Pragmatic trials in the time of a pandemic

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Background

- Randomised trials are crucial for estimating the effectiveness of interventions
- This is especially so within a pandemic - every day delay costs lives
- Pragmatic trials are especially important
- Pragmatic trials are an important component of pandemic evidence

Response to pandemic

- Initial international response was confused. Few countries initiated large rapid randomised trials and relied on: opinion, hearsay, observational evidence – much/most was misleading
- Some small double blind RCTs often led by drug companies were hopelessly underpowered

Some politicians don't require RCTs!

Bolsonaro Is Taking Hydroxychloroquine To Treat His Coronavirus

Carlie Porterfield Forbes Staff

Business

I cover breaking news.

Updated Jul 8, 2020, 12:21pm EDT

TOPLINE Shortly after announcing he had been infected with Covid-19, Brazilian President Jair Bolsonaro posted a video on his Facebook page that appears to show him taking a dose of hydroxychloroquine, an anti-malarial drug that has been dropped by health organizations after studies found evidence of it being both ineffective in treating the virus and having dangerous side effects.

Trump's tweets advocate hydroxychloroquine as big COVID-19 vaccine trials start

Salvadoran leader says he takes drug touted by Trump for coronavirus

By Reuters Staff

2 MIN READ

Hydroxychloroquine, the anti-malaria drug controversially used to fight COVID-19, was trending again after a string of retweets from president Donald Trump in favour of the medicine.

Some doctors don't use evidence either

The Honorable Doug Ducey
1700 West Washington St.
Phoenix, AZ 85007

Dear Governor Ducey:

This concerns your Executive Order forbidding prophylactic use of chloroquine (CQ) or hydroxychloroquine (HCQ) unless peer-reviewed evidence becomes available.

Attached and posted here (https://bit.ly/cqhcqresearch) is a summary of peer-reviewed evidence, indexed in PubMed, concerning the use of CQ and HCQ against coronavirus. We believe that there is clear and convincing evidence of benefit both pre-exposure and post-exposure.

In addition, Michael J. A. Robb, M.D., of Phoenix is compiling all reports as they come in. As of this date, the total number of reported patients treated with HCQ, with or without azithromycin and zinc, is 2,333. Of these, 2,137 or 91.6 percent improved clinically. There were 63 deaths, all but 11 in a single retrospective report from the Veterans Administration where the patients were severely ill.

Most of the data concerns use of HCQ for treatment, but one study included used the medication as prophylaxis with excellent results. Many nations, including Turkey and India, are protecting medical workers and contacts of infected persons prophylactically. According to worldometers.info, deaths per million persons from COVID-19 as of Apr 27 are 167 in the U.S., 33 in Turkey, and 0.6 in India.

Based on this evidence, we request that you rescind your Executive Orders impeding the use of CQ and HCQ and further order that administrative agencies not impose any requirements on the prescription of CQ, HCQ, azithromycin, or other drugs intended to treat or prevent coronavirus illness that do not apply equally to all approved medications that may be used off-label for any purpose.

Respectfully,

Michael J. A. Robb, M.D.
President, Arizona State Chapter of the Association of American Physicians and Surgeons

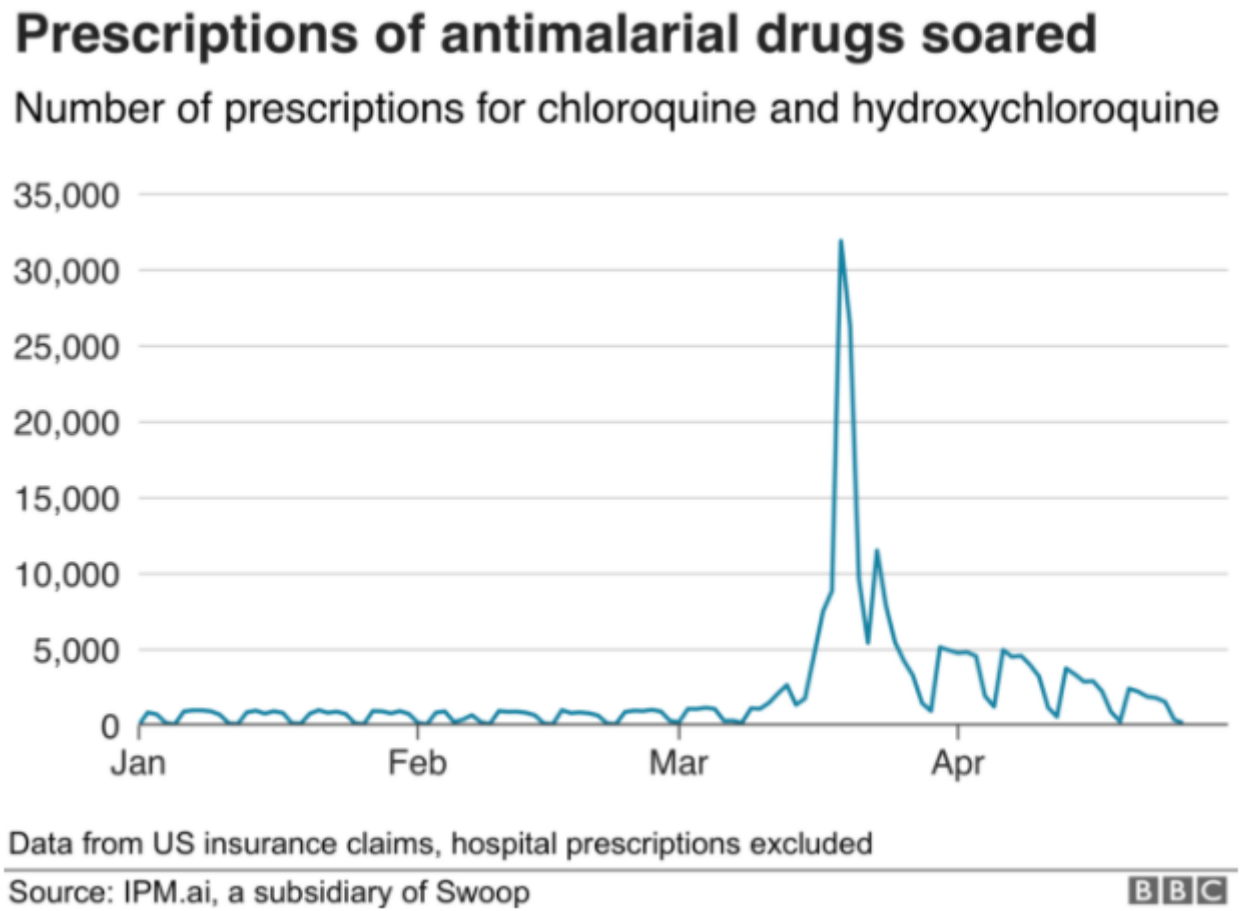
Jane M. Orient, M.D.
Executive Director, Association of American Physicians and Surgeons

https://www.youtube.com/watch?time_continue=229&v=xdwe9wXPctI&feature=emb_logo

Nor do some regulators!!!

On March 28, the FDA issued an Emergency Use Authorization, which allowed hydroxychloroquine and chloroquine products that were donated to the SNS to be distributed and used for adolescent and adult patients hospitalized with COVID-19 who cannot be part of a clinical trial.

Impact of publicity



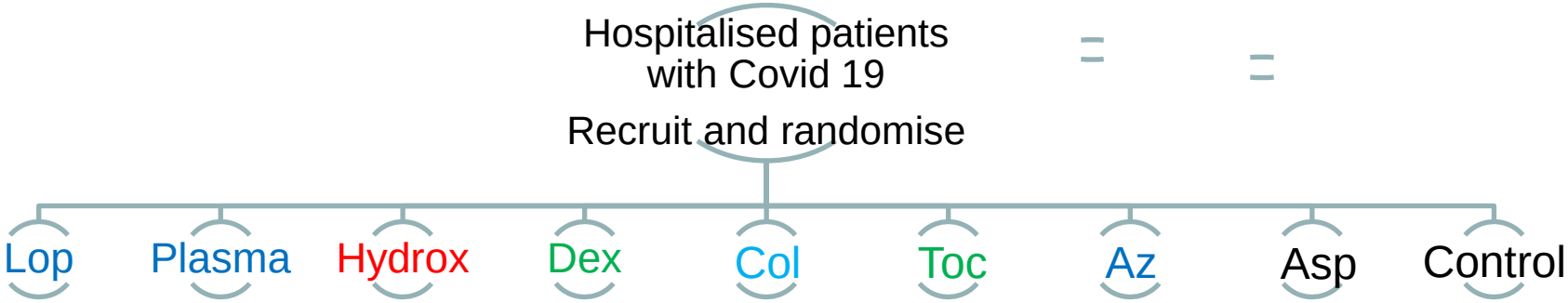
Large pragmatic trials are needed

- Lots of potential treatments – for example
  - » Hydoxycholoroquine
  - » Dexamethasone
  - » Convalescent plasma
  - » Azithromycin
  - » Lopinavir-ritonavir
  - » Tocilizumab
  - » Colchicine
  - » Aspirin
  - » REGN-COV2 antibody

RECOVERY trial

- A large multi-armed, factorial, platform **pragmatic** design to test several treatments for hospitalised Covid-19 patients in the UK
- Largest treatment trial in world (>35,000 patients in Feb 2021)
- **NOTE <10% of UK hospital patients!**
- Initially six treatments but later expanded: hydroxychloroquine, dexamethasone, lopinavir-ritonavir, azithromycin, convalescent plasma, aspirin, colchicine and second randomisation for deteriorating patients, tocilizumab.

Platform design



Trial procedures

- Emphasis on being simple and quick
  - » Internet patient enrolment
  - » Simple informed consent and data entry
  - » Simple randomisation via internet
  - » Data collected: physician and patient identity, age, sex, co-morbidity, pregnancy, COVID-19 onset date and severity, contraindications to study treatment

Randomisation

- Simple randomisation was used with a ratio of 2:1:1:1:1 if all the treatments were available at the hospital – if some treatments were missing then the allocation was restricted to available treatments
- Unequal allocation favouring control group
- Some arms may be paused if fluctuation in numbers make it infeasible to recruit to all treatments

Sample size calculation

- Unusually there was not an '*a priori*' sample size estimate. Once trial had started and some data had been collected on 28 day mortality the independent monitoring committee decided that a 20% mortality rate was likely and that a 4% absolute reduction was worthwhile
- This required 4,000 in control group and 2,000 in each of the intervention groups

Date	Action
10th March 2020	Trial protocol drafted
11th March 2020	WHO declares pandemic
19th March 2020	First RECOVERY patient recruited
23rd March 2020	UK enters first lockdown
14th May 2020	10,000th RECOVERY patient recruited
5th June 2020	Data monitoring committee recommends closure of hydroxychloroquine arm preliminary results
16th June 2020	Dexamethasone results released in press conference
29th June 2020	Results of lopinavir-ritonavir released
14th Sept 2020	REGN-COV2 added as an arm
6th Nov 2020	Aspirin added as an arm
9th Nov 2020	Convalescent plasma added as an arm
27th Nov 2020	Cochicine added as an arm
14th Dec 2020	Press release – no benefit of azithromycin
15th Jan 2021	Results of plasma 18% mortality in both groups
2nd Feb 2021	Baricitinib added as an arm
11th Feb 2021	Tocilizumab results released in press conference
5th March 2021	Colchicine results released 20% mortality vs 19% mortality

Race against time

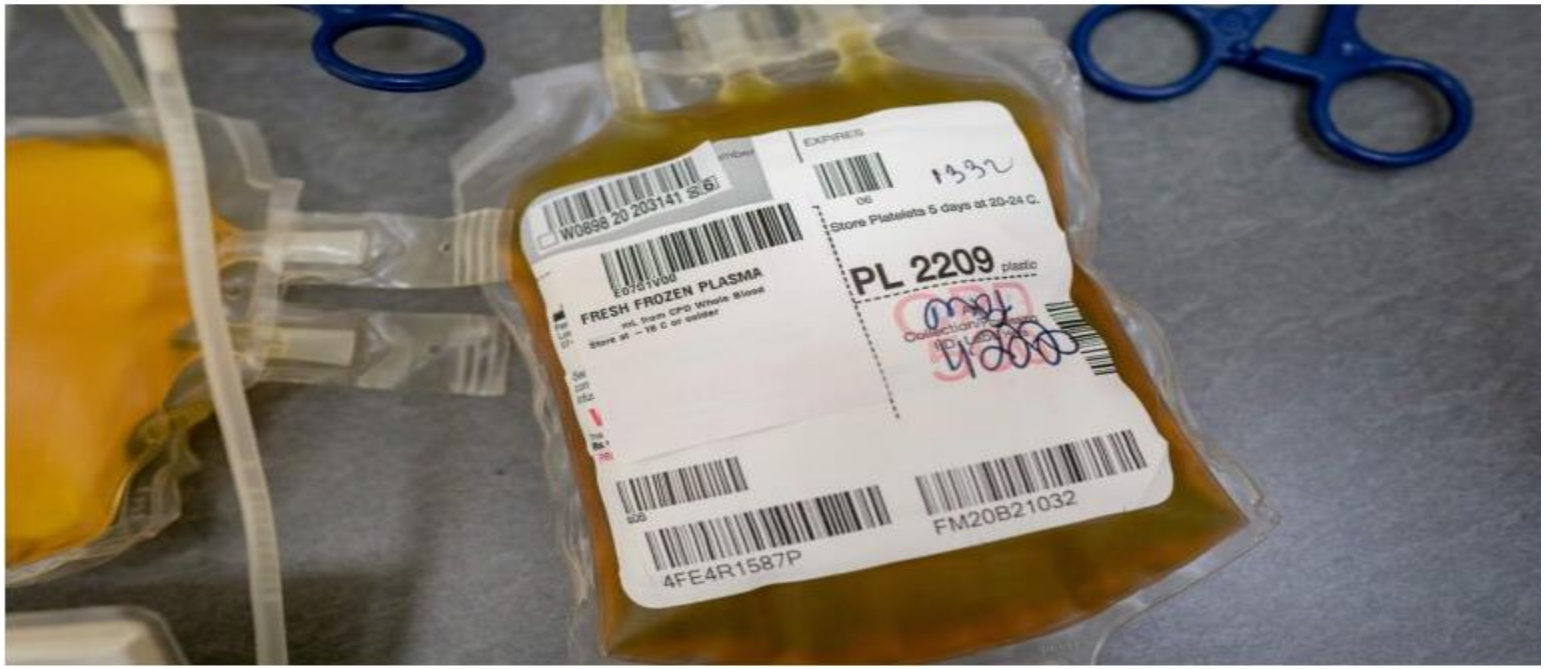
- Because it was a pandemic evidence is need NOW also political/regulator problems
- FDA in the USA is a particular problem for US trials as it was issuing EUAs on a regular basis for treatments based on limited and probably misleading evidence.

Convalescent Plasma

We don't know if convalescent plasma is effective against Covid-19. With the emergency authorization, we might never know

By ARTHUR L. CAPLAN / AUGUST 24, 2020

Reprints



Plasma and RECOVERY
15th January 2021

10,406 patients randomised.
NO evidence of a treatment effect

Meanwhile 100,000 patients in USA received plasma

The DMC reviewed data on patients randomised to convalescent plasma vs. usual care. The preliminary analysis based on 1873 reported deaths among 10,406 randomised patients shows no significant difference in the primary endpoint of 28-day mortality (18% convalescent plasma vs. 18% usual care alone; risk ratio 1.04 [95% confidence interval 0.95-1.14]; p=0.34). Follow-up of patients is ongoing and final results will be published as soon as possible.

Corticosteroid treatments

- In contrast, use of corticosteroids were not promoted by politicians or encouraged by the medical profession with international clinical guidelines arguing that there was little evidence of effectiveness in a Covid-19 population until the RECOVERY results

Corticosteroid Therapy

Table 5 | Recommendations for use of corticosteroids for covid-19 in global guidelines produced early in pandemic

Origin	Corticosteroid recommendations	Evidence base	Antimicrobials notes
WHO	Corticosteroid therapy contraindicated	Stockman LJ et al,[27] Rodrigo C et al,[28] Delaney et al,[29] Arabi YM et al[30]	Give empirical antimicrobials to treat all likely pathogens causing SARI
Italy	Not recommended for confirmed covid-19 patients, but low dose dexamethasone may be considered in patients with confirmed ARDS on ICU clinicians' indication	World Health Organization interim guidance,[9] Villar J et al[31]	Add antibiotic (empirical or targeted) according to clinical indications, health policies, or protocols in use
US CDC	Corticosteroids should be avoided unless indicated for other reasons (eg, COPD exacerbation or septic shock)	Zumla A et a,l[32] Arabi YM et al,[30] Russell et al,[33] Metlay JP et al[34]	
India	Not recommended for viral pneumonia or ARDS outside of clinical trials, unless indicated for other reason	No link to supporting evidence provided	Antibiotics not recommended/covered
Turkey	Not recommended routinely	No link to supporting evidence provided	Give empirical antimicrobials to treat all likely pathogens causing SARI
South Korea	Steroids not indicated in general but may be considered for other conditions, such as septic shock	No link to supporting evidence provided	Empirical antimicrobials for possible pathogens are recommended
France	Steroids not indicated for SARS-CoV-2 infection alone	Stockman LJ et al[27]	Routine use of antibiotics for treatment of covid-19 not recommended. However, antibiotics may be used if accompanying bacterial infection is suspected
Brazil	Not recommended for viral pneumonia or ARDS outside of clinical trials, unless indicated for other reasons	No link to supporting evidence provided	
Taiwan	Not recommended for viral pneumonia or ARDS outside of clinical trials, unless indicated for other reasons	No link to supporting evidence	Systematic coverage of bacterial infection/superinfection recommended in severe forms
Indonesia	Not recommended for viral pneumonia or ARDS outside of clinical trials, unless indicated for other reasons	No clear link to supporting evidence	
Spain	Not recommended	No clear link to supporting evidence	Give empirical antimicrobials to treat all likely pathogens that cause SARS
Malaysia	Not recommended unless indicated for other reasons (eg, COPD, septic shock)	No clear link to supporting evidence	Consider giving empirical antibiotics to treat other possible bacterial infection
Germany	Not recommended without clear indication	No clear link to supporting evidence	Give empirical antibiotics based on likely aetiology

ARDS=acute respiratory distress syndrome; COPD=chronic obstructive pulmonary disease; ICU=intensive care unit; SARI=severe acute respiratory illness; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Results - hydroxychloroquine

- On the 5th June 2020 initial results were released for hydroxychloroquine
  - » *“A total of 1542 patients were randomised to hydroxychloroquine and compared with 3132 patients randomised to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10). There was also no evidence of beneficial effects on hospital stay duration or other outcomes”*

https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19

Published Paper

Table 2. Primary and Secondary Outcomes.

Outcome	Hydroxychloroquine (N=1561)	Usual Care (N=3155)	Rate or Risk Ratio (95% CI)
	no./total no. (%)		
Primary outcome: 28-day mortality	421/1561 (27.0)	790/3155 (25.0)	1.09 (0.97–1.23)*
Secondary outcomes			
Discharge from hospital in ≤28 days	931/1561 (59.6)	1983/3155 (62.9)	0.90 (0.83–0.98)*
Invasive mechanical ventilation or death†	399/1300 (30.7)	705/2623 (26.9)	1.14 (1.03–1.27)‡
Invasive mechanical ventilation	128/1300 (9.8)	225/2623 (8.6)	1.15 (0.93–1.41)
Death	311/1300 (23.9)	574/2623 (21.9)	1.09 (0.97–1.23)

* The between-group difference was calculated as a rate ratio.
† Patients who were receiving invasive mechanical ventilation at randomization were excluded from this analysis.
‡ The between-group difference was calculated as a risk ratio.

N Engl J Med 2020;383:2030-40

Key points

- 23rd March first patients enrolled, by the 5th June the trial demonstrated that hydroxychloroquine was ineffective and probably harmful
- Rapid result improves patient health and probably reduces mortality from inappropriate use of the drug
- Politicians and doctors calling for its use were wrong.
- Regulators shouldn’t have approved

Results dexamethasone

- Boris Johnson announced the results in a press conference 16th June 2020.
  - » *Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).*

Press conference or peer review?

"I think it is irresponsible to release the results only in a press release; a press release is not evidence," says Tobias Kurth, professor of epidemiology and public health at the Charité Berlin University of Medicine and one of *The BMJ*'s statistical advisers. "This habit has to stop now. Even though we are in a difficult situation and urgently need to find something that works, it is important to show all the methods and data."

BMJ 2020;370:m2670

Delay = lost lives

- The New England Journal of Medicine published a peer review paper 1 month after the press release (15th July). The differences between the main findings were negligible.

- How many people would have died in the UK and the world in that time?

Estimated numbers of UK additional patients who survived up to 15th July due to RECOVERY.

Status	Proportion in each status as per RECOVERY Trial (Numbers admitted from 16th June to 15th July (6,980) of which 83% are eligible for dexamethasone) N = 5,793	Estimated deaths despite dexamethasone	Estimated deaths without dexamethasone
No Oxygen	24% (1,390)	14.0%* (195)	14.0% (195)
Oxygen alone	60% (3476)	22.0%** (765)	26.2%(911)
Ventilation	16% (927)	29.1%** (270)	41.4% (384)
Total deaths		1,230	1,490
Additional lives saved		**260**	

*Assumes steroids are not given to hospitalised but not oxygenated patients as per the results from the RECOVERY trial.
**Adjusted rather than observed differences between groups are used, which are 12.3 and 4.2% reduction in 28-day mortality for ventilated and oxygen supported patients, respectively.

Across EU 1,700? USA 1,272?

Are we good enough?

- At the first peak around 20,000 people with Covid in hospital at anyone time – ONLY 10% were recruited into RECOVERY
- During second peak 30,000 still only 10% recruited into trials

Estimated additional patients who survived up to 15th July with 50% recruitment to RECOVERY

Status	Proportion in each status as per the RECOVERY Trial (Numbers admitted from 9th April to 16th June (77,310) of which 83% are eligible for dexamethasone) N = 64,167	Steroid deaths	Usual care deaths
No Oxygen	24% (15,400)	14.0%* (2,156)	14.0% (2,156)
Oxygen alone	60% (38,500)	22.0%** (8,470)	26.2%(10,087)
Ventilation	16% (10267)	29.1%** (2988)	41.4% (4,251)
Total deaths		13,614	16,494
Additional lives saved		**2,880**	

*Assumes steroids are not given to hospitalised but not oxygenated patients as per the results from the RECOVERY trial. Knowleson, Torgerson F1000, 2020

EU = 19,000?, USA = 14,000? Norway = 8?

Facemasks do they work?

Pragmatic trial

Eligible persons were community-dwelling adults aged 18 years or older without current or prior symptoms or diagnosis of COVID-19 who reported being outside the home among others for at least 3 hours per day and who did not wear masks during their daily work. Recruitment involved media advertisements and contacting private companies and public organizations. Interested citizens had internet access to detailed study information and to research staff for questions (Part 3 of the Supplement). At baseline,

Participants were notified of allocation by e-mail, and study packages were sent by courier (Part 7 of the Supplement). Participants in the mask group were instructed to wear a mask when outside the home during the next month. They received 50 three-layer, disposable, surgical face masks with ear loops (TYPE II EN 14683 [Abena]; filtration rate, 98%; made in China). Participants in both groups received materials and instructions for antibody testing on receipt and at 1 month. They also received materials and

Do they work?

Table 2. Distribution of the Components of the Composite Primary Outcome

Outcome Component	Face Mask Group (*n* = 2392), *n* (%)	Control Group (*n* = 2470), *n* (%)	Odds Ratio (95% CI)*
Primary composite end point	42 (1.8)	53 (2.1)	0.82 (0.54–1.23)
Positive antibody test result†			
IgM	31 (1.3)	37 (1.5)	0.87 (0.54–1.41)
IgG	33 (1.4)	32 (1.3)	1.07 (0.66–1.75)
Positive SARS-CoV-2 RT-PCR	0 (0)	5 (0.2)	–
Health care–diagnosed SARS-CoV-2 or COVID-19	5 (0.2)	10 (0.4)	0.52 (0.18–1.53)

COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory

Remdesivir

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

ABSTRACT

BACKGROUND

Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), no antiviral agents have yet been shown to be efficacious.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Patients were randomly assigned to receive either

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Beigel at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Ln., Rm. 7E60, MSC 9826, Rockville, MD 20892-9826, or at jbeigel@niaid.nih.gov.

*A complete list of members of the

Remdesivir – placebo trial

- **METHODS**

- We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

- **RESULTS**

- A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test).

N Engl J Med 2020; 383:1813-1826 DOI: 10.1056/NEJMoa2007764

WHO Solidarity Trial

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

ABSTRACT

BACKGROUND

World Health Organization expert groups recommended mortality trials of four repurposed antiviral drugs — remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a — in patients hospitalized with coronavirus disease 2019 (Covid-19).

METHODS

We randomly assigned inpatients with Covid-19 equally between one of the trial drug regimens that was locally available and open control (up to five options, four active and the local standard of care). The intention-to-treat primary analyses examined in-hospital mortality in the four pairwise comparisons of each trial drug and its control (drug available but patient assigned to the same care without that drug). Rate ratios for death were calculated with stratification according to age and status regarding mechanical ventilation at trial entry.

RESULTS

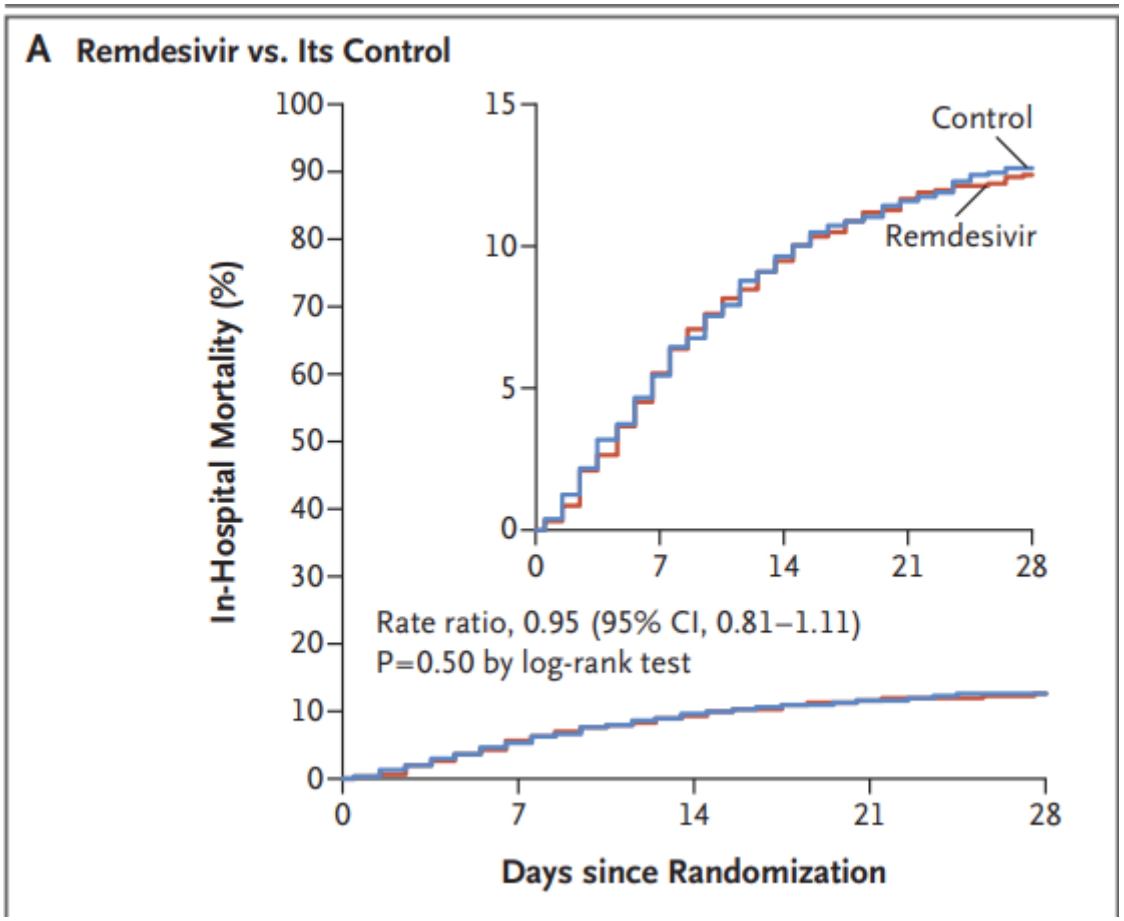
At 405 hospitals in 30 countries, 11,330 adults underwent randomization; 2750 were assigned to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. Adherence was 94 to 96% midway through treatment, with 2 to 6% crossover. In total, 1253 deaths were reported (median day of death, day 8; interquartile range, 4 to 14). The Kaplan–Meier 28-day mortality was 11.8% (39.0% if the patient was already receiving ventilation at randomization and 9.5% otherwise). Death occurred in 301 of 2743 patients receiving remdesivir and in 303 of 2708 receiving its control (rate ratio, 0.95; 95% confidence interval [CI], 0.81 to 1.11; P=0.50), in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving its control (rate ratio, 1.19; 95% CI, 0.89 to 1.59; P=0.23), in 148 of 1399 patients receiving lopinavir and in 146 of 1372 receiving its control (rate ratio, 1.00; 95% CI, 0.79 to 1.25; P=0.97), and in 243 of 2050 patients receiving interferon and in 216 of 2050 receiving its control (rate ratio, 1.16; 95% CI, 0.96 to 1.39; P=0.11). No drug definitely reduced mortality, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration.

CONCLUSIONS

These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. (Funded by the World Health Organization; ISRCTN Registry number, ISRCTN83971151; ClinicalTrials.gov number, NCT04315948.)

NEJM DOI: 10.1056/NEJMoa2023184

Remdesivir


A Remdesivir vs. Its Control
In-Hospital Mortality (%)
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
Days since Randomization
15
10
5
0
Control
Remdesivir
Rate ratio, 0.95 (95% CI, 0.81–1.11)
P=0.50 by log-rank test

No Effect

CONCLUSIONS

These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. (Funded by the World Health Organization; ISRCTN Registry number, ISRCTN83971151; ClinicalTrials.gov number, NCT04315948.)

ACTT-1, which examined remdesivir, was placebo-controlled,[6] which avoids any bias in time to discharge. In that trial, however, the proportion of lower-risk patients (i.e., those not already receiving high-flow oxygen or ventilation) happened to be appreciably greater in the remdesivir group than in the placebo group. This chance imbalance might account for some of the differences in time to recovery between ACTT-1 and the Solidarity trial.

Lucky escape!

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Cite this as: *BMJ* 2020;370:m2797
http://dx.doi.org/10.1136/bmj.m2797
Published: 13 July 2020

US purchases world stocks of remdesivir: why the rest of the world should be glad to be at the back of the queue

The remdesivir story may actually be good news for the rest of the world, argues James M Brophy

James M Brophy *professor of medicine and epidemiology*

On 30 June, the *Guardian* ran an article with the headline "US secures world stock of key covid-19 drug remdesivir," lamenting the monopolisation for "the next three months of one of the two drugs proven to work against covid-19, leaving none for the UK, Europe, or most of the rest of the world."[1] This "me first" attitude should surprise nobody familiar with

exemplified in a quote in the *Guardian* article from Andrew Hill, senior visiting research fellow at Liverpool University, stating, "Remdesivir would get people out of hospital more quickly, reducing the burden on the NHS, and might improve survival," and, "Once again we're at the back of the queue."

I would argue that in this case, it is good to be at the

In conclusion, yes, the US action is truly the apotheosis of a self-centred nation, but it is potentially beneficial for other countries. Better to have the plutocratic American healthcare system dominate this market with an expenditure of $1.5bn for such uncertain benefits. The money other countries save can surely be better spent on further research for this and other drugs as well as for public health measures, including testing, contact tracing, and maintaining universal healthcare, all notable lacunae in the American system.

Many trials too small

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A.S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M.D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.-D. Halvorsen, T.K. Thurber, Z. Dagher, A. Scherer, R.S. Wallwork, A.Y. Kim, S. Schoenfeld, P. Sen, T.G. Neilan, C.A. Perugino, S.H. Unizony, D.S. Collier, M.A. Matza, J.M. Yinh, K.A. Bowman, E. Meyerowitz, A. Zafar, Z.D. Drobni, M.B. Bolster, M. Kohler, K.M. D'Silva, J. Dau, M.M. Lockwood, C. Cubbison, B.N. Weber, and M.K. Mansour, for the BACC Bay Tocilizumab Trial Investigators*

ABSTRACT

BACKGROUND

The efficacy of interleukin-6 receptor blockade in hospitalized patients with coronavirus disease 2019 (Covid-19) who are not receiving mechanical ventilation is unclear.

METHODS

We performed a randomized, double-blind, placebo-controlled trial involving patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hyperinflammatory states, and at least two of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. Patients were randomly assigned in a 2:1 ratio to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight) or placebo. The primary outcome was intubation or death, assessed in a time-to-event analysis. The secondary efficacy outcomes were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline, both assessed in time-to-event analyses.

RESULTS

We enrolled 243 patients; 141 (58%) were men, and 102 (42%) were women. The median age was 59.8 years (range, 21.7 to 85.4), and 45% of the patients were Hispanic or Latino. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P=0.64), and the hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10; P=0.73). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had had worsening of disease. The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8 to 7.6) in the tocilizumab group and 4.9 days (95% CI, 3.8 to 7.8) in the placebo group (P=0.69). At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen. Patients who received tocilizumab had fewer serious infections than patients who received placebo.

CONCLUSIONS

Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Some benefit or harm cannot be ruled out, however, because the confidence intervals for efficacy comparisons were wide. (Funded by Genentech; ClinicalTrials.gov number, NCT04356937.)

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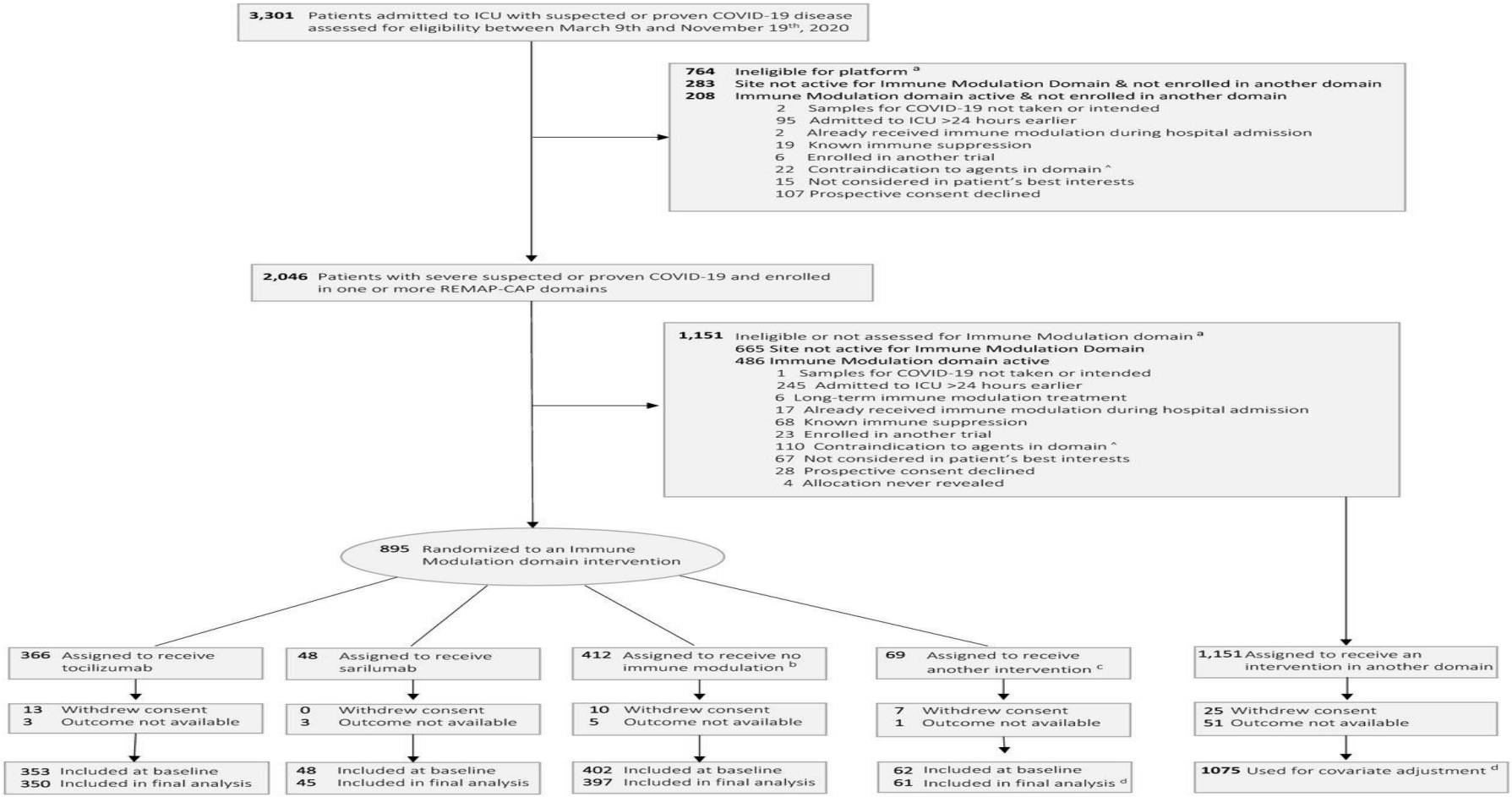
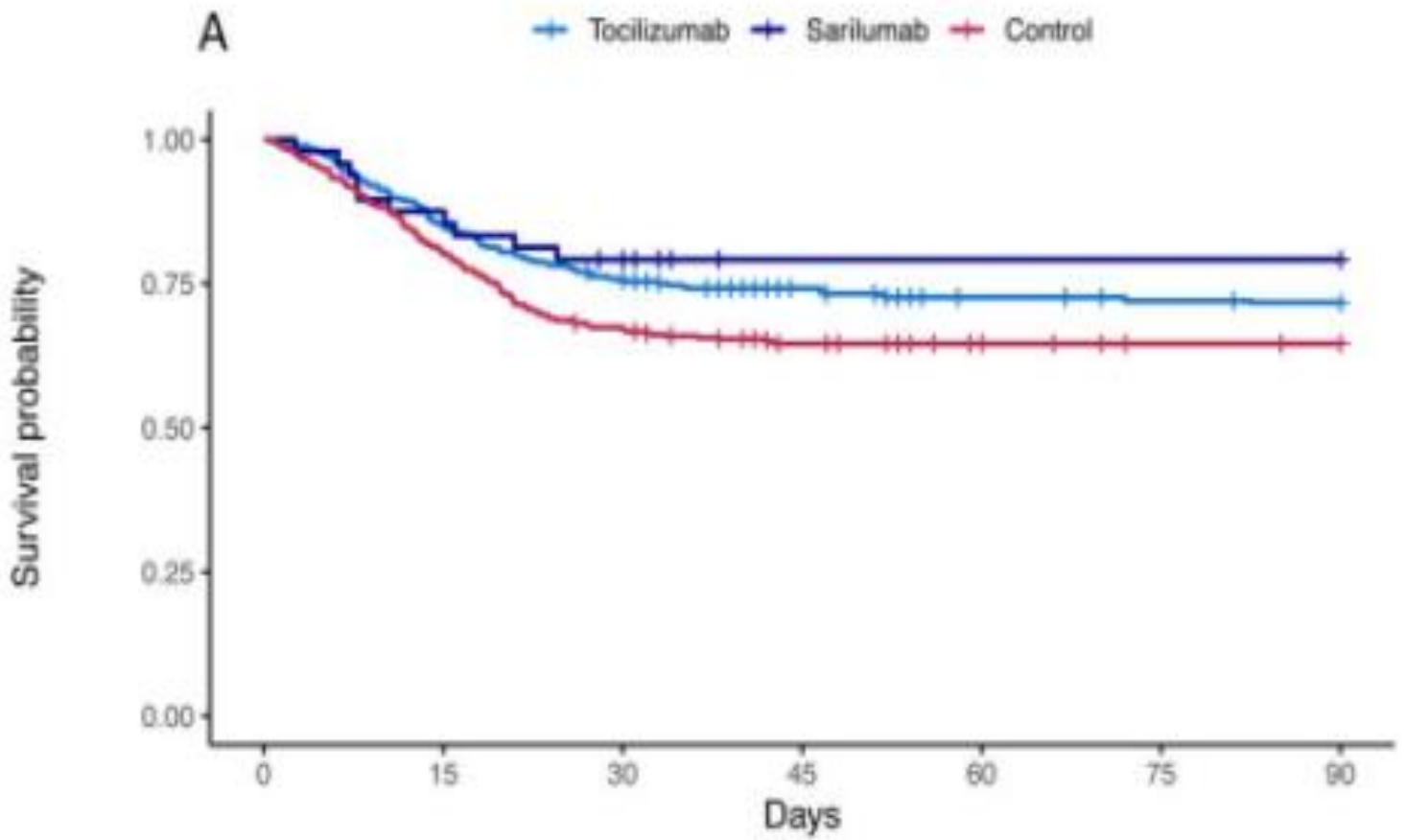
N Engl J Med 2020;383:2333-44

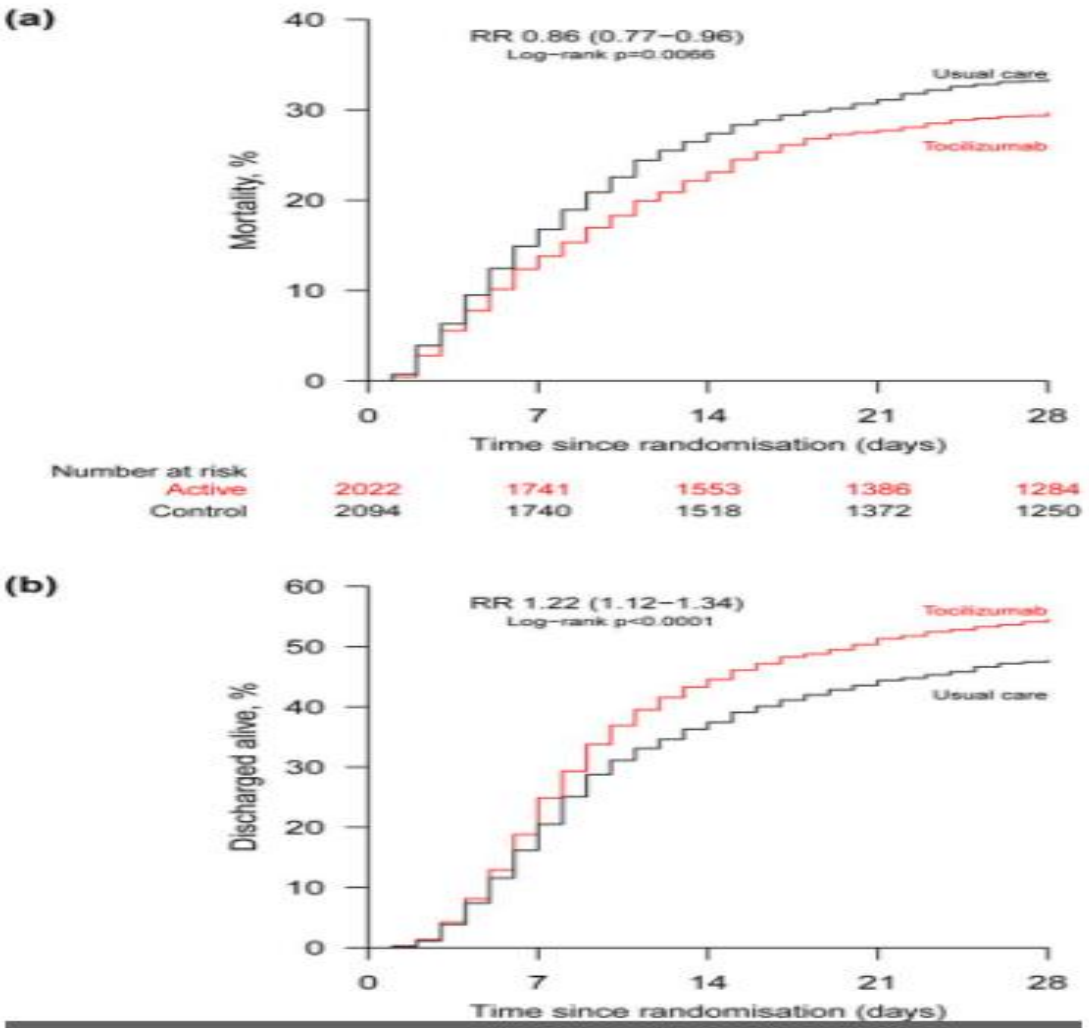
REMAP-CAP international platform trial



Results


A
Tocilizumab
Sarilumab
Control
Survival probability
1.00
0.75
0.50
0.25
0.00
0
15
30
45
60
75
90
Days

RECOVERY trial results for Tocilizumab (n = 4,116)



Effect of allocation to tocilizumab on (a) 28–day mortality and (b) discharge from hospital alive within 28 days of

Before we finish

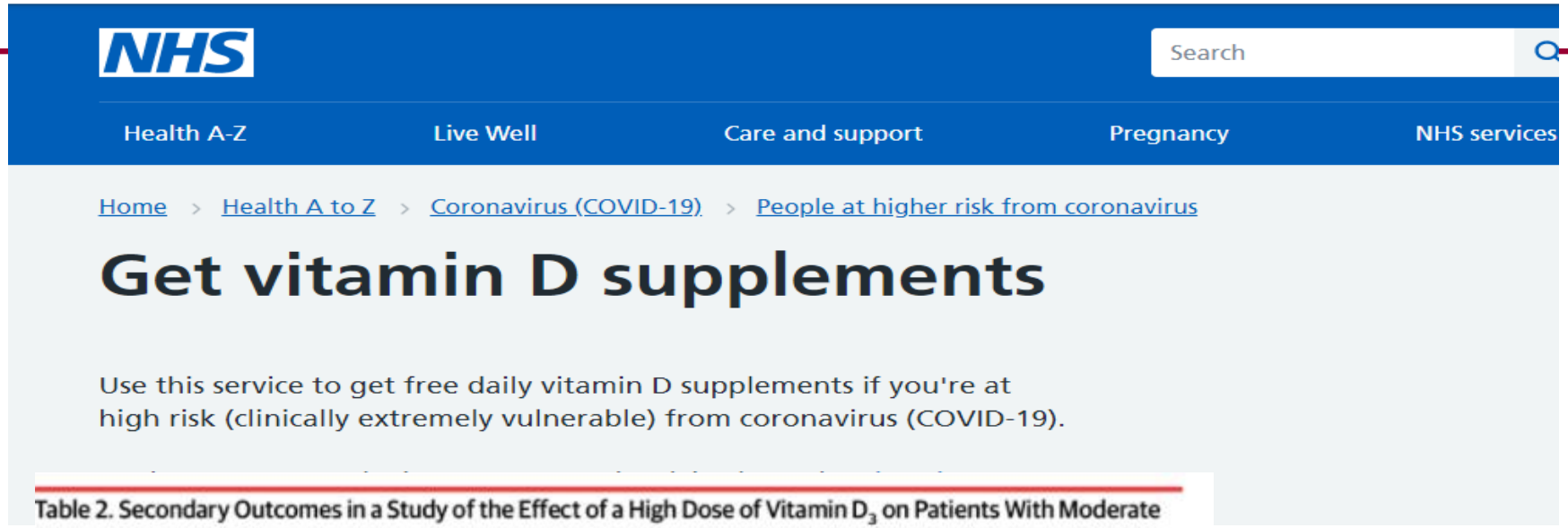


Table 2. Secondary Outcomes in a Study of the Effect of a High Dose of Vitamin D_3 on Patients With Moderate to Severe Coronavirus Disease 2019

Outcome	Patients (95% CI), %		Between-group difference (95% CI), %	*P* value
	Vitamin D_3 group	Placebo group		
All patients	n = 119	n = 118		
In-hospital mortality	7.6 (3.5 to 13.9)	5.1 (1.9 to 10.7)	2.5 (-4.1 to 9.2)	.43
Admission to intensive care unit	16.0 (9.9 to 22.5)	21.2 (14.2 to 29.7)	-5.2 (-15.1 to 4.7)	.30
Mechanical ventilation requirement	7.6 (3.5 to 13.9)	14.4 (8.6 to 22.1)	-6.8 (-15.1 to 1.2)	.09
Patients with 25-hydroxyvitamin D deficiency (<20 ng/mL)	n = 57	n = 58		
In-hospital mortality	7.0 (1.9 to 17.0)	1.7 (0.04 to 9.2)	5.3 (-3.3 to 15.1)	.21
Admission to intensive care unit	19.3 (10.0 to 31.9)	15.5 (7.4 to 27.4)	3.8 (-10.3 to 17.8)	.59
Mechanical ventilation requirement	7.0 (1.9 to 17.0)	8.6 (2.9 to 19.0)	-1.6 (-12.5 to 9.2)	>.99

JAMA. Published online February 17, 2021. doi:10.1001/jama.2020.26848

Conclusion

- To resolve clinical uncertainty we need large, pragmatic, RCTs
- The pandemic response is representative of what happens in non-pandemic situations
- Many/most evidence is poor
- All patients should be offered the chance to go into a RCT (not just 10% - 70-80% of UK cancer patients go into trials)