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RECOVERY Randomised Evaluation of COVID-19 Therapy

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

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on behalf of the RECOVERY trial investigators

www.recoverytrial.net

UKRI Medical Research Council

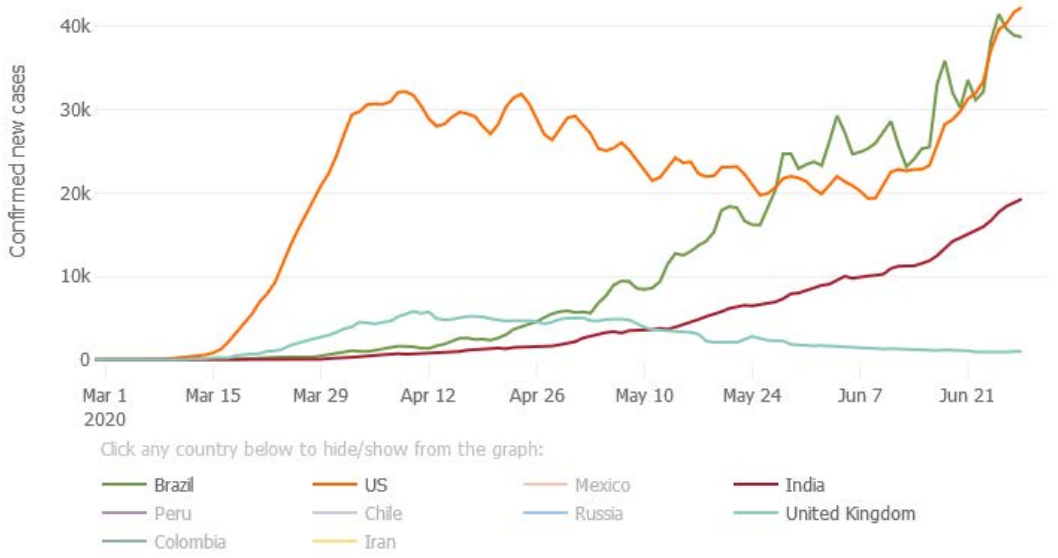
Background

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

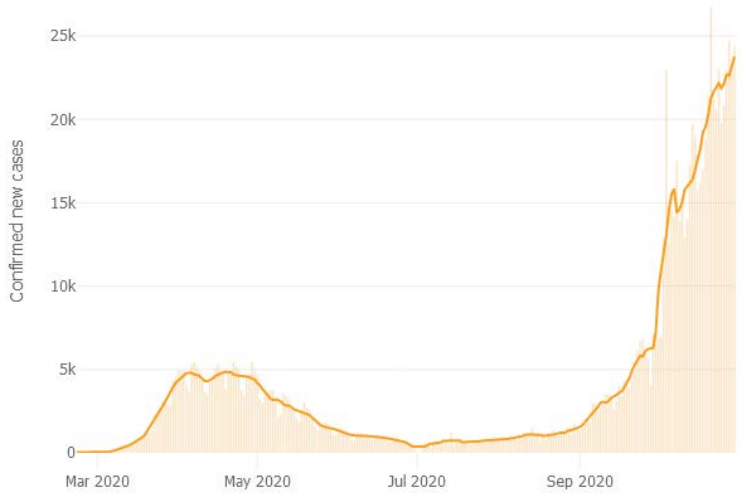


Background

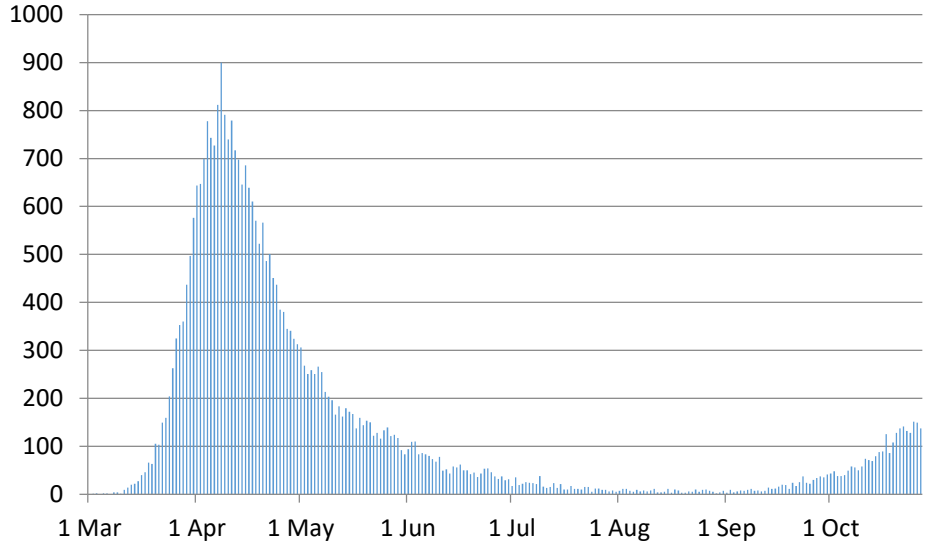
Unprecedented clinical challenge:

- 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**."

ISIS 2
Second International Study of Infarct Survival
NOTIFICATION OF DISCHARGE OR PRIOR DEATH

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

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

OR: PATIENT STICKER,
IF ALL DETAILS PROVIDED

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

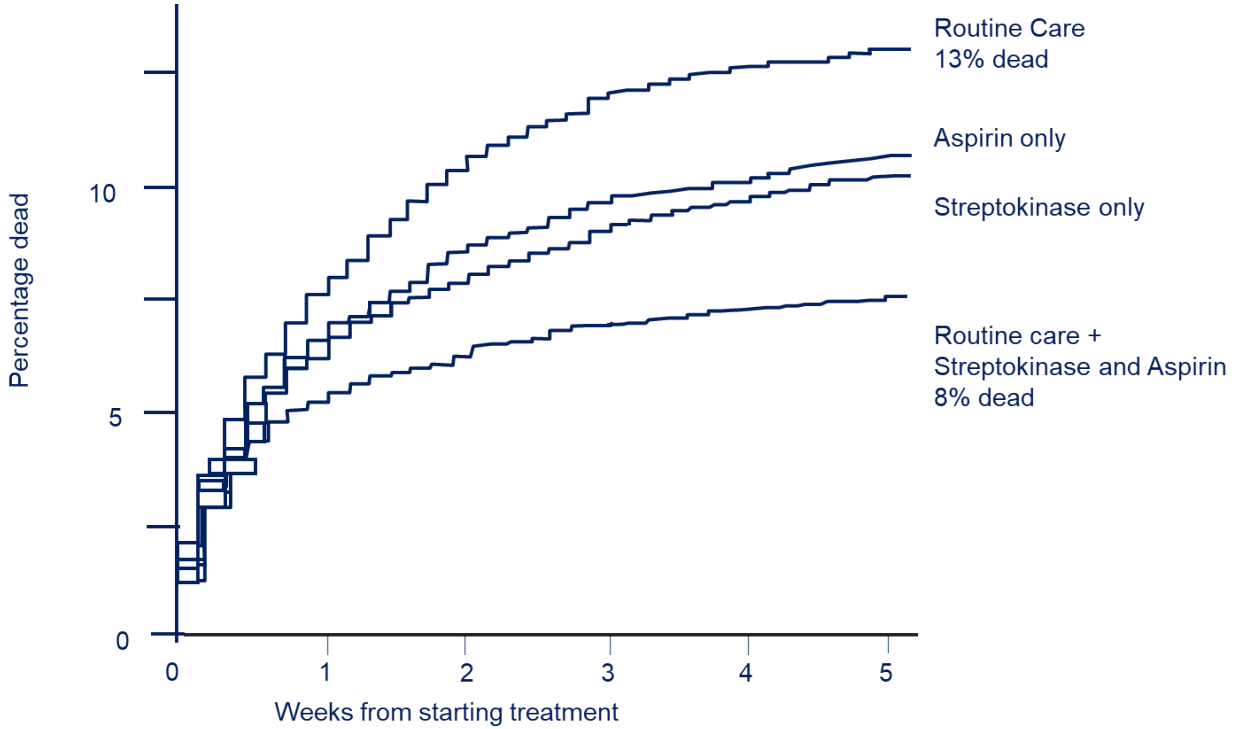
TICK ✓ TREATMENT IN HOSPITAL
Steroids prior to streptokinase/placebo infusion
Subcutaneous heparin
Intravenous heparin
Oral anticoagulant
Intravenous beta-blocker
Non-trial aspirin
Other anti-platelet agent(s)

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, FREEPOST, OXFORD OX2 6BR, 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 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 authorised 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.

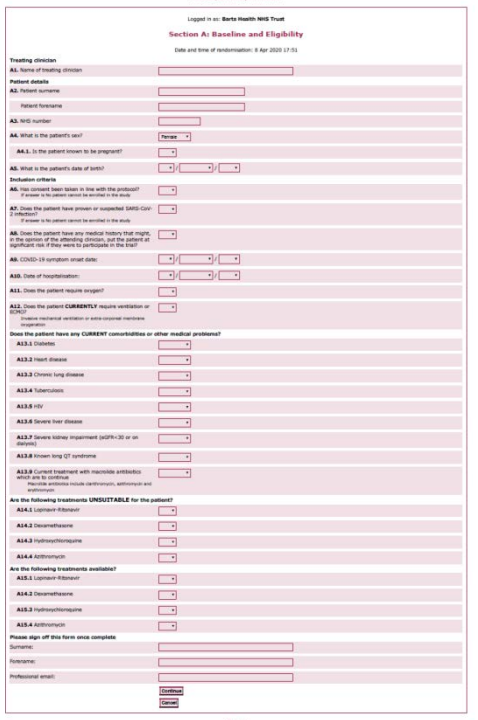
5. **Data stored on computer:** I understand that information about my progress in the study will be recorded on a computer database, and that this data will be stored on computers supervised by the University of Oxford. I understand that this information will be kept securely and confidentially.

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*



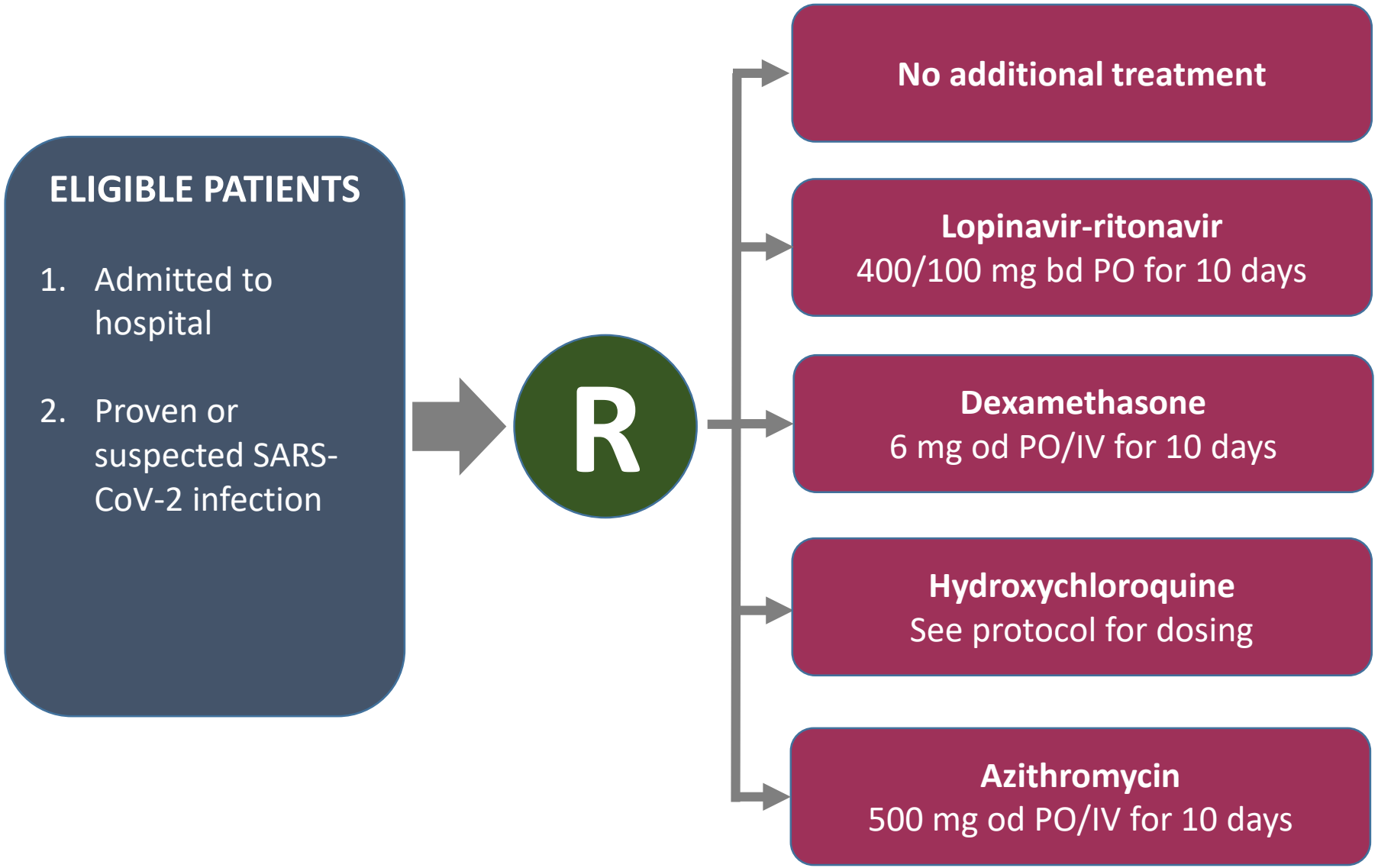
Section A: Baseline and Eligibility

RECOVERY trial design

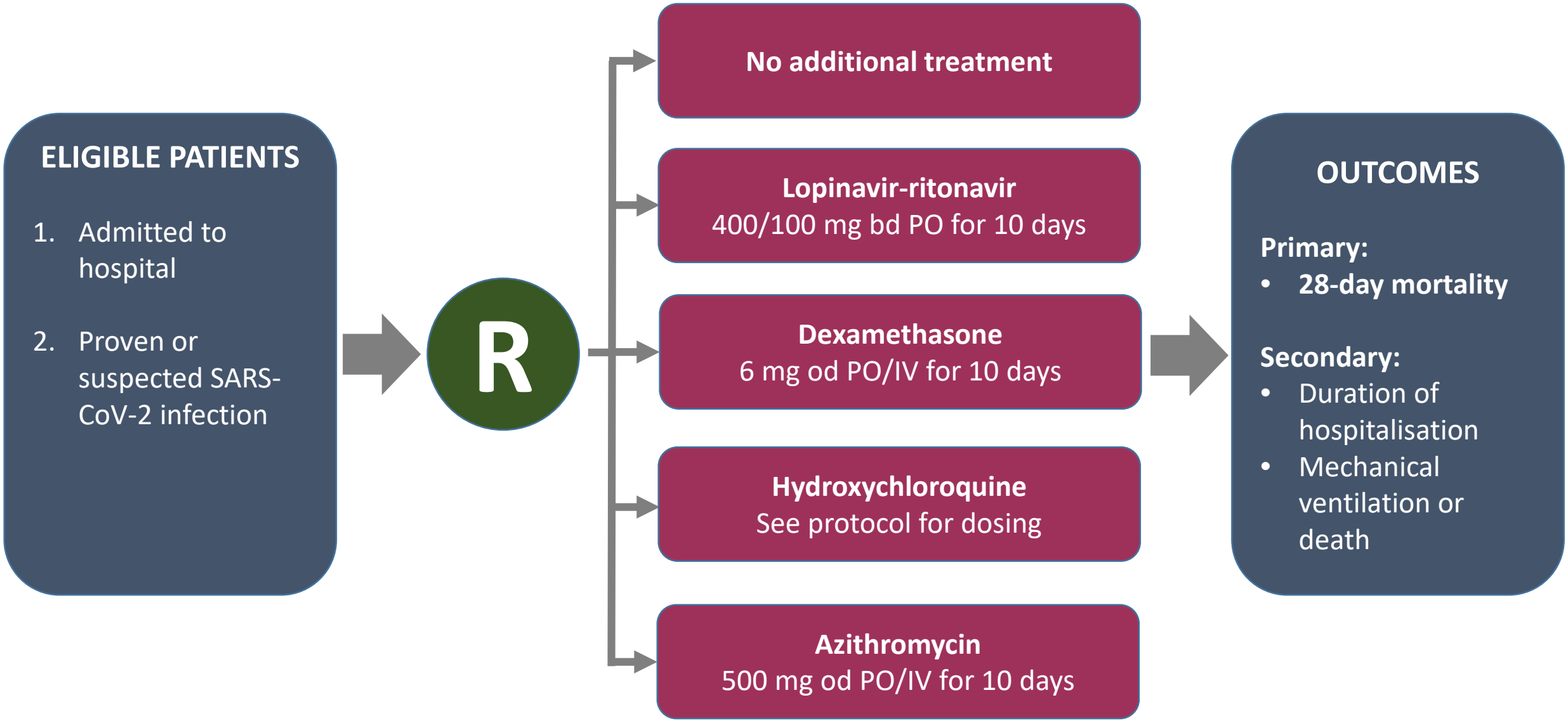
ELIGIBLE PATIENTS

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

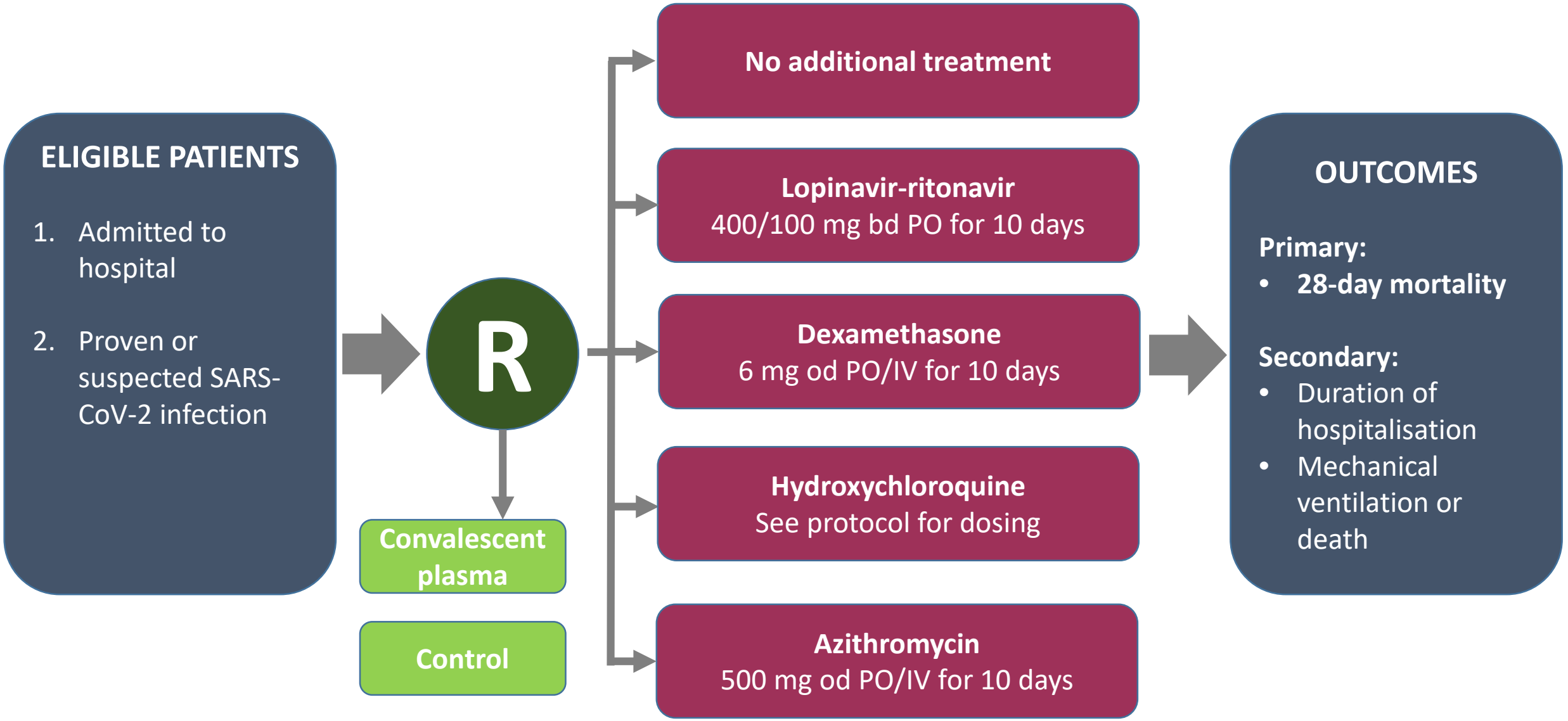
RECOVERY trial design



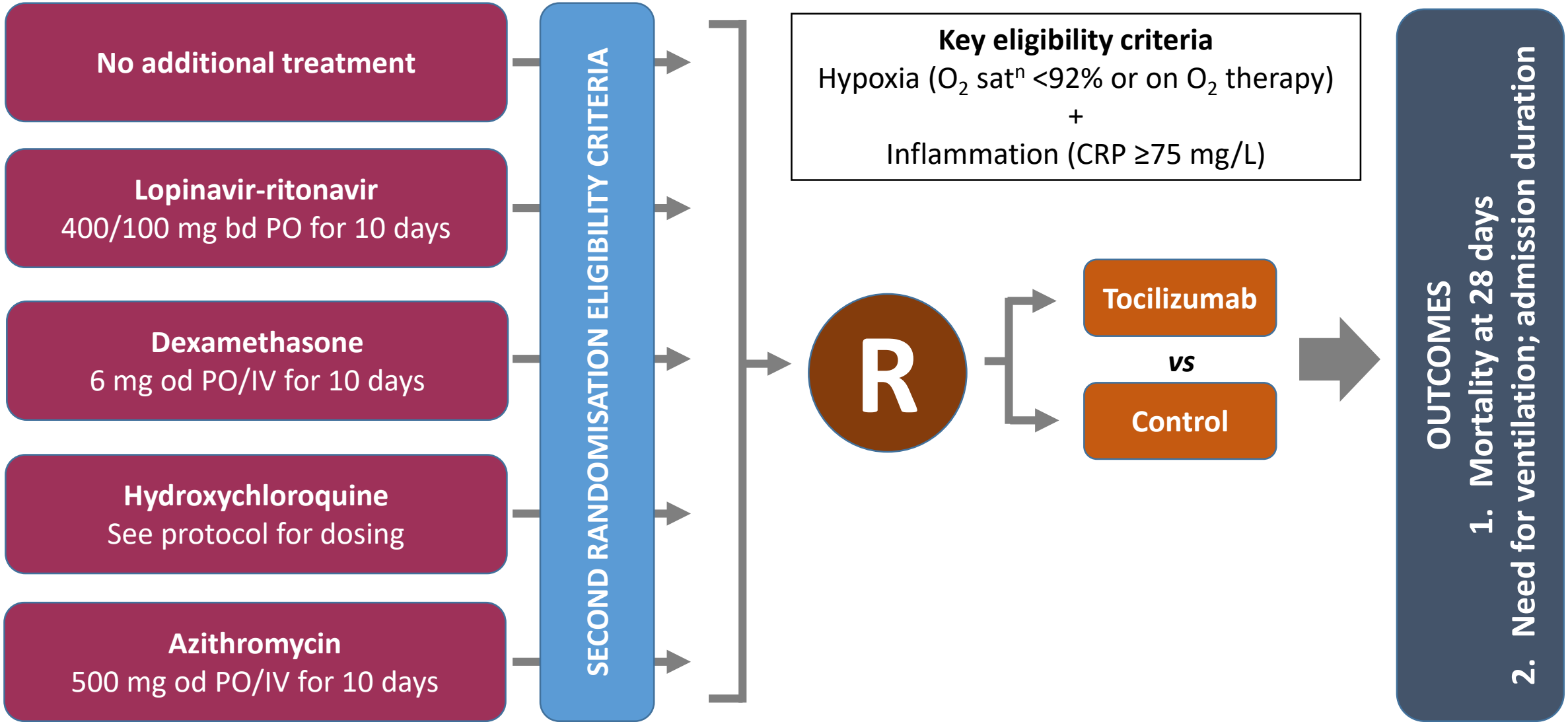
RECOVERY trial design



RECOVERY trial design



Adding a second randomisation



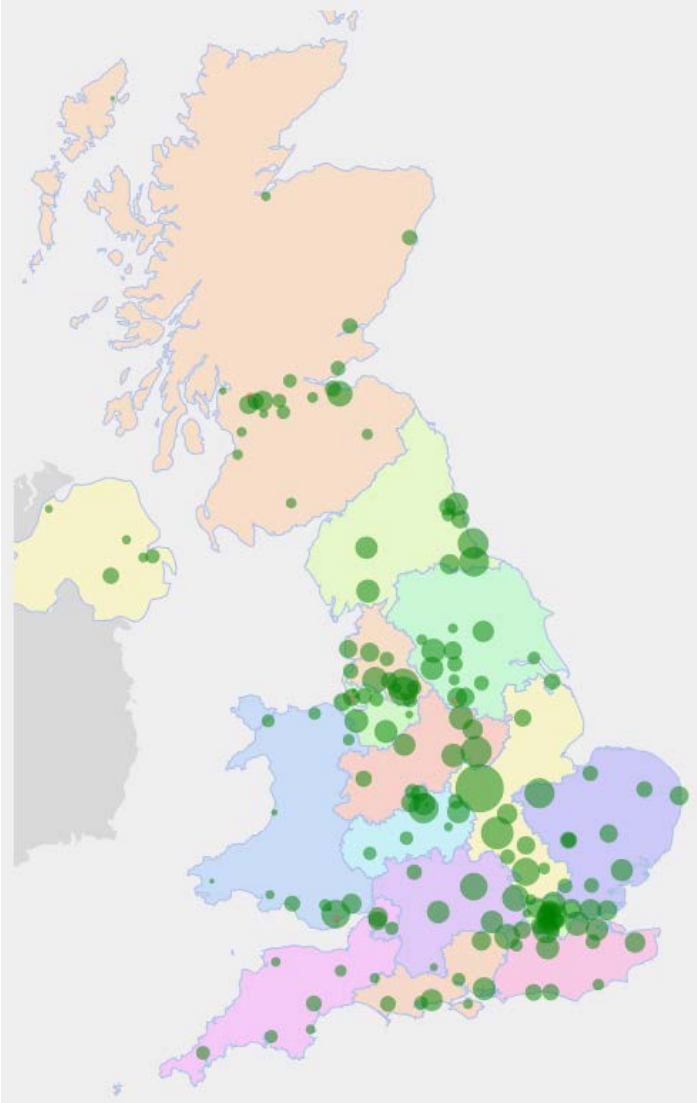
Follow-up

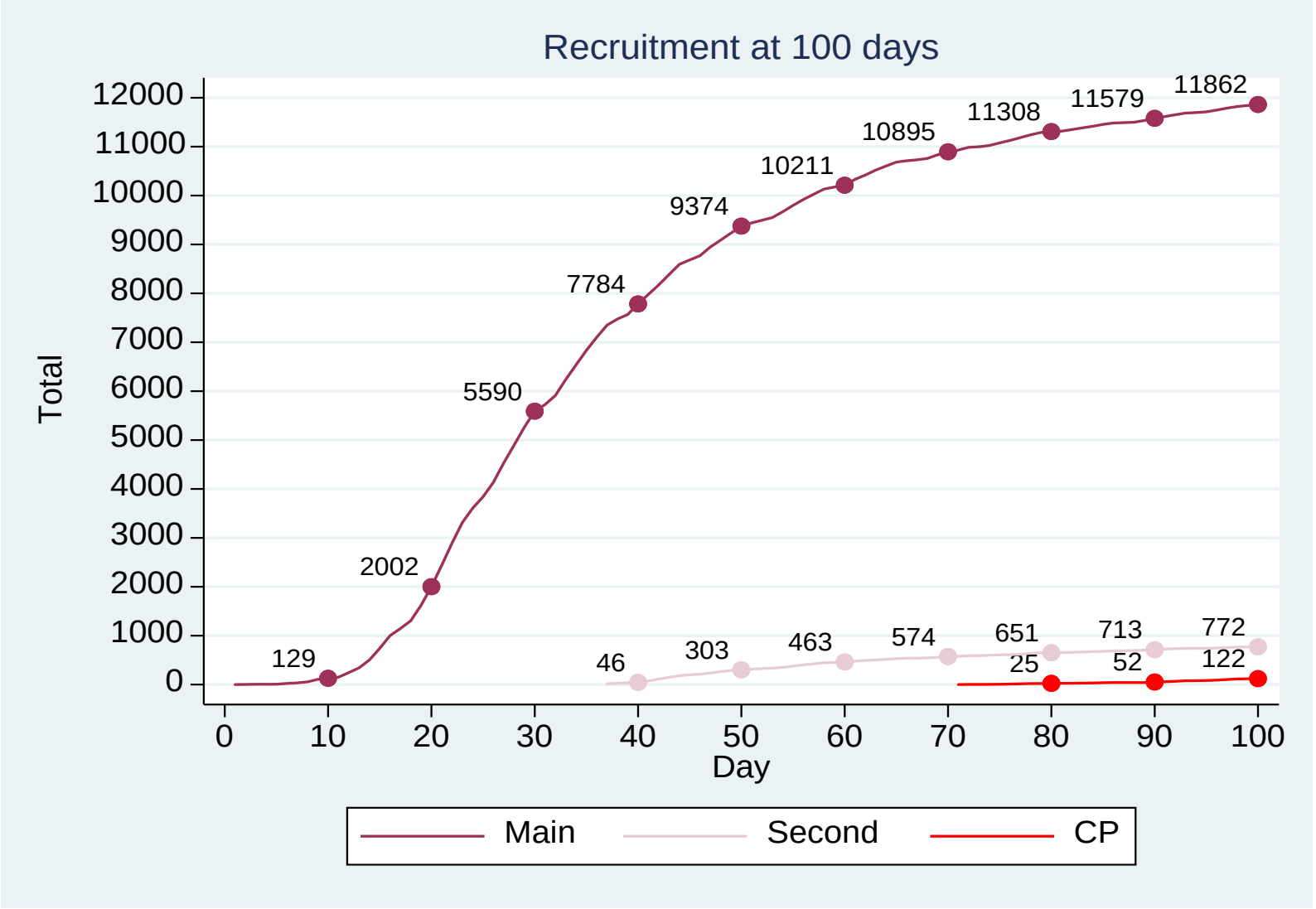
- **Simple on-line form at death, discharge or 28 days**
- **Additional assessment of safety of convalescent plasma at 72 hrs**
- **Linkage to national health data sources**
  - Vital status, death certificate
  - Coded hospital episode statistics (diagnoses, procedures)
  - Intensive Care audit data, 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

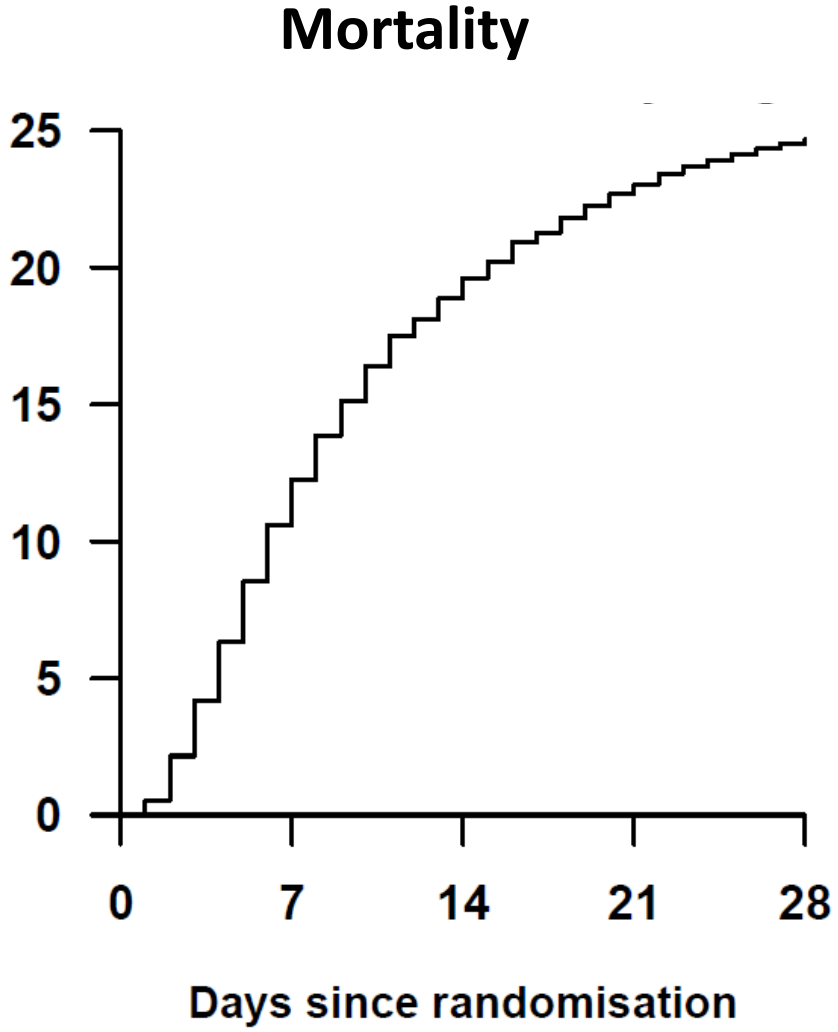




Characteristics at main randomisation (n=12102)

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%)

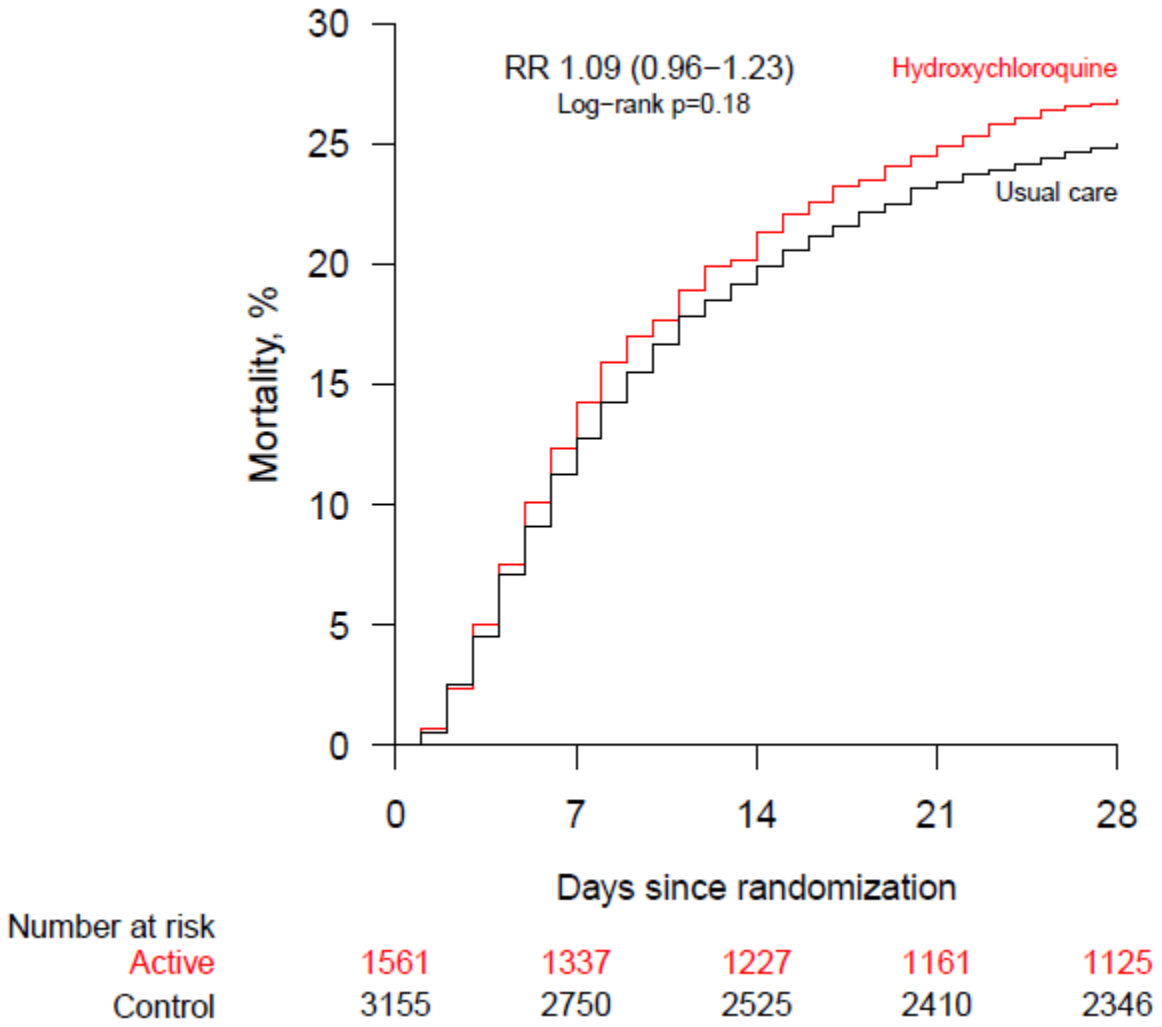
Mortality – overall and by patient characteristic



	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

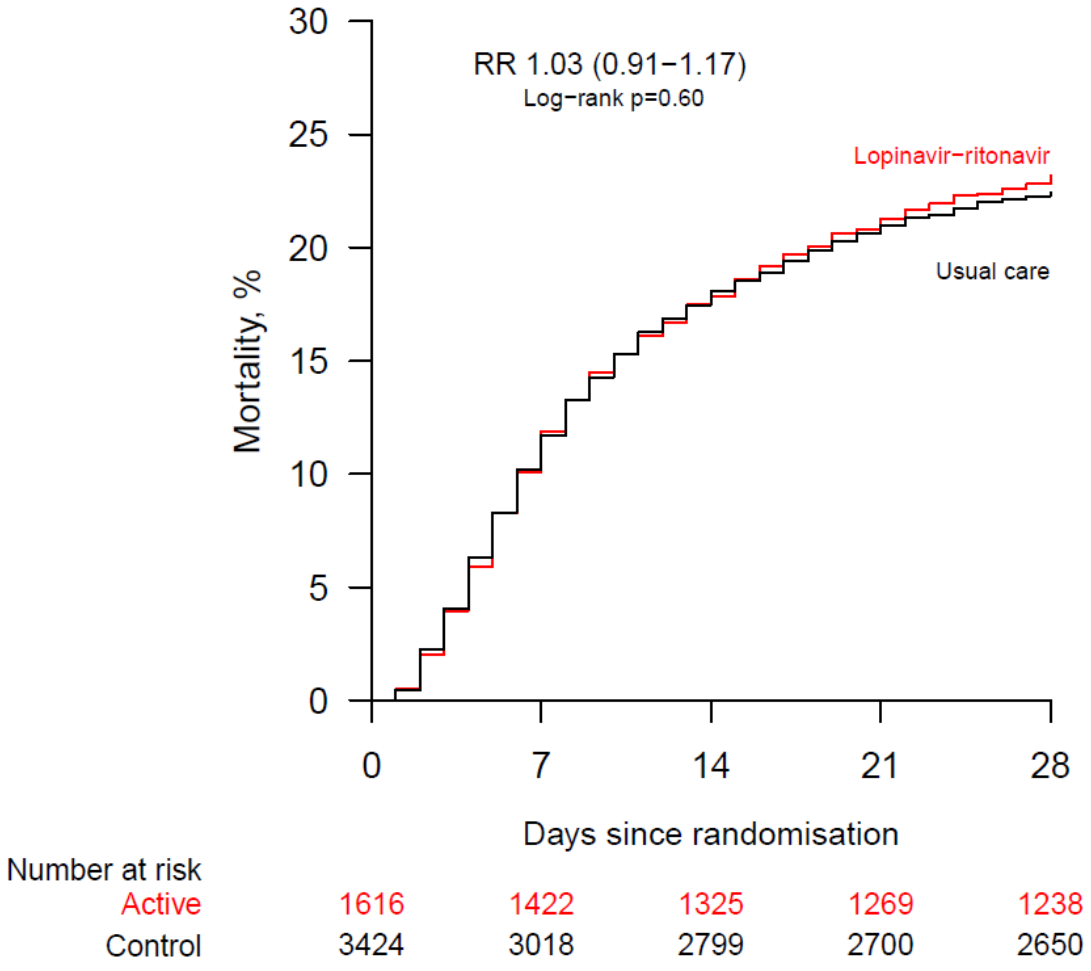
https://www.nejm.org/doi/10.1056/NEJMoa2022926



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

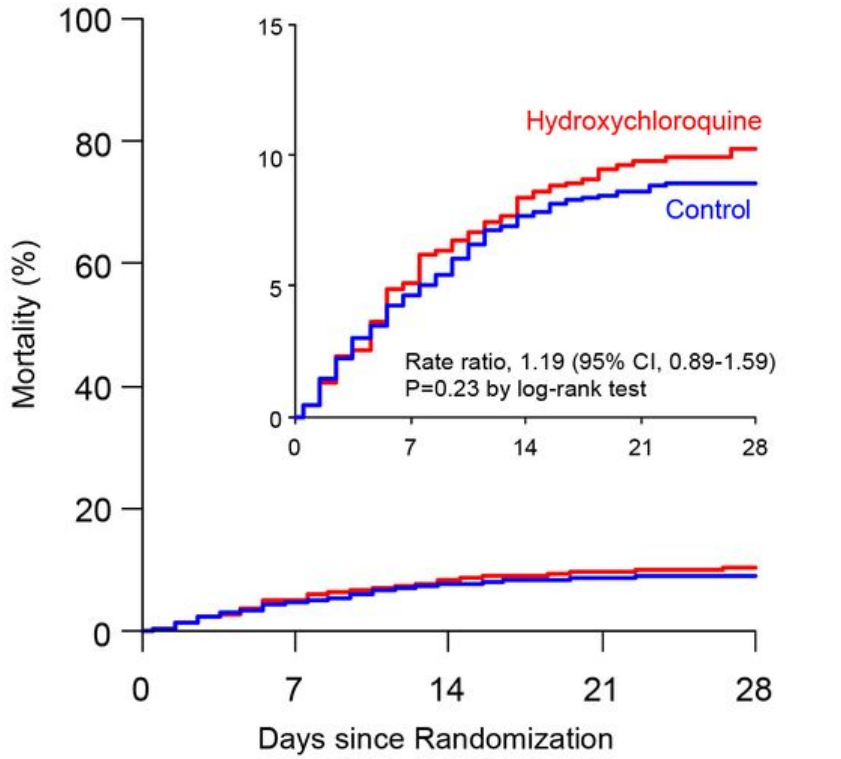


https://www.nejm.org/doi/10.1056/NEJMoa2022926

WHO SOLIDARITY:

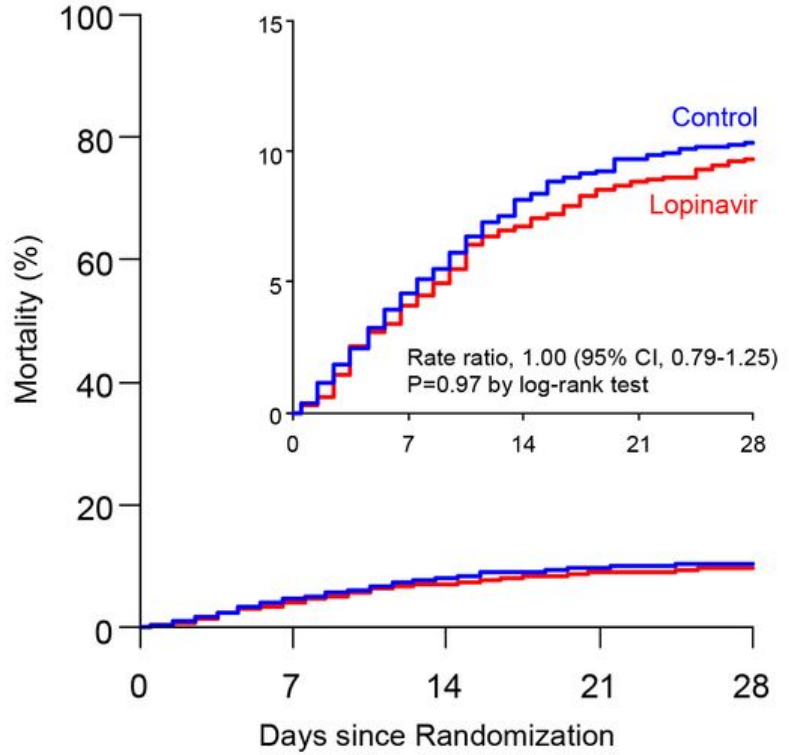
https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1

No effect of hydroxychloroquine or lopinavir on mortality



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

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



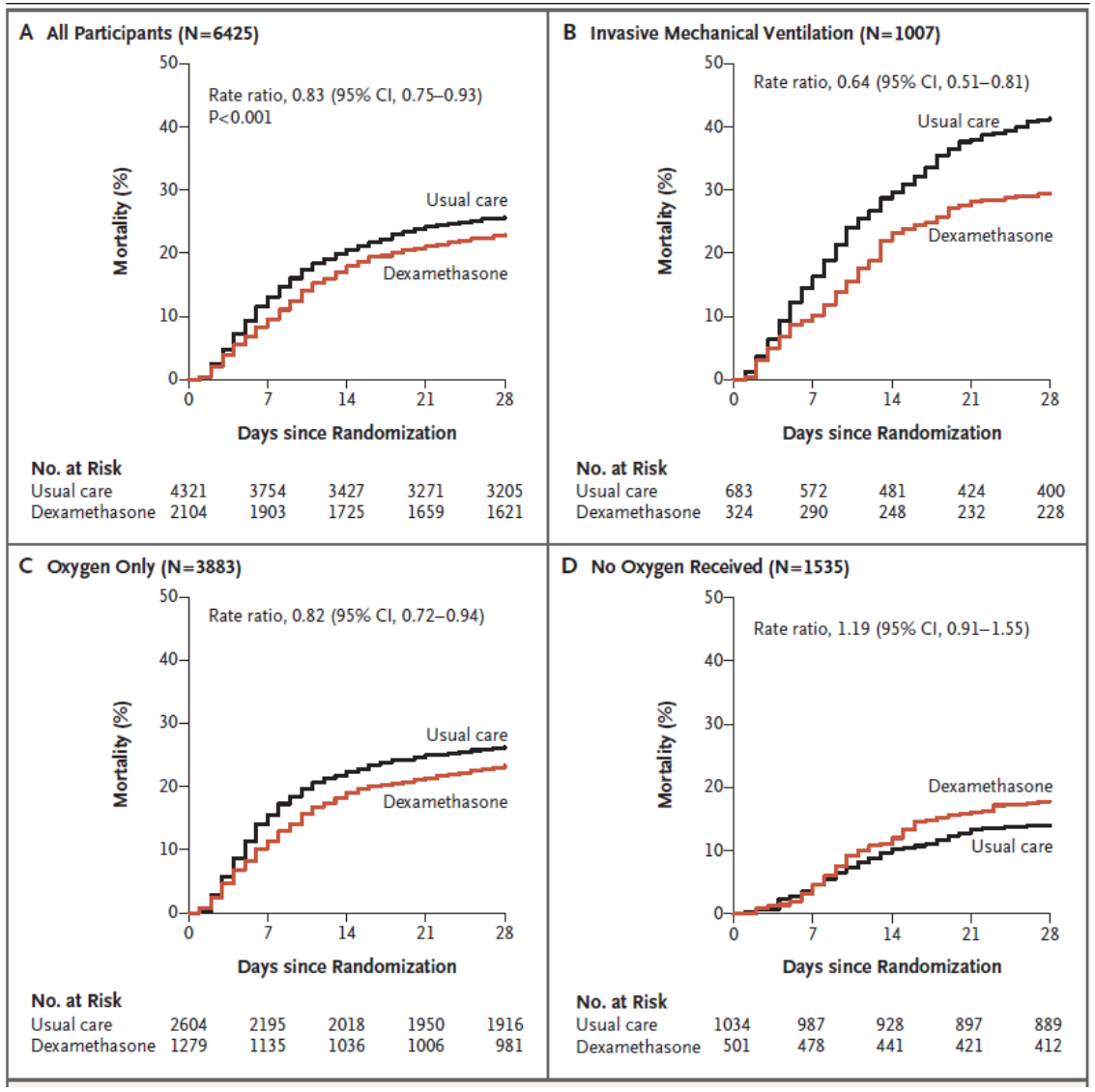
Numbers at risk at the start of each week, and numbers dying

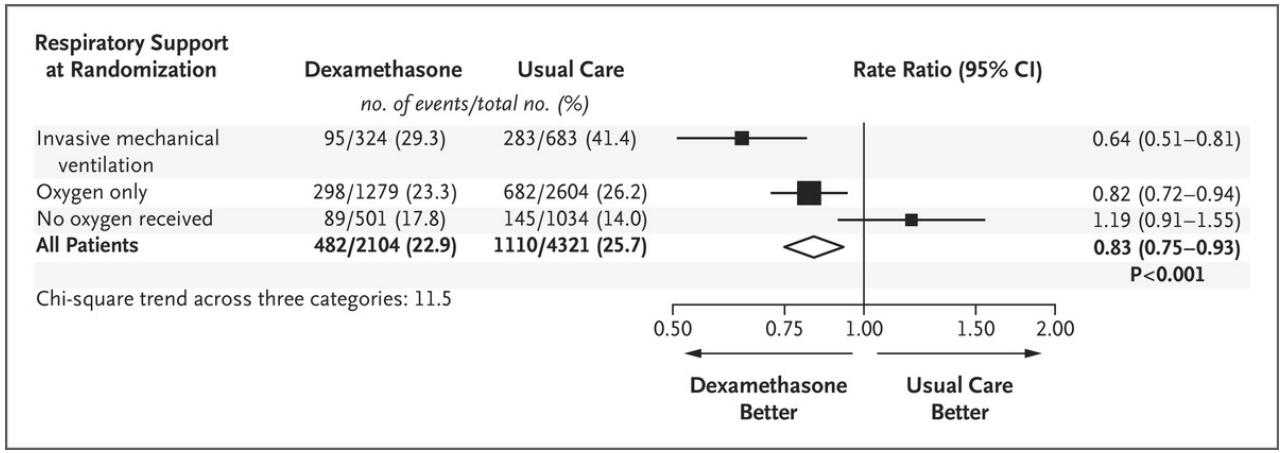
Lopinavir	1399	57	1333	42	1282	24	1257	15	1243	10
Control	1372	62	1293	48	1239	21	1216	10	1203	5

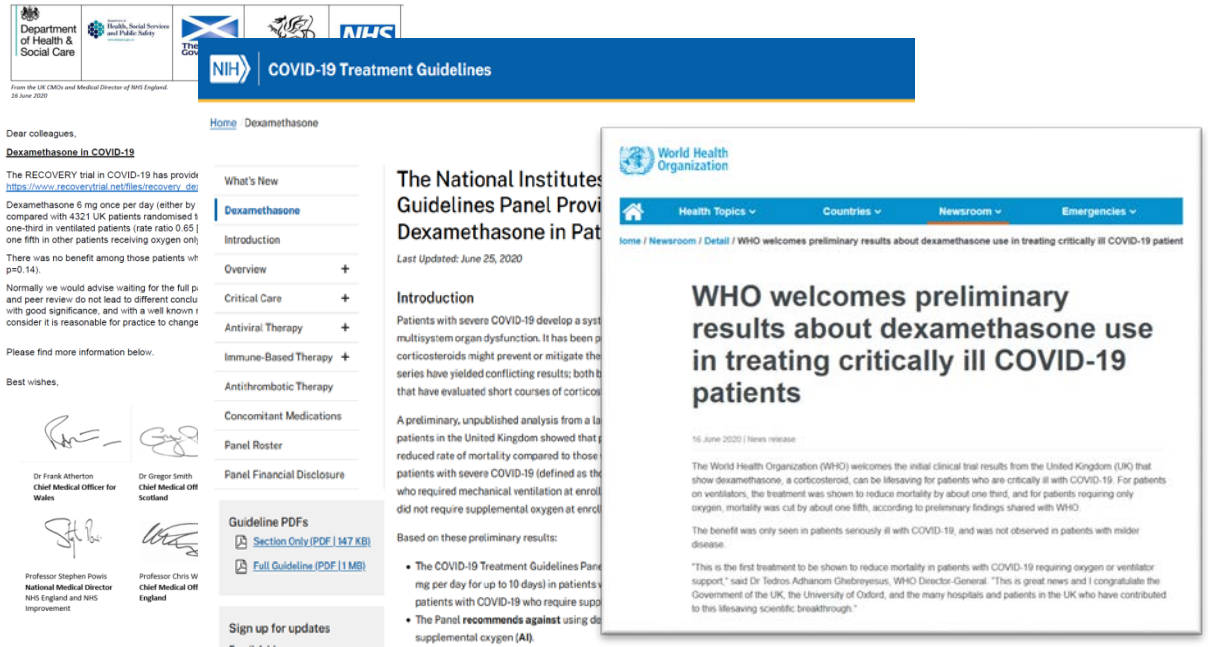
Dexamethasone:

Reduces mortality in patients requiring oxygen or ventilation

https://www.nejm.org/doi/full/10.1056/NEJMoa2021436





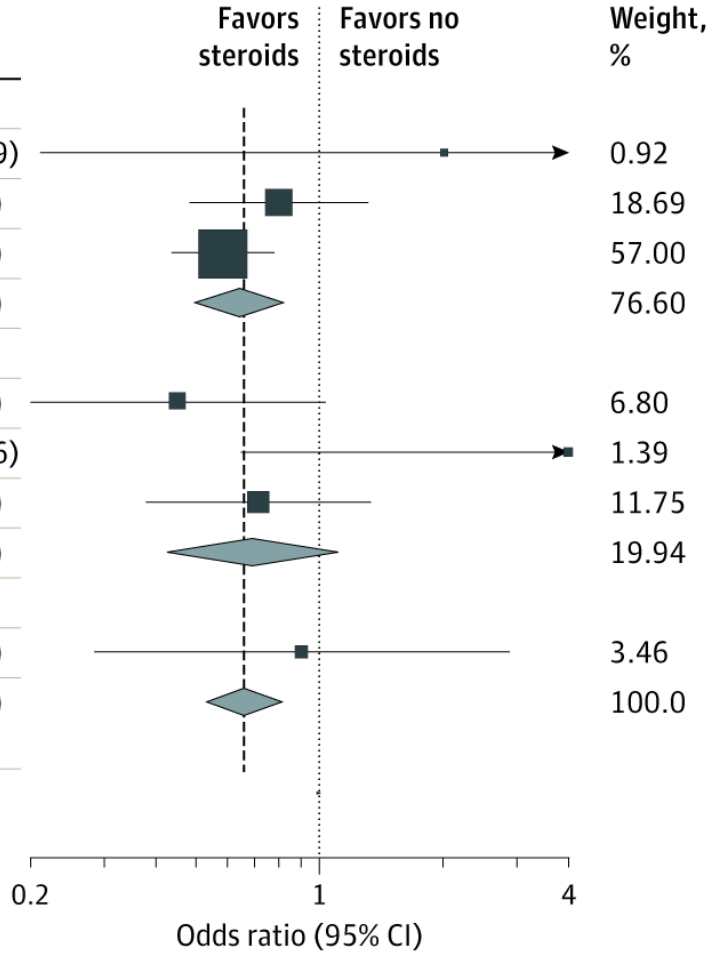


Corticosteroids & mortality
among critically ill patients with COVID-19

https://jamanetwork.com/journals/jama/fullarticle/2770279

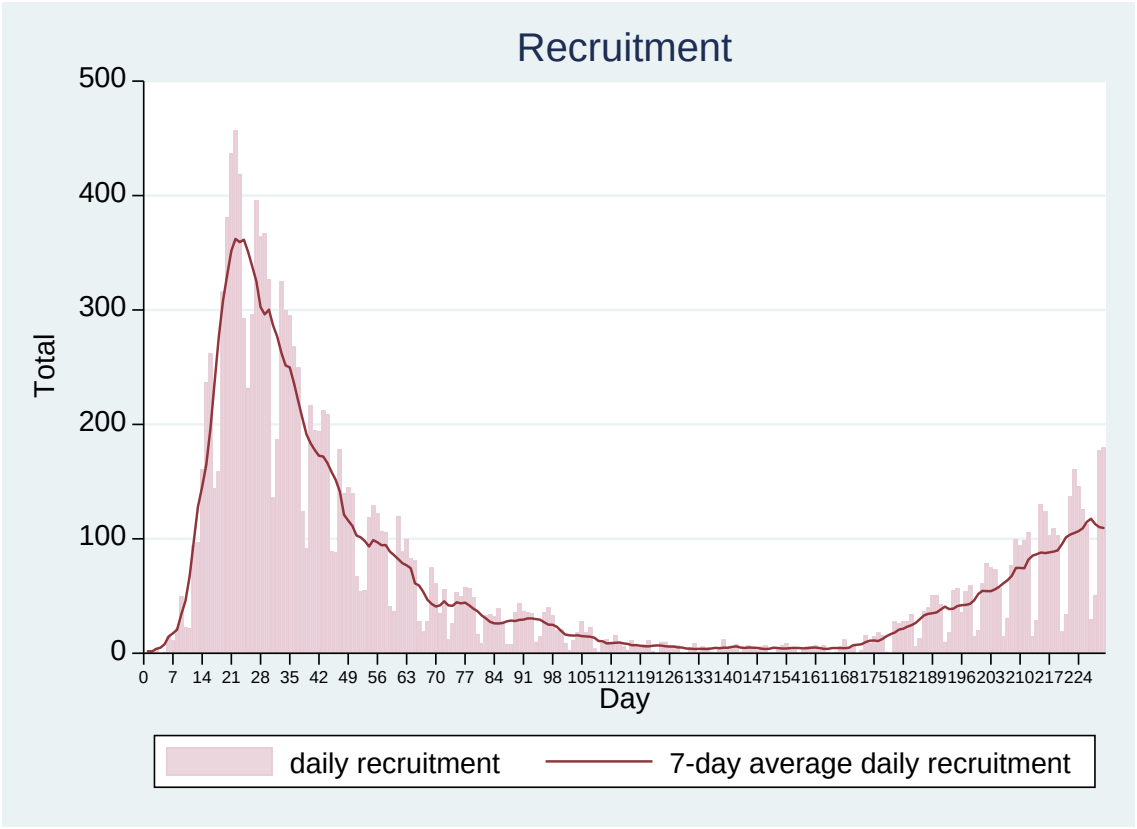
Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)
Dexamethasone					
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)
CoDEX	NCT04327401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

$P = .31$ for heterogeneity; $I^2 = 15.6\%$

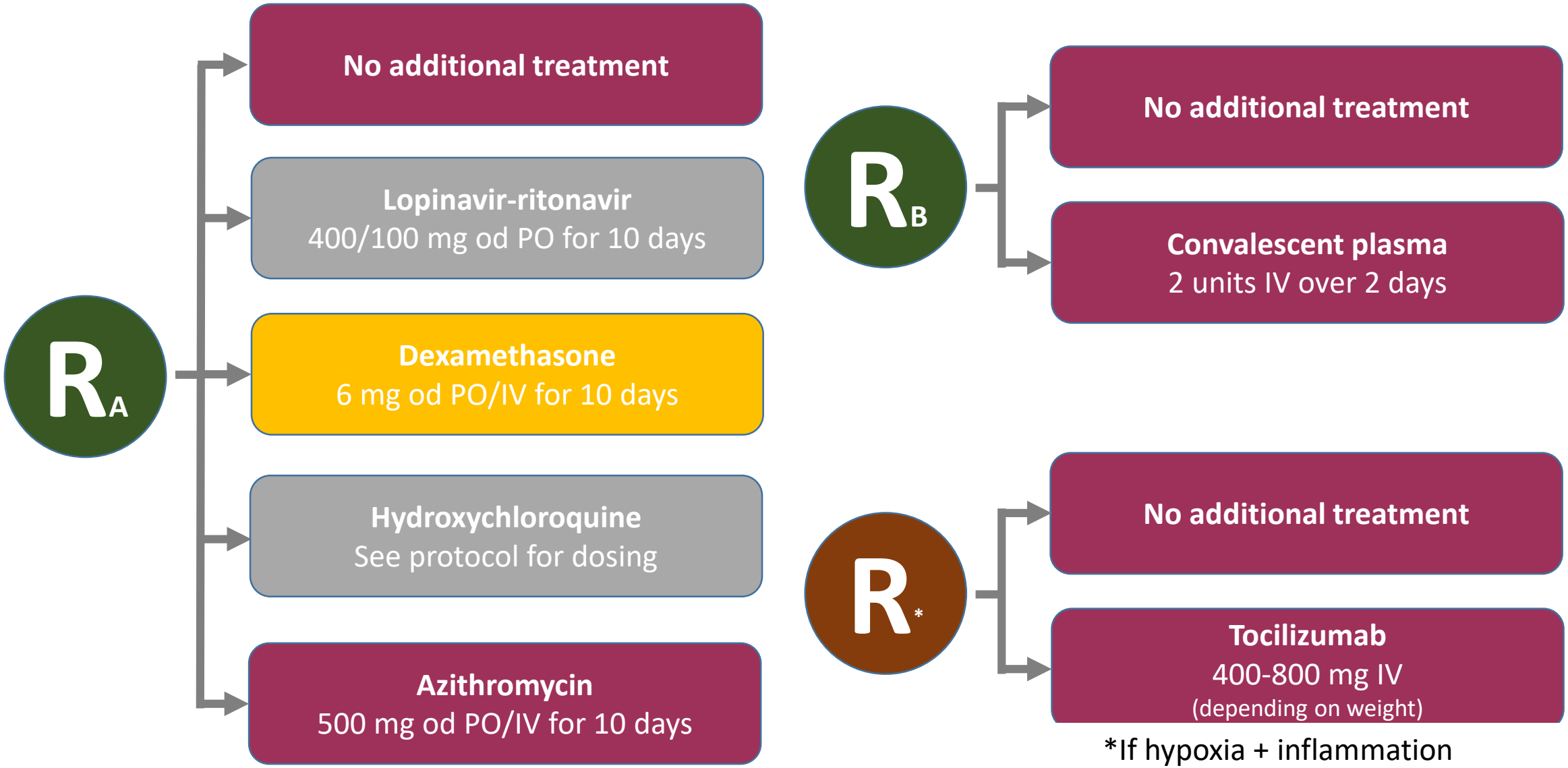


The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. JAMA 2020; doi:10.1001/jama.2020.17023

RECOVERY – the second wave is upon us

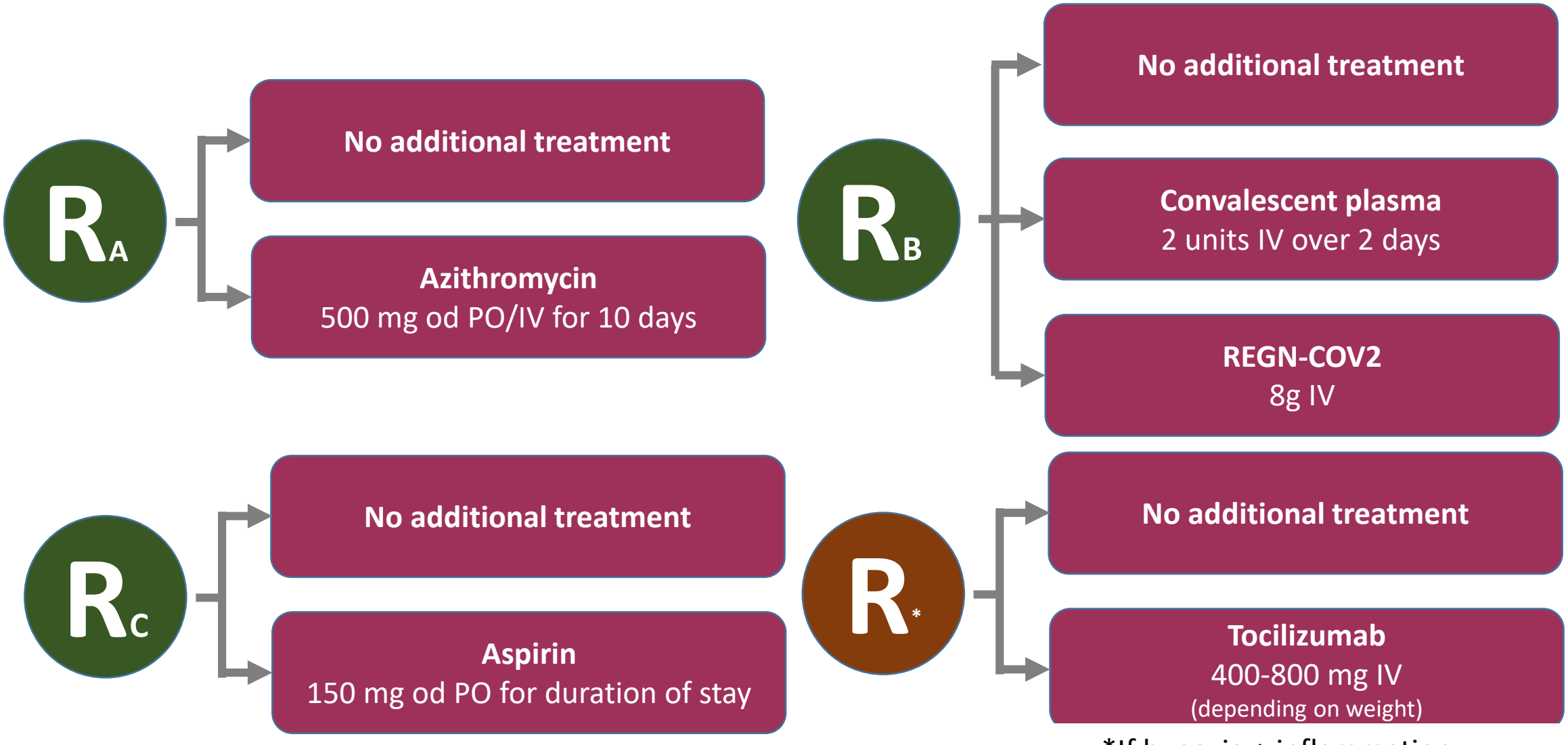


RECOVERY – studying multiple treatments



*If hypoxia + inflammation

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
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- National Institute for Health Research
- Bill & Melinda Gates Foundation
- Department of Health & Social Care

- NIHR Clinical Research Network
- NIHR Oxford Biomedical Research Centre
- Nuffield Department of Medicine
- NHS DigiTrials
- Medical Research Council Population Health Research Unit
- Nuffield Department of Population Health

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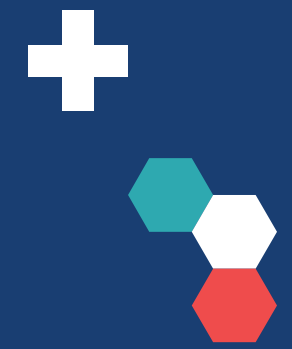
RECOVERY Randomised Evaluation of COVID-19 Therapy

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

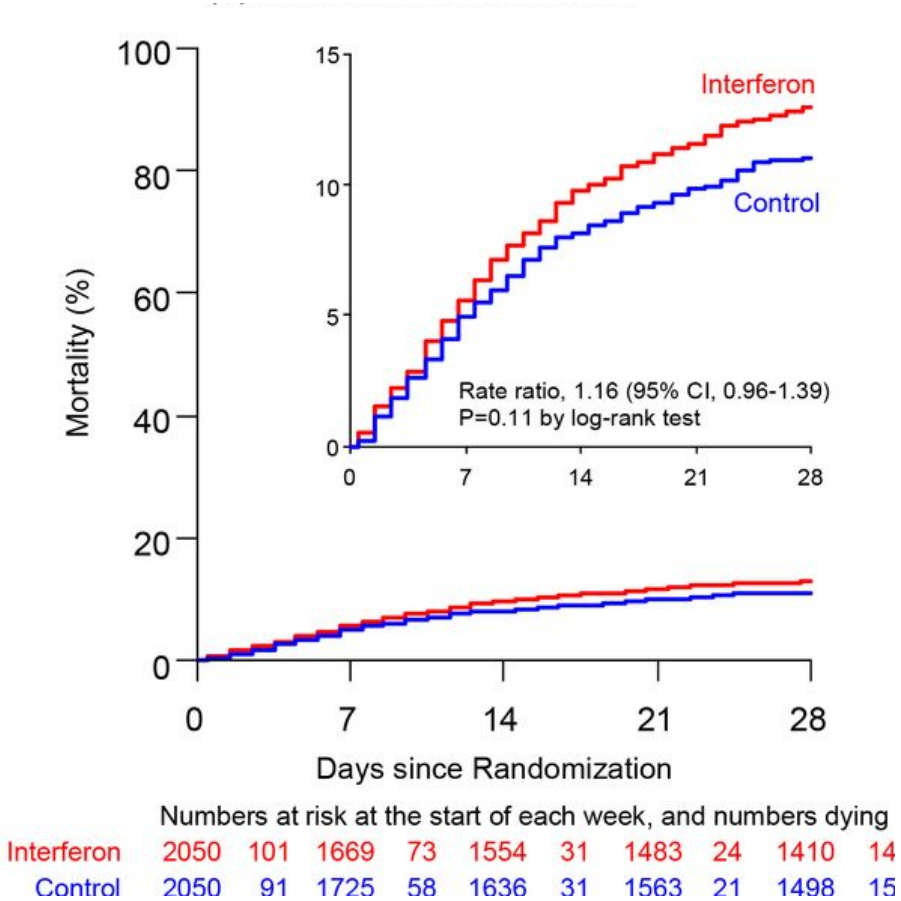
to the thousands of patients who participate

in this extraordinary project

UKRI Medical Research Council

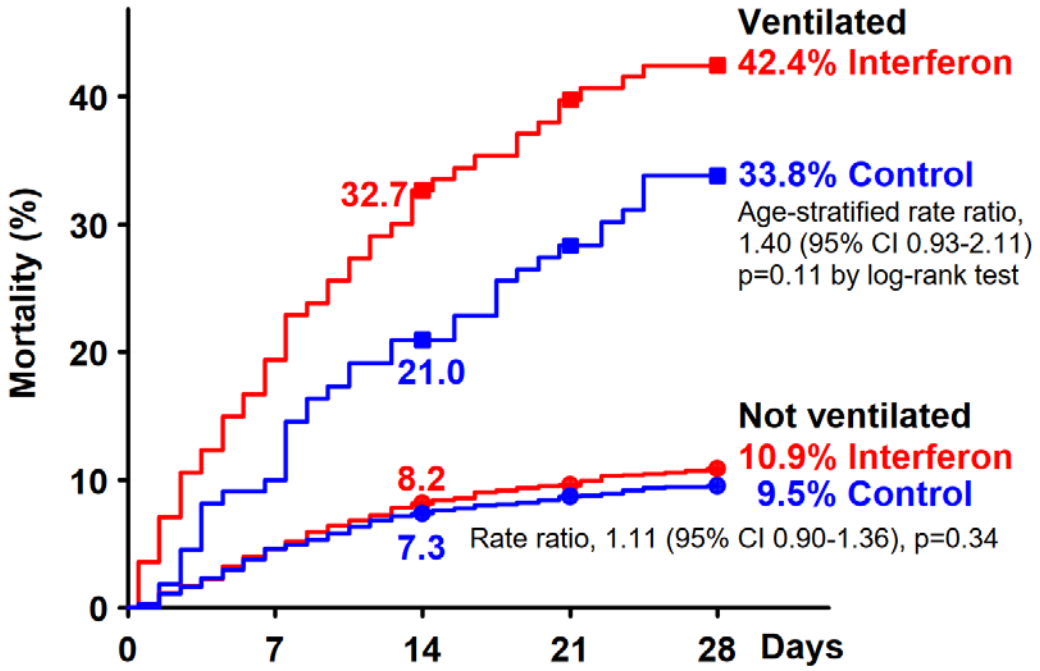
WHO SOLIDARITY:
No effect of interferon on mortality

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



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

Interferon	2050	101	1669	73	1554	31	1483	24	1410	14
Control	2050	91	1725	58	1636	31	1563	21	1498	15

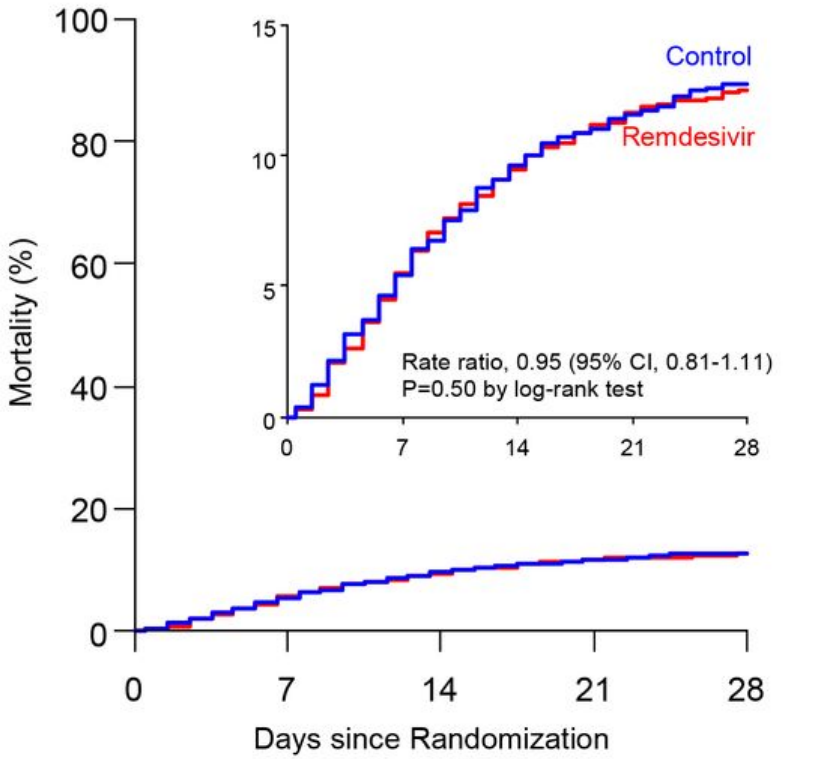


Nos. at risk at the start of each week, and nos. dying

Interferon	139	23	91	15	76	8	68	4	65	5	Ventilated
Control	130	11	99	12	86	8	78	6	72	3	
Interferon	1911	78	1578	58	1478	23	1415	20	1345	9	Not ventilated
Control	1920	80	1626	46	1550	23	1485	15	1426	12	

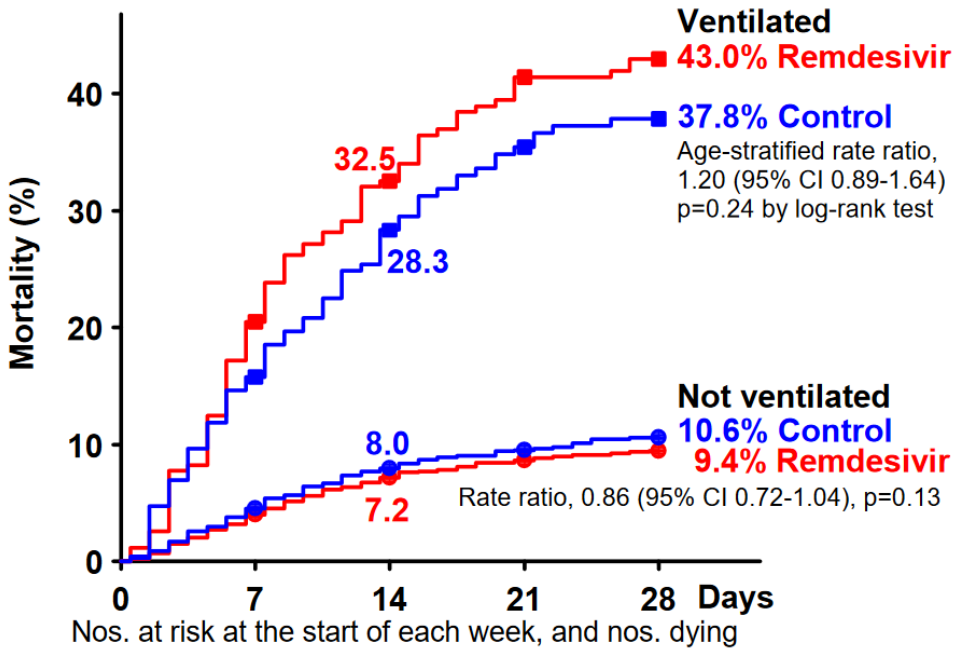
WHO SOLIDARITY:
No effect of remdesivir on mortality

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



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