**Before class on Tuesday Nov 24**:

- Read the excerpted material on the RECOVERY TRIAL and construct a written question on a (design or) statistical aspect. If relevant, specify where in which paragraph(s) it refers to. In case a lot of people come up with the same question, have a second (spare) one that might be less common. You are asked to also produce a written model answer for each question; answers should also be short and to the point.
- Do likewise for the SOLIDARITY TRIAL.

**In class**:

RECOVERY TRIAL

- JH will split the class into 2 teams; they will then meet in separate breakout rooms and agree on the order of the questions they will ask the other team, and which team member will ask which question.
- When we all re-assemble, a person from one team poses the 1st question for the other team to answer. Having heard the answer, the questioning team grades it.
- The teams will reverse roles, and repeat the process, etc.

SOLIDARITY TRIAL

- Same as above.

**The following was used in an introductory biostatistics course for summer school students in medicine and allied health sciences**[1]

EPIB-694 Principles of Inferential Statistics
Construction of a Statistical Exercise
Due: 5pm June 21, 2004

You are asked to construct an exercise along the lines of the homegrown ones which are being used in this course, suitable for testing or demonstrating understanding of basic principles of biostatistics. These principles are to be found in such texts as Colton or Moore and McCabe or as discussed in the lectures.

While you are free to invent the entire exercise, it will probably be easier (and more realistic) to base it on some report in a scientific journal (in your own specialty, or a general one*) or perhaps in the lay press. It should concern some health problem amenable to statistical investigation. Try to make the narrative as clear and as concise as you can. The exercise should comprise 5-7 questions requiring altogether about one hour for completion. You are asked also to produce a separate set of model answers; these should be equally short and to the point.

The questions may cover any part of this course (694) or the preceding one (693). Indeed, in the interests of time, and the June 21st deadline, it would be good to have 1 or 2 of the questions cover material from 693.

See examples of such an exercise, prepared by students in past years.

Your exercise and model answers will count for the indicated % of the marks in your final grade for this course. In assessing the quality of your exercise, we shall consider the extent to which the questions test understanding of important biostatistical principles in a clear, concise and unambiguous way. Credit will also be given for choice of subject and ingenuity in use of the available information.

The exercise, model answers and a copy of any published report(s) on which the exercise is based should be handed in by the deadline indicated.

JH got the idea of this exercise from Corbett McDonald; he believes, as JH does, that just as with surgery, the best way to learn the statistical material is to 'See one, do one, teach one'.

If you absolutely cannot find an article, JH has some you might select from – but he urges you to find one on your own.

[1] This older material is reproduced here in case it might be of help if you are ever asked to teach such a course.

# Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

RECOVERY TRIAL

The RECOVERY Collaborative Group*


## ABSTRACT

### BACKGROUND

Hydroxychloroquine and chloroquine have been proposed as treatments for coronavirus disease 2019 (Covid-19) on the basis of in vitro activity and data from uncontrolled studies and small, randomized trials.

### METHODS

In this randomized, controlled, open-label platform trial comparing a range of possible treatments with usual care in patients hospitalized with Covid-19, we randomly assigned 1561 patients to receive hydroxychloroquine and 3155 to receive usual care. The primary outcome was 28-day mortality.

### RESULTS

The enrollment of patients in the hydroxychloroquine group was closed on June 5, 2020, after an interim analysis determined that there was a lack of efficacy. Death within 28 days occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15). Consistent results were seen in all prespecified subgroups of patients. The results suggest that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98). Among the patients who were not undergoing mechanical ventilation at baseline, those in the hydroxychloroquine group had a higher frequency of invasive mechanical ventilation or death (30.7% vs. 26.9%; risk ratio, 1.14; 95% CI, 1.03 to 1.27). There was a small numerical excess of cardiac deaths (0.4 percentage points) but no difference in the incidence of new major cardiac arrhythmia among the patients who received hydroxychloroquine.

### CONCLUSIONS

Among patients hospitalized with Covid-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care. (Funded by UK Research and Innovation and National Institute for Health Research and others; RECOVERY ISRCTN number, ISRCTN50189673; ClinicalTrials.gov number, NCT04381936.)

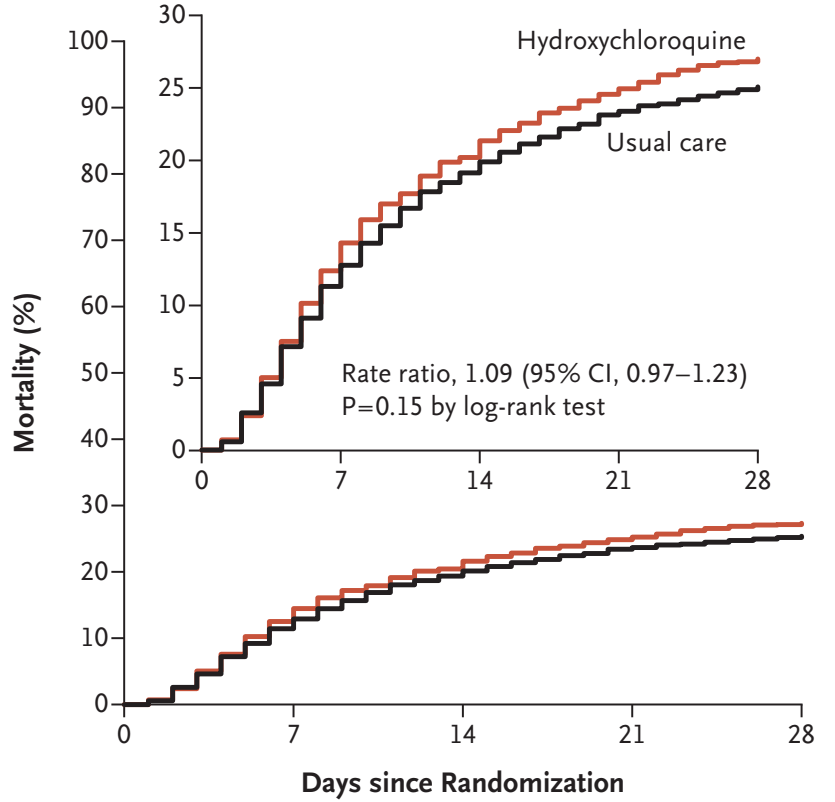




**Figure 2. Mortality at 28 Days.**

Death at 28 days (the primary outcome) occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group. The inset shows the same data on an expanded y axis.

## RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

This national clinical trial aims to identify treatments that may be beneficial for people hospitalised with suspected or confirmed COVID-19

The full article Effect of Hydroxychloroquine Hospitalized Patients with Covid-19 is found here.

## OUTCOME MEASURES

The primary outcome was all-cause mortality within 28 days after randomization; further analyses were specified at 6 months. Secondary outcomes were the time until discharge from the hospital and a composite of the initiation of invasive mechanical ventilation including extracorporeal membrane oxygenation or death among patients who were not receiving invasive mechanical ventilation at the time of randomization

## STATISTICAL ANALYSIS

For the primary outcome of 28-day mortality, we used the log-rank observed-minus-expected statistic and its variance both to test the null hypothesis of equal survival curves and to calculate the one-step estimate of the average mortality rate ratio in the comparison between the hydroxy-chloroquine group and the usual-care group. Kaplan-Meier survival curves were constructed to show cumulative mortality over the 28-day period. The same methods were used to analyze the time until hospital discharge, with censoring of data on day 29 for patients who had died in the hospital. We used the Kaplan-Meier estimates to calculate the median time until hospital discharge. For the pre-specified composite secondary outcome of invasive mechanical ventilation or death within 28 days (among patients who had not been receiving invasive mechanical ventilation at randomization), the precise date of the initiation of invasive mechanical ventilation was not available, so the risk ratio was estimated instead. Estimates of the between-group difference in absolute risk were also calculated.

All the analyses were performed according to the intention-to-treat principle. Pre-specified analyses of the primary outcome were performed in six subgroups, as defined by characteristics at randomization: age, sex, race, level of respiratory support, days since symptom onset, and predicted 28-day risk of death. (Details are provided in the Supplementary Appendix.)

Estimates of rate and risk ratios are shown with 95% confidence intervals without adjustment for multiple testing. The P value for the assessment of the primary outcome is two-sided. The full database is held by the trial team, which collected the data from the trial sites and performed the analyses, at the Nuffield Department of Population Health at the University of Oxford.

## SUPPLEMENTARY STATISTICAL METHODS

### *Sample size*

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned at the start of the COVID-19 pandemic. As the trial progressed, the Trial Steering Committee, blinded to the results of the study treatment comparisons, formed the view that if 28-day mortality was 20% then a comparison of at least 2000 patients allocated to active drug and 4000 to usual care alone would yield at least 90% power at two-sided P=0.01 to detect a proportional reduction of one-fifth (a clinically relevant absolute difference of 4 percentage points between the two arms).

### *Baseline-predicted risk*

Baseline-predicted risk of 28-day mortality was estimated through the formula $100 \times \exp(a)/(1+\exp(a))$, where $a =$

```
-1.23
- 2.85 (age < 50) - 2.03 (age 50 - 59) - 1.21 (age 60 - 69) - 0.51 (age 70 - 79)
+ 0.42 (male)
- 0.34 (> 7 days since symptom onset)
+ 0.86 (on oxygen only at randomization)
+ 2.18 (on invasive mechanical ventilation at randomization)
- 0.01 (history of diabetes)
+ 0.22 (history of heart disease)
+ 0.21 (history of chronic lung disease)
+ 0.50 (history of kidney disease).
```

These regression coefficients were derived from a multivariable logistic regression model using data from all trial participants who (at the time of data-lock) had complete 28-day mortality follow-up data. The regression model additionally adjusted for treatment allocation (with usual care designated the reference category) and for all possible two-way interactions between the above baseline characteristics and treatment allocation. These additional terms were ignored when calculating baseline-predicted risk, however, in order to ensure that the estimates corresponded to risk if assigned usual care. Patients were then subdivided into three approximately equally-sized groups (across all RECOVERY participants) on the basis of their predicted risk: $< 30\%$, $\geq 30\%$ to $< 45\%$, and $\geq 45\%$. Calculation of rate ratio The RR is derived from the log-rank observed minus expected statistic (O - E) and its variance (V) as the one-step estimate, through the formula exp([O - E] $\div$ V), and its 95% CI is given by $\exp([O-E] \div V \pm 1.96 \div V^{1/2})$. simulations were performed and presented as median values and 95% prediction intervals.

Ascertainment and classification of study outcomes Information on baseline

characteristics and study outcomes was collected through a combination of electronic case report forms (see below) completed by members of the local research team at each participating hospital and linkage to National Health Service, clinical audit, and other relevant health records. Full details are provided in the RECOVERY Definition and Derivation of Baseline Characteristics and Outcomes Document which was published online (www.recoverytrial.net) on 9 June 2020. Randomization form The Randomization form (shown below) was completed by trained study staff. It collected baseline information about the participant (including demographics, COVID-19 history, comorbidities and suitability for the study treatments) and availability of the study treatments. Once completed and electronically signed, the treatment allocation was displayed.

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Hydroxychloroquine for COVID-19

**Test version only (v6.08 - 05/06/20)**

**Randomisation Program**

Call Freefone **0800 138 5451** to contact the RECOVERY team for **URGENT** problems using the Randomisation Program or for medical advice
All **NON-URGENT queries** should be emailed to **recoverytrial@ndph.ox.ac.uk**

Logged in as: **Barts Health NHS Trust**

**Section A: Baseline and Eligibility**

Date and time of randomisation: 5 Jun 2020 13:32

**Treating clinician**

**A1.** Name of treating clinician

**Patient details**

**A2.** Patient surname

Patient forename

**A3.** NHS number ☐ Tick if not available

**A4.** What is the patient's date of birth? / /

**A5.** What is the patient's sex?

**Inclusion criteria**

**A6.** Has consent been taken in line with the protocol?
If answer is No patient cannot be enrolled in the study

**A7.** Does the patient have proven or suspected SARS-CoV-2 infection?
If answer is No patient cannot be enrolled in the study

**A8.** Does the patient have any medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial?

**A8B.** Is the patient willing to receive convalescent plasma?

**A9.** COVID-19 symptom onset date: / /

**A10.** Date of hospitalisation: / /

**A11.** Does the patient require oxygen?

**A12.** Does the patient **CURRENTLY** require ventilation or ECMO?
Invasive mechanical ventilation or extra-corporeal membrane oxygenation

**Does the patient have any CURRENT comorbidities or other medical problems?**

**A13.1** Diabetes

**A13.2** Heart disease

**A13.3** Chronic lung disease

**A13.4** Tuberculosis

**A13.5** HIV

**A13.6** Severe liver disease

**A13.7** Severe kidney impairment (eGFR<30 or on dialysis)

**A13.8** Known long QT syndrome

**A13.9** Current treatment with macrolide antibiotics which are to continue
Macrolide antibiotics include clarithromycin, azithromycin and erythromycin

**A13.10** Previous adverse reaction to blood or blood product transfusion

**Are the following treatments UNSUITABLE for the patient?**
**If you answer Yes it means you think this participant should NOT receive this drug.**

**A14.1** Lopinavir-Ritonavir

**A14.3** Azithromycin

**A14B.1** Convalescent plasma

**Are the following treatments available?**

**A15.1** Lopinavir-Ritonavir

**A15.3** Azithromycin

**A15B.1** Convalescent plasma

**Current medication**

**A16** Is the patient currently prescribed remdesivir?

**Please sign off this form once complete**

Surname:

Forename:

Professional email:

Continue

Cancel

Page 25 of 37

Home

Follow-up form

The Follow-up form collected information on study treatment adherence (including both the randomised allocation and use of other study treatments), vital status (including date and provisional cause of death if available), hospitalisation status (including date of discharge), respiratory support received during the hospitalisation, occurrence of any major cardiac arrhythmias and renal replacement therapy received.

28/05/2020 Follow-up

Hydroxychloroquine for COVID-19

## Follow-up

### Date of randomisation

**Patient's date of birth**

yyyy-mm-dd

**1. Which of following treatment(s) did the patient definitely receive as part of their hospital admission after randomisation?** *

*(NB Include RECOVERY study-allocated drug, only if given, PLUS any of the other treatments if given as standard hospital care)*

- [ ] No additional treatment
- [ ] Lopinavir-ritonavir
- [ ] Corticosteroid (dexamethasone, prednisolone or hydrocortisone)
- [ ] Hydroxychloroquine
- [ ] Azithromycin or other macrolide (eg, clarithromycin, erythromycin)
- [ ] Tocilizumab or sarilumab
- [ ] Remdesivir

**The following questions only appear if the treatments have been allocated at randomisation**

**Please select number of days the patient received lopinavir-ritonavir**

1 2 3 4 5 6 7 8 9 10

**Please select number of days the patient received corticosteroid (dexamethasone, prednisolone or hydrocortisone)**

1 2 3 4 5 6 7 8 9 10

**Please select number of days the patient received hydroxychloroquine**

1 2 3 4 5 6 7 8 9 10

**Please select number of days the patient received azithromycin** **This question and the following question cannot both be zero**

0 1 2 3 4 5 6 7 8 9 10

**Please select number of days the patient received other macrolides (eg, clarithromycin, erythromycin)**

0 1 2 3 4 5 6 7 8 9 10

**Please select number of doses of tocilizumab or sarilumab the patient received**

1 >1





28/05/2020 Follow-up

Hydroxychloroquine for COVID-19

**Please select number of days the patient received remdesivir**

1 2 3 4 5 6 7 8 9 10

### » Convalescent Plasma

**How many convalescent plasma infusions did the patient receive?**

***This is plasma given as part of trial, not any standard fresh frozen plasma or other blood products that the patient may have been given***

0 1 2

**Were any infusions stopped early for any reason ie, the patient did not receive the full amount?**

Yes No

**How many were stopped early?**

1 2

### » Health Status

**2. Was a COVID-19 test done for this patient?**

*(If multiple tests were done, and the results were positive and negative, please tick Yes – positive result and Yes – negative result)*

- [ ] Yes – positive result
- [ ] Yes – negative result
- [ ] Not done

**3. What is the patient's vital status?** *

- ◯ Alive
- ◯ Dead

**3.1 What is the patient's current hospitalisation status?**

Q3.1 is only completed if the patients is alive at Q3

- ● Inpatient
- ● Discharged

The patient has been enrolled in the trial for **NaN** days

**3.1.1 Date follow-up form completed** Q3.1.1 is only completed if patient is still an inpatient at Q3

yyyy-mm-dd

28/05/2020 Follow-up

Hydroxychloroquine for COVID-19

**3.1.1 What was the date of discharge?** Q3.1.1 is only completed if patient has been discharged at Q3

yyyy-mm-dd

**3.1 What was the date of death?** * Q3.1.1 is only completed if patient has died at Q3

yyyy-mm-dd

**3.2 What was the underlying cause of death?** *

*This can be obtained from the last entry in part 1 of the death certificate*

- ◯ COVID-19
- ◯ Other infection
- ◯ Cardiovascular
- ◯ Other

**Please give details**

**4. Did the patient require any form of assisted ventilation (ie, more than just supplementary oxygen)?** *

- ◯ Yes
- ◯ No

**Please answer the following questions:**

**4.1 For how many days did the patient require assisted ventilation?** *

**4.2 What type of ventilation did the patient receive?**

| | Yes | No | Unknown |
|---|---|---|---|
| **CPAP alone** | ◯ | ◯ | ◯ |
| **Non-invasive ventilation (eg, BiPAP)** | ◯ | ◯ | ◯ |
| **High-flow nasal oxygen (eg, AIRVO)** | ◯ | ◯ | ◯ |
| **Mechanical ventilation (intubation/tracheostomy)** | ◯ | ◯ | ◯ |
| **ECMO** | ◯ | ◯ | ◯ |

Hydroxychloroquine for COVID-19

**Total number of days the patient received invasive mechanical ventilation (intubation/tracheostomy) (from randomisation until discharge/death/28 days after randomisation)**

Complete if invasive mechanical ventilation (intubation/tracheostomy) is Yes

**5. Has the participant been documented to have a NEW cardiac arrhythmia at any point since the main randomisation?**

- ◯ Yes
- ◯ No
- ◯ Unknown

**5. Has the participant been documented to have a NEW cardiac arrhythmia at any point since the main randomisation?**

- ◯ Yes
- ◯ No
- ◯ Unknown

**5.1 Please select all of the following which apply**

**If Q5 is answered Yes, you must select at least one option here**

- ☐ Atrial flutter or atrial fibrillation
- ☐ Supraventricular tachycardia
- ☐ Ventricular tachycardia (including torsades de pointes)
- ☐ Ventricular fibrillation
- ☐ Atrioventricular block requiring intervention (eg, cardiac pacing)

**6. Did the patient require use of renal dialysis or haemofiltration?**

- ◯ Yes
- ◯ No

**7. Please enter UKOSS case ID if known** *

*Enter the full UKOSS case ID ie, COR_123*

**Complete only if patient was pregnant at randomisation**

*(select if you do not know the UKOSS case ID)*

☐ Not known

### *Cause of death*

Cause of death was recorded by the site staff on the Follow-up form. In addition, information about cause of death was obtained from death registration data in England, Wales and Scotland. Where cause of death information was available from both sources, the underlying cause of death from the death registration data was used (in preference to what was recorded on the Follow-up form). In the death registration data, the underlying cause of death is based on the death certificate information completed by the certifying doctor and is recorded using International Classification of Disease 10 codes. These were grouped into relevant categories as described in the Recovery Definition and Derivation of Baseline Characteristics and Outcomes document ( see www.recoverytrial.net ).

# SOLIDARITY TRIAL

The full article **Repurposed antiviral drugs for COVID-19 - interim WHO SOLIDARITY trial results** is found here.

MedRxiv (October 15) version



## Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results

WHO Solidarity trial consortium*


### ABSTRACT

**BACKGROUND**

WHO expert groups recommended mortality trials in hospitalized COVID-19 of four re-purposed antiviral drugs.

**METHODS**

Study drugs were Remdesivir, Hydroxychloroquine, Lopinavir (fixed-dose combination with Ritonavir) and Interferon-β1a (mainly subcutaneous; initially with Lopinavir, later not). COVID-19 inpatients were randomized equally between whichever study drugs were locally available and open control (up to 5 options: 4 active and local standard-of-care). The intent-to-treat primary analyses are of in-hospital mortality in the 4 pairwise comparisons of each study drug vs its controls (concurrently allocated the same management without that drug, despite availability). Kaplan-Meier 28-day risks are unstratified; log-rank death rate ratios (RRs) are stratified for age and ventilation at entry.

**RESULTS**

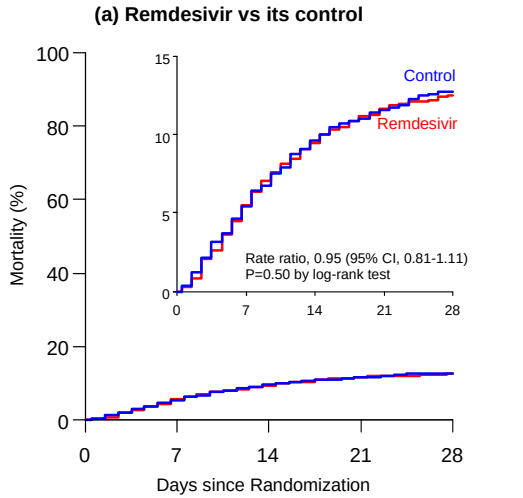
In 405 hospitals in 30 countries 11,266 adults were randomized, with 2750 allocated Remdesivir, 954 Hydroxychloroquine, 1411 Lopinavir, 651 Interferon plus Lopinavir, 1412 only Interferon, and 4088 no study drug. Compliance was 94-96% midway through treatment, with 2-6% crossover. 1253 deaths were reported (at median day 8, IQR 4-14). Kaplan-Meier 28-day mortality was 12% (39% if already ventilated at randomization, 10% otherwise). Death rate ratios (with 95% CIs and numbers dead/randomized, each drug vs its control) were: Remdesivir RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control), Hydroxychloroquine RR=1.19 (0.89-1.59, p=0.23; 104/947 vs 84/906), Lopinavir RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372) and Interferon RR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050). No study drug definitely reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalisation duration.

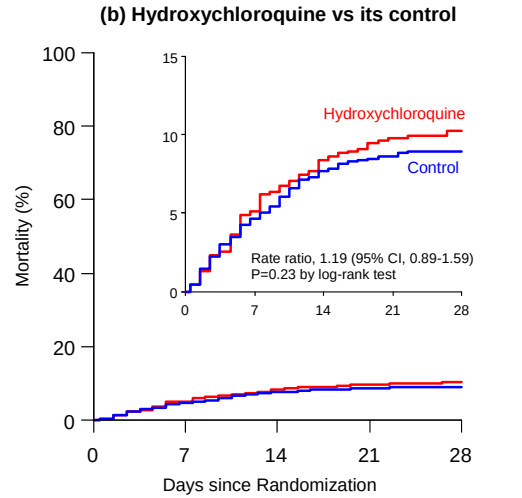
**CONCLUSIONS**

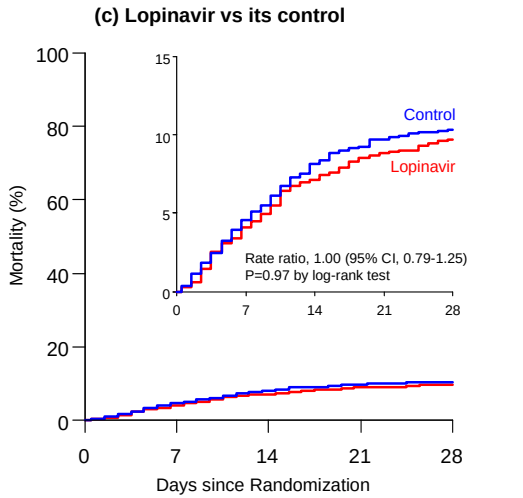
These Remdesivir, Hydroxychloroquine, Lopinavir and Interferon regimens appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay. The mortality findings contain most of the randomized evidence on Remdesivir and Interferon, and are consistent with meta-analyses of mortality in all major trials. (Funding: WHO. Registration: ISRCTN83971151, NCT04315948)

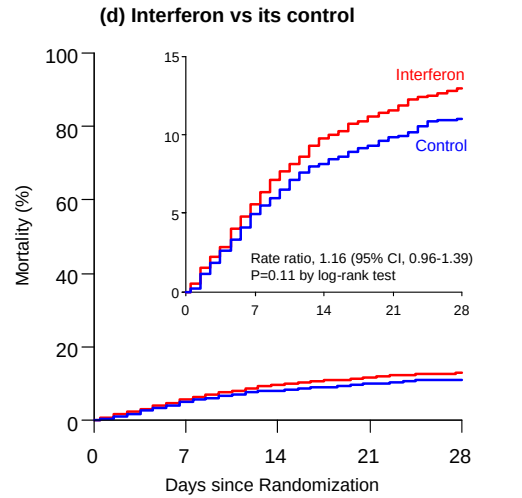

**Figure 2. Effects of (a) Remdesivir, (b) Hydroxychloroquine, (c) Lopinavir and (d) Interferon on 28-day mortality**

Kaplan-Meier graphs of in-hospital mortality. The inset shows the same data on an expanded y-axis.



## INTRODUCTION

A WHO COVID-19 research forum in February 2020 recommended evaluation of treatments in large randomized trials, and other WHO expert groups identified 4 re-purposed anti-viral drugs that might have at least a moderate effect on mortality: Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon-$\beta$1a.

In March 2020, WHO began a large, simple, multi-country, open-label randomized trial among hospital inpatients of the effects of these 4 drugs on in-hospital mortality. The trial was adaptive; unpromising drugs could be dropped and others added. Hydroxychloroquine and Lopinavir were eventually dropped, but others, such as monoclonal antibodies, will be added. We report interim mortality results for the original 4 drugs.

## METHODS

The protocol was designed to involve hundreds of potentially over-stressed hospitals in dozens of countries. Hence, no form-filling was required, and trial procedures were minimal but rigorous. Online randomization of consented patients (via a cloud-based GCP-compliant clinical data management system) took just a few minutes, as did online reporting of death in hospital or discharge alive (plus brief details of respiratory support in hospital and use of study drugs and certain non-study drugs). No other reporting was required unless doctors suspected an unexpected serious adverse reaction (SUSAR). National and global monitors resolved queries and checked progress and data completeness. Eligible patients were age $\geq$ 18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contra-indication to any study drug. Participants were randomized in equal proportions between control and whichever other study drugs were locally available (up to 5 options: these drugs, and local standard-of-care). Placebos were not used. Study drugs were Remdesivir, Hydroxychloroquine, Lopinavir-Ritonavir and Interferon (given with Lopinavir, until July 4). Hydroxychloroquine and Lopinavir were discontinued for futility on June 18 and July 4, 2020, respectively; Interferon is ceasing on October 16.

Daily doses were those already used for other diseases, but to maximize any efficacy without undue cardiac risk Hydroxychloroquine dosage was based on that for amoebic liver abscess, rather than the lower dosage for malaria. (Hydroxychloroquine slightly prolongs QT, and unduly high or rapid dosage might cause arrhythmias or hypotension.) All treatments were stopped at discharge; otherwise, regimens were:

- Remdesivir (intravenous): Day 0, 200mg; days 1-9, 100mg.
- Hydroxychloroquine (oral): Hour 0, four tablets; Hour 6, four tablets; Hour 12, begin two tablets twice daily for 10 days. Each tablet contained 200mg Hydroxychloroquine sulphate (155mg base/tablet; a little-used alternative involved 155mg chloroquine base/tablet).
- Lopinavir (oral): Two tablets twice daily for 14 days. Each tablet contained 200mg Lopinavir (plus 50mg Ritonavir, to slow hepatic clearance of Lopinavir). Other formulations were not provided, so ventilated patients received no study Lopinavir while unable to swallow.
- Interferon (mainly subcutaneous): Three doses over six days of 44$\mu$g subcutaneous Interferon-$\beta$1a; where intravenous interferon was available, patients on high-flow oxygen, ventilators or ECMO were instead to be given 10$\mu$g intravenously once daily for six days.

## ENDPOINTS

The protocol-specified primary objective was to assess effects on in-hospital mortality (ie, mortality during the original episode of hospitalization; follow-up ceased at discharge) not only in all patients but also in those with moderate COVID and in those with severe COVID (subsequently defined as ventilated when randomized). The protocol-specified secondary outcomes were initiation of ventilation and hospitalization duration. Although no placebos were used, appropriate analyses of these non-fatal outcomes can still be reliably informative. The CATCO add-on study in Canada and the Discovery add-on study in Europe (mostly France) recorded additional outcomes that will be reported elsewhere.

## SAMPLE SIZE

The protocol stated "The larger the number entered the more accurate the results will be, but numbers entered will depend on how the epidemic develops... it may be possible to enter several thousand hospitalised patients with relatively mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial." The Executive Group, blind to any findings, decided the timing of release of interim results.

## STATISTICAL ANALYSES

The four main sets of analyses involve the evenly randomized pairwise comparisons of each study drug vs its controls. The controls for those randomly allocated one particular drug were those patients who could by chance have been randomly allocated that drug (at that moment, in that hospital), but instead got allocated standard of care. If, for a particular study entrant, more than one study drug was available, allocation to standard of care would put that patient into the control group for each of them. Hence, there is partial overlap between the four control groups. Each comparison between a study drug and its controls, however, is evenly randomized (50/50) and unbiased,

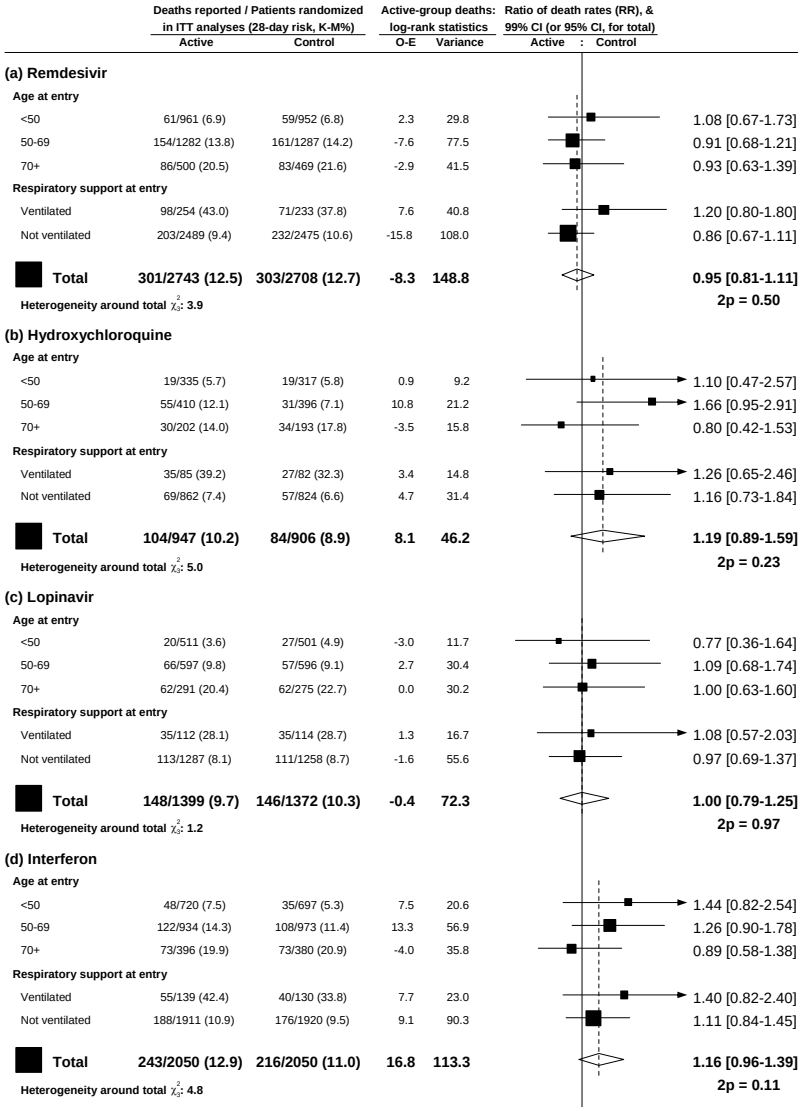
as both groups are affected equally by any differences between countries or hospitals and by any time trends in patient characteristics or standard of care.

All analyses relate mortality to allocated treatment (ie, they are intent-to-treat analyses). The overall mortality analyses were of all randomised patients (drug vs its control), and the only protocol-specified subgroup analyses are those considering separately patients with moderate and with severe COVID (ie, already ventilated; the type of ventilation was not recorded at study entry.) Unstratified Kaplan-Meier methods plot 28-day risk. Death rate ratios (RRs) and p-values are from log-rank analyses, stratified for 3x2=6 strata of age and ventilation at entry. If the stratified log-rank Observed minus Expected number of deaths is O-E with variance V, logeRR is calculated as (O-E)/V with variance 1/V and a The few currently uncertain death times were taken as day 7. Analyses censored patients with outcome not yet reported at day 0, and censored the few inter-hospital transfers at transfer. They did not censor patients discharged alive, as analyses were of mortality during the initial hospitalisation. Forest plots (with 95% CIs only for overall results, otherwise 99% CIs) and chi-squared statistics (sum of [O-E]2/V, with no p-value given) help interpret any apparent heterogeneity of treatment RRs between subgroups. Analyses used SASv9.4 and Rv4.02.

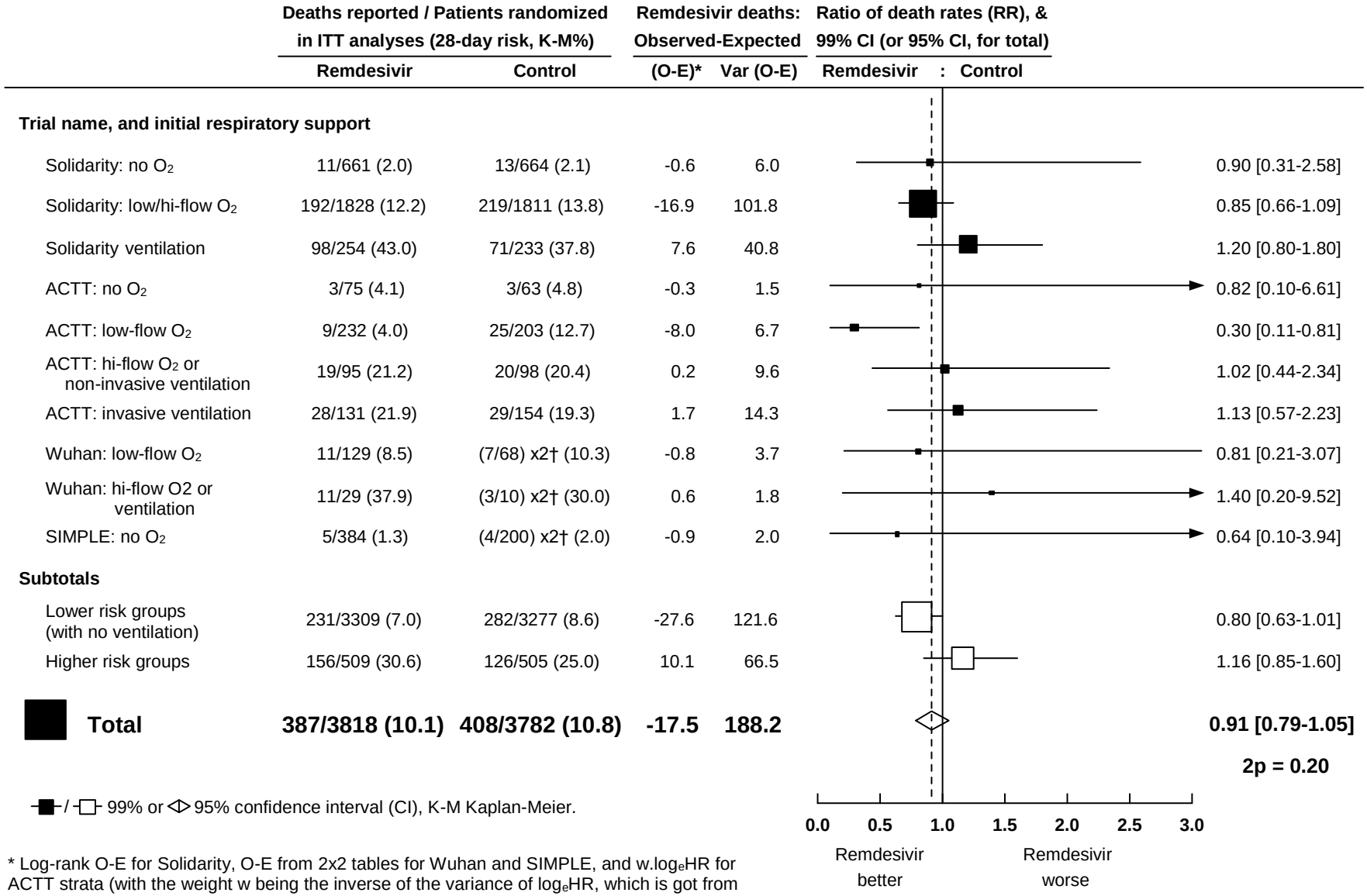
The Discussion includes meta-analyses of the major trial results, based on the inverse-variance-weighted average of b=log$_e$RR from each stratum of each trial, using odds ratios where hazard or death rate ratios were unavailable. (This weighted average is derived from the sums of [O-E] and of V over strata.) In general, the more deaths in a stratum the larger V is and, correspondingly, the smaller is the variance of log$_e$RR, so the more weight that stratum gets. The variance attributed to the result in each stratum and to the overall weighted average reflects only the play of chance at randomization. Homogeneity of different RRs is not needed for this weighted average to be informative.

**Figure 3. Rate ratios of any death, stratified by age and respiratory support at entry, (a) Remdesivir, (b) Hydroxychloroquine, (c) Lopinavir, (d) Interferon, each vs its control**





# Figure 4. Remdesivir vs control – Meta-analysis of mortality in trials of random allocation of hospitalised COVID-19 patients to Remdesivir or the same treatment without it




* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.log$_e$HR for ACTT strata (with the weight w being the inverse of the variance of log$_e$HR, which is got from the HR's CI). RR is got by taking log$_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the log$_e$RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

**FOR INTEREST ONLY** .

**FOR INTEREST ONLY**

The full article **Survival of SARS-CoV-2 and influenza virus on the human skin: Importance of hand hygiene in COVID-19** is found here.

Ryohei Hirose,[1,2*] Hiroshi Ikegaya,[3] Yuji Naito,[2] Naoto Watanabe, [1,2] Takuma Yoshida, [1,2] Risa Bandou,[1,3] Tomo Daidoji,[1] Yoshito Itoh,[2] Takaaki Nakaya[1]

[1] Department of Infectious Diseases, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.

[2] Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.

[3]Department of Forensics Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.





## Summary

The survival time of SARS-CoV-2 on the human skin was approximately 9 h, significantly longer than that of IAV (approximately 1.8 h). The longer survival of SARS-CoV-2 on the skin increases contact-transmission risk; however, hand hygiene can reduce this risk.

**Figure 1. Outline of the pathogen stability evaluation model and its reproducibility.** The pathogen stability evaluation model was constructed using human skin collected from forensic autopsy specimens (A). To evaluate the reproducibility of the model, influenza A virus (IAV) was applied to the six model skin samples and to the hand skin of six subjects (amount of virus: $1.0 \times 10^5$ FFU), and the titer of the remaining viruses on the skin was measured. The 95% confidence interval (red bar) of the viable virus titer on the model skin at each elapsed time was within the 95% confidence interval (blue bar) of the viable virus titer on the skin of live individuals (B).

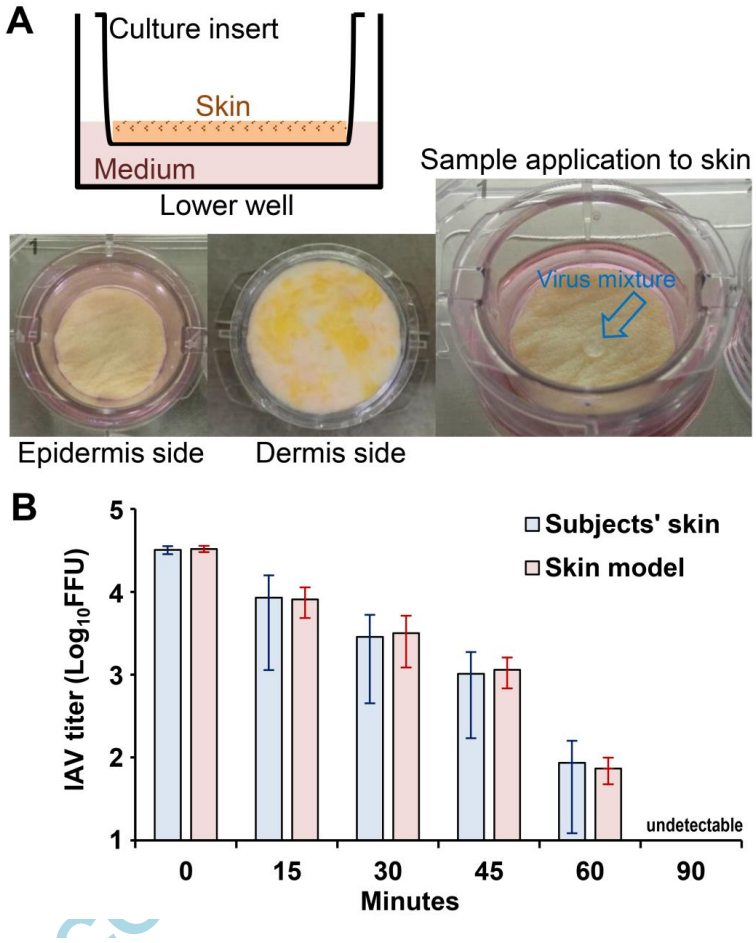


**Figure 2. (A–F) Fluctuations in the titer of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza A virus (IAV) surviving on the surface of stainless steel (A), borosilicate glass (B), polystyrene (C), and three skin samples [HS1 (D), HS2 (E), and HS3 (F)].** SARS-CoV-2/IAV was mixed with Dulbecco's modified Eagle's medium (DMEM) or mucus and applied in 5-μL aliquots to each surface (amount of virus: $1.0 \times 10^5$ FFU or $1.0 \times 10^5$ $TCID_{50}$, respectively). Each surface was incubated in a constant environment (temperature: 25 °C, humidity: 45–55%) for 0–120 h. The remaining viruses on the surface were then recovered in 1 ml of culture medium and titrated. For each measurement, three independent experiments were performed, and the results are expressed as the mean ± standard error of the mean. Bars referring to the data below the detection limit were omitted. See Supplementary Figure S1 and S2 for raw data.

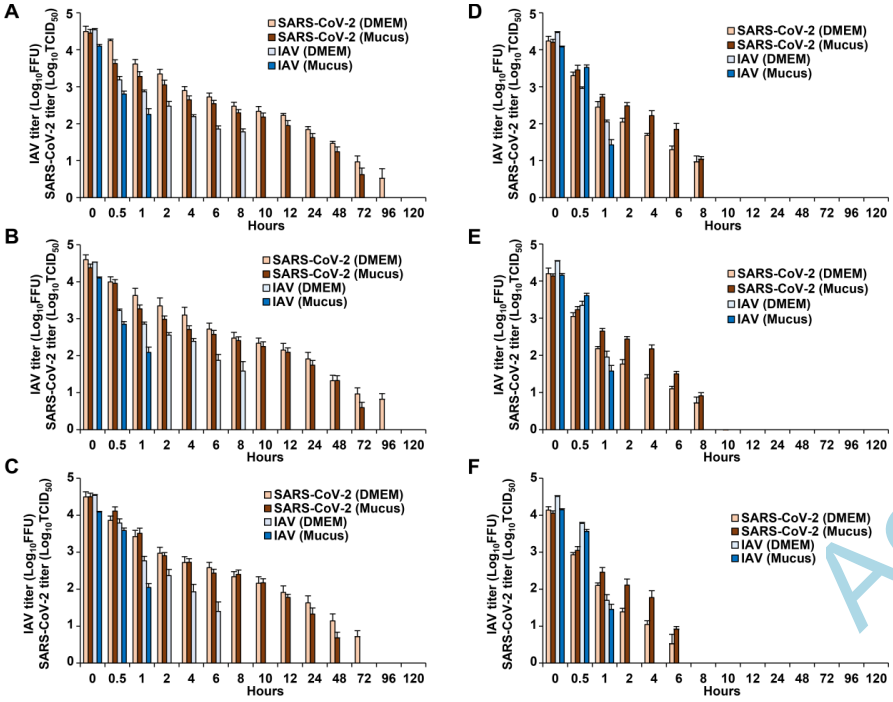



**Figure 3. Evaluation of the disinfection effectiveness of 80% (w/w) ethanol against SARS-CoV-2 (upper panel) and IAV (lower panel) on human skin.** Thirty minutes after the mixture of the DMEM/mucus and SARS-CoV-2/IAV was applied to each skin surface (HS1/HS2/HS3), 80% ethanol was further applied to the skin surfaces for 15 s, followed by disinfectant inactivation via dilution with culture medium. The surviving viruses on the skin surfaces were then titrated. For comparison, the surviving viruses on the skin surfaces in the absence of ethanol were also titrated over time. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IAV, influenza A virus; DMEM, Dulbecco's modified Eagle's medium. For each measurement, three independent experiments were performed, and the results are expressed as mean ± standard error values.

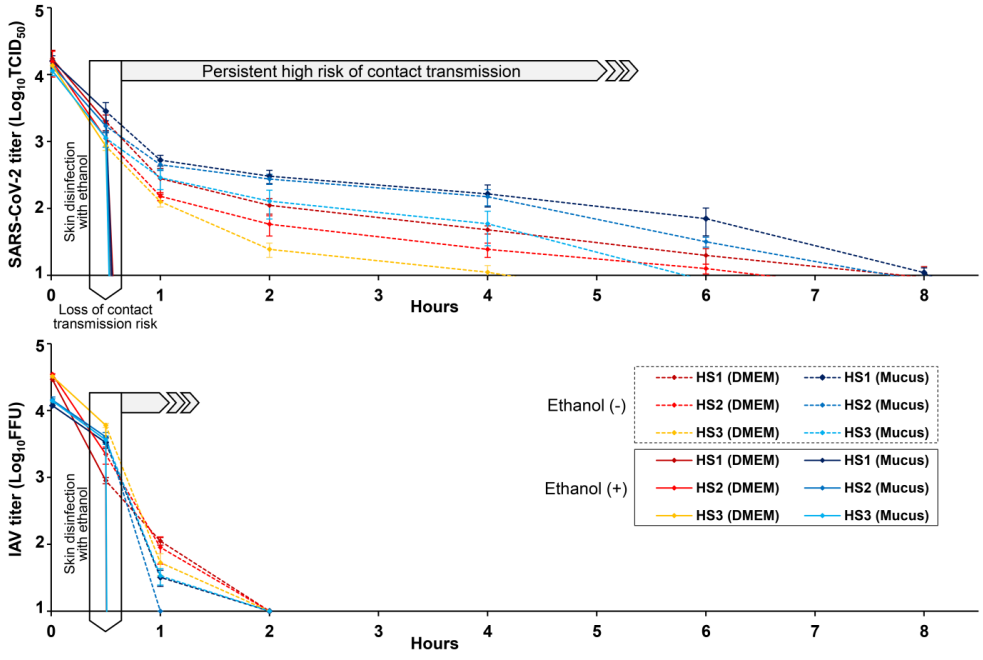


**Table 1. Survival time and half-life time of viruses on each surface.**

| | Survival time[1], hour, median (95% CI) | | | | Half-life time[2], hour, median (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | **IAV (DMEM)** | **SARS-CoV-2 (DMEM)** | **IAV (Mucus)** | **SARS-CoV-2 (Mucus)** | **IAV (DMEM)** | **SARS-CoV-2 (DMEM)** | **IAV (Mucus)** | **SARS-CoV-2 (Mucus)** |
| **Stainless steel** | 11.56 (10.11-13.22) | 84.29 (54.01-119.56) | 1.73 (1.57-1.91) | 64.51 (52.35-77.73) | 6.78 (5.84-7.97) | 32.62 (16.80-56.68) | 0.86 (0.76-0.98) | 25.53 (18.45-34.24) |
| **Borosilicate glass** | 10.61 (9.18-12.27) | 85.74 (56.27-119.80) | 1.73 (1.58-1.88) | 61.23 (49.03-74.44) | 6.13 (5.22-7.29) | 33.24 (17.59-56.49) | 0.85 (0.76-0.96) | 23.63 (17.16-31.86) |
| **Polystyrene** | 6.07 (5.05-7.27) | 58.07 (37.76-81.95) | 1.96 (1.76-2.18) | 35.92 (29.58-42.67) | 3.04 (2.40-3.87) | 22.58 (11.64-41.24) | 0.91 (0.80-1.04) | 13.17 (10.26-17.35) |
| **Human skin (HS total)** | 1.82 (1.65-2.00) | 9.04 (7.96-10.22) | 1.69 (1.57-1.81) | 11.09 (10.22-12.00) | 0.80 (0.72-0.90) | 3.53 (3.02-4.16) | 0.77 (0.71-0.84) | 4.16 (3.79-4.58) |
| **Human skin (HS1)** | 1.81 (1.64-2.00) | 10.93 (8.95-13.10) | 1.66 (1.47-1.88) | 12.24 (10.64-13.94) | 0.82 (0.73-0.93) | 4.13 (3.29-5.28) | 0.77 (0.66-0.89) | 4.47 (3.83-5.26) |
| **Human skin (HS2)** | 1.79 (1.50-2.13) | 9.45 (7.72-11.38) | 1.71 (1.51-1.94) | 12.2 (11.10-13.34) | 0.78 (0.64-0.98) | 3.75 (2.93-4.86) | 0.78 (0.67-0.91) | 4.51 (4.06-5.03) |
| **Human skin (HS3)** | 1.86 (1.50-2.27) | 6.14 (4.91-7.53) | 1.69 (1.49-1.91) | 8.13 (6.85-9.51) | 0.79 (0.63-1.04) | 2.36 (1.73-3.21) | 0.77 (0.67-0.90) | 3.13 (2.56-3.86) |

The elapsed time was defined as an explanatory variable (X-axis), and the log virus titer of IAV or SARS-CoV-2 was defined as an explained variable (Y-axis). A linear regression analysis with logarithmic link function was performed for each virus to create a curve of regression (see also Supplementary Figure S3).

[1]The measurement limits of the titers of IAV and SARS-CoV-2 were $10^1$ FFU and $10^{0.5}$ $TCID_{50}$, respectively; therefore, the survival times of IAV and SARS-CoV-2 were defined as the X values when the Y values of the regression curves were 1.0 and 0.5, respectively.

[2]The half-life time of each log virus titer was calculated from the slope of each regression line.

FOR INTEREST ONLY

# Remdesivir for the Treatment of Covid-19 — Preliminary 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), none have yet been shown to be efficacious.

**METHODS**

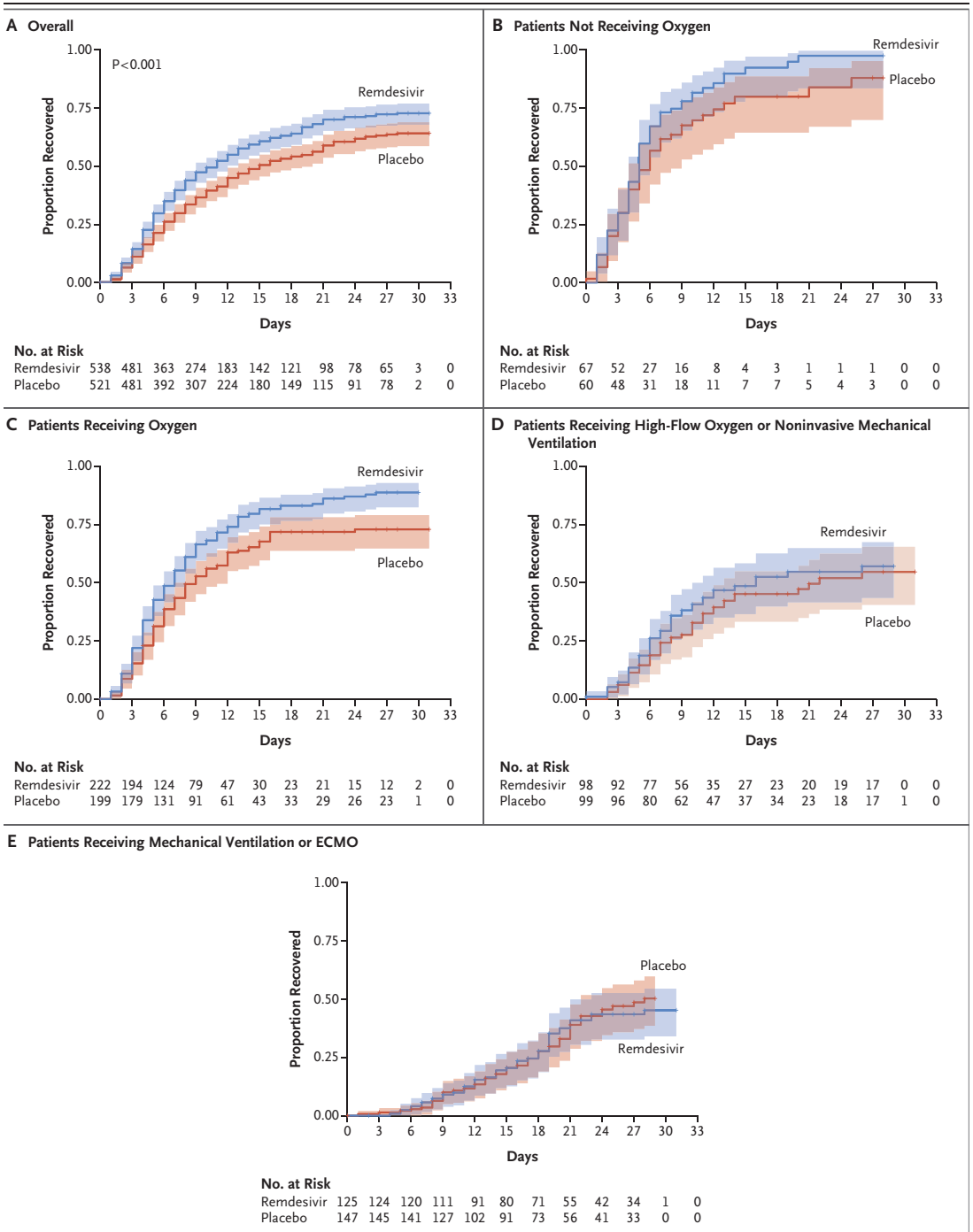
We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for 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 1063 patients underwent randomization. The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

**CONCLUSIONS**

Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACCT-1 ClinicalTrials.gov number, NCT04280705.)



# 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

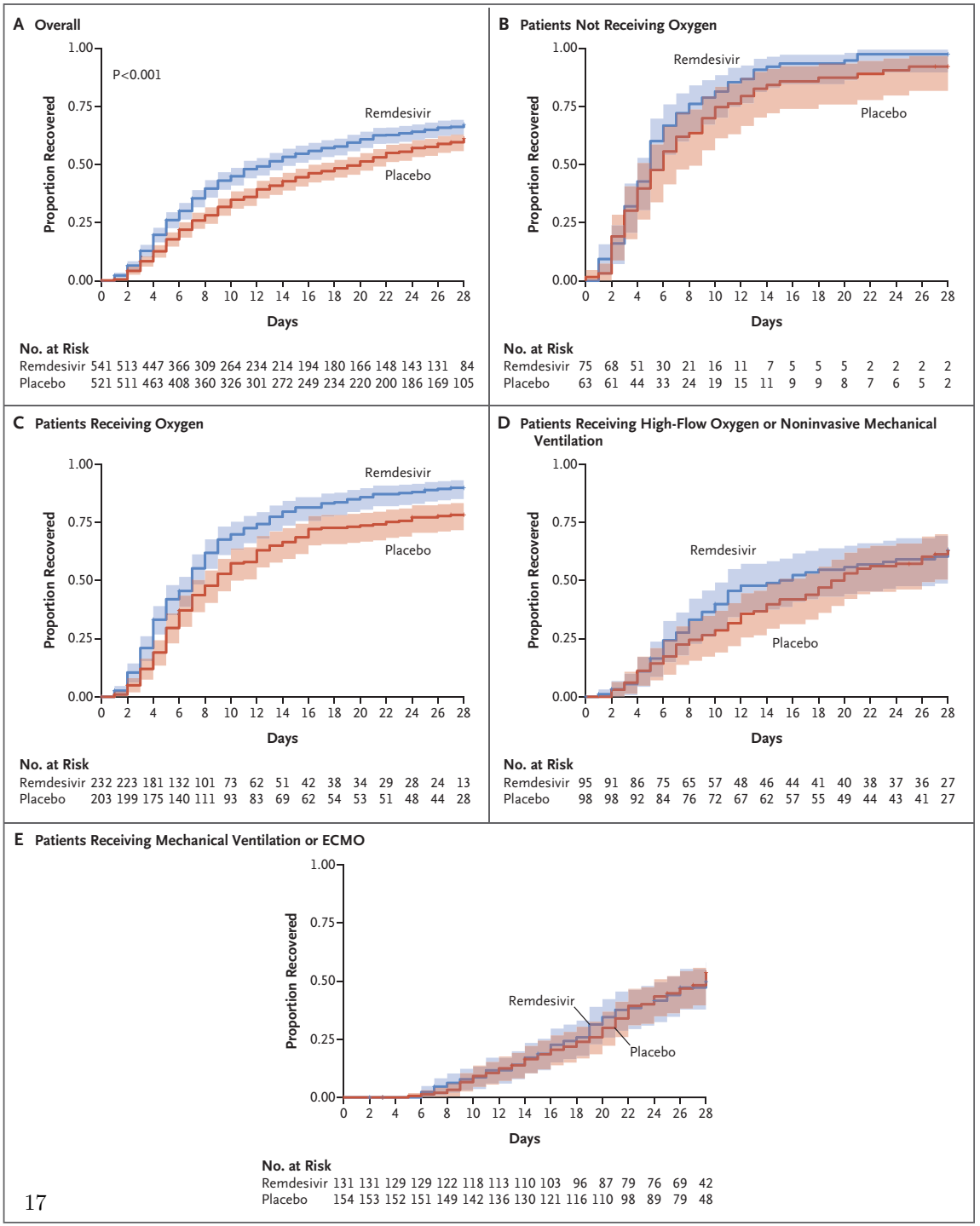
We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 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). In an analysis that used a proportional-odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).

### CONCLUSIONS

Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

## Supplementary Exercise

The full articles on the ACCT1 (Rendesivir) trial, as well as a Supplement that includes an expanded Statistical Analysis Plan, can be found in this single file.

Tue **2020-06-30** 9:04 PM.

Hi Jim. Hope all is well and you are surviving these crazy times.

I seem to recall you said at some point in the past that you were able to digitize pdf graphs

**Basically for Figure A on page 6 I want to calculate the AUC between the 2 curves as this will give the extra number of recovery days gained with the intervention. I think this is a more useful measure than giving the OR for recovery at arbitrary time points.**

Do you think that concept is reasonable. If so, are you able to calculate this area between the curves?

Cheers ..... Jay

Wed **2020-07-01** 2:54 PM Thanks Jim!

This confirms my gut instinct that while the relative metrics in the paper suggest a large benefit, when you look at absolute metrics, the benefit appear smaller.

Quickly looking at your digital plot, your calculations seem right. Each square represents 1 day and 5% difference. I quickly counted about 50 squares between the 2 curves so 50*0.05 = 2.5 people days which approximates your calculations.

This is less than the reported median difference of 4 days which I feel is an exaggeration of the true effect size. Not quite sure how to explain other than comparing than the benefits of examining the whole distributions versus looking at 1 time point.

In fact, I don't believe the choice of median times was mentioned as either a primary or secondary outcome. "The primary outcome measure was the time to recovery, defined as the first day, during the 28 days after enrollment," Moreover this trial suffers from enormous lost to follow-up if 28 days was the endpoint, ignoring deaths, it looks like 90% didn't reach the specified follow-up of 28 days. Maybe those missing people would have further shrunk the differences.

Like your `R` program. I see you haven't been swept up with the tidyverse / ggplot2 universe.

Interestingly about 2 hours ago, BMJ asked me to write an opinion piece about this Guardian article this Guardian article. Eventually we should do a formal cost-effectiveness piece on this drug - although it could be argued that it is a no-brainer in a public system to stay away from it and let the Americans over spend for these very modest benefits. I'll get back to you on this. Cheers

Tue **2020-10-13** 8:10 PM Hi Jim

These exercises look great. Wish I was back being a stats student!

Nice to see the reference to Clayton and Hill, I still have their textbook which remains among my favourites. Reminds me of a statistical epidemiology summer course i took from David Clayton many years ago in Florence. We had some intense ping pong games in the evenings!

So for remdesivir the opinion piece i wrote for the BMJ is found here

Big study apparently to be published this week will confirm no mortality benefit with remdesivir so another reason besides the cost not to be rushing out to be first in line to spend our limited health dollars on this particular drug. Glad for you to reference my email or anything else you think useful.

Stay healthy. Jay website: www.brophyj.com. twitter: @brophyj

James (Jay) Brophy MD PhD Professor of Medicine & Epidemiology (McGill University)

https://www.rte.ie/brainstorm/2020/1013/1171221-remdesivir-magic-bullet-covid-19-donald-trump-tests/

## Questions

1. Using the information in the Figure of the 'Remdesivir for the Treatment of Covid-19 — Preliminary Report' carry out the computation Dr Brophy proposed. [See JH for details on extracting data from K-M type curves in pdf files, as well as the article Recovering the raw data behind a non-parametric survival curve ] and some `R` code to extract graph co-ordinates from a PostScript file.]
2. Suggest a way to calculate a CI for the area between the curves.
3. In the 'Additional Statistical Analysis Details' section of the 'Supplementary Appendix to Manuscript Entitled Remdesivir for the Treatment of COVID-19 – Final Report' we read

   > The primary analysis was a log-rank test of time-to-recovery between remdesivir and placebo stratified by disease severity as defined above.

   Carry out the log-rank test.
4. We also read

   > The relevant treatment efficacy parameter is the "recovery rate ratio" (for remdesivir relative to placebo), which is akin to the hazard ratio in survival analysis but for the beneficial outcome of recovery.[2] The study was designed to achieve 85% power for detecting a recovery rate ratio of 1.35 with a two-sided type-I error rate of 5%. Enrollment continued through April 19, 2020 to ensure at least 400 recoveries and to address subgroup analysis.

   Carry out the sample size calculations (focusing on a minimum number of recoveries) based on (a) a binomial test that fixes the total number of recovered patients (as in the Mayo Lung Screening trial) and (b) the log of the recovery rate ratio; its variance is $1/E[n.r_0] + 1/E[n.r_1]$, where $n.r_0$ and $n.r_1$ are the numbers of recovered patients in the placebo and remdesivir arms respectively.

[2] "Two practical considerations result from considering time to a beneficial outcome. First, a recovery rate ratio greater than one indicates an improvement for remdesivir. Second, failure to recover and death are both censored at Day 29. Consequently, participants censored on the last observation day reflect two different states: death and failure to recover by Day 29. Hence, a breakdown of deaths by treatment arm is also important to understanding treatment efficacy. The key secondary analysis tested a difference in the ordinal score distribution between remdesivir and placebo at Day 15 using the "common odds ratio" from a proportional odds model, stratifying by baseline disease severity stratum."

**FOR INTEREST ONLY**

# Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*


## ABSTRACT

### BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

### METHODS

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

### RESULTS

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

### CONCLUSIONS

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)

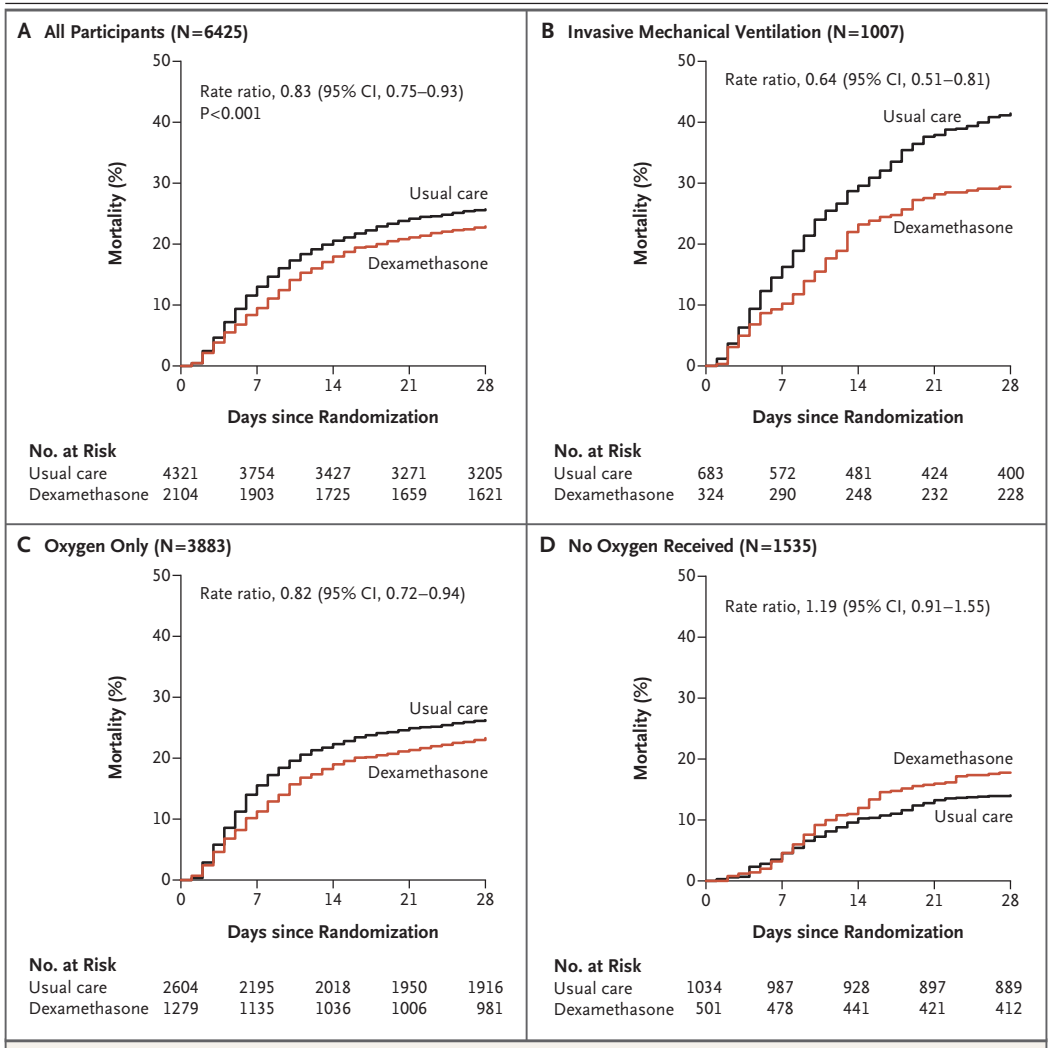




**Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.**

Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

## Supplementary Exercise

The full article Dexamethasone in Hospitalized Patients with Covid-19 – Preliminary Report is found here.

1. The Statistical Analysis section begins...

   > As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned at the start of the Covid-19 pandemic. As the trial progressed, the trial steering committee, whose members were unaware of the results of the trial comparisons, determined that if 28-day mortality was 20%, then the enrollment of at least 2000 patients in the dexamethasone group and 4000 in the usual care group would provide a power of at least 90% at a two-sided P value of 0.01 to detect a clinically relevant proportional reduction of 20% (an absolute difference of 4 percentage points) between the two groups. Consequently, on June 8, 2020, the steering committee closed recruitment to the dexa-methasone group, since enrollment had exceed- ed 2000 patients.

   Do your own power/sample size calculations and compare them with those above. State any assumptions you made.

2. Repeat the calculations for a design in which, rather than 1:2, the randomization was (a) 1:1 (b) 1:3. Comment on the lessons you learned from these calculations.

3. The section went on to say

   > For the primary outcome of 28-day mortality, the hazard ratio from Cox regression was used to estimate the mortality rate ratio. Among the few patients (0.1%) who had not been followed for 28 days by the time of the data cutoff on July 6, 2020, data were censored either on that date or on day 29 if the patient had already been discharged. That is, in the absence of any information to the contrary, these patients were assumed to have survived for 28 days. Kaplan–Meier survival curves were constructed to show cumulative mortality over the 28-day period.

4. Use the numbers in the Figure to verify that the censoring was indeed minimal and negligible.

5. How does this information simplify the calculation of the SE for the difference in 28-day mortality rates?

6. Calculate a 95% CI for ratio of the 28-day mortality rates (unlike the authors, you don't have the data to calculate the age-adjusted ratio.)

7. Is the ratio in patients receiving invasive mechanical ventilation significantly different from the ratio in those receiving oxygen without invasive mechanical ventilation?

8. For each of these two classes of patients, calculate the number needed to treat to prevent one death, and try to find the 'costs' of doing so. See the Dr Brophy's BMJ blog for the cost calculations for Remdesivir.

9. Use this trial to explain why, for doctors, knowing when there is effect modification (different slopes – or different effects – for different folks, or 'interaction' to statisticians ) is very important. 'Interactions' make in statistical models more complex, and the story more nuanced; one answer doesn't fit all, rather 'it depends'. But 'le bon traitement pour le bon patient' is central to good medical practice.