

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial



Prof Martin Landray

University of Oxford, UK

on behalf of the RECOVERY trial investigators

www.recoverytrial.net



Background

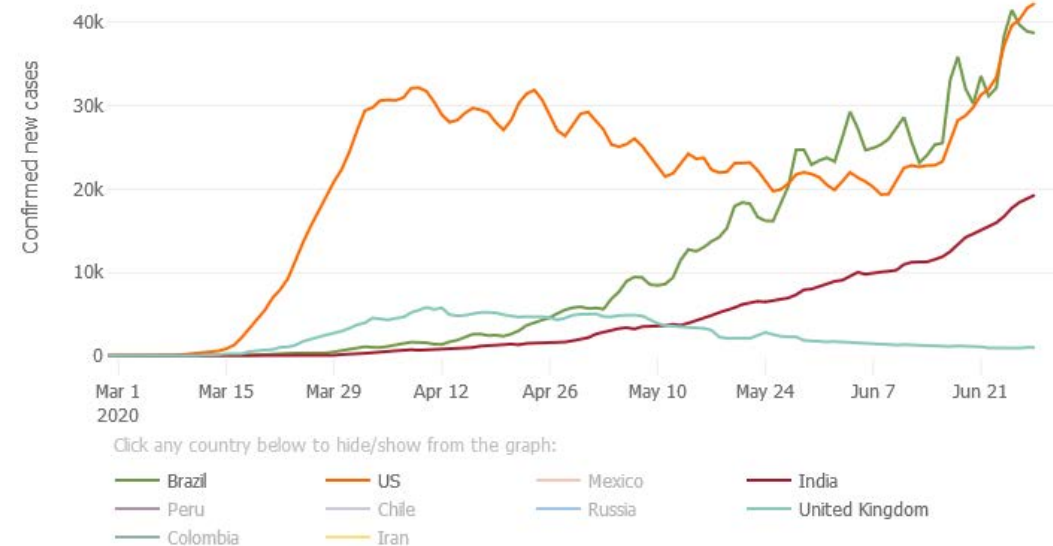
Pandemic caused by a new virus:

- For most people, self-limiting viral illness
- For hospitalised patients, 25-30% mortality
- For ventilated patients, 30-40% mortality

UK Cases



Cases in USA, UK, Brazil, and India



Background

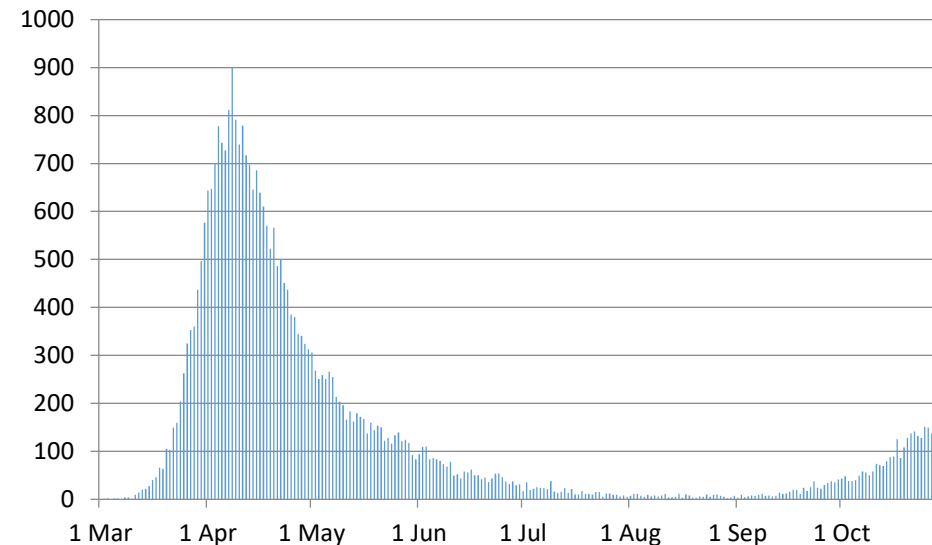
Unprecedented clinical challenge:

- Overstretched health service (availability of beds, staff, and ventilators)
- Huge time pressures and personal stress for frontline medical staff
- Large numbers of unwell, anxious, and often elderly patients

UK New Cases



UK Deaths



Selection of treatments

Huge uncertainty about treatment

- Many candidate drugs
- Many opinions (from many sources)
- No reliable data (uncontrolled case series, inconclusive randomized trials)
- Unlikely to be a single “big win” but moderate benefits would be important

Initial prioritisation principles

- Potentially effective (based on prior pre-clinical & clinical data)
- Major safety issues understood
- Sufficient treatment available for large-scale recruitment
- Potential to rapidly scale up as a clinical treatment (if shown to be effective)

Looking back to move forward...

STATISTICS IN MEDICINE, VOL. 3, 409–420 (1984)

WHY DO WE NEED SOME LARGE, SIMPLE RANDOMIZED TRIALS?

SALIM YUSUF* RORY COLLINS AND RICHARD PETO

Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, UK

The criteria for a good trial are similar in many serious diseases: first and foremost, ask an 'important' question and, secondly, answer it 'reliably'. These two very general criteria obviously require further elaboration, but even as they stand they can suggest some surprisingly specific consequences for clinical trial design. Particularly, they can be used to suggest both the possibility and the desirability of *large, simple randomized* trials of the effects on *mortality* of various *widely practicable* treatments for *common* conditions.

Lessons from the past...

Second International Study of Infarct Survival (ISIS2)

“By far the most important determinant of the success of ISIS is the extent to which, in those busy hospitals where the majority of acute MI patients are actually admitted, the responsible physicians and nurses choose to enter their patients. Hence, the extra work must be – and is – absolutely minimal.”

PATIENT IDENTIFIERS (Please PRINT)
(for central monitoring of certified causes of death)

Hospital: _____
Surname/Family name: _____
All given names: _____
Date of birth: day: _____ / month: _____ / year: _____
Address: _____
Maiden name: (if available) _____
Family doctor: (if available) _____

TICK **PRE-TREATMENT CHARACTERISTICS**

Female
 Previous myocardial infarction
 Previous diabetes

TICK **ANY DEVIATIONS FROM TRIAL TREATMENT**

STREPTOKINASE/PLACEBO infusion interrupted, or not given
 ASPIRIN/PLACEBO capsules pack interrupted, or not given

TICK **APPARENT SIDE-EFFECTS OF STREPTOKINASE/PLACEBO INFUSION**

Significant hypotension during, or just after, infusion
 Anaphylactic shock
 Rigor
 Rash
 Other (specify, eg, respiratory distress) _____

TICK **MAIN EVENTS (FATAL OR NOT) AFTER RANDOMISATION, AND ENTER DATE (FIRST) OCCURRED**
day / month / year

"Major" bleed (transfused) _____ and site(s) _____
 "Minor" bleed (not transfused) _____
 Cardiac rupture
 Reinfarction
 Ventricular fibrillation
 Other cardiac arrest
 Stroke, probable cerebral haemorrhage
 Stroke, infarct or unknown type _____ Likely residual disability (if alive): _____ Non-significant? _____ Moderate? _____ Severe? _____
 Discharge alive from hospital
 Death in hospital _____ and underlying cause, if not cardiac: _____

TICK **TREATMENT IN HOSPITAL**

Steroids prior to streptokinase/placebo infusion
 Subcutaneous heparin
 Intravenous heparin
 Oral anticoagulant
 Intravenous beta-blocker
 Non-trial aspirin
 Other anti-platelet agent(s) _____

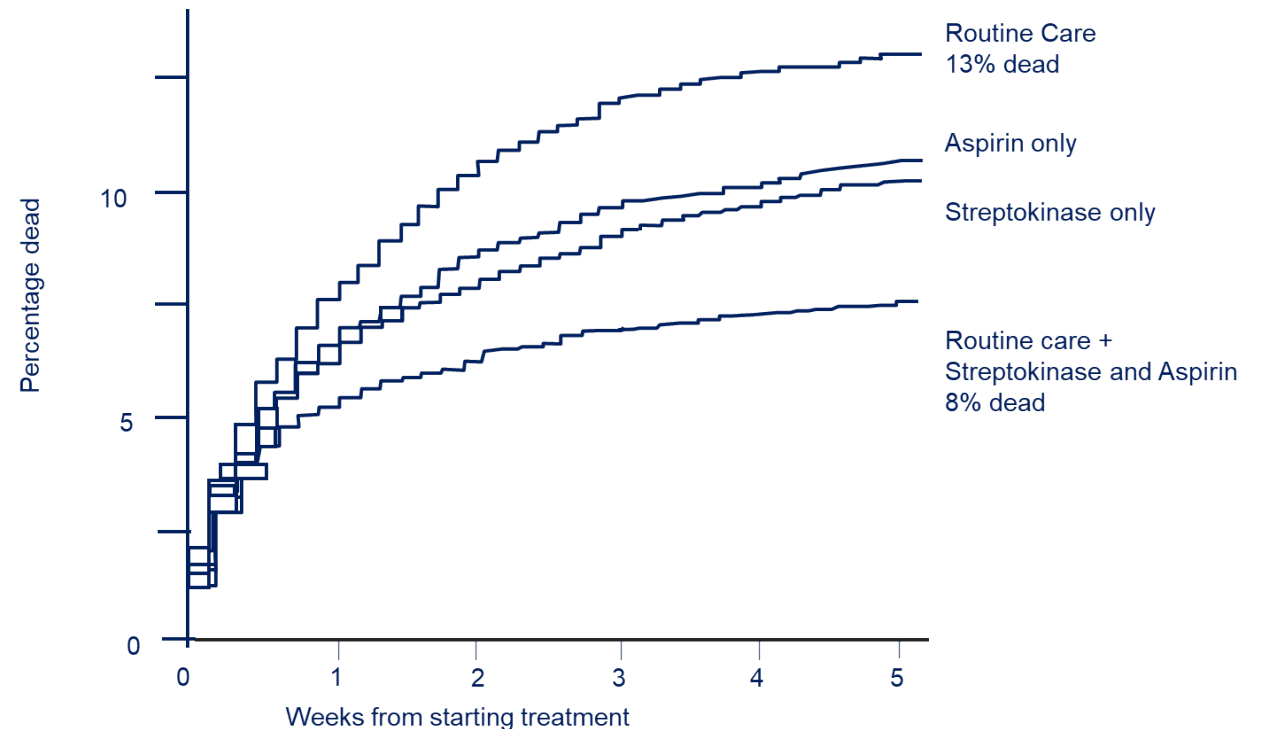
TICK **DRUGS ON DISCHARGE**

Oral anticoagulant
 Non-trial aspirin
 Other anti-platelet agent(s) _____
 Beta-blocker

NAME OF PERSON COMPLETING FORM (please PRINT): _____

PLEASE SEND: — TOP COPY OF THIS FORM (retain bottom green copy)
— AND PRE-RANDOMISATION ECG (original or good photocopy)
TO: ISIS-2, HREPOST, OXFORD OX2 0BB, UK (no stamp required within UK)

THANK YOU VERY MUCH



RECOVERY trial - Design

- **Simple eligibility:** Hospitalised patients with SARs-CoV-2
- **Important outcome:** mortality (use of ventilation, duration of hospitalisation)
- **Randomization:** assigns patient between suitable and available treatments
- **Follow-up:** 1 page case report form + extensive linkage to NHS datasets via NHS DigiTrials

- **Repurposed antivirals**

- Hydroxychloroquine
- Lopinavir-ritonavir

- **Immunomodulatory**

- Dexamethasone
- Azithromycin
- Tocilizumab

- **Targeted anti-SARS-CoV-2**

- Convalescent plasma

Randomised Evaluation of RECOVERY COVID-19 Therapy

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

Hospital: Patient Name:

1. Information about the study has been provided to me: I confirm that I have read and understood the Participant Information Leaflet (V1.0 13-Mar-2020) I have had the opportunity to consider the information and ask questions. These have been answered satisfactorily.

2. Voluntary participation: I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

3. Access to study data about me: I give permission for relevant sections of my medical notes and information collected during the study to be looked at, in confidence, by authorized individuals from this hospital, the University of Oxford, and regulatory authorities to check that the study is being carried out correctly.

4. Access to my medical information: I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be provided to the study coordinating centre both during and for up to 10 years after the scheduled follow-up period. I understand that information that identifies me will be passed securely to such bodies to make this possible and that I can opt out of this at any time by writing to the coordinating centre team.

5. Data stored on computer: I understand that information about my progress in the study will be recorded on a computer database, and that this data will be stored on computers supervised by the University of Oxford. I understand that this information will be kept securely and confidentially.

6. Agreement to take part: I have read the information (or had it read to me), had an opportunity to ask questions and agree to take part in the above study.

PRINTED name of participant Signature Today's date

PRINTED name of person taking consent Signature Today's date

*1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes

Logged in as: Berke Health NHS Trust

Section A: Baseline and Eligibility

Date and time of randomisation: 9 Apr 2020 17:55

Treating clinician

AE1. Name of treating clinician

Patient details

AE2. Patient surname

AE3. Patient forename

AE4. NHS number

AE5. What is the patient's sex?

AE6.1. Is the patient known to be pregnant?

AE6.2. Is the patient's date of birth?

Inclusion criteria

AE7. Has consent been taken in line with the protocol?

AE8. Does the patient have previous or suspected SARS-CoV-2 infection?

AE9. Does the patient have any medical history that might contraindicate or affect the safety of the study?

AE10. Date of COVID-19 symptom onset date

AE11. Date of hospitalisation

AE12. Does the patient require oxygen?

AE13. Does the patient CURRENTLY require ventilation or CPAP?

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

AE13.1 Diabetes

AE13.2 Heart disease

AE13.3 Chronic lung disease

AE13.4 Hypertension

AE13.5 HIV

AE13.6 Stroke/brain disease

AE13.7 Previous stroke treatment (pTICU) or an aneurysm

AE13.8 Previous long QT syndrome

AE13.9 Current treatment with immunosuppressants, steroids, anti-cancer drugs, immunosuppressants, anti-infectives and other immunosuppressants

Are the following treatments UNAVAILABLE for the patient?

AE14.1 Lopinavir-Ritonavir

AE14.2 Dexamethasone

AE14.3 Hydroxychloroquine

AE14.4 Azithromycin

Are the following treatments available?

AE15.1 Lopinavir-Ritonavir

AE15.2 Dexamethasone

AE15.3 Hydroxychloroquine

AE15.4 Azithromycin

Please sign off this form once complete

Signature

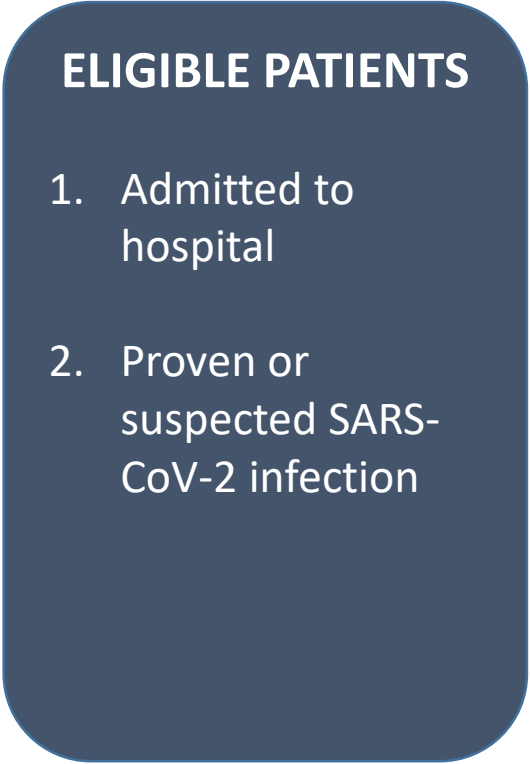
Professional name

Signature

Signature

RECOVERY trial design

ELIGIBLE PATIENTS

1. Admitted to hospital
 2. Proven or suspected SARS-CoV-2 infection
- 

RECOVERY trial design

ELIGIBLE PATIENTS

1. Admitted to hospital
2. Proven or suspected SARS-CoV-2 infection



No additional treatment

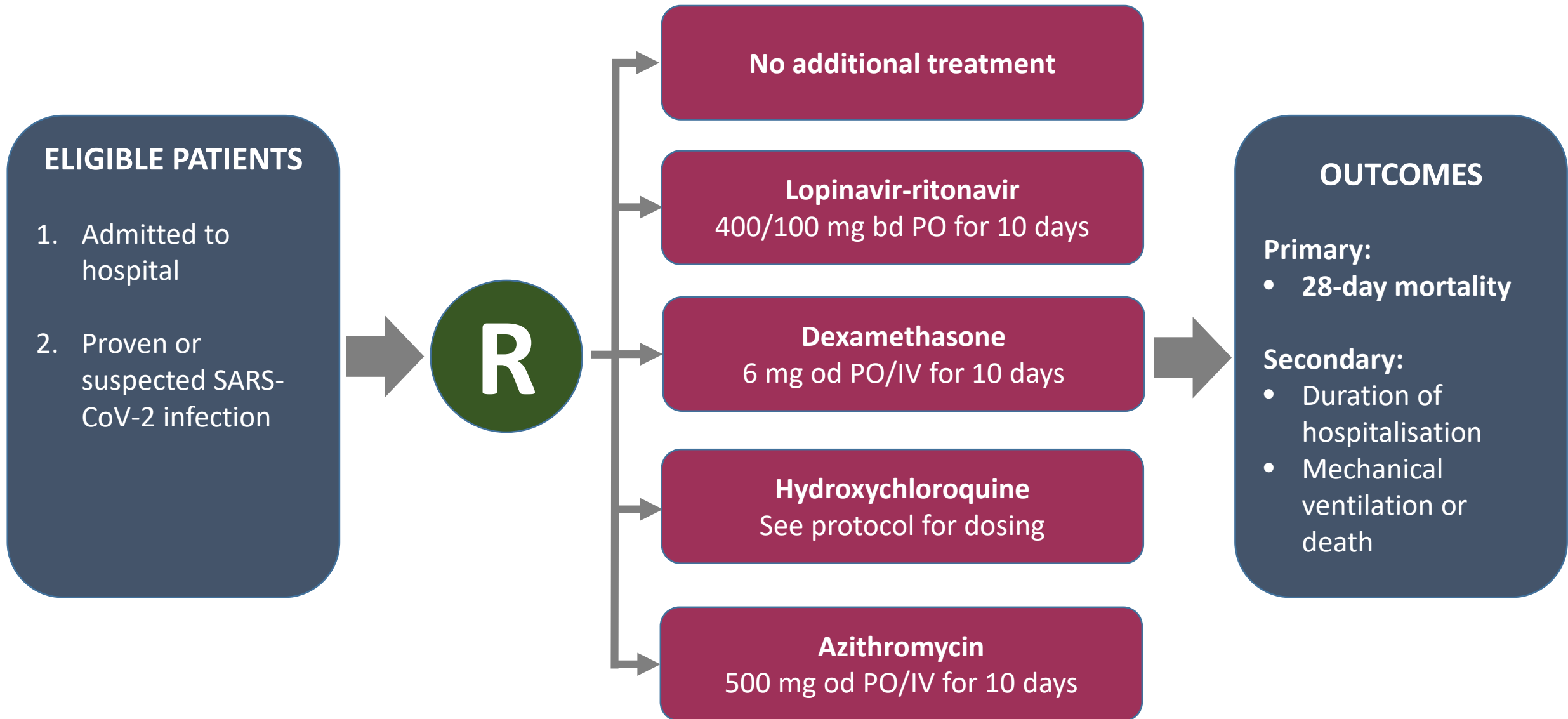
Lopinavir-ritonavir
400/100 mg bd PO for 10 days

Dexamethasone
6 mg od PO/IV for 10 days

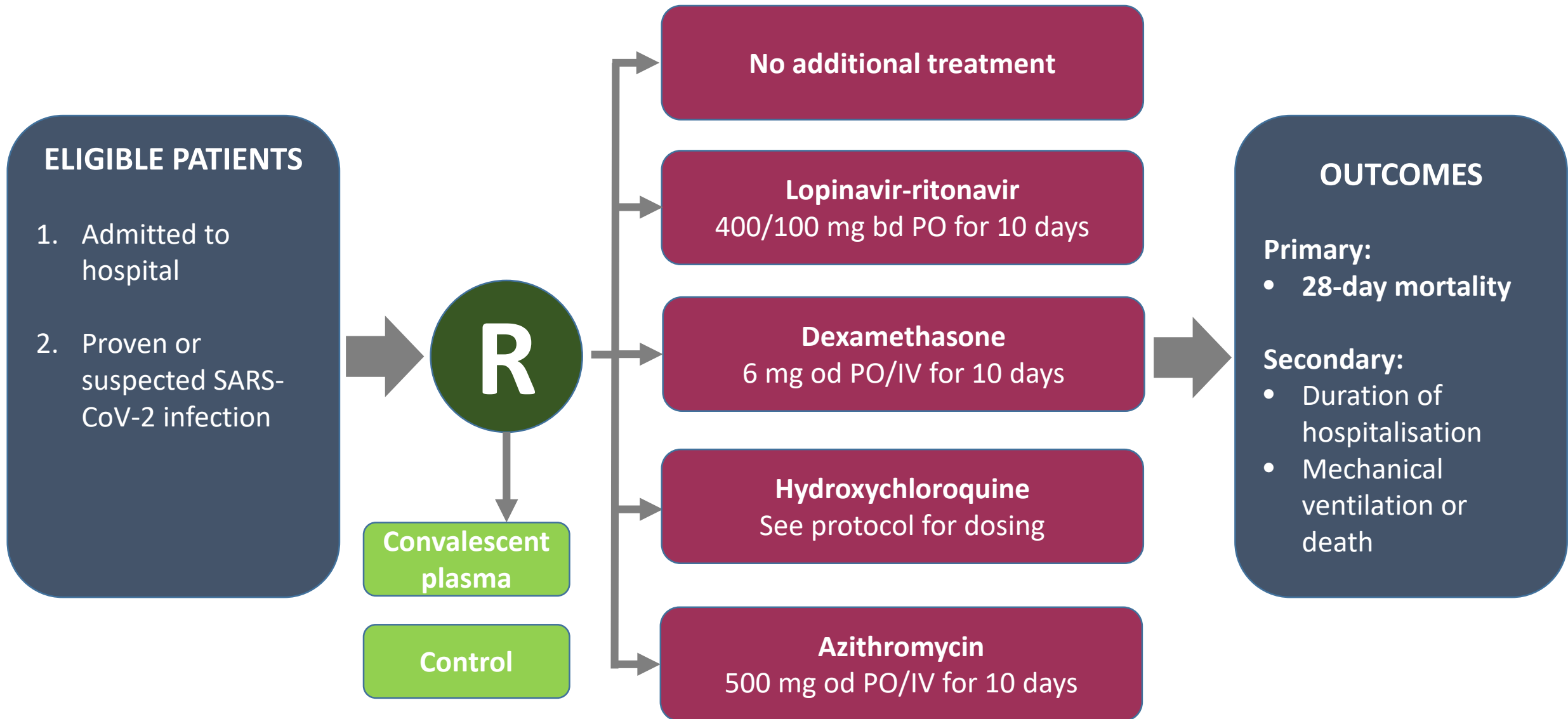
Hydroxychloroquine
See protocol for dosing

Azithromycin
500 mg od PO/IV for 10 days

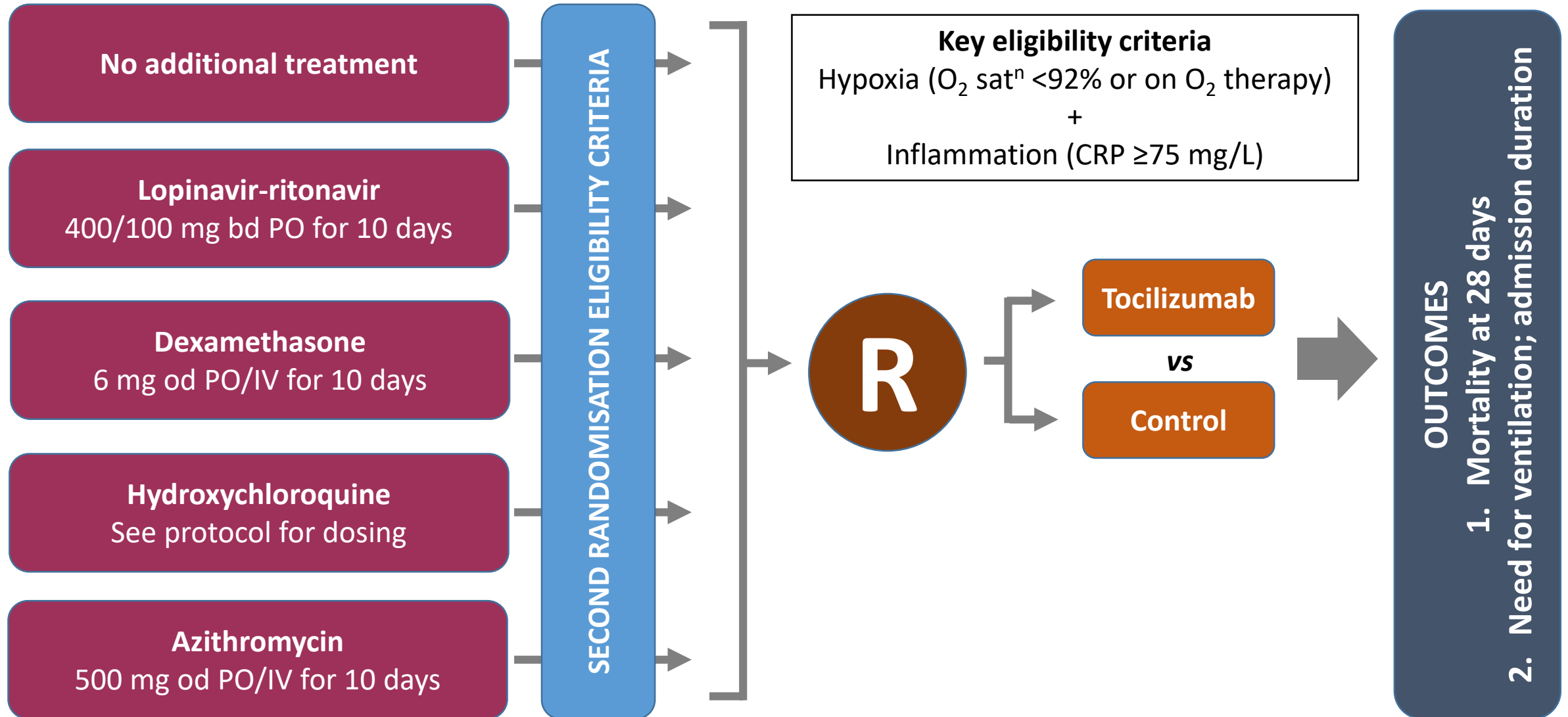
RECOVERY trial design



RECOVERY trial design



Adding a second randomisation



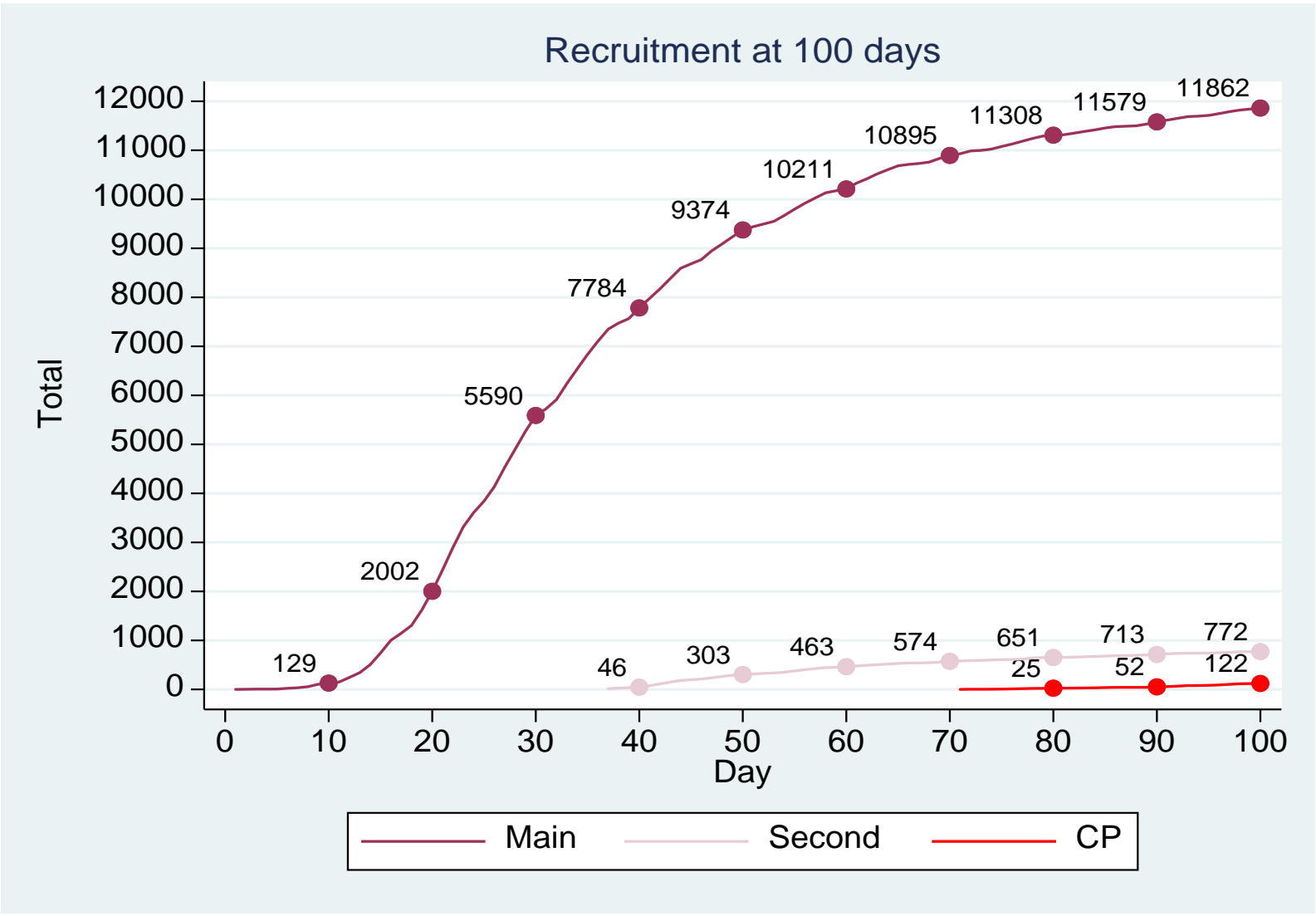
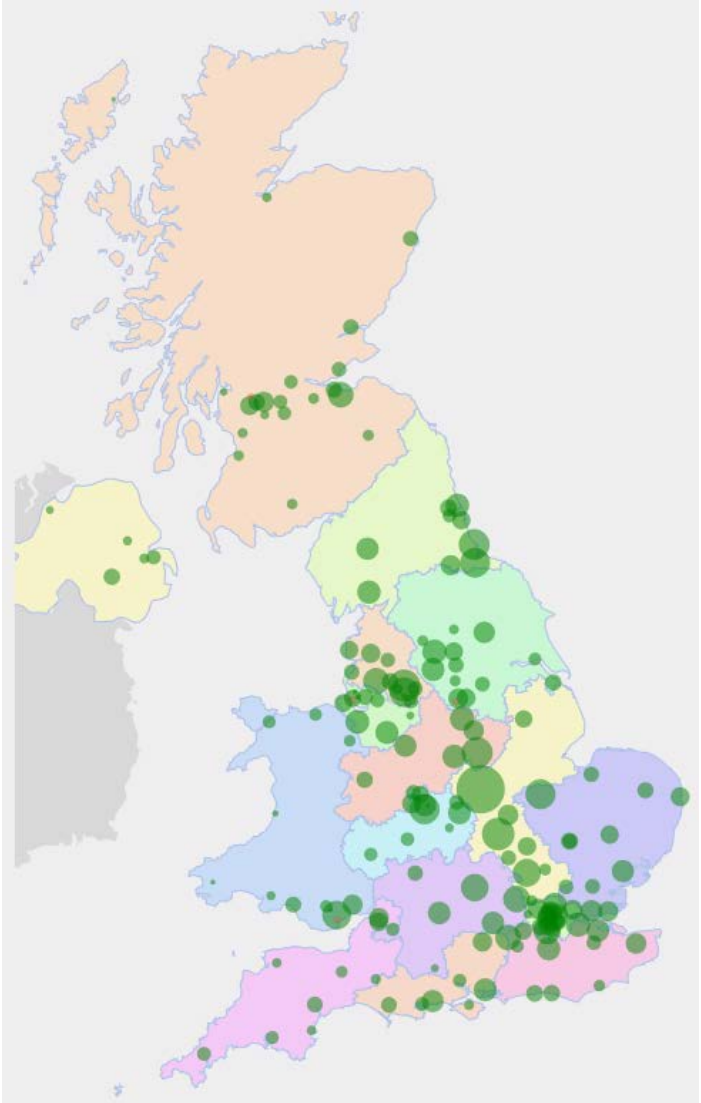
Follow-up

- **Simple on-line form at death, discharge or 28 days**
- **Additional assessment of safety of convalescent plasma at 72 hrs**
- **Linkage to national health data sources**
 - Vital status, death certificate
 - Coded hospital episode statistics (diagnoses, procedures)
 - Intensive Care audit data, SARS-CoV-2 PCR laboratory results
 - Primary care, national outpatient prescribing data
- **Pre-specified analyses at 6 months**
- **Permission to follow-up via record linkage for up to 10 years**

Adverse event reporting

- **Suspected Serious Adverse Reactions** – expedited reporting
- **All deaths (with cause of death)** – eCRF and record linkage
- **Other serious or non-serious adverse events** – not routinely captured
- **Additional assessments may be added** – e.g. cardiac arrhythmia, transfusion reactions
- **Emphasis on comparison with randomized control arm**
 - Independent Data Monitoring Committee

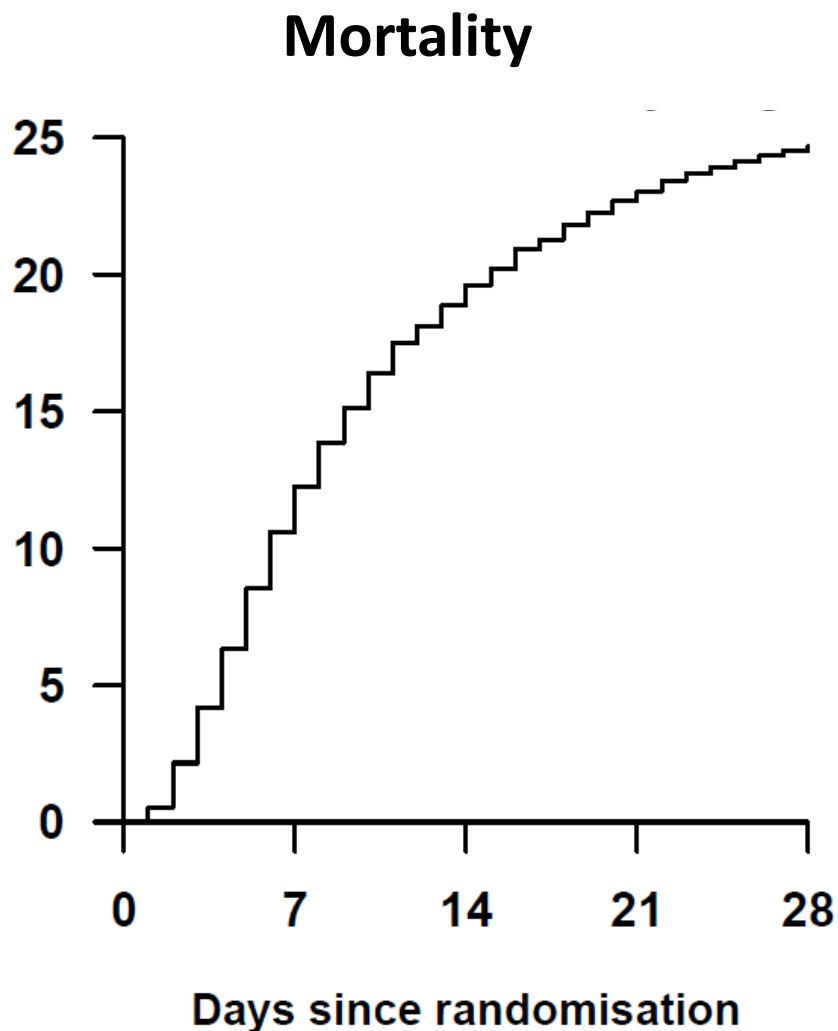
RECOVERY – rapid and widespread recruitment



Characteristics at main randomisation (n=12102)

Male sex		7539 (62%)
Age		66
Days since symptom onset (median)		8
Respiratory support	No oxygen required	3039 (25%)
	Supplemental oxygen only	7518 (62%)
	Ventilation/ECMO	1545 (13%)
Prior disease	Diabetes	3303 (27%)
	Cardiovascular disease	3410 (28%)
	Chronic lung disease	2731 (22%)

Mortality – overall and by patient characteristic



28-day mortality

Age (years)

<50	8%
50-59	14%
60-69	24%
70-79	33%
80+	40%

Sex

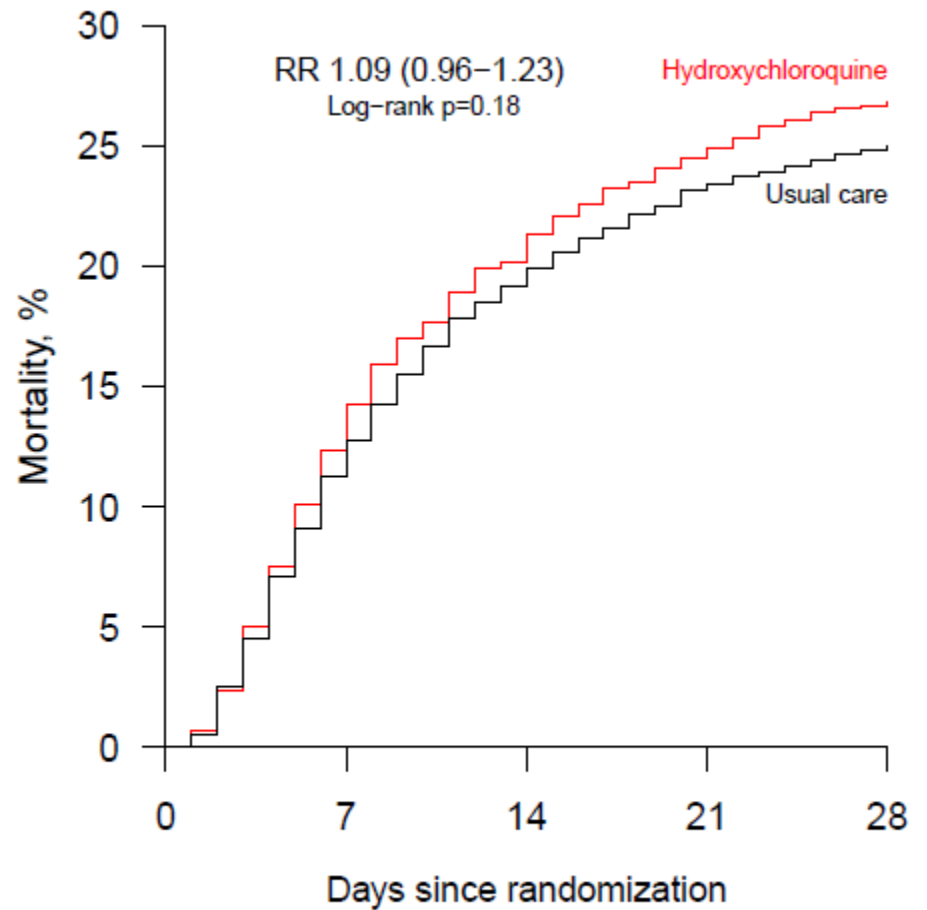
Female	19%
Male	26%

Respiratory support at enrolment

No oxygen	15%
Oxygen only	22%
Ventilation	35%

Hydroxychloroquine: No reduction in mortality

<https://www.nejm.org/doi/10.1056/NEJMoa2022926>



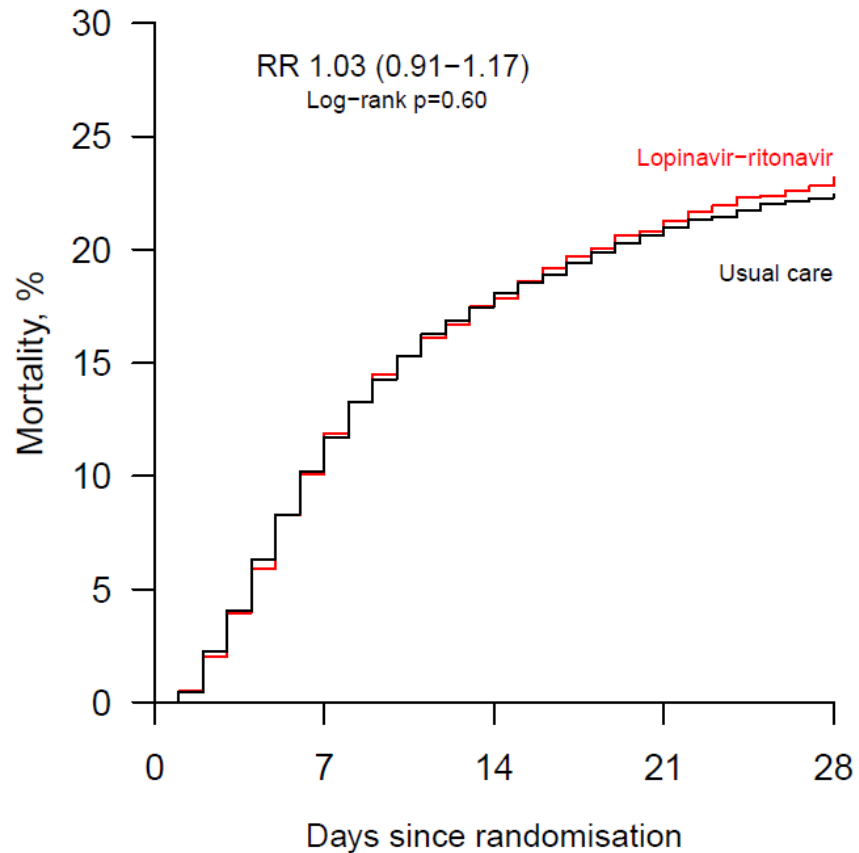
Number at risk	0	7	14	21	28
Active	1561	1337	1227	1161	1125
Control	3155	2750	2525	2410	2346



<https://www.nejm.org/doi/10.1056/NEJMoa2022926>

Lopinavir-ritonavir: No reduction in mortality

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32013-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32013-4/fulltext)



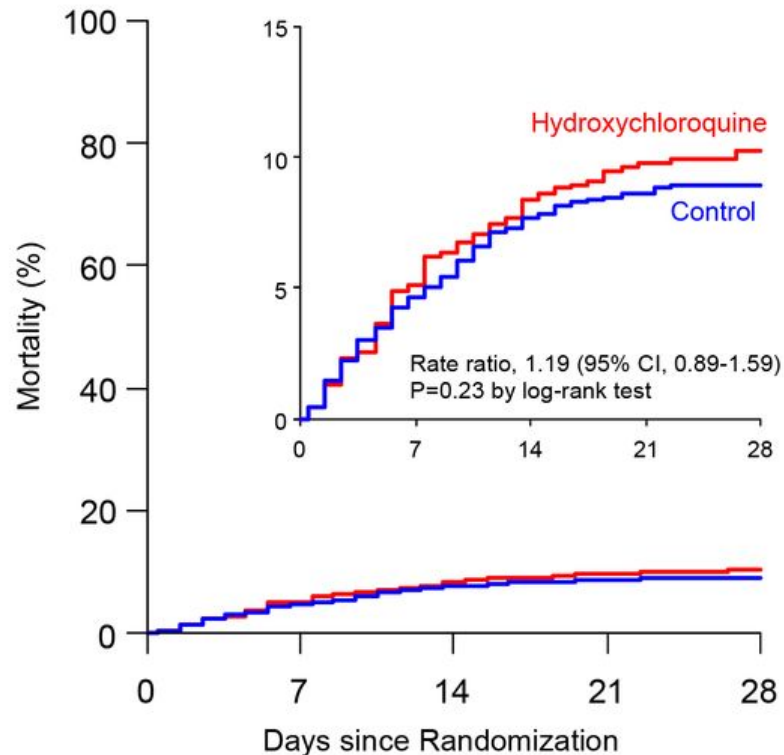
Number at risk	0	7	14	21	28
Active	1616	1422	1325	1269	1238
Control	3424	3018	2799	2700	2650



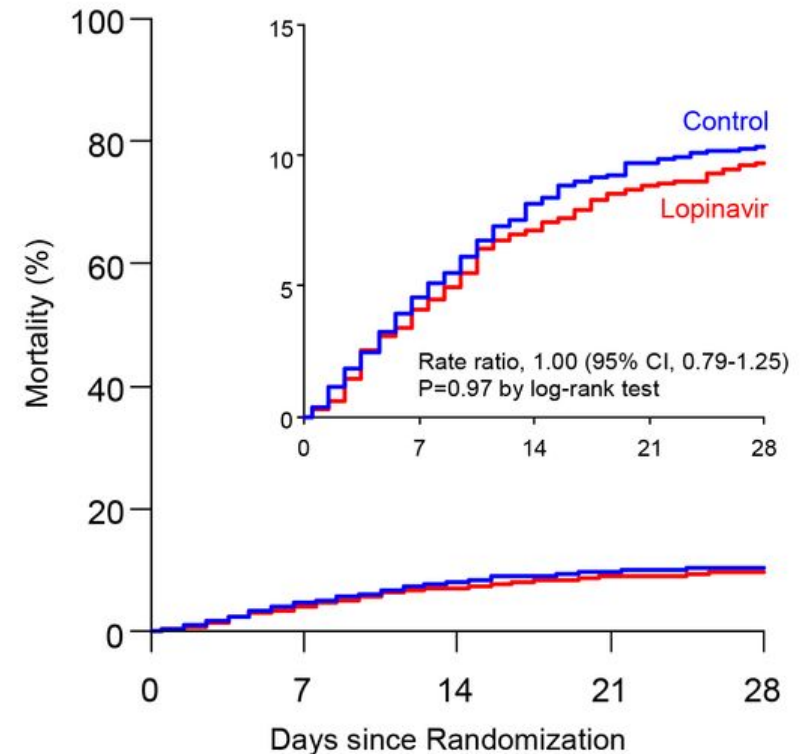
<https://www.najm.org/doi/10.1056/NEJMoa2022926>

WHO SOLIDARITY:

No effect of hydroxychloroquine or lopinavir on mortality

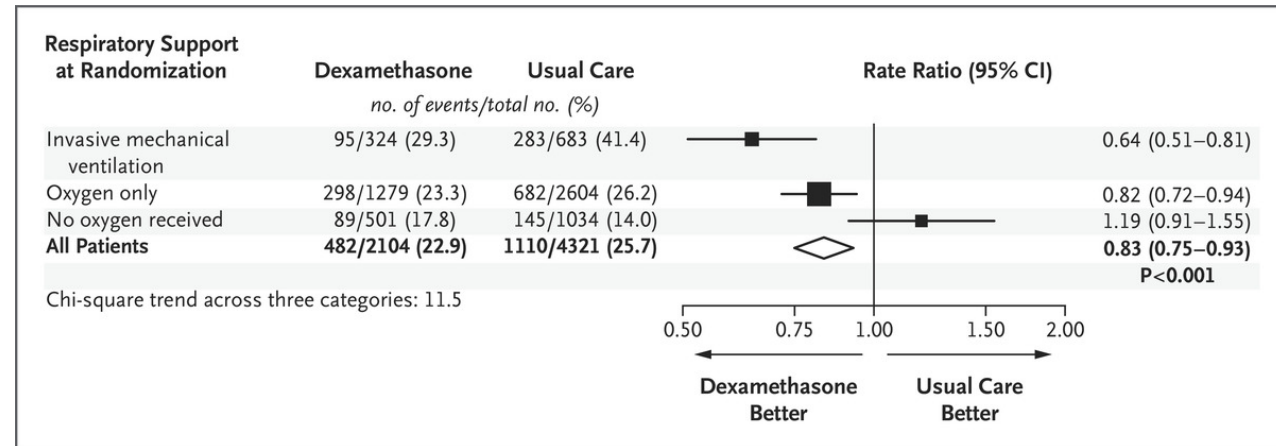
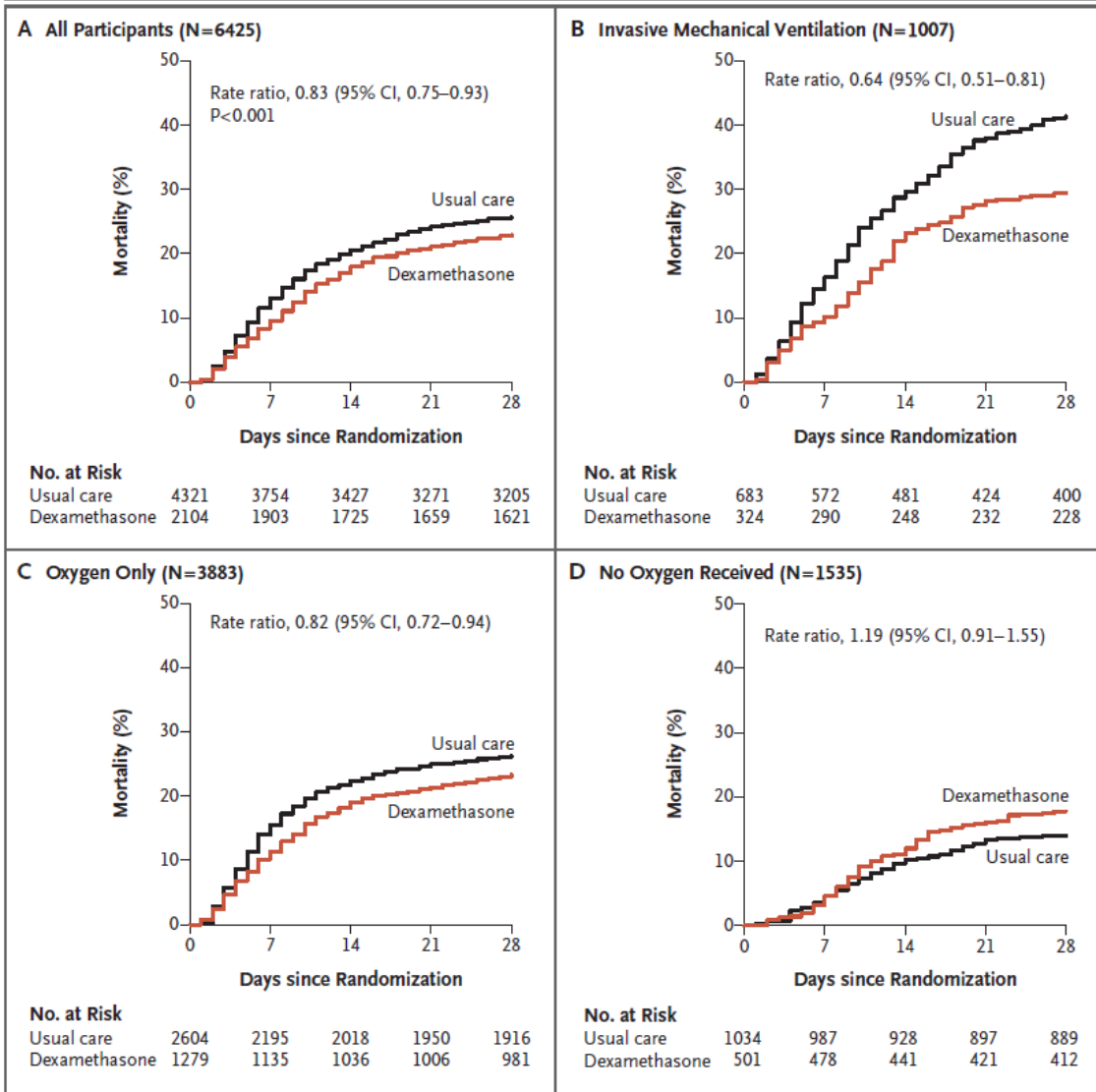


	0	7	14	21	28					
Hydroxyc .	947	48	889	31	854	13	838	6	833	6
Control	906	42	853	27	823	8	814	4	809	3



	0	7	14	21	28					
Lopinavir	1399	57	1333	42	1282	24	1257	15	1243	10
Control	1372	62	1293	48	1239	21	1216	10	1203	5

Dexamethasone: Reduces mortality in patients requiring oxygen or ventilation



From the UK GCMs and Medical Director of NHS England, 28 June 2020

Dear colleagues,
Dexamethasone in COVID-19

The RECOVERY trial in COVID-19 has provided evidence that dexamethasone 6 mg once per day (either by comparison with 4321 UK patients randomised 1 one-third in ventilated patients (rate ratio 0.65) or one fifth in other patients receiving oxygen only). There was no benefit among those patients who were not receiving oxygen (rate ratio 1.19).

Normally we would advise waiting for the full peer review, but given the importance of this information, we have decided to issue this guidance now. We will continue to monitor the evidence and update this guidance as more information becomes available.

Please find more information below.

Best wishes,

Dr Frank Atherton
Chief Medical Officer for Wales

Dr Gregor Smith
Chief Medical Officer for Scotland

Professor Stephen Powis
National Medical Director
NHS England and NHS Improvement

Professor Chris Whitty
Chief Medical Officer
England

COVID-19 Treatment Guidelines

The National Institutes of Health Guidelines Panel Provides Recommendations on Dexamethasone in Patients with COVID-19

Last Updated: June 25, 2020

Introduction

Patients with severe COVID-19 develop a systemic inflammatory response and multiorgan dysfunction. It has been hypothesized that corticosteroids might prevent or mitigate this response. However, several studies have yielded conflicting results: both that corticosteroids may be beneficial and that they may be harmful.

A preliminary, unpublished analysis from a large clinical trial in the United Kingdom showed that treatment with dexamethasone reduced the rate of mortality compared to those patients with severe COVID-19 (defined as those who required mechanical ventilation at enrollment or died) who did not require supplemental oxygen at enrollment.

Based on these preliminary results:

- The COVID-19 Treatment Guidelines Panel recommends dexamethasone 6 mg per day for up to 10 days in patients with severe COVID-19 who require supplemental oxygen (A).
- The Panel recommends against using dexamethasone in patients who do not require supplemental oxygen (A).

WHO welcomes preliminary results about dexamethasone use in treating critically ill COVID-19 patients

16 June 2020 | News release

The World Health Organization (WHO) welcomes the initial clinical trial results from the United Kingdom (UK) that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth, according to preliminary findings shared with WHO.

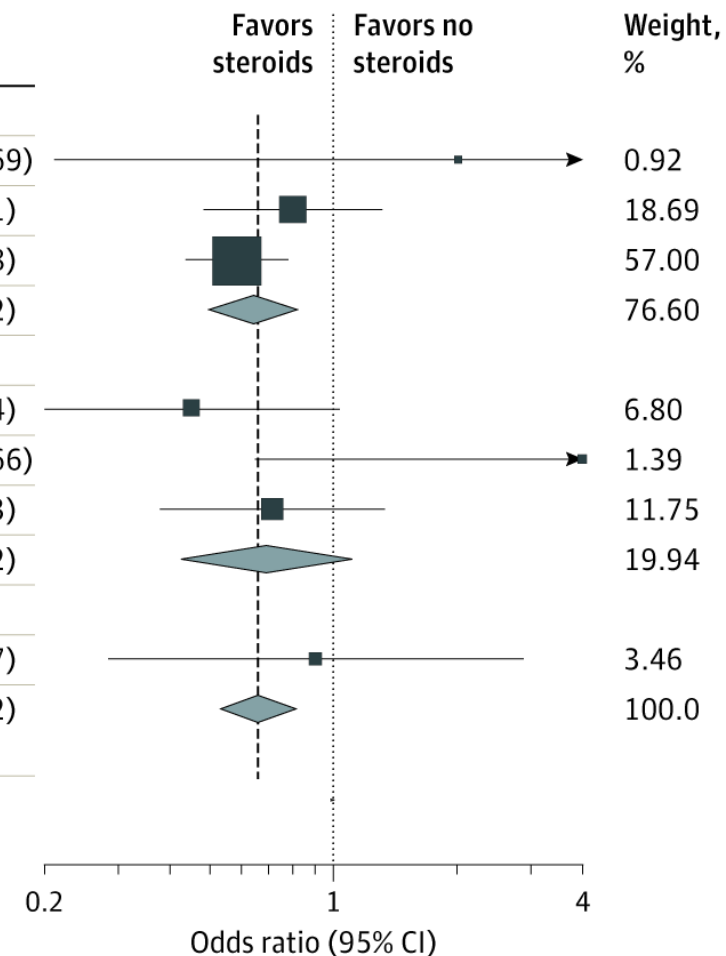
The benefit was only seen in patients seriously ill with COVID-19, and was not observed in patients with milder disease.

"This is the first treatment to be shown to reduce mortality in patients with COVID-19 requiring oxygen or ventilator support," said Dr Tedros Adhanom Ghebreyesus, WHO Director-General. "This is great news and I congratulate the Government of the UK, the University of Oxford, and the many hospitals and patients in the UK who have contributed to this lifesaving scientific breakthrough."

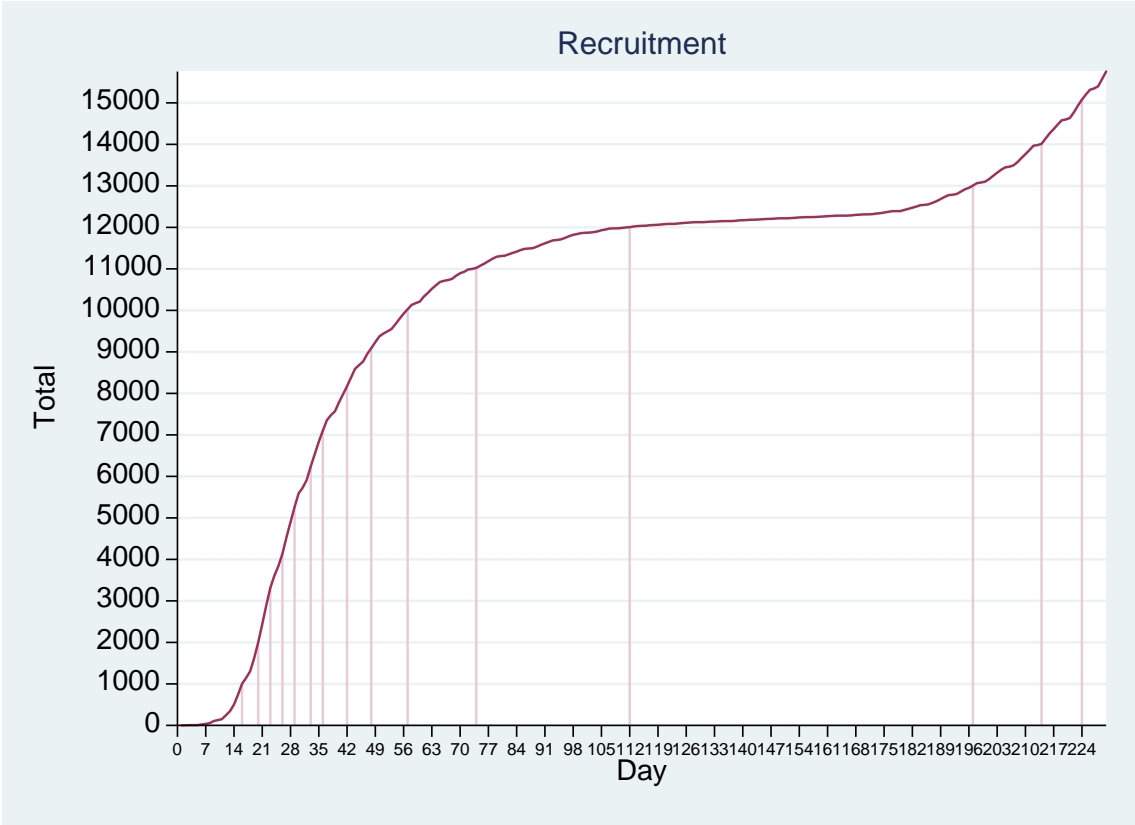
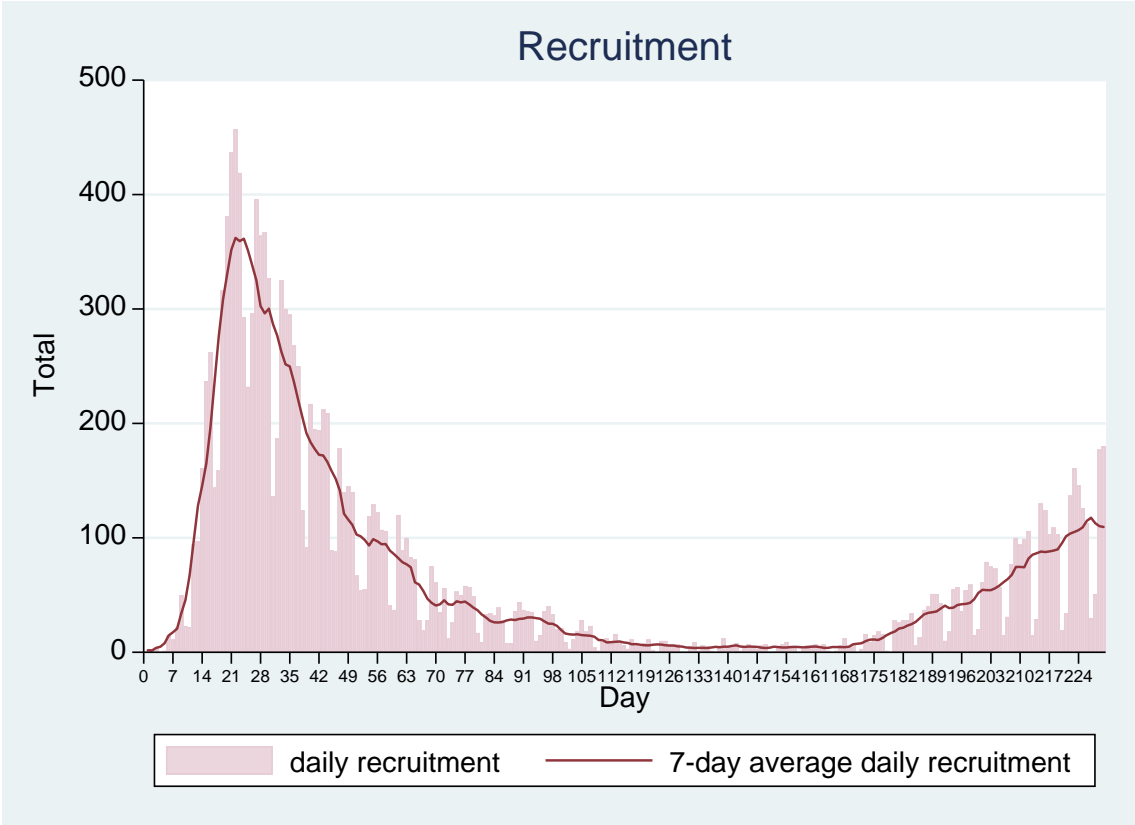
Corticosteroids & mortality among critically ill patients with COVID-19

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients		Odds ratio (95% CI)	Weight, %
			Steroids	No steroids		
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0

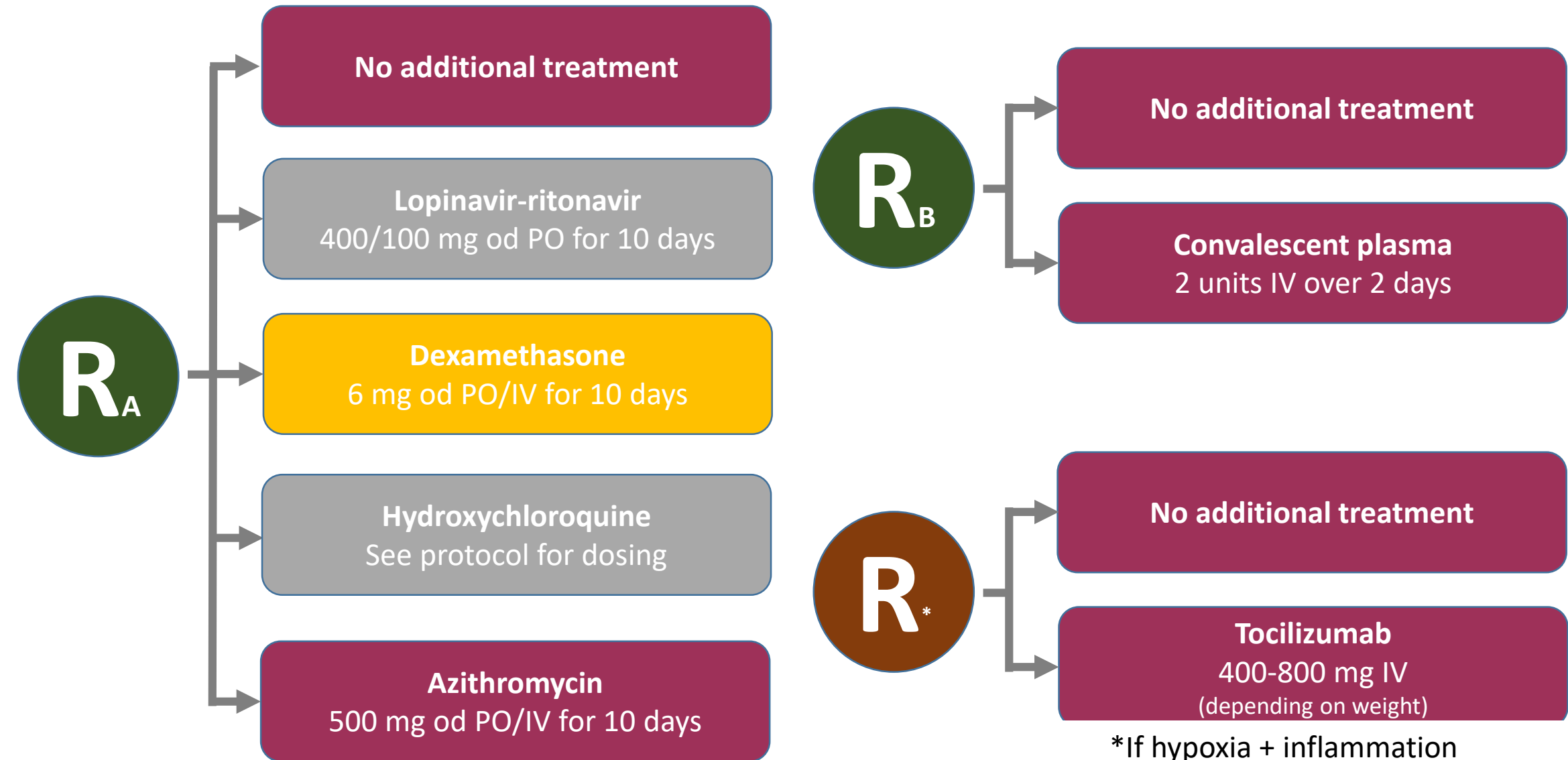
P = .31 for heterogeneity; *I*² = 15.6%



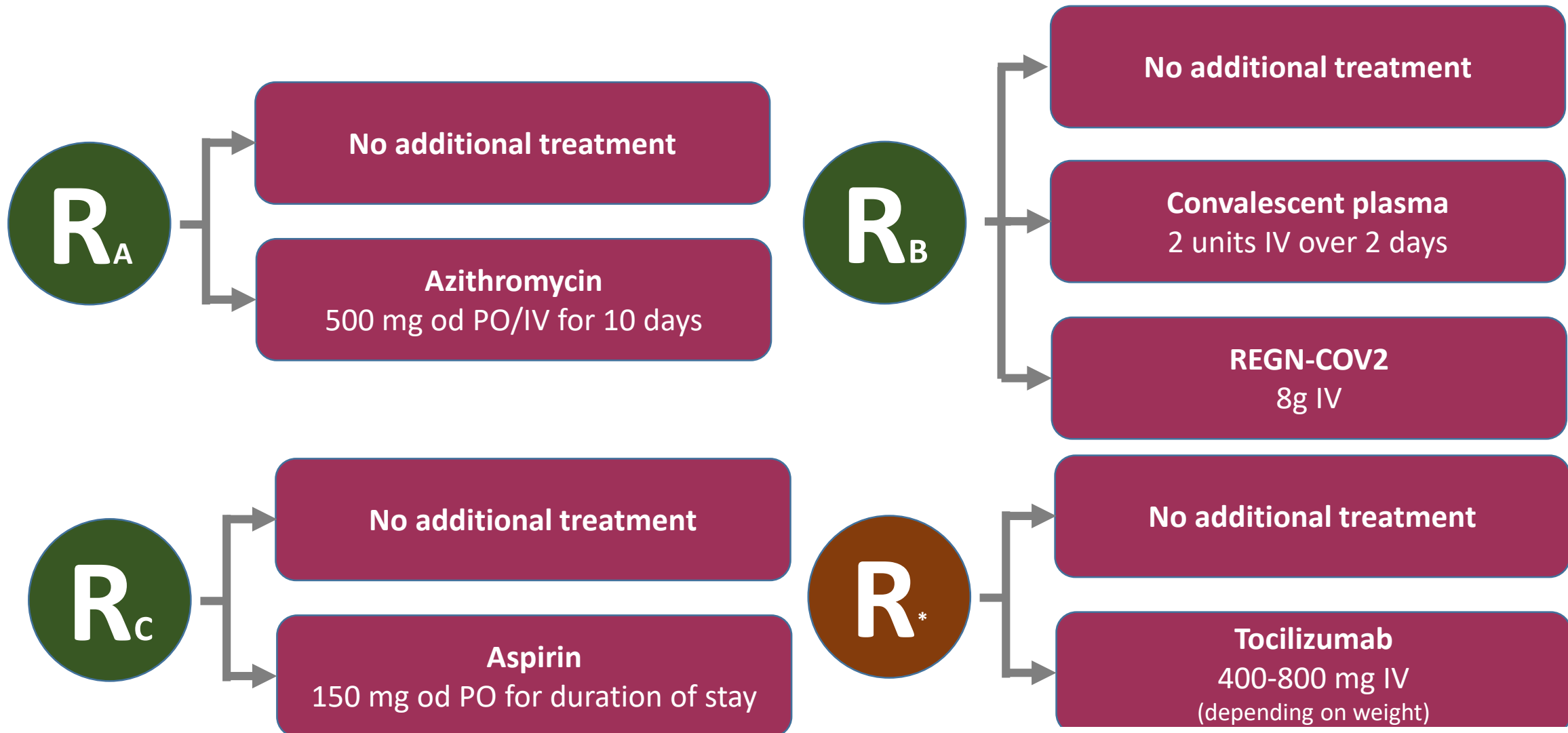
RECOVERY – the second wave is upon us



RECOVERY – studying multiple treatments



RECOVERY – studying multiple treatments



*If hypoxia + inflammation

Lessons learned

- Arbitrary use of unproven treatments must be avoided
- Randomized trials are a critical component of high quality clinical care
- Requires leadership, collaboration, and infrastructure
- But trials must be:
 - Feasible for patients and clinical staff
 - Inclusive of relevant patient groups
 - Focused on outcomes that matter
 - Sufficiently large to produce clear results
- Compelling results change practice

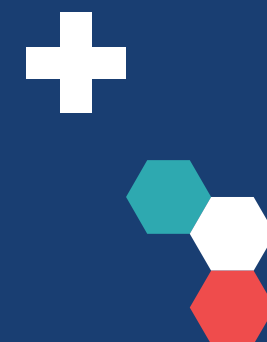
These lessons are not just important for the current COVID-19 pandemic but also for the tackling the burden of cardiovascular and other common, non-communicable diseases

Acknowledgements



- UK Research & Innovation
- Wellcome Trust
- Department for International Development
- National Health Service in England, Wales, Scotland, and Northern Ireland
- NIHR Clinical Research Network
- NIHR Oxford Biomedical Research Centre
- Nuffield Department of Medicine
- National Institute for Health Research
- Bill & Melinda Gates Foundation
- Department of Health & Social Care
- NHS DigiTrials
- Medical Research Council Population Health Research Unit
- Nuffield Department of Population Health

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial



with enormous thanks

to the very many doctors, nurses, and other healthcare and
research staff at over 176 NHS hospitals

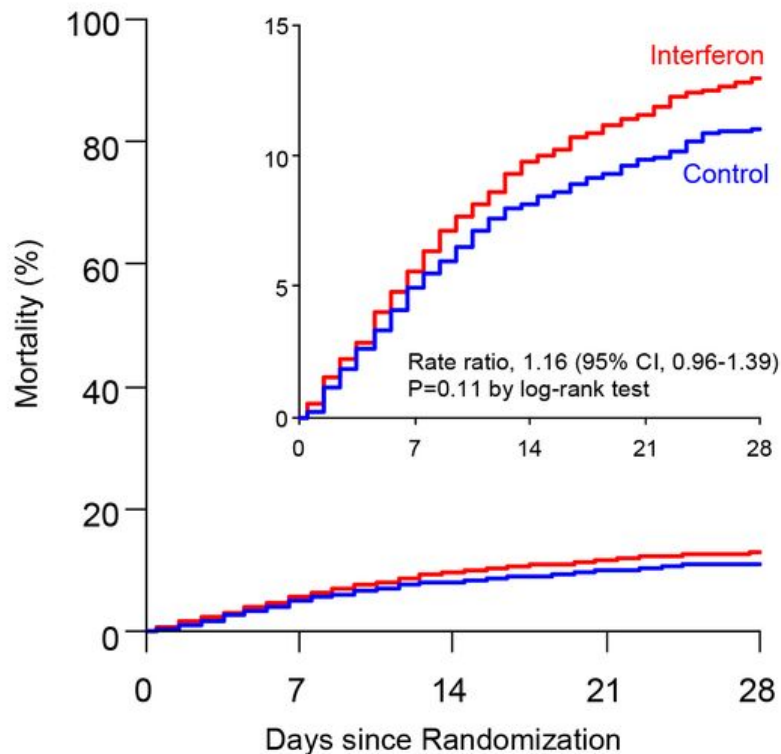
and, most importantly

to the thousands of patients who participate

in this extraordinary project



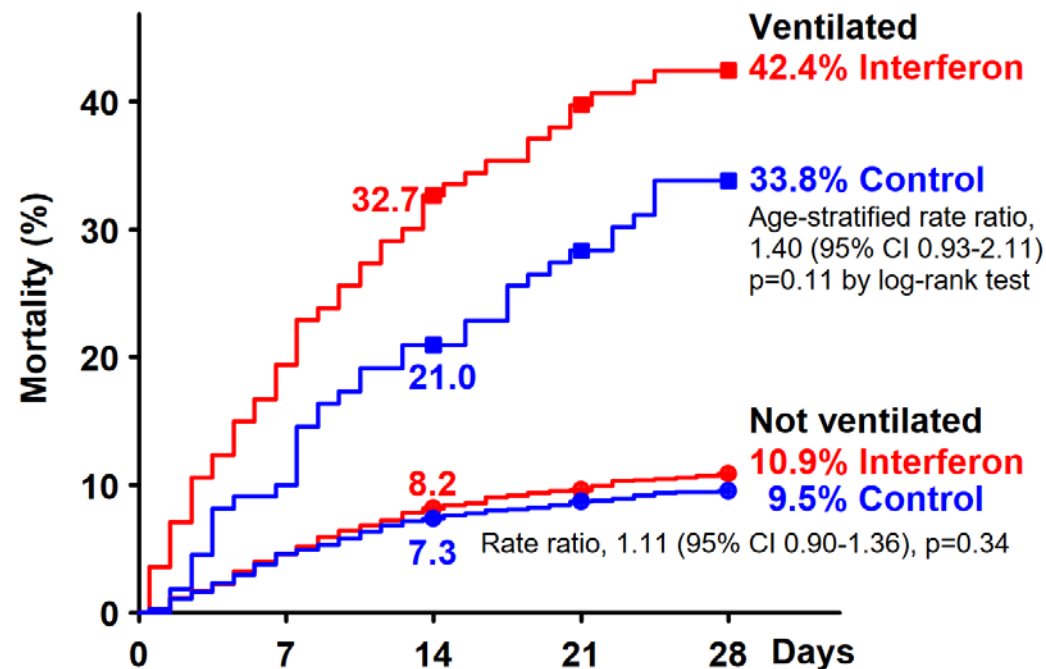
WHO SOLIDARITY: No effect of interferon on mortality



Numbers at risk at the start of each week, and numbers dying

	0	7	14	21	28
Interferon	2050	101	1669	73	1554
Control	2050	91	1725	58	1636

	0	7	14	21	28
Interferon	2050	101	1669	73	1554
Control	2050	91	1725	58	1636

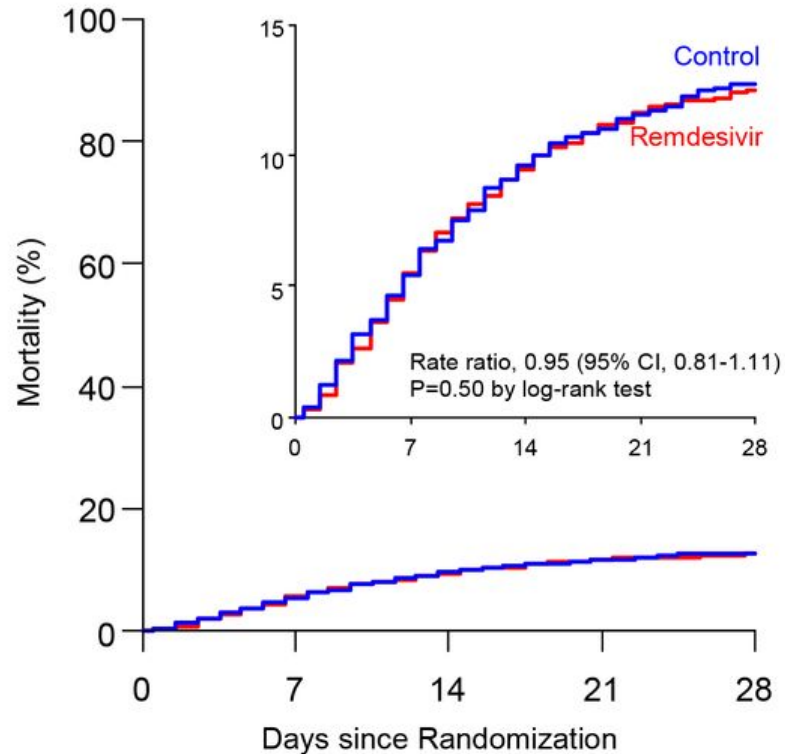


Nos. at risk at the start of each week, and nos. dying

	0	7	14	21	28
Interferon	139	23	91	15	76
Control	130	11	99	12	86

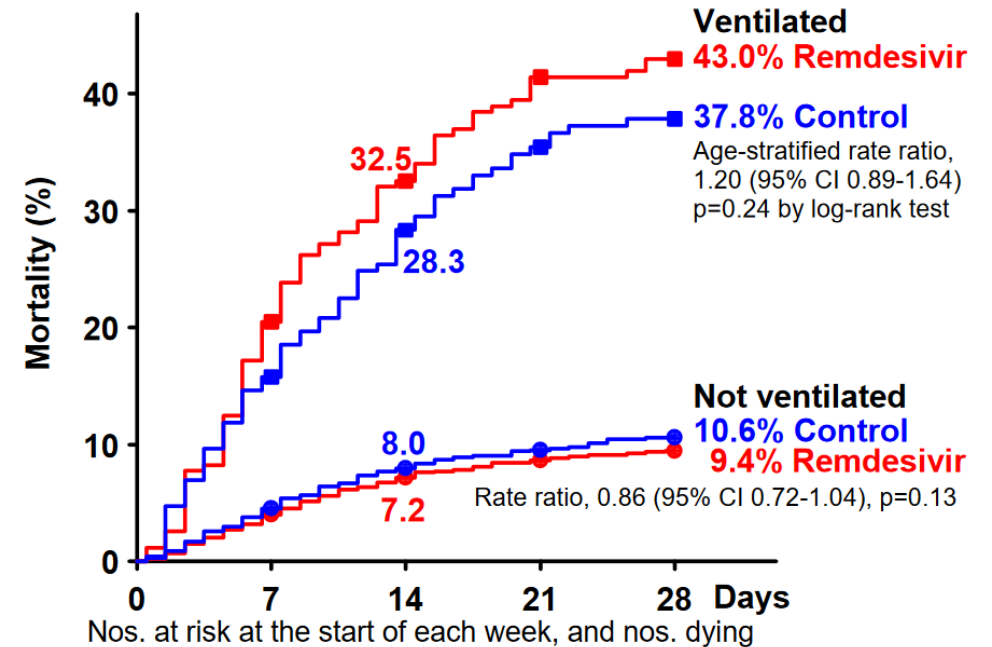
	0	7	14	21	28
Interferon	1911	78	1578	58	1478
Control	1920	80	1626	46	1550

WHO SOLIDARITY: No effect of remdesivir on mortality



Numbers at risk at the start of each week, and numbers dying

Remdesivir	2743	129	2159	90	2029	48	1918	18	1838	16
Control	2708	126	2138	93	2004	43	1908	27	1833	14



Nos. at risk at the start of each week, and nos. dying

Remdesivir	254	44	167	25	138	18	118	3	112	8	Ventilated
Control	233	29	151	22	123	12	108	5	102	3	
Remdesivir	2489	85	1992	65	1891	30	1800	15	1726	8	Not ventilated
Control	2475	97	1987	71	1881	31	1800	22	1731	11	

Meta-analysis: No effect of remdesivir on mortality

<https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1>

