



American College
of Medical Toxicology

Medical and Public Health Considerations of COVID-19

Web-based Series Addressing Emerging Topics of Importance



ACES/ARBS, NSAIDS, REMDESIVIR & UPDATES FROM THE FRONT LINES

APRIL 1, 2020

WEBINAR SERIES PARTNERS

American Academy of Clinical Toxicology (AACT)

American Academy of Emergency Medicine (AAEM)

American Association of Poison Control Centers (AAPCC)

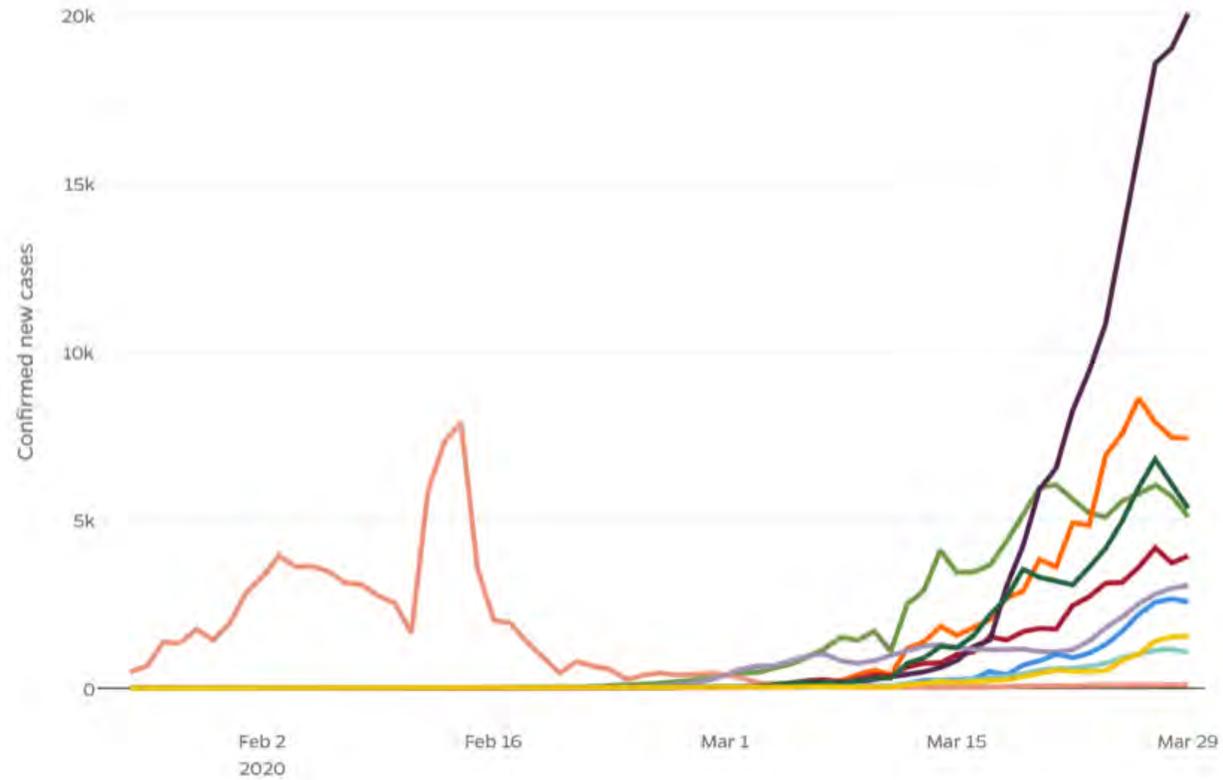
American College of Medical Toxicology (ACMT)

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European Association of Poison Centers and Clinical Toxicologists (EAPCCT)

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Outbreak evolution for the current 10 most affected countries



Click any country below to hide/show from the graph:

- Italy
- Spain
- China
- France
- US
- Iran
- United Kingdom
- Netherlands
- Germany
- Belgium

CONFLICT OF INTEREST

NONE OF OUR SPEAKERS HAVE ANY CONFLICTS OF
INTEREST TO DISCLOSE

NSAIDS AND ACES/ARBS

MEDICAL & PUBLIC HEALTH CONSIDERATIONS DURING THE COVID19 PANDEMIC

April 1, 2020



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 [@EMPoisonPharmD](https://twitter.com/EMPoisonPharmD)



Joshua D. King, MD

Assistant Professor, Medicine and Pharmacy; Medical Director, Maryland Poison Center; Associate Program Director, Nephrology Fellowship, University of Maryland

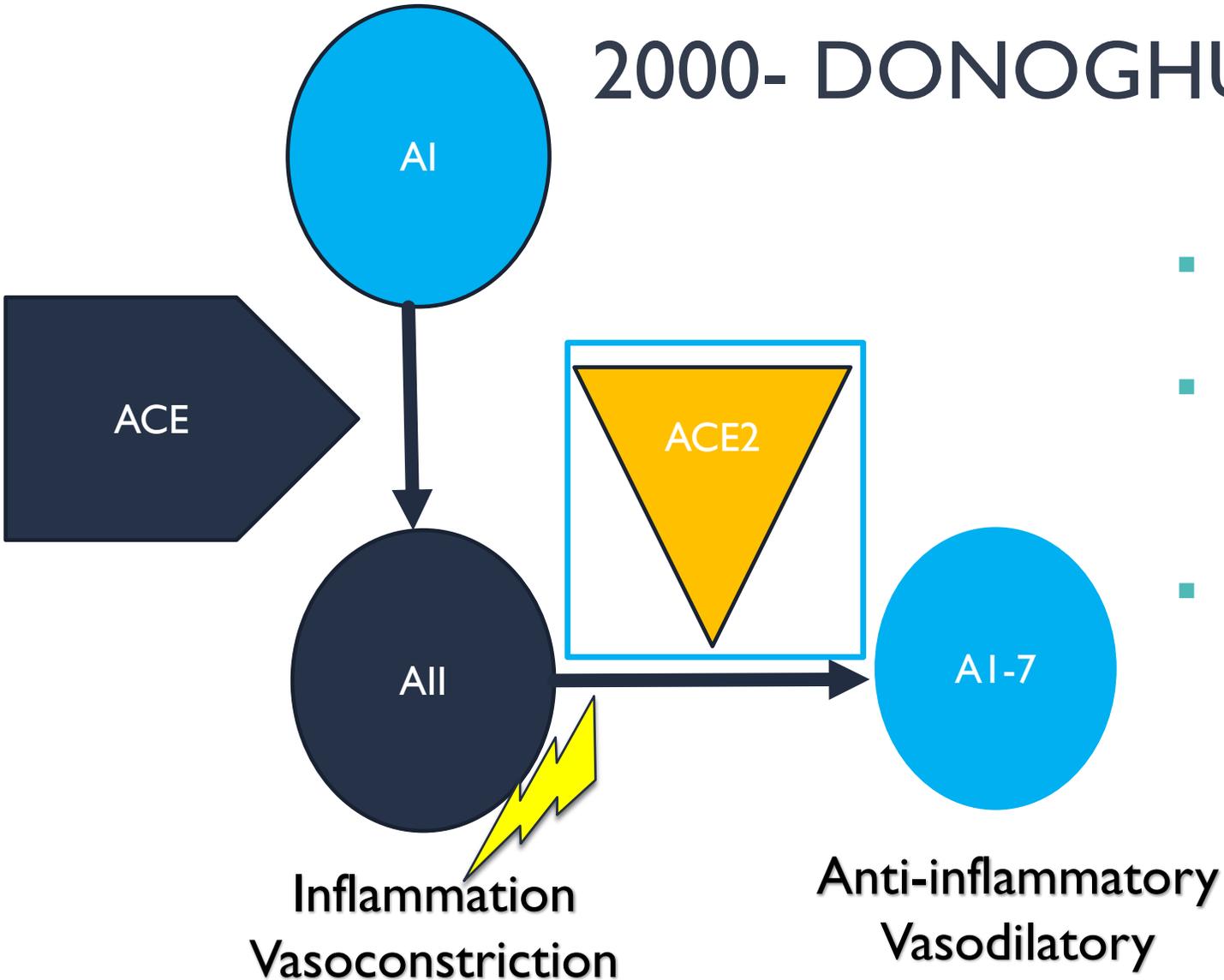
JDKing@som.umaryland.edu

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OBJECTIVES

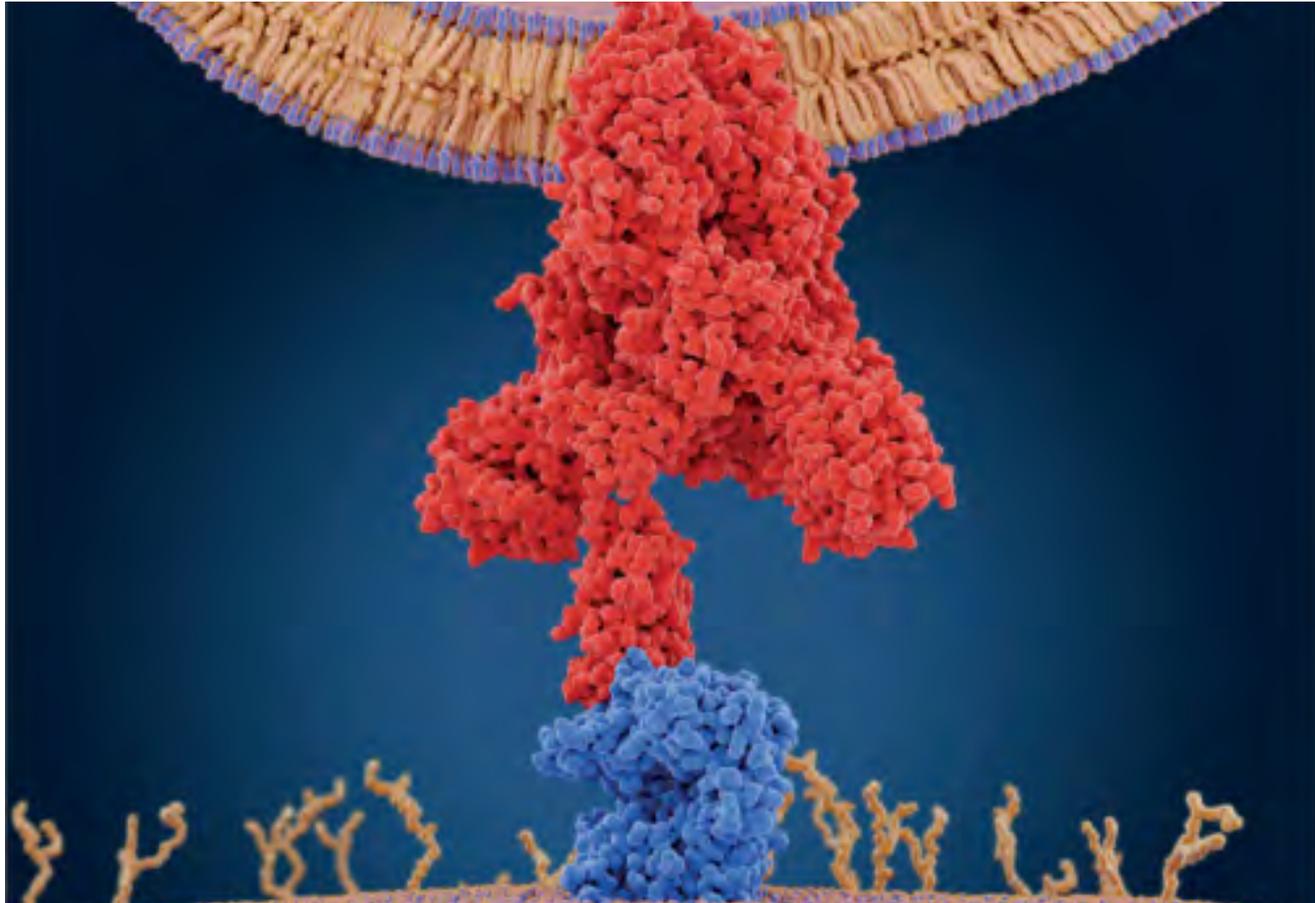
-
- Understand role of ACE2 in SARS-CoV2 (nCoV19) viral entry
 - Understand the impact of NSAIDS on ACE2
 - Discuss the roles NSAIDS may play in COVID 19 severity

2000- DONOGHUE ET AL.



- Discovery of Angiotensin Converting Enzyme 2 (ACE2) protein
- Counter part to ACE1
 - Creates angiotensin II (All)
 - Pro-inflammatory, vasoconstrictor
- ACE2
 - Degrades pro inflammatory All to AI-7
 - Anti-inflammatory, vasodilatory

2003- LI ET AL.



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- ACE2 determined to be docking site SARS-CoV spike protein (cellular attachment protein)
- Binding site for corona virus cell entry
- ACE2 docking for SARS-CoV2 highly likely

LANCET- MARCH 11

| Comorbidity present (vs not present) | | | | |
|--------------------------------------|-----------------------|---------|----------------------|------|
| Chronic obstructive lung disease | 5.40 (0.96-30.40) | 0.056 | .. | .. |
| Coronary heart disease | 21.40 (4.64-98.76) | <0.0001 | 2.14 (0.26-17.79) | 0.48 |
| Diabetes | 2.85 (1.35-6.05) | 0.0062 | .. | .. |
| Hypertension | 3.05 (1.57-5.92) | 0.0010 | .. | .. |

Respiratory rate, breaths per min

Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?

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

- Lancet letter
 - Observed fatal cases of COVID frequently had conditions treated with drugs that increase ACE2
 - Despite large confounding by age
 - Concern that drugs that increase ACE2 may increase disease burden
 - ACE inhibitor/ARB
 - “Ibuprofen”

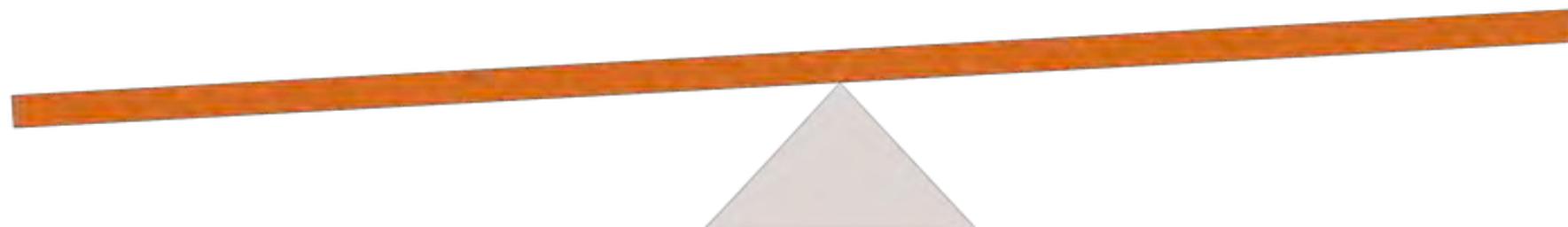
ACE2 MODULATORS

Decrease
ACE2

Angiotensin II
Diabetes
Inflammation

Increase
ACE2

NSAID
Thiazolidiones
ACE/ARB
Mineralocorticoid antagonists
Pressure overloaded disease (heart failure)



MARCH 14-18 FRENCH MINISTER OF HEALTH, WHO NHS FDA BMI



Olivier Véran
@olivierveran

⚠️ **#COVID-19** | Taking anti-inflammatory drugs (ibuprofen, cortisone, ...) could be an aggravating factor of the infection. If you have a fever, take paracetamol. If you are already on anti-inflammatory drugs or in doubt, ask your doctor for advice.



BMJ 2020;368:m1086 doi: 10.1136/bmj.m1086 (Published 17 March 2020)

Page 1 of 1



NEWS

Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists

Michael Day

At present, based on currently available information, WHO does not recommend against the use of ibuprofen.

We are also consulting with physicians treating COVID-19 patients and are not aware of reports of any negative effects of ibuprofen, beyond the usual known side effects that limit its use in certain populations.

WHO is not aware of published clinical or population-based data on this topic.

Could ibuprofen worsen disease for people with COVID-19?



WHO

At this time, FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms. The agency is investigating this issue further and will communicate publicly when more information is available. However, all prescription NSAID labels warn that “the pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.”

FDA

There is currently no strong evidence that ibuprofen can make coronavirus (COVID-19) worse.

But until we have more information, take paracetamol to treat the symptoms of coronavirus, unless your doctor has told you paracetamol is not suitable for you.

If you are already taking ibuprofen or another non-steroidal anti-inflammatory (NSAID) on the advice of a doctor, do not stop taking it without checking first.

NHS

Viral Misinformation

Hi all- just passing along info... I figured I would share what I got from a friend whose sister is a nurse at NYU...

Information from Vienna's laboratory studying COVID-19 say vast majority of people who died had ibuprofen/ Advil in their system so do not take it!! Those who recovered did not take ibuprofen so if you have symptoms, take Paracetamol only!!! Looks like this virus thrives on ibuprofen so don't do it and tell everyone you

J&J's Tylenol production at maximum capacity as coronavirus boosts demand

Michael Erman

3 MIN READ



NEW YORK (Reuters) - Johnson & Johnson is running its Tylenol

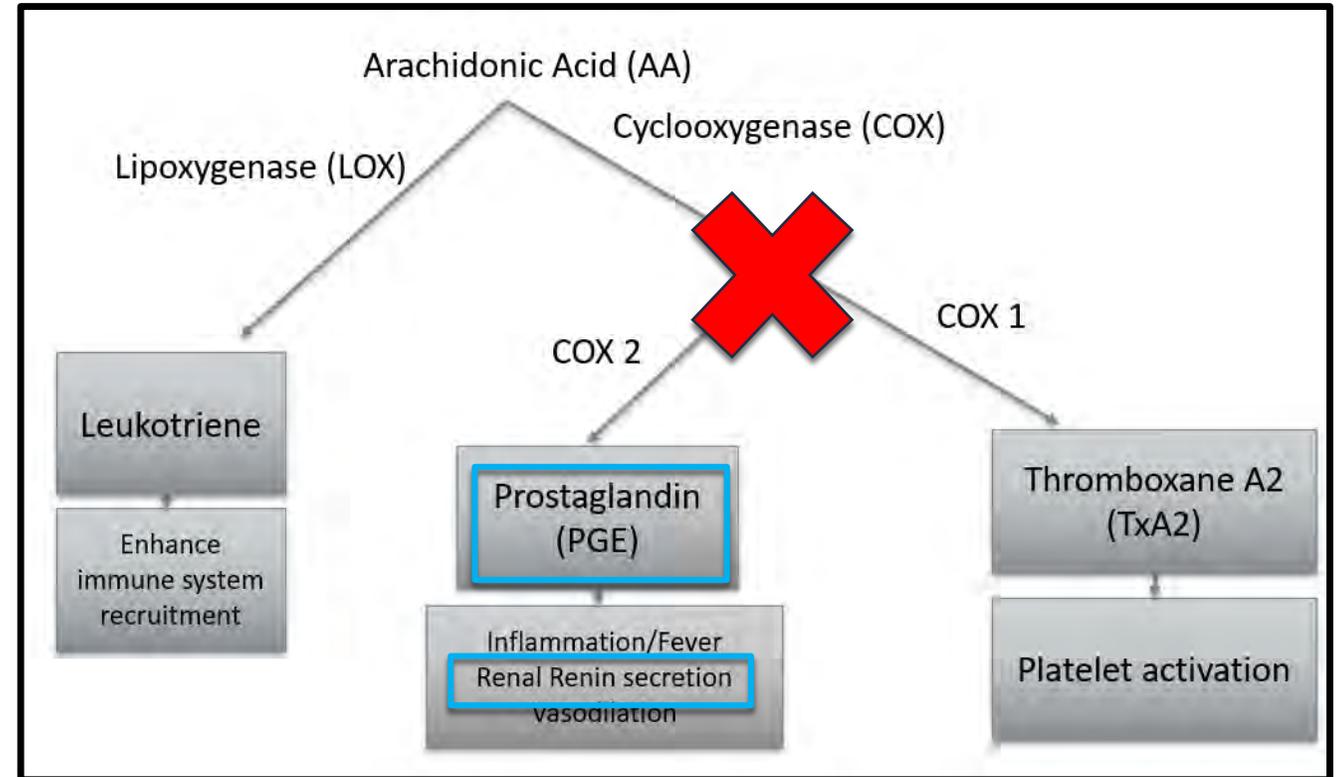
Michael Erman. J&J's Tylenol production at maximum capacity as coronavirus boosts demand. <https://www.reuters.com/article/us-health-coronavirus-johnson-johnson/jjs-tylenol-production-at-maximum-capacity-as-coronavirus-boosts-demand-idUSKBN2I62FU>. Accessed 3/31/2020

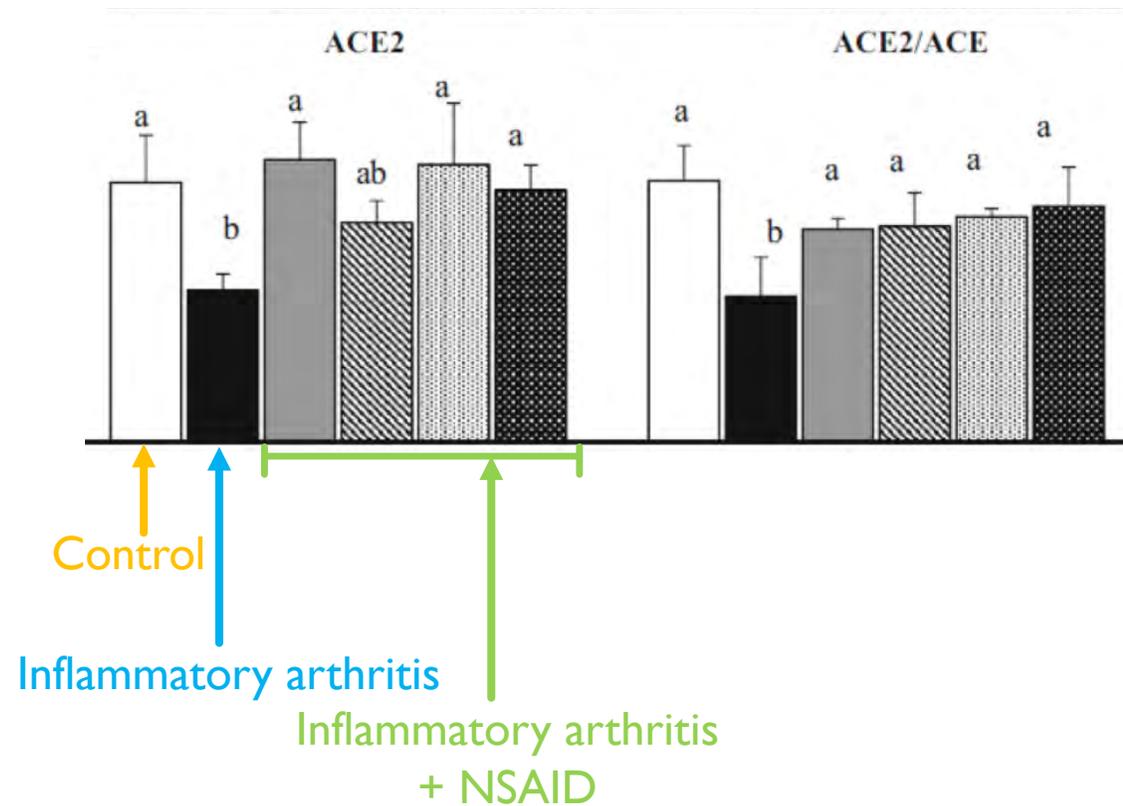
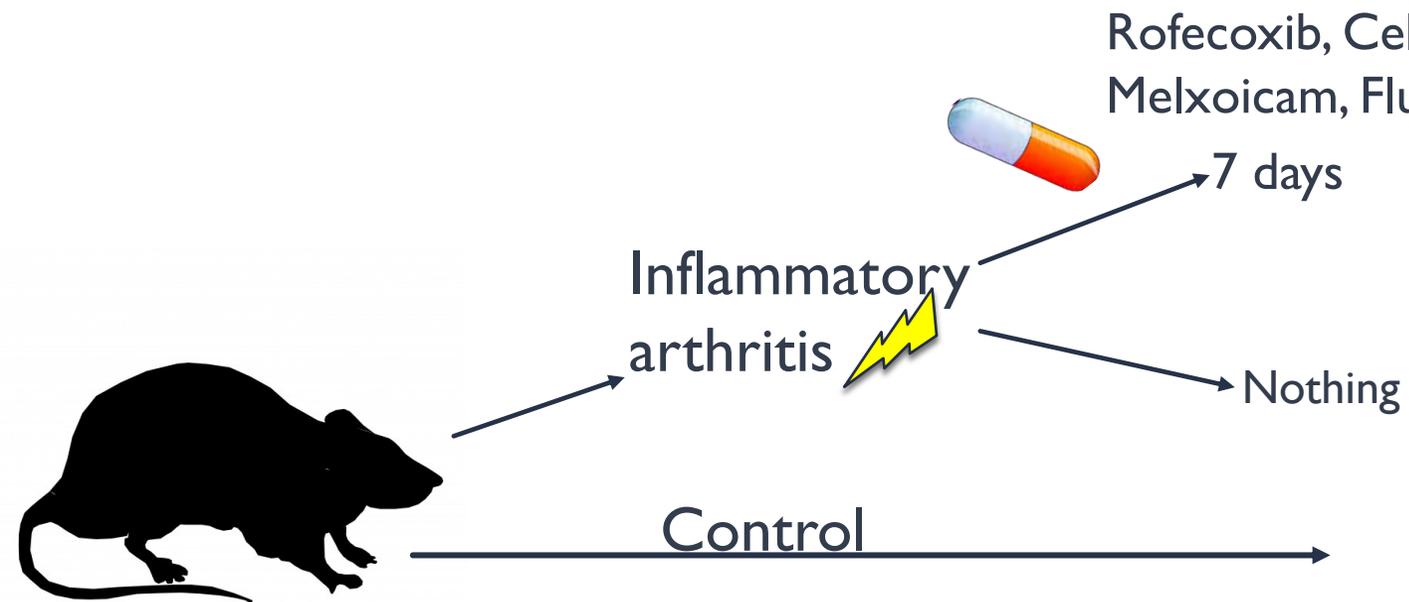
SO, WHAT EXACTLY IS GOING?

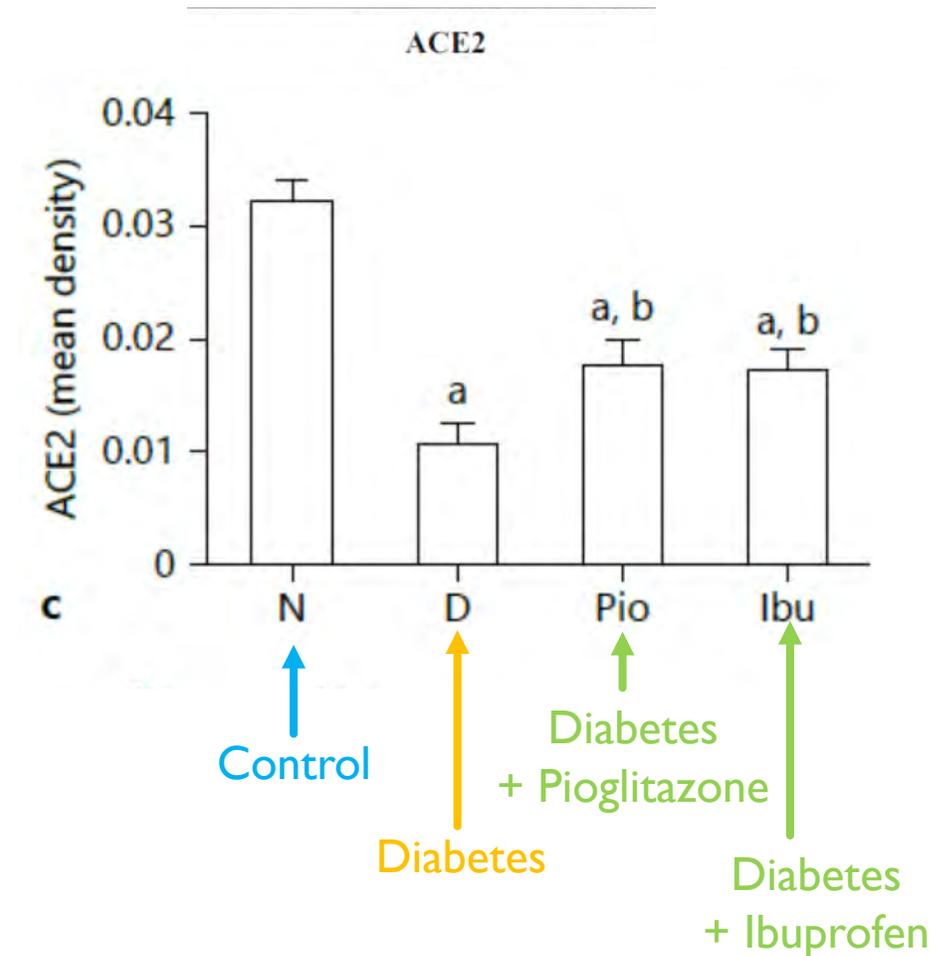
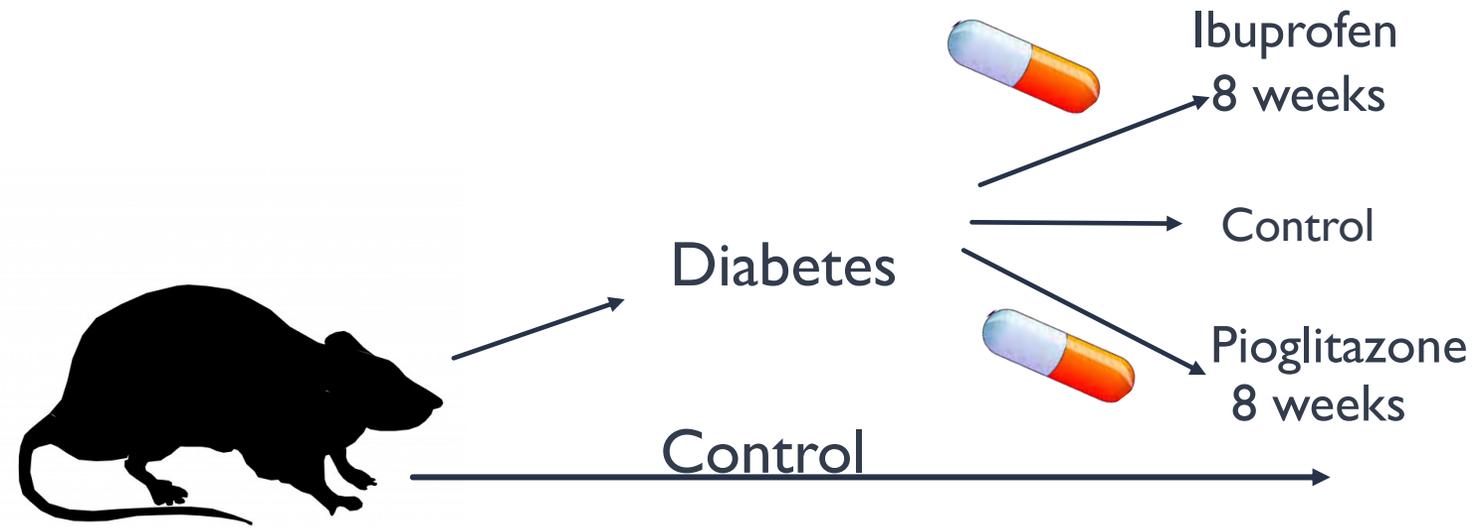


BIOLOGIC PLAUSABILITY

- NSAID Mechanism
 - COX 1 and 2 inhibition
 - ↑ACE2
- NSAID
 - ↓ Renal PGE synthesis
 - Inhibit renin secretion
 - ↓ angiotensin II
 - ↑ACE2
- Acetaminophen
 - Decrease ↓ PGE in brain
 - No ACE2 modulation



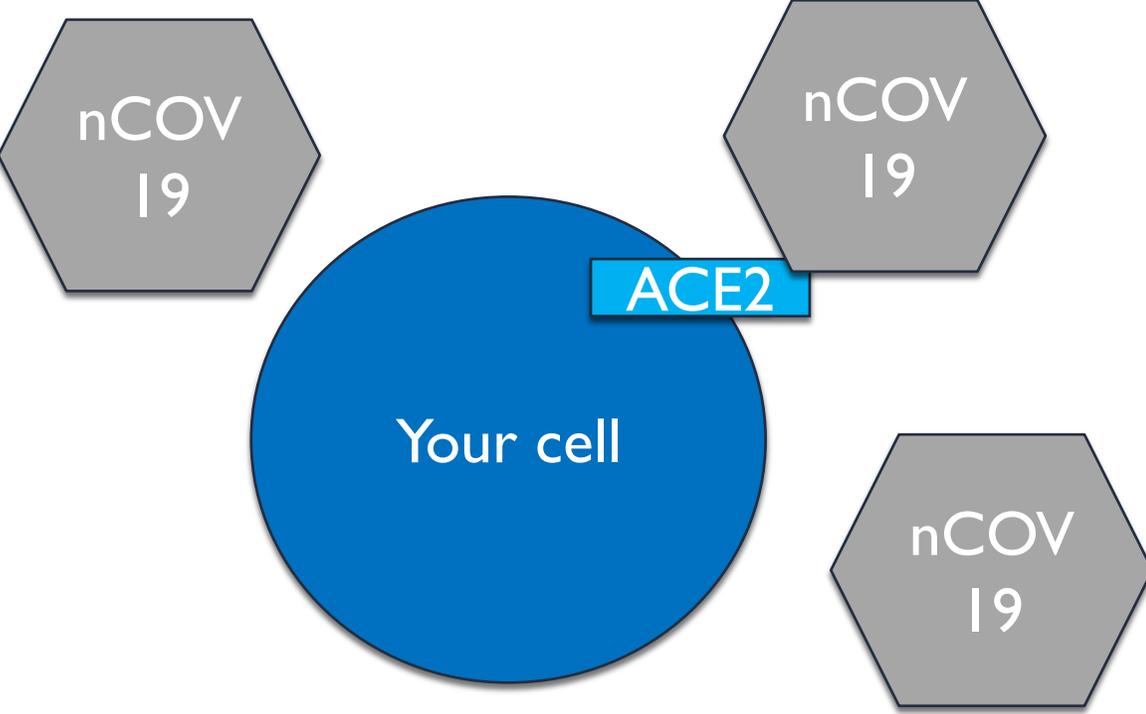






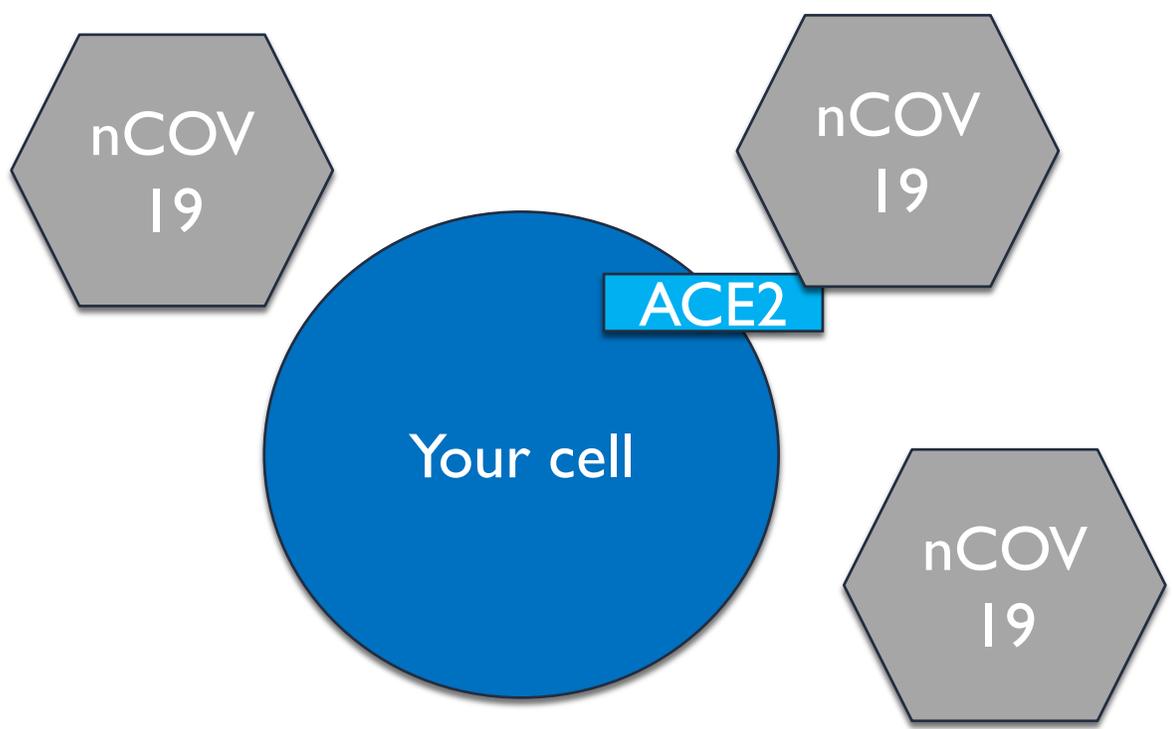
HOW DOES ACE2
UPREGULATION
IMPACT COVID 19?

ACE2 UPREGULATION INCREASED INFECTIVITY?

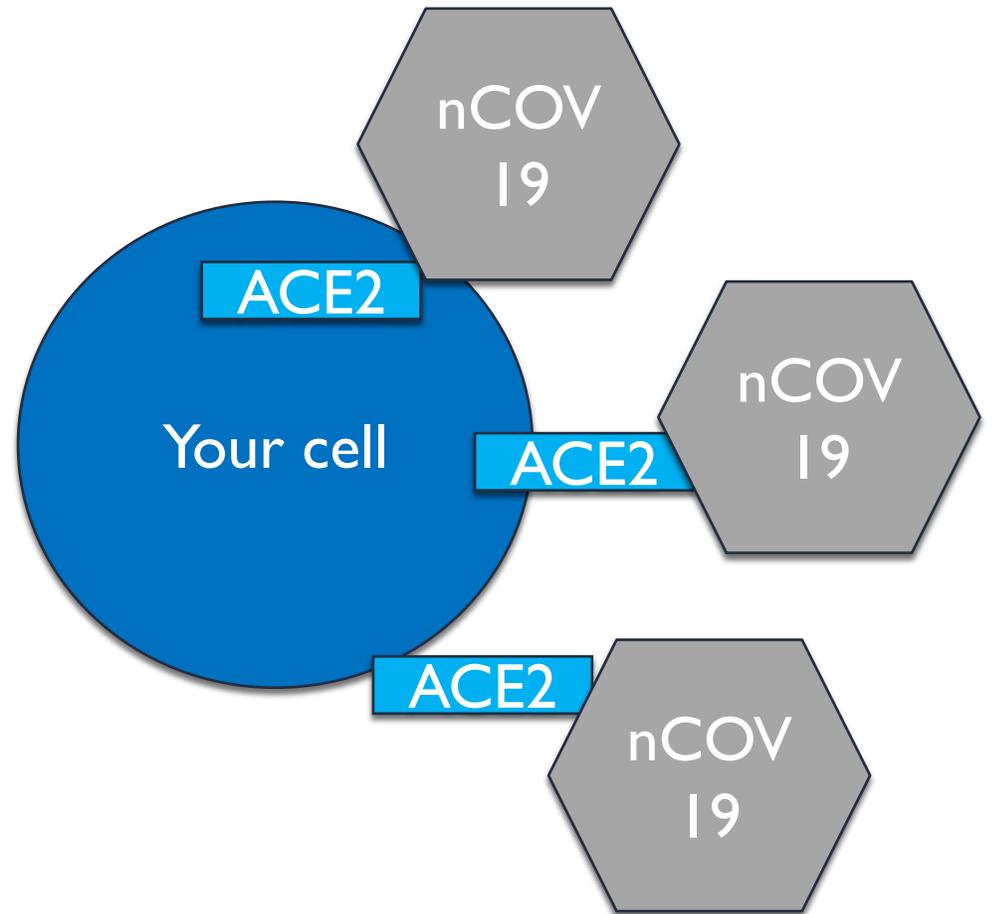


Less ACE2

ACE2 UPREGULATION INCREASES INFECTIVITY?



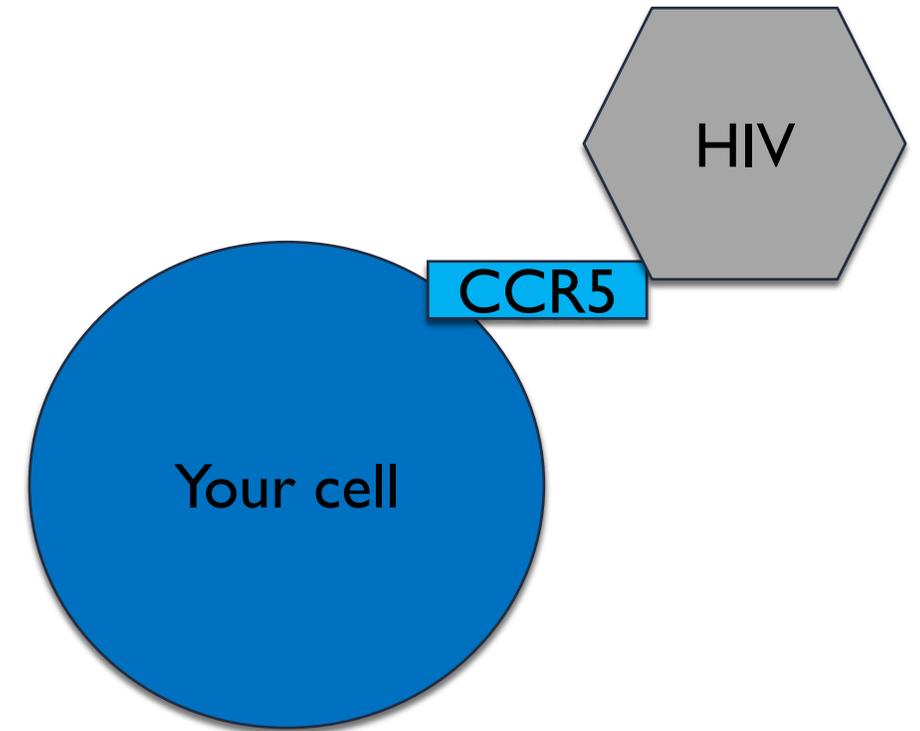
Less ACE2



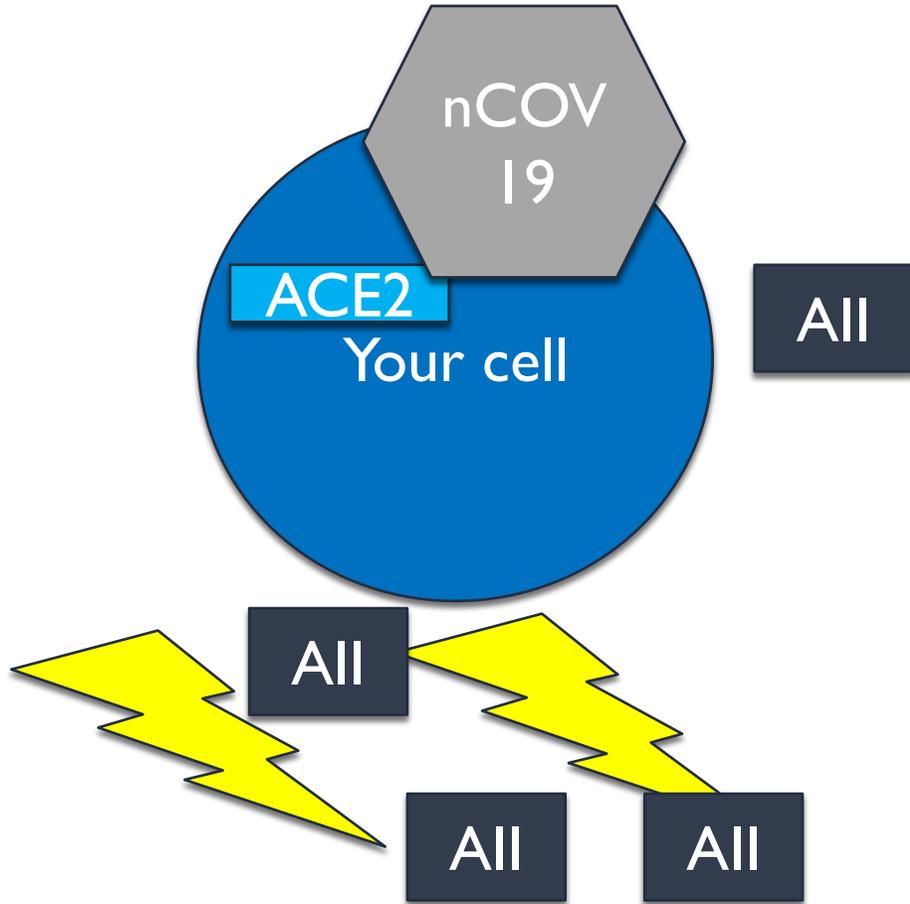
More ACE2

DOWN REGULATION, GOOD FOR VIRUS?

- HIV- secretes a downregulating nef protein
 - Aid in endocytosis
 - May prevent HIV secondary strain super infection
- SARS-CoV2 also down regulates ACE2
 - May lead to worse COVID19 disease

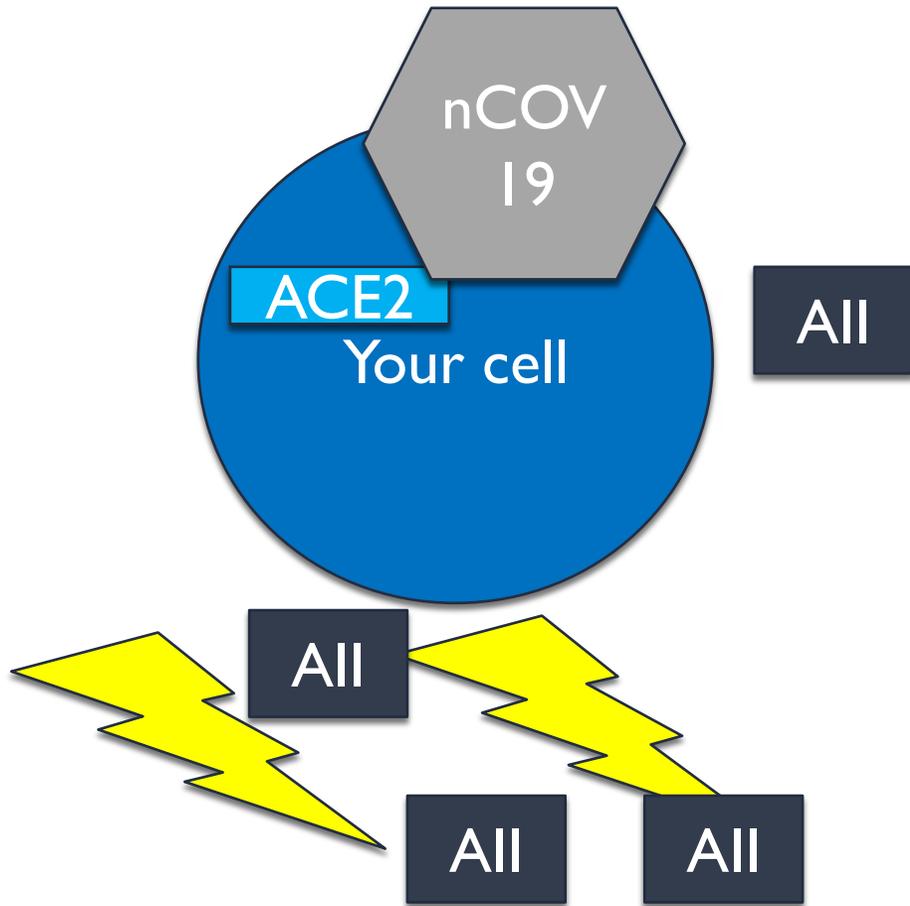


ACE2-DOWN REGULATION PATHOGENESIS

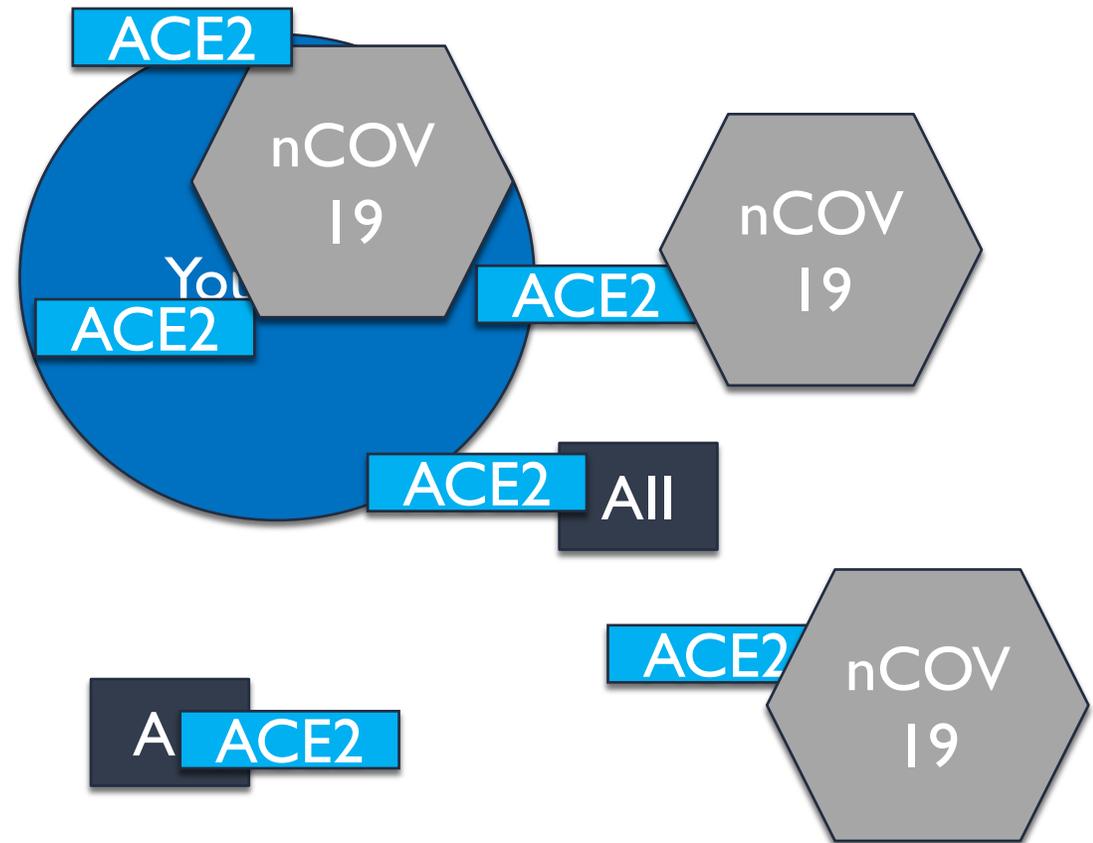


More inflammation

ACE2-DOWN REGULATION PATHOGENESIS

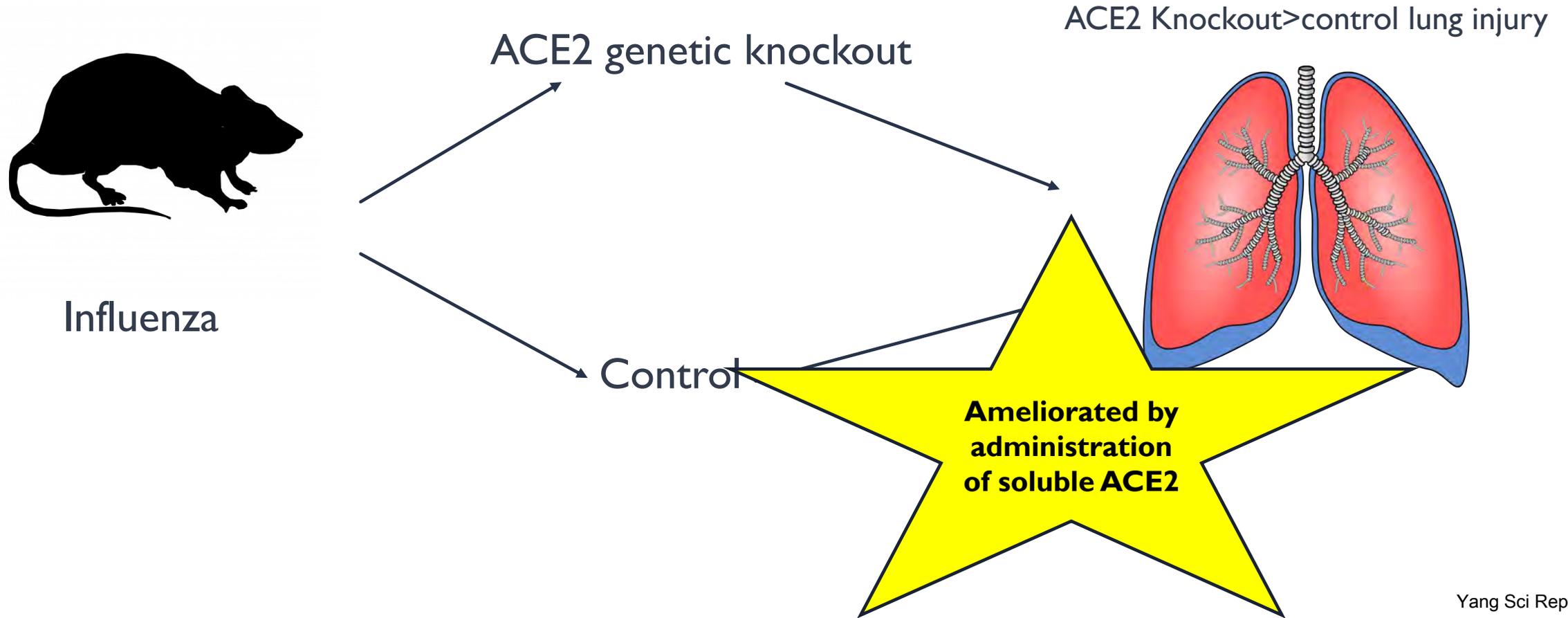


More inflammation

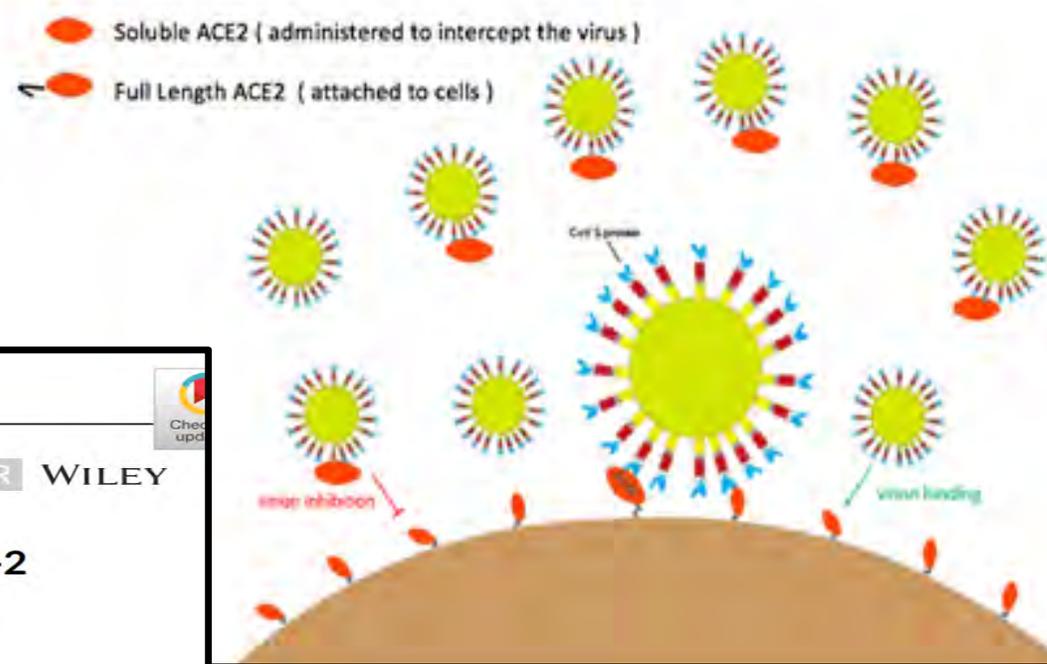


Less inflammation

ACE2 knock out worsens pathogenesis in animal model of influenza



THERAPEUTIC ACE2



Received: 25 February 2020 | Accepted: 27 February 2020
DOI: 10.1002/ddr.21656

COMMENTARY

DDR WILEY

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics

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Abstract

At the time of writing this commentary (February 2020), the coronavirus COVID-19 epidemic has already resulted in more fatalities compared with the SARS and MERS coronavirus epidemics combined. Therapeutics that may assist to contain its rapid spread and reduce its high mortality rates are urgently needed. Developing vaccines against the SARS-CoV-2 virus may take many months. Moreover, vaccines based on viral-encoded peptides may not be effective against future coronavirus epidemics, as virus mutations could make them futile. Indeed, new Influenza virus strains emerge every year, requiring new immunizations. A tentative suggestion based on existing therapeutics, which would likely be resistant to new coronavirus mutations, is to use available angiotensin receptor 1 (AT1R) blockers, such as losartan, as therapeutics for reducing the aggressiveness and mortality from SARS-CoV-2 virus infections. This idea is based on observations that the angiotensin-converting enzyme 2 (ACE2) very

CORRESPONDENCE | MARCH 13 2020

Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy?

Daniel Batlle ; Jan Wysocki; Karla Satchell

Check for updates

Clin Sci (Lond) (2020) 134 (5): 543–545.

<https://doi.org/10.1042/CS20200163> Article history

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ACE2-NSAIDS

Known Knowns

- Theoretically plausible
 - NSAIDS increase ACE2
- Animal experimental data supports this
 - Animal studies > 7 days exposure
 - Confounded by ACE2 diseases (arthritis diabetes)
 - Impact on healthy individual not clear
- Animal data does not equal human experimental data
 - No human ACE2/NSAID literature
 - Some drugs like ACE/ARB show variable impact on human ACE2 (Vaduganathan et al.)

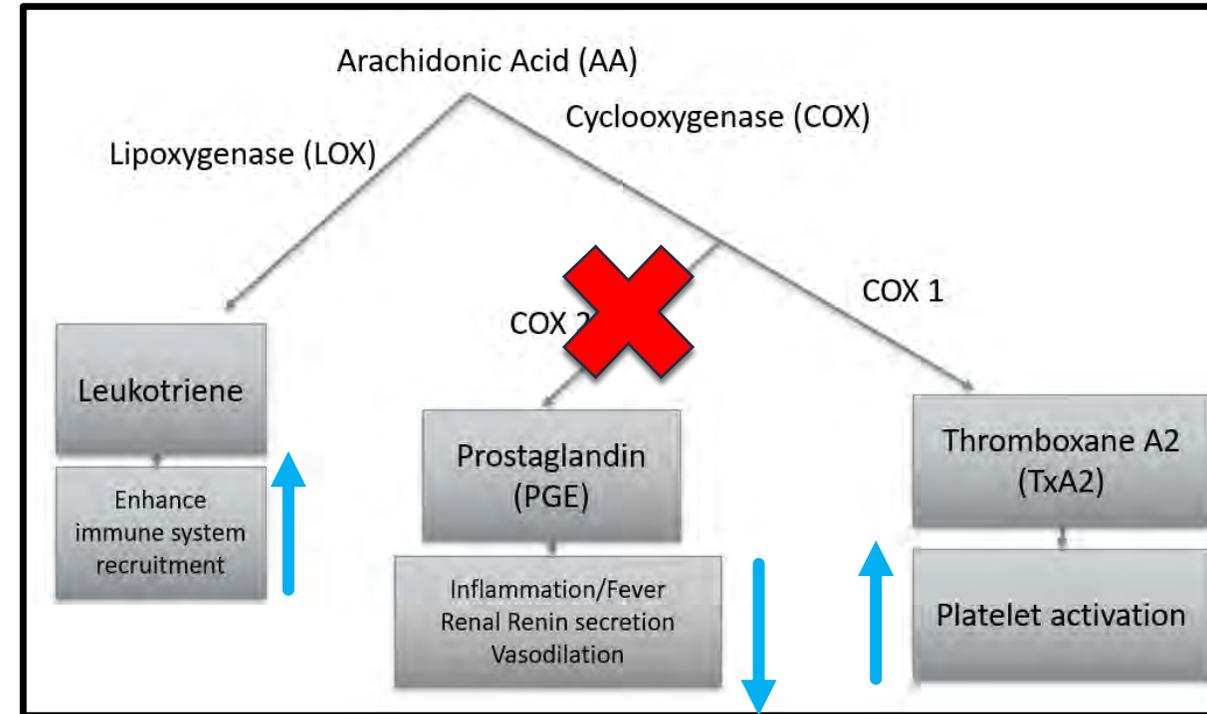
Known unknowns

- Does ACE2 regulation modify disease severity?
- Are clinical outcomes different among patients taking NSAID and have COVID19?

- No randomized control trials on use of NSAID in COVID19
- No studies registered with clinicaltrials.gov evaluating NSAID use
- No COVID19 cohort or interventional studies have on NSAID use

OLD RISKS, NEW DISEASE

- NSAID Mechanism
 - COX 1 and 2 inhibition
- Thrombosis- ↑ TxA2 (Black Box Warning) (COX2>COX1)
 - Increased risk of CVA/AMI with NSAID use alone, URI alone, and further increase with both (Wen et al.)
- Increased complications?- Leukotriene ↑
 - NSAID induced bronchospasm (Sturtevant et al.)
 - Increased empyema in children with URI reported (Le Bourgeois et al.)
- ↓ PGE Gastric/Renal
 - Increased risk of GI bleed (decreased GI mucosal secretions)
 - Pre-renal acute kidney injury
- Efficacy
 - 899 URI patients, no significant difference between APAP and IBU for URI symptoms (Little et al.)



TAKE AWAY

- Change in NSAID prescribing due to COVID19 premature
 - More clinical outcome data needed
 - Continue long term NSAID (aspirin, gout, osteoarthritis)
- Be aware of their current risk profile
- Additional resources
 - Oxford Center for Evidence Based Medicine (CEBM)
 - <https://www.cebm.net/covid-19/nsaids-in-acute-respiratory-infection/>
 - Perspective-
 - Little P. Non-steroidal anti-inflammatory drugs and covid-19. BMJ. 2020 Mar 27;368:m1185. doi: 10.1136/bmj.m1185. PubMed PMID: 32220865.

| NSAID Candidates | Consider avoiding |
|---|---|
| <ul style="list-style-type: none">• Patients with low risk for adverse effect• Unable to tolerate acetaminophen• Break through analgesia/anti pyretic | <ul style="list-style-type: none">• Advanced age• History of thrombosis• History of peptic ulcer of gastrointestinal bleed• Asthma• Renal disease |

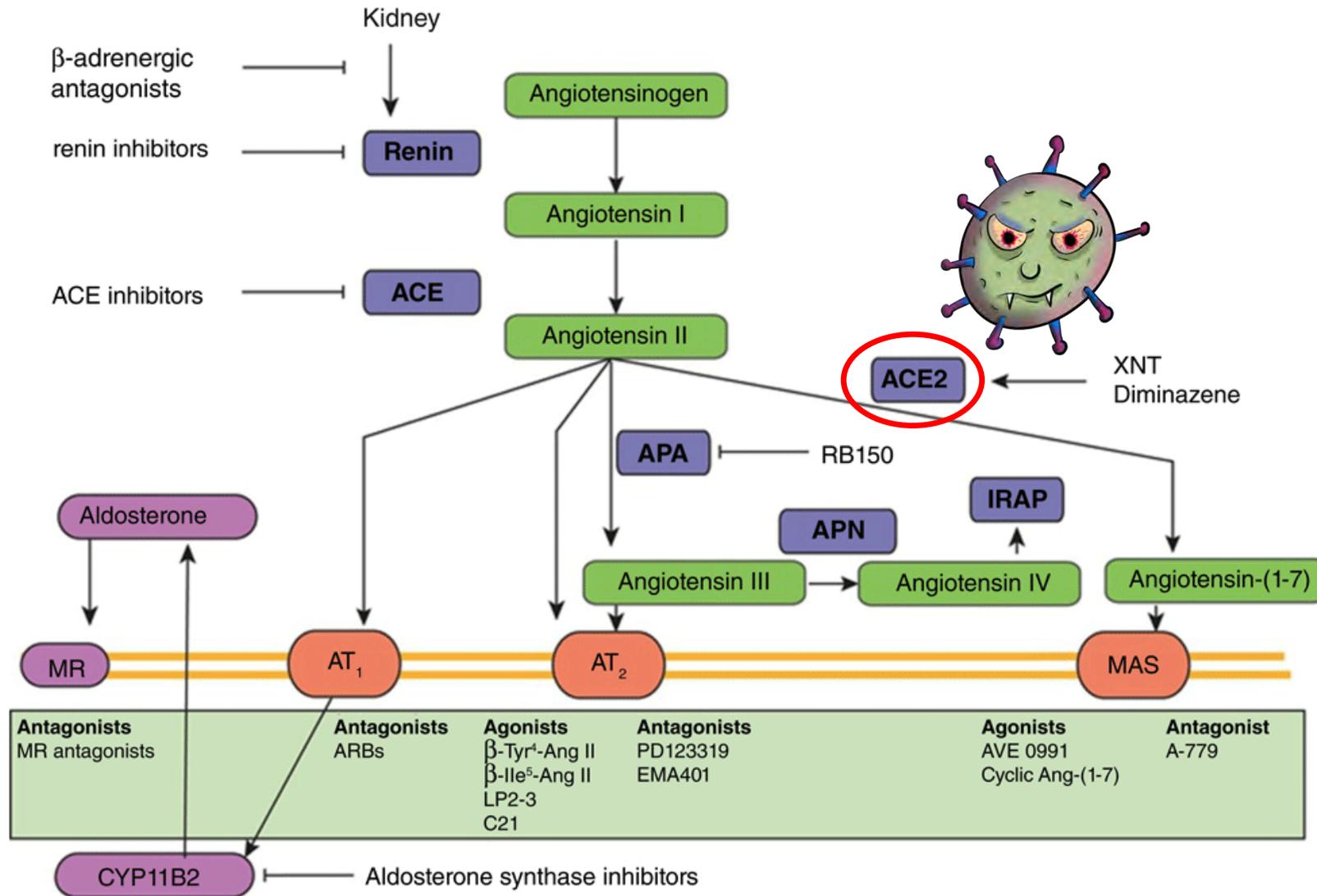
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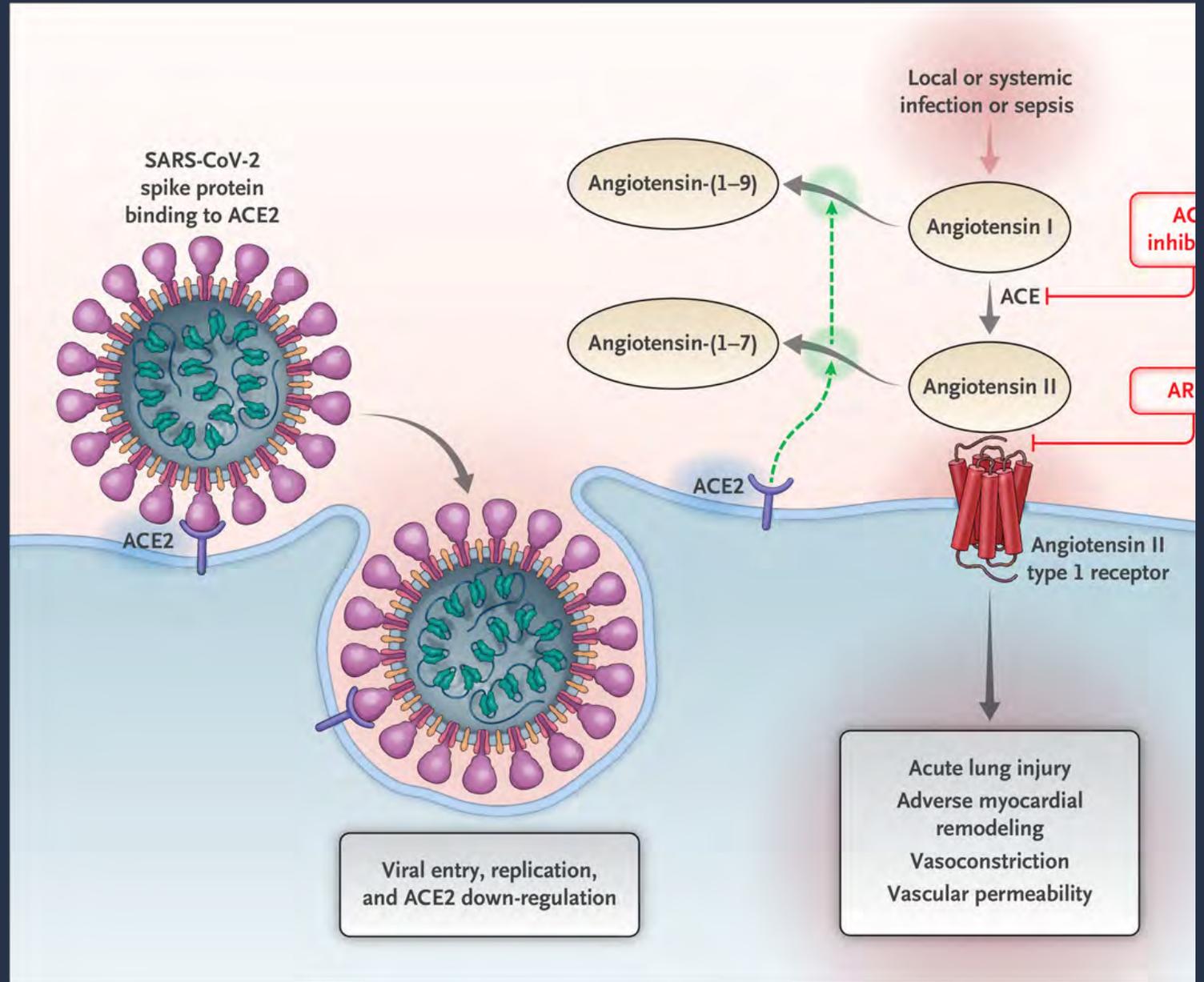
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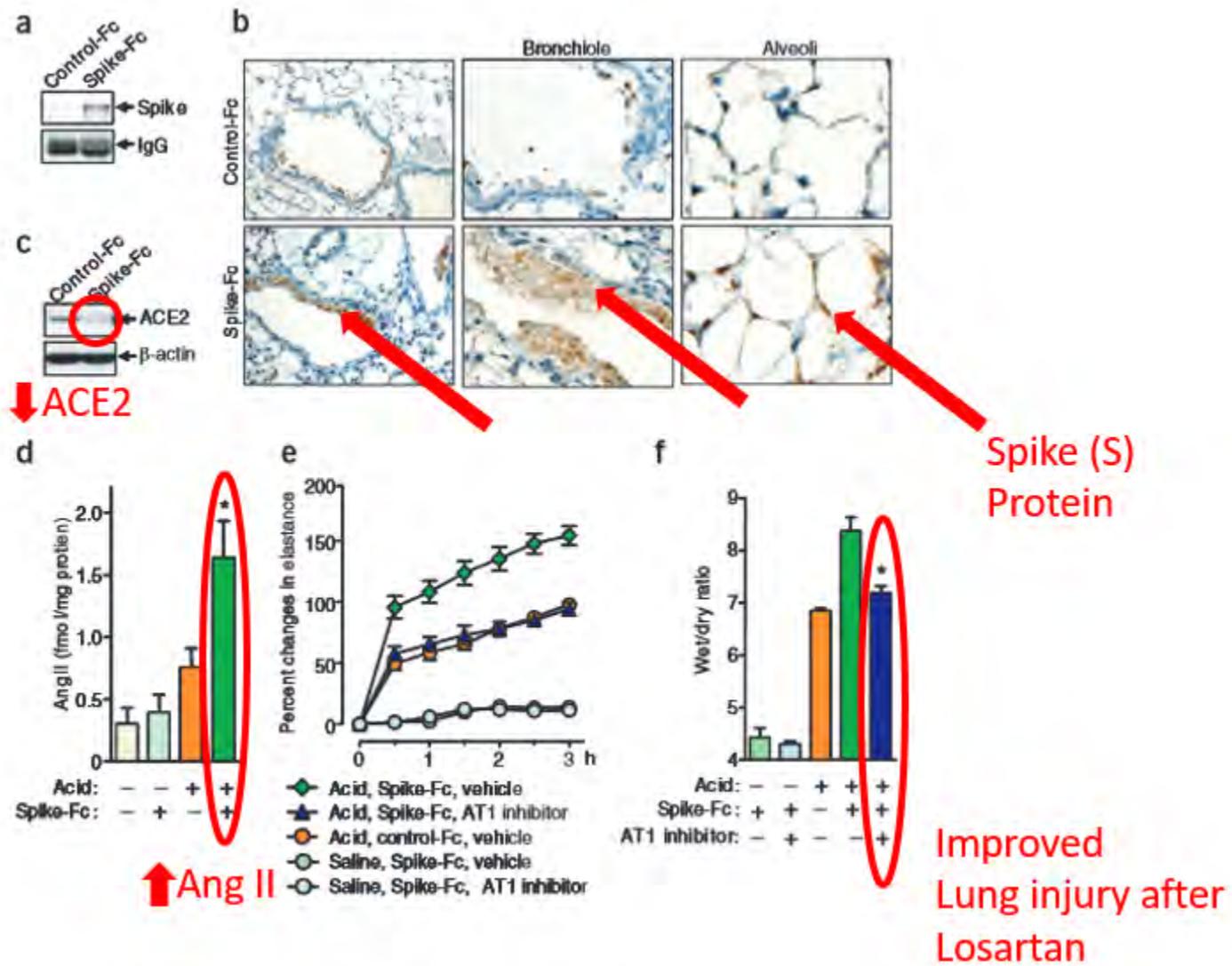
Figure 1. New and existing drugs interfering with the renin-angiotensin (Ang) system cascade.



Ghazi L and Drawz P. Advances in understanding the renin-angiotensin-aldosterone system (RAAS) in blood pressure control and recent pivotal trials of RAAS blockade in heart failure and diabetic nephropathy [version 1]. F1000Research 2017, 6:297 (doi: 10.12688/f1000research.9692.1)

Interaction between SARS-CoV-2 and the Renin-Angiotensin-Aldosterone System.

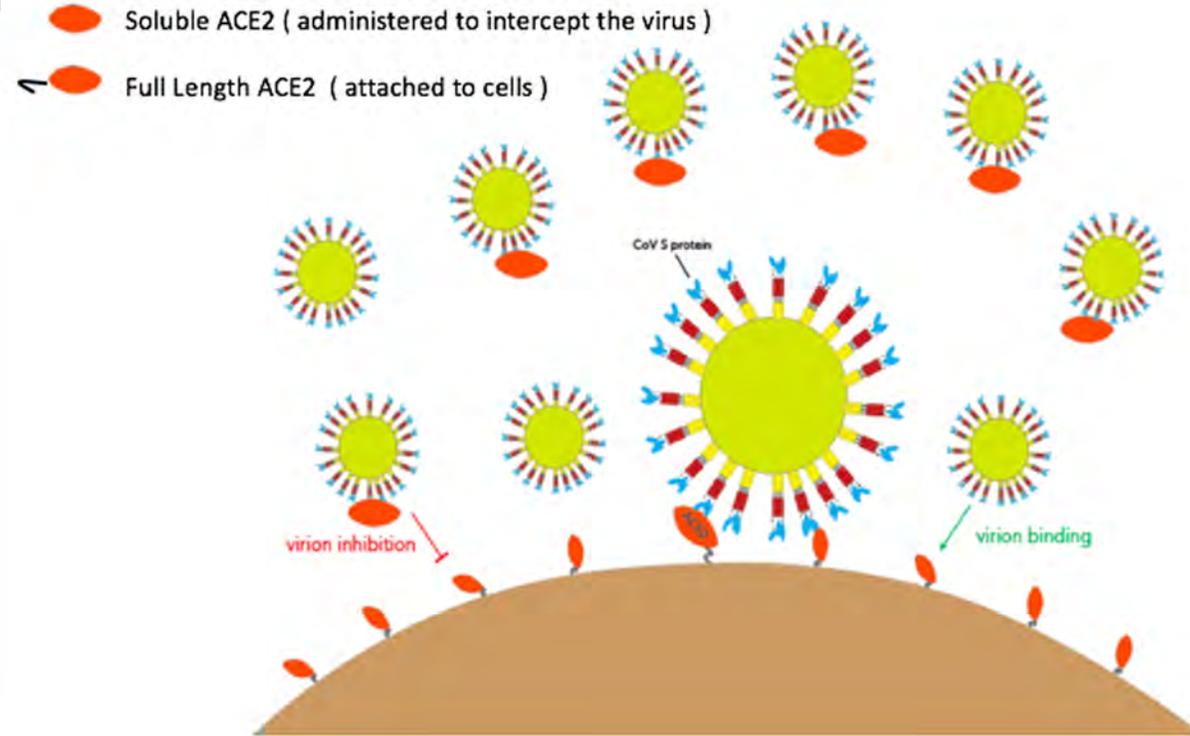




Kuba et al. Nature Medicine volume 11, pp 875–879 (2005)

Sparks MA, Hiremath S et al. "The Coronavirus Conundrum: ACE2 and Hypertension Edition" NephJC <http://www.nephjc.com/news/covidace2>
 Accessed 3/31/2020.

Figure 1



Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy?

- Ang II → lung injury
- Unclear upregulation of ACE2 in humans
- ARB → more ACE2 on cells → less lung injury in animal models
- ACEI improve pneumonia outcomes
- SARS-CoV2 downregulates ACE2, decreasing levels

Hypothesis: More ACE2 could be good

- Ang II ↓ in shock
- Upregulation of ACE2 → more viral entry?
- ARBs increase ACE2 in the gut → fecal-oral spread of SARS-CoV2
- Ang II → decreased ACE2 on cells → less viral entry?
- Anecdotal benefit of Ang II used as a pressor in COVID

Hypothesis: Less ACE2 is good

ACEI/ARB: Beneficial

ACEI/ARB: Harmful

| Society | Summary of recommendations | Last Statement Update |
|--|---|-----------------------|
| European Society of Hypertension | Recommend continuing ACEis/ARBs due to lack of evidence to support differential use in COVID-19 patients. In those with severe symptoms or sepsis, antihypertensive decisions should be made on a case-by-case basis taking into account current guidelines | March 12, 2020 |
| European Society of Cardiology Council on Hypertension | Strongly encourage continuing ACEis/ARBs due to lack of evidence to support discontinuing | March 13, 2020 |
| Hypertension Canada | Recommend continuing ACEis/ARBs due to lack of evidence that patients with hypertension or those treated with ACEis/ARBs are at higher risk of adverse outcomes from COVID-19 infection | March 13, 2020 |
| Canadian Cardiovascular Society | Strongly encourage continuing ACEis/ARBs and Angiotensin Receptor Nephilysin Inhibitors due to a lack of clinical evidence to support withdrawal of these agents | March 15, 2020 |
| The Renal Association, United Kingdom | Strongly encourage continuing ACEis/ARBs due to unconvincing evidence that these medications increase risk | March 15, 2020 |
| International Society of Hypertension | Strongly recommend that the routine use of ACEis/ARBs to treat hypertension should not be influenced by concerns about COVID-19 in the absence of compelling data that ACEis/ARBs either improve or worsen susceptibility to COVID-19 infection nor do they affect the outcomes of those infected | March 16, 2020 |
| American College of Physicians | Encourage continuing ACEis/ARBs because there is no evidence linking them to COVID-19 disease severity, and discontinuation of antihypertensive therapy without medical indication could in some circumstances result in harm | March 16, 2020 |
| Spanish Society of Hypertension | Recommend that ACEis/ARBs should not be empirically stopped in patients who are already taking them; in seriously ill patients, changes should be made on a case-by-case basis | March 16, 2020 |
| American Heart Association, Heart Failure Society of America, American College of Cardiology | Recommend continuing ACEis/ARBs for all patients already prescribed them | March 17, 2020 |
| European Renal Association - European Dialysis and Transplant Association | Recommend continuing ACEis/ARBs in COVID-19 infection patients due to a lack of evidence to support differential use and the discontinuation of ACEis/ARBs in COVID-19 patients | March 17, 2020 |
| American Society of Pediatric Nephrology | Strongly recommend continuing ACEis/ARBs until new evidence to the contrary becomes available | March 17, 2020 |
| High Blood Pressure Research Council of Australia | Recommend continuing routine use of ACEis/ARBs. Patients should not cease blood pressure lowering medications unless advised to do so by their physician | March 18, 2020 |
| Australian Diabetes Society | Recommend that usual antihypertensive therapy is continued given that speculation about risk of ACE inhibitors and ARBs is purely theoretical | March 29, 2020 |

Sparks MA, Hiremath S et al.
 "The Coronavirus Conundrum:
 ACE2 and Hypertension
 Edition" NephJC
<http://www.nephjc.com/news/covidace2> Accessed 3/31/2020.

ONGOING TRIALS

- Observational
 - Italy: Retrospective, ACEI or ARB use (CODIV-ACE)
 - UK: Matched prospective case-control ACEI vs not
 - Wuhan, China: Case-control ACEI vs not
- Investigational
 - Minnesota: outpatient losartan 25 mg vs placebo
 - Minnesota: inpatient losartan 25 mg vs placebo

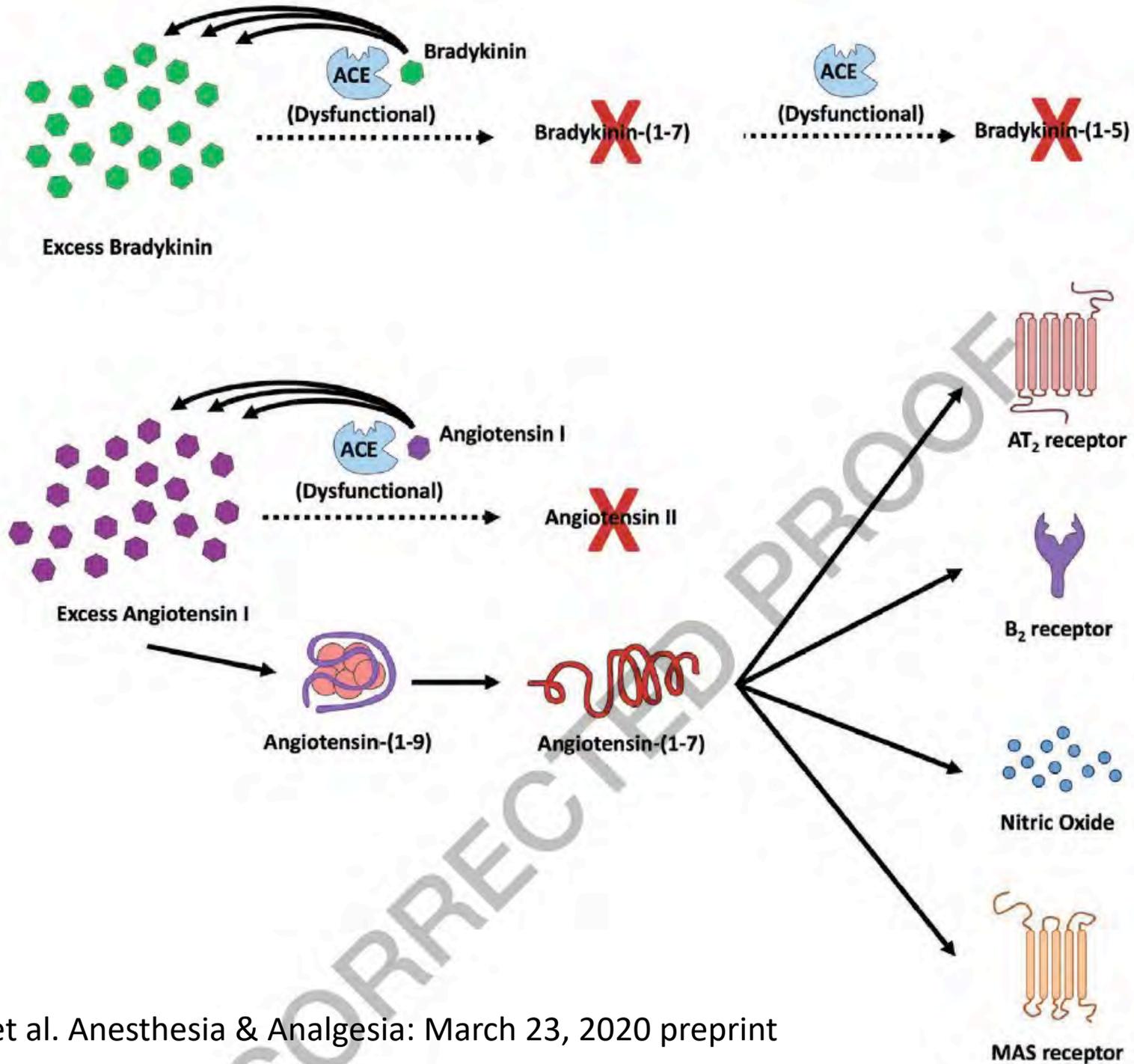
Angiotensin II for the Treatment of COVID-19–Related Vasodilatory Shock

Jonathan H. Chow, MD, Michael A. Mazzeffi, MD, MPH, and Michael T. McCurdy, MD

Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients

Yingxia Liu, Fengming Huang, Jun Xu, Penghui Yang, Yuhao Qin, Mengli Cao, Zhaoqin Wang, Xiaohe Li, Shaogeng Zhang, Lu Ye, Jingjun Lv, Jie Wei, Tuxiu Xie, Hong Gao, Kai-Feng Xu, Fusheng Wang, Lei Liu, Chengyu Jiang

doi: <https://doi.org/10.1101/2020.03.20.20039586>



ACEI AND ARB RETROSPECTIVE DATA

- 78 patients in China with COVID-19 and HTN
- For age > 65 with HTN (46 pts), severe disease was greatly reduced in those who took ARBs prior to hospitalization
- ...based on 10 patients on ARBs

Figure 1

medRxiv preprint doi: <https://doi.org/10.1101/2020.03.20.20039586>. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

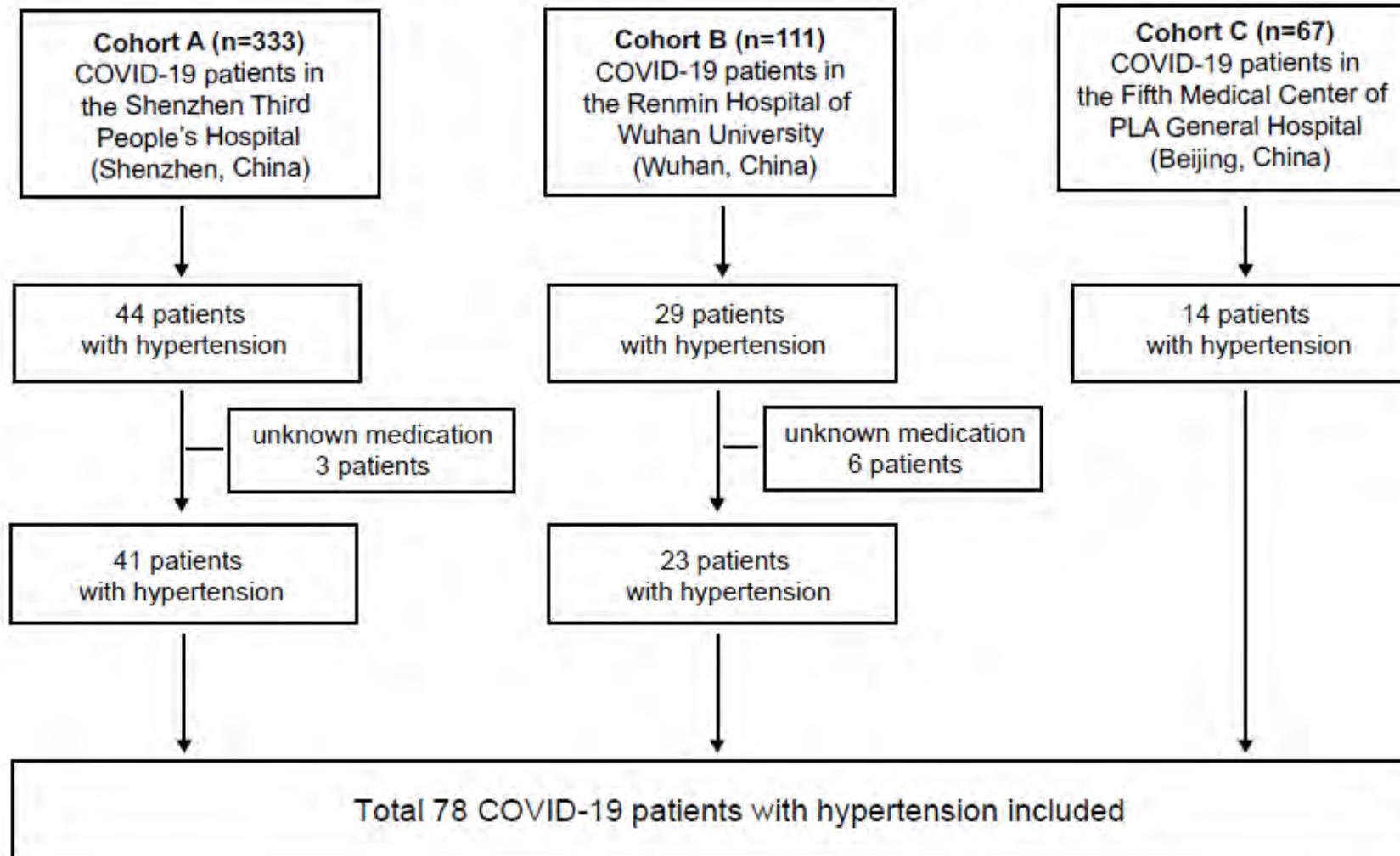


Table 1. Association between antihypertensive use and disease severity of COVID-19 patients older than 65 years old with hypertension comorbidity

| Characteristics | Total patients (n=46) | Severe patients (n=28) | Mild patients (n=18) | Unadjusted | | | Adjusted | | |
|-----------------------------------|-----------------------|------------------------|----------------------|------------|-------------|---------|----------|-------------|---------|
| | | | | OR | 95% CI | p value | OR | 95% CI | p value |
| Antihypertensive use, n(%) | | | | | | | | | |
| No use | 8 (17.4) | 7 (25) | 1 (5.6) | ref | | ref | ref | | ref |
| CCB | 26 (56.5) | 18 (64.3) | 8 (44.4) | 0.791 | 0.548-1.141 | 0.403 | 0.359 | 0.036-3.58 | 0.382 |
| ARB | 10 (21.7) | 3 (10.7) | 7 (38.9) | 0.343 | 0.128-0.916 | 0.025 | 0.250 | 0.064-0.976 | 0.046 |
| ACEI | 2 (4.3) | 1 (3.6) | 1 (5.6) | 0.571 | 0.139-2.342 | 0.378 | — | — | — |
| Thiazide | 3 (6.5) | 0 (0) | 3 (16.7) | — | — | — | — | — | — |
| BB | 7 (15.2) | 3 (10.7) | 4 (22.2) | 0.49 | 0.2-1.198 | 0.119 | — | — | — |

ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; BB, beta blocker.

OR, odds ratio; CI, confidence interval.

Adjustment was by multivariable logistic regression modeling with sex variable

| | Total patients (n=46) | Severe patients (n=28) | Mild patients (n=18) | Unadjusted | | | Adjusted | | |
|-----------------|-----------------------|------------------------|----------------------|------------|-------------|---------|----------|-------------|---------|
| | | | | OR | 95% CI | p value | OR | 95% CI | p value |
| No use | 8 (17.4) | 7 (25) | 1 (5.6) | ref | | ref | ref | | ref |
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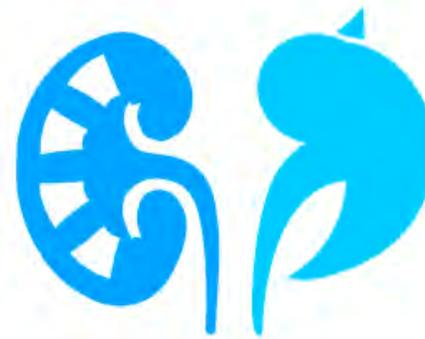
WHAT CAN BE SAID CONFIDENTLY?

- **It is uncertain** if ACEIs and ARBs worsen or improve outcomes of COVID-19
- Patients chronically taking ACEIs or ARBs **should not stop therapy** pending trials given **clear benefit in heart failure, HTN, and CKD**, plus the **uncertain risk-benefit ratio in COVID**
- **It is uncertain** if angiotensin II is of additional benefit or detriment in treatment of COVID-19

Many researchers (work shown and not)
Matt Sparks, Swapnil Hiremath, and the rest of the
Nephrology / Hypertension online community

THANK YOU

PLEASE REACH OUT WITH ANY QUESTIONS



#NephJC



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 [@nephrotox](https://twitter.com/nephrotox)

REMDESIVIR (GS-5734)

A REVIEW OF PERTINENT DRUG INFORMATION FOR SARS-COV-2

April 1, 2020

Matt Davis, PharmD

Infectious Diseases Pharmacist

UCLA Ronald Reagan Medical Center

Mrdavis@mednet.ucla.edu

 @mattdavis | 38



REMEDESIVIR (GS-5734)

Mechanism of Action: Interference with viral RNA-dependent RNA polymerase; premature termination of viral RNA transcription

Status: Investigational, COVID-19 Phase III trials ongoing

Formulation: Intravenous only

Dosing: 200 mg IV loading dose, then 100 mg IV daily for 5-10 days

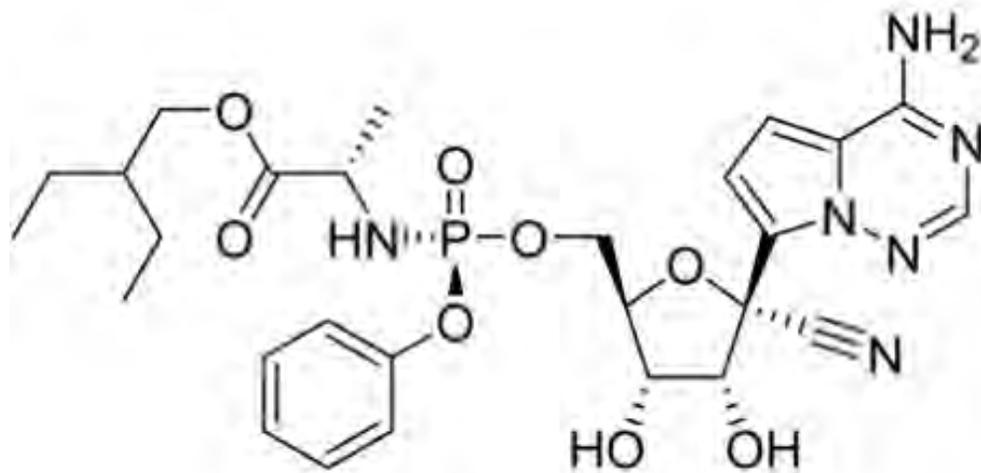
Pediatric Dosing: 5 mg/kg IV loading dose (max 200 mg), then 2.5 mg/kg IV daily (max 100 mg)

Manufacturer: Gilead Sciences

*Optimal duration currently under investigation

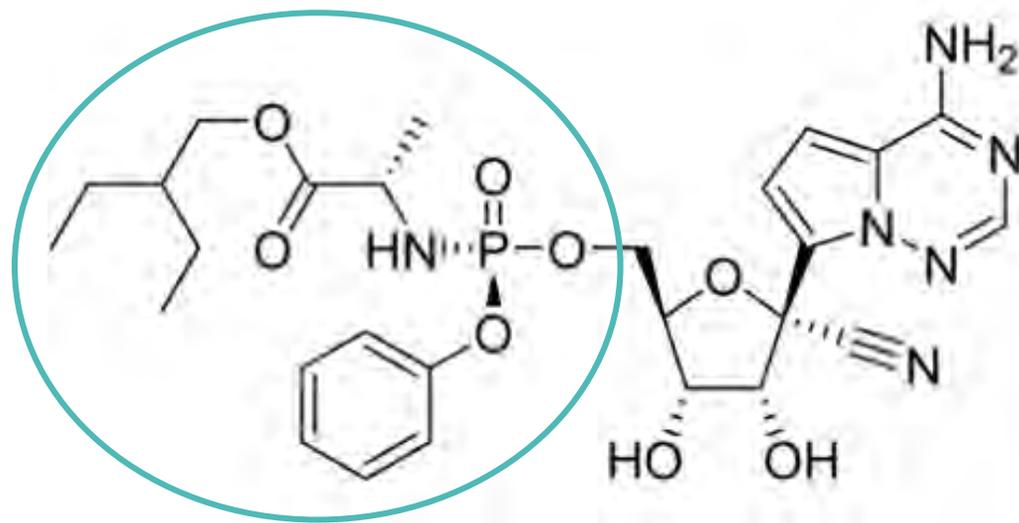
Tchesnokov;Viruses 2019.

REMDESIVIR STRUCTURE ACTIVITY RELATIONSHIP



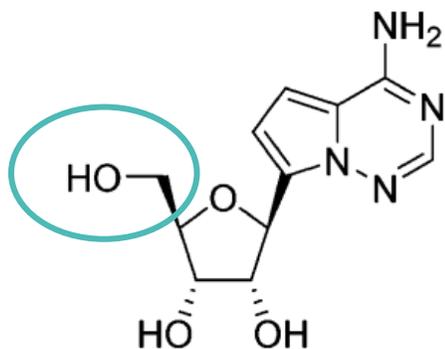
Monophosphoramidate 1'Cyano
C-adenosine Nucleoside Analog

REMDESIVIR STRUCTURE ACTIVITY RELATIONSHIP



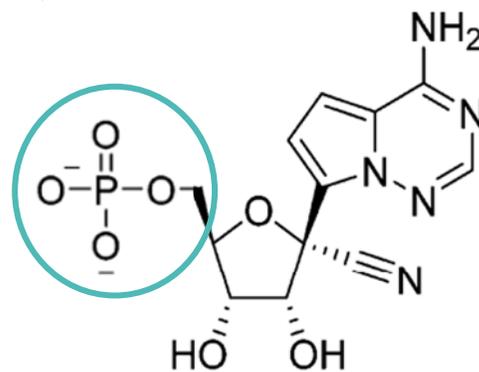
Monophosphoramidate 1'Cyano
C-adenosine Nucleoside Analog

REMDESIVIR STRUCTURE ACTIVITY RELATIONSHIP



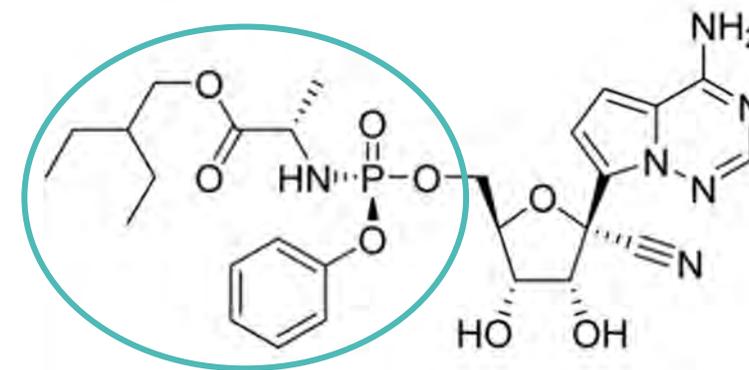
C-Adenosine Analog

Rate limiting phosphorylation



Monophosphate Form

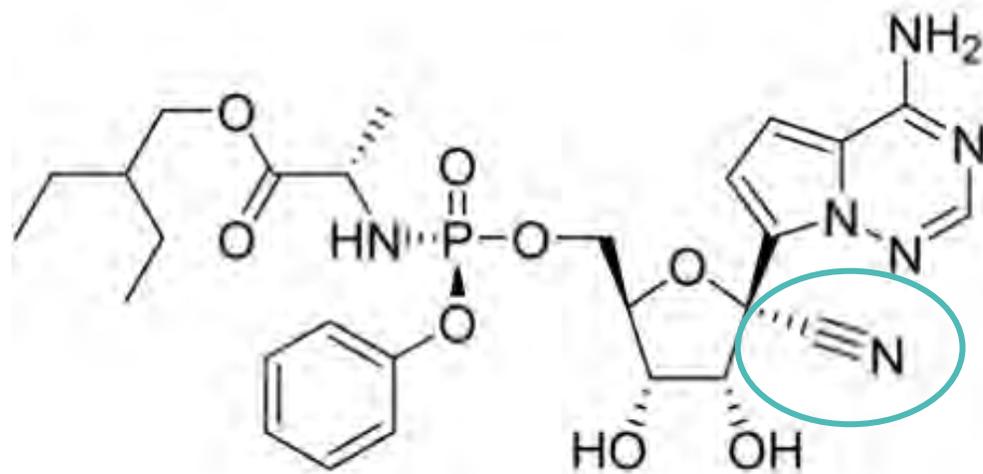
Charge reduces permeability



Remdesivir

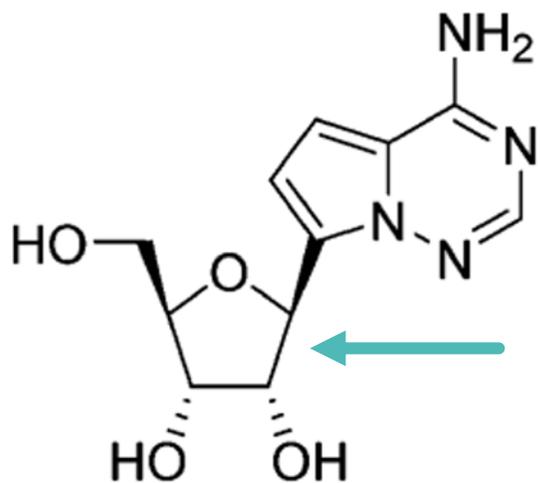
Neutral charge, bypasses rate limiting step

REMDESIVIR STRUCTURE ACTIVITY RELATIONSHIP



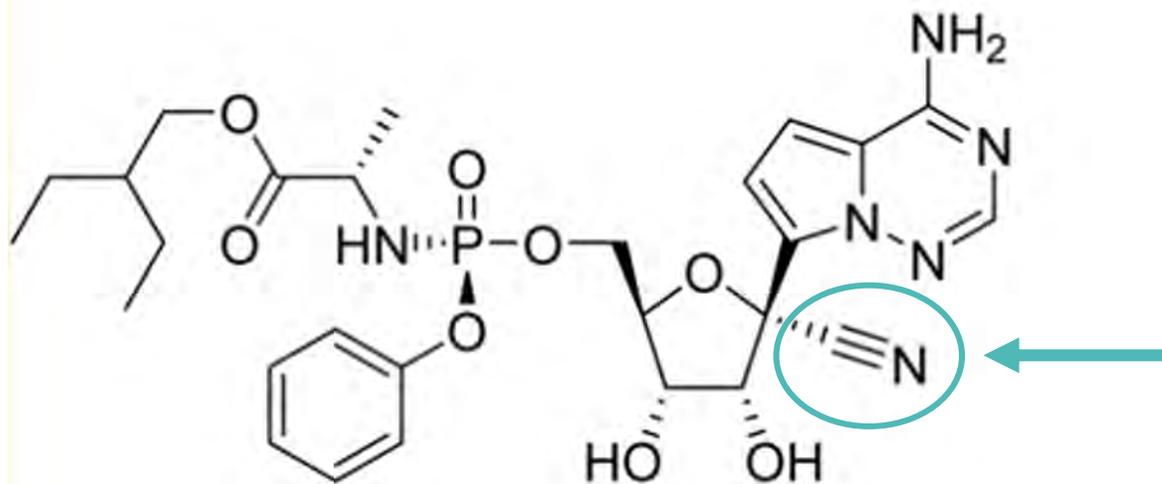
Monophosphoramidate **1'-Cyano**
C-adenosine Nucleoside Analog

REMDESIVIR STRUCTURE ACTIVITY RELATIONSHIP



C-Adenosine Analog

Poor selectivity, highly cytotoxic



Remdesivir

1'Cyano modification confers selectivity

REMDESIVIR (GS-5734) PHARMACOKINETICS

- **Distribution:** Unbound 12.1%; Widely distributed
 - Bladder, kidneys, liver, prostate gland, salivary gland (mandibular), pancreas
 - Seminal vesicle, epididymis, testes
 - Poorly crosses blood-brain barrier
- **Metabolism:** Phosphoramidate prodrug activated by esterases; CYP3A4 substrate
- **Elimination:** Rats - Urine 63%, feces 27.8%

| Parameter | Remdesivir (GS-5734) | Nucleoside Metabolite (GS-441524) |
|------------------|----------------------|-----------------------------------|
| C _{max} | 2.6 µg/mL | 0.14-0.15 µg/mL |
| T _{max} | - | 2.75-4 hr |
| Half-life | 0.84-1.04 hr | 20.4-25.3 hr |

SAFETY

- Multiple-dose, 5-14 days
 - Any TEAE - 56-72%; All Grade 1-2
 - **ALT/AST increase**
 - Onset 5-25 days; resolution 3-47 days
 - Phlebitis
 - Constipation
 - Dyspepsia
 - Extremity pain
 - Headache
 - Nausea
- Ebola RCT
 - Single patient experienced hypotension and cardiac arrest after RDV initiation; cannot be distinguished from fulminant Ebola

SAFETY

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- Ebola RCT
 - Single patient experienced hypotension and cardiac arrest after RDV initiation; cannot be distinguished from fulminant Ebola

Sulfobutylether- β Cyclodextrin (SBECD)

Remdesivir 150 mg solution - **9 g**

Remdesivir 150 mg lyophilized powder - **4.5 g**

Voriconazole 400 mg - **6.4 g**

Does **NOT** meet NIOSH/ASHP criteria for a hazardous compound

Consult updated pharmacy instructions from Gilead for additional information

IN VITRO ACTIVITY

Filoviridae

- Ebola
- Marburg

Paramyxoviridae

- Measles
- Mumps
- Nipah
- Hendra

Pneumoviridae

- Respiratory Syncytial Virus
- Human Metapneumovirus

Orthocoronaviridae

- HCoV-NL63
- HCoV-OC43
- HCoV-229E
- HCoV-HKUI
- MERS
- SARS-CoV-1
- SARS-CoV-2

HCoV = Human Coronavirus; MERS = Middle East Respiratory Syndrome;
SARS = Severe Acute Respiratory Syndrome

Brown; Antivir Res 2019.
Lo; Sci Rep 2017.
Sheahan; Sci Transl Med 2017.

IN VITRO ACTIVITY

| Virus | EC50 (cells) | CC50 (cells) | Selectivity Index |
|------------|---|------------------------|-------------------|
| SARS-CoV-2 | 0.77 μM (Vero E6) | >100 μ M (Vero E6) | >130 |
| SARS-CoV-1 | 0.069 μ M (HAE) | > 10 μ M (HAE) | >144 |
| MERS | 0.074 μ M (HAE) | > 10 μ M (HAE) | >135 |
| Ebola | 0.086 μ M (MCr) | 6.1 (Hep-2) | N/A |

EC50 = 50% effective concentration; CC50 = 50% cytotoxic concentration; Selectivity Index = CC50/EC50; Vero E6 = African monkey kidney cells; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells

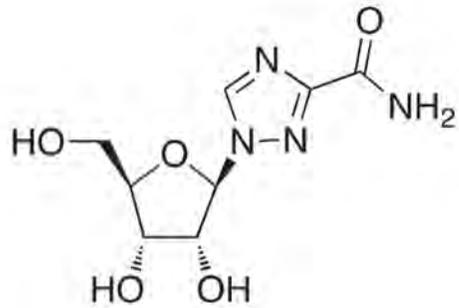
Gordon; J Bio Chem 2020.
Sheahan; Sci Transl Med 2017.
Agostini; Am Soc Micro 2018.
Yao; CID 2020.

IN VITRO ACTIVITY

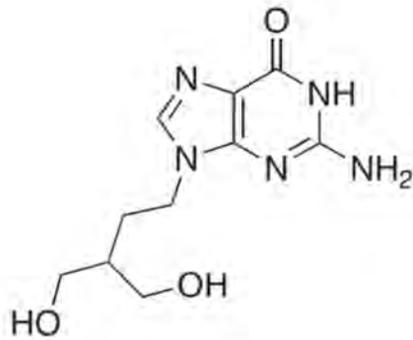
| Virus | EC50 (cells) | CC50 (cells) | Selectivity Index |
|------------|--|------------------------|-------------------|
| SARS-CoV-2 | 0.77 μM (Vero E6) | >100 μ M (Vero E6) | >130 |
| SARS-CoV-1 | SARS-CoV-2 EC ₅₀ | > 10 μ M (HAE) | >144 |
| MERS | Ribavirin 109.5 μ M Penciclovir 95.96 μ M | > 10 μ M (HAE) | >135 |
| Ebola | Favipiravir 61.9 μ M Hydroxychloroquine 0.77 μ M Chloroquine 1.13-5.47 μ M | 6.1 (Hep-2) | N/A |

Gordon; J Bio Chem 2020.
 Sheahan; Sci Transl Med 2017.
 Agostini; Am Soc Micro 2018.
 Yao; CID 2020.

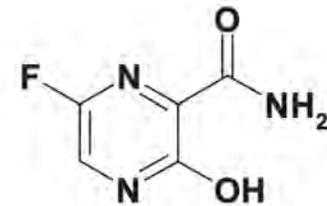
CORONAVIRUSES AND PROOFREADING



Ribavirin

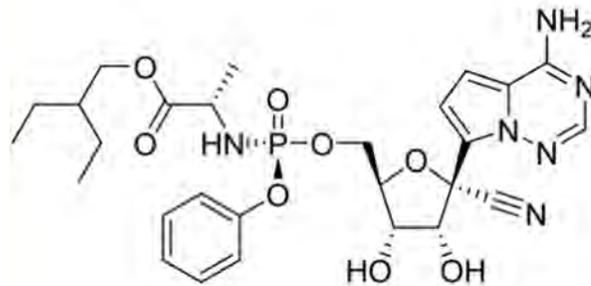


Penciclovir



Favipiravir

Removed by
proofreading



Remdesivir

Maintains activity;
high fitness cost

Agostini; mBio 2018.
Smith; PLoS Pathog 2013.
Wang; Cell Res 2020.
Jordan; AAC 2018.

IN VIVO ANIMAL PROPHYLAXIS

| Virus | Virologic | Clinical/Pathologic | Survival |
|-------------------|-----------|---------------------|----------|
| SARS-CoV-1 | ✓ | ✓ | ✓ |
| MERS | ✓ | ✓ | ✓ * |

*MERS-infected mice showed improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir

IN VIVO ANIMAL TREATMENT

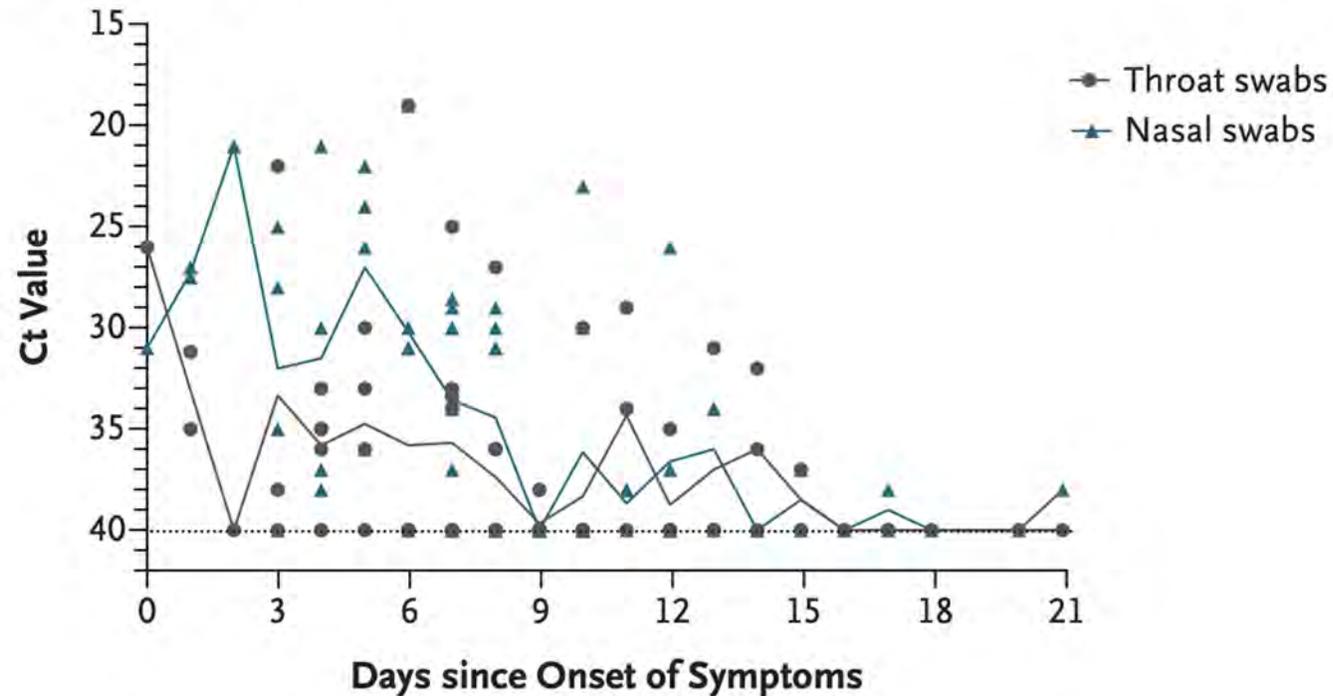
| Virus | Virologic | Clinical/Pathologic | Survival |
|-------------------|-----------|---------------------|--|
| SARS-CoV-1 | ✓ | ✓ | <div style="display: flex; justify-content: space-around;"> ✓ (Day 1) ✗ (Day 2) </div> |
| MERS | ✓ | ✓ | ✗* |
| Ebola | ✓ | ✓ | --- |

*MERS-infected mice did not show improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir; Macaques in Ebola model were euthanized if deemed clinically moribund

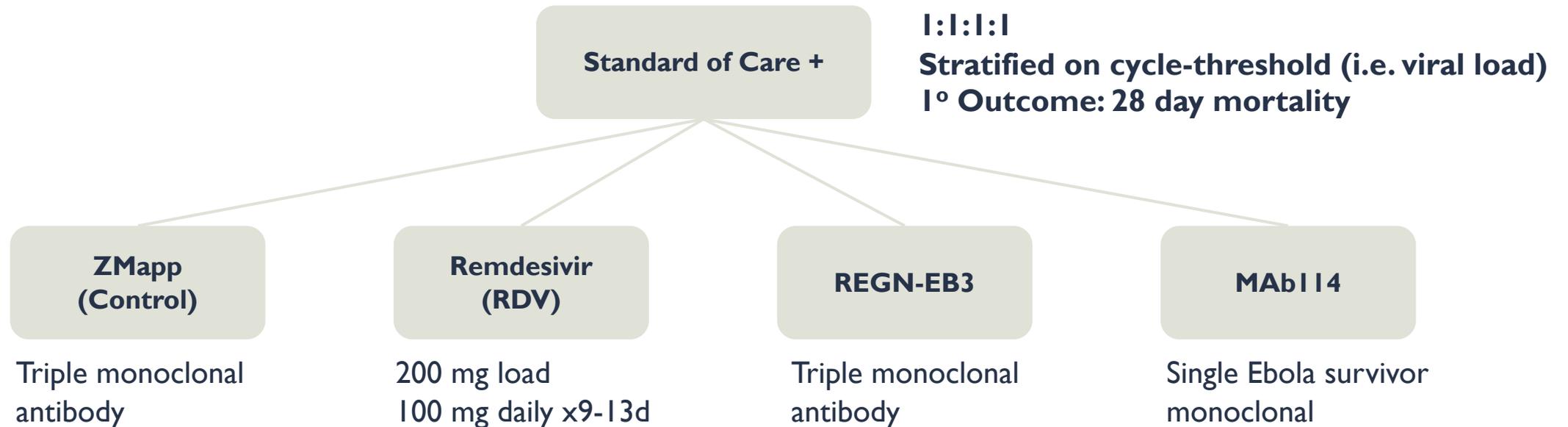
Agostini; mBio 2018.
Smith; PLoS Pathog 2013.
Wang; Cell Res 2020.
Jordan; AAC 2018.

“A drug that inhibits viral replication may be of little use once virus replication has reached its peak...”

C Aggregated Ct Values



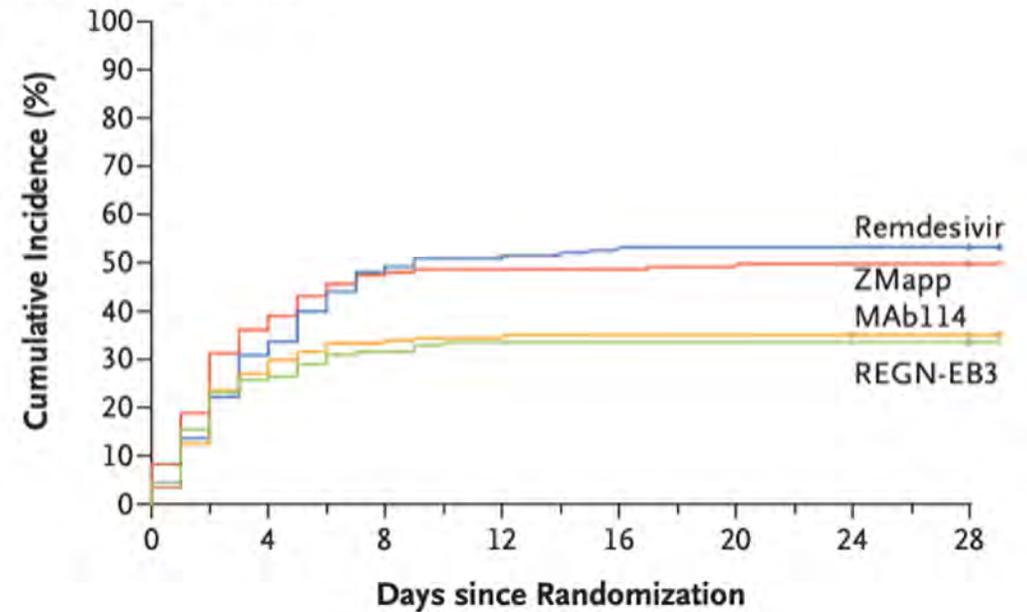
RANDOMIZED, CONTROLLED EBOLA TRIAL



RANDOMIZED, CONTROLLED EBOLA TRIAL

- Similar duration of symptoms (~5.5 days)/viral load
 - Per day OR 1.12 (1.00-1.24)
- Baseline characteristics generally well matched
 - Higher SCr/LFTs in ZMapp/RDV (sicker?)
- ZMapp and RDV arms halted; mortality signal

A Incidence of Death, Overall

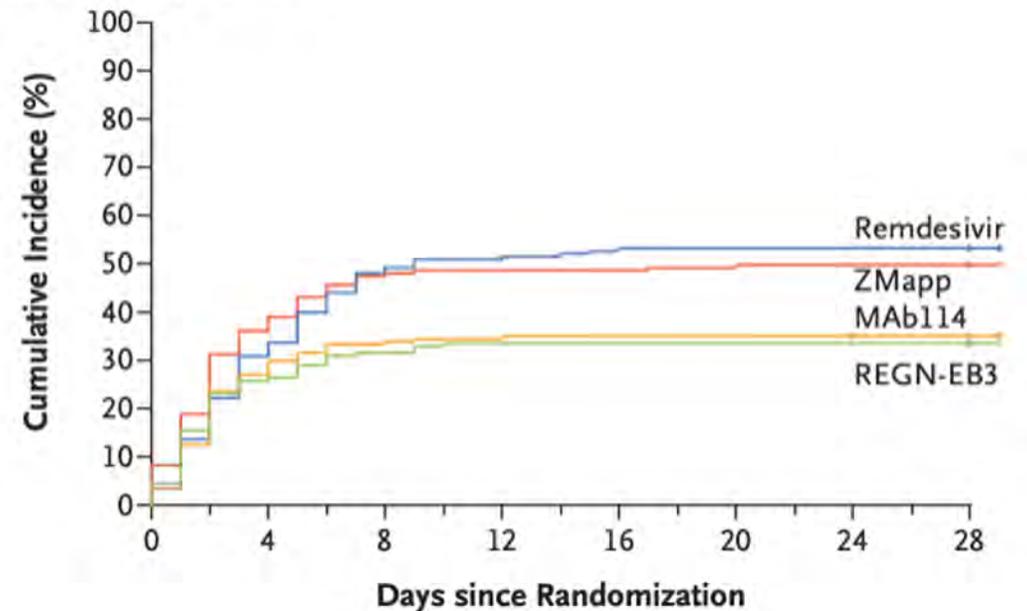


RANDOMIZED, CONTROLLED EBOLA TRIAL

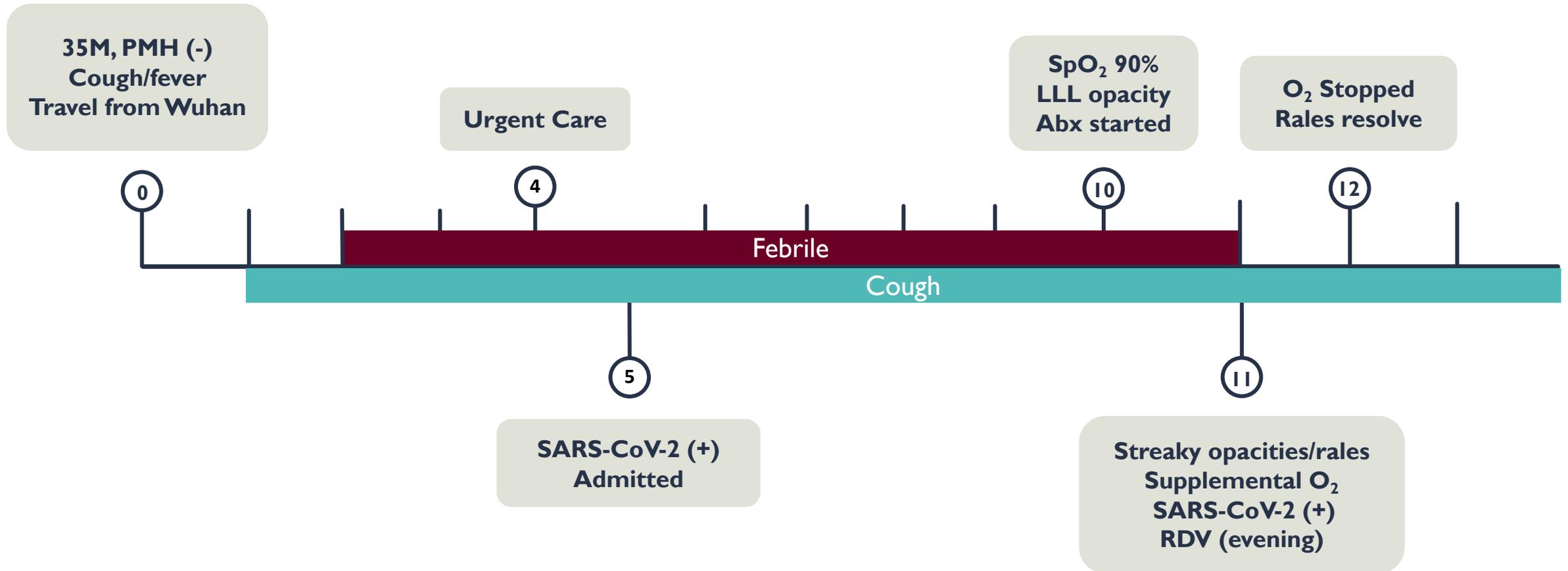
- Similar duration of symptoms (~5.5 days)/viral load
 - Per day OR 1.12 (1.00-1.24)
- Baseline characteristics generally well matched
 - Higher SCr/LFTs in ZMapp/RDV (sicker?)
- ZMapp and RDV arms halted; mortality signal

Started too late? (latest start day 3)
Flaw in animal model?
Standard of care/resources?

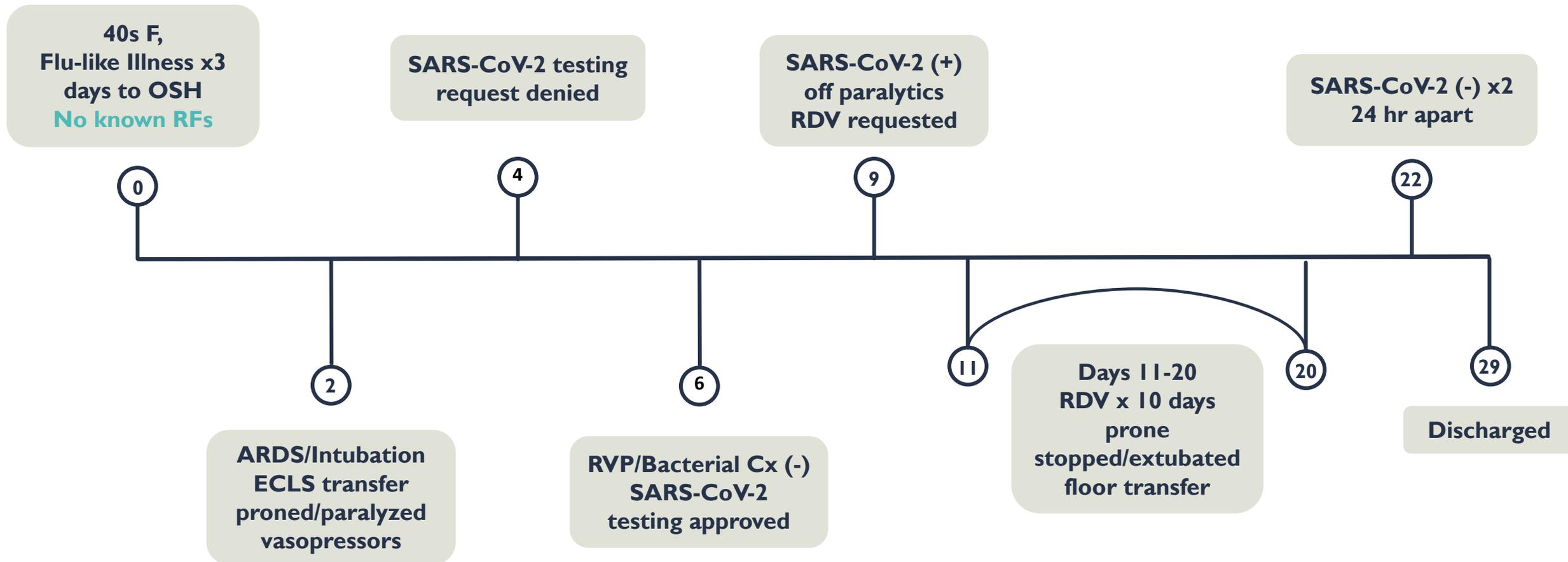
A Incidence of Death, Overall



FIRST U.S. COVID-19 CASE REPORT



FIRST U.S. COMMUNITY TRANSMITTED CASE REPORT



Sanville; CID 2020.

ARDS = Acute respiratory distress syndrome; ECLS = extracorporeal life support; RVP = Respiratory viral panel

CONCLUDING REMARKS

- Current data insufficient to draw definitive conclusions
- Seemingly well tolerated in published COVID-19 cases
- Clinical trials and compassionate use ongoing

“[...] scientists are **patiently waiting** for the final results of these ongoing trials.”

CURRENT INVESTIGATIONS

| Trial | Sponsor | Population | Intervention | Renal | Completion* |
|----------------------|---------|---------------------------------|---------------------------|------------------|-------------|
| Adaptive | NIAID | n = 440 | RDV vs. PCB; Adaptive | eGFR < 50 mL/min | 4/1/2023 |
| Moderate | Gilead | SpO ₂ ≥ 94%; n = 600 | 5 vs. 10 days RDV vs. SOC | CrCl < 50 mL/min | 5/2020 |
| Severe* | Gilead | SpO ₂ < 94%; n = 400 | 5 vs. 10 days RDV | CrCl < 50 mL/min | 5/2020 |
| Expanded | USAMR | U.S. DoD-Affiliates; All age | RDV | eGFR < 30 mL/min | -- |
| Mild/Mod (Ch) | CMU | SpO ₂ > 94%; n = 308 | RDV vs. PCB | eGFR < 30 mL/min | 4/27/2020 |
| Severe (Ch) | CMU | SpO ₂ < 94%; n = 453 | RDV vs. PCB | eGFR < 30 mL/min | 5/1/2020 |

RDV = remdesivir; PCB = placebo; USAMR = U.S. Army Medical R&D Command; CMU = Capital Medical University, Beijing

*All data current as of 3/31/2020, subject to change

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THANK YOU

PLEASE REACH OUT WITH ANY QUESTIONS

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UPDATES FROM THE FRONT LINE



Davide Lonati, MD, FEAPCCT

- EAPCCT General Secretary
- Poison Control Centre and National Toxicology Information Centre, Toxicology Unit
- IRCCS Maugeri Hospital and University of Pavia (Italy)

Alex Manini, MD, MS, FACMT, FAACT

- Professor
- Division of Medical Toxicology, Department of Emergency Medicine
- The Icahn School of Medicine at Mount Sinai
Elmhurst Hospital Center



Cameron Kyle-Sidell, MD

- Lead Intensivist, ICU-X
- Critical Care Medicine, Maimonides Medical Center

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Q&A

ON-DEMAND RESOURCES

- All webinars are recorded and posted to the ACMT website
- PDFs of webinar slides are also available on the website
- Questions? Email: info@acmt.net

www.acmt.net/COVID-19_Webinars

NEXT WEBINAR



Topic To Be Announced on Monday 4/6



Wednesday, April 8, 2020
@ 3:00 PM EDT