COVID-19
ONLINE EDUCATIONAL PROGRAM

Update on Therapeutics for COVID-19

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academic medical education

Disclosures

- **The speaker is a consultant to and has received honoraria and/or research support from the following companies:**
  - Atea
  - Gilead
  - GlaxoSmithKline
  - Merck
  - Novartis
  - ViiV

Outline

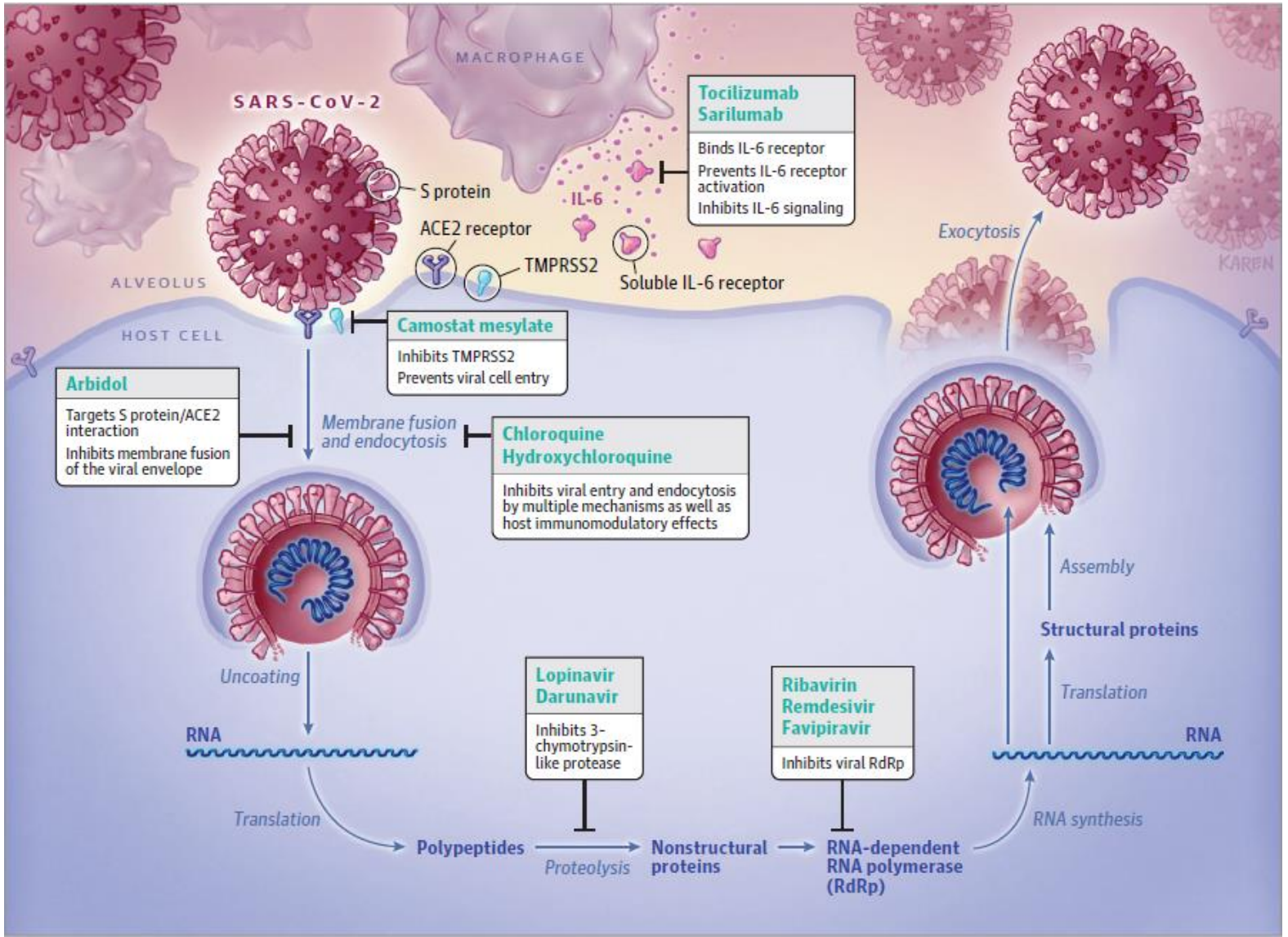
- Potential therapeutic interventions for COVID-19
- Antivirals
- Immune response modifiers
- Renin-angiotensin-aldosterone system inhibitors
- Convalescent serum
- Challenges in conducting drug trials for viral respiratory infections

Treatment options for COVID-19

- **Antiviral drugs**
- **Anti-inflammatory drugs**
- **ACE inhibitors and angiotensin receptor blockers**
- **Convalescent serum**

Antiviral Therapeutics

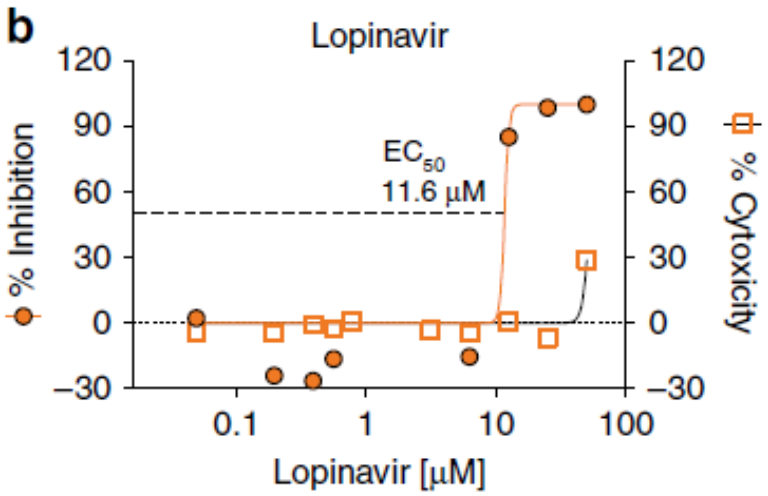
SARS-CoV-2 lifecycle and points of inhibition

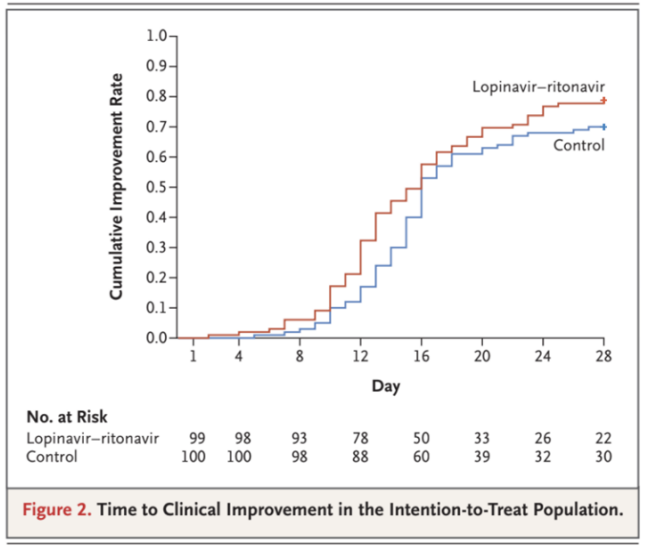


Sanders et al JAMA 2020

Lopinavir/ritonavir

- **Inhibit SARS-CoV-2 cysteine proteases?**
- **Modest evidence of in vitro activity[1]**
- **Retrospective case-control series suggest benefit in SARS[2,3]**
- **RCT in patients with severe COVID-19 showed no clinical benefit[4]**
  - Possible benefit if started early in disease (prior to day 12)?



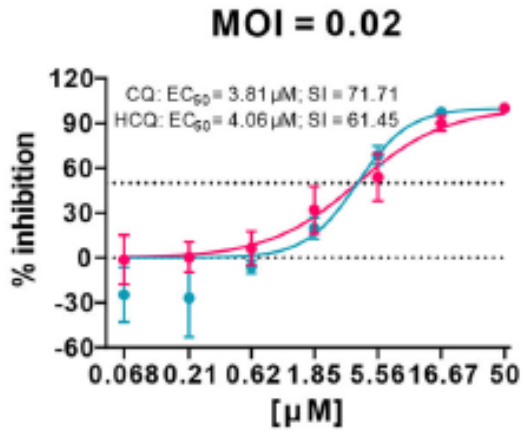


1. Sheahan TP et al Nat Commun 2020
2. Chu CM et al Thorax 2004
3. Chan KS et al Hong Kong Med J 2003
4. Cao B et al N Engl J Med 2020

Hydroxychloroquine

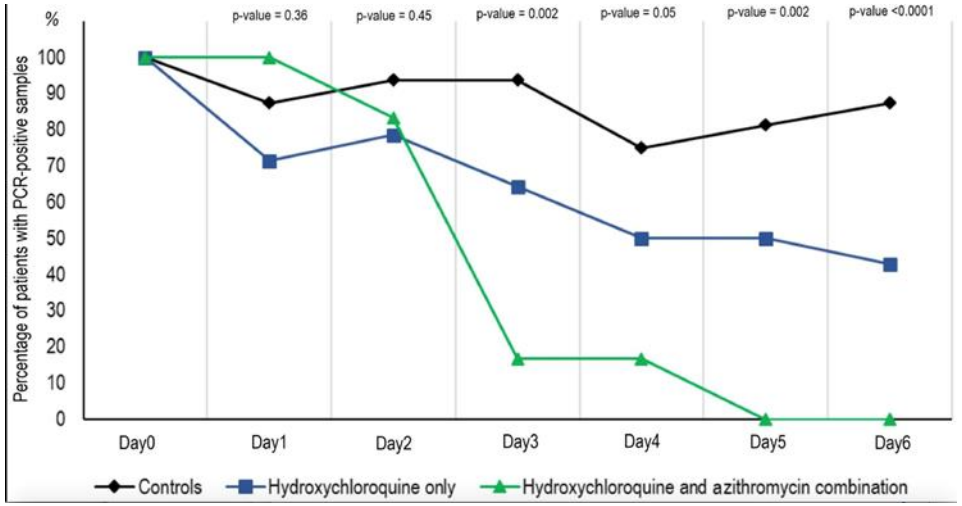
- **Two potential modes of action**
  - Antiviral (inhibits acidification of endosomal vesicles)
  - Anti-inflammatory

- **In vitro evidence for antiviral activity[1]**



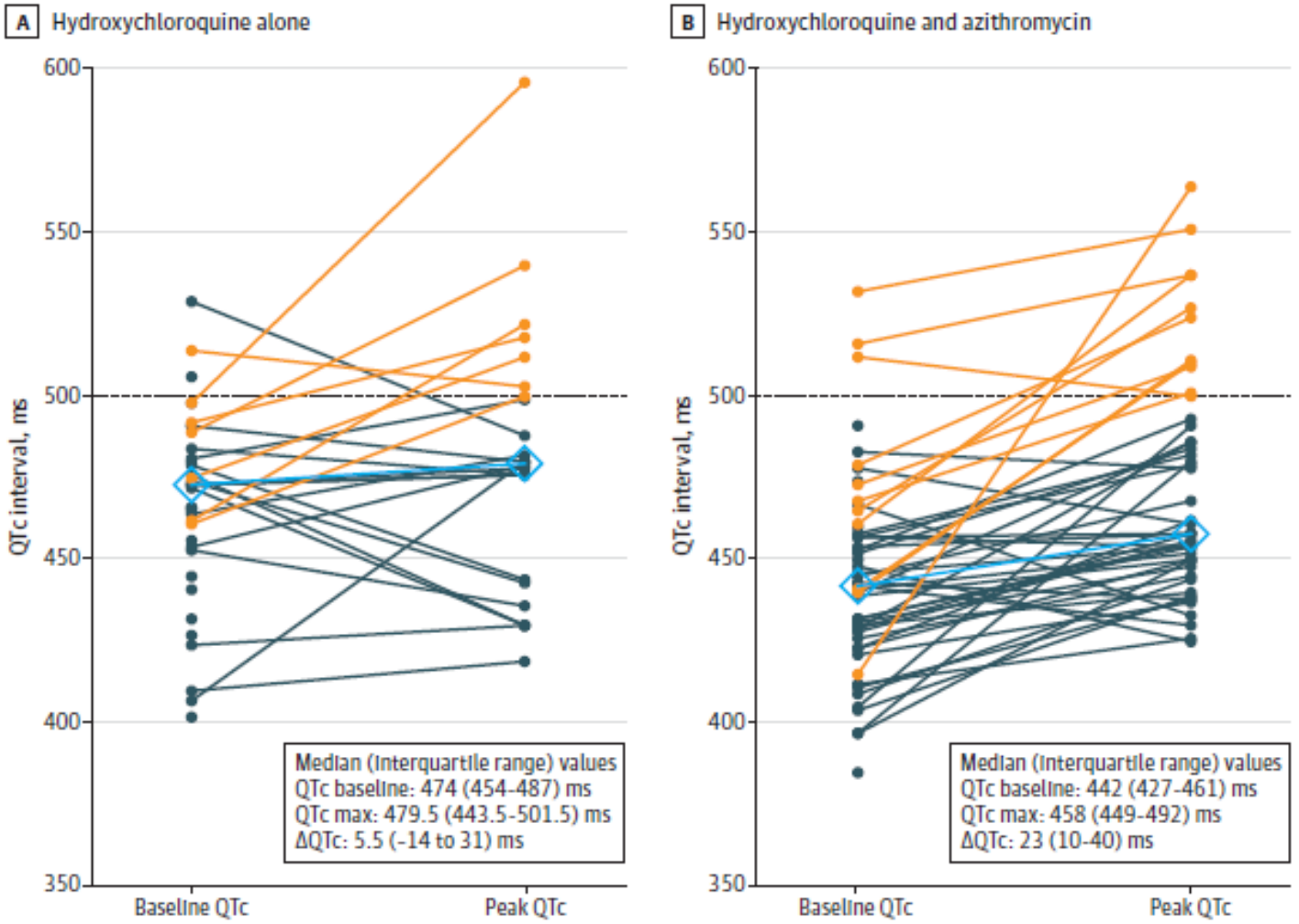
- **Mixed results from small clinical trials[2,3,4]**

- **One trial suggests faster reduction of SARS-CoV-2 shedding from oropharynx[4]**



1. Liu J et al Cell Discovery 2020
2. Cortegiani A et al J Crit Care 2020
3. Chen Z et al medRxiv 2020
4. Gautret P et al Int J Antimicrob Agents 2020
5. Molina JM et al Med Mal Infect 2020

QTc prolongation with HCQ ± azithromycin



Mercuro NJ et al JAMA Cardiol 2020

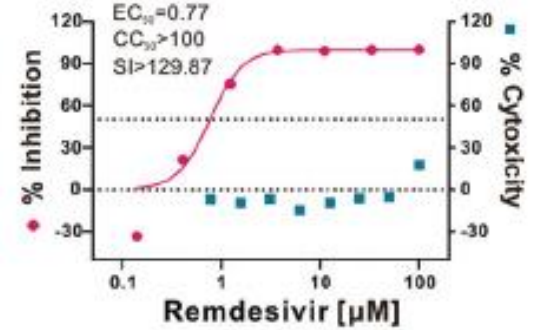
Outcomes of open-label HCQ use in VA hospitals

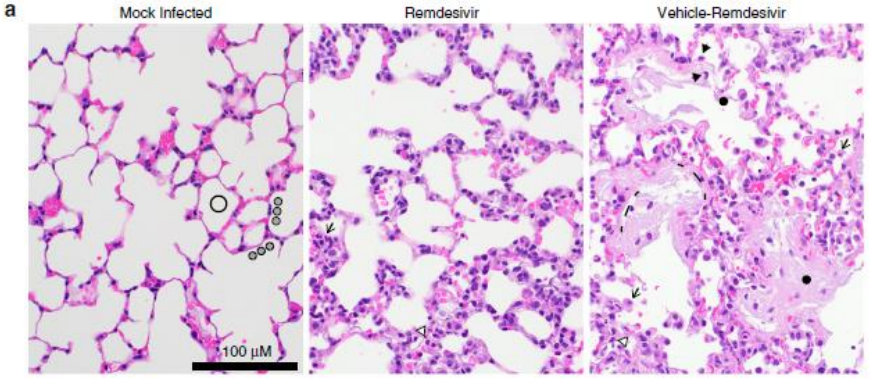
Outcome	HC N=97	HC+AZ N=113	No HC N=158	P value
Death – no. (%)	27 (27.8)	25 (22.1)	18 (11.4)	0.003
Discharge – no. (%)	70 (72.2)	88 (77.9)	140 (88.6)	

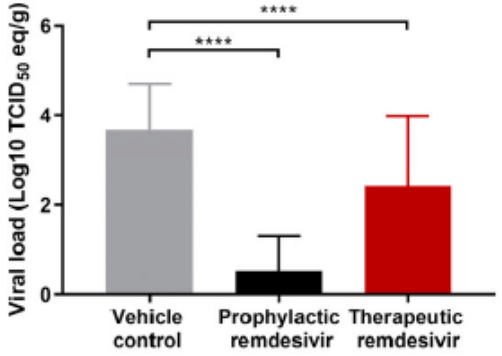
HC=hydroxychloroquine; AZ=azithromycin

Remdesivir

- **RNA polymerase inhibitor with in vitro activity against Ebola, SARS, MERS and SARS-CoV-2[1,2]**
- **Inferior to bNAbs against Ebola[3]**
- **Effective against MERS in murine and NHP models[1,4]**
- **Numerous ongoing RCT in moderate and severe COVID-19**

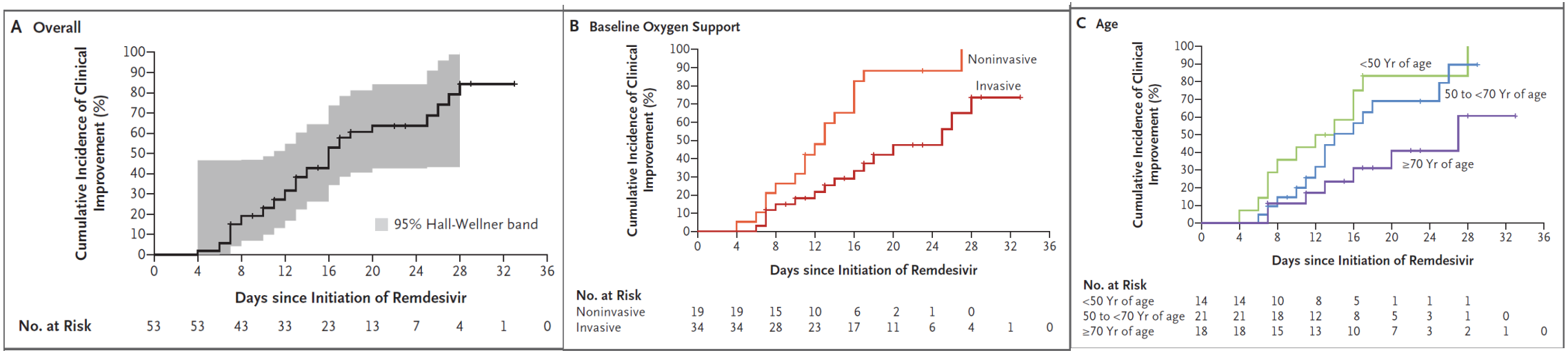






1. Sheahan TP et al Nat Commun 2020
2. Wang M et al Cell Res 2020
3. Mulangu S et al N Engl J Med 2019
4. de Witt E et al Proc Nat Acad Sci USA 2020

Open-label experience with remdesivir in patients with severe COVID-19



Grein J et al N Engl J Med 2020

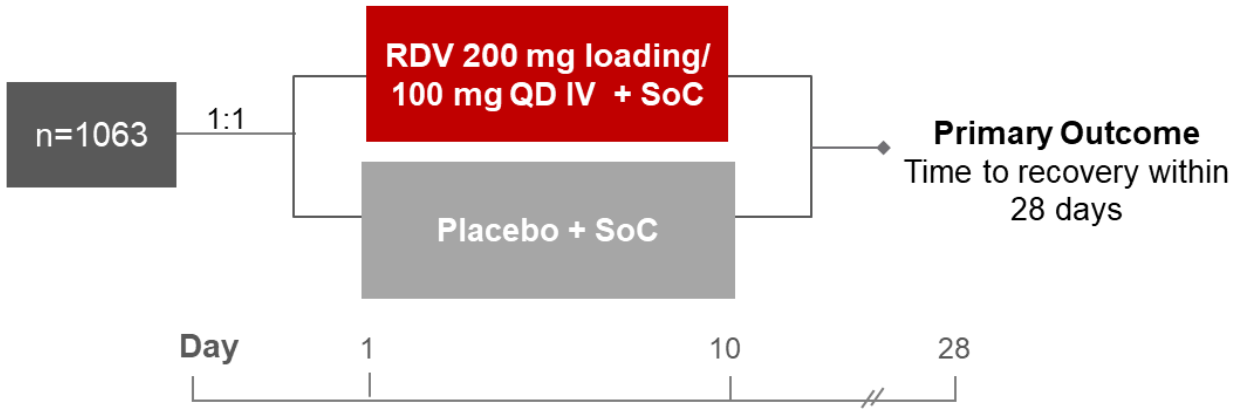
Remdesivir clinical trials

- **Compassionate use protocol (US)**
  - SaO_2 ≤94% on room air or requirement for supplemental O_2
- **ACTT-1 study: RDV vs placebo**
  - SaO_2 ≤94% or requirement for supplemental O_2 or mechanical ventilation and pulmonary infiltrates; N=
- **Severe disease (China): RDV vs placebo**
  - SaO_2 ≤94% and pulmonary infiltrates; N=237
- **SIMPLE study (Severe): RDV 5 vs 10 days**
  - SaO_2 ≤94% or requirement for supplemental O_2; if intubated, <5 days
- **SIMPLE study (Moderate): RDV 5 vs 10 days vs placebo**
  - SaO_2 ≥94% and pulmonary infiltrates

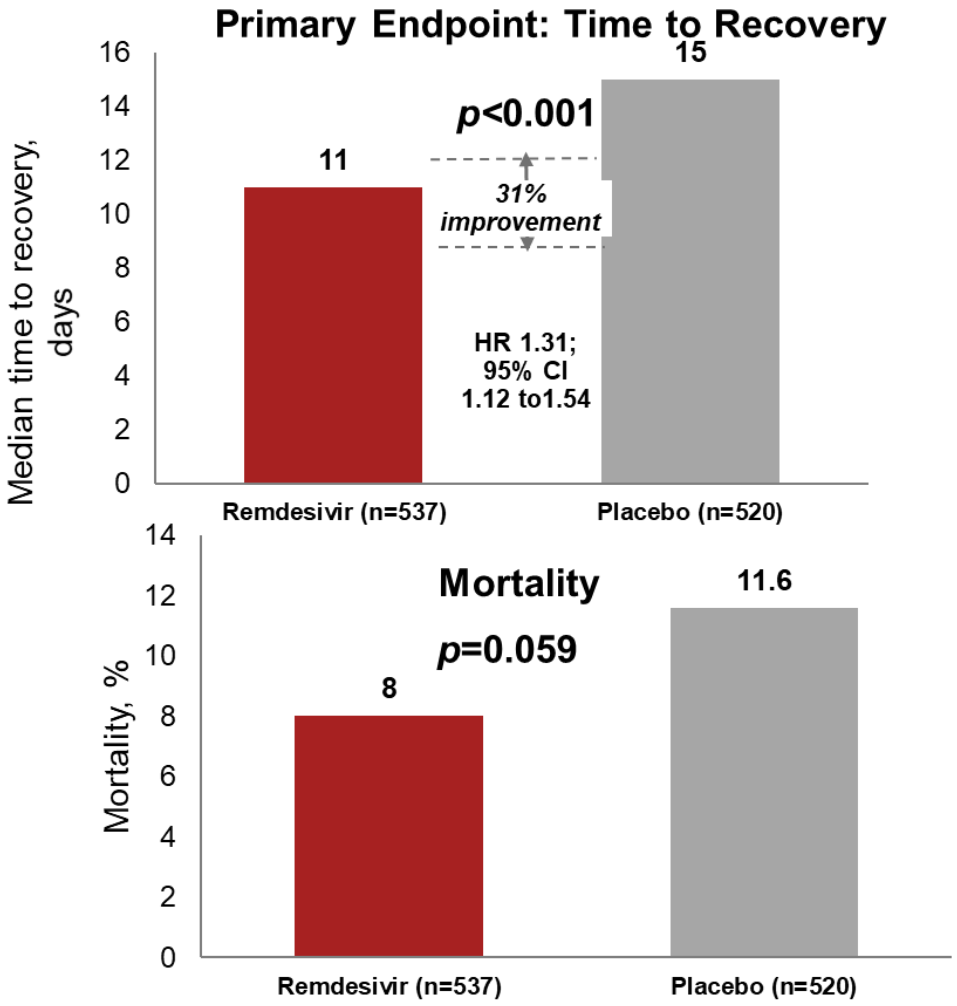
ACTT-1 Study

NIAID ACTT-1 Study Design

A randomized, double-blind, placebo-controlled, multicenter global trial in hospitalized adult patients with COVID-19



Preliminary analysis of primary endpoint after 606 recoveries were attained

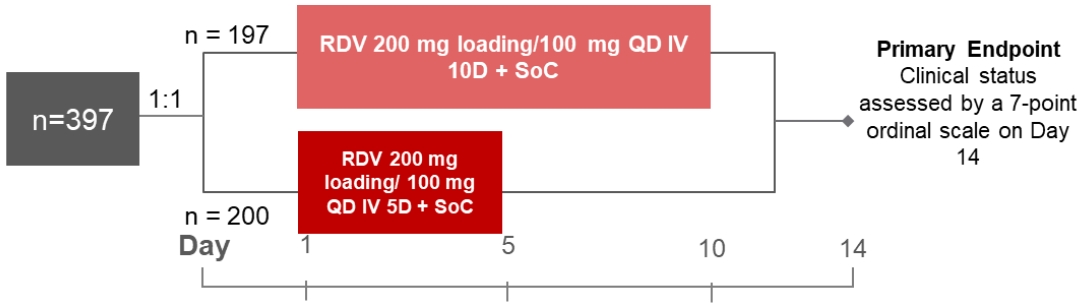


Source: Gilead Sciences

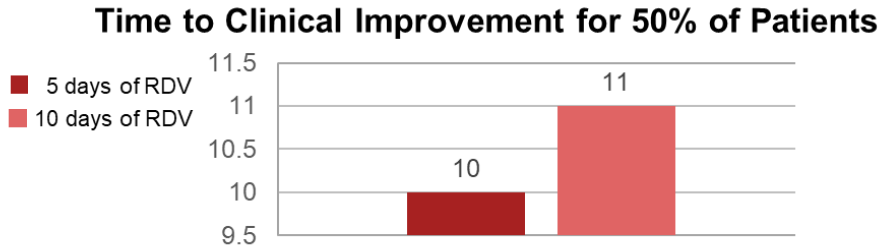
Remdesevir “severe” trial: GS-US-540-5773

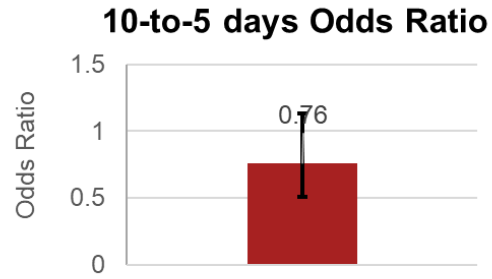
Study GS- US 540-5774

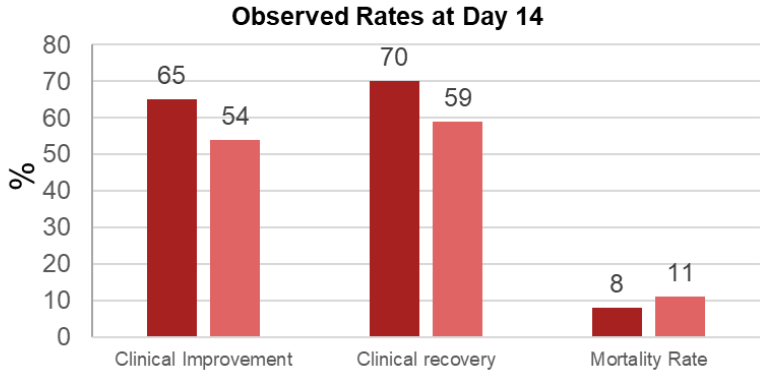
Randomized, open-label, multicenter trial



Clinical improvement was defined as an improvement of two or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death. Patients achieved clinical recovery if they no longer required oxygen support or were discharged from the hospital.



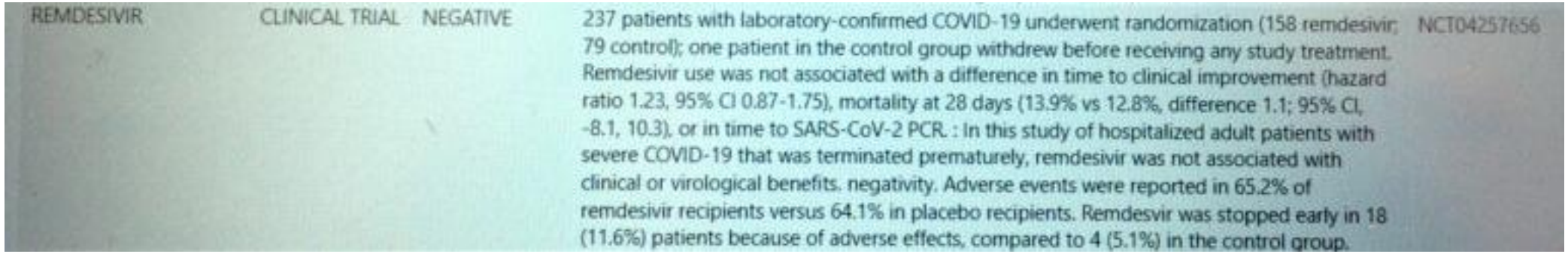




Source: Gilead Sciences

China study of remdesivir

- **RCT of remdesivir vs placebo in severe disease**
  - SaO_2 ≤94% and pulmonary infiltrates
  - Study terminated for futility due to under-enrollment
- **Top-line results unintentionally leaked by WHO**



- **HR for time to clinical improvement 1.23 (95% CI, 0.87-1.75)**
- **28-day mortality 13.9% vs 12.8% (delta 1.1%; 95% CI, -8.1, 10.3)**
- **Remdesivir stopped early for AEs in 11.6% vs 5.1% in placebo**

Source: STAT

Remdesivir EUA

Remdesivir (GS-5734™) is authorized for use under an EUA only for the treatment of patients with suspected or laboratory-confirmed SARS-CoV-2 infection and severe COVID-19. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen, mechanical ventilation, and/or extracorporeal membrane oxygenation (ECMO). Remdesivir is authorized for adult or pediatric patients who are admitted to a hospital and for whom use of an IV agent is clinically appropriate. Remdesivir must be administered intravenously.

Distribution of the authorized remdesivir will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Gilead will supply remdesivir to authorized distributors, or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed.

Remdesivir EUA terms

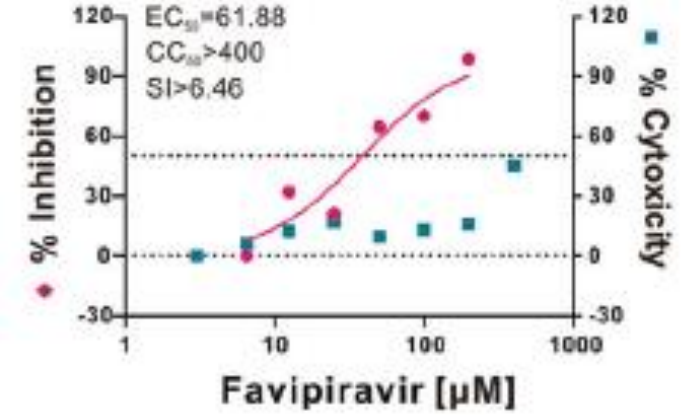
• The suggested dose for adults and pediatric patients weighing ≥40 kg requiring invasive mechanical ventilation and/or ECMO is a single loading dose of 200 mg infused intravenously over 30 to 120 minutes on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously over 30 to 120 minutes for 9 days (days 2 through 10).

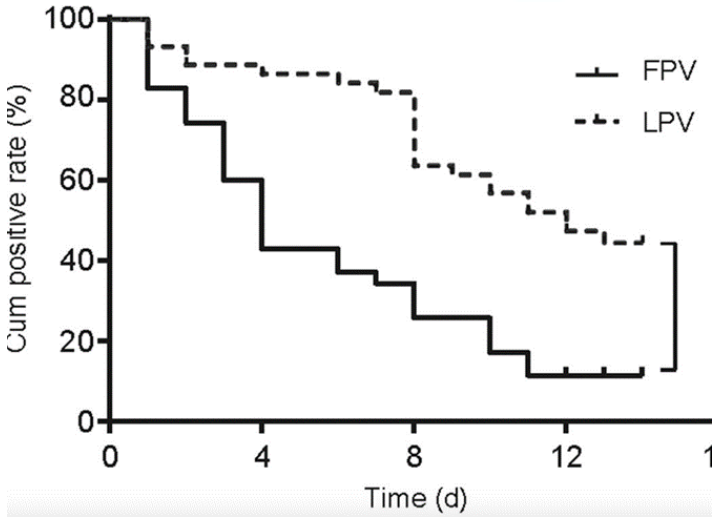
• The suggested dose for adults and pediatric patients weighing ≥40 kg not requiring invasive mechanical ventilation and/or ECMO is a single dose of 200 mg infused intravenously over 30 to 120 minutes on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously over 30 to 120 minutes for 4 days (days 2 through 5). If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).

- Can administer empirically while awaiting SARS-CoV-2 test results
- Must provide patient and/or caregiver information consistent with the “Fact Sheet for Patients and Parents/Caregivers” prior to the patient receiving remdesivir.
- Must obtain eGFR at baseline
- Should monitor LFTs
- Not recommended for patients with eGFR <30 mL/min
- Must collect and report SAEs and dosing errors

Favipiravir

- “Broad spectrum” viral RNA polymerase inhibitor
- Approved for use against influenza in Japan
- Active in vitro against SARS-CoV-2[1]
- Non-randomized pilot study showed faster clearance of SARS-CoV-2 vs LPV/RTV[2]
- Several trials planned or underway

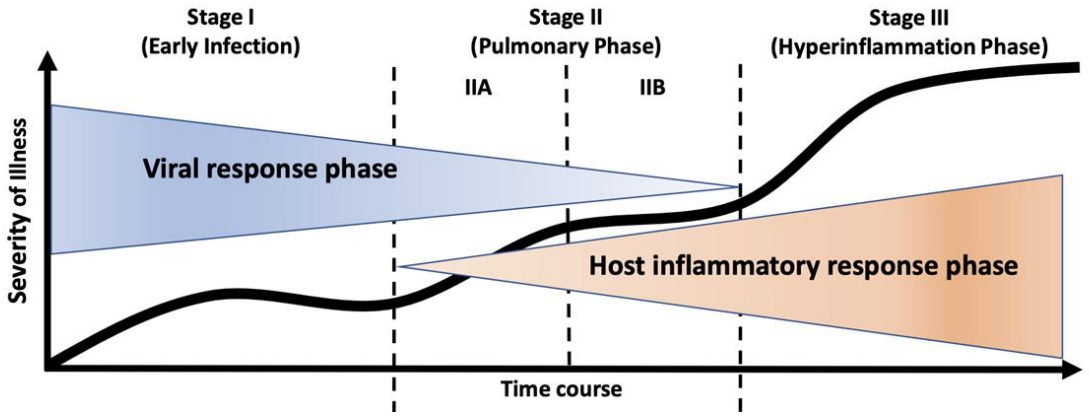


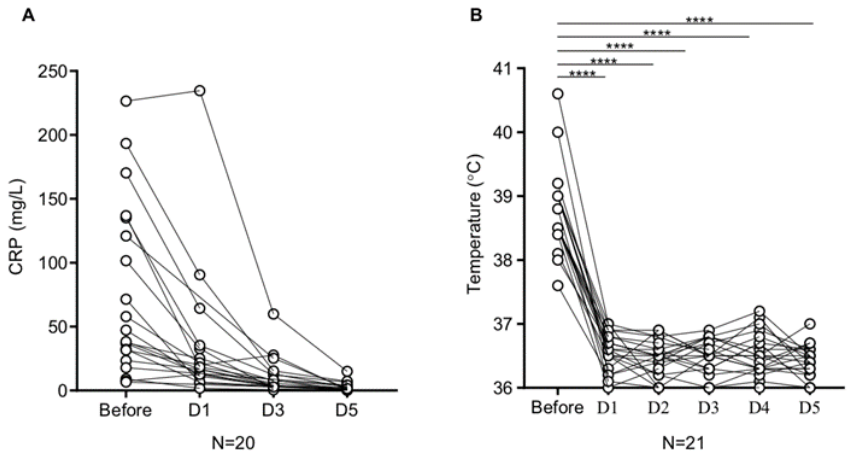


1. Wang M et al Cell Res 2020
2. Cai Q et al Bioengineering 2020

Anti-inflammatory drugs

Immune response modifiers





- **Second phase of COVID-19 characterized by immune activation, “cytokine storm” and high levels of IL-6**
- **mAbs that block the IL-6/IL-6R access may be effective in preventing/moderating immune-mediated lung injury**
- **Pilot study of tocilizumab showed decrease in CRP, fever**

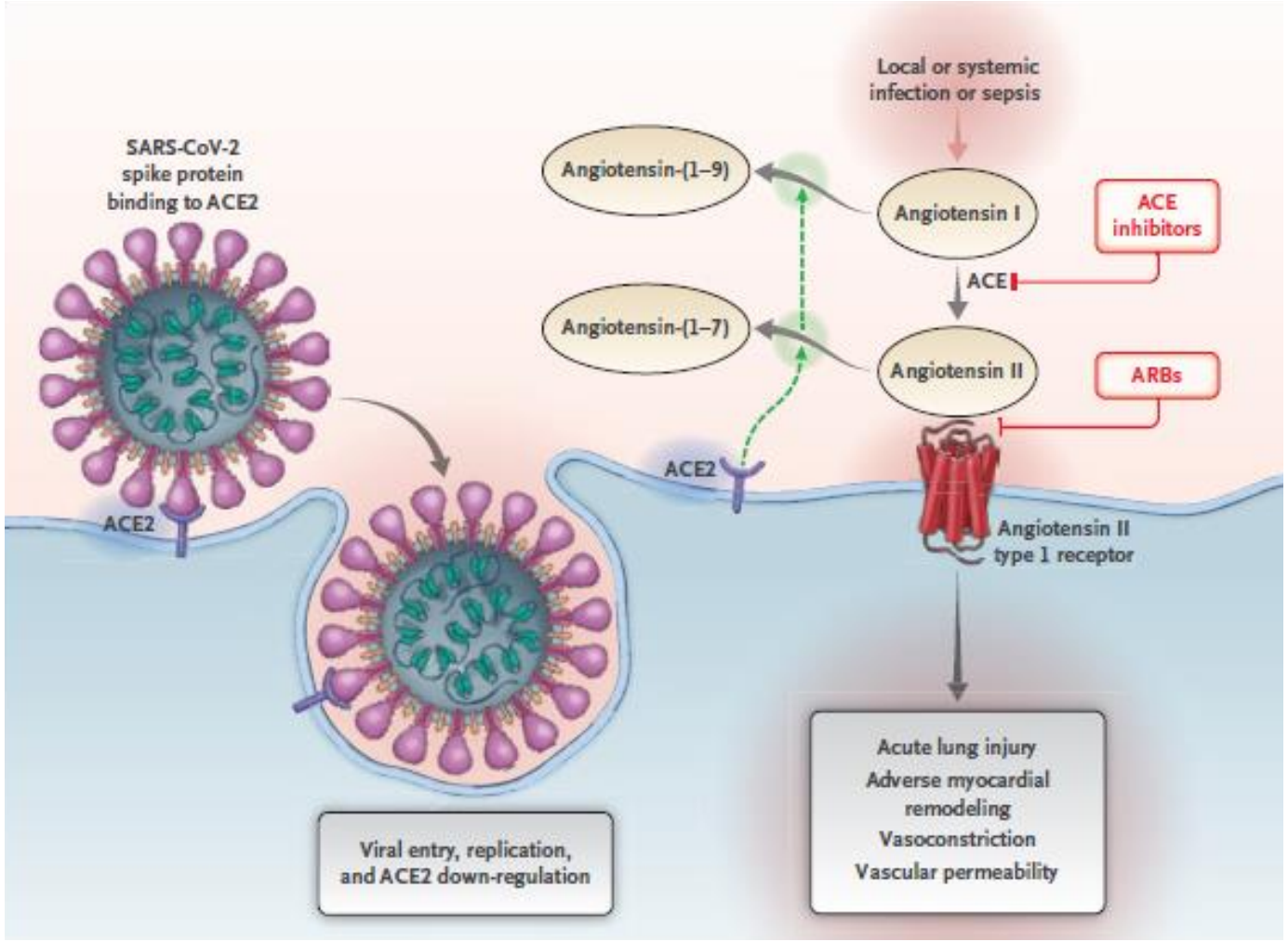
Siddiqi HK J Heart Lung Transplant 2020
Xu 2020 chinaXiv:202003.00026v1

Ongoing or planned trials of immunomodulators for COVID-19

- Tocilizumab
- Sarilumab
- Clazakizumab
- Canakinumab
- Ibrutinib
- Ruxolitinib
- Others…

Renin-angiotensin-aldostserone system

Renin-angiotensin-aldosterone system inhibitors



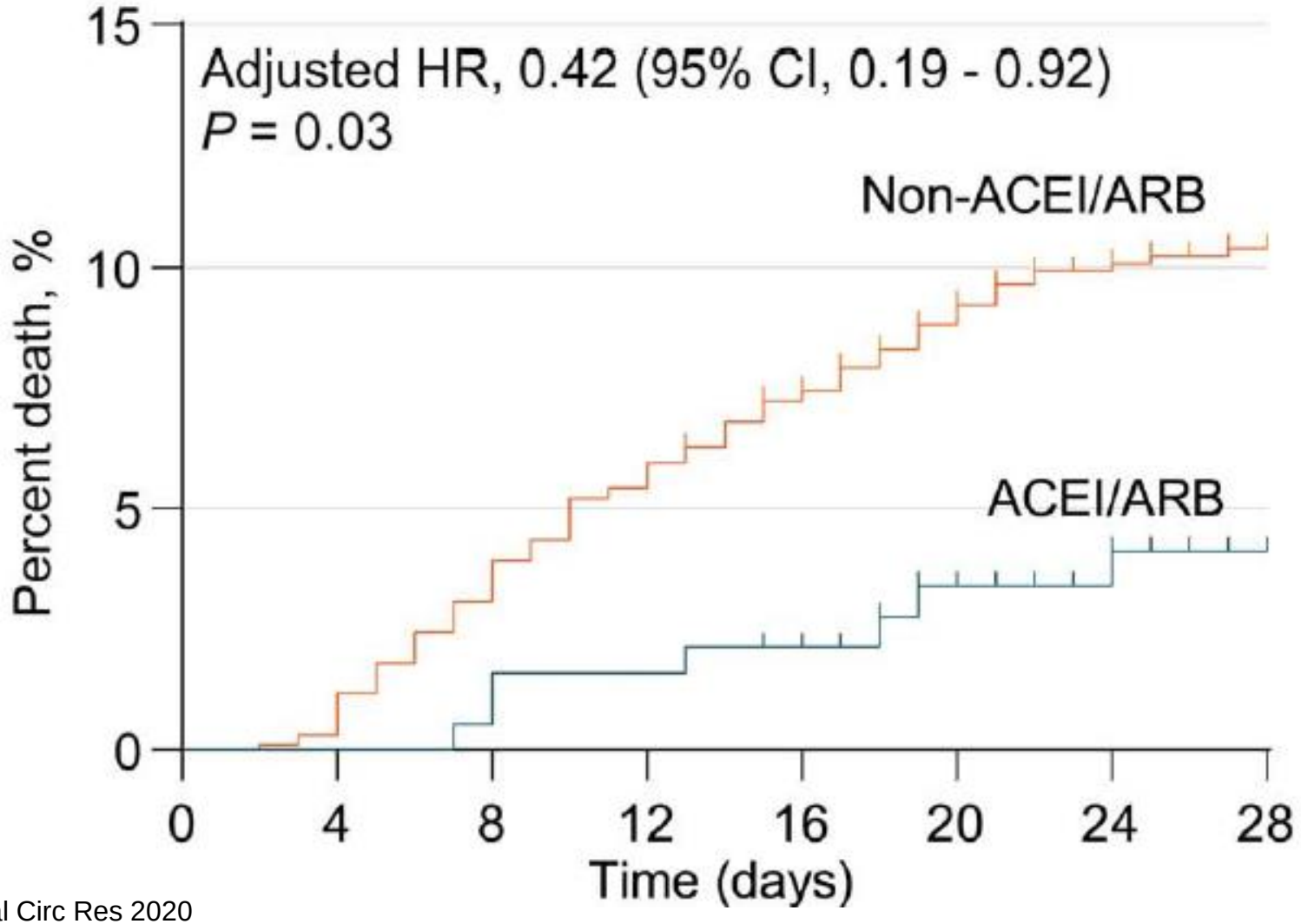
Vaduganathan M et al N Engl J Med 2020

RAAS inhibitors

- **Angiotensin-converting enzyme and angiotensin II receptor blockers increase levels of ACE2**
  - Might potentiate SARS-CoV-2 entry
- **SARS-CoV-2 infection down-regulates ACE2 expression**
- **Could result in unopposed angiotensin II accumulation and RAAS activation**
- **RAAS blockade limits lung injury in mice due to exposure to SARS-CoV-1 spike protein**
- **Net benefit/harm of ACE inhibitors and ARBs in setting of COVID-19 is unknown at present**

Vaduganathan M et al N Engl J Med 2020

Effect of RAAS inhibitors on clinical outcomes in hypertensive patients with COVID-19

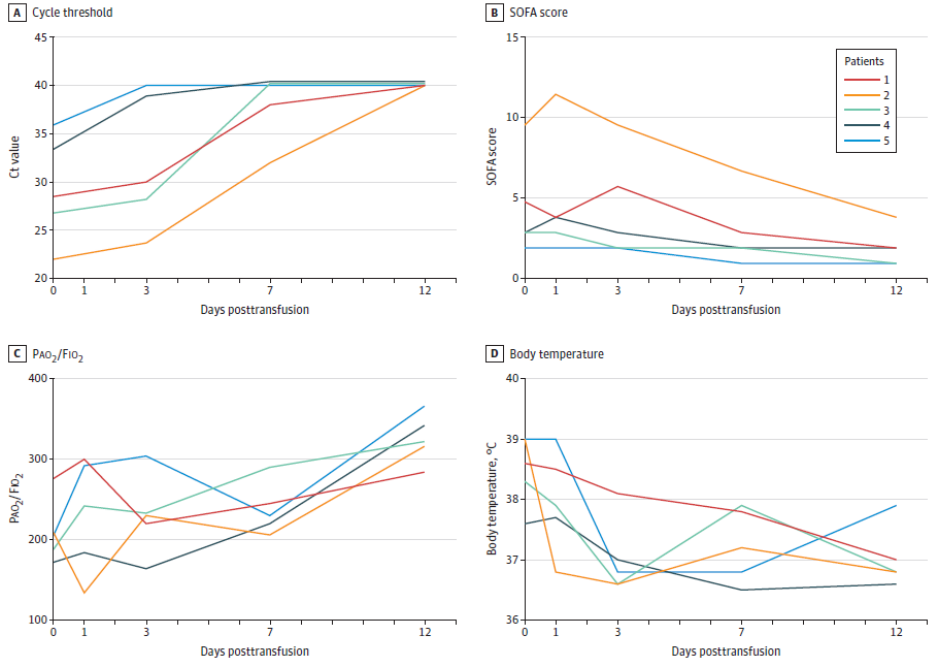


Zhang P et al Circ Res 2020

Convalescent serum

Convalescent serum

- **Convalescent serum from survivors of COVID-19 infection may contain high titers of neutralizing Ab**
- **Convalescent serum has shown some benefit in treatment of avian (H1N5) and H1N1 influenza and MERS**
- **Uncontrolled pilot study (N=5) suggested possible benefit in patients with COVID-19**
  - 4 of 5 weaned from ventilator
- **Theoretical concerns regarding enhancing antibodies**
- **Clinical trials planned/underway**



Shen C et al JAMA 2020

Challenges in conducting trials of therapeutics for respiratory viral pathogens

- Studies in influenza have shown maximal benefit when drug is started within first few days after symptom onset
- Accelerated viral clearance from respiratory secretions may not correlate with faster clinical improvement
- Immune-mediated lung injury unlikely to be modified by antivirals
- Availability of several candidates as approved drugs available by prescription complicates conduct of controlled trials
- Combinations of antiviral and anti-inflammatory drugs may be required for maximal benefit

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