Higher dose corticosteroids in patients admitted to hospital with COVID-19 who are hypoxic but not requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial

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Summary

Background Low-dose corticosteroids have been shown to reduce mortality for patients with COVID-19 requiring oxygen or ventilatory support (non-invasive mechanical ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation). We evaluated the use of a higher dose of corticosteroids in this patient group.

Methods This randomised, controlled, open-label platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) is assessing multiple possible treatments in patients hospitalised for COVID-19. Eligible and consenting adult patients with clinical evidence of hypoxia (ie, receiving oxygen or with oxygen saturation <92% on room air) were randomly allocated (1:1) to either usual care with higher dose corticosteroids (dexamethasone 20 mg once daily for 5 days followed by 10 mg dexamethasone once daily for 5 days or until discharge if sooner) or usual standard of care alone (which included dexamethasone 6 mg once daily for 10 days or until discharge if sooner). The primary outcome was 28-day mortality among all randomised participants. On May 11, 2022, the independent data monitoring committee recommended stopping recruitment of patients receiving no oxygen or simple oxygen only due to safety concerns. We report the results for these participants only. Recruitment of patients receiving ventilatory support is ongoing. The RECOVERY trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Findings Between May 25, 2021, and May 13, 2022, 1272 patients with COVID-19 and hypoxia receiving no oxygen (eight [1%]) or simple oxygen only (1264 [99%]) were randomly allocated to receive usual care plus higher dose corticosteroids (659 patients) versus usual care alone (613 patients, of whom 87% received low-dose corticosteroids during the follow-up period). Of those randomly assigned, 745 (59%) were in Asia, 512 (40%) in the UK, and 15 (1%) in Africa. 248 (19%) had diabetes and 769 (60%) were male. Overall, 123 (19%) of 659 patients allocated to higher dose corticosteroids versus 75 (12%) of 613 patients allocated to usual care died within 28 days (rate ratio 1·59 [95% CI 1·20–2·10]; p=0·0012). There was also an excess of pneumonia reported to be due to non-COVID infection (64 cases [10%] *vs* 37 cases [6%]; absolute difference 3·7% [95% CI 0·7–6·6]) and an increase in hyperglycaemia requiring increased insulin dose (142 [22%] *vs* 87 [14%]; absolute difference 7·4% [95% CI 3·2–11·5]).

Interpretation In patients hospitalised for COVID-19 with clinical hypoxia who required either no oxygen or simple oxygen only, higher dose corticosteroids significantly increased the risk of death compared with usual care, which included low-dose corticosteroids. The RECOVERY trial continues to assess the effects of higher dose corticosteroids in patients hospitalised with COVID-19 who require non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation.

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See **Online** for appendix

Introduction

The randomised evaluation of COVID-19 therapy (RECOVERY) trial has previously shown that the use of corticosteroids (using dexamethasone 6 mg once daily for 10 days or until discharge if sooner) reduces the risk of death in patients admitted to hospital with COVID-19 and hypoxia.[1] Subsequent findings that additional immunosuppression with an IL-6 receptor blocker or a Janus kinase (JAK) inhibitor further reduces the risk of death in these patients raises the question of whether simply increasing the dose of corticosteroid, rather than adding other immunomodulators, could confer additional benefits at substantially lower cost.[2,3]

Initially, the dose of dexamethasone chosen for the RECOVERY trial was 6 mg once daily on the basis that there is considerable experience of the safe use of similar doses of corticosteroids for exacerbations of asthma and chronic obstructive pulmonary disease. However, the optimal corticosteroid dose in COVID-19 treatment has not been determined. Higher doses of corticosteroids

Research in context

Evidence before this study

We searched MEDLINE, Embase, medRxiv, and the WHO International Clinical Trials Registry Platform between Sept 1, 2019, and Jan 13, 2023, for randomised controlled trials comparing the effect of different doses of systemic corticosteroids in patients hospitalised with COVID-19 receiving no or simple oxygen at randomisation, using the search terms: (Coronavirus infection OR SARS-CoV-2 OR SARS-CoV2 OR SARSCoV2 OR COVID OR COVID-19 OR COVID19 OR 2019-nCoV OR Coronavirus OR Coronavirinae) AND (corticosteroid* OR dexamethasone OR glucocorticoid* OR steroid* OR hydrocortisone OR methylprednisolone OR prednisolone OR betamethasone) and using validated filters to select for randomised controlled trials. No language restrictions were applied. We identified 13 relevant randomised trials with results available that assessed different doses of corticosteroids in patients hospitalised with COVID-19, at least some of whom were receiving simple oxygen therapy at randomisation: seven studies assessed higher dose dexamethasone (12–24 mg per day) and six assessed methylprednisolone (60–1000 mg per day), all compared with lower dose dexamethasone (6–8 mg per day; appendix p 34). Four of the trials included only a non-critically ill population and the remainder included a mixed illness severity population. 12 of the trials have been fully published, of which six were considered to have low risk of bias for the 28-day mortality outcome and six having some concerns (including lack of information about randomisation process, lack of information about prespecified analyses, crossover between randomised groups, and post-randomisation exclusion of patients in the analysis population). All but one of the trials had found no significant difference in mortality between the treatment groups. The exception was a small trial by Gautam and colleagues comparing methylprednisolone (2 mg/kg per day for 3 days then 1 mg/kg per day for 3 days) with dexamethasone (8 mg daily for 10 days) that included 140 patients and 18 deaths and reported that methylprednisolone was associated with significantly improved mortality at 10 days (appendix p 34). There was no information in the trial report about the randomisation process or whether the trial was analysed as prespecified, conferring some concerns over risk of bias.

Added value of this study

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is the largest randomised trial of the effect of different doses of corticosteroids in patients hospitalised with COVID-19 and included patients from three continents. We found that among patients with hypoxia on simple or no oxygen, randomisation to higher dose corticosteroids (dexamethasone 20 mg daily for 5 days followed by dexamethasone 10 mg for 5 days, or until discharge if sooner) versus usual care (which included dexamethasone 6 mg once daily in 87% of participants) resulted in an increased risk of all-cause mortality.

Implications of all the available evidence

Among hospitalised patients with COVID-19 who require oxygen or ventilatory support, low-dose corticosteroids reduce the risk of death. However, among patients requiring simple oxygen only, higher doses of corticosteroids increase the risk of death compared with low-dose corticosteroids. It remains unclear whether using a higher dose of corticosteroids is beneficial among patients requiring non-invasive or invasive ventilation—the RECOVERY trial continues to study this.

have been used in non-COVID acute respiratory distress syndrome and in other COVID-19 clinical trials with reported clinical benefit; however, these trials have been mostly restricted to patients with severe or critical illness, and the trials that have directly compared higher corticosteroid doses with the lower doses used in RECOVERY have been inconclusive.[4–11] A WHO meta-analysis of randomised controlled trials in patients who are critically ill with COVID-19 has indicated similar mortality benefits with lower and higher dose corticosteroids, but estimates were imprecise.[7]

In April, 2021, the UK COVID-19 Therapeutics Advisory Panel (CTAP) recommended that the RECOVERY trial study higher dose corticosteroids.[12] Therefore, the RECOVERY trial established a randomised evaluation of the effects of higher dose corticosteroids versus usual care for adult patients who had been admitted to hospital with COVID-19 and had clinical evidence of hypoxia. Usual care for patients with hypoxia and COVID-19 includes low-dose corticosteroids. On May 11, 2022, the independent data monitoring committee recommended that this comparison be halted for those patients receiving no oxygen or simple oxygen only on the grounds of safety. Here we report the results for these patients. Recruitment to this comparison continues as planned for patients receiving non-invasive ventilation or invasive mechanical ventilation.

Methods

Study design and participants

The RECOVERY trial is an investigator-initiated, individually randomised, controlled, open-label, platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19. Details of the trial design and results for other possible treatments (low-dose dexamethasone, hydroxychloroquine, lopinavir–ritonavir, azithromycin, tocilizumab, convalescent plasma, colchicine, aspirin, casirivimab plus imdevimab, and baricitinib) have been published previously. The trial is underway at hospital organisations in the UK, supported by the National Institute for Health Research Clinical Research Network, and in south and southeast Asia and Africa. Of these, 81 hospitals in the UK, five in Nepal, two in Indonesia, two in Viet Nam, two in South Africa,

and one in Ghana enrolled participants in the evaluation of higher dose corticosteroids (appendix pp 2–31). The trial is coordinated by the Nuffield Department of Population Health at the University of Oxford (Oxford, UK), the trial sponsor. The trial is being conducted in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines. The protocol was approved by all relevant regulatory authorities and ethics committees in each participating country (appendix p 32). The protocol and statistical analysis plan are available in the appendix (pp 71–152) with additional information available on the study website.

Patients aged at least 18 years admitted to hospital were eligible for the study if they had clinically suspected or laboratory-confirmed SARS-CoV-2 infection, clinical evidence of hypoxia (ie, receiving oxygen with or without other forms of respiratory support, or with oxygen saturations <92% on room air), and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial. Patients were not eligible for the comparison of higher dose corticosteroid versus usual care if there was a known contraindication to short-term use of corticosteroids, suspected or confirmed influenza, or current use of nirmatrelvir–ritonavir, ritonavir, or other potent CYP3A inhibitors. Screening for endemic infections (eg, tuberculosis or *Strongyloides stercoralis*) was at the discretion of the managing physician, according to their usual practice for patients receiving higher dose corticosteroids. The use of other immunomodulatory therapies, such as IL-6 or JAK inhibitors, was not contraindicated, as patients receiving these agents remain at high risk of death from inflammatory lung disease and previous concerns about their use in combination with low-dose corticosteroids proved unfounded.[2,3] However, investigators were advised to consider the total burden of such therapy in combination with higher dose corticosteroids. Written informed consent was obtained from all patients, or a legal representative if patients were too unwell or unable to provide consent.

Randomisation and masking

Baseline data were collected using a web-based case report form that included demographics, level of respiratory support, major comorbidities, suitability of the study treatment for a particular patient, SARS-CoV-2 vaccination status, and treatment availability at the study site (appendix pp 44–47).

Eligible and consenting patients were assigned in a 1:1 ratio to either usual standard of care plus higher dose corticosteroids or usual standard of care alone (which includes low-dose corticosteroids, usually dexamethasone 6 mg once daily for 10 days or until discharge if sooner) using web-based simple (unstratified) randomisation with allocation concealed until after randomisation (appendix pp 42–44).[13,14] Patients allocated to higher dose corticosteroid were to receive oral or intravenous dexamethasone 20 mg daily for 5 days followed by dexamethasone 10 mg for 5 days, or until discharge if sooner (a dosing regimen used in several previous COVID-19 trials and consistent with the CTAP recommendation).[7,11,12] Dexamethasone could be given orally or intravenously at the discretion of the managing physician. Alternative corticosteroid regimens for pregnant women are described in the protocol (appendix p 80).

As a platform trial, and in a factorial design, patients could be simultaneously randomly assigned to other treatment groups: empagliflozin versus usual care, sotrovimab versus usual care, and molnupiravir versus usual care. The use of any non-trial treatments was left to the discretion of the managing physician. Additional details of when these factorial randomisations were open are provided in the appendix (pp 42–44). Participants and local study staff were not masked to the allocated treatment. Other than members of the Data Monitoring Committee, all individuals involved in the trial were masked to aggregated outcome data while recruitment and 28-day follow-up were ongoing.

For the **RECOVERY study website** see http://www.recoverytrial.net

Procedures

An online follow-up form was completed by site staff when patients were discharged, had died, or at 28 days after random assignment, whichever occurred first (appendix pp 48–56). Information was recorded on adherence to allocated trial treatment, receipt of other COVID-19 treatments, duration of admission, receipt of respiratory or renal support, new cardiac arrhythmia, thrombosis, clinically significant bleeding, non-COVID infection, metabolic complications (collected from July 28, 2021, onwards), and vital status (including cause of death). In addition, in the UK, routinely collected health-care and registry data were obtained, including information on vital status at day 28 (with date and cause of death); discharge from hospital; and receipt of respiratory support or renal replacement therapy. For sites outside the UK, an additional case report form (appendix p 58) collected vital status at day 28 (if not already reported on follow-up form).

Outcomes

Outcomes were assessed at 28 days after randomisation, with additional analyses specified at 6 months. The primary outcome was 28-day all-cause mortality. Secondary outcomes were time to discharge from hospital and the composite outcome of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Prespecified subsidiary clinical outcomes were use of invasive or non-invasive ventilation and use of renal dialysis or haemofiltration among patients not receiving such treatment at randomisation. Prespecified safety outcomes were cause-specific mortality, major cardiac arrhythmia, thrombotic and major bleeding events,

metabolic complications, and infections other than COVID-19. The diagnosis of other infections, which included non-COVID-19 pneumonia, was at the discretion of the managing physician based on their usual practice, with no diagnostic criteria specified in the protocol. Information on suspected serious adverse reactions was collected in an expedited fashion to comply with regulatory requirements. Details of the methods used to ascertain and derive outcomes are provided in the appendix (pp 153–175).

Statistical analysis

All analyses were limited to the subgroup of patients on no oxygen or simple oxygen at randomisation. For all outcomes, intention-to-treat analyses compared patients randomly assigned to higher dose corticosteroids with patients randomly assigned to usual care. For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were used to both test the null hypothesis of equal survival curves (ie, the log-rank test) and to calculate the one-step estimate of the average mortality rate ratio. We constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period. We used the same method to analyse time to hospital discharge with patients who died in hospital right censored on day 29. Median time to discharge was derived from Kaplan-Meier estimates. For the composite secondary outcome of progression to invasive mechanical ventilation or death within 28 days, and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or haemofiltration, the precise dates were not available and so the risk ratio was estimated instead.

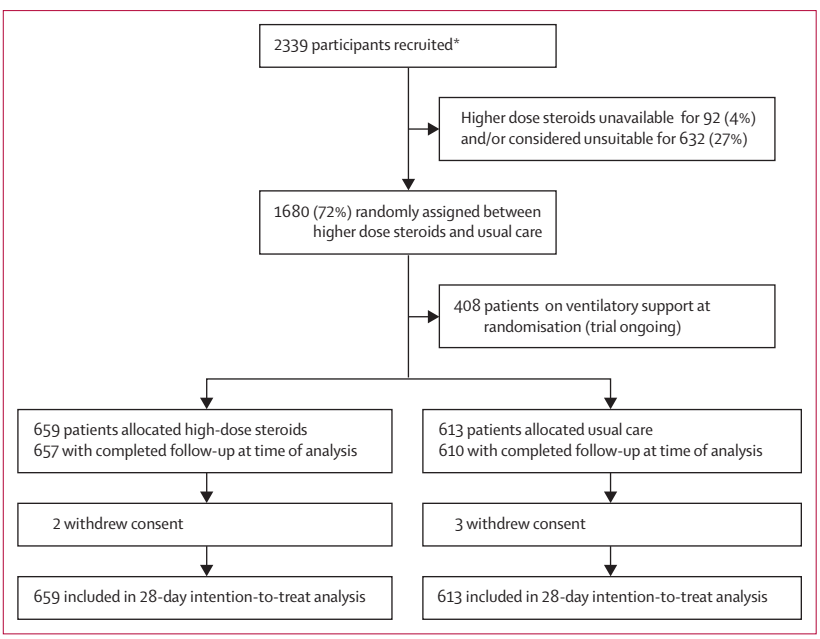

Figure 1: **Trial profile**
Higher dose corticosteroid unavailable and higher dose corticosteroid considered unsuitable are not mutually exclusive. *Number recruited overall during period that participants on no oxygen or simple oxygen only could be recruited into the higher dose corticosteroid comparison.

Estimates of rate ratio and risk ratios (both denoted RR) are shown with 95% CIs. For the primary outcome of 28-day mortality, a sensitivity analysis adjusted for age was done using Cox regression.

Since the analyses presented here relate only to the subset of participants who were on no oxygen or simple oxygen only at randomisation, any analyses of the primary outcome in further subgroups defined by different baseline characteristics must be considered exploratory in nature. With that caveat, we present analyses of the primary outcome by age, sex, ethnicity, days since symptom onset, and place of recruitment (UK, elsewhere) with χ^2 tests for heterogeneity or trend, as appropriate. We have not presented analyses by subgroups for the secondary or other outcomes. Results for the prespecified other clinical outcomes and safety outcomes are presented. The full database is held by the study team that collected the data from study sites and did the analyses at the Nuffield Department of Population Health (University of Oxford, Oxford, UK).

For the primary outcome of 28-day mortality, the results from RECOVERY were subsequently included in a meta-analysis of results from all previous randomised trials of higher dose versus low-dose corticosteroids in patients who had been hospitalised with COVID-19 who were largely or wholly receiving simple oxygen or no oxygen. For each trial, we compared the observed number of deaths among patients allocated higher dose corticosteroids with the expected number if all patients were at equal risk (ie, we calculated the observed minus expected statistic [o−e], and its variance v). For RECOVERY, these were taken as the log-rank observed minus expected statistic and its variance but for other trials, where the exact timing of each death was not available, these were calculated from standard formulae for 2×2 contingency tables. We then combined trial results using the log of the mortality rate ratio calculated as the inverse-variance weighted average S/V with variance 1/V (and hence with 95% CI $S/V \pm 1{\cdot}96/\sqrt{V}$), where S is the sum over all trials of (O−E) and V is the sum over all trials of v.[15]

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned. However, the intention for this comparison was to continue recruitment until sufficient primary outcomes had accrued to have 90% power to detect a proportional risk reduction of 20% at 2p=0·01.

The independent data monitoring committee reviewed unblinded analyses of the study data and any other information considered relevant to the trial at intervals of around 1–2 months (depending on speed of enrolment) and was charged with determining whether, in their view, the randomised comparisons in the study provided evidence on mortality that was strong enough (with a range of uncertainty around the results that was narrow enough) to affect national and global treatment strategies (appendix p 59).

On May 11, 2022, the data monitoring committee recommended stopping recruitment to the higher dose corticosteroid comparison for patients who require no oxygen or simple oxygen only at randomisation due to safety concerns (appendix p 60). The data monitoring committee encouraged continuing recruitment of all those patients who, at random assignment, required either non-invasive ventilation (including high-flow nasal oxygen and continuous positive airway pressure), invasive mechanical ventilation, or extracorporeal membrane oxygenation.

On May 13, 2022, recruitment of patients on oxygen or simple oxygen only to this comparison was stopped, and investigators were notified and advised not to administer further higher dose corticosteroids to this group as part of the trial. Follow-up of all patients continued as planned. The regulatory authorities and ethics committees in each participating country were notified. Trial procedures were changed as an urgent safety measure and the protocol was subsequently modified and approved accordingly. Recruitment and follow-up of patients receiving non-invasive ventilation or invasive mechanical ventilation remains open.

Analyses were performed using SAS version 9.4 and R version 4.0.3. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Recruitment to the evaluation of higher dose corticosteroids commenced on May 25, 2021, outside the UK and on Dec 29, 2021, in the UK (following closure of the baricitinib comparison) and ended worldwide for patients receiving no oxygen or simple oxygen on May 13, 2022, following the data monitoring committee recommendation. Of 1680 patients enrolled in this comparison during this period, 1272 patients receiving no oxygen or simple oxygen only were included in this evaluation. Of these, 659 were randomly allocated to higher dose corticosteroids and 613 patients were randomly allocated to usual care (figure 1). The mean age of these participants was 61·1 years (SD 17·5; appendix p 62) with those randomly allocated to higher dose corticosteroids on average 1·9 years younger than those allocated usual care (table 1). 745 (59%) participants were in Asia, 512 (40%) in the UK, and 15 (1%) in Africa. 248 (19%) had a history of diabetes and 1264 (99%) were receiving simple oxygen (appendix p 62).

The follow-up form was completed for 657 patients (>99%) in the higher dose corticosteroid group and 610 patients (>99%) in the usual care group. Among patients with a completed follow-up form, 601 (91%) allocated to higher dose corticosteroid were reported to have received higher dose corticosteroids compared with

	Higher dose steroids (n=659)	Usual care (n=613)
Age, years	60·2 (18·3)	62·1 (16·6)
<70	426 (65%)	395 (64%)
70–79	128 (19%)	123 (20%)
≥80	105 (16%)	95 (15%)
Sex		
Male	393 (60%)	376 (61%)
Female	266 (40%)	237 (39%)
Country		
Ghana	1 (<1%)	0
Indonesia	41 (6%)	31 (5%)
Nepal	317 (48%)	288 (47%)
South Africa	11 (2%)	3 (<1%)
Viet Nam	40 (6%)	28 (5%)
UK	249 (38%)	263 (43%)
Ethnicity		
White	227 (34%)	227 (37%)
Black	5 (1%)	9 (1%)
Asian	363 (55%)	325 (53%)
Other	3 (<1%)	6 (1%)
Unknown	61 (9%)	46 (8%)
Time since symptom onset, days	7 (4–10)	7 (4–10)
Time since admission to hospital, days	1 (0–2)	1 (1–3)
Respiratory support received		
None	5 (1%)	3 (<1%)
Simple oxygen	654 (99%)	610 (100%)
Previous diseases		
Diabetes	129 (20%)	119 (19%)
Heart disease	186 (28%)	165 (27%)
Chronic lung disease	135 (20%)	134 (22%)
Tuberculosis	5 (1%)	5 (1%)
HIV	3 (<1%)	3 (<1%)
Severe liver disease*	5 (1%)	7 (1%)
Severe kidney impairment†	22 (3%)	18 (3%)
Any of the above	338 (51%)	307 (50%)
SARS-CoV-2 PCR test result		
Positive	623 (95%)	581 (95%)
Negative	5 (1%)	4 (1%)
Unknown	31 (5%)	28 (5%)
Received a COVID-19 vaccine	358 (54%)	317 (52%)
Use of other treatments at the time of randomisation		
Remdesivir	221 (34%)	206 (34%)
Tocilizumab	57 (9%)	46 (8%)
Plan to use tocilizumab within the next 24 h	26 (4%)	26 (4%)

Data are mean (SD), n (%), or median (IQR). Three pregnant women were randomly assigned. *Defined as requiring ongoing specialist care. †Defined as estimated glomerular filtration rate <30 mL/min per 1·73 m².

Table 1: **Baseline characteristics by treatment allocation**

seven (1%) allocated to usual care (appendix p 63). Among those with a completed follow-up form allocated usual care, 530 (87%) received low-dose dexamethasone. Use of other treatments for COVID-19 was broadly similar among patients allocated higher dose corticosteroids and among those allocated usual care, with two-fifths receiving remdesivir and a tenth receiving an IL-6 antagonist during the follow-up period (appendix p 63).

Primary and secondary outcome data are known for more than 99% of randomly assigned patients. Allocation to higher dose corticosteroids was associated with a significant increase in the primary outcome of 28-day mortality compared with usual care alone: 123 (19%) of 659 patients in the higher dose corticosteroid group died versus 75 (12%) of 613 patients in the usual care group (rate ratio 1·59 [95% CI 1·20–2·10]; p=0·0012; figure 2, table 2). A similar proportional risk increase was seen in analyses restricted to participants with a positive SARS-CoV-2 PCR test (RR 1·66 [95% CI 1·25–2·20], p=0·0005) or adjusted for baseline age (RR 1·62 [1·21–2·15], p=0·0011). In exploratory analyses, the proportional effect of higher dose corticosteroids on mortality was consistent across all five pre-specified subgroups (all interaction p values ≥0·10; figure 3), including by region of recruitment and by ethnicity. Because of the potential for higher dose corticosteroids to cause hyperglycaemic complications, a post-hoc subgroup analysis of 28-day mortality was performed by baseline diabetes status. This analysis showed no evidence of heterogeneity between the 248 patients with diabetes (RR 1·20 [0·62–2·32]) and the 1024 without diabetes (1·69 [1·24–2·30]); p value for heterogeneity 0·36.

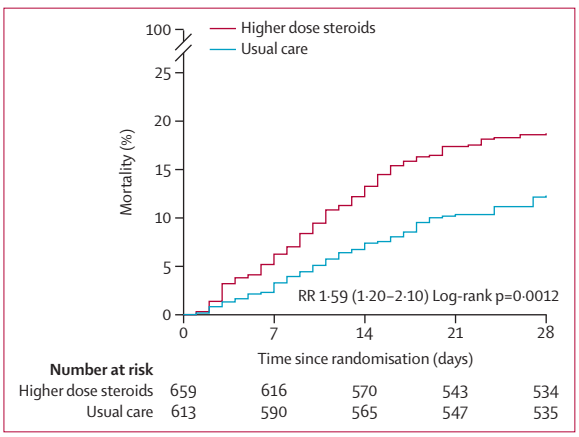

Figure 2: **Effect of allocation to higher dose corticosteroids or usual care (lower dose corticosteroids) on 28-day mortality in patients receiving no oxygen or simple oxygen only**
RR=rate ratio.

	Higher dose steroids (n=659)	Usual care (n=613)	RR (95% CI)
Primary outcome			
28-day mortality	123 (19%)	75 (12%)	1·59 (1·20–2·10)
Secondary and subsidiary outcomes			
Median (IQR) duration of hospitalisation, days	9 (5–17)	9 (5–16)	..
Discharged from hospital alive within 28 days	526 (80%)	504 (82%)	0·92 (0·81–1·05)
Invasive mechanical ventilation or death within 28 days	131 (20%)	80 (13%)	1·52 (1·18–1·97)
Use of ventilation	119 (18%)	85 (14%)	1·30 (1·01–1·68)
Non-invasive ventilation	108 (16%)	83 (14%)	1·21 (0·93–1·58)
Invasive mechanical ventilation	22 (3%)	14 (2%)	1·46 (0·75–2·83)
Renal replacement therapy*	11/658 (2%)	8/613 (1%)	1·28 (0·52–3·16)

Data are n (%) or n/N (%), unless otherwise indicated. RR=rate ratio for the outcomes of 28-day mortality and hospital discharge, and risk ratio for other outcomes. *Analyses exclude those on haemodialysis or haemofiltration at randomisation.

Table 2: **Effect of allocation to higher dose corticosteroid on key study outcomes**

Systematic review identified seven previous trials of higher dose versus lower dose corticosteroids among hospitalised patients who were largely or wholly receiving simple oxygen or no oxygen, which included a total of 113 deaths among 1193 patients (appendix p 68). After inclusion of the 28-day mortality results from RECOVERY into this meta-analysis, the mortality rate ratio from the eight trials was 1·35 (1·07–1·70; p=0·011).

Discharge alive within 28 days was similar among those allocated to higher dose corticosteroids compared with usual care (526 [80%] *vs* 504 [82%]; rate ratio 0·92 [95% CI 0·81–1·05]; median 9 days [IQR 5–17] *vs* 9 days [5–16]; table 2). Allocation to higher dose corticosteroids was associated with a higher risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (131 [20%] *vs* 80 [13%], risk ratio 1·52 [95% CI 1·18–1·97]; table 2). There were no significant differences in use of ventilation or receipt of haemodialysis or haemofiltration (table 2).

Three-quarters of the deaths within 28 days were attributed to COVID-19 (appendix p 64). Allocation to higher dose corticosteroids was associated with an increase in pneumonia reported as not due to COVID-19 (64 [10%] *vs* 37 [6%], absolute risk increase 3·7% [95% CI 0·7–6·6]; table 3), but there were no significant differences in the rates of other presentations of non-SARS-CoV-2 infection, new onset cardiac arrhythmia, thrombotic events, or clinically significant bleeding (table 3, appendix p 65). Allocation to higher dose corticosteroids was associated with an increase in clinically significant hyperglycaemia (ketoacidosis, hyperglycaemic hyperosmolar state, or hyperglycaemia requiring new use of insulin) occurring in 142 (22%) versus 87 (14%) participants (absolute risk increase 7·4% [95% CI 3·2–11·5]; table 3). There were five reports of a serious adverse reaction believed to be related to treatment with higher dose corticosteroids, all of which resolved; four related to hyperglycaemia and one related to gastrointestinal bleeding (appendix p 66).

Discussion

In this large, randomised trial, allocation to higher dose corticosteroids significantly increased 28-day mortality for patients with hypoxia requiring simple oxygen or no

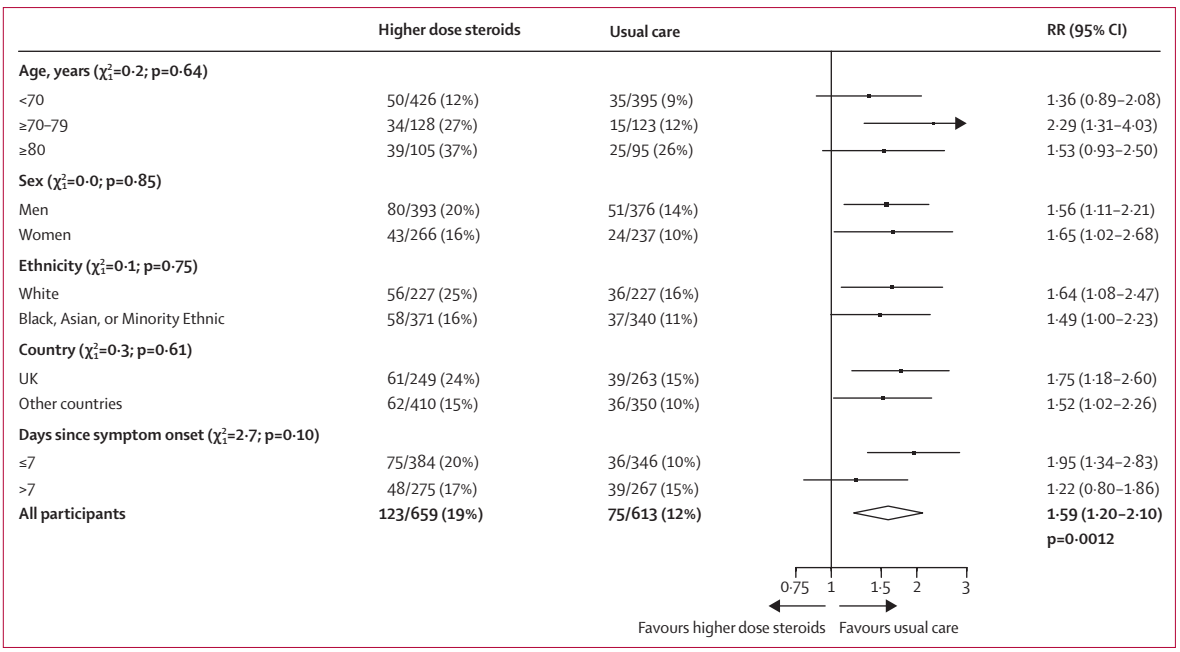

Figure 3: **Effect of allocation to higher dose corticosteroids or usual care (low-dose corticosteroids) on 28-day mortality in patients receiving no oxygen or simple oxygen only by other baseline characteristics**

Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. The ethnicity subgroup excludes those with missing data, but these patients are included in the overall summary diamond. RR=rate ratio. χ^2 values and their corresponding p values are tests for heterogeneity or trend.

oxygen. There was also an increase in the risk of pneumonia due to non-COVID-19 causes and in hyperglycaemic episodes requiring new use of insulin. The increase in mortality appeared similar among patients with and without diabetes, suggesting it is not primarily mediated by hyperglycaemia, and was similar among patients from the UK and from Asia, suggesting it is not limited to areas with a high prevalence of tuberculosis.

Strengths of the RECOVERY trial are that it was randomised, had a large sample size, had broad eligibility criteria, and that more than 99% of patients in this analysis had been followed up for the primary outcome. The trial was also conducted in areas with high (south and southeast Asia, and Africa) and low (UK) prevalence of tuberculosis and other infections. The study has some limitations: this randomised trial was open label (ie, participants and local hospital staff were aware of the assigned treatment), which could potentially lead to bias in outcomes that might be affected by knowledge of treatment allocation, such as the diagnosis of hyperglycaemia or non-SARS-CoV-2 infections. However, the primary outcome of death is unambiguous and unlikely to be affected by knowledge of allocated treatment (and there was no evidence in this study that knowledge of allocated treatment affected the use of other COVID-19 therapies or led to a reluctance to initiate ventilatory support in those allocated higher dose corticosteroids; appendix p 63, table 2). Information on radiological, virological, or physiological outcomes was

	Higher dose steroids (n=659)	Usual care (n=613)	Absolute difference (95% CI)
Non-SARS-CoV-2 infection			
Pneumonia	64 (10%)	37 (6%)	3·7% (0·7 to 6·6)
Urinary tract	12 (2%)	9 (1%)	0·4% (–1·0 to 1·7)
Biliary	0	0	..
Other intra-abdominal	0	1 (<1%)	–0·2% (–0·5 to 0·2)
Blood stream	7 (1%)	3 (<1%)	0·6% (–0·4 to 1·5)
Skin	1 (<1%)	3 (<1%)	–0·3% (–1·0 to 0·3)
Other	9 (1%)	13 (2%)	–0·8% (–2·2 to 0·7)
Any non-SARS-CoV-2 infection	81 (12%)	58 (9%)	2·8% (–0·6 to 6·2)
Metabolic complications*			
Ketoacidosis	1 (<1%)	1 (<1%)	0·0% (–0·4 to 0·4)
Hyperglycaemic hyperosmolar state	5 (1%)	2 (<1%)	0·4% (–0·4 to 1·2)
Other hyperglycaemia requiring new use of insulin	138 (21%)	86 (14%)	6·9% (2·8 to 11·1)
Any clinically significant hyperglycaemia	142 (22%)	87 (14%)	7·4% (3·2 to 11·5)
Severe hypoglycaemia	2 (<1%)	2 (<1%)	0·0% (–0·6 to 0·6)
New cardiac arrhythmia†	13 (2%)	8 (1%)	0·7% (–0·7 to 2·1)
Thrombotic events†	8 (1%)	13 (2%)	–0·9% (–2·3 to 0·5)
Clinically significant bleeds†	8 (1%)	4 (1%)	0·6% (–0·5 to 1·6)

*Information on metabolic complications was added to the follow up form on July 28, 2021. Of the 1267 (>99%) randomly assigned participants with a follow-up form completed, 1062 (84%) had information on metabolic complications recorded. †Details of these events are presented in the appendix (p 65).

Table 3: **Effect of allocation to higher dose corticosteroid on non-SARS-CoV-2 infection, metabolic complications, new cardiac arrhythmia, thrombotic events, and clinically significant bleeds**

not collected. Only about 10% of participants in this evaluation of higher dose corticosteroids received an IL-6 antagonist or baricitinib so we are unable to assess any possible interactions between corticosteroid dose and other immunomodulatory treatments. The enrolment of patients on no oxygen or simple oxygen was closed early on the basis of an interim analysis by the independent data monitoring committee. Consequently, it is possible that the size of the hazards presented is an over-estimate of the true effects of higher dose corticosteroids.[16] Indeed, when combined in a meta-analysis of other trials of lower-risk patients, the estimated RR was somewhat lower, although still significant.

Before the COVID-19 pandemic, the role of corticosteroids in acute lung injury was unclear.[17] This understanding began to change when the RECOVERY trial showed a clear reduction in 28-day mortality with the use of 6 mg dexamethasone once daily for up to 10 days in patients with COVID-19 requiring oxygen therapy.[1] The benefit of corticosteroids among patients who are critically ill with COVID-19 was subsequently confirmed in other randomised controlled trials and in a meta-analysis.[7,18] A broader meta-analysis of the effects of corticosteroids in both COVID-19-related acute respiratory distress syndrome and non-COVID-19 acute respiratory distress syndrome has reported that corticosteroids probably reduce mortality regardless of the cause.[19]

Previous difficulties in determining the role of corticosteroids in acute lung injury might have arisen because the benefits and hazards of their use could vary by dose, comorbidities, and the severity of lung injury (which is reflected in the level of respiratory support required).[19,20] The initial dexamethasone result from RECOVERY showed a clear difference in effect of low-dose corticosteroids by disease severity, with the greatest benefit seen in the most severely ill. 28-day mortality was reduced by about a third in those requiring invasive mechanical ventilation or extracorporeal membrane oxygenation, with a more modest reduction of a fifth in those requiring simple oxygen or non-invasive ventilation, and no benefit observed in those not requiring oxygen.[1]

The results we present in this Article show that in patients with COVID-19 and hypoxia who require only simply oxygen therapy, a higher dose of corticosteroids (dexamethasone 20 mg once daily for 5 days followed by 10 mg once daily for 5 days or until discharge if sooner) is harmful compared with usual care (which included use of low-dose corticosteroids). In contrast to our results for patients on simple oxygen, trials of higher dose versus low-dose corticosteroids in patients requiring higher levels of respiratory support seem to rule out a substantial hazard, which is in keeping with the fact that no safety concern has yet been identified in these patients in RECOVERY. In the COVIDICUS trial of 546 patients in intensive care, which compared the same dexamethasone regimens used in RECOVERY, higher dose dexamethasone showed no evidence of substantial hazard and results were consistent with both moderate benefit or harm (RR 0·96 [95% CI 0·69–1·33]).[11] The COVID STEROID 2 trial evaluated an intermediate dose of dexamethasone (12 mg daily) versus low dose (6 mg daily) in 1000 patients with COVID-19 requiring 10 L/min or more oxygen or mechanical ventilation.[10] In this trial, the intermediate dose was associated with non-significantly lower mortality, and was inconsistent with a substantial hazard (RR 0·86 [95% CI 0·68–1·08]). As such, it remains an open question whether increasing the dose of corticosteroids above 6 mg dexamethasone per day is helpful for patients with COVID-19 requiring non-invasive or invasive mechanical ventilation—the RECOVERY trial continues to seek an answer for that question.

In summary, this large, randomised trial demonstrated that, compared with standard dose corticosteroids, use of higher dose corticosteroids increases mortality for patients with COVID-19 and hypoxia who are not receiving non-invasive or invasive mechanical ventilation.

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Contributors
This manuscript was initially drafted by PWH and MJL, further developed by the writing committee, and approved by all members of the trial steering committee. PWH, BB, RLH, JA, JKB, MB, LCC, JD, SNF, TJ, EJ, KJ, WSL, MM, AMo, AMu, KR, GT, RH, and MJL designed the trial and study protocol. MM, LP, MC, GP-A, EK, MR, RKJ, NTP, US, DP, PNT, NN, ES, LM, RS, and the data linkage team at the RECOVERY Coordinating Centre, and the health records and local clinical centre staff listed in the appendix collected the data. JRE and NS had access to the study data and did the statistical analysis. All authors contributed to data interpretation and critical review and revision of the manuscript. PWH and MJL had access to the study data and had final responsibility for the decision to submit for publication. MJL, PWH, JRE, and NS verified the data.

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Declaration of interests
We declare no competing interests or financial relationships relevant to the submitted work to disclose. No form of payment was given to anyone to produce the manuscript. The Nuffield Department of Population Health at the University of Oxford has a staff policy of not accepting honoraria or consultancy fees directly or indirectly from industry.

Data sharing
The protocol, consent form, statistical analysis plan, definition, and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant study materials are available online at http://www.recoverytrial.net. As described in the protocol, the trial steering committee will facilitate the use of the study data and approval will not be unreasonably withheld. Deidentified participant data will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However,

the steering committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The steering committee will have the right to review and comment on any draft manuscripts before publication. Data will be made available in line with the policy and procedures described at https://www.ndph.ox.ac.uk/data-access. Those wishing to request access should complete the form at https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx and e-mail it to data.access@ndph.ox.ac.uk.

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