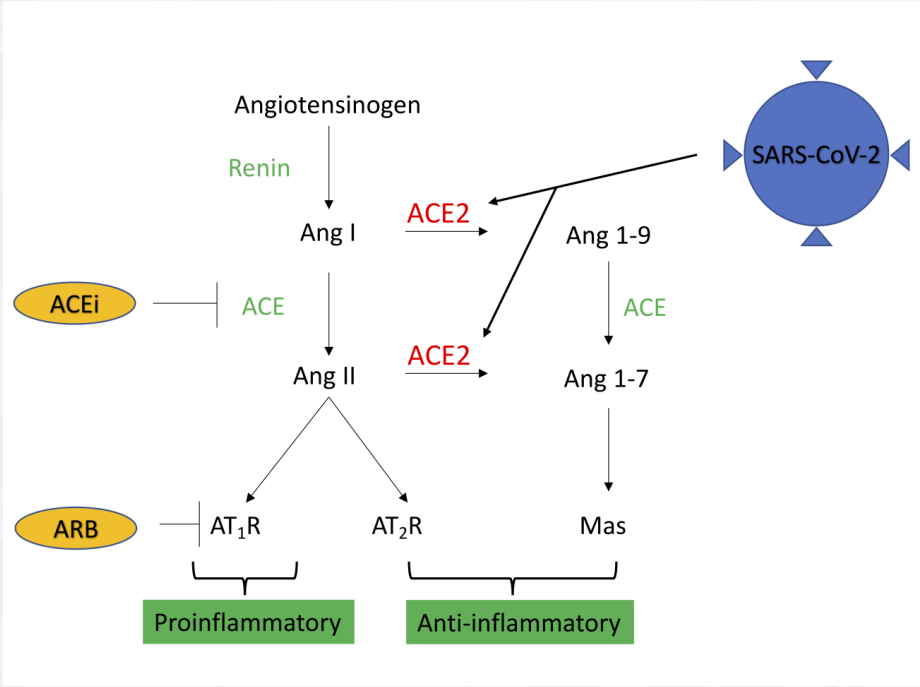
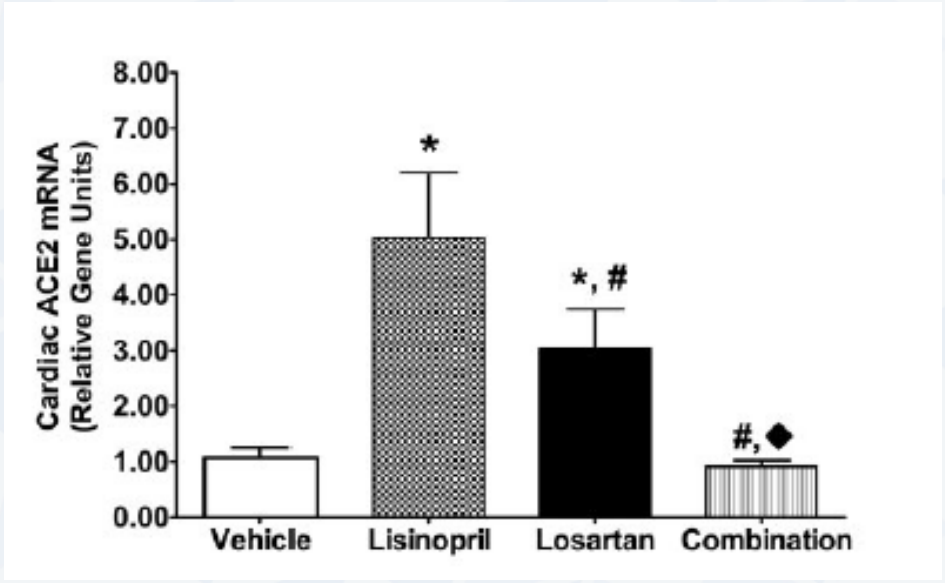
Hanff TC, et al. *Clin Infect Dis.* March 26, 2020 [Epub ahead of print] doi: 10.1093/cid/ciaa329
Givertz MM. *Circulation.* 2001;104(5):E14–E18.

RAS and COVID-19

- SARS-CoV-1 binding to ACE2 led to ACE2 **downregulation** & increased Angiotensin II[1]
  - ACE & Ang II promote lung disease progression in murine pneumonia model[2]
- ACEI & ARB **upregulated** ACE2 expression in animal models[3]
  - ACE2 mRNA increased by ~5- and ~3-fold in Lewis rats exposed to lisinopril and losartan, respectively





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3. Ferrario CM, et al. *Circulation*. 2005 May 24;111(20):2605-10.
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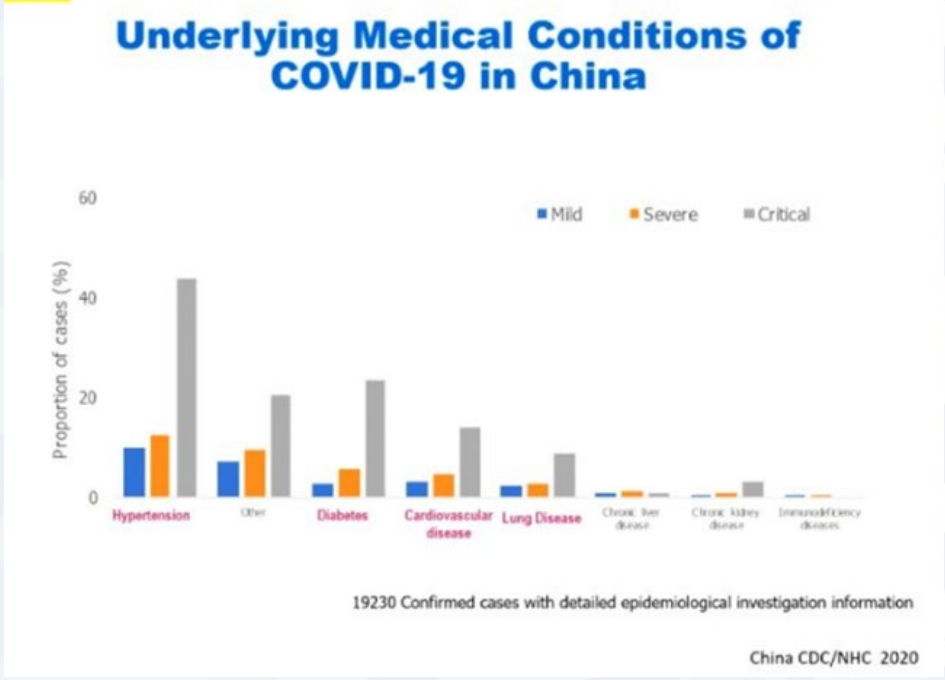
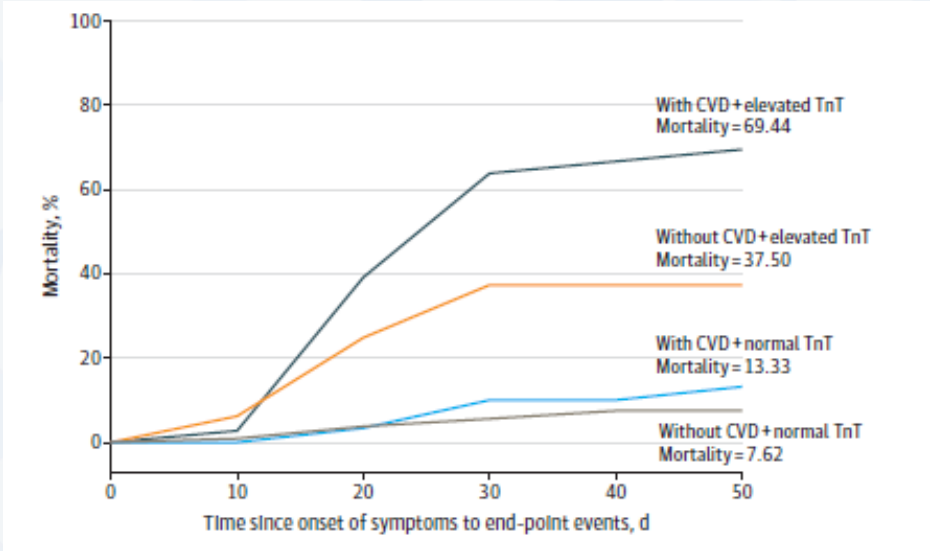
ACEI/ARB Use and COVID-19

- ? Potential to increase risk of SARS-CoV-2 attachment and COVID-19 among ACEI/ARB-treated patient[1]
  - **NOT** substantiated by **any** human data
  - *Urgent research priority*
- ACEI/ARB may reduce lung injury in some viral pneumonias[2]
  - Prevented ACE & Angiotensin II lung disease progression in a murine pneumonia model[2]
- COVID-19 patients with CV disease may experience worse outcomes[3,4]





TnT, troponin.

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3. Zheng YY, et al. *Nat Rev Cardiol.* March 5, 2020 [Epub ahead of print] doi: 10.1038/s41569-020-0360-5
4. Guo T, et al. *JAMA Cardiol*. March 27, 2020 [Epub ahead of print] doi: 10.1001/jamacardio.2020.1017
5. Wu Z. CROI. March 10, 2020. http://www.croiwebcasts.org/console/player/44710?mediaType=audio& Accessed March 29, 2020.

Potential Pros & Cons of ACEI/ARB for COVID-19 Infection

Minimize COVID-related cardiovascular and lung damage

Continued cardio-renal protection

Increased susceptibility to COVID-19

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Professional Societies Statements on Use of ACEIs/ARBs & COVID-19

Society	Summary of Recommendations
European Society of Hypertension	Continue ACEIs/ARB
European Society of Cardiology Council on Hypertension	Strongly encourage continuing ACEIs/ARBs
Hypertension Canada	Recommend continuing ACEIs/ARBs
Canadian Cardiovascular Society	Strongly encourage continuing ACEIs/ARBs
The Renal Association, United Kingdom	Strongly encourage continuing ACEIs/ARBs
International Society of Hypertension	Strongly recommend routine use of ACEIs/ARBs
American College of Physicians	Encourage continuing ACEIs/ARBs
Spanish Society of Hypertension	Recommend that ACEIs/ARBs
American Heart Association, Heart Failure Society of America, American College of Cardiology	Recommend continuing ACEIs/ARBs
European Renal Association- European Dialysis and Transplant Association	Recommend continuing ACEIs/ARBs
American Society of Pediatric Nephrology	Strongly recommend continuing ACEIs/ARBs
High Blood Pressure Research Council of Australia	Recommended continuing routine use of ACEIs/ARBs

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The Coronavirus Conundrum: ACE2 and Hypertension Edition. http://www.nephjc.com/news/covidace2. Accessed March 26, 2020.

ACE/ARB in Hospitalized COVID+ Adults with HTN

Zhang P, et al. China

n=1,128 – 17% ACE/ARB

Outcome: mortality

MV regression analysis and propensity score matching

Mortality: ACE/ARB 3.4% v. 9.8% no ACE/ARB (p<0.05)

- **aOR 0.42 (95% CI, 0.19 0.92) and p-score aOR 0.37 (95% CI 0.15, 0.89)**

NO HARM, ? BENEFIT

Li J, et al. China.

n=362 – 32% ACE/ARB

Outcome: disease severity or mortality

No statistical adjustment

NO difference in severity or mortality

NO HARM

Zhang P, et al. *Circ Res*. April 17, 2020. [epub ahead of print] doi:10.1161/CIRCRESAHA.120.317134
Li J, et al. JAMA Cardiol. 2020;e201624.

HTN, hypertension

ACE/ARB in Hospitalized COVID+ Adults with HTN (con't)

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

Bean DM, et al. UK.

n=205, 18% ACE within 7 days of symptom onset or in hospital

Outcome: mortality or need for ICU care

MV regression analysis

Mortality or ICU: ACE 14% vs. 29% no ACE

- **aOR 0.29 (95% CI, 0.10, 0.75)**

NO HARM, ? BENEFIT

Tedeschi S, et al. Italy.

n=311 – 32% ACE/ARB

Outcome: mortality

MV regression analysis

42% mortality – older, comorbid cohort

Only SOFA score and age predicted mortality

NO HARM

Bean DM, et al. https://doi.org/10.1101/2020.04.07.20056788 . Accessed May 6, 2020.
Tedeschi S, et al. *Clin Infect Dis*. April 27, 2020 [epub ahead of print} doi:10.1093/cid/ciaa492

HTN, hypertension

ACE/ARB in Hospitalized COVID+ Adults with HTN (con't)

NEJM et al. New York City.

12,594; 46.8% COVID+ & 17% severe disease

Outcomes: i) COVID+ test, ii) severe disease (ICU, ventilatory support, mortality)

Exposure: HTN meds including ACE/ARB

Propensity score MV modeling

No difference in any HTN medication exposure and outcomes of interest

NO HARM

SUMMARY

- ACE/ARBS are not harmful in hospitalized COVID+ adults with hypertension (China, UK, Italy and US)
  - N= 5 observational studies
  - ? Benefit
- Ongoing RCTs to study the impact of ACE/ARB as COVID "therapy"

HTN, hypertension

Reynolds HR, et al. *N Engl J Med*. 2020;10.1056/NEJMoa2008975.

ACEI/ARB – Therapeutic Potential for COVID-19

- COVID-19 more common in patients with diabetes mellitus and cardiovascular disease[1]
  - Mortality 12-fold higher in these populations for SARS-CoV-1 (2003)[2]
- COVID-19 induces myocardial injury (elevated troponin)[3,4]
  - Worse COVID-19 outcomes among with CV disease and elevated troponin[5]
- SARS-CoV-2 binding causes ACE2 downregulation
  - Increased pulmonary vascular permeability & pulmonary edema
  - ACEI and ARB can mitigate this effect[6,7]
- Ongoing losartan (ARB) trials for outpatients and inpatients with COVID-19[8,9]

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1. Yang J, et al. *Int J Infect Dis.* March 12, 2020. [Epub ahead of print]. doi: 10.1016/j.ijid.2020.03.017
2. Booth CM, et al. *JAMA*. 2003;289:2801-2809.
3. Wang D, et al. *JAMA*. 2020;323:1061-1069.
4. Zheng YY, et al. *Nat Rev Cardiol.* March 5, 2020 [Epub ahead of print] doi: 10.1038/s41569-020-0360-5
5. Guo T, et al. *JAMA Cardiol*. March 27, 2020 [Epub ahead of print] doi: 10.1001/jamacardio.2020.1017
6. Imai Y, et al. *Nature*. 2005;436:112-116.
7. Kuba K, et al. *Nat Med*. 2005;11:875-879.
8. ClinicalTrials.gov. Identifier: NCT04311177. March 17, 2020. https://clinicaltrials.gov/ct2/show/NCT04311177.
9. ClinicalTrials.gov. Identifier: NCT04312009. March 17, 2020. https://clinicaltrials.gov/ct2/show/NCT04312009.

NSAIDs and non-COVID-19 Respiratory Tract Infections (RTI)

- NSAID exposure linked to higher rates of complications following RTI[1]
  - Review of observational studies
- Pleuropulmonary complications more common with NSAID use in Danish cohort with community acquired pneumonia (n=59,250)[2]
  - 3.8% compared to 2.3% among those without NSAID exposure
  - **Adjusted risk ratio of 1.81 (95% CI, 1.60–2.05)**
- Trial of UK primary care patients with RTI (>3 years of age; n=889) randomized to paracetamol, ibuprofen, or both[3]
  - **No difference between groups in mean symptom severity on days 2-4**
  - Re-consultations with new/unresolved symptoms or complications:
    - *12% paracetamol and 20% ibuprofen – aRR 1.67 (95% CI, 1.12 to 2.38)*

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1. Voiriot G, et al. *J Clin Med.* 2019;8:E786.
2. Basille D, et al. *Am J Respir Crit Care Med*. 2018;198:128-31.
3. Little P, et al. *BMJ.* 2013;347:f6041..

NSAIDs and COVID-19

- ACE2 **may** be upregulated by ibuprofen
  - *Mentioned in one letter to the editor* – no citation provided[1]
- *"Ibuprofen could **ameliorate the cardiac fibrosis in diabetic rats** by **reduction of the ACE**/AngII/AT1-R axis and **enhancement of the ACE2**/Ang(1-7)/Mas-R axis…"* [2]
- NSAIDs also blunted IgM and IgG synthesis in stimulated human peripheral blood mononuclear cells[3]
- French Health Minister suggested avoiding NSAIDS in COVID-19 on Twitter[4]
  - **Gained traction on social media**
- NO published data to support ibuprofen avoidance in COVID-19
- NO "scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms."[5]

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2. Qiao W, et al. *Cardiology.* 2015;131:97–106.
3. Bancos S, et al. *Cell Immunol.* 2009;258(1):18-28.
4. Olivier Veran. Available at: https://twitter.com/olivierveran/status/1238776545398923264. Accessed March 23, 2020.
5. FDA. March 19, 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19. Accessed March 23, 2020.

List of Key Organizations and Individuals that Do NOT Recommend Ibuprofen Avoidance in COVID-19

- U.S. Food and Drug Administration (FDA)[1]
- World Health Organization (WHO)[2]
- European Medicines Agency (EMA)[3]
  - *"When starting treatment for fever or pain in COVID-19, patients and healthcare professionals should consider all available treatment options including paracetamol and NSAIDs. Each medicine has its own benefits and risks…"*
- David Aronoff, MD, Carlos del Rio, MD and Anthony Fauci, MD

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1. FDA. March 19, 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19. Accessed March 23, 2020.
2. WHO. March 18, 2020. Available at: https://twitter.com/WHO/status/1240409217997189128 Accessed March 23, 2020.
3. EMA. March 18, 2020. Available at: https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19. Accessed March 23, 2020.
4. https://news.vumc.org/2020/03/18/ibuprofen-and-covid-19%E2%80%88a-doctors-guidance/ Accessed March 26, 2020.
5. https://www.npr.org/sections/health-shots/2020/03/18/818026613/advice-from-france-to-avoid-ibuprofen-for-covid-19-leaves-experts-baffled Accessed March 26, 2020.
6. https://www.npr.org/2020/03/19/818518651/is-it-safe-to-take-ibuprofen-and-nsaids-for-covid-19-symptoms. Accessed March 26, 2020.

Guidelines – NSAIDs and COVID-19

Guideline	Recommendations
NIH[1]	• "Persons w/ COVID-19 taking NSAIDS for a co-morbid condition should continue therapy (AIII)." • "no difference in the strategy of antipyretic use (e.g., with acetaminophen or NSAIDs) as in patients with or without COVID-19 (AIII)."
NICE[2]	• "Advise patients to take paracetamol or ibuprofen if they have fever and other symptoms that antipyretics would help treat"
IDSA[3]	• "no causal evidence of adverse outcomes with NSAIDs in the management of COVID-19 have been published" • "RCTs are needed to better understand the safety of NSAIDS in the management of patients with COVID-19"
SCCM[4]	• "The use of NSAIDs to treat fever in patients with COVID-19 continues to be debated. Until more evidence is available, we suggest using acetaminophen/paracetamol to treat fever

NIH, National Institutes of Health; NICE, National Institute for Health and Care Excellence; IDSA, Infectious Diseases Society of America; SCMM, Society of Critical Care Medicine.

"…no evidence of severe adverse events, acute health care utilization, long-term survival, or quality of life in patients with COVID-19, as a result of the use of NSAIDs." – WHO[5]

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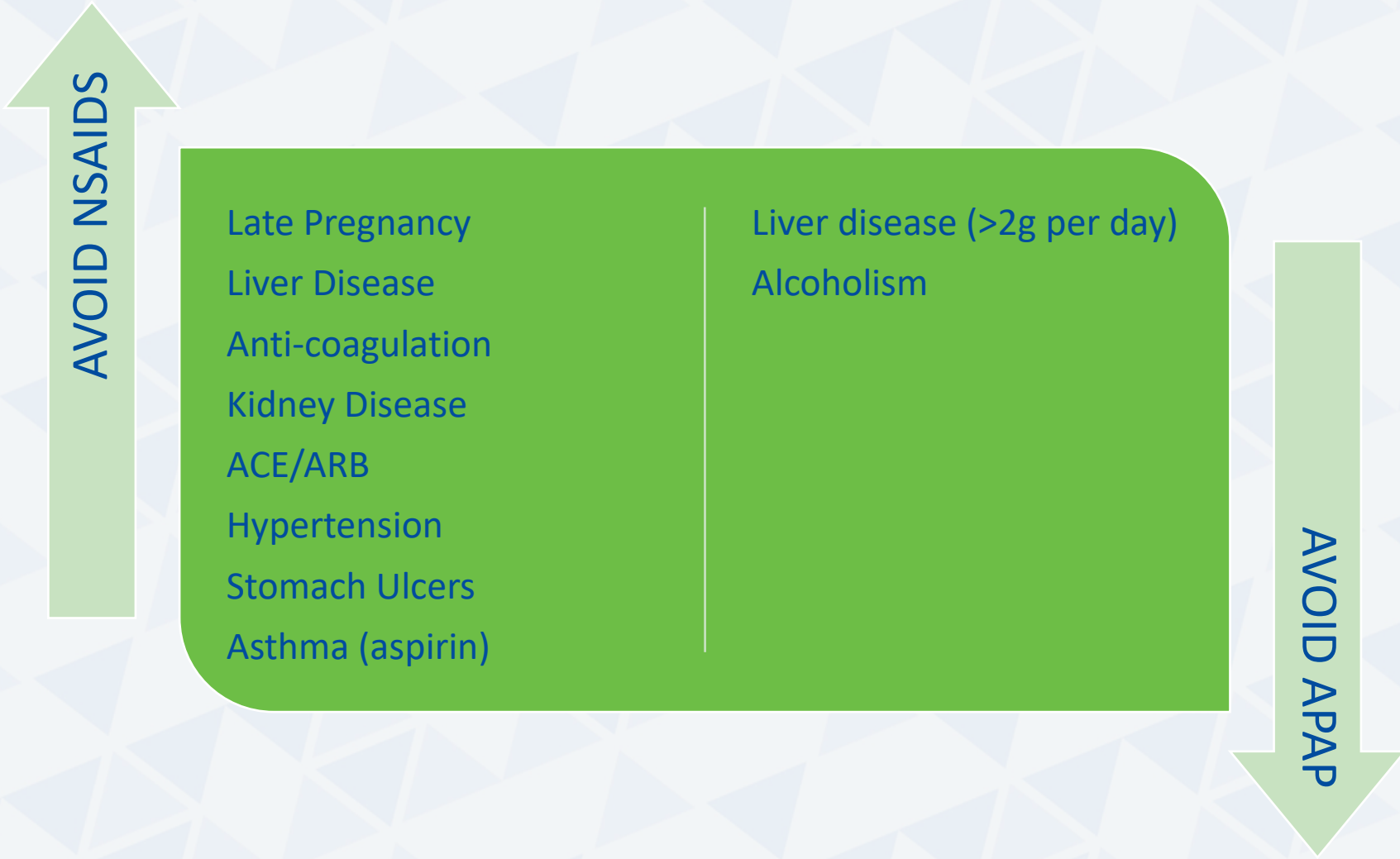
1. NIH. April 21, 2020. https://www.covid19treatmentguidelines.nih.gov/concomitant-medications/
2. NICE. April 30, 2020. https://www.nice.org.uk/guidance/ng163/chapter/5-Managing-fever
3. Bhimraj A, et al. Clin Infect Dis. April 27, 2020. [epub ahead of print] doi:10.1093/cid/ciaa478
4. Alhazzani W, et al. Crit Care Med. March 27, 2020. [epub ahead of print] doi:10.1097/CCM.0000000000004363
5. WHO. April 19, 2020. https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19

NSAIDs v. Acetaminophen (APAP): Clinical Pearls

- Available over the counter (OTC)
  - Combination cough/cold products
- Used by millions
- Analgesics are a common cause of acute poison center use in the U.S.[1]
  - Intentional and unintentional



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1. Bronstein AC, et al. *Clin Toxicol (Phila).* 2012;50(10):911–1164.

NSAIDs– Therapeutic Potential for COVID-19

- Indomethacin:
  - Demonstrated cytotoxic activity vs. SARS-CoV-1[1]
  - Identified as a potential SARS-CoV-2 treatment using protein-protein interaction mapping[2] bioRxiv THE PREPRINT SERVER FOR BIOLOGY
- Naproxen:
  - Can bind the nucleoprotein of influenza A and may be active vs. SARS-CoV-2[3]
  - Naproxen vs. standard of care in critically-ill COVID+ patients - NCT04325633[4]
    - Randomized, open label study in France (estimated n=584)
    - Rationale is putative anti-viral activity and known anti-inflammatory activity
    - **Naproxen 250mg BID + lansoprazole 30mg daily (for GI protection) vs. standard of care**
    - **Primary outcome: 30-day mortality**
    - Numerous secondary endpoints

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1. Amici C, et al. Antivir Ther. 2006;11(8):1021-1030.
2. Gordon DE, et al. https://www.biorxiv.org/content/10.1101/2020.03.22.002386v1.full.pdf Accessed May 6, 2020.
3. Lejal N, et al. *Antimicrob Agents Chemother*. 2013;57(5):2231-2242.
4. ClinicalTrials.gov. Identifier:NCT04325633. May 6, 2020. https://clinicaltrials.gov/ct2/show/record/NCT04325633?view=record

Conclusions

- No reason to avoid ACEIs/ARBs in COVID-19 patients
  - Patients should continue as prescribed, d/c may do more harm than good

- No reason to avoid NSAIDs in COVID-19 patients
  - Patients should continue as prescribed
  - Anti-inflammatory selection based on patient-level factors, not COVID-19

- **More research needed on <u>concomitant, non-antimicrobial</u> pharmacotherapy in COVID-19 patients**

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