



COVID-19 therapeutics update

- Ivermectin
- Remdesivir

July 27th, 2021

Reviewing studies

Individual Studies

- Who was included
- How were patients allocated to treatment
 - Random vs. Non-random
 - Confounding factors
- Do the results match the methods
 - Look for cherrypicking

Meta-Analysis

- How were the studies identified
- Were treatments comparable
- Did they define outcomes the same way
- Patient groups comparable



Ivermectin

- What: anti-parasitic (strongyloides, scabies)
- *In vitro*: antiviral (dengue, SARS-CoV2)
 - at concentrations >50-fold the anti-parasitic effect
- Pros: Older drug, available, \$



New (old) data on Ivermectin

Open Forum Infectious Diseases

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Article Contents

[Abstract](#)[Supplementary data](#)[Comments \(2\)](#)

ACCEPTED MANUSCRIPT

Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection

Andrew Hill , Anna Garratt, Jacob Levi, Jonathan Falconer, Leah Ellis, Kaitlyn McCann, Victoria Pilkington, Ambar Qavi, Junzheng Wang, Hannah Wentzel

Open Forum Infectious Diseases, ofab358, <https://doi.org/10.1093/ofid/ofab358>

Published: 06 July 2021 **Article history ▼**



New (old) data on Ivermectin

- N = 24 RCTs with 3328 participants

8
Published
studies

9
Pre-prints
(i.e. not peer
reviewed)

1
Trial
regis-
try

6
Unpublished
results

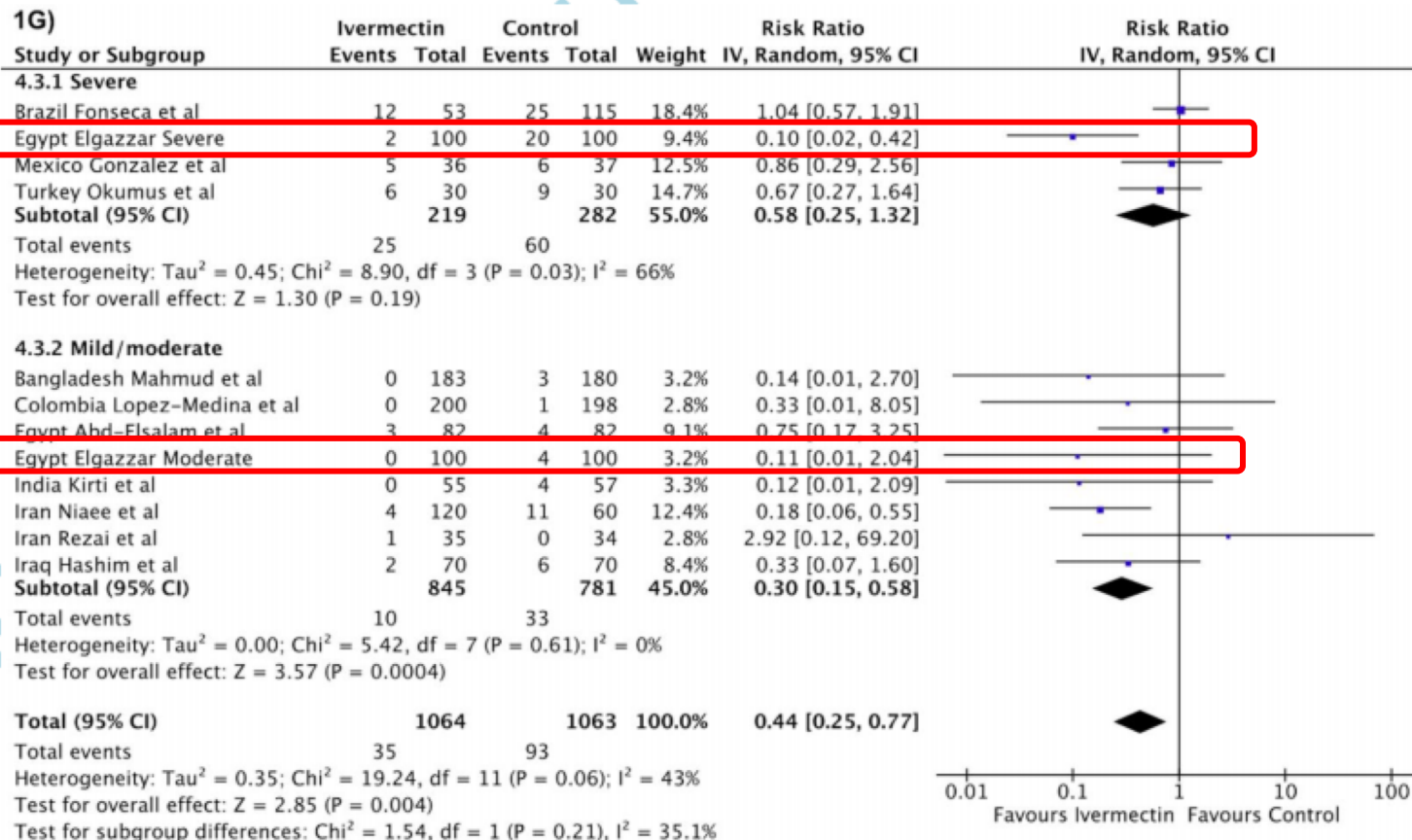
- Primary Outcome: All-cause mortality from randomization to end of follow-up
 - Excluding pts hospitalized within 12h of randomization



Outcomes

Mortality: 35/1064 (3%) vs. 93/1063 (8.7%)

Figure 1G



Study Design and Limitations

- 9/24 studies rated as low-risk of bias
- 10/24 placebo-controlled
- Range of doses (0.1 mg/kg - 24 mg) for 1 dose – 1 week
- 3 studies used doxycycline + ivermectin

Perhaps most puzzling is the degree and extent of benefit identified – across disease stages, dosing regimens, and viral and clinical outcomes- which strains belief, particularly for a disease that has been characterized by narrow therapeutic window for most other interventions.



Article Contents

Abstract

Supplementary data

Comments (0)

ACCEPTED MANUSCRIPT

Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials FREE

Yuani M Roman, MD, MPH, Paula Alejandra Burela, BSc,
Vinay Pasupuleti, MD, PhD, Alejandro Piscoya, MD, Jose E Vidal, MD, PhD,
Adrian V Hernandez, MD, PhD 

Clinical Infectious Diseases, ciab591, <https://doi.org/10.1093/cid/ciab591>

Published: 28 June 2021 **Article history ▼**

-Included RCTs reporting
benefit or harm outcomes
for treatment of COVID-19
Excluded studies utilizing
IVM for ppx

Primary outcome: all-cause
mortality, length of
hospital stay and AE

256 citations found plus 9
pre-prints identified
published until 3/2021

12 full text articles
included



Reviewing studies

Individual Studies

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 - Random vs. Non-random
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- Do the results match the methods
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Meta-Analysis

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- Were treatments comparable
- Did they define outcomes the same way
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Visual summary of recommendation



Population

This recommendation applies only to people with these characteristics:



Patients with confirmed covid-19

Disease severity

Non-severe

Absence of signs of severe or critical disease

Severe

SpO₂<90% on room air

Respiratory rate >30 in adults

Raised respiratory rate in children

Signs of severe respiratory distress

Critical

Requires life sustaining treatment

Acute respiratory distress syndrome

Sepsis

Septic shock



Interventions

IL-6 receptor blockers

Interleukin-6 receptor blockers



Recommendation in favour (strong)

Ivermectin



Recommendation against (except in clinical trials)

Hydroxychloroquine



Recommendation against (strong)

Lopinavir-ritonavir



Recommendation against (strong)

Remdesivir



Recommendation against (weak)

Corticosteroids



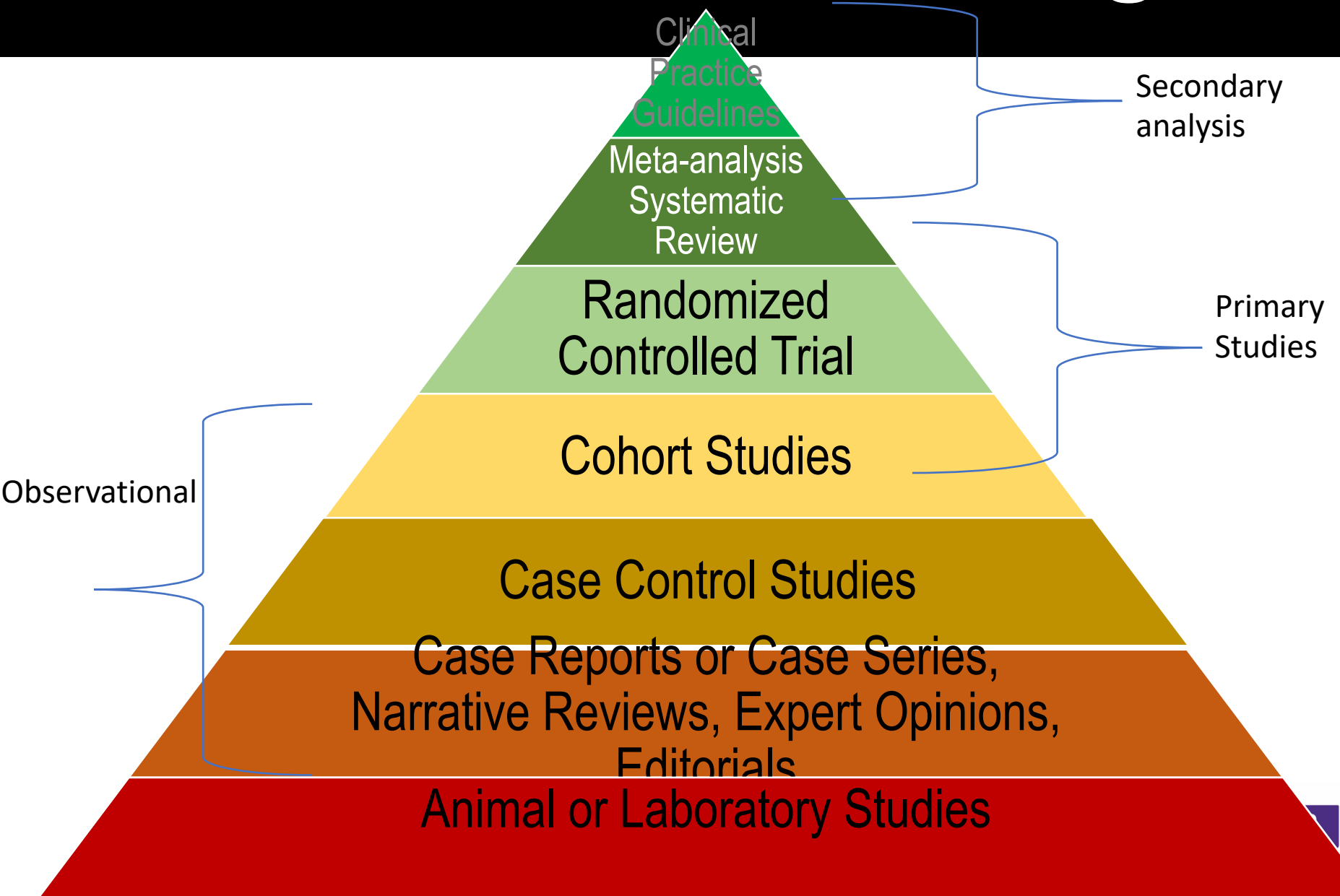
Recommendation against (weak)



Recommendation in favour (strong)



Data and Decision making



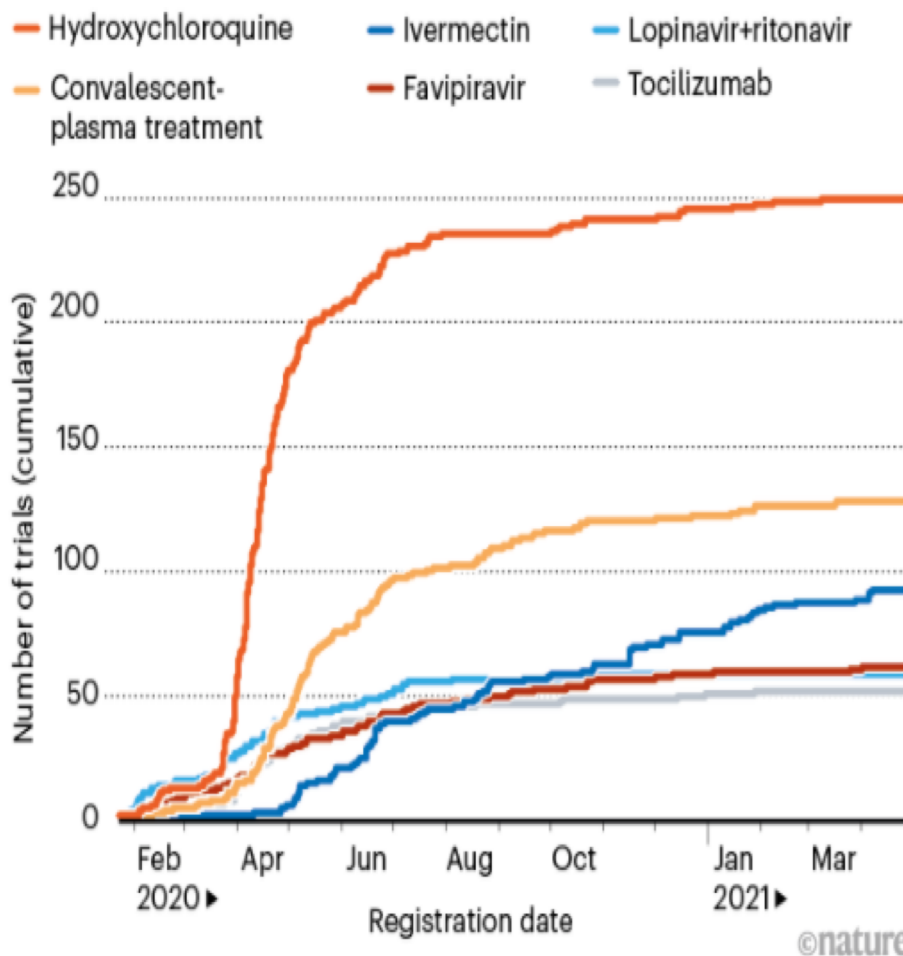
**HCQ is still
being
studied!?!**

June 2021

<https://www.nature.com/articles/d41586-021-01246-x>

TOO MANY TRIALS?

Studies assessing drugs against COVID-19 included 250 trials of hydroxychloroquine — a duplication that researchers say represents wasted effort.

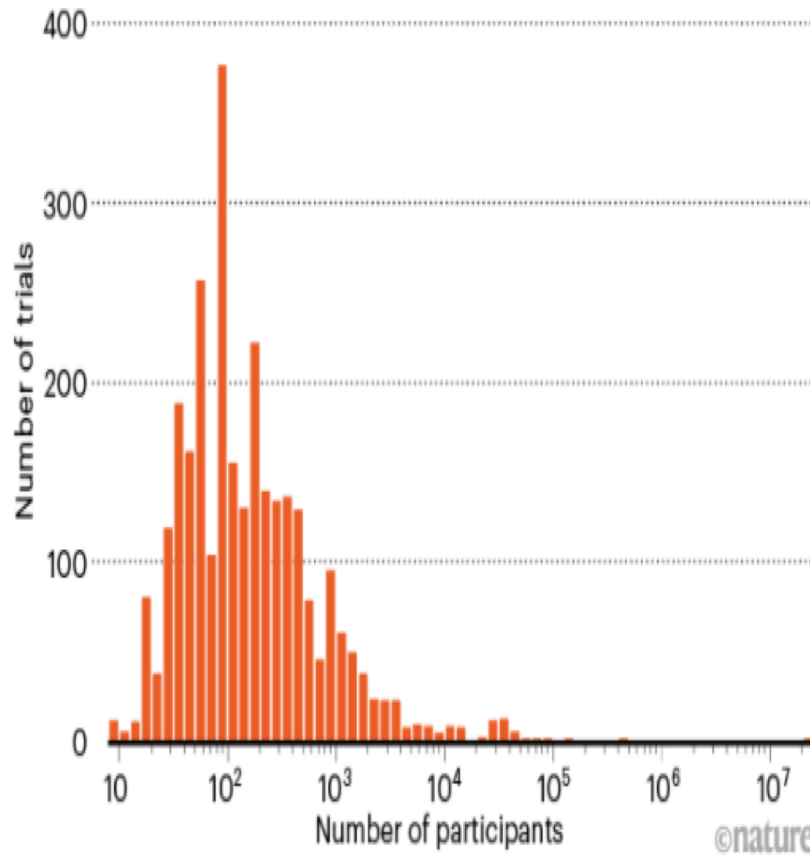


Source: COVID-NMA

Lack of quality data

SMALL SAMPLES

In one database of COVID-19 trials, 40% stated that they were enrolling fewer than 100 patients – a sample size that is generally too small to be useful.



June 2021

<https://www.nature.com/articles/d41586-021-01246-x>



Credible
Resource

S

peer reviewed
free access



COVID-19 Treatment Guidelines

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

[VIEW GUIDELINES](#)

Credit NIAID-RML

IDSA Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 4/14/2021

thebmj

covid-19

Research ▾

Education ▾

News & Views ▾

Practice » Rapid Recommendations

A living WHO guideline on drugs for covid-19

BMJ 2020 ; 370 doi:<https://doi.org/10.1136/bmj.m3379> (Published 04 September 2020)

Cite this as: *BMJ* 2020;370:m3379





Remdesivir Versus Standard-of-Care for Severe Coronavirus Disease 2019 Infection: An Analysis of 28-Day Mortality

Study Design

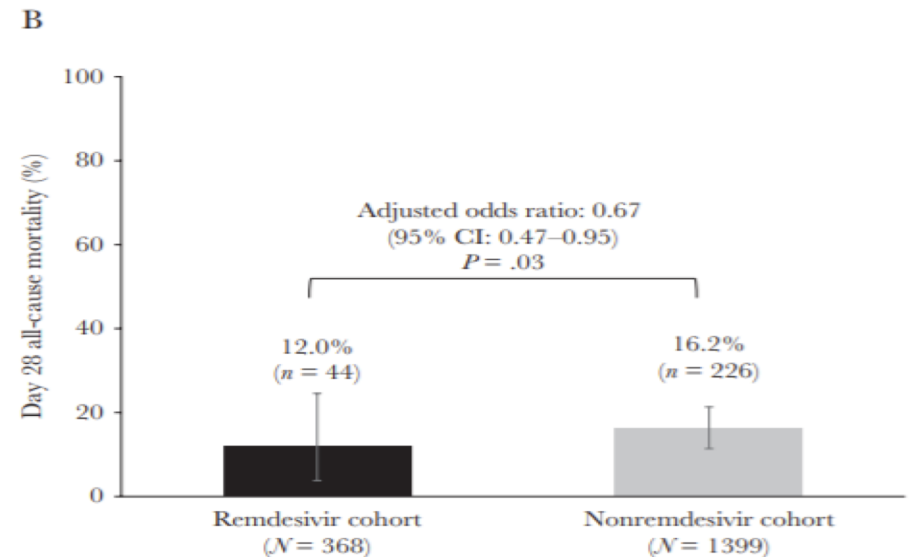
Phase 3, randomized, open-label study comparing Remdesivir 5 vs 10 days

- used previously published data

Propensity score matching to compare populations

Outcome: 14 day clinical recovery and 28 day mortality

Outcome



Limitations

- comparing prospective and retrospective data
- open-label treatment
- unproven treatments used
- time period before steroids used



Original Investigation | Infectious Diseases

Association of Remdesivir Treatment With Survival and Length of Hospital Stay Among US Veterans Hospitalized With COVID-19

Michael E. Ohl, MD, MSPH; Donald R. Miller, ScD; Brian C. Lund, PharmD; Takaaki Kobayashi, MD; Kelly Richardson Miell, PhD; Brice F. Beck, MA; Bruce Alexander, PharmD; Kristina Crothers, MD; Mary S. Vaughan Sarrazin, PhD

Study design:

retrospective cohort study used data from the Veterans Health Administration

Propensity scoring to match

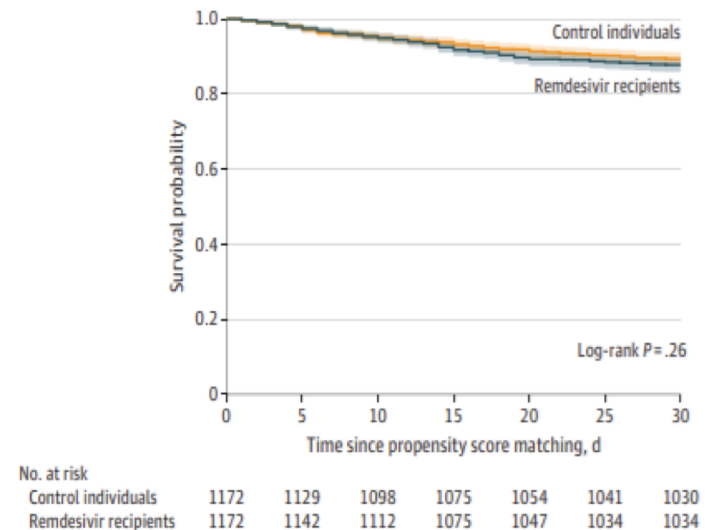
Outcomes: Time to death within 30 days of Remdesivir treatment
n=5898

2374 Remdesivir vs 3524 no Remdesivir

Time period: 5/1/20 to 10/8/20

doi:10.1001/jamanetworkopen.2021.14741

Figure 2. Kaplan-Meier Survival Curves for Remdesivir Recipients and Control Individuals in the Propensity Score-Matched Cohort

**Limitations:**

- observational
- Not all patients had matching cohort
- missing data of symptom onset and amount supplemental O2



Article Contents

[Abstract](#)[Supplementary data](#)[Comments \(0\)](#)

ACCEPTED MANUSCRIPT

Clinical improvement, outcomes, antiviral activity, and costs associated with early treatment with remdesivir for patients with COVID-19 FREE

Study Design:

Retrospective cohort
of patients hospitalized in Hong
Kong

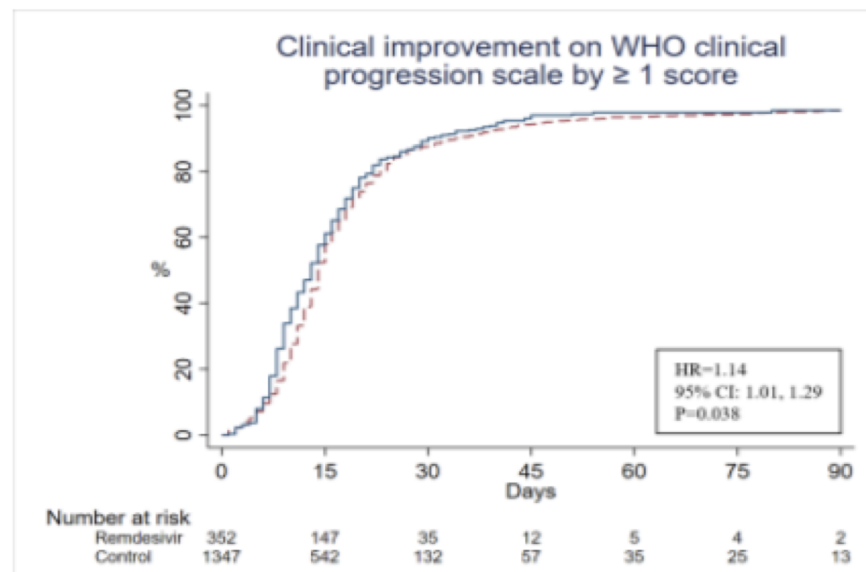
Propensity matching

Objectives: time to clinical
improvement, hospital
discharge, in-hospital death

n=352 Remdesivir

n=1,347 control

Time period: 1/21/20 to 1/31/21

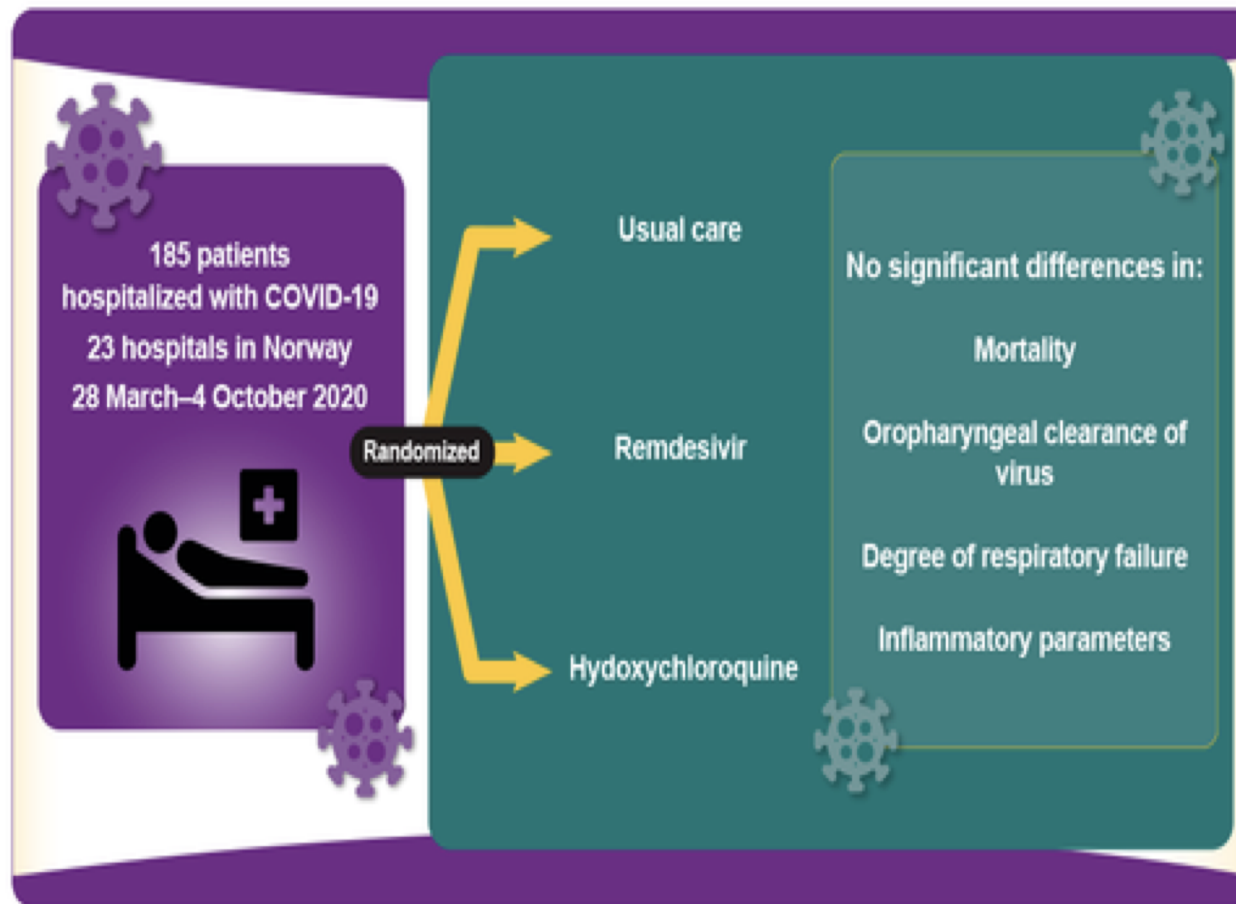


Limitations:

- moderate COVID-19 disease
- heterogeneity amongst population



Do remdesivir and hydroxychloroquine affect outcomes of patients hospitalized with COVID-19?



Annals
of Internal Medicine

Barratt-Due A, Olsen IC, Neovius-Henriksen K, et al. NOR-Solidarity trial. Evaluation of the effects of remdesivir and hydroxychloroquine on viral clearance in COVID-19: A randomized trial. *Ann Intern Med*. 2021. [Epub ahead of print]. doi:10.7326/M21-0653
<http://ajphjournals.org/doi/10.7326/M21-0653>

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Should this new data change my practice?



All retrospective studies



Most studies conducted in 2020



I still rely on the original Randomized, placebo controlled study





Therapeutic Management of Hospitalized Adults With COVID-19

Last Updated: July 8, 2021

Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII).^a There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • Remdesivir^{ch,c} (e.g., for patients who require minimal supplemental oxygen) (BIIa) • Dexamethasone^d plus remdesivir^{ch,c} (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII) • Dexamethasone^d (when combination therapy with remdesivir cannot be used or is not available) (BI)
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • Dexamethasone^d (AI) • Dexamethasone^d plus remdesivir^{ch,c} (BIII) For patients who were recently hospitalized^d with rapidly increasing oxygen needs and systemic inflammation: • Add either baricitinib^{la} (BIIa) or tocilizumab^{lh} (BIIa) to one of the two options above
Hospitalized and Requires IMV or ECMO	For most patients: • Dexamethasone^d (AI) For patients who are within 24 hours of admission to the ICU: • Dexamethasone^d plus tocilizumab^{lh} (BIIa)

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion



Previous slides...

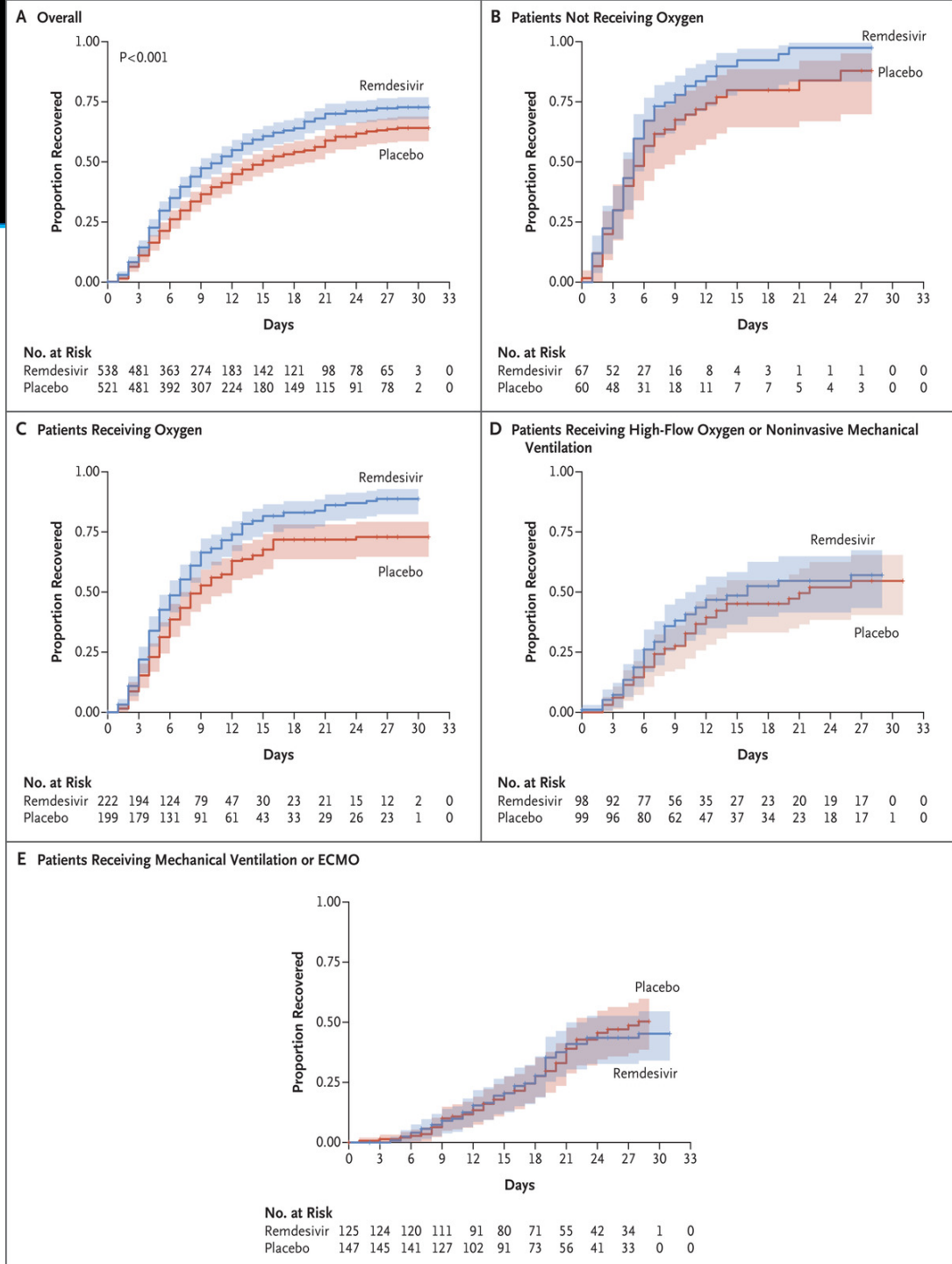


ACTT-1

Randomized controlled trial
IV Remdesivir x 10 days, any
hospitalized pt with COVID-19

The primary outcome was the time
to recovery, defined by either
discharge from the hospital or
hospitalization for infection-control
purposes only.

Majority of patients included were
on supplemental oxygen



WHO does not endorse IV Remdesivir

Figure S1. Effects on in-hospital mortality of (a) remdesivir,

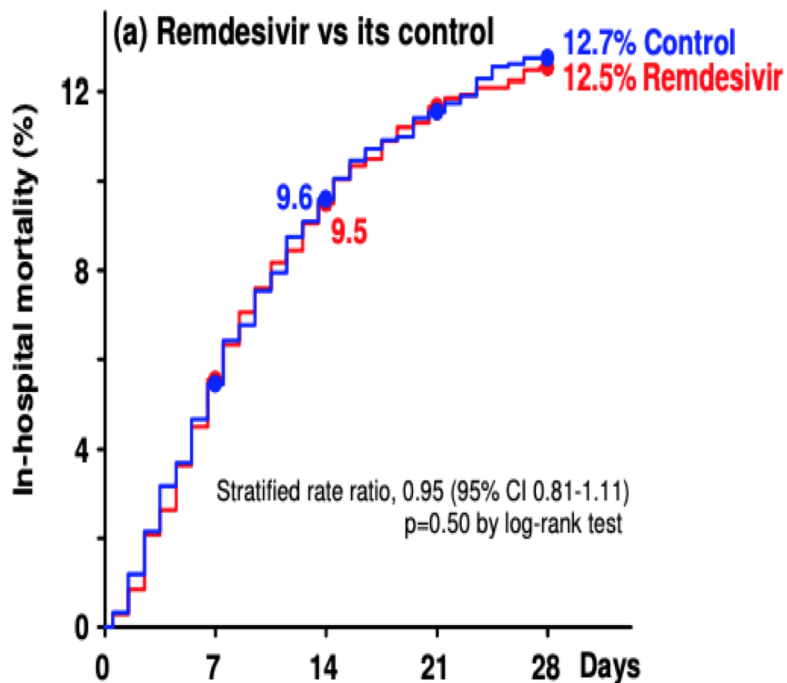
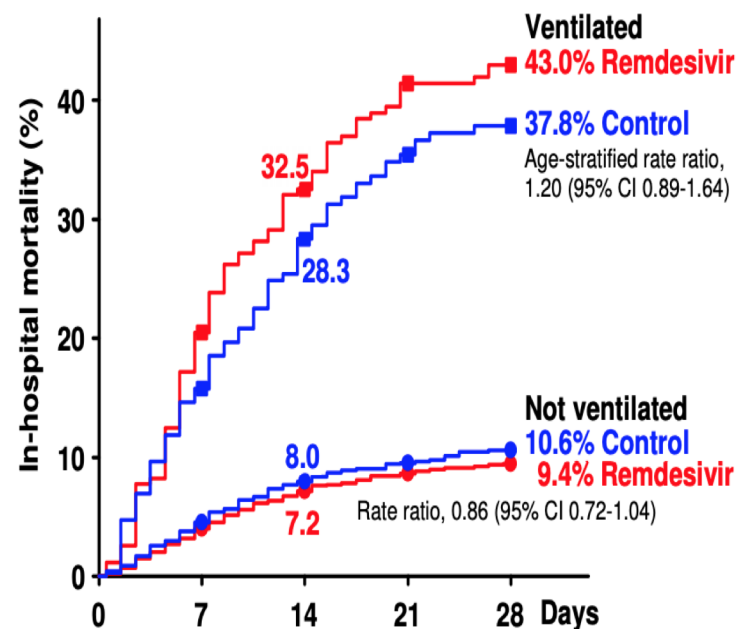


Figure S2. Subdivision by ventilation at randomization of the apparent effects of remdesivir on the probability of death in hospital from any cause



- No diff in survival, irrespective of ventilation status

Supplemental Appendix 1, Supplementary online material for. (n.d.).
<https://doi.org/10.1056/NEJMoa2023184>



Remdesivir for SEVERE disease

IDSA:

In hospitalized patients with severe COVID-19, the IDSA panel **suggests remdesivir** over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence)

NIH:

- the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients in this group (e.g., those who require increasing amounts of supplemental oxygen) (**BIII**).

WHO:

- <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>
<https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/>
<https://www.bmj.com/content/370/bmj.m3379>
Do not recommend for any patient due to low certainty of evidence



QUESTION What is the effect of ivermectin on duration of symptoms in adults with mild COVID-19?

CONCLUSION This randomized trial found that a 5-day course of ivermectin compared with

POPULATION

231 Women
167 Men



Adult patients with mild COVID-19 and symptoms for 7 days or fewer

LOCATIONS

1

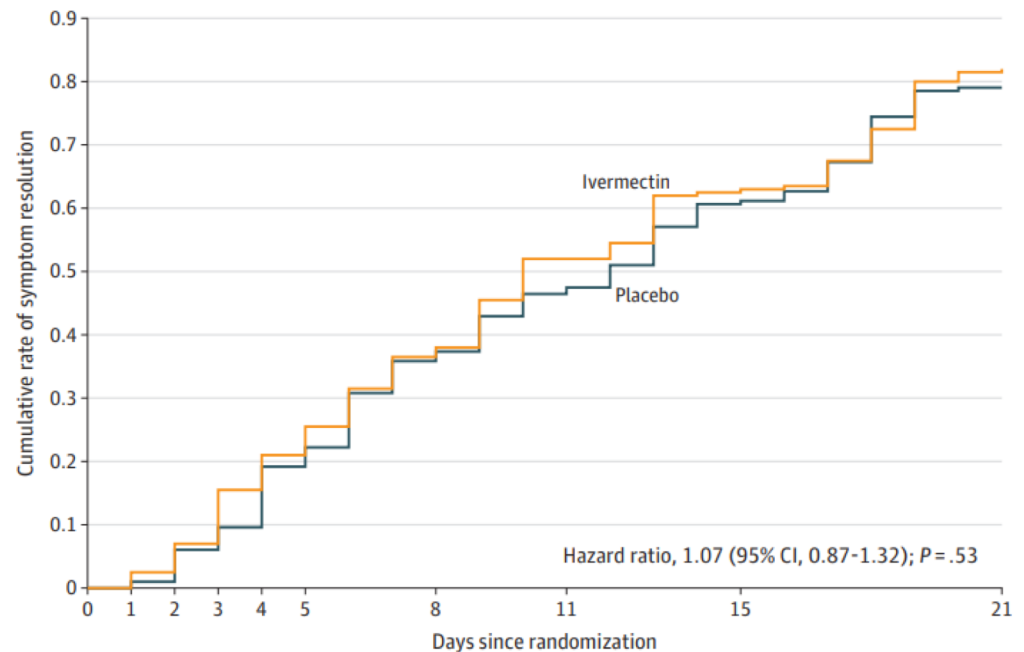
Site in Cali, Colombia



Ivermectin
Oral ivermectin
300 µg
per day

PRIMA

Figure 2. Time to Resolution of Symptoms in the Primary Analysis Population



Hazard ratio, 1.07 (95% CI, 0.87-1.32); P=.53

[illegible]

López-Medina E, López P, Hurtado IC, et al. Effect of
JAMA. Published online March 4, 2021. doi:10.1001

IDSA and FDA weigh in

Overview of IDSA COVID-19 Treatment Guidelines

Version 4.1.0 – March 5, 2021

		Setting and severity of illness			
		Ambulatory care: mild-to-moderate disease	Hospitalized: mild-to-moderate disease without need for suppl. oxygen	Hospitalized: severe but non-critical disease (spO ₂ <94% on room air)	Hospitalized: critical disease (e.g., in ICU needing MV, or septic shock, ECMO)
17-18	Ivermectin	Suggests against use except in a clinical trial ⊕○○○	NA	Suggests against use except in a clinical trial ⊕○○○	NA

Why You Should Not Use Ivermectin to Treat or Prevent COVID-19

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03/05/2021

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COVID-19. We've been living with it for what sometimes seems like forever. Given the number of deaths that have occurred from the disease, it's perhaps not surprising that

