ORIGINAL ARTICLE

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

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.)

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (Covid-19), emerged in China in late 2019 from a zoonotic source.[1] The majority of Covid-19 infections are either asymptomatic or result in only mild disease. However, in a substantial proportion of infected persons, the infection leads to a respiratory illness requiring hospital care,[2] which can progress to critical illness with hypoxemic respiratory failure and lead to prolonged ventilatory support.[3-6] Among the patients with Covid-19 who have been admitted to hospitals in the United Kingdom, the case fatality rate is approximately 30%.[7]

Hydroxychloroquine and chloroquine, two 4-aminoquinoline drugs that were developed more than 70 years ago and have been used to treat malaria and rheumatologic conditions, have been proposed as treatments for Covid-19. Chloroquine has been shown to have in vitro activity against a variety of viruses, including SARS-CoV-2 and the related SARS-CoV-1.[8-13] The exact mechanism of antiviral action is uncertain, but these drugs increase the pH of endosomes that the virus uses for cell entry and also interfere with the glycosylation of angiotensin-converting–enzyme 2 (ACE2), which is the cellular receptor of SARS-CoV, and of associated gangliosides.[10,14] The 4-aminoquinoline levels that are required to inhibit SARS-CoV-2 replication in vitro are higher than the free plasma levels that have been observed in the prevention and treatment of malaria.[15] These drugs generally have an acceptable side-effect profile and are inexpensive and widely available. After oral administration, they are rapidly absorbed, even in severely ill patients. Therapeutic hydroxychloroquine levels could be expected to be reached in human lung tissue shortly after an initial loading dose.

In small preclinical studies of SARS-CoV-2 infection in animals, prophylaxis or treatment with hydroxychloroquine had no beneficial effect on clinical disease or viral replication.[16] A clinical benefit and an antiviral effect from the administration of these drugs alone or in combination with azithromycin in patients with Covid-19 have been reported in some observational studies[17-21] but not in others.[22-24] The results of a few small trials of hydroxychloroquine or chloroquine for the treatment of Covid-19 have been inconclusive, whereas one larger randomized, controlled trial involving patients who were hospitalized with mild-to-moderate Covid-19 showed that hydroxychloroquine (at a dose of 400 mg twice daily, with or without azithromycin) did not improve clinical status at day 15, as compared with usual care.[25-29] Here, as part of the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, we report the results of a comparison between hydroxychloroquine and usual care involving patients hospitalized with Covid-19.

METHODS

TRIAL DESIGN AND OVERSIGHT

The RECOVERY trial is an investigator-initiated platform trial to evaluate the effects of potential treatments in patients hospitalized with Covid-19. The trial is being conducted at 176 hospitals in the United Kingdom. (Details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) The investigators were assisted by the National Institute for Health Research Clinical Research Network, and the trial is coordinated by the Nuffield Department of Population Health at the University of Oxford, the trial sponsor. Although patients are no longer being enrolled in the hydroxychloroquine, dexamethasone, and lopinavir–ritonavir groups, the trial continues to study the effects of azithromycin, tocilizumab, convalescent plasma, and REGN-COV2 (a combination of two monoclonal antibodies directed against the SARS-CoV-2 spike protein). Other treatments may be studied in the future. The hydroxychloroquine that was used in this phase of the trial was supplied by the U.K. National Health Service (NHS).

Hospitalized patients were eligible for the trial if they had clinically-suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial. Initially, recruitment was limited to patients who were at least 18 years of age, but the age limit was removed as of May 9, 2020.

Written informed consent was obtained from all the patients or from a legal representative if they were too unwell or unable to provide consent. The trial was conducted in accordance with Good Clinical Practice guidelines of the International Conference on Harmonisation and was approved by the U.K. Medicines and Healthcare Products

Regulatory Agency (MHRA) and the Cambridge East Research Ethics Committee. The protocol with its statistical analysis plan are available at NEJM.org, with additional information in the Supplementary Appendix and on the trial website at www.recoverytrial.net.

The initial version of the manuscript was drafted by the first and last authors, developed by the writing committee, and approved by all members of the trial steering committee. The funders had no role in the analysis of the data, in the preparation or approval of the manuscript, or in the decision to submit the manuscript for publication. The first and last members of the writing committee vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan.

RANDOMIZATION AND TREATMENT

We collected baseline data using a Web-based case-report form that included demographic data, level of respiratory support, major coexisting illnesses, the suitability of the trial treatment for a particular patient, and treatment availability at the trial site. Using a Web-based unstratified randomization method with the concealment of trial group, we assigned patients to receive either the usual standard of care or the usual standard of care plus hydroxychloroquine or one of the other available treatments that were being evaluated. The number of patients who were assigned to receive usual care was twice the number who were assigned to any of the active treatments for which the patient was eligible (e.g., 2:1 ratio in favor of usual care if the patient was eligible for only one active treatment group, 2:1:1 if the patient was eligible for two active treatments, etc.).

For some patients, hydroxychloroquine was unavailable at the hospital at the time of enrollment or was considered by the managing physician to be either definitely indicated or definitely contraindicated. Patients with a known prolonged corrected QT interval on electrocardiography were ineligible to receive hydroxychloroquine. (Coadministration with medications that prolong the QT interval was not an absolute contraindication, but attending clinicians were advised to check the QT interval by performing electrocardiography.) These patients were excluded from entry in the randomized comparison between hydroxychloroquine and usual care.

In the hydroxychloroquine group, patients received hydroxychloroquine sulfate (in the form of a 200-mg tablet containing a 155-mg base equivalent) in a loading dose of four tablets (total dose, 800 mg) at baseline and at 6 hours, which was followed by two tablets (total dose, 400 mg) starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until discharge, whichever occurred earlier (see the Supplementary Appendix).[15] The assigned treatment was prescribed by the attending clinician. The patients and local trial staff members were aware of the assigned trial groups.

PROCEDURES

A single online follow-up form was to be completed by the local trial staff members when each trial patient was discharged, at 28 days after randomization, or at the time of death, whichever occurred first. Information was recorded regarding the adherence to the assigned treatment, receipt of other treatments for Covid-19, duration of admission, receipt of respiratory support (with duration and type), receipt of renal dialysis or hemofiltration, and vital status (including cause of death). Starting on May 12, 2020, extra information was recorded on the occurrence of new major cardiac arrhythmia. In addition, we obtained routine health care and registry data that included information on vital status (with date and cause of death) and discharge from the hospital.

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. Decisions to initiate invasive mechanical ventilation were made by the attending clinicians, who were informed by guidance from NHS England and the National Institute for Health and Care Excellence. Subsidiary clinical outcomes included cause-specific mortality (which was recorded in all patients) and major cardiac arrhythmia (which was recorded in a subgroup of patients). All information presented in this report is based on a data cutoff of September 21, 2020. Information

regarding the primary outcome is complete for all the trial patients.

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 hydroxychloroquine 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 prespecified 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. Prespecified 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.

The independent data monitoring committee was asked to review unblinded analyses of the trial data and any other information that was considered to be relevant at intervals of approximately 2 weeks. The committee was then charged with determining whether the randomized comparisons in the trial provided evidence with respect to mortality that was strong enough (with a range of uncertainty around the results that was narrow enough) to affect national and global treatment strategies. In such a circumstance, the committee would inform the members of the trial steering committee, who would make the results available to the public and amend the trial accordingly. Unless that happened, the steering committee, investigators, and all others involved in the trial would remain unaware of the interim results until 28 days after the last patient had been randomly assigned to a particular treatment group.

On June 4, 2020, in response to a request from the MHRA, the independent data monitoring committee conducted a review of the data and recommended that the chief investigators review the unblinded data for the hydroxychloroquine group. The chief investigators and steering committee members concluded that the data showed no beneficial effect of hydroxychloroquine in patients hospitalized with Covid-19. Therefore, the enrollment of patients in the hydroxychloroquine group was closed on June 5, 2020, and the preliminary result for the primary outcome was made public. Investigators were advised that any patients who were receiving hydroxychloroquine as part of the trial should discontinue the treatment.

RESULTS

PATIENTS

From March 25 to June 5, 2020, a total of 11,197 patients underwent randomization; of these patients, 7513 (67%) were eligible to receive hydroxychloroquine (i.e., the patient had no known indication for or contraindication to hydroxychloroquine, and the drug was available in the hospital at the time) (Fig. 1). Of the eligible patients, 1561 were assigned to receive hydroxychloroquine and 3155 were assigned to receive usual care; the remainder of the patients were randomly assigned to one of the other treatment groups.

The mean (±SD) age of the patients in this trial was 65.4±15.3 years (Table 1 and Table S1 in the Supplementary Appendix). A total of 38% of the patients were female; 18% were Black or Asian or had a minority ethnic background. No children were enrolled. A history of diabetes was present in 27% of patients, heart disease in 26%, and chronic lung disease in 22%, with 57% having at least one major coexisting illness that was recorded. In this analysis, 90% of the patients

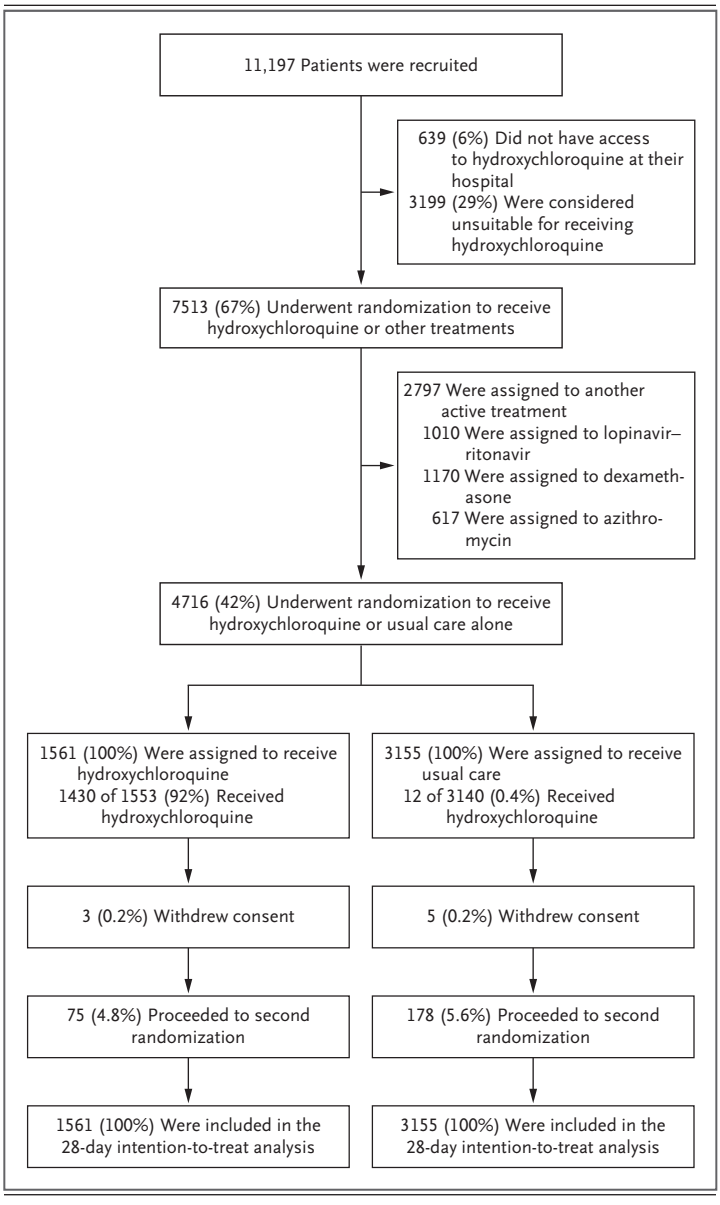

Figure 1. Enrollment and Outcomes in the RECOVERY Trial.

The enrollment number that is shown is the total number of patients in the RECOVERY platform trial during the period in which adult patients could be recruited for the comparison between hydroxychloroquine and usual care. Patients could have more than one reason for not participating in the hydroxychloroquine trial. At the time of this analysis, data from the trial follow-up form were available for 1553 of 1561 patients (99.5%) in the hydroxychloroquine group and for 3140 of 3155 patients (99.5%) in the usual-care group. The subgroup of patients who later underwent a second randomization to tocilizumab versus usual care in the RECOVERY trial included 37 of 1561 patients (2.4%) in the hydroxychloroquine group and 89 of 3155 patients (2.8%) in the usual care group. In addition, 6 patients were randomly assigned to receive either convalescent plasma or usual care alone (1 patient [0.1%] in the hydroxychloroquine group and 5 patients [0.2%] in the usual-care group) in accordance with protocol version 6.0. Among the 167 sites at which at least 1 patient was assigned to receive hydroxychloroquine, the median number of patients who underwent randomization was 20 (interquartile range, 11 to 41).

had laboratory-confirmed SARS-CoV-2 infection, with the result not known for less than 1%. At randomization, 17% were receiving invasive mechanical ventilation including extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither.

A total of 1430 patients in the hydroxychloroquine group (92%) received at least one dose (Table S2). The median duration of treatment was 6 days (interquartile range, 3 to 10 days). In addition, 12 patients (0.4%) in the usual-care group received hydroxychloroquine. The frequency of use of azithromycin or other macrolide drug during the follow-up period was similar in the hydroxychloroquine group and the usual-care group (18.6% vs. 20.3%), as was the use of dexamethasone (9.1% vs. 9.2%). Remdesivir was administered to less than 0.1% of the patients in each group.

PRIMARY OUTCOME

Death at 28 days occurred in 421 of 1561 patients (27.0%) in the hydroxychloroquine group and in 790 of 3155 patients (25.0%) in the usual-care group (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15) (Fig. 2). Similar results were seen across all six prespecified subgroups (Fig. 3). In a post hoc exploratory analysis that was restricted to the 4266 patients (90.5%) with a positive SARS-CoV-2 test result, the result was similar to the overall result (rate ratio, 1.09; 95% CI, 0.96 to 1.23).

SECONDARY OUTCOMES

Patients in the hydroxychloroquine group had a longer duration of hospitalization than those in the usual-care group (median, 16 days vs. 13 days) and a lower probability of discharge alive within 28 days (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98) (Table 2). Among the patients who

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hydroxychloroquine (N=1561)	Usual Care (N=3155)
Age		
Mean ±SD	65.2±15.2	65.4±15.4
Distribution — no. (%)		
<70 yr	925 (59.3)	1873 (59.4)
≥70 to <80 yr	342 (21.9)	630 (20.0)
≥80 yr	294 (18.8)	652 (20.7)
Sex — no. (%)		
Male	960 (61.5)	1974 (62.6)
Female†	601 (38.5)	1181 (37.4)
Race or ethnic group — no. (%)‡		
White	1181 (75.7)	2298 (72.8)
Black, Asian, or minority ethnic group	264 (16.9)	593 (18.8)
Unknown	116 (7.4)	264 (8.4)
Median no. of days since symptom onset (IQR)§	9 (5–14)	9 (5–13)
Median no. of days since hospitalization (IQR)	3 (1–6)	3 (1–5)
Respiratory support — no. (%)		
No oxygen received	362 (23.2)	750 (23.8)
Oxygen only	938 (60.1)	1873 (59.4)
Invasive mechanical ventilation	261 (16.7)	532 (16.9)
Previous disease — no. (%)		
Any of the listed conditions	882 (56.5)	1807 (57.3)
Diabetes	427 (27.4)	856 (27.1)
Heart disease	422 (27.0)	789 (25.0)
Chronic lung disease	334 (21.4)	712 (22.6)
Tuberculosis	4 (0.3)	9 (0.3)
HIV infection	8 (0.5)	13 (0.4)
Severe liver disease¶	18 (1.2)	46 (1.5)
Severe kidney impairment‖	111 (7.1)	261 (8.3)
SARS-CoV-2 test result — no. (%)		
Positive	1399 (89.6)	2867 (90.9)
Negative	156 (10.0)	275 (8.7)
Unknown	6 (0.4)	13 (0.4)

* Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, IQR interquartile range, and SD standard deviation.
† Among the women, 2 in the hydroxychloroquine group and 4 in the usual-care group were pregnant.
‡ Race or ethnic group is reported as it was recorded in the patient's electronic health record.
§ Data regarding the number of days since symptom onset were missing for 9 patients in the hydroxychloroquine group and 9 patients in the usual-care group.
¶ Severe liver disease was defined as a diagnosis that resulted in ongoing specialist care.
‖ Severe kidney impairment was defined as an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area.

were not undergoing invasive mechanical ventilation at baseline, the number of patients who had progression to the prespecified composite secondary outcome of invasive mechanical ventilation or death was higher among those in the hydroxychloroquine group than among those in the usual-care group (risk ratio, 1.14; 95% CI, 1.03 to 1.27).

OTHER PRESPECIFIED OUTCOMES

There was no difference between the hydroxychloroquine group and the usual-care group in 28-day mortality that was ascribed to Covid-19 (24.0% vs. 23.5%). However, patients in the hydroxychloroquine group had a greater risk of death from cardiac causes (mean [±SE] excess, 0.4±0.2 percentage points) and from non–SARS-CoV-2 infection (mean excess, 0.4±0.2 percentage points) (Table S3). Data regarding the occurrence of new major cardiac arrhythmia were collected for 735 of 1561 patients (47.1%) in the hydroxychloroquine group and 1421 of 3155 patients (45.0%) in the usual-care group, after collection of this information was added to the follow-up form on May 12, 2020. Among these patients, there were no significant differences between the hydroxychloroquine group and the usual-care group in the frequency of supraventricular tachycardia (7.6% vs. 6.0%), ventricular tachycardia or fibrillation (0.7% vs. 0.4%), or atrioventricular block requiring intervention (0.1% vs. 0.1%) (Table S4). There was one report of a serious adverse reaction that was deemed by investigators to be related to hydroxychloroquine: a case of torsades de pointes, from which the patient recovered without undergoing intervention. Among the patients who were not receiving renal dialysis or hemofiltration at randomization, the percentage who went on to receive such treatment during the follow-up period was the same in the hydroxychloroquine group and the usual-care group (7.9% vs. 7.9%) (Table S5).

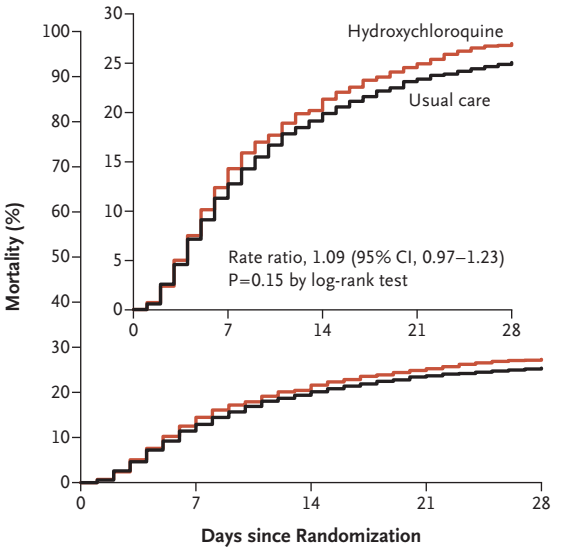

Figure 2. Mortality at 28 Days.

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.

DISCUSSION

In this analysis of the RECOVERY trial, we determined that hydroxychloroquine was not an effective treatment for patients hospitalized with Covid-19. The lower boundary of the confidence limit for the primary outcome ruled out any reasonable possibility of a meaningful mortality benefit. The results were consistent across subgroups according to age, sex, race, time since illness onset, level of respiratory support, and baseline-predicted risk. In addition, the results suggest that the patients who received hydroxychloroquine had a longer duration of hospitalization and, among those who were not undergoing mechanical ventilation at baseline, a higher risk of invasive mechanical ventilation or death than those who received usual care.

The RECOVERY trial is a large, pragmatic, randomized, controlled platform trial designed to assess the effect of potential treatments for Covid-19 on 28-day mortality. Approximately 15% of the patients who were hospitalized with Covid-19 in the United Kingdom during the trial period were enrolled, and the percentage of patients in the usual-care group who died was consistent with the hospitalized case fatality rate among hospitalized patients in the United Kingdom and elsewhere.[7,30,31] Only essential data were

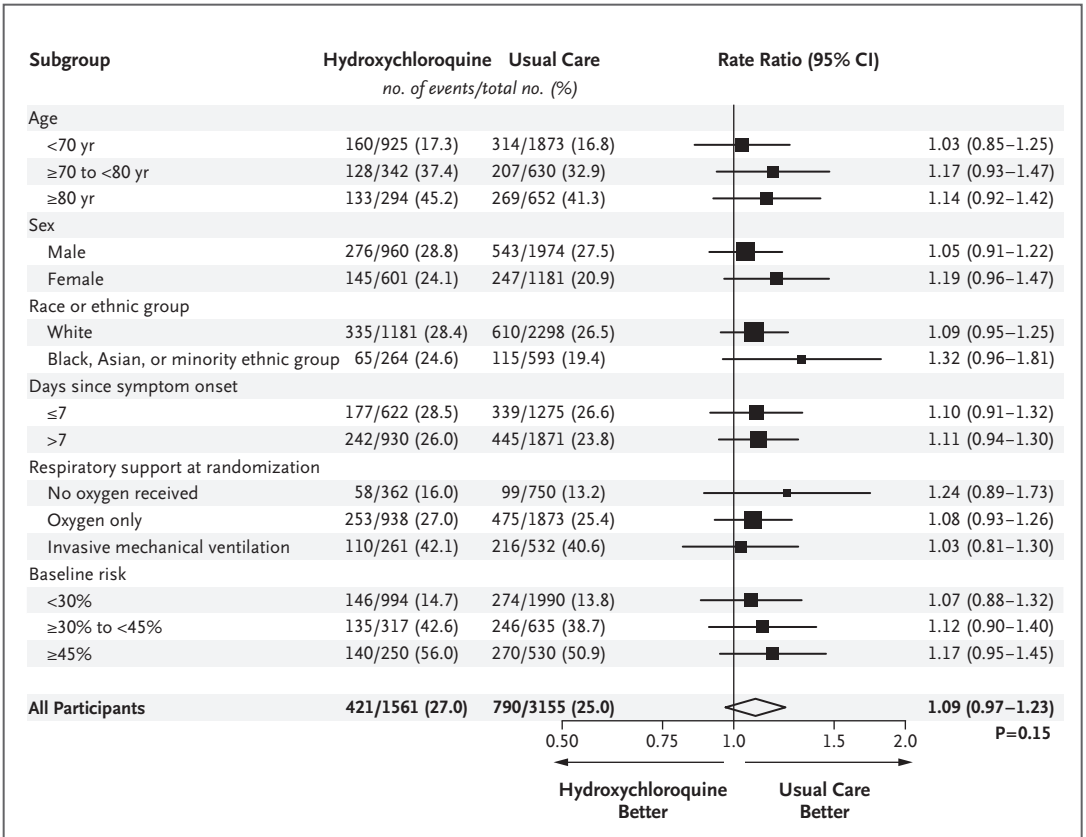

Figure 3. Mortality at 28 Days, According to Subgroup.

The size of the squares representing rate ratios is proportional to the amount of statistical information that was available for each comparison. The method that was used for calculating the baseline-predicted risk in each subgroup is described in the Supplementary Appendix. Race or ethnic group was recorded in the patient's electronic health record.

collected at hospital sites, with additional information (including long-term mortality) ascertained through linkage with routine data sources. We did not collect information on physiologic, electrocardiographic, laboratory, or virologic measurements.

Hydroxychloroquine has been proposed as a treatment for Covid-19 largely on the basis of its in vitro SARS-CoV-2 antiviral activity and on data from observational studies reporting effective reduction in viral loads. However, the 4-aminoquinoline drugs are relatively weak antiviral agents.[15] The demonstration of therapeutic efficacy of hydroxychloroquine in severe Covid-19 would require rapid attainment of efficacious levels of free drug in the blood and respiratory epithelium.[32] Thus, to provide the greatest chance of providing benefit in life-threatening Covid-19, the dose regimen in our trial was designed to result in rapid attainment and maintenance of plasma levels that were as high as safely possible.[15] These levels were predicted to be at the upper end of those observed during steady-state treatment of rheumatoid arthritis with hydroxychloroquine.[33] Our dosing schedule was based on pharmacokinetic modeling of hydroxychloroquine that referenced a SARS-CoV-2 50% effective concentration of 0.72 μM, as scaled to whole-blood levels and on the assumption that cytosolic levels in the respiratory epithelium are in dynamic equilibrium with blood levels.[8,15,34]

The primary concern with short-term, high-dose 4-aminoquinoline regimens is cardiovascular toxicity. Hydroxychloroquine causes predictable prolongation of the corrected QT interval on electrocardiography, which is exacerbated by coadministration with azithromycin, as widely prescribed in Covid-19 treatment.[16-18] Although

Table 2. Primary and Secondary Outcomes.

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

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

torsades de pointes has been described, serious cardiovascular toxicity has been infrequently reported, despite the high prevalence of cardiovascular disease in hospitalized patients, the common occurrence of myocarditis in Covid-19, and the extensive use of hydroxychloroquine and azithromycin together. The exception is a Brazilian study that was stopped early because of cardiotoxicity. However, in that study, chloroquine was administered at a base dose of 600 mg twice daily for 10 days, a higher total dose than those that were used in other trials, including the RECOVERY trial.[35,36] Pharmacokinetic modeling in combination with information regarding blood levels and mortality from a case series involving 302 patients with chloroquine overdose predicts that a chloroquine regimen that was equivalent to the hydroxychloroquine regimen used in our trial should have an acceptable safety profile.[36] There was a small absolute excess of cardiac mortality of 0.4 percentage points in the hydroxychloroquine group on the basis of very few events, but we did not observe excess mortality in the first 2 days of treatment with hydroxychloroquine, the time when early effects of dose-dependent toxicity might be expected. Furthermore, the data presented here did not show any excess in ventricular tachycardia or ventricular fibrillation in the hydroxychloroquine group.

These findings indicate that hydroxychloroquine is not an effective treatment for hospitalized patients with Covid-19 but do not address its use as prophylaxis or in patients with less severe SARS-CoV-2 infection managed in the community. A review of Covid-19 treatment guidelines that was produced early in the pandemic showed that chloroquine or hydroxychloroquine was recommended in China, France, Italy, the Netherlands, and South Korea.[37] In the United States, the use of chloroquine and hydroxychloroquine was permitted in certain hospitalized patients under an Emergency Use Authorization (EUA) of the Food and Drug Administration (FDA). A retrospective cohort study involving 1376 patients with Covid-19 who were admitted to the hospital in New York City in March and April 2020 showed that 59% of the patients received hydroxychloroquine.[22,38] Since our preliminary results were made public on June 5, 2020, the FDA has revoked the EUA for chloroquine and hydroxychloroquine,[39] and the World Health Organization (WHO) and the National Institutes of Health have ceased trials of its use in hospitalized patients on the grounds of a lack of benefit. The WHO has released preliminary results from the SOLIDARITY trial on the effectiveness of hydroxychloroquine in hospitalized patients with Covid-19 that are consistent with the results from the RECOVERY trial.[40]

The views expressed in this article are those of the authors and not necessarily those of the National Health Service (NHS), the National Institute for Health Research (NIHR), or the Department of Health and Social Care.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2022926

Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19

SUPPLEMENTARY APPENDIX

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The views expressed in this publication are those of the authors and not necessarily those of the National Health Service (NHS), the National Institute for Health Research or the Department of Health and Social Care (DHCS).

Supplementary Methods

Study organization

The RECOVERY trial is an investigator-initiated, individually randomized, open-label, controlled trial to evaluate the efficacy and safety of a range of putative treatments in patients hospitalized with COVID-19. The protocol is available at NEJM.org. The trial was conducted at 176 National Health Service (NHS) hospital organizations in the United Kingdom. The trial was coordinated by a team drawn from the Clinical Trial Service Unit and the National Perinatal Epidemiology Clinical Trials Unit within the Nuffield Department of Population Health at University of Oxford, the trial sponsor. Support for local site activities was provided by the National Institute for Health Research Clinical Research Network.

Treatment supply to local sites was supported by National Health Service (NHS) England and Public Health England. Access to relevant routine health care and registry data was supported by NHS DigiTrials, the Intensive Care National Audit and Research Centre, Public Health Scotland, National Records Service of Scotland, and the Secure Anonymised Information Linkage (SAIL) at University of Swansea.

Protocol changes

RECOVERY is a randomized trial among patients hospitalized for COVID-19. All eligible patients receive usual standard of care in the participating hospital and are randomly allocated between no additional treatment and one of several active treatment arms. Over time, additional treatment arms have been added (see Table). In version 4.0 of the protocol, a second randomization was introduced for those trial participants with hypoxia (oxygen saturation <92% on air or receiving oxygen) and inflammation (C-reactive protein ≥75 mg/dL), comparing the addition of tocilizumab vs. control on top of the treatment assigned in the first randomization. In version 6.0, a factorial design was introduced to the first randomization such that participants were also randomized to convalescent plasma vs. no additional treatment. As outlined in the protocol, if one or more of the active treatments was not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then random allocation was between the remaining treatment arms.

The original and final protocol are included in the supplementary material to this publication, together with summaries of the changes made.

Table. Protocol changes to treatment comparisons

Protocol version	Date	Randomization	Treatment arms
1.0	13-Mar-2020	Main (part A)	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid Nebulised Interferon-ß-1a (never activated)
2.0	23-Mar-2020	Main (part A)	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid Hydroxychloroquine

Protocol version	Date	Randomization	Treatment arms
3.0	07-Apr-2020	Main (part A)	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid Hydroxychloroquine Azithromycin
4.0	14-Apr-2020	Main (part A) Second[a]	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid Hydroxychloroquine Azithromycin No additional treatment Tocilizumab
5.0	24-Apr-2020	-	(no change – extension to children <18 years old)
6.0	14-May-2020	Main (part A) Main (part B factorial) Second[a]	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid[b] Hydroxychloroquine[c] Azithromycin No additional treatment Convalescent plasma No additional treatment Tocilizumab

[a] for patients with (a) oxygen saturation <92% on air or requiring oxygen or children with significant systemic disease with persistent pyrexia; and (b) C-reactive protein ≥75 md/dL)
[b] enrolment of adults ceased 8 June 2020 as more than 2,000 patients had been recruited to the active arm
[c] enrolment ceased 5 June 2020 when the Data Monitoring Committee advised that the Chief Investigators review the unblinded data.

Selection of hydroxychloroquine dose

The hydroxychloroquine dose regimen was based on previous pharmacokinetic modelling of plasma and whole blood hydroxychloroquine concentrations in healthy volunteers, the treatment of malaria and in rheumatological conditions.[1] The choice of dose and predicted safety margins were also informed by pharmacometric studies of chloroquine in the treatment of both severe and uncomplicated malaria and in self-poisoning.[2] In-vitro studies suggest that high concentrations of hydroxychloroquine are required for maximal effects, although inhibitory concentrations derived from static Vero cell cultures are likely to provide, at best, an approximate guide to required in-vivo concentrations.[3] Hydroxychloroquine plasma concentrations in short course regimens are determined primarily by distribution rather than elimination.[1] We reasoned that the target respiratory epithelium was likely to be in a dynamic equilibrium with free plasma concentrations. The objective therefore was to design a regimen that provided free plasma concentrations that were as high as safely possible throughout the treatment period. As a parenteral formulation is not generally available, dosing was designed around currently available hydroxychloroquine sulfate tablets (200mg salt: 155 mg base equivalent). To achieve loading while allowing adequate

distribution, the loading doses (4 tablets) were given at 0 and 6 hours and from 12 hours maintenance doses (2 tablets) were given 12 hourly.

The dosing regimen was based on pharmacometric modelling:[1] All pharmacokinetic models were coded and simulated using the pharmacometric software NONMEM v.7.4.3 (Icon Development Solution, Ellicott City, MD). A small study in healthy volunteers was used for dose simulations[4], reporting a 3-compartment disposition model with a terminal elimination half-life of 50 days. Reported true coefficients and exponents were used to derive mean pharmacokinetic parameters for simulations. Both short course treatments[5] and repeated dosing to steady-state[6] were simulated, to ensure that model-derived concentrations captured the reported drug measurements, resulting in a relative bioavailability parameter of 60% to scale model predictions to reported concentrations. A fixed value of 30% between-patient variability was added exponentially in all parameters in order to capture the approximately 4- to 5-fold variability seen in observed whole blood measurements. Allometric scaling of clearance (exponent of 0.75) and volume (exponent of 1) parameters was implemented in order to simulate different weight groups. A total of 1,000 stochastic simulations were performed and presented as median values and 95% prediction intervals.[1]

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 x exp(a)/(1 + exp(a)), where a = −1.23 − 2.85 (if age <50) − 2.03 (if age 50−59) − 1.21 (if age 60−69) − 0.51 (if age 70−79) + 0.42 (if male) − 0.34 (if >7 days since symptom onset) + 0.86 (if on oxygen only at randomization) + 2.18 (if on invasive mechanical ventilation at randomization) − 0.01 (if history of diabetes) + 0.22 (if history of heart disease) + 0.21 (if history of chronic lung disease) + 0.50 (if 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%, ≥30% to <45%, and ≥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] ÷ V), and its 95% CI is given by exp([O – E] ÷ V ± 1.96 ÷ √V).

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.

The following modifications were made to the Randomization form during the trial:

Randomization form version	Date of release	Major modifications from previous version
1.0	19-Mar-20	Initial version (protocol V1.0)
2.0	25-Mar-20	For protocol V2.0 • Hydroxycholoroquine added as treatment • Known long QT syndrome added to comorbidities • Severe depression removed from comorbidities
3.0	09-Apr-20	For protocol V3.0 • Azithromycin added as treatment • Suspected SARS-CoV-2 infection included in eligibility criteria
[Second randomization form introduced]	23-Apr-20	For protocol 4.0 • Eligibility criteria for second randomization • Tocilizumab vs control as treatment allocations
4.0	09-May-20	For protocol V5.0 • Age ≥18 years removed from eligibility criteria • Additional questions on child's age and weight added
5.0	21-May-20	For protocol V6.0 • Convalescent plasma added as treatment
6.0	28-May-20	Baseline use of remdesivir

RECOVERY
Randomised Evaluation of COVID-19 Therapy

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

Home

Follow-up form

The Follow-up form (shown on the next page) 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.

The following modifications were made to the Follow-up form during the trial:

Follow-up form version	**Date of release**	**Modifications from previous version**
1.0	30-Mar-20	Initial version
2.0	09-Apr-20	Information on other treatments used during admission: • Azithromycin, IL-6 receptor antagonist Fact and result of SARS-CoV-2 PCR test
3.0	09-Apr-20	Update to functionality; no changes to questions
4.0	23-Apr-20	Duration of treatments added
5.0	12-May-20	Capture of major cardiac arrhythmias added
6.0	28-May-20	Updates to wording of questions. Information on other treatments used during admission: • Remdesivir, convalescent plasma

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

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

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	◯	◯	◯

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

5.1 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).

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Supplementary Tables

Table S1: Baseline characteristics of patients considered unsuitable for randomization to hydroxychloroquine compared with those randomized to hydroxychloroquine versus usual care

	Randomized (n=4716)	Considered unsuitable (n=3199)
Age, years	65.4 (15.3)	67.3 (16.1)
<70	2798 (59.3%)	1712 (53.5%)
≥70 to <80	972 (20.6%)	678 (21.2%)
≥80	946 (20.1%)	809 (25.3%)
Sex		
Male	2934 (62.2%)	2017 (63.1%)
Female	1782 (37.8%)	1182 (36.9%)
Race		
White	3479 (73.8%)	2381 (74.4%)
BAME	857 (18.2%)	508 (15.9%)
Unknown	380 (8.1%)	310 (9.7%)
Number of days since symptom onset	9 (5-13)	8 (4-12)
Number of days since hospitalization	3 (1-5)	2 (1-4)
Respiratory support received		
No oxygen received	1112 (23.6%)	834 (26.1%)
Oxygen only	2811 (59.6%)	2043 (63.9%)
Invasive mechanical ventilation	793 (16.8%)	322 (10.1%)
Previous diseases		
Diabetes	1283 (27.2%)	918 (28.7%)
Heart disease	1211 (25.7%)	1020 (31.9%)
Chronic lung disease	1046 (22.2%)	758 (23.7%)
Tuberculosis	13 (0.3%)	13 (0.4%)
HIV	21 (0.4%)	19 (0.6%)
Severe liver disease	64 (1.4%)	76 (2.4%)
Severe kidney impairment	372 (7.9%)	330 (10.3%)
Any of the above	2689 (57.0%)	1995 (62.4%)

Results are count (%), mean ± standard deviation, or median (inter-quartile range). The 'oxygen only' group includes non-invasive ventilation. Severe liver disease defined as requiring ongoing specialist care. Severe kidney impairment defined as estimated glomerular filtration rate <30 mL/min/1.73m².

Table S2: Treatments given, by randomized allocation

	Treatment allocation	
	Hydroxychloroquine (n=1561)	**Usual care (n=3155)**
Compliance data available	1553	3140
Hydroxychloroquine received	1430 (92.1%)	12 (0.4%)
Other treatments received		
Dexamethasone	142 (9.1%)	288 (9.2%)
Lopinavir-Ritonavir	2 (0.1%)	6 (0.2%)
Azithromycin or other macrolides	289 (18.6%)	638 (20.3%)
Tocilizumab or sarilumab	34 (2.2%)	84 (2.7%)
Remdesivir	1 (0.1%)	2 (0.1%)
Not recorded	3 (0.2%)	0 (0.0%)

Percentages are of those with a completed follow-up form. Remdesivir only became available for use in the UK under the Medicines & Healthcare Products Regulatory Agency Emergency Access to Medicines Scheme on 26 May 2020, 13 days prior to closure of the hydroxychloroquine arm of the study.

Of those allocated hydroxychloroquine who received at least one dose, 69% received it either every day or nearly every day they were in hospital (missing at most 1 dose) while 84% received it on at least half the days they were in hospital.

Table S3: Effect of allocation to hydroxychloroquine on cause-specific 28-day mortality

Cause of death	Treatment allocation		Absolute percent difference (SE)
	Hydroxychloroquine (n=1561)	Usual care (n=3155)	
COVID	374 (24.0%)	743 (23.5%)	0.4 (1.32)
Other infection	8 (0.5%)	5 (0.2%)	0.4 (0.19)
Cardiac	9 (0.6%)	4 (0.1%)	0.4 (0.20)
Stroke	2 (0.1%)	4 (0.1%)	0.0 (0.11)
Other vascular	1 (0.1%)	2 (0.1%)	0.0 (0.08)
Cancer	9 (0.6%)	10 (0.3%)	0.3 (0.22)
Other medical	15 (1.0%)	21 (0.7%)	0.3 (0.29)
External	2 (0.1%)	0 (0.0%)	0.1 (0.09)
Unknown cause	1 (0.1%)	1 (<0.05%)	0.0 (0.07)
Total: 28-day mortality	**421 (27.0%)**	**790 (25.0%)**	**1.9 (1.36)**

RR=Rate Ratio. CI=confidence interval.

Table S4: Effect of allocation to hydroxychloroquine on new major cardiac arrhythmia

	Treatment allocation	
	Hydroxychloroquine (n=1561)	**Usual care (n=3155)**
Number with follow-up form*	735	1421
Atrial flutter or atrial fibrillation	46 (6.3%)	74 (5.2%)
Other supraventricular tachycardia	10 (1.4%)	18 (1.3%)
Subtotal: Supraventricular tachycardia	56 (7.6%)	85 (6.0%)
Ventricular tachycardia	3 (0.4%)	5 (0.4%)
Ventricular fibrillation	2 (0.3%)	0 (0.0%)
Subtotal: Ventricular tachycardia or fibrillation	5 (0.7%)	5 (0.4%)
Atrioventricular block requiring intervention	1 (0.1%)	1 (0.1%)
Total: Any major cardiac arrhythmia	**60 (8.2%)**	**90 (6.3%)**

* Information on new cardiac arrhythmias was only collected on follow-up forms from 12 May 2020 onwards; percentages are of those with such a form completed.

Table S5: Effect of allocation to hydroxychloroquine on need for renal replacement therapy (RRT) among those not on RRT at randomization

	Treatment allocation		
	Hydroxychloroquine (n=1561)	Usual care (n=3155)	RR (95% CI)
Need for renal replacement therapy (among those not on RRT at randomisation)	120/1520 (7.9%)	241/3050 (7.9%)	1.00 (0.81-1.23)

RR=Risk Ratio. CI=confidence interval.