CADTH COVID-19 PANDEMIC

COVID-19 CADTH Health Technology Review

Chloroquine or Hydroxychloroquine to Prevent or Treat COVID-19

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

This report reviews the current scientific evidence on the potential benefits and harms of chloroquine or hydroxychloroquine.

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Questions or requests for information about this report can be directed to **requests@cadth.ca**.

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Tables

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Version	Date	Summary of revisions
1.0	August 17, 2020	Information accurate as of July 14, 2020
2.0	April 23, 2021	Information accurate as of November 20, 2020

Abbreviations

COVID-19	coronavirus disease 2019
DSMB	data safety and monitoring board
ECMO	extracorporeal membrane oxygenation
EUA	emergency use authorization
ICU	intensive care unit
IgG	immunoglobulin G
IQR	interquartile range
ITT	intention to treat
NIH	US National Institutes of Health
PCR	polymerase chain reaction
QTc	corrected QT
RCT	randomized controlled trial
RNA	ribonucleic acid
RT-PCR	reverse transcription–polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SpO2	oxygen saturation measured by pulse oximetry

Key Messages

This report reviews the current scientific evidence on the potential benefits and harms of chloroquine and hydroxychloroquine for the prevention or treatment of coronavirus disease 2019 (COVID-19).

A total of 17 key studies were included in this review. The evidence comes from 14 treatment trials and 3 prevention trials.

CloroCovid-19 (Borba et al.[1]) was a randomized, double-blind, controlled trial evaluating 2 different dosages of chloroquine. CloroCovid-19[1] was designed to assess the safety and efficacy of 2 different chloroquine dosages in patients hospitalized with severe COVID-19. This study was terminated early because of concerns raised by an independent data safety and monitoring board (DSMB) surrounding the greater incidence of lethality and presence of serious cardiac events in the high-dosage group compared with the low-dosage group. Accordingly, the corrected QT (QTc) interval prolongation and increased lethality associated with higher dosages of chloroquine suggest that high dosages of chloroquine should not be recommended for patients with severe COVID-19. Due to statistical power concerns from a premature termination of recruitment, the study did not demonstrate a statistically significant difference in treatment efficacy between the 2 treatment dosages. Notable limitations of this study pertain to the higher prevalence of older patients, with more heart disease in the high-dosage group, and the lack of a standard of care or placebo group.

Tang et al.[2] was an open-label, randomized controlled trial (RCT) assessing the combination of hydroxychloroquine and standard of care compared with standard of care alone in adults with mild-to-moderate COVID-19. This study was terminated early by an independent data and safety monitoring committee due to a decline in eligible new cases of COVID-19 in China. Findings from this study suggest that administering hydroxychloroquine did not result in a higher probability of negative conversion of SARS-CoV-2 infection when compared with standard of care alone. Also, adverse events were more prevalent in the hydroxychloroquine group. Findings may be attributed to early termination of the study and a smaller sample size than anticipated.

The Davoodi et al.[3] study was an open-label RCT designed to compare the effectiveness of febuxostat (a drug approved in Canada for lowering uric acid in patients with gout) and hydroxychloroquine for the management of patients with moderate COVID-19. While there was no difference in the effectiveness of febuxostat compared with hydroxychloroquine in the treatment of patients with COVID-19, this study was unable to demonstrate the absolute effect of either of these treatments, given that this study lacked a placebo or standard of care comparator.

Cavalcanti et al.[4] reported the findings of a multi-centre, randomized, open-label, controlled trial conducted in Brazil. The objective of this study was to assess whether hydroxychloroquine, either alone or in combination with azithromycin, could improve the clinical status of patients with mild-to-moderate COVID-19 at 15 days after hospital admission. Findings from this study suggest there was no difference in the 15-day ordinal clinical status outcome among those treated with hydroxychloroquine, azithromycin, or hydroxychloroquine in combination with azithromycin. While those with a confirmed COVID-19 diagnosis had a higher prevalence of chronic obstructive pulmonary disease, a lower prevalence of diabetes, and were less likely to receive supplemental oxygen than those without a confirmed diagnosis, sensitivity analyses for the primary outcome did not demonstrate a statistically significant effect of the treatments between groups.

Skipper et al.[5] reported the findings of a randomized, double-blind, placebo-controlled trial conducted in the US and Canada (including 40 states and 3 provinces). The objective of this study was to assess whether starting hydroxychloroquine therapy within the first few days of COVID-19 symptoms could alter the course of COVID-19 by reducing symptom severity and duration. Findings from this study suggest there was no statistically significant difference in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups. Patients in each treatment group were relatively balanced in terms of demographics and comorbidities. To assess the success of the masking, the authors surveyed the participants in both groups at day 14 to identify whether they believed they were receiving the placebo or the treatment. Due to the low percentages of participants correctly identifying their treatment group, the authors concluded that the masking was generally effective. A limitation of this study pertains to the lack of definition or reference for illness severity, which influences the external validity of the findings.

Abd-Elsalam et al.[6] reported the findings of a multi-centre open-label RCT with 194 patients with confirmed COVID-19 infections recruited at 3 tertiary referral centres in Egypt. The objective of this study was to evaluate the safety and efficacy of hydroxychloroquine added to standard of care versus standard of care alone in patients with COVID-19. Findings from this study suggest that the effects of hydroxychloroquine plus standard of care did not differ from standard of care alone regarding mean recovery duration, the need for mechanical ventilation, or mortality. Notable limitations of this study pertain to the potential for imbalances between the 2 treatment groups, and inconsistencies among reporting statistical findings.

Horby et al.[7] reported the findings of a multi-centre, randomized, open-label, controlled study involving 4,716 hospitalized patients. This study was part of the larger RECOVERY trial assessing the effect of various treatments on patients with COVID-19 at 176 hospitals in the UK. The objective of this study was to assess whether hydroxychloroquine is an effective treatment for patients with COVID-19. Enrolment was terminated early after an interim analysis by an independent data monitoring committee determined that there was a lack of efficacy with hydroxychloroquine in patients hospitalized with COVID-19. There was no statistically significant difference in 28-day mortality when comparing the hydroxychloroquine plus standard of care group with the standard of care alone group. These results were consistent across all pre-specified subgroups, including age, sex, race or ethnic group, days since symptom onset, respiratory support at randomization, and baseline risk. Limitations of this study involve methodological concerns of insufficient power and a lack of control for multiple comparisons.

Lyngbakken et al.[8] reported the findings of a pragmatic, single-site, open-label RCT with 53 patients with confirmed COVID-19 infections recruited from March to May 2020 at Akershus University Hospital in Norway. The objective of this study was to evaluate the safety of hydroxychloroquine therapy on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) oropharyngeal viral load in patients hospitalized with moderately severe COVID-19.The trial was terminated prematurely due to the decreasing incidence of COVID-19 in Norway. Findings from this study suggested there was no difference between the 2 groups in the rate of decline in SARS-CoV-2 viral load in the oropharynx from baseline through the first 96 hours after randomization. Limitations of this study include insufficient power and a lack of control for multiple comparisons. Also, there were imbalances between the treatment groups, with the hydroxychloroquine plus standard of care group being younger and having a higher percentage of males.

Mitjà et al.[9] reported the findings of a multi-centre, randomized, open-label, controlled study involving 293 non-hospitalized patients recruited in 3 health administrative regions in Catalonia, Spain. The objective of this study was to assess whether treatment with hydroxychloroquine was more efficacious than the absence of this treatment for outpatients with mild COVID-19. Findings from this study suggest there is no substantive difference in the reduction in viral load in nasopharyngeal swabs when comparing the hydroxychloroquine group with the standard of care group at days 3 or 7. Limitations of this study include the concomitant use of cobicistat-boosted darunavir and the lack of a definition of standard of care.

The WHO Solidarity Trial Consortium[10] reported the interim findings of a multi-centre, randomized, open-label, controlled study involving 11,330 hospital inpatients conducted in 405 hospitals in 30 countries. The objective of this study was to evaluate the effectiveness of 4 drugs, including remdesivir, hydroxychloroquine, lopinavir, and interferon, compared with open control (defined as the standard of care where the patient was located) on in-hospital mortality of patients with COVID-19. While there were 4 active treatment groups, only the results of the hydroxychloroquine group and associated controls are pertinent to this report. Recruitment was terminated for hydroxychloroquine due to futility. Findings from this study suggest there is no difference in the 28-day mortality outcome between the 2 groups. Limitations of this study involve premature termination of recruitment.

Ulrich et al.[11] reported the findings of a double-blind, multi-centre, randomized, controlled study involving 128 patients recruited at various hospitals in the New York City metropolitan area. The objective of this study was to evaluate the efficacy and safety of hydroxychloroquine in hospitalized patients with confirmed COVID-19. Recruitment for this study was terminated early due to decreased COVID-19 admissions at the recruitment sites. Findings from this study suggest that hydroxychloroquine does not prevent severe outcomes or improve clinical scores among patients hospitalized with COVID-19. Notable limitations of this study involve concerns of insufficient power and imbalances between the treatment groups, with the hydroxychloroquine group having a lower proportion of patients with a body mass index of 30 kg/m^2 or greater.

Khamis et al.[12] reported the findings of a randomized, open-label, controlled study involving 89 patients recruited at the Royal Hospital in Muscat, Oman. The objective of this study was to evaluate the therapeutic effectiveness of favipiravir combined with inhaled interferon beta-1b versus hydroxychloroquine in adult patients hospitalized with moderate-to-severe COVID-19 pneumonia. Findings from this study suggest there is no difference in clinical outcomes between the 2 treatment groups. The limitations of this study involve concerns of insufficient power and imbalances between the treatment groups on kidney function; patients randomized to favipiravir were more likely to have moderate, severe, or end-stage kidney disease compared with patients randomized to hydroxychloroquine. Furthermore, there were methodological concerns surrounding statistical adjustment for baseline differences between treatment groups, and a lack of control for multiple comparisons.

Self et al.[13] reported the findings of a blinded, multi-centre, randomized, placebo-controlled clinical trial involving 479 patients recruited at 34 hospitals in the US. The objective was to determine whether hydroxychloroquine is an efficacious treatment for adults hospitalized with COVID-19. Recruitment for this study was terminated at the fourth interim analysis after the DSMB determined it would be futile for the study to continue. No statistical difference was found in clinical status at day 14 between patients with COVID-19 treated with hydroxychloroquine compared with placebo. The authors noted that some patients

enrolled in the study were treated with open-label remdesivir (21.7%), azithromycin (19.0%), and corticosteroids (18.4%), which may hinder the ability to assess toxicity associated with hydroxychloroquine alone.

Brown et al.[14] reported the findings of a randomized, open-label, multi-centre, controlled study involving 85 patients recruited at 13 hospitals in Utah, US. The objective of this study was to assess the efficacy of hydroxychloroquine compared with azithromycin among hospitalized patients with COVID-19. The DSMB providing oversight for this study recommended that the study cease enrolment based on findings from the interim analysis on the first 60 patients with 14-day follow-up. Findings from this study suggest there is no difference in clinical outcomes between the 2 treatment groups. A limitation of this study surrounds the low power resulting from a recruitment below the calculated sample size.

Boulware et al.[15] was a randomized, double-blind, placebo-controlled trial designed to assess whether hydroxychloroquine could prevent symptomatic infection after SARS-CoV-2 exposure. This study was terminated early based on poor conditional power. This study demonstrated that the incidence of new COVID-19 illnesses did not differ significantly when comparing participants receiving hydroxychloroquine prophylaxis and those receiving placebo. Furthermore, more patients had an adverse event with hydroxychloroquine than with placebo. Findings may be attributed to early termination of the study and a smaller sample size than anticipated.

Abella et al.[16] reported the findings of a randomized, double-blind, placebo-controlled trial with 132 patients in 2 tertiary urban hospitals in Philadelphia, US. The objective of this study was to evaluate the efficacy of hydroxychloroquine to prevent transmission of SARS-CoV-2 in hospital-based health care workers with exposure to patients with COVID-19 using a pre-exposure prophylaxis strategy. After the second interim analysis was conducted, the DSMB recommended early termination of the study, given that only 4 patients in the hydroxychloroquine group and 3 patients in the placebo group had converted to positive SARS-C0V-2 status. Findings from this study suggest there was no statistically significant difference in the proportion of COVID-19 positivity when comparing the hydroxychloroquine group with the placebo group. A limitation of this study relates to baseline differences in the treatment and control groups: females were more prevalent in the hydroxychloroquine group, and hypertension was more common in the placebo group.

Rajasingham et al.[17] reported the findings of a randomized, double-blind, placebo-controlled trial with 1,483 patients recruited online in the US and Manitoba, Canada. The objective of this study was to determine the effectiveness of hydroxychloroquine as pre-exposure prophylaxis in health care workers at high risk of SARS-CoV-2 exposure in a randomized, placebo-controlled clinical trial setting. An interim analysis conducted once 100 patients had completed the observation period identified that it was futile to continue recruiting patients and study recruitment was terminated. Findings from this study suggest that pre-exposure prophylaxis with hydroxychloroquine did not significantly reduce laboratory-confirmed COVID-19 or COVID-19–compatible illness among health care workers. Findings may be attributed to early termination of the study and a smaller sample size than anticipated.

The evidence available at this time regarding the clinical efficacy and safety of chloroquine or hydroxychloroquine in COVID-19 is limited in terms of quality. The clinical studies described in this report are associated with several limitations, including small sample sizes and inconsistencies related to standard of care comparators. The available evidence suggests that chloroquine or hydroxychloroquine is ineffective for the treatment or prevention of COVID-19.

Introduction

Chloroquine was first used in clinical practice in 1947 as a preventive treatment for malaria. Hydroxychloroquine is a metabolite of chloroquine and was developed in 1955 in an attempt to reduce the toxicity associated with chloroquine. Both drugs have been shown to have antiviral properties in vitro against various viruses.[18] The alkaline nature of these 2 drugs may contribute to their antiviral effect, as it appears that this property inhibits the pH-dependent steps of viral replication.[19,20] Some early studies suggested that chloroquine and hydroxychloroquine have an antiviral effect on the coronavirus associated with COVID-19.[20]

At the beginning of the pandemic, preliminary results from non-randomized trials evaluating the use of hydroxychloroquine for the treatment of COVID-19 showed mixed results.[21-23] In addition, several RCTs have been published or are close to completion.

This report reviews the current scientific evidence on the potential benefits and harms of hydroxychloroquine and chloroquine, when used as monotherapy or in combination with other medications, for the prevention of COVID-19 in patients at risk or in the treatment of patients with COVID-19. This will be the final update of this report.

Clinical Evidence

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources, including Ovid MEDLINE, Ovid Embase, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were chloroquine, hydroxychloroquine, and COVID-19. Search filters were applied to limit retrieval to RCTs or controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2019 and November 20, 2020.

Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov, COVID-19 studies from WHO via clinicaltrials.gov, and Health Canada's Clinical Trials Database.

Selection Criteria

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. Studies of interest were selected for review according to the criteria outlined in Table 1.

Non-randomized studies, single-arm trials, case series, case reports, conference reports, editorials, letters to the editor, and press releases were excluded from the evidence review.

Table 1: Selection Criteria

Population	• Patients with SARS-CoV2 infection (COVID-19) (i.e., treatment trials) • Patients at risk for COVID-19 (i.e., pre- and post-exposure prophylaxis or prevention trials)
Intervention	Chloroquine or hydroxychloroquine (used as monotherapy or combination therapy)
Comparators	• Standard of care • Placebo • Other pharmacotherapies • Chloroquine or hydroxychloroquine
Outcomes	**Treatment** • Clinical efficacy (e.g., time to clinical improvement, time to recovery) • Investigation and monitoring (e.g., change in medical imaging, incidence of undetectable viral RNA in nasopharyngeal or oropharyngeal swabs) **Prevention** • Clinical efficacy (e.g., test conversion, incidence of new COVID-19 symptoms, hospitalization) **Harms** • TEAEs, SAEs, WDAEs, deaths
Study design	Randomized controlled trials published in full (excluding pre-prints)

COVID-19 = coronavirus disease 2019; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Literature Search Results

The initial literature search identified 4 RCTs that met the inclusion criteria. The updated literature search identified 11 additional treatment trials and 2 prevention RCTs.

Study Characteristics

The characteristics of the studies of interest for this report are summarized in Table 2, Table 3, Table 4, Table 5, Table 6, Table 7.

Table 2: Characteristics of RCTs – Treatment Trials (CloroCovid-19, Borba et al., Tang et al., and Davoodi et al.)

		Treatment trials		
		CloroCovid-19, Borba et al.[1]	Tang et al.[2]	Davoodi et al.[3]
DESIGNS AND POPULATIONS	**Trial registration number**	NCT04323527	Chinese RCT number: ChiCTR2000029868	Iranian clinical trials identification number: IRCT2019072704434N1
	Status	Terminated early	Terminated early	Completed
	Trial completion date	June 7, 2020	February 29, 2020	April 10, 2020
	Funding	The Government of the Amazonas State, Farmanguinhos (Fiocruz), Superintendencia da Zona Franca de Manaus, Coordination for the Improvement of Higher Education Personnel, Fundacao de Amparo a Pesquisa do Estado do Amazonas, and federal funds facilitated by the Brazilian Senate	The Emergent Projects of National Science and Technology, National Natural Science Foundation of China, National Key Research and Development Program of China, Shanghai Municipal Key Clinical Specialty, National Innovative Research Team of High-Level Local Universities in Shanghai, Shanghai Key Discipline for Respiratory Diseases, National Major Scientific and Technological Special Project for Significant New Drugs Development, Key Projects in the National Science and Technology Pillar Program During the Thirteenth Five-Year Plan Period	Mazandaran University of Medical Science, Sari, Iran (identification number: 7294)
	Study design	Parallel, double-blind, phase IIb	Multi-centre, open label	Open label
	Locations	1 hospital in Manaus, Western Brazilian Amazon	16 government-designated COVID-19 treatment centres in 3 provinces in China (Hubei, Henan, and Anhui)	1 fever clinic in Sari (Iran)
	Randomized, N	81	150	60

		Treatment trials		
		CloroCovid-19, Borba et al.[1]	Tang et al.[2]	Davoodi et al.[3]
	Inclusion criteria	• ≥ 18 years old • Hospitalized patients • Clinical suspicion of COVID-19 (i.e., history of fever and any respiratory symptom, e.g., cough or rhinorrhea), with respiratory rate higher than 24 rpm and/or heart rate higher than 125 bpm (in the absence of fever) and/or peripheral oxygen saturation lower than 90% on ambient air and/or shock (i.e., arterial pressure lower than 65 mm Hg, with the need for vasopressor medicines, oliguria, or a lower level of consciousness)	• ≥ 18 years old • Ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens with real-time RT-PCR • Consent not to be enrolled in other clinical trials during the study period • Pneumonia on CT scan of the chest was not mandatory for inclusion	• Chest CT finding compatible with COVID-19 infection, together with other symptoms of coronavirus infection; bilateral and peripheral ground-glass and consolidative pulmonary opacities were the hallmarks of CT findings • Any symptoms of respiratory tract involvement, including cough, dyspnea, or tachypnea, together with a history of contact with a known case of COVID-19 • Creatinine clearance > 60 mL/minute
	Exclusion criteria	• < 18 years old	• < 18 years old • Severe conditions, including malignancies, heart, liver, or kidney disease, or poorly controlled metabolic diseases • Unsuitability for oral administration • Pregnancy or lactation • Allergy to hydroxychloroquine • Inability to cooperate with investigators due to cognitive impairments or poor mental status • Severe hepatic impairment (for example, Child-Pugh class C score, alanine aminotransferase more than 5-fold the upper limit) • Severe renal impairment (estimated glomerular filtration rate ≤ 30 mL/minute/1.73 m^2) or receipt of continuous renal replacement therapy, hemodialysis, or peritoneal dialysis • In the original protocol, patients with severe COVID-19 were excluded; considering that the anti-inflammatory property of hydroxychloroquine might favour disease regression, patients with severe COVID-19 were included (change approved by the ethics committee on February 17, 2020)	• Patients with suspected COVID-19 pneumonia who had severe underlying diseases, such as cardiovascular, lung, or kidney diseases • Patients with severe pneumonia needing hospitalization • Patients who were unable to take oral medications • Concurrent use of azathioprine, didanosine, mercaptopurine, or pegloticase (due to drug interaction with FBX)

		Treatment trials		
		CloroCovid-19, Borba et al.[1]	Tang et al.[2]	Davoodi et al.[3]
Drugs	**Intervention(s)**	High-dosage chloroquine diphosphate (600 mg chloroquine diphosphate twice daily for 10 days)	Hydroxychloroquine administered within 24 hours after randomization, with a loading dose of 1,200 mg daily for 3 days, followed by a maintenance dose of 800 mg daily for the remaining days (total treatment duration was 2 weeks for patients with mild-to-moderate disease and 3 weeks for those with severe disease). The dose of hydroxychloroquine was adjusted when adverse events were related to hydroxychloroquine, as judged by investigators	FBX 80 mg administered once daily for 5 days following randomization
	Comparator(s)	Low-dosage chloroquine diphosphate (450 mg twice daily on day 1 and once daily for 4 days) with placebo tablets to standardize the frequency and duration with the high-dosage chloroquine group	Standard of care; minimum requirements for the standard of care included the provision of intravenous fluids, supplemental oxygen, regular laboratory testing, SARS-CoV-2 testing, hemodynamic monitoring, and intensive care, as well as the ability to deliver concomitant medications	Hydroxychloroquine 200 mg administered twice daily for 5 days following randomization
Duration	Treatment duration	10 days	14 days for patients with mild-to-moderate disease, and 21 days for patients with severe disease	5 days
	Follow-up	28 days from randomization	28 days from randomization	14 days after the initiation of treatment
Outcomes	**Primary end point**	Lethality by day 28	Negative conversion of SARS-CoV-2 by day 28 and whether patients with severe COVID-19 had clinical improvement by day 28[a]	Frequency of hospitalization
	Secondary end points	• Lethality on day 13 (presented by authors as primary outcome) • Participant clinical status • Laboratory examinations[b] • Electrocardiogram on days 13 and 28 • Daily clinical status during hospitalization, duration of mechanical ventilation (if applicable), and supplementary oxygen (if applicable) • Time (in days) from treatment initiation to death • Safety outcomes, including the occurrence of adverse events during treatment, serious adverse events, and	• Alleviation of clinical symptoms within 28 days[c] • Probability of negative conversion at day 4, 7, 10, 14, or 21 • Improvement in CRP, ESR, TNF-alpha, IL-6, and absolute blood lymphocyte count at day 28 • Improvement in lung lesions on chest radiology at day 28 • All-cause death at day 28 • Disease progression in patients with mild-to-moderate disease at day 28 • Additional secondary outcomes were to be captured for severe patients and are listed in the protocol (e.g., clinical improvement) but not reported, given that only 2 patients were enrolled with severe disease • Safety outcomes included any adverse event, serious adverse	• Clinical improvements (e.g., resolution of fever, cough, and dyspnea) • Improvement of CT findings at day 14 after initiation of the treatment • Laboratory examinations (e.g., lymphocytes count, CRP values) • Safety outcomes were not captured

		Treatment trials		
		CloroCovid-19, Borba et al.[1]	Tang et al.[2]	Davoodi et al.[3]
		premature or temporary discontinuation of treatment were evaluated	event, and non-serious adverse event	
NOTES	**Publications**	Borba et al.[1]	Tang et al.[2]	Davoodi et al.[3]

bpm = beats per minute; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FBX = febuxostat; IL-6 = interleukin-6; RCT = randomized controlled trial; rpm = respirations per minute; RT-PCR = reverse transcription–polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNF= tumour necrosis factor.

[a] Negative conversion of SARS-CoV-2 is defined as 2 consecutive reports of a negative result for SARS-CoV-2 at least 24 hours apart, without a subsequent report of a positive result by the end of the study.

[b] Hematology and biochemistry tests were performed through automated machines. Two nasopharyngeal or 1 oropharyngeal swab sample was submitted to viral ribonucleic acid extraction using the QIAamp Viral RNA Mini Kit (QIAGEN). Specimens were considered positive if both viral targets showed a cycle threshold lower than 40.00.

[c] The definition of the alleviation of clinical symptoms was the resolving from fever to an axillary temperature of 36.6°C or below, normalization of SpO_2, blood oxygen saturation (> 94% on room air), and the disappearance of respiratory symptoms, including nasal congestion, cough, sore throat, sputum production, and shortness of breath.

Table 3: Characteristics of RCTs – Treatment Trials (Cavalcanti et al., Skipper et al., and Abd-Elsalam et al.)

		Treatment trials		
		Cavalcanti et al.[4]	Skipper et al.[5]	Abd-Elsalam et al.[6]
DESIGNS AND POPULATIONS	**Trial registration number**	NCT04322123	NCT04308668	NCT04353336
	Status	Completed	Completed	Completed
	Trial completion date	June 2, 2020	May 20, 2020	December 23, 2030
	Funding	The Coalition COVID-19 Brazil, and EMS Pharma	Private donors	Tanta University
	Study design	Multi-centre, open-label, 3-group study	Multi-centre, double blind, placebo controlled	Multi-centre, open label
	Locations	55 hospitals in Brazil	Internet recruitment in US (40 states), and Canada (Quebec, Manitoba, and Alberta)	3 university hospitals in Egypt
	Randomized, N	667	491	194
	Inclusion criteria	• ≥ 18 years old • Hospitalized with suspected or confirmed COVID-19 with ≤ 14 days since symptom onset	• ≥ 18 years old • 3 groups of participants were included: ○ non-hospitalized adults with ≤ 4 days of symptoms and either PCR-confirmed SARS-CoV-2 infection or symptoms after a high-risk exposure to a person with PCR-confirmed COVID-19 within the past 14 days[a] ○ health care workers who had COVID-19–compatible symptoms and high-risk	• Patients admitted to 1 of 3 hospitals managing patients with confirmed COVID-19

		Treatment trials		
		Cavalcanti et al.[4]	Skipper et al.[5]	Abd-Elsalam et al.[6]
			exposure but whose contact had pending PCR results were enrolled after symptom review by an infectious diseases physician ○ patients with high-risk exposure who were asymptomatic at the time of their consent for a companion post-exposure prophylaxis trial that had the same inclusion and exclusion criteria, but who became symptomatic before starting their study medicine on day 1 and were analyzed as part of this trial	
	Exclusion criteria	• Use of supplemental oxygen at a rate of more than 4 litres per minute as administered by a nasal cannula or at a level of at least 40% as administered by a Venturi mask • Use of oxygen administered by a high-flow nasal cannula or invasive or non-invasive ventilation • Previous use of chloroquine, hydroxychloroquine, azithromycin, or any other macrolide antibiotic for more than 24 hours before enrolment (and since the onset of symptoms) • A history of severe ventricular tachycardia or electrocardiographic findings with a corrected QT interval of at least 480 milliseconds	• < 18 years old • Hospitalized • Symptoms > 4 days (per inclusion criteria) • Hydroxychloroquine allergy • Retinal eye disease • Known glucose-6-phosphate dehydrogenase deficiency • Known chronic kidney disease (stage 4 or 5 or receiving dialysis) • Known porphyria • Weight less than 40 kg • Receiving chemotherapy • Current use of chloroquine or hydroxychloroquine • Current use of cardiac antiarrhythmic drugs, including flecainide, amiodarone, digoxin, procainamide, or sotalol • In Canada, additional exclusions mandated by regulatory authorities were: pregnancy; breastfeeding; severe diarrhea or vomiting; known cirrhosis with encephalopathy or ascites; known prolonged cardiac QT interval, ventricular arrhythmia, or history of sudden cardiac death; or use of QT-prolonging medicines • On April 20, 2020, additional US exclusions were added	• Patients who had an allergy or contraindication to hydroxychloroquine • Pregnant and lactating females • Patients with cardiac problems (chronic heart failure or prolonged QT interval on electrocardiogram)

		Treatment trials		
		Cavalcanti et al.[4]	Skipper et al.[5]	Abd-Elsalam et al.[6]
			for weight less than 50 kg, structural or ischemic heart disease, personal or family history of cardiac QT prolongation, and use of QT-prolonging medications • Use of the following medications: azithromycin clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ketoconazole, itraconazole, mefloquine, amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, bupropion, venlafaxine, haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone, methadone, sumatriptan, zolmitriptan	
Drugs	**Intervention(s)**	The first intervention group was standard of care plus hydroxychloroquine 400 mg twice daily for 7 days. The second intervention group was standard of care plus hydroxychloroquine 400 mg twice daily for 7 days, plus azithromycin 500 mg once daily for 7 days	Hydroxychloroquine 800 mg (4 tablets of 200 mg at once), then 600 mg (3 tablets) 6 to 8 hours after initial dose, then 600 mg (3 tablets) once daily for 4 more days (5 days in total)	Hydroxychloroquine 400 mg twice daily (on day 1), followed by 200 mg twice daily added to the standard of care treatment adopted by the Egyptian MOH for 15 days[b]
	Comparator(s)	Standard of care. Standard of care was at the discretion of the treating physicians. The use of glucocorticoids, other immunomodulators, antibiotic drugs (except macrolides in the hydroxychloroquine only or standard of care group), and antiviral drugs was allowed	Placebo tablets of folic acid: 400 mcg as an identical regimen for the control group. In Canada, the placebo tablets were lactose. In case of gastrointestinal upset, the total daily dose was divided into 2 or 3 doses	Standard of care for 15 days
Duration	**Phase**			
	Treatment duration	7 days	5 days	15 days
	Follow-up	15 days after hospital admission	14 days after randomization	28 days after the initiation of treatment
Outcomes	**Primary end point**	Clinical status at 15 days based on a 7-level ordinal scale[c]	An ordinal outcome by day 14 of: not hospitalized, hospitalized, intensive care unit stay, or death	Percentage of recovery within 28 days
	Secondary end points	• Clinical status at 7 days evaluated with a 6-level ordinal scale	• Symptom severity at day 5 and day 14 by 10-point visual analogue scale[d]	• Need for mechanical ventilation • Death

		Treatment trials		
		Cavalcanti et al.[4]	Skipper et al.[5]	Abd-Elsalam et al.[6]
		• Indication for intubation within 15 days • Receipt of supplemental oxygen administered by a high-flow nasal cannula or non-invasive ventilation between randomization and 15 days • Duration of hospital stay • In-hospital death • Thromboembolic complications • Acute kidney injury • The number of days alive and free from respiratory support up to 15 days	• Nominal incidence of all hospitalizations and deaths Incidence of study medicine withdrawal	• Duration to negative PCR • Duration to clinical improvement • Duration to hospital discharge
NOTES	**Publications**	Cavalcanti et al.[4]	Skipper at al.[5]	Abd-Elsalam et al.[6]

COVID-19 = coronavirus disease 2019; MOH = medical officer of health; O_2 = oxygen; PaO_2 = partial pressure of oxygen; PCR = polymerase chain reaction; RCT = randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] High-risk exposure was defined as an immediate household contact or a close occupational exposure to someone with COVID-19 (for example, health care worker or first responder).

[b] Standard of care included acetaminophen, oxygen, fluids (according to assessment), empiric antibiotics (cephalosporins), oseltamivir, if needed (75 mg per 12 hours for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO_2 < 60 mm Hg, O_2 saturation < 90% despite oxygen or non-invasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock.

[c] Scores on the scale were defined as follows: a score of 1 indicated not hospitalized with no limitations on activities; 2, not hospitalized but with limitations on activities; 3, hospitalized and not receiving supplemental oxygen; 4, hospitalized and receiving supplemental oxygen; 5, hospitalized and receiving oxygen supplementation administered by a high-flow nasal cannula or non-invasive ventilation; 6, hospitalized and receiving mechanical ventilation; and 7, death.

[d] Zero indicated no symptoms and 10 indicated severe symptoms.

Table 4: Characteristics of RCTs – Treatment Trials (Horby et al., Lyngbakken et al., and Mitjà et al.)

		Treatment trial		
		Horby et al.[7]	Lyngbakken et al.[8]	Mitjà et al.[9]
DESIGNS AND POPULATIONS	**Trial registration number**	NCT04381936	NCT04316377	NCT04304053
	Status	HCQ treatment arm terminated early	Terminated early	Completed
	Trial completion date	Enrolment of patients in the HCQ group closed on June 5, 2020	May 25, 2020	May 26, 2020
	Funding	UK Research and Innovation and National Institute for Health Research	European Union's Horizon 2020 research and innovation program (grant agreement 871029)	Crowdfunding campaign "JoEmCorono," Laboratorios Rubio, Laboratorios Gebro Pharma, Zurich Seguros, SYNLAB Barcelona, and Generalitat de Catalunya
	Study design	Multi-centre, open label	Open label, pragmatic	Multi-centre, open label
	Locations	176 hospitals in the UK	Norway, single-centre study (Akershus	Recruitment through electronic registry in 3 health

		Treatment trial		
		Horby et al.[7]	Lyngbakken et al.[8]	Mitjà et al.[9]
			University Hospital)	administrative regions in Catalonia, Spain
	Randomized, N	4,716	53	293
	Inclusion criteria	• ≥ 18 years old (initial inclusion criteria revised to include all ages as of May 9, 2020) • Hospitalized with clinically suspected or laboratory-confirmed SARS-CoV-2 infection • No medical history that might put the patient at substantial risk if they were to participate in the trial (based on the opinion of the attending clinician)	• ≥ 18 years old • Hospitalized • Moderately severe disease (NEWS2 score ≤ 6) • SARS-CoV-2 positive nasopharyngeal swab	• ≥ 18 years old • Mild symptoms of COVID-19 (i.e., fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, or influenza-like illness) for less than 5 days before enrolment • Not hospitalized • Positive PCR test for SARS-CoV-2 in the baseline nasopharyngeal swab
	Exclusion criteria	• < 18 years old (initial exclusion criteria revised to include all ages as of May 9, 2020) • Patients with a known or prolonged corrected QT interval on electrocardiography	• Requiring ICU admission at screening • History of psoriasis • Reduced hearing/tinnitus • Visual impairment • Known adverse reaction to HCQ sulphate • Pregnancy • Prolonged QT interval (> 450 milliseconds)	• Patient with moderate-to-severe COVID-19 disease (e.g., required hospitalization) • Any condition that might preclude following the study procedures safely (e.g., mental disability) • Known allergy or hypersensitivity to study drugs • Known retinal and severe liver or renal diseases • History of cardiac arrhythmia • Known QT prolongation or other diseases that could be exacerbated by study drugs (e.g., psoriasis) • Active treatment with medications that are contraindicated with study drugs • Known HIV infection • Females who were pregnant or breastfeeding
Drugs	**Intervention(s)**	200 mg tablets of HCQ sulphate in a loading dose of 4 tablets (800 mg) at baseline and at 6 hours, followed by 2 tablets (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	HCQ 400 mg twice daily for 7 days plus standard of care	HCQ 800 mg on day 1, followed by 400 mg once daily for 6 days. Initially, the protocol included the use of HCQ and cobicistat-boosted darunavir combined treatment, but it was changed to HCQ alone after the recommendation of the pharmaceutical company not to use cobicistat-boosted

		Treatment trial		
		Horby et al.[7]	Lyngbakken et al.[8]	Mitjà et al.[9]
				darunavir combined treatment due to lack of activity in vitro and negative results in human clinical trials of closely related HIV protease inhibitors
	Comparator(s)	Usual care[a]	Standard of care for 7 days; standard of care included medical treatment in accordance with local and national guidelines	Usual care for 7 days
DURATION	**Phase**			
	Treatment duration	10 days	7 days	7 days
	Follow-up	28 days after randomization or a time of death, whichever came first	30 days after randomization	28 days after the initiation of treatment
OUTCOMES	**Primary end point**	All-cause mortality within 28 days after randomization	The rate of decline in SARS-CoV-2 viral load in the oropharynx from baseline through the first 96 hours after randomization	The reduction of viral RNA load in nasopharyngeal swabs at days 3 and 7 after treatment start
	Secondary end points	• Time until hospital discharge • 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 • Cause-specific mortality (recorded in all patients) • Major cardiac arrhythmia (recorded in a subgroup of patients)	• In-hospital mortality • Mortality at 30 days • Clinical status on a 7-point ordinal scale at 14 days after randomization[b] • Duration of hospital admission after randomization • Change in degree of illness as quantified by NEWS2 from randomization to 96 hours	• Clinical progression measured by a simplified version of the WHO progression scale • Time from randomization to complete resolution of symptoms within the 28-day follow-up period
NOTES	**Publications**	Horby et al.[7]	Lyngbakken at al.[8]	Mitjà et al.[9]

COVID-19 = coronavirus disease 2019; HCQ = hydroxychloroquine; ICU = intensive care unit; NEWS2 = National Early Warning Score 2; PCR = polymerase chain reaction; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

[a] No further information on what constitutes "usual care" was provided in either the original publication or the supplemental appendix.

[b] 1 = dead; 2 = hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation; 3 = hospitalized, on non-invasive ventilation or high-flow oxygen devices; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, not requiring supplemental oxygen; 6 = not hospitalized, but unable to resume normal activities, 7 = not hospitalized, with resumption of normal activities.

Table 5: Characteristics of RCTs – Treatment Trials (WHO Solidarity Trial Consortium, Ulrich et al., and Khamis et al.)

		Treatment trials		
		WHO Solidarity Trial Consortium[10]	Ulrich et al.[11]	Khamis et al.[12]
Designs and populations	**Trial registration number**	NCT04315948	NCT04369742	Not identified
	Status	Terminated early	Terminated early	Terminated early
	Trial completion date	June 19, 2020	May 12, 2020	June 22, 2020
	Funding	World Health Organization	The New York University Grossman School of Medicine, the National Center for Advancing Translational Sciences, National Institutes of Health	No funding was received for this study
	Study design	Multi-centre, open label	Multi-centre, double blind, placebo controlled	Open label
	Locations	405 hospitals in 30 countries	NYU Langone Health (Tisch Hospital and Kimmel Pavilion, NYU Langone — Brooklyn Hospital and NYU Winthrop Hospital), NYC Health and Hospitals/Bellevue Hospital Center, and State University of New York Downstate Medical Center	The Royal Hospital (Muscat, Oman)
	Randomized, N	1,863	128	89
	Inclusion criteria	• ≥ 18 years old • Hospitalized with a diagnosis of COVID-19 • Not known to have received any trial drug • Not expected to be transferred elsewhere within 72 hours • In the physician's view, had no contraindication to any trial drug	• Hospitalized patients with a positive SARS-CoV-2 RT-PCR within 72 hours of enrolment • At least 1 COVID-19 symptom (e.g., fever, cough, dyspnea, nausea, diarrhea, myalgia, anosmia, dysgeusia) • Written informed consent	• Age 18 to 75 years • SARS-CoV-2 infection confirmed by RT-PCR test on respiratory tract specimens • Moderate-to-severe COVID-19 pneumonia according to the WHO interim guidelines case definitions • The interval between symptoms onset and randomization was not > 10 days • For female patients: Evidence of post-menopause status or, for pre-menopause patients, negative pre-treatment serum or urine pregnancy test • Eligible patients of child-bearing age (male or female) had to agree to take effective contraceptive measures (including hormonal contraception,

		Treatment trials		
		WHO Solidarity Trial Consortium[10]	**Ulrich et al.**[11]	**Khamis et al.**[12]
				barrier methods or abstinence) with their partner during the study period and for at least 7 days following the last study treatment • Not participating in any other interventional drug clinical study before completion of the present trial
	Exclusion criteria	• Excluded if any of the available study drugs were contraindicated (e.g., because of patient characteristics, chronic liver or heart disease, or some concurrent medication) • Patients who did not consent or had uncertain consent	Patients who: • met the primary end point (admitted to the ICU, mechanical ventilation, extracorporeal membrane oxygenation [ECMO], and/or vasopressor use) at enrolment • had received any doses of HCQ or chloroquine within 30 days • were unable to take oral medications • were allergic to study treatment medications • had a baseline corrected QT (QTc) interval of > 500 milliseconds • were on concomitant therapy with antiarrhythmic medications (flecainide, amiodarone, digoxin, procainamide, propafenone) or antipsychotic drugs (thioridazine, or pimozide) • had a history of cardiac arrest, retinal disease, or glucose-6-phosphate dehydrogenase deficiency	• Age > 75 years • Refractory nausea, vomiting, or chronic gastrointestinal disorders • Inability to swallow the study drug or had undergone extensive bowel resection, which may affect adequate absorption of favipiravir • Severe liver disease (underlying liver cirrhosis or alanine aminotransferase /aspartate aminotransferase elevated more than 5 times the upper limit of normal) • Gout or history of gout or hyperuricemia • Known severe renal impairment with creatinine clearance of < 30 mL/minute or had received continuous renal replacement therapy, hemodialysis, or peritoneal dialysis • Known allergy or hypersensitivity to favipiravir • Pregnant or lactating women
Drugs	**Intervention(s)**	HCQ (oral) was 4 tablets (800 mg) at hour 0, 4 tablets (800 mg) at hour 6 and, starting at hour 12, 2 tablets (400 mg) twice daily for 10 days; each tablet contained 200 mg of HCQ sulphate	HCQ prescribed at 400 mg (two 200 mg tablets) twice daily on day 1 followed by 200 mg (1 tablet) twice daily for days 2 through 5	Favipiravir 1,600 mg prescribed on day 1 followed by 600 mg twice a day for a maximum of 10 days. The dose was reduced to 800 mg on day 1, then 400 mg twice a day if the patient experienced a liver injury adverse event of grade ≥ 3

		Treatment trials		
		WHO Solidarity Trial Consortium[10]	Ulrich et al.[11]	Khamis et al.[12]
				In addition to favipiravir, inhaled interferon beta-1b was prescribed at a dose of 8 million IU (0.25 mcg) twice a day for 5 days
	Comparator(s)	Standard of care as defined in each local hospital where HCQ was used	Placebo calcium citrate tablets, 200 mg prescribed at an identical regimen as HCQ for the control group	HCQ 400 mg twice daily on day 1 followed by 200 mg twice daily for 7 days
DURATION	**Phase**			
	Treatment duration	10 days	5 days	11 days for intervention 8 days for comparator
	Follow-up	Until death or hospital discharge	30 days after randomization	14 days after assignment
OUTCOMES	**Primary end point**	In-hospital mortality before or after day 28	• The proportion of patients meeting a severe COVID-19 progression composite end point at day 14 • The primary safety outcome is the cumulative incidence of SAEs, grade 3 or 4 adverse events, and/or discontinuation of therapy at day 30	• Time from assignment to clinical recovery • The normalization of inflammatory markers • Improvement in oxygen saturation that was maintained for at least 72 hours
	Secondary end points	• Initiation of mechanical ventilation • Hospitalization duration	• Change in an 8-point ordinal COVID-19 clinical severity score[a] • The primary composite outcome and mortality at day 30 • Hospital length of stay • Fever-free days • Oxygen-free days • SARS-CoV-2 viral clearance on nasopharyngeal PCR • Clinically significant changes from baseline to follow-up (day 6 or day 3 if day 6 was unavailable) in creatinine, hepatic, and hematology laboratory results • Changes in inflammatory markers (C-reactive protein, lactic acid dehydrogenase, ferritin, interleukin-6) and coagulation factors	• Deterioration or aggravation of pneumonia • ICU admission rate • Mortality within 14 days of assignment

		Treatment trials		
		WHO Solidarity Trial Consortium[10]	Ulrich et al.[11]	Khamis et al.[12]
			(D dimer) associated with severe COVID-19	
NOTES	**Publications**	WHO Solidarity Trial Consortium[10]	Ulrich et al.[11]	Khamis et al.[12]

COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; HCQ = hydroxychloroquine; ICU = intensive care unit; IU = international unit; NYU = New York University; PCR = polymerase chain reaction; QTc = corrected QT; RT-PCR = reverse transcription–polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

[a] The ordinal scores were defined as follows: 1 = death; 2 = ventilator; 3 = hospitalized, on non-invasive ventilation or high-flow nasal cannula; 4 = hospitalized, on supplemental oxygen; 5 = hospitalized, not on oxygen, ongoing medical care; 6 = hospitalized, not on oxygen, not requiring ongoing care; 7 = outpatient, limitation on activities or home O_2; 8 = outpatient, no limitation on activities.

Table 6: Characteristics of RCTs – Treatment Trials (Self et al. and Brown et al.)

		Treatment trial	
		Self et al.[13]	Brown et al.[14]
DESIGNS AND POPULATIONS	**Trial registration number**	NCT04332991	NCT04329832
	Status	Terminated early	Terminated early
	Trial completion date	July 17, 2020	June 19, 2020
	Funding	The National Heart, Lung, and Blood Institute of the US National Institutes of Health	Heart and Lung Research Foundation, Intermountain Research and Medical Foundation, and Office of the Associate Vice President for Research, University of Utah Health Sciences
	Study design	Multi-centre, blinded, placebo-controlled	Multi-centre, open label
	Locations	34 hospitals in the US	13 hospitals in Utah, US
	Randomized, N	479	85
	Inclusion criteria	• ≥ 18 years old • Hospitalized for less than 48 hours or in an emergency department with anticipated hospitalization • Symptoms of acute respiratory infection for less than 10 days, defined as 1 or more of the following: ○ cough ○ fever (> 37.5°C or 99.5°F) ○ shortness of breath (operationalized as any of the following: subjective shortness of breath reported by patient or surrogate; tachypnea with respiratory rate ≥ 22 per minute; hypoxemia, defined as SpO_2 < 92% on room air, new receipt of supplemental oxygen to maintain SpO_2 ≥ 92%, or increased supplemental oxygen to maintain SpO_2 ≥ 92% for a patient on chronic oxygen therapy) ○ sore throat	• Hospitalized patients • Symptomatic laboratory-confirmed COVID-19 • Enrolled within 10 days of a positive test for COVID-19

		Treatment trial	
		Self et al.[13]	Brown et al.[14]
		• Laboratory-confirmed SARS-CoV-2 infection within the past 10 days prior to randomization	
	Exclusion criteria	• Prisoner • Pregnancy • Breastfeeding • Unable to randomize within 10 days after onset of acute respiratory infection symptoms • Unable to randomize within 48 hours after hospital arrival • Seizure disorder • Porphyria cutanea tarda • QTc interval > 500 milliseconds on electrocardiogram within 72 hours prior to enrolment • Diagnosis of long QT syndrome • Known allergy to hydroxychloroquine, chloroquine, or amodiaquine • Receipt in the 12 hours prior to enrolment, or planned administration during the 5-day study period, of any of the following medications that treating clinicians feel cannot be substituted for another medication: amiodarone, cimetidine, dofetilide, phenobarbital, phenytoin, sotalol • Receipt of > 1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrolment • Inability to receive enteral medications • Refusal or inability to be contacted on day 15 for clinical outcome assessment if discharged prior to day 15 • Previous enrolment in this trial • The treating clinical team does not believe equipoise exists regarding the use of hydroxychloroquine for the treatment of this patient	• Excluded for ethical reasons (e.g., incarcerated) • Safety reasons (e.g., known long QT syndrome, seizure disorder, or renal or liver failure)
DRUGS	**Intervention(s)**	Hydroxychloroquine sulphate 400 mg twice a day for the first 2 doses and then 200 mg twice a day for the subsequent 8 doses for a total of 10 doses over 5 days	Hydroxychloroquine sulphate 400 mg twice a day on the first day followed by 200 mg twice daily for the following 4 days (total dose of 2,400 mg)
DRUGS	**Comparator(s)**	Matching placebo in the same dosing frequency as the intervention	Azithromycin 500 mg on the first day followed by 250 mg daily for the following 4 days (total dose of 1,500 mg)
DURATION	**Phase**		
DURATION	Treatment duration	5 days	5 days
DURATION	Follow-up	28 days after randomization	28 days after randomization

		Treatment trial	
		Self et al.[13]	**Brown et al.**[14]
Outcomes	**Primary end point**	The clinical status 14 days after randomization assessed with a 7-category ordinal scale (the COVID Outcomes Scale) recommended by the World Health Organization[a]	The 8-category World Health Organization COVID Ordinal Scale for Clinical Improvement at day 14[b]
	Secondary end points	• Time to recovery, defined as time to reaching level 5, 6, or 7 on the COVID Outcomes Scale, which is the time to the earlier of final liberation from supplemental oxygen or hospital discharge • All-location, all-cause 14-day mortality (assessed on study day 15) • All-location, all-cause 28-day mortality (assessed on study day 29) • COVID Outcomes Scale on study days 3, 8, and 29 • Composite of death or receipt of ECMO through day 28 • Oxygen-free days through day 28 • Ventilator-free days through day 28 • Vasopressor-free days through day 28 • ICU-free days through day 28 • Hospital-free days through day 28	• Hospital-free days by day 28 of follow-up • Ventilator-free days by day 28 of follow-up • ICU-free days by day 28 of follow-up • Safety outcomes assessed from day 1 through day 5
Notes	**Publications**	Self et al.[13]	Brown at al.[14]

COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; QTc = corrected QT; RCT = randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation measured by pulse oximetry.

[a] The COVID Outcomes Scale consists of 7 mutually exclusive categories: 1 = death; 2 = hospitalized, receiving ECMO or invasive mechanical ventilation; 3 = hospitalized, receiving non-invasive mechanical ventilation or nasal high-flow oxygen therapy; 4 = hospitalized, receiving supplemental oxygen without positive pressure or high flow; 5 = hospitalized, not receiving supplemental oxygen; 6 = not hospitalized and unable to perform normal activities; and 7 = not hospitalized and able to perform normal activities.

[b] Outcomes of this 8-category scale were as follows: 1 = no limitation of activities, 2 = limitation of activities, 3 = no oxygen therapy, 4 = oxygen by mask or nasal cannula, 5 = non-invasive ventilation or high-flow oxygen, 6 = invasive mechanical ventilation without other organ support, 7 = invasive mechanical ventilation with other organ support, and 8 = death.

Table 7: Characteristics of RCTs – Prevention Trials

		Prevention trial		
		Boulware et al.[15]	Abella et al.[16]	Rajasingham et al.[17]
Designs and populations	**NCT number**	NCT04308668	NCT04329923	NCT04328467
	Status	Terminated early	Terminated early	Terminated early
	Trial completion date	May 6, 2020	August 4, 2020	July 13, 2020
	Funding	Practice Assessment Unit of the McGill University Health Centre and the McGill Interdisciplinary Initiative in Infection and Immunity — Emergency COVID-19 Research Funding program, Manitoba Medical Service Foundation and Research Manitoba, Northern Alberta Clinical Trials and Research Centre — COVID-19 Clinical Research Grant	Philanthropic donations from Leonard and Madlyn Abramson and Mark and Cecilia Vonderheide	Jan and David Baszucki, Steve Kirsch, the Rainwater Charitable Foundation, the Alliance of Minnesota Chinese Organizations, the Minnesota Chinese Chamber of Commerce, the University of Minnesota Foundation, Manitoba Medical Service Foundation and Research Manitoba, Rising Pharmaceuticals, the National Institutes of Health's National Center for Advancing Translational Sciences
	Study design	Randomized, double-blind, placebo-controlled trial	Randomized, double-blind, multi-centre, placebo-controlled trial	Randomized, double blind, placebo controlled
	Locations	Participants were enrolled through a secure internet-based survey nationwide in the US and in Canada in the provinces of Quebec, Manitoba, and Alberta. The survey was facilitated by social media outreach, as well as traditional media	Two tertiary hospitals in the Pennsylvania medical system: • Hospital of the University of Pennsylvania • Penn Presbyterian Medical Center	Participants were enrolled through an internet-based survey nationwide in the US and in Manitoba, Canada
	Randomized, N	821	132	1,483
	Inclusion criteria	• ≥ 18 years old • Household or occupational exposure to a person with confirmed COVID-19 at a distance of less than 6 feet for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure) or while wearing a face mask but no eye shield (moderate-risk exposure)	• Health care workers at either study hospital • Worked 20 hours or more per week in hospital-based units • No known history of SARS-CoV-2 infection • Did not have symptoms suggestive of COVID-19 in the 2 weeks before enrolment, including cough, fever, or shortness of breath • Physicians, nurses, certified nursing assistants, emergency technicians, and	• ≥ 18 years old • Health care workers with ongoing exposure to persons with COVID-19 • High-risk exposure included "working in an emergency department or intensive care unit, on a dedicated COVID-19 hospital ward, as a first responder, or whose job description included regularly performing aerosol-generating procedures (e.g., anesthesiologists or otolaryngologists), and included physicians, nurses, advanced

		Prevention trial		
		Boulware et al.[15]	**Abella et al.**[16]	**Rajasingham et al.**[17]
			respiratory therapists were eligible; enrolment was focused on staff members in the emergency department and dedicated COVID-19 units	practice providers, and other personnel (e.g., respiratory therapists)"

	Exclusion criteria	• Patients who:
		  ○ were < 18 years of age
		  ○ were hospitalized
		  ○ had symptoms of COVID-19 or PCR-proven SARS-CoV-2 infection
		  ○ had a hydroxychloroquine allergy, retinal eye disease, glucose-6-phosphate dehydrogenase deficiency, chronic kidney disease, porphyria, weight less than 40 kg, receiving chemotherapy
		  ○ had concomitant medication usage[a]
		  ○ concurrently using azithromycin, hydroxychloroquine, or cardiac arrythmia medications
		• Exclusions specific to Canada include pregnancy, breastfeeding, severe diarrhea or vomiting, known cirrhosis with encephalopathy or ascites, known prolonged cardiac QT interval prolongation or QT-prolonging medications, and weight less than 50 kg
		• On April 20, 2020, the FDA required additional exclusions of structural or ischemic heart disease, personal or family history of cardiac QT prolongation, or QT-prolonging medications, and weight less than 50 kg
			• < 18 years of age
			• History of a positive SARS-CoV-2 test result
			• Prisoners or other detained persons
			• Allergy or sensitivity to hydroxychloroquine
			• Glucose-6-phosphate dehydrogenase deficiency
			• Pregnant or lactating or positive pregnancy test during pre-medication examination
			• Receiving any treatment drug for SARS-CoV-2 within 14 days prior to screening evaluation (off label, compassionate use, or trial-related)
			• Enrolment into another interventional COVID-19 study
			• Known history of retinal disease, including but not limited to age-related macular degeneration
			• Taking any of the following medications that prolong QTc interval: chlorpromazine, haloperidol, droperidol, quetiapine, olanzapine, amisulpride, thioridazine
			• History of interstitial lung disease or chronic pneumonitis unrelated to COVID-19
			• Due to risk of disease exacerbation, patients with porphyria or psoriasis were ineligible, unless the disease was well controlled and they were under the care of a specialist for the disorder who
				• Patients who reported active or prior COVID-19 (either confirmed or symptom-compatible illness)
				• No expected exposure to patients
				• Contraindications to hydroxychloroquine

		Prevention trial		
		Boulware et al.[15]	Abella et al.[16]	Rajasingham et al.[17]
			agreed to monitor the patient for exacerbations • Patients with serious intercurrent illness that required active infusion therapy, intense monitoring, or frequent dose adjustments for medication, including but not limited to infectious disease, cancer, autoimmune disease, cardiovascular disease • Patients who had undergone major abdominal, thoracic, spine or CNS surgery in the last 2 months, or planned to undergo surgery during study participation • Patients receiving cytochrome P450 enzyme-inducing anticonvulsant drugs (i.e., phenytoin, carbamazepine, phenobarbital, primidone, or oxcarbazepine) within 4 weeks of the start of the study treatment • History or evidence of increased cardiovascular risk, including any of the following: ○ Left ventricular ejection fraction less than the institutional lower limit of normal; baseline echocardiogram was not required ○ Current clinically significant uncontrolled arrhythmias (exception: patients with controlled atrial fibrillation) ○ History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrolment	

		Prevention trial		
		Boulware et al.[15]	Abella et al.[16]	Rajasingham et al.[17]
			○ Current ≥ class II congestive heart failure as defined by New York Heart Association	
Drugs	**Intervention(s)**	Hydroxychloroquine sulphate (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days); if participants had gastrointestinal upset, they were advised to divide the daily dose into 2 or 3 doses	Hydroxychloroquine 600 mg administered as 3 tablets of 200 mg once daily, taken orally for 8 weeks	There were 2 treatment groups; participants in both treatment groups were given a loading dose of 400 mg of hydroxychloroquine (two 200 mg tablets) twice separated by 6 to 8 hours. Following the loading dose, participants in the first treatment group were administered 400 mg (two 200 mg tablets) once weekly for 12 weeks, whereas participants in the second treatment group were administered 400 mg (two 200 mg tablets) twice weekly for 12 weeks
	Comparator(s)	Placebo folate tablets, which were similar in appearance to the hydroxychloroquine tablets, were prescribed as an identical regimen for the control group	Placebo consisted of custom-moulded identically sized and shaped microcrystalline cellulose tablets taken orally for 8 weeks with identical instructions as for hydroxychloroquine (prepared for this trial by Temple IDS and Temple University, Philadelphia, Pennsylvania)	Placebo (folic acid) prescribed in a matched fashion, including a loading dose of 2 tablets followed by 2 tablets once or twice weekly for 12 weeks
Duration	**Phase**			
	Treatment duration	5 days	8 weeks	12 weeks
	Follow-up	14 days	4 weeks and 8 weeks	4 weeks and 12 weeks
Outcomes	**Primary end point**	The incidence of either laboratory-confirmed COVID-19 or illness compatible with COVID-19 within 14 days[b]	The rate of conversion to SARS-CoV-2–positive status via NP swab during the 8 weeks of study participation	COVID-19–free survival time by laboratory-confirmed or probable compatible illness. Laboratory-confirmed COVID-19 was defined as a self-reported positive SARS-CoV-2 PCR; the definition of COVID-19–compatible symptoms was based on guidance from the US Council for State and Territorial Epidemiologists[b]

		Prevention trial		
		Boulware et al.[15]	**Abella et al.**[16]	**Rajasingham et al.**[17]
	Secondary end points	• Incidence of hospitalization for COVID-19 or death • Incidence of PCR-confirmed SARS-CoV-2 infection • Incidence of COVID-19 symptoms[b] • Incidence of discontinuation of the trial intervention owing to any cause • Severity of symptoms (if any) at days 5 and 14 according to a visual analogue scale (scores ranged from 0 [no symptoms] to 10 [severe symptoms]) • Safety outcomes, including adverse events, serious adverse events, and withdrawals due to adverse events	• Adverse event rate • Rate of serologic antibody positivity for either nucleocapsid or spike protein antigens • ECG changes after 4 weeks of treatment • Clinical outcomes for any participants who became SARS-CoV-2 positive and/or developed COVID-19 symptoms within the 8-week study period	• Incidence of confirmed SARS-CoV-2 • Incidence of possible COVID-19 • Incidence of hospitalization • Death • Other adverse events
NOTES	**Publications**	Boulware et al.[15]	Abella et al.[16]	Rajasingham et al.[17]

CNS = central nervous system; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; IDS = Investigational Drug Service; NP = nasopharyngeal; PCR = polymerase chain reaction; QTc = corrected QT; RCT = randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Concomitant medication usage included the use of: hydroxychloroquine, chloroquine, amiodarone, digoxin, procainamide, sotalol, azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ketoconazole, itraconazole, mefloquine, amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, Wellbutrin, venlafaxine, haloperidol, lithium, quetiapine, thioridazine, ziprasidone, methadone, sumatriptan, and zolmitriptan.

[b] COVID-19–related symptoms were based on the US Council of State and Territorial Epidemiologists criteria for confirmed cases (positivity for SARS-Cov-2 on PCR assay), probable cases (the presence of cough, shortness of breath, or difficulty breathing, or the presence of 2 or more symptoms of fever, chills, rigours, myalgia, headache, sore throat, and new olfactory and taste disorders), and possible cases (the presence of 1 or more compatible symptoms, which could include diarrhea).

Study Design Characteristics of Treatment Trials

CloroCovid-19

Borba et al. reported the findings of a parallel, double-blind, randomized, phase IIb clinical trial with 81 patients hospitalized with SARS-CoV-2. This study was conducted from March 23 to April 5, 2020 at a tertiary care facility in Manaus, Brazilian Amazon. The objective of this study was to evaluate the safety and efficacy of 2 chloroquine dosages in patients with severe COVID-19.[1]

Patients were eligible for enrolment in the study if they were 18 years or older, hospitalized with a clinical suspicion of COVID-19, and had a respiratory rate and heart rate greater than 24 breaths per minute and 125 beats per minute, respectively, and peripheral oxygen saturation below 90%.

The intervention and comparator groups were based on different dosages of chloroquine tablets. Patients were randomized in a 1:1 ratio to either receive the high-dosage chloroquine "(600 mg CQ [chloroquine]; 4 × 150 mg tablets twice daily for 10 days; total dose 12 g) or low-dosage CQ (450 mg CQ; 3 × 150 mg tablets and 1 placebo tablet twice daily on day 0, 3 × 150 mg tablets plus 1 placebo tablet once a day followed by 4 placebo tablets from day 1 to day 4, then 4 placebo tablets twice daily from day 5 to day 9; total dose 2.7 g)."[1] Upon entry into the study, patients in each treatment arm also received 2 g of ceftriaxone daily for 7 days, 500 mg of azithromycin daily for 5 days, and 150 mg of oseltamivir daily for 5 days in patients with a suspected influenza infection.

An independent DSMB was assembled to review the protocol and activities of the study. Originally, the required sample size for this trial was 220 patients per treatment arm (440 total); however, the trial was terminated early, as recommended by the DSMB, due to safety concerns resulting from an unplanned interim analysis on the first 81 patients. Because of a greater incidence in lethality in the high-dosage chloroquine group compared with the low-dosage chloroquine group, and the presence of serious cardiac events, the DSMB made the recommendation that all patients be unmasked and revert the high-dosage group to the treatment regime prescribed for the low-dosage group.

The original primary end point was lethality by day 28; however, the authors presented analyses until day 13 because of the early termination of the study. Lethality on day 13 was identified as a secondary outcome in the original methodology, in addition to clinical status, laboratory examinations, electrocardiograms, duration of mechanical ventilation, supplementary oxygen, and the time from treatment initiation to death. Clinical parameters to assess safety and efficacy were measured daily, and then at days 13 and 28 for discharged patients, whereas laboratory outcomes and electrocardiograms were performed as needed. The QIAamp Viral RNA (ribonucleic acid) Mini Kit was used to diagnose COVID-19 with viral ribonucleic extraction from either nasopharyngeal or oropharyngeal swabs. Safety outcomes, including the occurrence of adverse events during treatment, serious adverse events, and premature or temporary discontinuation of treatment were evaluated.[1]

Tang et al.

Tang et al. reported the findings of a multi-centre, open-label, RCT with 150 laboratory-confirmed COVID-19 patients admitted to 1 of 16 government-designated COVID-19 treatment centres in China. This study was conducted from February 11 to February 29, 2020. The objective of this study was to compare the efficacy and safety of hydroxychloroquine plus standard of care compared with standard of care alone in adults with COVID-19.[2]

Patients 18 years of age or older with a confirmed ongoing SARS-CoV-2 infection were eligible for inclusion in the study. Patients were not permitted to participate if they did not meet the age requirement or if they experienced other severe conditions (e.g., malignancies, hepatic impairment). Full details of inclusion and exclusion criteria are provided in Table 2. Inclusion criteria were amended on February 17, 2020 to include patients with severe COVID-19.

Hydroxychloroquine was administered to the intervention group within 24 hours of randomization at an initial dose of 1,200 mg daily for 3 days followed by 800 mg daily for 2 weeks for patients with mild-to-moderate disease and 3 weeks for patients with severe disease. Dosages were adjusted accordingly for patients experiencing adverse events. Both the patients receiving the intervention and the comparator received the standard of care, and neither patients nor investigators were blinded to the treatment assignment. Standard of care was based on clinical practice guidelines for the treatment of COVID-19 in China and included regular laboratory testing, hemodynamic monitoring, and concomitant medications.

The primary outcomes were initially identified to be both the negative conversion of SARS-CoV-2 defined by 10 days and the clinical improvement of patients with severe COVID-19 by day 28. However, the negative conversion outcome was extended to 28 days and early termination of the study resulted in the inability to assess the clinical improvement outcome. Secondary outcomes included adverse events and the probability of negative conversion at day 4, 7, 10, 14, or 21. Respiratory tract specimens were obtained from patients on screening and at the follow-up visits on days 4, 7, 10, 14, 21, and 28. While the exhaustive list of secondary outcomes can be found in Table 2, other secondary outcomes explored clinical improvement and disease progression. The criteria to assess the alleviation of clinical symptoms included the resolution of a fever below 36.7°C, normalization of oxygen saturation measured by pulse oximetry (SpO_2), and resolution of respiratory symptoms. Safety outcomes were also measured.[2]

Davoodi et al.

Davoodi et al. reported the findings of an open-label, RCT with 60 outpatients with COVID-19 infections from March 16, 2020 until April 10, 2020 at the Mostafavian Fever Clinic in Sari (Iran). The objective of this study was to compare the effectiveness of febuxostat and hydroxychloroquine for the management of patients with a COVID-19 infection.[3]

Eligible patients included those with both a CT finding compatible with COVID-19 in addition to symptoms of a current COVID-19 infection. Patients were excluded from participation in the study if they had a severe underlying condition or disease (e.g., cardiovascular or lung-related) or were on medication regimens that have contraindications with febuxostat.

Patients were randomized to either receive 80 mg of febuxostat daily for 5 days in the intervention group (n = 30) or 200 mg of hydroxychloroquine twice daily for 5 days in the comparator group (n = 30). Patients in either treatment arm were given 325 mg of acetaminophen to control fever, as needed. The primary outcome was the frequency of hospitalization, whereas secondary end points included both clinical improvements (e.g., temperature, cough) and improvement in CT findings assessed at 14 days after the initial treatment. Each of the 5 lobes of the patients' lungs were assessed and then given an overall score of 0 to 100. Higher scores implied worse lung involvement. Safety outcomes were not collected.[3]

Cavalcanti et al.

Cavalcanti et al. reported the findings of a multi-centre, randomized, open-label, controlled study involving 667 patients with suspected or confirmed COVID-19 recruited between March 29 to June 2, 2020 at 55 hospitals in Brazil. The objective of this study was "to assess whether hydroxychloroquine, either alone or in combination with azithromycin, could improve the clinical status of patients with mild-to-moderate COVID-19 at 15 days after hospital admission."[4]

Eligible patients for the study included adults 18 years or older who had been hospitalized with COVID-19 and had experienced symptoms for 2 weeks or less. Patients excluded from the study included those who required supplemental oxygen, previous use of study medications or any other medications, and had a history of cardiovascular illness.

This trial included 2 intervention groups and 1 comparator (control) group. Patients in the first intervention group were administered 400 mg of hydroxychloroquine twice daily for 7 days, whereas patients in the second intervention group were administered the same dosage and frequency of hydroxychloroquine plus 500 mg of azithromycin once daily for 7 days. Both intervention groups and the comparator were provided with the standard of care, which was at the discretion of the physicians. Use of glucocorticoids, other immunomodulators, antibiotic drugs, and antiviral drugs was permitted under the standard of care. The use of study medications administered to the treatment groups was not allowed in the control group and the use of a macrolide antibiotic was not allowed in any study group.

The primary outcome was clinical status, which was assessed at 15 days post-hospitalization and evaluated using a 7-level ordinal scale. The ordinal scores were defined as: "a score of 1 indicated not hospitalized with no limitations on activities; 2, not hospitalized but with limitations on activities; 3, hospitalized and not receiving supplemental oxygen; 4, hospitalized and receiving supplemental oxygen; 5, hospitalized and receiving oxygen supplementation administered by a high-flow nasal cannula or non-invasive ventilation; 6, hospitalized and receiving mechanical ventilation; and 7, death."[4] There were multiple secondary outcomes assessed in this study, the first of which was the clinical status at 7 days. This was evaluated using a 6-level ordinal scale defined as: "1, not hospitalized; 2, hospitalized and not using supplemental oxygen; 3, hospitalized and using supplemental oxygen; 4, hospitalized and using oxygen supplementation via high-flow nasal cannula or non-invasive ventilation; 5, hospitalized and on mechanical ventilation; 6, death."[4] Other secondary outcomes of interest included an indication for intubation within 15 days, receipt of supplemental oxygen, duration of stay, death, thromboembolic complications, acute kidney injury, and the number of days alive and free from respiratory support up to 15 days.

Skipper et al.

Skipper et al. reported the findings of a multi-centre, randomized, blinded study conducted from March 22 through May 20, 2020 in the US (40 states), and Canada (Quebec, Manitoba, and Alberta). The objective of this study was "to assess whether starting hydroxychloroquine therapy within the first few days of COVID-19 symptoms could alter the course of COVID-19 by reducing symptom severity and duration."[5]

All patients in this study were adults 18 years or older and were randomized to 1 of 3 groups. The first group included non-hospitalized patients experiencing 4 or fewer days of symptoms that either had a positive reverse transcriptase polymer chain reaction (RT-PCR) test, or high-risk exposure to an individual who tested positive with RT-PCR within the past 2 weeks. The second group of patients included health care workers who were symptomatic and had high-risk exposure to an individual with pending RT-PCR results, whereas patients in the third group were those who were both at high risk of exposure and asymptomatic. Patients excluded from the study included those who were under the age cut-off, hospitalized, or receiving contraindicated medications.

Patients enrolled into the trial were randomized to either the treatment group or the placebo group. Those in the treatment group (intervention) received 800 mg of hydroxychloroquine (four 200 mg tablets) on entry on day 1, followed by 600 mg (three 200 mg tablets) 6 to 8 hours after the loading dose, and then 600 mg once daily for 4 additional days for a total treatment duration of 5 days. Patients in the placebo group (comparator) received 400 mcg tablets of folic acid prescribed at the same frequency and duration as the intervention group. Canadian patients in the placebo group received lactose tablets in place of folic acid.

The original primary outcome for this study was a 4-level ordinal patient clinical status outcome, which was assessed at day 14. The 4 ordinal levels were: "not hospitalized, hospitalized, intensive care unit (ICU), or death."[5] There were multiple secondary outcomes assessed in this study, the first of which was the symptom severity at day 5 and day 14 measured by a 10-point visual analogue scale, where increased scores were attributed to increased symptom severity. Additional secondary outcomes included the incidence of hospitalizations, deaths, and study medication withdrawal. However, an interim analysis conducted on April 24, 2020 identified power concerns surrounding the low frequency of patients in the hospitalized and death categories. Accordingly, a DSMB approved changing the primary outcome to the change in overall symptom severity over 14 days as measured by a 10-point visual analogue scale, which was originally a secondary outcome.

Abd-Elsalam et al.

Abd-Elsalam et al. reported the findings of a multi-centre, open-label randomized study with 194 patients recruited from March to June 2020 at 3 tertiary hospitals in Egypt. The objective of this study was "to evaluate the safety and efficacy of hydroxychloroquine added to the standard of care versus the standard of care alone in patients with COVID-19."[6]

Eligible patients included those admitted to hospital with a confirmed COVID-19 diagnosis. Patients were excluded from participation in the study if they had contraindications to the study medication, or if they had cardiovascular problems. Females who were pregnant or lactating were also excluded from participation.

Patients enrolled into the trial were randomized to either the treatment group or the comparator group. Patients in the treatment group (n = 97) were administered hydroxychloroquine 400 mg twice daily on the first day, followed by 200 mg twice daily plus

standard of care for 15 days. In contrast, patients in the comparator group (n = 97) received the standard of care for 15 days. Standard of care included any of the following treatments deemed appropriate by the attending physician: paracetamol, oxygen, fluids, cephalosporins, and invasive or non-invasive mechanical ventilation. It should be noted that paracetamol is called acetaminophen in Canada.

The primary outcome of this study was the percentage of recovery within 28 days. Secondary outcomes included the need for mechanical ventilation and death by day 28, the duration to a negative PCR test, the duration to clinical improvement, and the duration to hospital discharge.

Horby et al.

Horby et al. conducted a multi-centre, randomized, open-label, controlled study involving 4,716 hospitalized patients. This study was part of the larger RECOVERY trial assessing the effect of various treatments in patients with COVID-19. The study portion that included hydroxychloroquine was conducted from March 25 to June 5, 2020 at 176 hospitals in the UK. The objective of this study was "to assess whether hydroxychloroquine was an effective treatment for patients with COVID-19. Enrolment was closed on June 5, 2020 after an interim analysis by an independent data monitoring committee determined there was a lack of efficacy of hydroxychloroquine in patients hospitalized with COVID-19."[7]

Eligible patients for enrolment into the study included those who were 18 years or older (initial inclusion criteria but revised to include all ages as of May 9, 2020), hospitalized with SARS-CoV-2 infection, and no medical history that might put the patient at risk. Patients were excluded if they were under 18 years old (initial exclusion criteria but revised to include all ages as of May 9, 2020) or if they had cardiovascular risks.

This trial included 1 intervention group and 1 comparator (usual care) group. Patients in the intervention group were administered 800 mg of hydroxychloroquine (200 mg tablets) at baseline and again at 6 hours. This was followed by 400 mg 12 hours after the initial dose, and 400 mg every 12 hours for the following 9 days or until discharge, whichever occurred first. Patients in the comparator groups were provided with the usual standard of care, which was not described in the publication.

The primary outcome of this study was all-cause mortality within 28 days after randomization, whereas secondary outcomes included the time until discharge, initiation of invasive mechanical ventilation, death, cause-specific mortality, and major cardiac arrhythmia.[7]

Lyngbakken et al.

Lyngbakken et al. reported the findings of an open-label randomized study with 53 patients recruited from March through to May 2020 at Akershus University Hospital in Norway. The objective of this study was "to evaluate the safety of hydroxychloroquine on SARS-CoV-2 oropharyngeal viral kinetics in patients hospitalized with moderately severe COVID-19."[8]

Eligible patients included those 18 years or older, SARS-CoV-2 positive, and with a National Early Warning Score 2 (NEWS2) score of 6 or less.[24] Patients were excluded if they were admitted to an ICU on hospital admission; had a history of psoriasis, hearing, or visual impairment; had contraindications to the study medications; or had pregnancy or cardiovascular risks.

Patients enrolled into the trial were randomized to either the treatment group or the standard of care group. Patients in the treatment group (n = 27) were administered 400 mg

of hydroxychloroquine twice daily for 7 days plus standard of care, whereas patients in the comparator group (n = 26) received the standard of care for the same duration. Standard of care included treatment in accordance with local and national guidelines.

The primary outcome of this study was the rate of decline in SARS-CoV-2 viral load at 96 hours after randomization. There were multiple secondary outcomes assessed in this study. The first of these was the clinical status measured on a 7-point ordinal scale at 14 days after randomization. The ordinal scores were defined as: "1, dead; 2, hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO]; 3, hospitalized, on non-invasive ventilation or high-flow oxygen devices; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, not requiring supplemental oxygen; 6, not hospitalized, but unable to resume normal activities; 7, not hospitalized, with resumption of normal activities."[8] Other secondary outcomes included in-hospital mortality, mortality at 30 days, duration of hospital admission after randomization, and the change in degree of illness at 96 hours.

Mitjà et al.

Mitjà et al. reported the findings of a multi-centre, open-label, randomized study involving 293 non-hospitalized patients enrolled between March 17 and May 26, 2020, at 3 health administrative regions in Catalonia, Spain. The objective of this study was "to assess whether treatment with hydroxychloroquine would be more efficacious than absence of this treatment for outpatients with mild COVID-19."[9]

Eligible patients included non-hospitalized individuals who were 18 years or older experiencing mild symptoms of COVID-19 for less than 5 days prior to enrolment and had a positive SARS-CoV-2 test at baseline. Exclusion criteria for this study were patients under 18 years old; moderate or severe COVID-19 symptoms; pre-existing medical conditions; contraindications to study medications; presence of retinal, liver, or renal disease; cardiovascular risks; concomitant treatment with active treatment with contraindicated medications; or known HIV infection.

This trial included 1 intervention group and 1 comparator (usual care) group. Patients in the intervention group were administered 800 mg of hydroxychloroquine prescribed on day 1, followed by 400 mg once daily for 6 days. Patients in the comparator groups were provided with usual care for the same duration, which was not directly specified in the publication. The initial protocol included the use of cobicistat-boosted darunavir with hydroxychloroquine; however, the protocol was adapted to remove cobicistat-boosted darunavir due insufficient efficacy data in support of darunavir to treat COVID-19.

The primary outcome was the reduction of viral RNA load at days 3 and 7, whereas secondary outcomes included clinical progression, time from randomization to complete resolution of symptoms, and safety outcomes.

WHO Solidarity Trial Consortium

The WHO Solidarity Trial Consortium reported the interim findings of a multi-centre, randomized, open-label, controlled study involving 11,330 patients enrolled in 405 hospitals in 30 countries. The objective of this study was "to evaluate the effectiveness of 4 drugs, including, remdesivir, hydroxychloroquine, lopinavir, and interferon on in-hospital mortality of patients with COVID-19."[10] While there were 4 treatment groups, only the results of the hydroxychloroquine group and associated controls are pertinent to this report. Recruitment

began in March 2020 and was terminated for hydroxychloroquine on June 19, 2020 due to futility.[10]

Eligible patients for enrolment into the study included hospitalized patients who were 18 years or older with a diagnosis of COVID-19 and who had not received or were not contraindicated for study medications. Eligible patients were also required to be at the hospital for 3 days.

Patients were excluded based on drug contraindications or if there was no or uncertain consent.

This trial included 4 intervention groups and a non-mutually exclusive comparator (standard of care) group for each intervention group. Patients in the 4 intervention groups were assigned either remdesivir, hydroxychloroquine, lopinavir, or interferon. Patients in the hydroxychloroquine group (n = 954) were administered 800 mg of hydroxychloroquine (200 mg tablets) at hour 0, 800 mg at hour 6, and, starting at hour 12, 400 mg twice daily for 10 days. Patients in the comparator groups (n = 4,088) were provided with the standard of care that was defined in their local hospital for the same duration.

The primary outcome was in-hospital mortality before or after day 28, whereas secondary outcomes included initiation of mechanical ventilation and hospitalization duration.

Ulrich et al.

Ulrich et al. reported the findings of a double-blind, multi-centre, randomized, controlled study involving 128 patients that was conducted between April 17 and May 12, 2020 at various hospitals in the New York City metropolitan area. The objective of this study was "to evaluate the efficacy and safety of hydroxychloroquine in hospitalized patients with confirmed COVID-19."[11]

Eligible patients for enrolment in the study included those who had a positive RT-PCR test, at least 1 COVID-19 symptom, and informed consent. Patients were excluded if they met the primary end point at enrolment, had received study medication, were unable to consume or allergic to study the medications, or had cardiac risks or retinal disease.

This trial included 1 intervention group and 1 comparator (placebo) group. Patients in the intervention group were administered hydroxychloroquine 400 mg (200 mg tablets) twice daily on day 1 followed by 200 mg twice daily for days 2 through 5. Patients in the comparator groups were provided with placebo calcium citrate 200 mg tablets prescribed at a regimen identical to the administration of hydroxychloroquine in the intervention group.

The primary outcome was the proportion of patients meeting a severe COVID-19 progression composite end point at day 14, whereas the primary safety outcome was the cumulative incidence of adverse events, serious adverse events, and discontinuation of therapy. There were multiple secondary outcomes assessed in this study, the first of which was the change in an 8-point ordinal COVID-19 clinical severity score. The ordinal scores were defined as follows: 1, death; 2, ventilator; 3, hospitalized, on non-invasive ventilation or high-flow nasal cannula; 4, hospitalized, on supplemental oxygen; 5, hospitalized, not on oxygen, ongoing medical care; 6, hospitalized, not on oxygen, not requiring ongoing care; 7, outpatient, limitation on activities or home O_2; 8, outpatient, no limitation on activities. Other secondary outcomes included "mortality at day 30, hospital stay duration, fever- and oxygen-free days, viral clearance, and clinically improvement from baseline to follow-up on laboratory values and inflammatory markers."

Khamis et al.

Khamis et al. reported the findings of a randomized, open-label, controlled study involving 89 patients recruited from June 22 to August 13, 2020 at the Royal Hospital in Muscat, Oman. The objective of this study was "to evaluate the therapeutic effectiveness of favipiravir combined with inhaled interferon beta-1b, versus hydroxychloroquine, in adult patients hospitalized with moderate to severe COVID-19 pneumonia."[12]

Eligible patients for enrolment into the study included those 18 years or older with a confirmed SARS-CoV-2 infection and moderate-to-severe COVID-19 pneumonia. Eligible patients of child-bearing age (male or female) had to agree to take effective contraceptive measures during the study period. Post-menopause females needed to show evidence of post-menopause, and pre-menopausal women needed to demonstrate a negative pre-treatment serum. Co-enrolment in any other clinical drug study was prohibited. Patients were excluded if they were older than 75 years of age; had a gastrointestinal, liver, or renal disorder; were unable to consume or allergic to the trial medication; or were pregnant or lactating.

This trial included 1 intervention group and 1 comparator group. Patients in the intervention group were administered 1,600 mg of favipiravir on day 1 followed by 600 mg twice a day for up to 10 days. In addition to favipiravir, interferon beta-1b was prescribed at a dose of 8 million IU (0.25 mcg) twice a day for 5 days. Patients in the comparator group were prescribed 400 mg of hydroxychloroquine twice daily on day 1 followed by 200 mg twice daily for 7 days.

The primary outcomes were the time from assignment to clinical recovery, and the normalization of inflammatory markers and improvement in oxygen saturation. Secondary outcomes included deterioration/aggravation of pneumonia defined as defined as "SpO_2 of 93% or PaO_2/FiO_2 of 300 mm Hg or RR of 30/min without oxygen inhalation and requiring oxygen therapy or more advanced breath support,"[12] ICU admission rate, and mortality within 14 days of assignment.

Self et al.

Self et al. conducted a blinded, multi-centre, randomized, controlled trial involving 479 patients recruited from April 2 to June 19, 2020, at 34 hospitals in the US. The objective was "to determine whether hydroxychloroquine was an efficacious treatment for adults hospitalized with COVID-19."[13]

Eligible patients included hospitalized, or soon to be hospitalized, individuals 18 years of age or older with symptoms and confirmed SARS-CoV-2 infection. Patients were excluded if they were incarcerated, were pregnant or breastfeeding, epileptic, had cardiovascular risks, had an allergy to the study medications, or had previous enrolment in this trial.

This trial included 1 intervention group and 1 comparator (placebo) group. Patients in the intervention group were administered 400 mg of hydroxychloroquine twice a day for the first 2 doses and then 200 mg twice a day for the subsequent 8 doses, for a total of 10 doses over 5 days. Patients assigned to the placebo group received matching placebo at the same dosing frequency.

The primary outcome was the clinical status 14 days after randomization assessed with a 7-category ordinal scale (the COVID Outcomes Scale) recommended by the World Health Organization. The scale consisted of 7 mutually exclusive categories: "1, death;

2, hospitalized, receiving extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation; 3, hospitalized, receiving non-invasive mechanical ventilation or nasal high-flow oxygen therapy; 4, hospitalized, receiving supplemental oxygen without positive pressure or high flow; 5, hospitalized, not receiving supplemental oxygen; 6, not hospitalized and unable to perform normal activities; and 7, not hospitalized and able to perform normal activities."[13] Secondary outcomes included: time to recovery, all-cause mortality survival through day 28, hospital discharge, clinical status assessed with the 8-category COVID Ordinal Scale for Clinical Improvement, oxygen-free days, ventilator-free days, vasopressor-free days, ICU-free days, and hospital-free days.

Brown et al.

Brown et al. conducted a randomized, open-label, multi-centre, controlled study involving 85 patients recruited between April 3 and June 19, 2020, at 13 hospitals in Utah, US. The objective of this study was "to assess the relative efficacy of hydroxychloroquine compared with azithromycin among hospitalized patients with COVID-19."[14]

Patients were eligible for the study if they were hospitalized, symptomatic, and had laboratory-confirmed COVID-19. Patients were also required to be enrolled within 10 days of a positive COVID-19 test. Patients were excluded for ethical and safety reasons.

This trial included 1 intervention group and 1 comparator group. Patients in the intervention group were administered 400 mg of hydroxychloroquine twice on day 1 followed by 200 mg twice daily for the following 4 days. Patients in the comparator group were prescribed 500 mg of azithromycin on day 1 followed by 250 mg of azithromycin daily for the following 4 days.

The primary outcome was the day 14 assessment on the COVID Ordinal Scale for Clinical Improvement. Outcomes of this scale were 1 = no limitation of activities, 2 = limitation of activities, 3 = no oxygen therapy, 4 = oxygen by mask or nasal cannula, 5 = non-invasive ventilation or high-flow oxygen, 6 = invasive mechanical ventilation without other organ support, 7 = invasive mechanical ventilation with other organ support, and 8 = death. Secondary outcomes included hospital-free days by 28 days of follow-up, ventilator-free days by 28 days of follow-up, ICU-free days by 28 days of follow-up, and safety outcomes assessed daily through day 5.

Study Design Characteristics of Prevention Trial

Boulware et al.

Boulware et al. reported the findings of a randomized, double-blind, placebo-controlled trial with 821 patients across the US and parts of Canada testing hydroxychloroquine as post-exposure prophylaxis. The objective of this study was to assess whether hydroxychloroquine could prevent symptomatic infection after SARS-CoV-2 exposure.[15]

Eligible participants were enrolled through an internet-based survey nationwide in the US and in Canada in the provinces of Quebec, Manitoba, and Alberta, and included adults with a household or occupational exposure to someone with confirmed COVID-19. Exposure was categorized as either "high-risk exposure," for individuals who had "household or occupational exposure to someone with confirmed COVID-19 at a distance of less than 6 feet for more than 10 minutes while wearing neither a face mask nor an eye shield," or "moderate-risk exposure" for "wearing a face mask but no eye shield." Individuals who were

hospitalized, under the age requirements, tested positive for COVID-19, or exhibited symptoms of COVID-19 at enrolment were excluded from the study.

Within 4 days after household or occupational exposure to an individual with confirmed COVID-19, the investigators randomly assigned participants to receive either placebo or hydroxychloroquine. The treatment regimen for the hydroxychloroquine group was 800 mg of hydroxychloroquine at entry into the study, followed by 600 mg of hydroxychloroquine 6 to 8 hours after the initial dosage, followed by 600 mg daily for an additional 4 days. While initial sample size estimations required 750 people per treatment group, the trial was halted at the third interim analysis on May 6, 2020, on the basis of a conditional power of less than 1%, and was deemed futile to continue.

The primary outcome was incidence of either laboratory-confirmed COVID-19 or illness compatible with COVID-19 within 14 days. Secondary outcomes included the incidence of confirmed SARS-CoV-2 infection, the incidence of COVID-19 symptoms, the incidence of COVID-19–related hospitalization, and symptom severity measured at days 5 and 14. Safety outcomes were also reported.[15]

Abella et al.

Abella et al. reported the findings of a randomized, double-blind, placebo-controlled trial with 132 patients in 2 tertiary urban hospitals that were part of a single health system in Philadelphia, Pennsylvania. The objective of this study was "to evaluate the efficacy of hydroxychloroquine to prevent transmission of SARS-CoV-2 in hospital-based health care workers with exposure to patients with COVID-19 using a pre-exposure prophylaxis strategy."[16]

Eligible participants included health care workers who were working at either study hospital who had no history or symptoms of SARS-CoV-2 infection prior to enrolment. Participants were excluded if they had previously tested positive for SARS-CoV-2, were allergic to the study medications, or had retinal or cardiac disease.

Patients enrolled into the trial were randomized to either the treatment group or the placebo group. Those in the treatment group received 600 mg of hydroxychloroquine (200 mg tablets) daily for 8 weeks. Patients in the placebo group received a size-matched placebo prescribed at the same frequency and duration as the intervention group.

The primary outcome of this study was the rate of conversion to SARS-CoV-2–positive status. Secondary outcomes included the rates of adverse events related to serologic antibody positivity. Other secondary outcomes included electrocardiogram changes and clinical outcomes for participants who tested positive for SARS-CoV-2 or developed COVID-19 symptoms.

An interim analysis was conducted once 100 of the targeted total of 200 patients had completed the 8-week study period. The interim analysis identified a z score of −0.42, which was lower than the threshold (−0.27) to declare futility; therefore, it was determined futile to continue recruiting patients.

Rajasingham et al.

Rajasingham et al. reported the findings of a randomized, double-blind, placebo-controlled trial with 1,483 patients recruited online in the US and Manitoba, Canada. The objective of this study was "to determine the effectiveness of hydroxychloroquine as pre-exposure

prophylaxis in health care workers at high risk of SARS-CoV-2 exposure in a randomized, placebo-controlled clinical trial setting."[17]

Eligible participants included health care workers 18 years or older with ongoing exposure to individuals with COVID-19. Participants were excluded if they reported active or prior COVID-19 (either confirmed or symptom-compatible illness), or if they had contraindications to the study medication.

Patients enrolled into the trial were randomized in a 2:2:1:1 ratio to receive either 1 of the 2 hydroxychloroquine dosages or matching placebo. Participants in both treatment groups were given an initial dose of 400 mg of hydroxychloroquine (200 mg tablets) twice on day 1. Following the initial dose, participants in the first treatment group were administered 400 mg of hydroxychloroquine once weekly for 12 weeks, whereas participants in the second treatment group were administered 400 mg twice weekly for the same duration. Patients in the 2 placebo groups received a placebo (folic acid) prescribed at the same frequency and duration as the study drug in each of the intervention groups.

The primary outcome of this study was COVID-19–free survival time. Secondary outcomes included the incidence of confirmed SARS-CoV-2 detection and the incidence of possible COVID-19, hospitalization, death, and adverse events.

An independent DSMB reviewed the data after 25% of participants had completed 4 weeks of follow-up. Authors noted that "before the first interim analysis on May 21, 2020, it became apparent that we would not meet our initial enrolment goal of 3,150 participants."[17] Accordingly, the principal investigator proposed to the DSMB that enrolment be stopped at the first interim analysis due to an inability to recruit participants.

Evidence Results for the Treatment Trials

Patient Disposition

The patient disposition tables for all trials are provided in Appendix 1.

CloroCovid-19

Of the 131 patients who were screened, 50 patients were excluded because of ineligibility (48 patients) or refusal to participate (2 patients). Reasons for ineligibility were not reported. A total of 40 patients and 41 patients were randomized to the low-dosage chloroquine group and the high-dosage chloroquine group, respectively.[1]

Tang et al.

Of the 191 patients who were screened, 41 patients did not meet the eligibility criteria. The reasons for ineligibility were not reported. A total of 150 patients were randomized, with 75 patients allocated to each of the 2 groups. One patient in the standard of care group received hydroxychloroquine in error, while 6 patients in the hydroxychloroquine group did not receive treatment because of withdrawal of consent (3 patients) or refusal of treatment (3 patients).[2]

Davoodi et al.

The number of patients screened for inclusion in the Davoodi et al. trial were not reported. A total of 60 patients were randomized, with 30 patients allocated to each of the 2 groups. One patient withdrew from the febuxostat group for failure to take the laboratory tests and 5 patients withdrew from the hydroxychloroquine group (3 patients did not take the

laboratory tests, 1 patient changed physicians, and 1 patient withdrew because of other reasons). The population analyzed included 29 patients and 25 patients in the febuxostat and hydroxychloroquine groups, respectively.[3]

Cavalcanti et al.

Of the 760 patients who were screened, 57 were excluded because they did not meet the inclusion criteria (n = 34) or met the exclusion criteria (n = 23). Reasons for not meeting the inclusion criteria included not having suspected or confirmed COVID-19 (n = 19), having symptoms for more than 14 days (n = 11), and being in the hospital for more than 48 hours (n = 9). Patients meeting the exclusion criteria: were using oxygen supplementation greater than 4 litres per minute (n = 12), needed invasive ventilation (n = 12) or non-invasive ventilation (n = 2), had chronic renal failure (n = 8), were under 18 years old (n = 2), were pregnant (n = 2), had a history of chronic liver disease or pancreatitis (n = 2), or were excluded for other reasons that were not disclosed (n = 4). An additional 36 patients were eligible but not randomized, since 35 did not consent and 1 was duplicated.[4]

Skipper et al.

The 6,924 patients who were screened for eligibility were first stratified into 2 groups. The first group included 2,237 patients who were symptomatic or tested positive, and the second group included 4,687 patients who were asymptomatic. Of the 2,237 who were symptomatic or tested positive, 180 did not complete the enrolment survey and 1,665 did not meet the eligibility criteria. Of the resulting 392 patients who were symptomatic or tested positive who were randomly assigned, 1 patient was administratively withdrawn since they were already concurrently enrolled in the post-exposure prophylaxis trial. This yielded 391 patients in the symptomatic or tested-positive group who were randomly assigned and included in the analysis.[5]

Among the 4,687 asymptomatic patients, 3,528 did not meet eligibility criteria and 238 did not complete the enrolment survey. Of the 921 remaining asymptomatic patients, 821 were still asymptomatic at day 1 and excluded from the treatment study. This yielded 100 patients initially asymptomatic but symptomatic by day 1 who were randomly assigned and included in the analysis.

The 391 patients from the symptomatic or tested-positive group were aggregated with the 100 patients from the initially asymptomatic but asymptomatic by day 1 group, for a combined total of 491 patients to be randomly assigned. Of the 491 patients, 244 were assigned to the hydroxychloroquine group and 247 were assigned to the placebo group. Of the 244 patients assigned to the hydroxychloroquine group, 13 were lost to follow-up and 19 had missing vital status data, which resulted in 212 patients who contributed to the primary end point. Of the 247 patients assigned to the placebo group, 13 were also lost to follow-up and 23 had missing vital status data, which resulted in 211 patients who contributed to the primary end point.

Abd-Elsalam et al.

The number of patients screened for inclusion in the Abd-Elsalam et al. trial was not reported. A total of 194 patients were randomized, with 97 patients allocated to each of the 2 groups. There is no information on whether any patients withdrew from the trial. The population analyzed included the 97 patients in both the hydroxychloroquine group and standard of care group.[6]

Horby et al.

Of the 11,197 patients screened for participation in the RECOVERY trial, 639 did not have access to hydroxychloroquine at their hospital and 3,199 patients were considered unsuitable for receiving hydroxychloroquine. A total of 7,513 patients underwent randomization to receive hydroxychloroquine or other treatments. Of the 7,513 patients who underwent randomization for the RECOVERY trial, 2,797 were assigned to another active treatment: 1,010 were assigned to lopinavir plus ritonavir, 1,170 were assigned to dexamethasone, and 617 were assigned to azithromycin. A total of 4,716 patients underwent randomization to receive either hydroxychloroquine (n = 1,561) or usual care (n = 3,155). Three patients withdrew from the hydroxychloroquine group and 5 patients withdrew from the usual care group. The 1,561 patients randomized to the hydroxychloroquine group and the 3,155 patients assigned to the usual care group were included in the 2-day intention-to-treat (ITT) analysis.[7]

Lyngbakken et al.

The number of patients screened for inclusion in the Lyngbakken et al. trial was not reported. A total of 53 patients were randomized, with 27 patients assigned to the hydroxychloroquine plus standard of care group, and 26 patients assigned to the standard of care group. All patients assigned to either the treatment or comparator received the allocated intervention. Only 1 patient was lost to follow-up and this patient was assigned to the standard of care group. Only 1 patient was excluded from the analyses due to missing data at baseline, and this patent was assigned to the hydroxychloroquine plus standard of care group. A total of 26 patients were analyzed in the hydroxychloroquine plus standard of care group, and 25 patients were analyzed in the standard of care group.[8]

Mitjà et al.

Of the 760 confirmed cases of COVID-19 that were assessed for eligibility, 400 were not considered for inclusion at the initial phone assessment. Of the 400 patients who were excluded, 29 were more than 5 days since the onset of symptoms, 76 were severely ill or required hospital admission, 5 had a predefined exclusion disease, 14 died before enrolment, 24 had contraindicated concomitant medication, 7 were pregnant or breastfeeding, 133 had dementia or mental illness and were not able to consent, 84 did not consent, and 28 had had previous treatment with hydroxychloroquine. A total of 353 patients were enrolled and randomized. Of the 169 patients assigned to the intervention group, 1 did not have any follow-up polymerase chain reaction (PCR) testing, and 32 had a negative RT-PCR test at baseline. This resulted in 136 patients who were eligible for the ITT sample. Among these patients, 14 were excluded during the follow-up (4 had more than 5 days since the start of symptoms, 1 was severely ill, 3 had a contraindicated concomitant medication, 3 were lost to follow-up, and 3 had treatment compliance under 80%). This resulted in 122 patients with complete follow-up in the per-protocol sample for the intervention group. In contrast, of the 184 patients assigned to the control arm, 2 withdrew consent and 25 had a negative RT-PCR test at baseline. This resulted in 157 patients who were eligible for the ITT sample. Among these patients, 9 were excluded during the follow-up (4 were more than 5 days since the start of symptoms and 5 were lost to follow-up). This resulted in 148 patients with complete follow-up in the per-protocol sample for the intervention group.[9]

WHO Solidarity Trial Consortium

Of the 11,330 patients who underwent randomization, 1,863 were directed toward the hydroxychloroquine and control group. These patients were further randomized to either receive hydroxychloroquine (n = 954) or to the control group (n = 909). Among those assigned to the hydroxychloroquine group, 7 had no or unknown consent to follow-up. This resulted in 947 patients being included in the ITT analysis. Among these patients, 932 died or left the hospital, 12 entered the trial on or before June 19 and were still inpatients in late September, and 3 entered the trial on or before June 19 and were not reported in late September.[10]

In comparison, only 3 patients assigned to the control group had no or unknown consent to follow-up, which resulted in 906 patients included in the ITT analysis. Among these patients, 891 died or left the hospital, 13 entered the trial on or before June 19 and were still an inpatient in late September, and 2 entered the trial on or before June 19 and were not reported in late September.

Ulrich et al.

Of the 764 patients who were screened for eligibility, 633 were excluded. This left 131 patients who were enrolled. Removing the 3 patients who were excluded pre-randomization, 128 patients were randomized in the ITT analysis, with 67 in the hydroxychloroquine group and 61 in the placebo group. Among those in the hydroxychloroquine group, 7 were lost to follow-up on day 14 and 14 were lost to follow-up on day 30. In contrast, 4 were lost to follow-up on day 14 and 11 were lost to follow-up on day 30 in the placebo group. The safety and per-protocol analysis population consisted of 63 and 50 patients in the hydroxychloroquine group, respectively, and 59 and 50 patients in the placebo group, respectively.[11]

Khamis et al.

Khamis et al. did not report the number of patients screened, excluded, or lost to follow-up. The only details provided are that 89 patients were randomized, with 44 assigned to the favipiravir group and 45 assigned to the hydroxychloroquine group.[12]

Self et al.

Of the 1,889 patients who were screened for eligibility, 11 were excluded. This left 1,878 patients who were screened with complete screening data. Of these 1,878 patients, a further 837 met the exclusion criteria. Reasons for exclusion from the study included symptoms of an acute respiratory infection for greater than 10 days (n = 291), more than 48 hours since randomization (n = 210), a QTc interval greater than 500 milliseconds (n = 117), and other or non-categorized reasons (n = 288). Among the 1,041 who were eligible, 562 patients were eligible but not randomized because they refused to participate (n = 337) due to a language barrier (n = 47), because they were enrolled in another clinical trial (n = 46), because a legally authorized representative or research staff was unavailable (n = 45), or for other reasons (n = 88). This left 479 patients who were randomized, with 242 randomized to the hydroxychloroquine group and 237 randomized to the placebo group. All of the 242 patients randomized to the hydroxychloroquine group and 237 patients randomized to the placebo group were included in the primary analysis.[13]

Brown et al.

Of the 829 patients who were screened for eligibility, 195 were excluded because they did not meet the inclusion criteria and 423 were excluded for meeting at least 1 of the exclusion criteria. Common exclusion criteria included those who had recovered or were being discharged (n = 122), had a prolonged QTc interval at baseline (n = 55), or were on dialysis (N = 53). Consequently, 211 patients were approached to participate in the study; however, 126 patients declined to participate. This left 85 patients who were randomized to either the hydroxychloroquine group (n = 42) or the azithromycin group (n = 43).[14]

Baseline Characteristics

CloroCovid-19

The baseline demographic and clinical characteristics of the patients included in the CloroCovid-19 trial are presented in Appendix 2. The mean age in the low-dosage group was 47.4 years (standard deviation [SD] = 13.3), whereas the mean age in the high-dosage group was 54.7 years (SD = 13.7). Comorbidities included hypertension, diabetes, cardiac disease, and asthma among 37%, 18.5%, 0%, and 3.8% of the low-dosage group, respectively, whereas these comorbidities were present among 53.6%, 32.1%, 17.9%, and 10.7% of the high-dosage group, respectively. In addition, all patients received ceftriaxone and azithromycin, and 86.6% and 92.5% of patients in the low- and high-dosage groups received oseltamivir, respectively.[1]

Tang et al.

The baseline demographic and clinical characteristics of patients included in Tang et al. are presented in Appendix 2. The mean age in the hydroxychloroquine group was 48.0 years (SD = 14.1), whereas the mean age in the standard of care group was 44.1 years (SD = 15.0). Of the comorbidities reported, diabetes and hypertension were the most common. Specifically, 16% and 12% of the hydroxychloroquine and standard of care groups had diabetes, respectively, and 8% and 4% of the hydroxychloroquine and standard of care groups had hypertension, respectively. A total of 63% of patients in the hydroxychloroquine group and 57.3% in the standard of care group were on other drug treatments prior to randomization. Regarding disease severity, the proportion of mild, moderate, and severe cases were relatively balanced between the hydroxychloroquine group and the standard of care group, with 20%, 79%, and 1% in the hydroxychloroquine group, respectively, and 9%, 89%, and 1% in the standard of care group, respectively.[2]

Davoodi et al.

The baseline demographic and clinical characteristics of patients included in the Davoodi et al. study are presented in Appendix 2. The mean age in the febuxostat group was 58 years (standard error [SE] = 1.47), whereas the mean age in the hydroxychloroquine group was 57.3 years (SE = 2.2). Diabetes and lung disease were the only reported comorbidities. Specifically, 27.6% and 28% of patients in the febuxostat and hydroxychloroquine groups had diabetes, respectively, whereas 0% and 4% of patients in the febuxostat and hydroxychloroquine groups had hypertension, respectively.[3]

Cavalcanti et al.

The baseline demographic and clinical characteristics of the patients included in Cavalcanti et al. are presented in Appendix 2. The mean age in the hydroxychloroquine plus azithromycin group was 49.6 years (SD = 14.2), whereas the mean age in the

hydroxychloroquine-only group was 51.3 years (SD = 14.5), and 49.9 years (SD = 15.1) in the control group. Males comprised 56.7%, 64.3%, and 54.2% of the participants in the hydroxychloroquine plus azithromycin group, hydroxychloroquine-alone group, and control group, respectively. The most common comorbidities included hypertension, diabetes, current or former smoker, and obesity, which were present among 37.3%, 18.4%, 7.8%, and 13.4% of patients in the hydroxychloroquine plus azithromycin group, respectively; 42.5%, 21.3%, 5.4%, and 16.7% of patients in the hydroxychloroquine-alone group, respectively; and 36.6%, 17.6%, 6.6%, and 16.3% of patients in the control group, respectively.[4]

Skipper et al.

The baseline demographic and clinical characteristics of patients included in the Skipper et al. study are presented in Appendix 2. The median age in the hydroxychloroquine group was 41 years (interquartile range [IQR], 33 to 49), whereas the median age in the placebo group was 39 years (IQR, 31 to 50). Females comprised 58.0% of the hydroxychloroquine group and 54.5% of the placebo group. The majority of patients in the hydroxychloroquine group (66.0%) and the placebo group (69.7%) reported no comorbidities. Hypertension, asthma, and diabetes were the only comorbidities recorded, with 10.8%, 13.2%, and 3.8% in the hydroxychloroquine group, respectively, and 10.9%, 9.5%, and 3.3% in the placebo group, respectively.[5]

Abd-Elsalam et al.

The baseline demographic and clinical characteristics of the patients included in Abd-Elsalam et al. are presented in Appendix 2. The mean age in the hydroxychloroquine plus standard of care group was 40.35 years (SD = 18.65), whereas the mean age in the standard of care group was 41.09 years (SD = 20.07). Males comprised 57.7% of the participants in the hydroxychloroquine plus standard of care group, and 59.8% of the standard of care group. While detailed comorbidities were not specified, comorbidities were present among 15.5% of the hydroxychloroquine group and 12.4% of the standard of care group.[6]

Horby et al.

The baseline demographic and clinical characteristics of patients included in the Horby et al. study are presented in Appendix 2. The mean age in the hydroxychloroquine group was 65.2 years (SD = 15.2), whereas the mean age in the usual care group was 65.4 years (SD = 15.4). Males comprised 61.5% of the hydroxychloroquine group and 62.6% of the usual care group. The majority of patients in the hydroxychloroquine group (56.5%) and the usual care group (57.3%) reported at least 1 comorbidity. Diabetes, heart disease, and chronic lung disease were the most common comorbidities recorded, with 27.4%, 27.0%, and 21.4% in the hydroxychloroquine group, respectively, and 27.1%, 25.0%, and 22.6% in the usual care group, respectively.[7]

Lyngbakken et al.

The baseline demographic and clinical characteristics of patients included in Lyngbakken et al. are presented in Appendix 2. The median age in the hydroxychloroquine plus standard of care group was 56 years (IQR, 41 to 72), whereas the median age in the standard of care group was 69 years (IQR, 51 to 74). Males comprised 70.4% of the participants in the hydroxychloroquine plus standard of care group, and 61.5% of the standard of care group. The most common comorbidities included hypertension, obesity,

and obstructive pulmonary disease, which were present among 22.2%, 19.2%, and 18.5% of the hydroxychloroquine plus standard of care group, respectively, and 42.3%, 42.3%, and 34.6 % of the standard of care group, respectively.[8]

Mitjà et al.

The baseline demographic and clinical characteristics of patients included in the Mitjà et al. study are presented in Appendix 2. The mean age in the hydroxychloroquine group was 41.6 years (SD = 12.4), whereas the mean age in the standard of care group was 41.7 years (SD = 12.6). Females comprised 65.6% of the hydroxychloroquine group and 72.1% of the standard of care group. The majority of patients in the hydroxychloroquine group (52.2%) and the standard of care group (54.1%) reported at least 1 comorbidity. Nervous system disease, cardiovascular disease, and metabolic disease were the most common comorbidities recorded with 14.0%, 14.7%, and 6.6% of patients in the hydroxychloroquine group, respectively, and 13.4%, 9.6%, and 9.0% of patients in the standard of care group, respectively.[9]

WHO Solidarity Trial Consortium et al.

The baseline demographic and clinical characteristics of patients included in the WHO Solidarity Trial Consortium study are presented in Appendix 2. There were 335 patients younger than 50 years old in the hydroxychloroquine group and 317 patients in that same age stratification in the control group. There were 410 patients aged 50 to 69 years in the hydroxychloroquine group, and 396 patients in the same age stratification in the control group. Lastly, there were 202 patients in the 70 years of age stratification in the hydroxychloroquine group, and 193 patients in the same age stratification in the control group. There were 574 males in the hydroxychloroquine group and 535 males in the control group.[10]

Diabetes, heart disease, and chronic lung disease were the most commonly reported baseline comorbid conditions. Diabetes was reported among 199 of the patients in the hydroxychloroquine group and 205 of the patients in the control group. Heart disease was reported among 193 of the patients in the hydroxychloroquine group and 194 of the patients in the control group. Chronic lung disease was reported among 62 of the patients in the hydroxychloroquine group and 66 of the patients in the control group.

Ulrich et al.

The baseline demographic and clinical characteristics of patients included in the Ulrich et al. study are presented in Appendix 2. The mean age in the hydroxychloroquine group was 66.5 years (SD = 16.4), whereas the mean age in the placebo group was 65.8 years (SD = 16.0). Males comprised 67.2% of the hydroxychloroquine group and 50.8% of the placebo group. Hypertension, diabetes, and cardiovascular disease (other than hypertension) were the most common comorbidities recorded with 53.7%, 28.4%, and 31.3% of patients in the hydroxychloroquine group, respectively, and 62.3%, 36.1%, and 21.3% of patients in the placebo group, respectively.[11]

Khamis et al.

The baseline demographic and clinical characteristics of patients included in the Khamis et al. study are presented in Appendix 2. The mean age in the favipiravir group was 54 years (SD = 15), whereas the mean age in the hydroxychloroquine group was 56 years (SD = 16). Males comprised 64% of the favipiravir group and 53% of the hydroxychloroquine group. Diabetes, hypertension, and heart disease were the most common comorbidities recorded with 39%, 55%, and 16% of patients in the favipiravir group, respectively, and 51%, 53%, and 13% of patients in the hydroxychloroquine group, respectively.[12]

Self et al.

The baseline demographic and clinical characteristics of patients included in the Ulrich et al. study are presented in Appendix 2. The median age in the hydroxychloroquine group was 58 years (IQR, 45 to 69), whereas the median age in the placebo group was 57 years (IQR, 43 to 68). Females comprised 44.2% of the hydroxychloroquine group and 44.3% of the placebo group. Hypertension, diabetes, and chronic kidney disease were the most common comorbidities recorded with 56.2%, 36.4%, and 11.6% of patients in the hydroxychloroquine group, respectively, and 49.4%, 32.9%, and 5.9% of patients in the placebo group, respectively.[13]

Brown et al.

The baseline demographic and clinical characteristics of patients included in the Brown et al. study are presented in Appendix 2. The median age in the hydroxychloroquine group was 51 years (IQR, 42 to 60), whereas the median age in the azithromycin group was 58 years (IQR, 43 to 68). Females comprised 44% of the hydroxychloroquine group and 33% of the azithromycin group. Approximately half of patients had comorbidities.[14]

Diabetes, chronic pulmonary disease, and mild liver disease were the most common comorbidities recorded with 21%, 21%, and 11% of patients in the hydroxychloroquine group, respectively, and 30%, 26%, and 19% of patients in the azithromycin group, respectively.

Efficacy

CloroCovid-19

The clinical efficacy results for Borba et al. are reported in Table 8.[1]

Lethality by Day 13

- A total of 6 patients (15.0%) in the low-dosage chloroquine group died compared with 16 patients (39.0%) in the high-dosage chloroquine group (odds ratio = 3.6; 95% confidence interval [CI], 1.2 to 10.6).

Viral RNA

- Viral RNA was detected in 5 (83.3%) and 14 (87.5%) deceased patients in the low-dosage and high-dosage chloroquine groups, respectively.

Table 8: Clinical Outcomes for CloroCovid-19

	CloroCovid-19[1]	
	Chloroquine low dosage (N = 40)	Chloroquine high dosage (N = 41)
Lethality by day 13		
Group-specific lethality, n (%)	6 (15.0)	16 (39.0)
Odds ratio (95% CI)	3.6 (1.2 to 10.6)	
P value	0.03	
Viral RNA		
Detection of viral RNA in deceased patients, n/N (%)	5/6 (83.3)	14/16 (87.5)

CI = confidence interval; RNA = ribonucleic acid.

Tang et al.

The clinical efficacy results for Tang et al. are reported in Table 9.[2] Although clinical improvement in patients with severe COVID-19 by day 28 was a planned primary outcome, the authors stated that because only 2 patients with severe COVID-19 were included in the study and because the study was stopped early, these results were not reported.[2]

Negative Conversion of SARS-CoV-2 by Day 28

- There was no difference in the number of patients with negative conversion of SARS-CoV-2 (percentage difference = 4.1; 95% CI, –10.3 to 18.5).
- There was no difference in the time to negative conversion of SARS-CoV-2 (hazard ratio = 0.85; 95% CI, 0.58 to 1.23).

Alleviation of Clinical Symptoms by Day 28

- There were no differences in the probability of alleviation of clinical symptoms (difference = –6.6%; 95% CI, – 41.3 to 28.0).
- There were no differences in the time to alleviation of clinical symptoms (1.01; 95% CI, 0.59 to 1.74 days).

Table 9: Clinical Outcomes for Tang et al.

	Tang et al.[2]	
	Hydroxychloroquine plus standard of care (N = 75)	Standard of care (N = 75)
Negative conversion of SARS-CoV-2[a]		
Patients with negative conversion by day 28, n (%)	53 (70.7)	56 (74.7)
Probability of negative conversion by day 28, % (95% CI)[b]	85.4 (73.8 to 93.8)	81.3 (71.2 to 89.6)
Difference, % (95% CI)	4.1 (−10.3 to 18.5)	
P value[c]	0.34	
Time to negative conversion of SARS-CoV-2		
Median, days (95% CI)	8 (5 to 10)	7 (5 to 8)
Hazard ratio (95% CI)	0.85 (0.58 to 1.23)	
P value[c]	0.34	
Alleviation of clinical symptom by day 28		
Probability of alleviation of clinical symptoms, % (95% CI)	59.9 (45.0 to 75.3)	66.6 (39.5 to 90.9)

	Tang et al.[2]	
	Hydroxychloroquine plus standard of care (N = 75)	Standard of care (N = 75)
Difference, % (95% CI)	−6.6 (−41.3 to 28.0)	
P value[c]	0.97	
Time to alleviation of clinical symptoms		
Median, days (95% CI)	19	21
Hazard ratio (95% CI)	1.01 (0.59 to 1.74)	
P value[c]	0.97	

CI = confidence interval; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Defined as 2 consecutive reports of a negative result for SARS-CoV-2 at least 24 hours apart without a subsequent report of a positive result by the end of the study.

[b] Using the Kaplan-Meier method.

[c] Using the log-rank test.

Davoodi et al.

The clinical efficacy results for Davoodi et al. are reported in Table 10.[3]

Hospitalization

- In the febuxostat group, 10.3% of patients (3 of 29) were hospitalized due to more severe symptoms compared with 12.5% of patients (3 of 25) in the hydroxychloroquine group.

Mortality

- There were no differences in the frequency of mortality between the 2 groups (data not reported).

ICU Care

- There were no differences in the frequency of ICU stays between the 2 groups (data not reported).

CT Lung Involvement at Day 14

- There were no statistically significant differences between the 2 groups in the mean percentage of reduction in lung involvement (7.3% with febuxostat and 8% with hydroxychloroquine; P value not reported).
- There were no statistically significant differences between the 2 groups in the number of patients with negative lung involvement (31% with febuxostat and 32% with hydroxychloroquine; P value not reported).

Clinical Status at Day 5

- While the mean respiratory rate was approximately 17 breaths per minute for both groups, more patients in the hydroxychloroquine group were reported to have a respiratory rate equal to or greater than 20 breaths per minute (12.0% versus 6.9% with febuxostat) and more patients with hydroxychloroquine had dyspnea (17.4% versus 10.7% with febuxostat).

Laboratory Findings at Day 5

- The number of patients with lymphopenia included 8 patients (28.6%) in the febuxostat group and 7 (30.4%) patients in the hydroxychloroquine group.

- The number of patients with an elevated C-reactive protein included 14 patients (50.0%) in the febuxostat group and 12 patients (60.0%) in the hydroxychloroquine group.

Table 10: Clinical Outcomes for Davoodi et al.

	Davoodi et al.[3]	
	Febuxostat N = 30	Hydroxychloroquine N = 30
Hospitalization		
Patients hospitalized due to more severe symptoms, n/N (%)	3/29 (10.3)	3/25 (12.5)
CT lung involvement		
Mean percentage of lung involvement at day 5, (SE)	7.3 (11.7)	8 (11.8)
Mean percentage reduction in lung involvement (adjusted)[a] at day 14, (SE)	47.4 (17)	58.3 (13.7)
P value	NS	
Patients with negative CT lung involvement at day 14, n/N (%)	9/29 (31)	8/25 (32)
P value	NS	
Clinical status at day 5		
Respiratory rate, mean number of breaths per minute (SE)	17.3 (0.5)	17.4 (0.5)
Patients with respiratory rate ≥ 20 breaths per minute, n (%)	2 (6.9)	3 (12.0)
Laboratory values status at day 5		
Patients with lymphopenia (< 1,500 count per µL), n (%)	8 (28.6)	7 (30.4)
Patients with elevated CRP, n (%)	14 (50.0)	12 (60.0)

CRP = C-reactive protein; NS = not significant; SE = standard error.

[a] Adjusted according to the following formula: ([Initial Total Lung Involvement – Day 14 Total Long Involvement] ÷ Initial Total Lung Involvement) × 100.

Cavalcanti et al.

The clinical efficacy results for Cavalcanti et al. are reported in Table 11.[4] The results reported are from the modified ITT population.

Clinical Status Measured With a Seven-Level COVID Outcomes Scale at 15 Days

- There was no statistically significant difference in the proportion of patients having a higher score when comparing the hydroxychloroquine plus azithromycin group with the control group (odds ratio = 0.99; 95% CI, 0.57 to 1.73; P = 1.00).
- There was no statistically significant difference in the proportion of patients having a higher score when comparing the hydroxychloroquine-alone group with the control group (odds ratio = 1.21; 95% CI, 0.69 to 2.11; P = 1.00).
- There was no statistically significant difference in the proportion of patients having a higher score when comparing the hydroxychloroquine plus azithromycin group with the hydroxychloroquine group (odds ratio = 0.82; 95% CI, 0.47 to 1.43; P = 1.00).

Secondary Outcomes

- There were no significant differences in any of the secondary outcomes when comparing the hydroxychloroquine plus azithromycin group with the control group, the hydroxychloroquine-alone group with the control group, or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group.
  - There was no statistically significant difference in the odds of having a higher median score in clinical status assessed on the 6-level ordinal scale at 7 days when comparing the hydroxychloroquine plus azithromycin group with the control group (odds ratio = 0.81; 95% CI, 0.54 to 1.22), the hydroxychloroquine-alone group with

the control group (odds ratio = 0.92; 95% CI, 0.61 to 1.38), or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (odds ratio = 0.89; 95% CI, 0.58 to 1.34).

- There was no statistically significant difference in the number of days free from respiratory support within 15 days when comparing the hydroxychloroquine plus azithromycin group with the control group (mean difference = 0.1; 95% CI, −0.7 to 0.9), the hydroxychloroquine-alone group with the control group (mean difference = −0.2; 95% CI, −1.1 to 0.6), or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (mean difference = 0.3; 95% CI, −0.6 to 1.1).
- There was no statistically significant difference in the use of high-flow nasal cannula or non-invasive ventilation within 15 days when comparing the hydroxychloroquine plus azithromycin group with the control group (odds ratio = 1.10; 95% CI, 0.60 to 2.03), the hydroxychloroquine-alone group with the control group (odds ratio = 1.19; 95% CI, 0.65 to 2.21), or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (odds ratio = 0.92; 95% CI, 0.50 to 1.70).
- There was no statistically significant difference in the use of mechanical ventilation within 15 days when comparing the hydroxychloroquine plus azithromycin group with the control group (odds ratio = 1.77; 95% CI, 0.81 to 3.87), the hydroxychloroquine-alone group with the control group (odds ratio = 1.15; 95% CI, 0.49 to 2.70), or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (odds ratio = 1.54; 95% CI, 0.71 to 3.35).
- There was no statistically significant difference in the duration of hospital stay when comparing the hydroxychloroquine plus azithromycin group with the control group (mean difference = 0.9; 95% CI, −0.3 to 2.1), the hydroxychloroquine-alone group with the control group (mean difference = 0.2; 95% CI, −1.0 to 1.3), or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (mean difference = 0.7; 95% CI, −0.6 to 1.9).
- There was no statistically significant difference in the number of in-hospital deaths when comparing the hydroxychloroquine plus azithromycin group with the control group (hazard ratio = 0.64; 95% CI, 0.18 to 2.21), the hydroxychloroquine-alone group with the control group (hazard ratio = 1.47; 95% CI, 0.48 to 4.53), or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (hazard ratio = 0.43; 95% CI, 0.13 to 1.45).
- There was no statistically significant difference in the number of thromboembolic complications within 15 days when comparing the hydroxychloroquine plus azithromycin group with the control group (odds ratio = 0.89; 95% CI, 0.31 to 2.54), the hydroxychloroquine-alone group with the control group (odds ratio = 1.39; 95% CI, 0.53 to 3.65), or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (odds ratio = 0.64; 95% CI, 0.24 to 1.68).
- There was no statistically significant difference in the number of acute kidney injuries within 15 days when comparing the hydroxychloroquine plus azithromycin group with the control group (odds ratio = 1.18; 95% CI, 0.44 to 3.20), the hydroxychloroquine-alone group with the control group (odds ratio = 0.88; 95% CI, 0.29 to 2.63), or the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (odds ratio = 1.35; 95% CI, 0.47 to 3.84).

Table 11: Clinical Outcomes for Cavalcanti et al.

	Cavalcanti et al.[4] (modified ITT population)		
	Hydroxychloroquine plus azithromycin N = 172	Hydroxychloroquine N = 159	Control N = 173
Primary outcome: Clinical status measured with a 7-level ordinal scale at 15 days[a]			
Median score (IQR)	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)
Score distribution, n (%)			
1: Not hospitalized with no limitations on activities	118 (68.6)	102 (64.2)	117 (67.6)
2: Not hospitalized but with limitations on activities	22 (12.8)	27 (17.0)	29 (16.8)
3: Hospitalized, not receiving supplemental oxygen	15 (8.7)	12 (7.5)	8 (4.6)
4: Hospitalized, receiving supplemental oxygen	5 (2.9)	6 (3.8)	5 (2.9)
5: Hospitalized, receiving non-invasive ventilation or high-flow nasal cannula	0	2 (1.3)	2 (1.2)
6: Hospitalized, receiving mechanical ventilation	9 (5.2)	5 (3.1)	7 (4.0)
7: Death	3 (1.7)	5 (3.1)	5 (2.9)
Secondary outcomes			
Clinical status measured with a 6-level ordinal scale at 7 days			
Median score (IQR)	2 (1 to 3)	2 (1 to 2)	2 (1 to 3)
Score distribution, n (%)			
1: Not hospitalized	84 (48.8)	67 (42.1)	75 (43.4)
2: Hospitalized, not receiving supplemental oxygen	38 (22.1)	53 (33.3)	45 (26.0)
3: Hospitalized, receiving supplemental oxygen	31 (18.0)	25 (15.7)	38 (22.0)
4: Hospitalized, receiving non-invasive ventilation or high-flow nasal cannula	3 (1.7)	2 (1.3)	4 (2.3)
5: Hospitalized, receiving mechanical ventilation	15 (8.7)	10 (6.3)	9 (5.2)
6: Death	1 (0.6)	2 (1.3)	2 (1.2)
Number of days free from respiratory support within 15 days,[e] days, mean (SD)	11.1 (4.9)	11.2 (4.9)	11.1 (4.9)
Use of high-flow nasal cannula or non-invasive ventilation within 15 days, n (%)	16 (9.3)	17 (10.7)	16 (9.2)
Use of mechanical ventilation within 15 days, n (%)	19 (11.0)	12 (7.5)	12 (6.9)
Duration of hospital stay, mean days (SD)[f]	10.3 (8.4)	9.6 (6.5)	9.5 (7.2)
In-hospital death, n (%)[f,g]	5 (2.9)	7 (4.4)	6 (3.5)
Thromboembolic complications within 15 days, n (%)	2 (1.2)	3 (1.9)	2 (1.2)
Acute kidney injury within 15 days, n (%)	6 (3.5)	4 (2.5)	5 (2.9)

	Cavalcanti et al.[4] (modified ITT population)		
	Hydroxychloroquine plus azithromycin N = 172	Hydroxychloroquine N = 159	Control N = 173
Effect estimates	**Hydroxychloroquine plus azithromycin versus control**	**Hydroxychloroquine versus control**	**Hydroxychloroquine plus azithromycin versus hydroxychloroquine**
Primary outcome, OR (95% CI)	0.99 (0.57 to 1.73)[c]	1.21 (0.69 to 2.11)[c]	0.82 (0.47 to 1.43)[c]
Secondary outcome, OR (95% CI)	0.81 (0.54 to 1.22)	0.92 (0.61 to 1.38)	0.89 (0.58 to 1.34)
Number of days free from respiratory support within 15 days,[e] MD (95% CI)	0.1 (−0.7 to 0.9)	−0.2 (−1.1 to 0.6)	0.3 (−0.6 to 1.1)
Use of high-flow nasal cannula or non-invasive ventilation within 15 days, OR (95% CI)	1.10 (0.60 to 2.03)	1.19 (0.65 to 2.21)	0.92 (0.50 to 1.70)
Use of mechanical ventilation within 15 days, OR (95% CI)	1.77 (0.81 to 3.87)	1.15 (0.49 to 2.70)	1.54 (0.71 to 3.35)
Duration of hospital stay, MD[f] (95% CI)	0.9 (−0.3 to 2.1)	0.2 (−1.0 to 1.3)	0.7 (−0.6 to 1.9)
In-hospital death, HR[f,g] (95% CI)	0.64 (0.18 to 2.21)	1.47 (0.48 to 4.53)	0.43 (0.13 to 1.45)
Thromboembolic complications within 15 days, OR (95% CI)	0.89 (0.31 to 2.54)	1.39 (0.53 to 3.65)	0.64 (0.24 to 1.68)
Acute kidney injury within 15 days, OR (95% CI)	1.18 (0.44 to 3.20)	0.88 (0.29 to 2.63)	1.35 (0.47 to 3.84)

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; ITT = intention to treat; MD = mean difference; OR = odds ratio; SD = standard deviation.

[a] Plus-minus values are means, plus or minus the SD. The modified ITT population included patients who had undergone randomization and who had a confirmed diagnosis of coronavirus disease 2019 (COVID-19). Effect estimates are mean differences (for the outcomes of the number of days free from respiratory support within 15 days and the duration of hospital stay), HRs (for the outcome of in-hospital death), or ORs (for all other outcomes). ORs for the ordinal outcome at 7 days and at 15 days that are lower than 1 indicate a benefit for treatment groups compared with control. CADTH used the Lipsitz method to test proportionality of odds with a P value of 0.15. The widths of the CIs for the secondary outcomes were not adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

[b] The ordinal outcome assessed at 15 days was evaluated on the 7-level scale. ORs lower than 1 indicate treatment benefit.

[c] P = 1.00 for all comparisons. P values for the 3 two-by-two comparisons for the primary outcome were adjusted with the use of Bonferroni correction for multiple comparisons.

[d] The ordinal outcome assessed at 7 days was evaluated on a 6-level scale, in which levels 1 and 2 from the 7-level scale were combined as level 1 (no hospitalization). Data were available for 171 patients assigned to receive hydroxychloroquine plus azithromycin, for 157 in the hydroxychloroquine-alone group, and for 173 in the control group. Effects were calculated after multiple imputations. OR values lower than 1 indicate treatment benefit.

[e] Data were available for 169 patients assigned to receive hydroxychloroquine plus azithromycin, 157 patients in the hydroxychloroquine-alone group, and 171 patients in the control group. Effects were calculated after multiple imputation.

[f] As of June 4, 2020, a total of 21 patients were still in the hospital (range of duration of follow-up, 22 to 49 days): 8 patients were assigned to receive hydroxychloroquine plus azithromycin; there were 5 patients in the hydroxychloroquine-alone group and 8 in the control group. These patients were considered to be discharged alive.

[g] A total of 18 patients died in the hospital. HRs are shown for this analysis. The causes of death were as follows: among patients assigned to receive hydroxychloroquine plus azithromycin, 5 patients died (the cause of death was COVID-19–related acute respiratory failure or septic shock in all patients); among patients assigned to receive hydroxychloroquine, 7 patients died (the cause of death was COVID-19–related acute respiratory failure or septic shock in 6 patients and abdominal-wall hemorrhage with shock in 1 patient). Six patients died in the control group (the cause of death was COVID-19–related acute respiratory failure or septic shock in 5 patients and myocardial infarction in 1 patient).

Skipper et al.

The clinical efficacy results for Skipper et al. are reported in Table 12.[5]

Ten-Point Visual Analogue Scale Outcome at 14 Days

There was no statistically significant difference in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups (absolute difference = −0.27; 95% CI, −0.61 to 0.07 points; P = 0.117).

Subgroup Analyses

- **Biological sex:** There was no statistically significant interaction in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups (absolute difference for males = −0.5; 95% CI, −1.02 to 0.03 points; P = 0.28; absolute difference for females = −0.11; 95% CI, −0.56 to 0.34 points; P = 0.28).
- **Age:** There was no statistically significant interaction in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups (absolute difference for patients aged 18 to 35 years = −0.16; 95% CI, −0.68 to 0.36 points; absolute difference for patients aged 36 to 50 years = −0.28; 95% CI, −0.78 to 0.23 points; absolute difference for patients aged > 50 years = −0.45; 95% CI, −1.27 to 0.38 points; P = 0.73).
- **Duration of symptoms:** There was no statistically significant interaction in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups (absolute difference for less than a day = −0.10; 95% CI, −0.58 to 0.38 points; absolute difference for 1 to 2 days = −0.66; 95% CI, −1.29 to −0.02 points; absolute difference for 3 to 4 days = 0.0; 95% CI, −0.69 to 0.68 points; P = 0.28).
- **SARS-CoV-2 testing:** There was no statistically significant interaction in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups (absolute difference for PCR-confirmed patients = −0.11; 95% CI, −0.75 to 0.52 points; absolute difference for probable COVID-19 = −0.36; 95% CI, −0.74 to 0.03 points; P = 0.51).
- **Exposure contact:** There was no statistically significant interaction in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups (absolute difference for PCR-confirmed patients = −0.18; 95% CI, −0.60 to 0.23 points; absolute difference for exposure not confirmed or unknown patients = −0.44; 95% CI, −1.03 to 0.15 points; P = 0.51).
- **Final diagnosis:** There was no statistically significant interaction in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups (absolute difference for PCR-confirmed patients = −0.11; 95% CI, −0.75 to 0.52 points; absolute difference for contact PCR-positive patients = −0.27; 95% CI, −0.71 to 0.18 points; absolute difference for probable case only = −0.55; 95% CI, −1.33 to 0.23 points; P = 0.68).

Table 12: Clinical Outcomes for Skipper et al.

Change in symptom severity score over 14 days, overall and by a priori subgroups	Skipper et al.[5]				
	Hydroxychloroquine		Placebo		Absolute difference in symptom severity (95% CI)
	Mean change from baseline (SE)	N	Mean change from baseline (SE)	N	
Overall	–2.60 (0.12)	212	–2.33 (0.12)	211	–0.27 (−0.61 to 0.07)
P value	0.117				
Biological sex					
Male	–2.88 (0.19)	88	–2.38 (0.18)	94	–0.50 (−1.02 to 0.03)
Female	–2.38 (0.16)	123	–2.27 (0.17)	115	–0.11 (−0.56 to 0.34)
P value	0.28				
Age					
18 to 35 years old	–2.89 (0.20)	69	–2.73 (0.18)	83	–0.16 (−0.68 to 0.36)
36 to 50 years old	–2.48 (0.17)	94	–2.20 (0.19)	78	–0.28 (−0.78 to 0.23)
> 50 years old	–2.36 (0.30)	49	–1.91 (0.30)	50	–0.45 (−0.27 to 0.38)
P value	0.73 (0.060)[a]				
Duration of symptoms					
< 1 day	–1.91 (0.17)	86	–1.81 (0.18)	83	–0.10 (−0.58 to 0.38)
1 to 2 days	–3.21 (0.24)	67	–2.55 (0.22)	78	−0.66 (−1.29 to −0.02)
3 to 4 days	–2.89 (0.24)	59	–2.88 (0.26)	50	0.0 (−0.69 to 0.68)
P value	0.28 (0.93)[a]				
SARS-CoV-2 PCR testing					
PCR confirmed	–2.21 (0.23)	73	–2.10 (0.23)	72	–0.11 (−0.75 to 0.52)
Not confirmed	–2.80 (0.14)	139	–2.45 (0.14)	139	–0.36 (−0.74 to 0.03)
P value	0.51				
Exposure contact					
PCR confirmed	–2.49 (0.15)	134	–2.30 (0.15)	146	–0.18 (−0.60 to 0.23)
Not confirmed or unknown	–2.82 (0.20)	78	–2.38 (0.22)	65	–0.44 (−1.03 to 0.15)
P value	0.51				
Final diagnosis					
PCR confirmed	–2.21 (0.23)	73	–2.10 (0.23)	72	–0.11 (−0.75 to 0.52)
Contact PCR positive	–2.71 (0.16)	92	–2.44 (0.16)	104	–0.27 (−0.71 to 0.18)
Probable case only	–3.01 (0.26)	47	–2.46 (0.30)	35	–0.55 (−1.33 to 0.23)
P value	0.68				

CI = confidence interval; PCR = polymerase chain reaction; SE = standard error.

[a] P values for trend of continuous variables are in parentheses.

Abd-Elsalam et al.

The clinical efficacy results for Abd-Elsalam et al. are reported in Table 13.[6]

Disease Severity After 28 Days

- There was no significant difference in disease severity when comparing the hydroxychloroquine plus standard of care group with the standard of care group (P = 0.06).

Death

- There was no significant difference in the proportion of participants who died when comparing the hydroxychloroquine plus standard of care group (6.1%) with the standard of care group (5.1%; P = 0.76).

Mechanical Ventilation

- There was no significant difference in the proportion of participants requiring mechanical ventilation when comparing the hydroxychloroquine plus standard of care group (4.1%) with the standard of care group (5.2%; P = 0.75).

Need for ICU

- There was no significant difference in the proportion of participants requiring admission to an ICU when comparing the hydroxychloroquine plus standard of care group (11.3%) with the standard of care group (13.4%; P = 0.83).

Duration to Negative PCR

- There was no significant difference in the mean time to negative PCR when comparing the hydroxychloroquine plus standard of care group (17.01 days; SD = 2.98) with the standard of care group (17.64 days; SD = 2.45; P = 0.11).

Duration to Clinical Improvement

- There was no significant difference in the mean time to clinical improvement when comparing the hydroxychloroquine plus standard of care group (9.43 days; SD = 1.87 days) with the standard of care group (9.52 days; SD = 2.94 days; P = 0.80).

Duration to Hospital Discharge

- There was no significant difference in the mean time to hospital discharge when comparing the hydroxychloroquine plus standard of care group (11.04 days; SD = 2.71 days) with the standard of care group (11.27 days; SD = 2.19; P = 0.52).

Table 13: Clinical Outcomes for Abd-Elsalam et al.

	Abd-Elsalam et al.[6]	
	Hydroxychloroquine plus standard of care (N = 97)	Standard of care (N = 97)
Disease severity after 28 days, n (%)		
Recovered	52 (53.6)	33 (34.0)
Mild	23 (23.7)	39 (40.2)
Moderate	8 (8.2)	11 (11.3)
Severe	8 (8.2)	9 (9.2)
Death	6 (6.1)	5 (5.1)
P value	0.06	
Death		
n, (%)	6 (6.1)	5 (5.1)
P value	0.76	

	Abd-Elsalam et al.[6]	
	Hydroxychloroquine plus standard of care (N = 97)	Standard of care (N = 97)
Mechanical ventilation		
n, (%)	4 (4.1)	5 (5.2)
P value	0.75	
Need for ICU		
n, (%)	11 (11.3)	13 (13.4)
P value	0.83	
Duration to negative PCR		
Mean, days (SD)	17.01 (2.98)	17.64 (2.45)
P value	0.11	
Duration to clinical improvement		
Mean, days (SD)	9.43 (1.87)	9.52 (2.94)
P value	0.80	
Duration to hospital discharge		
Mean, days (SD)	11.04 (2.71)	11.27 (2.19)
P value	0.52	

CI = confidence interval; ICU = intensive care unit; SD = standard deviation.

Horby et al.

The clinical efficacy results for Horby et al. are reported in Table 14.[7]

28-Day Mortality

- There was no significant difference in the 28-day mortality when comparing the hydroxychloroquine plus standard of care group with the standard of care group (27.0% versus 25.0%; rate ratio = 1.09; 95% CI, 0.97 to 1.23; P = 0.15). Results were consistent across all pre-specified subgroups, including age, sex, race or ethnic group, days since symptom onset, respiratory support at randomization, and baseline risk.

Discharge From Hospital in 28 or Fewer Days

- Patients in the hydroxychloroquine group were statistically significantly less likely to be discharged from the hospital alive within 28 days than those in the usual care group (59.6% versus 62.9%; rate ratio = 0.90; 95% CI, 0.83 to 0.98).

Intensive Mechanical Ventilation or Death

- Patients in the hydroxychloroquine group had a statistically higher frequency of mechanical ventilation or death than those in the usual care group (30.7% versus 26.9%; rate ratio = 1.14; 95% CI, 1.03 to 1.27).

Death From Specific Causes

- Patients in the hydroxychloroquine group had a greater risk of death from cardiac causes (mean excess of 0.4; SE = 0.2) and from non–SARS-CoV-2 infection (mean excess of 0.4; SE = 0.2).

Occurrence of New Major Cardiac Arrythmia

- When comparing the hydroxychloroquine group with the usual care group, there were no significant differences in the frequency of supraventricular tachycardia (7.6% versus 6.0%), ventricular tachycardia or fibrillation (0.7% versus 0.4%), or atrioventricular block requiring intervention (0.1% versus 0.1%).

Need for Renal Replacement Therapy

- There was no difference in the percentage of patients who required renal dialysis or hemofiltration during the follow-up when comparing the hydroxychloroquine group (7.9%) with the usual care group (7.9%).

Table 14: Clinical Outcomes for Horby et al.

	Horby et al.[7]	
	Hydroxychloroquine (N = 1,561)	Usual care (N = 3,155)
Primary outcome, n/N (%)		
28-day mortality	421/1561 (27.0)	790/3155 (25.0)
Rate ratio (95% CI)	1.09 (0.97 to 1.23)	
P value	0.15	
Secondary outcomes, n/N (%)		
Discharge from hospital in ≤ 28 days	931/1561 (59.6)	1983/3155 (62.9)
Rate ratio (95% CI)	0.90 (0.83 to 0.98)	
Intensive mechanical ventilation or death	399/1300 (30.7)	705/2623 (26.9)
Risk ratio (95% CI)	1.14 (1.03 to 1.27)	
Intensive mechanical ventilation	128/1,300 (9.8)	225/2,623 (8.6)
Risk ratio (95% CI)	1.15 (0.93 to 1.41)	
Death	311/1,300 (23.9)	574/2,623 (21.9)
Risk ratio (95% CI)	1.09 (0.97 to 1.23)	
Mortality at 28 days, subgroup analyses, n/N (%)		
Age		
< 70 years	160/925 (17.3)	314/1873 (16.8)
Rate ratio (95% CI)	1.03 (0.85 to 1.25)	
≥ 70 to < 80 years	128/342 (37.4)	207/630 (32.9)
Rate ratio (95% CI)	1.17 (0.93 to 1.47)	
≥ 80 years	133/294 (45.2)	269/652 (41.3)
Rate ratio (95% CI)	1.14 (0.92 to 1.42)	
Sex		
Male	276/960 (28.8)	543/1974 (27.5)
Rate ratio (95% CI)	1.05 (0.91 to 1.22)	
Female	145/601 (24.1)	247/1181 (20.9)
Rate ratio (95% CI)	1.19 (0.96 to 1.47)	
Race or ethnic group		
White	335/1,181 (28.4)	610/2,298 (26.5)
Rate ratio (95% CI)	1.09 (0.95 to 1.25)	
Black, Asian, or minority ethnic group	65/264 (24.6)	115/593 (19.4)
Rate ratio (95% CI)	1.32 (0.96 to 1.81)	
Days since symptom onset		
≤ 7	177/622 (28.5)	339/1275 (26.6)
Rate ratio (95% CI)	1.10 (0.91 to 1.32)	
> 7	242/930 (26.0)	445/1,871 (23.8)
Rate ratio (95% CI)	1.11 (0.94 to 1.30)	

	Horby et al.[7]	
	Hydroxychloroquine (N = 1,561)	Usual care (N = 3,155)
Respiratory support at randomization		
No oxygen received	58/362 (16.0)	99/750 (13.2)
Rate ratio (95% CI)	1.24 (0.89 to 1.73)	
Oxygen only	253/938 (27.0)	475/1,873 (25.4)
Rate ratio (95% CI)	1.08 (0.93 to 1.26)	
Invasive mechanical ventilation	110/261 (42.1)	216/532 (40.6)
Rate ratio (95% CI)	1.03 (0.81 to 1.30)	
Baseline risk		
< 30%	146/994 (14.7)	274/1,990 (13.8)
Rate ratio (95% CI)	1.07 (0.88 to 1.32)	
≥ 30% to < 45%	135/317 (42.6)	246/635 (38.7)
Rate ratio (95% CI)	1.12 (0.90 to 1.40)	
≥ 45%	140/250 (56.0)	270/530 (50.9)
Rate ratio (95% CI)	1.17 (0.95 to 1.45)	
Effect of allocation to hydroxychloroquine on cause-specific 28-day mortality		
Cause of death, n (%)		
COVID-19	374 (24.0)	743 (23.5)
Absolute percent difference (SE)	0.4 (1.32)	
Other infection	8 (0.5)	5 (0.2)
Absolute percent difference (SE)	0.4 (0.19)	
Cardiac	9 (0.6)	4 (0.1)
Absolute percent difference (SE)	0.4 (0.20)	
Stroke	2 (0.1)	4 (0.1)
Absolute percent difference (SE)	0.0 (0.11)	
Other vascular	1 (0.1)	2 (0.1)
Absolute percent difference (SE)	0.0 (0.08)	
Cancer	9 (0.6)	10 (0.3)
Absolute percent difference (SE)	0.3 (0.22)	
Other medical	15 (1.0)	21 (0.7)
Absolute percent difference (SE)	0.3 (0.29)	
External	2 (0.1)	0 (0.0)
Absolute percent difference (SE)	0.1 (0.09)	
Unknown cause	1 (0.1)	1 (< 0.05)
Absolute percent difference (SE)	0.0 (0.07)	
Effect of allocation to hydroxychloroquine on new major cardiac arrhythmia, n (%)		
Number with follow-up form	735	1,421
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)

	Horby et al.[7]	
	Hydroxychloroquine (N = 1,561)	Usual care (N = 3,155)
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)
Effect of allocation to hydroxychloroquine on need for RRT among those not on RRT at randomization		
Need for RRT (among those not on RRT at randomization), n/N (%)	120/1,520 (7.9%)	241/3,050 (7.9%)
Risk ratio (95% CI)	1.00 (0.81 to 1.23)	

CI = confidence interval; COVID-19 = coronavirus disease 2019; RRT = rental replacement therapy; SE = standard error.

Lyngbakken et al.

The clinical efficacy results for Lyngbakken et al. are reported in Table 15.[8]

Rate of Reduction in SARS-CoV-2 Viral Load

- There was no significant difference in rate of reduction in SARS-CoV-2 viral load at 24 hours when comparing the hydroxychloroquine plus standard of care group (0.24; 95% CI, 0.03 to 0.46) with the standard of care group (0.14; 95% CI, −0.10 to 0.37).

Died in Hospital

- Only 1 patient in both the hydroxychloroquine plus standard of care group (3.7%) and the standard of care alone group (3.9%) died in hospital.

Clinical Status at 14 Days Post-Randomization

- There was no statistically significant difference in the cumulative odds ratio of the clinical status at 14 days post-randomization when comparing the hydroxychloroquine plus standard of care group with the standard of care group (odds ratio = 1.11; 95% CI, 0.31 to 4.01).

Time From Hospitalization to Hospital Discharge

- There was no statistically significant difference in the log rank of the time from hospitalization to hospital discharge when comparing the hydroxychloroquine plus standard of care group with the standard of care group (P = 0.71).

Change in NEWS2 Score From Randomization to 96 Hours Post-Randomization

- There was a difference in change in NEWS2 from randomization to 96 hours post-randomization when comparing the hydroxychloroquine plus standard of care group (0.47; 95% CI, −0.58 to 1.53) with the standard of care group (0.29; 95% CI, −1.40 to 1.76); however, this change in NEWS2 score was not statistically significant (mean difference = 0.18; 95% CI, −1.40 to 1.76).

Table 15: Clinical Outcomes for Lyngbakken et al.

	Lyngbakken et al.[8]	
	Hydroxychloroquine plus standard of care (N = 26)[a]	Standard of care (N = 25)[a]
Primary outcome		
Rate of reduction in SARS-CoV-2 viral load, log_{10} RNA copies/mL over a 24-hour period, (95% CI)	0.24 (0.03 to 0.46)	0.14 (−0.10 to 0.37)
Reduction difference (95% CI)	0.11 (−0.21 to 0.43)	
Secondary outcomes		
Died in hospital, n (%)	1 (3.7)	1 (3.9)
Clinical status on 7-point ordinal scale at 14 days post-randomization, n (%)		
1: Dead	1 (3.8)	1 (4.0)
2: Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation	0 (0)	1 (4.0)
3: Hospitalized, on non-invasive ventilation or high-flow oxygen devices	1 (3.8)	0 (0)
4: Hospitalized, requiring supplemental oxygen	0 (0)	2 (8.0)
5: Hospitalized, not requiring supplemental oxygen	1 (3.8)	0 (0)
6: Not hospitalized, but unable to resume normal activities	3 (11.5)	2 (8.0)
7: Not hospitalized, with resumption of normal activities	20 (76.9)	19 (76.0)
Cumulative odds ratio (95% CI)	1.11 (0.31 to 4.01)	
Time from hospitalization to hospital discharge, P value	0.71	
Change in NEWS2 from randomization to 96 hours post-randomization, marginal mean change (95% CI)	0.47 (−0.58 to 1.53)	0.29 (−0.88 to 1.46)
Mean difference (95% CI)	0.18 (−1.40 to 1.76)	

CI = confidence interval; NEWS2 = National Early Warning Score 2; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] For all outcomes except for the died in hospital outcome, there were 26 patients in the hydroxychloroquine plus standard of care group and 25 patients in the standard of care group.

Mitjà et al.

The clinical efficacy results for Mitjà et al. are reported in Table 16.[9]

Viral Load Reduction

- There were no substantive differences in the reduction in viral load in nasopharyngeal swabs when comparing the hydroxychloroquine group with the standard of care group at day 3 or 7. There was a difference of 0.01 (95% CI, −0.28 to 0.29) in the hydroxychloroquine group at day 3, and a difference of −0.07 (95% CI, −0.44 to 0.29) in the hydroxychloroquine group at day 7.

Hospitalization

- The clinical outcome of risk of hospitalization was similar in the control arm (7.1%; 11 of 157 patients) and the intervention arm (5.9%; 8 of 136 patients) (risk ratio = 0.75; 95% CI, 0.32 to 1.77).

Mechanical Ventilation

- No patients required mechanical ventilation.

Table 16: Clinical Outcomes for Mitjà et al.

	Mitjà et al.[9]			
	N	Hydroxychloroquine N = 157	Standard of care N = 136	Absolute difference[a]
		Mean (SE)	Mean (SE)	
Primary outcome				
Viral load reduction in nasopharyngeal swabs from baseline (log_{10} copies/mL) (CI)				
Day 3	271	−1.41 (0.15)	−1.41 (0.14)	0.01
Day 7	211	−3.44 (0.19)	−3.37 (0.18)	0.07
Secondary outcomes				
Not hospitalized with resolution of symptoms at home	290	128 (94.1)	143 (92.3)	
Hospitalization not requiring mechanical ventilation[b]	290	8 (5.9)	11 (7.1)	0.75 (0.32 to 1.77)[c]
Hospitalization requiring mechanical ventilation	290	0 (0.0)	0 (0.0)	
Death	290	0 (0.0)	0 (0.0)	

CI = confidence interval; SE = standard error.

[a] None of the estimated mean differences or risk ratios were statistically significant.

[b] Estimated through a mixed-effects regression model.

[c] Risk ratio.

WHO Solidarity Trial Consortium

The clinical efficacy results for the WHO Solidarity Trial Consortium are reported in Table 17.[10]

In-Hospital Mortality Rate Ratio

- There was no statistically significant difference in the rate of mortality between the hydroxychloroquine group and the control group (rate ratio = 1.19; 95% CI, 0.89 to 1.59; P = 0.23).
- There were no statistically significant differences in the rate of mortality between the treatment group and the control group among the stratified subgroup analyses (less than 50 years old, 50 to 69 years old, 70 years old or older, no mechanical ventilation at entry, and mechanical ventilation at entry).

Ventilation

- The clinical outcome of the need for initiating ventilation was similar in the hydroxychloroquine group (8.7%) and the control group (8.0%).

Hospital Duration

- The percentage of patients ever reported as discharged who were still in the hospital at various times was similar in the hydroxychloroquine group and the control group at 7 days (n = 64 and n = 54, respectively), 14 days (n = 23 and n = 20, respectively), and 21 days (n = 11 and n = 10, respectively).

Table 17: Clinical Outcomes for WHO Solidarity Trial Consortium

	WHO Solidarity Trial Consortium[10]		
	Hydroxychloroquine	Control	Rate ratio
Primary outcome: In-hospital mortality rate ratio			
Sex, n/N (%)			
Male	80/574 (12.9)	50/535 (9.1)	1.52 (0.97 to 2.40)
Female	24/373 (6.2)	34/371 (8.7)	0.69 (0.35 to 1.36)
Age at entry, n/N (%)			
< 50	19/335 (5.7)	19/317 (5.8)	1.10 (0.47 to 2.57)
50 to 69	55/410 (12.1)	31/396 (7.1)	1.66 (0.95 to 2.91)
≥ 70	30/202 (14.0)	34/193 (17.8)	0.80 (0.42 to 1.53)
Days from hospital admission to randomization, n/N (%)			
0	23/296 (7.8)	20/281 (6.8)	1.06 (0.48 to 2.34)
1	39/317 (10.8)	29/312 (9.0)	1.19 (0.63 to 2.26)
≥ 2	42/334 (12.0)	35/313 (10.8)	1.21 (0.67 to 2.19)
Respiratory support at entry, n/N (%)			
No O_2	8/345 (2.3)	5/341 (1.2)	1.56 (0.37 to 6.54)
Low-flow or high-flow O_2	61/517 (10.8)	52/483 (10.5)	1.11 (0.68 to 1.80)
Ventilation	35/85 (39.2)	27/82 (32.3)	1.26 (0.65 to 2.46)
Bilateral lung lesions, n/N (%)			
No images taken at entry	20/137 (11.9)	18/118 (14.8)	1.02 (0.44 to 2.36)
Yes	78/656 (11.6)	63/618 (9.8)	1.19 (0.77 to 1.85)
No	6/154 (3.3)	3/170 (1.8)	2.16 (0.34 to 13.77)
Current smoking, n/N (%)			
Yes	14/92 (14.2)	8/82 (9.9)	2.09 (0.59 to 7.41)
No	90/855 (9.8)	76/824 (8.8)	1.14 (0.76 to 1.71)
Diabetes, n/N (%)			
Yes	35/199 (17.8)	20/205 (8.3)	1.87 (0.92 to 3.81)
No	69/748 (8.2)	64/701 (9.1)	1.02 (0.65 to 1.61)
Heart disease, n/N (%)			
Yes	25/193 (12.0)	20/194 (9.9)	1.25 (0.58 to 2.74)
No	79/754 (9.8)	64/712 (8.7)	1.16 (0.75 to 1.79)
Chronic liver disease, n/N (%)			
Yes	2/15 (6.7)	3/14 (21.4)	0.21 (0.01 to 3.14)
No	102/932 (10.3)	81/892 (8.7)	1.22 (0.83 to 1.79)
Chronic lung disease, n/N (%)			
Yes	9/62 (14.7)	7/66 (10.7)	1.27 (0.35 to 4.65)
No	95/885 (9.9)	77/840 (8.8)	1.17 (0.79 to 1.75)
Asthma, n/N (%)			
Yes	3/41 (7.4)	4/46 (6.7)	1.16 (0.11 to 11.85)
No	101/906 (10.4)	80/860 (9.1)	1.19 (0.81 to 1.75)
Corticosteroids at entry or later, n/N (%)			

	WHO Solidarity Trial Consortium[10]		
	Hydroxychloroquine	Control	Rate ratio
Yes	33/140 (23.3)	31/140 (22.2)	1.42 (0.71 to 2.83)
No	71/807 (8.0)	53/766 (6.5)	1.24 (0.78 to 1.97)
Geographic location,[a] n/N (%)			
Europe or Canada	24/286 (6.7)	17/267 (6.1)	1.38 (0.61 to 3.09)
Latin America	28/97 (27.9)	21/96 (20.8)	1.50 (0.70 to 3.21)
Asia and Africa	52/564 (9.0)	46/543 (8.2)	1.15 (0.67 to 1.95)
Scheduled hydroxychloroquine dose, n/N (%)			
Full dose	89/796 (10.8)	71/755 (9.1)	1.22 (0.81 to 1.85)
Half dose (discovery)	15/151 (7.5)	13/151 (8.0)	1.19 (0.45 to 3.19)
Total, n/N (%)	104/947 (10.2)	84/906 (8.9)	1.19 (0.89 to 1.59)
P value			0.23
Secondary outcomes			
Ventilation, n (%)	75 (8.7)	66 (8.0)	NA
Patients ever reported as discharged who were still in the hospital at various times, %			
On day 7	64	54	NA
On day 14	23	20	NA
On day 21	11	10	NA

NA = not applicable; O_2 = oxygen.

[a] Wastefully fine stratification, by country and within country, by the 6 strata of age and ventilation yielded a rate ratio of 1.30 (95% CI, 0.96 to 1.76), with no good evidence of between-country rate ratio heterogeneity.

Ulrich et al.

The clinical efficacy results for Ulrich et al. are reported in Table 18.[11]

Severe Disease Composite at Day 14

- There was no statistically significant difference in severe disease progression at day 14 between the hydroxychloroquine group (16.4%) and the placebo group (9.8%; P = 0.350).

Primary Safety Composite at Day 30

- There was no statistically significant difference in the primary safety composite at day 30 between the hydroxychloroquine group (34.3%) and the placebo group (31.1%; P = 0.620).

Severe Disease Composite at Day 30

- There was no statistically significant difference in the severe disease progression at day 30 between the hydroxychloroquine group (19.4%) and the placebo group (9.8%; P = 0.166).

Mortality at Day 30

- There was no statistically significant difference in mortality at day 30 between the hydroxychloroquine group (10.4%) and the placebo group (9.8%; P = 1.000).

Length of Stay

- There was no statistically significant difference in the average length of hospital stay from admission to discharge between the hydroxychloroquine group (10.3 days) and the placebo group (5.92 days; P = 0.053).

COVID-19 Severity Score at Day 14

- There was no statistically significant difference in the COVID-19 severity score at day 14 between the hydroxychloroquine group and the placebo group (P = 0.354).

QTc Interval Change From Baseline

- There was a statistically significant difference in the mean change in QTc interval between the hydroxychloroquine group (16 milliseconds) and the placebo group (2.1 milliseconds) in which the QTc interval was longer in the hydroxychloroquine group (P = 0.029).

Electrocardiogram Changes: QT Interval Greater Than 500 Milliseconds

- There was no statistically significant difference in the QT interval of greater than 500 milliseconds between the hydroxychloroquine group (4.5%) and the placebo group (1.6%; P = 0.680).

Inflammatory Laboratory Changes on Follow-Up: D Dimer

- There was a statistically significant difference in the mean D dimer after follow-up between the hydroxychloroquine group (836 ng/mL) and the placebo group (−288 ng/mL; P = 0.047).

SARS-CoV-2 Follow-Up RT-PCR

- There was no statistically significant difference in the proportion of negative SARS-CoV-2 RT-PCR tests at follow-up between the hydroxychloroquine group (11.9%) and the placebo group (16.4%; P = 0.639).

Co-Enrolment in Other Trials

- There was no statistically significant difference in the proportion of patients who were co-enrolled in other trials between the hydroxychloroquine group (19.4%) and the placebo group (21.3%; P = 0.962).

Table 18: Clinical Outcomes for Ulrich et al.

	Ulrich et al.[11]		
	Hydroxychloroquine N = 67	Placebo N = 61	P value
Primary outcomes			
Severe disease composite (day 14)[a]	11 (16.4)	6 (9.8)	0.350
Death	3 (4.5)	5 (8.2)	0.659
ICU admission	9 (13.4)	5 (8.2)	0.452
Mechanical ventilation	5 (7.5)	4 (6.6)	1.000
ECMO	0 (0)	0 (0)	NA
Vasopressor use	3 (4.5)	3 (4.9)	1.000
Unknown	7 (10.4)	4 (6.6)	639
Primary safety composite (day 30)[b]	23 (34.3)	19 (31.1)	0.620
Unknown	11 (16.4)	7 (11.5)	0.783
Secondary outcomes			
Severe disease composite (day 30)	13 (19.4)	6 (9.8)	0.166
Death	7 (10.4)	6 (9.8)	1.000
ICU admission	9 (13.4)	3 (4.9)	0.153
Mechanical ventilation	5 (7.5)	3 (4.9)	0.778
ECMO	0 (0)	0 (0)	NA

	Ulrich et al.[11]		
	Hydroxychloroquine N = 67	Placebo N = 61	P value
Vasopressor use	2 (3.0)	2 (3.3)	1.000
Lost to follow-up	14 (20.9)	11 (18.0)	0.853
COVID-19 severity score at day 14[c]			0.354
1: Death	3 (4.5)	5 (8.2)	NA
2: Ventilator or ECMO	2 (3.0)	0 (0)	NA
3: Hospitalized, on NIV or high-flow nasal cannula	7 (10.4)	2 (3.3)	NA
4: Hospitalized, on supplemental oxygen	4 (6.0)	1 (1.6)	NA
5: Hospitalized, not on O_2, ongoing medical care	2 (3.0)	0 (0)	NA
6: Hospitalized, not on O_2, not requiring ongoing care	1 (1.5)	2 (3.3)	NA
7: Outpatient, limitation on activities or home O_2	13 (19.4)	18 (29.5)	NA
8: Outpatient, no limitation on activities	28 (41.8)	29 (47.5)	NA
Unknown	7 (10.4)	4 (6.6)	NA
30-day mortality	7 (10.4)	6 (9.8)	1.000
Fever-free days (temperature < 100.4°F), mean (SD)	6.40 (0.94)	6.31 (1.33)	0.631
O_2 supplementation–free days, mean (SD)	4.63 (2.44)	4.43 (2.40)	0.640
Length of stay, mean (SD), days			
Admission to discharge	9.75 (10.3)	6.80 (5.92)	0.053
Electrocardiogram changes[d]			
QT interval > 500 milliseconds	3 (4.5)	1 (1.6)	0.680
Corrected QT interval (Bazett formula) change from baseline, mean (SD), milliseconds	16.0 (30.0)	2.10 (25.3)	0.029
No follow-up electrocardiogram	26 (38.8)	22 (36.1)	0.891
Safety laboratory changes on follow-up[e]			
Creatinine > 1.5 × baseline	5 (7.5)	2 (3.3)	0.515
AST > 3 × ULN (if baseline normal) or 1.5 × baseline	7 (10.4)	4 (6.6)	0.639
ALT > 3 × ULN (if baseline normal) or 1.5 × baseline	3 (4.5)	4 (6.6)	0.898
Platelet count decrease to < 75 10^9/L	5 (7.5)	1 (1.6)	0.255
Bilirubin > 1.5 × ULN (if baseline normal) or 1.5 × baseline	1 (1.5)	1 (1.6)	1.000
Inflammatory laboratory changes on follow-up[e]			
Ferritin, mean (SD), ng/mL	9.56 (786)	–378 (2,420)	0.302
C-reactive protein, mean (SD), mg/L	–19.9 (78.1)	–24.9 (114)	0.792
LDH, mean (SD), U/L	–2.65 (153)	–45.1 (162)	0.194
D dimer, mean (SD), ng/mL	836 (3,550)	–288 (1,700)	0.047
Interleukin-6, mean (SD), pg/mL	85.8 (245)	17.9 (98.7)	0.251
SARS-CoV-2 follow-up RT-PCR			
Positive	29 (43.3)	20 (32.8)	0.299
Interval between positive tests, median (IQR), days	6 (4)	6 (3)	0.674
Negative	8 (11.9)	10 (16.4)	0.639
Interval between tests if negative, median (IQR), days	8 (3)	6 (4)	0.51
No follow-up RT-PCR performed	30 (44.8)	31 (50.8)	0.612

	Ulrich et al.[11]		
	Hydroxychloroquine N = 67	Placebo N = 61	P value
Concomitant medications and clinical trial co-enrolment by treatment group			
Antibacterial drugs			
Azithromycin	13 (19.4)	17 (27.9)	0.357
Ceftriaxone	19 (28.4)	12 (19.7)	0.348
Anticoagulation			
VTE prophylaxis[b]	39 (58.2)	30 (49.2)	0.463
Therapeutic anticoagulation[c]	22 (32.8)	24 (39.3)	0.535
Antiplatelet drugs	25 (37.3)	13 (21.3)	0.096
Off-label COVID-19 therapies	27 (40.3)	14 (23.0)	0.056
Zinc	13 (19.4)	5 (8.2)	0.117
Corticosteroids	7 (10.4)	6 (9.8)	1.000
Tocilizumab	3 (4.5)	2 (3.3)	1.000
Lopinavir plus ritonavir	1 (1.5)	0 (0)	1.000
Remdesivir	1 (1.5)	0 (0)	1.000
Co-enrolment in other trials	13 (19.4)	13 (21.3)	0.962
Convalescent plasma	7 (10.4)	10 (16.4)	0.466
Clazakizumab	4 (6.0)	0 (0)	0.153
Remdesivir (ACTT-2)	0 (0)	1 (1.6)	0.962
Anticoagulation (PROTECT study)[e]	2 (3.0)	1 (1.6)	1.000

ACTT-2 = Adaptive COVID-19 Treatment Trial 2; AST = aspartate aminotransferase; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; LDH = lactate dehydrogenase; NA = not applicable; NIV = non-invasive ventilation; ng = nanogram; O_2 = oxygen; RT-PCR = reverse transcription–polymerase chain reaction; SD = standard deviation; ULN = upper limit of normal; VTE = venous thromboembolism.

[a] Number of patients with composite end point is less than the sum of each category, as some patients achieved multiple components of the composite end point.

[b] Primary safety composite: Serious adverse event and/or grade 3 or 4 adverse event and/or discontinuation of therapy for any reason. Eight (4 placebo, 4 hydroxychloroquine) of these end points were positive due to nursing error (medication not provided on discharge) or the patient was unable to confirm outpatient compliance.

[c] Wilcoxon rank sum test was used for COVID-19 score.

[d] Follow-up electrocardiogram performed at day 6 or, if discharged prior, on day of discharge.

[e] Day 6 laboratory results compared with baseline; if day 6 was not available, day 3 laboratory results were used to calculate. The number of patients with missing data for all laboratory measures did not differ significantly between the hydroxychloroquine and placebo arms.

Khamis et al.

The clinical efficacy results for Khamis et al. are reported in Table 19.[12]

C-Reactive Protein

- There was no statistically significant difference in C-reactive protein between the favipiravir group (50 mg/dL; IQR, 14 to 130) and the hydroxychloroquine group (33 mg/dL; IQR, 1 to 79; P = 0.413).

Ferritin

- There was no statistically significant difference in ferritin between the favipiravir group (1,107 mcg/dL; IQR, 539 to 1,404) and the hydroxychloroquine group (993 mcg/dL; IQR, 295 to 1,650; P = 0.968).

Lactate Dehydrogenase

- There was no statistically significant difference in lactate dehydrogenase between the favipiravir group (452 U/L; IQR, 351 to 554) and the hydroxychloroquine group (366 U/L; IQR, 338 to 427; P = 0.259).

Interleukin-6

- There was no statistically significant difference in interleukin-6 between the favipiravir group (138 pg/mL; IQR, 25 to 742) and the hydroxychloroquine group (143 pg/mL; IQR, 113 to 478; P = 0.410).

Length of Hospital Stay

- There was no statistically significant difference in the length of hospital stay between the favipiravir group (7 days; IQR, 4 to 12) and the hydroxychloroquine group (7 days; IQR, 3 to 11; P = 0.948).

Transferred to ICU

- There was no statistically significant difference in the number of patients transferred to ICU between the favipiravir group (n = 8; 18.2%) and the hydroxychloroquine group (n = 8; 17.8%; P = 0.960).

Discharged Home

- There was no statistically significant difference in the number of patients discharged between the favipiravir group (n = 29; 65.9%) and the hydroxychloroquine group (n = 31; 68.9%; P = 0.764).

Oxygen Saturation at Discharge

- There was no statistically significant difference in oxygen saturation between the favipiravir group (94%; IQR, 93 to 96) and the hydroxychloroquine group (95%; IQR, 93 to 96; P = 0.324).

Died

- There was no statistically significant difference in the number of patients who died between the favipiravir group (n = 5; 11.4%) and the hydroxychloroquine group (n = 6; 13.3%; P = 0.778).

Table 19: Clinical Outcomes for Khamis et al.

	Khamis et al.[12]		
	Favipiravir N = 45	Hydroxychloroquine N = 44	P value
Inflammatory parameters			
C-reactive protein, mg/dL (IQR)	50 (14 to 130)	33 (14 to 79)	0.413
Ferritin, mcg/L (IQR)	1,107 (539 to 1,404)	993 (295 to 1,650)	0.968
Lactate dehydrogenase, U/L (IQR)	452 (351 to 554)	366 (338 to 427)	0.259
Interleukin-6, pg/mL (IQR)	138 (25 to 742)	143 (113 to 478)	0.410
Length of hospital stay, days (IQR)	7 (4 to 12)	7 (3 to 11)	0.948
Outcomes, n (%)			
Transferred to ICU, n (%)	8 (18.2)	8 (17.8)	0.960
Discharged home, n (%)	29 (65.9)	31 (68.9)	0.764
Oxygen saturation at discharge, n (IQR)	94 (93 to 96)	95 (93 to 96)	0.324
Died, n (%)	5 (11.4)	6 (13.3)	0.778

ICU = intensive care unit; IQR = interquartile range; pg = picogram.

Self et al.

The clinical efficacy results for Self et al. are reported in Table 20.[13]

COVID Outcomes Scale Score at 14 Days

- There was no statistically significant difference in the COVID Outcomes Scale score at 14 days between the hydroxychloroquine group and the placebo group (odds ratio = 1.02; 95% CI, 0.73 to 1.42).

COVID Outcomes Scale Score at 2 Days

- There was no statistically significant difference in the COVID Outcomes Scale score at 2 days between the hydroxychloroquine group and the placebo group (odds ratio = 1.28; 95% CI, 0.90 to 1.81).

COVID Outcomes Scale Score at 7 Days

- There was no statistically significant difference in the COVID Outcomes Scale score at 7 days between the hydroxychloroquine group and the placebo group (odds ratio = 1.16; 95% CI, 0.84 to 1.61).

COVID Outcomes Scale Score at 28 Days

- There was no statistically significant difference in the COVID Outcomes Scale score at 28 days between the hydroxychloroquine group and the placebo group (odds ratio = 0.97; 95% CI, 0.69 to 1.38).

All-cause, All-Location Death at 14 Days

- There was no statistically significant difference in the all-cause, all-location death at 14 days between the hydroxychloroquine group and the placebo group (odds ratio = 1.56; 95% CI, 0.68 to 3.57).

All-cause, All-Location Death at 28 Days

- There was no statistically significant difference in the all-cause, all-location death at 28 days between the hydroxychloroquine group and the placebo group (odds ratio = 1.07; 95% CI, 0.54 to 2.09).

Time to Recovery in Days

- There was no statistically significant difference in the time to recovery in days between the hydroxychloroquine group and the placebo group (odds ratio = 0.97; 95% CI, 0.69 to 1.35).

Composite of Death or ECMO Through 28 Days

- There was no statistically significant difference in the composite of death or ECMO through 28 days between the hydroxychloroquine group and the placebo group (odds ratio = 1.13; 95% CI, 0.60 to 2.14).

Hospital-Free Days

- There was no statistically significant difference in the number of hospital-free days between the hydroxychloroquine group and the placebo group (odds ratio = 1.17; 95% CI, 0.85 to 1.61).

Oxygen-Free Days

- There was no statistically significant difference in the number of oxygen-free days between the hydroxychloroquine group and the placebo group (odds ratio = 0.96; 95% CI, 0.68 to 1.34).

ICU-Free Days

- There was no statistically significant difference in the number of ICU-free days between the hydroxychloroquine group and the placebo group (odds ratio = 1.26; 95% CI, 0.84 to 1.88).

Ventilator-Free Days

- There was no statistically significant difference in the number of ventilator-free days between the hydroxychloroquine group and the placebo group (odds ratio = 1.26; 95% CI, 0.76 to 2.08).

Vasopressor-Free Days

- There was no statistically significant difference in the number of vasopressor-free days between the hydroxychloroquine group and the placebo group (odds ratio = 1.03; 95% CI, 0.61 to 1.72).

Table 20: Clinical Outcomes for Self et al.

	Self et al.[13]			
	Hydroxychloroquine N = 242	Placebo N = 237	Unadjusted absolute difference (95% CI)[a]	Adjusted odds ratio or odds ratio (95% CI)[b]
Primary outcome				
COVID Outcomes Scale score at 14 days, median (IQR)	6 (4 to 7)	6 (4 to 7)	0[c]	1.02 (0.73 to 1.42)
Secondary outcomes				
COVID Outcomes Scale score, median (IQR)[d]				
At 2 days	4 (3 to 5)	4 (3 to 5)	0[c]	1.28 (0.90 to 1.81)
At 7 days	5 (4 to 7)	6 (3 to 6)	−1 (−2 to 0)	1.16 (0.84 to 1.61)
At 28 days	6 (6 to 7)	6 (6 to 7)	0 (−1 to 1)	0.97 (0.69 to 1.38)
All-cause, all-location death, n/N (%)				
At 14 days	18/241 (7.5)	14/236 (5.9)	1.5 (−2.9 to 6.0)	1.56 (0.68 to 3.57)

	Self et al.[13]			
	Hydroxychloroquine N = 242	Placebo N = 237	Unadjusted absolute difference (95% CI)[a]	Adjusted odds ratio or odds ratio (95% CI)[b]
At 28 days	25/241 (10.4)	25/236 (10.6)	−0.2 (−5.7 to 5.3)	1.07 (0.54 to 2.09)
Time to recovery in days, median (IQR)	5 (1 to 14)	6 (1 to 15)	−1 (−3 to 1)	0.97 (0.69 to 1.35)
Composite of death or ECMO through day 28, n/N (%)	29/241 (12.0)	28/236 (11.9)	0.2 (−5.6 to 6.0)	1.13 (0.60 to 2.14)
Support-free days through day 28, median (IQR)				
Hospital-free days	21 (11 to 24)	20 (10 to 24)	1 (−1 to 3)	1.17 (0.85 to 1.61)
Oxygen-free days	21 (0 to 27)	20 (0 to 27)	1 (−2 to 4)	0.96 (0.68 to 1.34)
ICU-free days	28 (21 to 28)	28 (18 to 28)	0 (0 to 0)	1.26 (0.84 to 1.88)
Ventilator-free days	28 (28 to 28)	28 (28 to 28)	0[c]	1.26 (0.76 to 2.08)
Vasopressor-free days	28 (28 to 28)	28 (28 to 28)	0[c]	1.03 (0.61 to 1.72)

aOR = adjusted odds ratio; CI = confidence interval; COVID = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; OR = odds ratio; SAE = serious adverse event.

[a] For multilevel ordinal variables (COVID Outcomes Scale and support-free outcomes), the unadjusted absolute difference was calculated as the median value for the hydroxychloroquine group minus the median value for the placebo group; CIs were computed based on quantile regression using the PROC QUANTREG procedure. For dichotomous variables, the unadjusted absolute difference was calculated as the percentage of participants with the outcome in the hydroxychloroquine group minus the percentage of participants with the outcome in the placebo group; CIs for binomial risk differences were computed using the aWald or Agresti-Coull method.

[b] Models for the primary and secondary outcomes were constructed with trial group assignment (hydroxychloroquine versus placebo) as the independent variable, the outcome as the dependent variable, and the following co-variables: age, sex, baseline COVID Outcome Scale category, baseline Sequential Organ Failure Assessment score, and duration of acute respiratory infection symptoms prior to randomization. Multi-variable proportional odds models were used for the COVID Outcomes Scale outcomes and support-free outcomes. Multi-variable logistic regression models were used for death outcomes. Systematically collected safety events and SAEs were analyzed with simple logistic regression models without co-variable adjustment. ORs greater than 1.0 indicated more favourable outcomes for patients in the hydroxychloroquine group compared with the placebo group for the following outcomes: COVID Outcomes Scale score (aOR > 1.0 indicated a higher score on the scale) and support-free days (aOR > 1.0 indicated more support-free days). ORs > 1.0 indicated less favourable outcomes for patients in the hydroxychloroquine group compared with the placebo group for the following outcomes: death (aOR > 1.0 indicated more death) and systematically collected safety events. ORs > 1.0 indicated more safety events and more SAEs.

[c] CIs for the absolute difference were not calculated for ordinal variables with identical medians and IQRs in the hydroxychloroquine and placebo groups.

[d] The COVID Outcomes Scale is a 7-category ordinal scale that classifies a patient's clinical status.[19] The 7 categories are 1: death; 2: hospitalized, receiving ECMO or invasive mechanical ventilation; 3: hospitalized, receiving non-invasive mechanical ventilation or nasal high-flow oxygen therapy; 4: hospitalized, receiving supplemental oxygen; 5: hospitalized, not receiving supplemental oxygen; 6: not hospitalized and unable to perform normal activities; and 7: not hospitalized and able to perform normal activities.

Brown et al.

The following are some of the clinical efficacy results for Brown et al.; further information is reported in Table 21.[14]

Primary Ordinal Regression Model

- The posterior median odds ratio for a less favourable COVID Ordinal Scale for Clinical Improvement score at 14 days was 1.07 (95% credible interval [CrI], 0.63 to 1.83) for the hydroxychloroquine arm compared with the azithromycin arm. The odds ratio is consistent with a small benefit of azithromycin over hydroxychloroquine, given there is a 60% probability of hydroxychloroquine being worse than azithromycin.

COVID Ordinal Scale for Clinical Improvement at 7 Days

- The median posterior odds ratio for a less favourable COVID Ordinal Scale for Clinical Improvement score at 7 days was 1.16 (95% CrI, 0.68 to 1.96) for the hydroxychloroquine arm compared with the azithromycin arm. The odds ratio is consistent with a small benefit of azithromycin over hydroxychloroquine.

Hospital-Free Days at 28 Days

- The median posterior odds ratio for hospital-free days at 28 days was 0.91 (95% CrI, 0.54 to 1.54) for the hydroxychloroquine arm compared with the azithromycin arm. The odds ratio is consistent with a small benefit of azithromycin over hydroxychloroquine.

ICU-Free Days at 28 Days

- The median posterior odds ratio for ICU-free days at 28 days was 0.85 (95% CrI, 0.50 to 1.46) for the hydroxychloroquine arm compared with the azithromycin arm. The odds ratio is consistent with a small benefit of azithromycin over hydroxychloroquine.

Table 21: Clinical Outcomes for Brown et al.

	Brown et al.[14]
Primary outcome	
Primary ordinal regression model	Odds ratio
Odds ratio for a less favourable score COVID Ordinal Outcome at 14 days in the hydroxychloroquine arm compared with the azithromycin arm (95% CrI)	1.07 (0.63 to 1.83)[a]
Posterior probabilities from primary ordinal regression model for 14-day	Probability
P1 = Pr(OR < 1: any benefit of hydroxychloroquine over azithromycin)	0.40
P2 = Pr(OR < 1/1.25: at least moderate benefit of hydroxychloroquine over azithromycin	0.14
P3 = Pr(OR > 1): any benefit of azithromycin over hydroxychloroquine	0.60
P4 = Pr(OR > 1.25): at least moderate benefit of azithromycin over hydroxychloroquine	0.29
P5 = Pr(1 ÷ 1.2 < OR < 1.2): negligible difference between the 2 drugs	0.48
Secondary outcomes	
End point name	Odds ratio (95% CrI)
COVID Ordinal Scale for Clinical Improvement score at 7 days	1.16 (0.68 to 1.96)[a]
Hospital-free days at 28 days	0.91 (0.54 to 1.54)[b]
ICU-free days at 28 days	0.85 (0.50 to 1.46)[b]
28-day mortality	Too few events

COVID-19 = coronavirus disease 2019; CrI = credible interval; ICU = intensive care unit; OR = odds ratio; P = posterior probability; Pr = probability.

[a] An OR > 1 favours azithromycin over hydroxychloroquine for this comparison.

[b] An OR < 1 favours azithromycin over hydroxychloroquine for this comparison.

Harms (Table 22, 23, 24, 24, and 26) and detailed harms outcomes for all trials are reported in Appendix 3.

CloroCovid-19

The number of patients who experienced an adverse event, a serious adverse event, or an adverse event leading to drug discontinuation were not reported in the publication by Borba et al.[1]

Borba et al. reported laboratory safety data until day 13. More patients in the low-dosage chloroquine group (22.2%) experienced a decrease in hemoglobin of more than 3 g/dL or a

decrease equal to or greater than 30% from baseline compared with the high-dosage chloroquine group (19.2%). Serum creatinine increases of 30% or more from baseline were reported in 46.7% of patients in the low-dosage chloroquine group and in 39.1% of patients in the high-dosage chloroquine group. Creatine kinase and creatine phosphokinase myocardial band were increased in 50.0% and 53.8% of patients in the high-dosage chloroquine group, respectively. This compared with 31.6% and 23.1% of patients in the low-dosage chloroquine group, respectively. A QTc interval greater than 500 milliseconds was seen in 11.1% of the patients in the low-dosage chloroquine group compared with 18.9% of the patients in the high-dosage chloroquine group. Two patients (2.7%) in the high-dosage chloroquine group experienced ventricular tachycardia compared with no patients in the low-dosage chloroquine group.[1]

Tang et al.

In Tang et al., 30% and 8.8% of patients in the hydroxychloroquine group and the standard of care group experienced an adverse event, respectively. Diarrhea (10%) and vomiting (2.8%) were the most frequent adverse events in the hydroxychloroquine group; no patients in the standard of care group reported diarrhea or vomiting.[2]

Disease progression and upper respiratory tract infection were considered serious adverse events, which were reported in 1 patient each in the hydroxychloroquine group. No patients experienced a serious adverse event in the standard of care group. Adverse events leading to drug discontinuation were not reported.[2]

Davoodi et al.

The number of patients who experienced an adverse event, a serious adverse event, or an adverse event leading to drug discontinuation were not reported in Davoodi et al.[3]

Cavalcanti et al.

In Cavalcanti et al., 39.3% of the patients in the hydroxychloroquine plus azithromycin group experienced an adverse event, whereas 33.7% and 22.6% of the patients in the hydroxychloroquine-alone group and standard of care group experienced adverse events, respectively. QTc interval prolongation was more common in both the hydroxychloroquine plus azithromycin group (14.7%) and the hydroxychloroquine-alone group (14.6%) when compared with the standard of care group (1.7%). Also, elevated liver enzyme levels were more common among the hydroxychloroquine plus azithromycin group (10.9%) compared with the standard of care group (3.4%).[4]

Two patients in the hydroxychloroquine plus azithromycin group died, whereas no patients from the other treatment groups died in the safety population.

Skipper et al.

In Skipper et al., 43.4% of the patients in the hydroxychloroquine group experienced adverse events, whereas 21.8% of the patients in the placebo group experienced adverse events. Upset stomach, diarrhea, and neurologic side effects were the most common adverse events, with 31.1%, 23.6%, and 9.4% of the patients in the hydroxychloroquine group experiencing these symptoms, respectively, and 12.3%, 9.5%, and 6.2% of the patients in the placebo group experiencing these symptoms, respectively. There were 4 hospitalizations and 1 hospitalized death among the hydroxychloroquine group, and 10 hospitalizations and 1 hospitalized death among the placebo group; however, it should

be noted that 2 of the hospitalizations among the control group were not related to COVID-19.[5]

Abd-Elsalam et al.

The number of patients who experienced an adverse event, a serious adverse event, or an adverse event leading to drug discontinuation were not reported in the publication by Abd-Elsalam et al.[6]

Horby et al.

In Horby et al., the only harms reported involved new major cardiac arrythmias, which were only captured among a subset of the population that was randomized to each group. Of the 735 patients in the hydroxychloroquine group for which cardiac harms data were collected, 8.2% (n = 60) reported a major cardiac arrythmia. In comparison, of the 1,421 patients in the usual care group for which cardiac harms data were collected, 6.3% (n = 90) reported a major cardiac arrythmia. Only 1 patient in the hydroxychloroquine group experienced a serious adverse event, a case of torsades de pointes.[7]

Lyngbakken et al.

In Lyngbakken et al., there were a total of 125 adverse events reported in the hydroxychloroquine plus standard of care group, and a total of 112 adverse events reported in the standard of care group. Adverse events included visual disturbances, gastrointestinal discomfort, diarrhea, headache, nausea, and dizziness; however, the authors did not discern which categories of adverse events were most prevalent. In terms of serious adverse events, 18.5% (n = 5) of patients in the hydroxychloroquine plus standard of care group experienced a serious adverse event, and 23.1% (n = 6) of patients in the standard of care group experienced a serious adverse event. Serious adverse events included acute respiratory distress syndrome (n = 1), pneumonia (n = 2), respiratory failure (n = 7), and urinary tract infection (n = 1).[8]

Mitjà et al.

In Mitjà et al., 72.0% and 8.7% of patients in the hydroxychloroquine group and the standard of care group experienced an adverse event, respectively. Also, 4.8% and 6.6% of patients in the hydroxychloroquine group and the standard of care group experienced a serious adverse event, respectively, though none of the serious adverse events were adjudicated by the pharmacovigilance group as related to hydroxychloroquine. No patients in either group required mechanical ventilation or died during the study. Diarrhea, nausea, and abdominal pain were the most frequent adverse events in the hydroxychloroquine group.[9]

WHO Solidarity Trial Consortium

The number of patients who experienced an adverse event, a serious adverse event, or an adverse event leading to drug discontinuation were not reported in the WHO Solidarity Trial Consortium.[10]

Ulrich et al.

In Ulrich et al., 56.7% of the patients in the hydroxychloroquine group experienced adverse events, whereas 59.0% of the patients in the placebo group experienced adverse events. There was no statistically significant difference in the frequency of adverse events between the 2 groups (P = 0.933). Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, or constipation), rash, and headaches were the most common adverse events, with 25.4%, 1.5%, and 1.5% of the patients in the hydroxychloroquine group experiencing these symptoms, respectively, and 16.4%, 6.6%, and 3.3% of the patients in the placebo group experiencing these symptoms, respectively. There were 14 severe adverse events among the hydroxychloroquine group, and 13 among the placebo group.[11]

Khamis et al.

The authors of Khamis et al. noted there were no major side effects, such as hyperuricemia, deranged liver enzymes, or QTc interval prolongation experienced in either group.[12]

Self et al.

In Self et al., 5.8% of patients (n = 50) in the hydroxychloroquine group experienced adverse events, whereas 4.6% of patients (n = 39) in the placebo group and control group experienced adverse events. Cytopenia, aspartate aminotransferase, or alanine aminotransferase greater than or equal to twice the normal limit, and cardiac arrest treated with cardiopulmonary resuscitation (CPR) were the most common adverse events, with 38.0%, 20.7%, and 4.1% of the patients in the hydroxychloroquine group experiencing these symptoms, respectively, and 36.7%, 27.4%, and 1.7% of the patients in the placebo group experiencing these symptoms, respectively. There were 18 serious adverse events among 14 patients (5.8%) in the hydroxychloroquine group and 12 serious adverse events among 11 patients (4.6%) in the placebo group.[13]

Brown et al.

In Brown et al., adverse events and safety outcomes within the first 5 days were both common and similar between the 2 groups. Specifically, 95% of patients (n = 39) in the hydroxychloroquine group experienced adverse events, whereas 100% of patients (n = 42) in the azithromycin group experienced adverse events. The only notable difference between the 2 groups involved the development of acute kidney injury, which was present among 17% of patients (n = 6) in the hydroxychloroquine group and 0% of patients in the azithromycin group.[14]

Table 22: Summary of Harms – Treatment Trials (CloroCovid-19, Tang et al. and Davoodi et al.)

	CloroCovid-19 Borba et al.[1]		Tang et al.[2]		Davoodi et al.[3]	
	CQ low dosage N = 40	CQ high dosage N = 41	HCQ plus SoC N = 70	SoC N = 80	FBX N = 30	HCQ N = 30
Adverse events, n (%)	NR	NR	19 (27.1)	7 (8.8)	NR	NR
Serious adverse events, n (%)	NR	NR	2 (2.8)	0	NR	NR
Withdrawals due to adverse events, n (%)	NR	NR	NR	NR	NR	NR

CQ = chloroquine; FBX = febuxostat; HCQ = hydroxychloroquine; NR = not reported; SoC = standard of care.

Table 23: Summary of Harms – Treatment Trials (Cavalcanti et al., Skipper et al., and Abd-Elsalam et al.)

	Cavalcanti et al.[4] (safety population)			Skipper et al.[5]		Abd-Elsalam et al.[6]	
	HCQ plus AZ N = 239	HCQ N = 199	Control N = NR	HCQ N = 212	Placebo N = 211	HCQ plus SoC N = 97	SoC N = 97
Adverse events, n (%)[a]	94 (39.3)	67 (33.7)	NR	92 (43.4)	46 (21.8)	NR	NR
Serious adverse events, n (%)	5 (2.1)	2 (1.0)	NR	0	0	NR	NR
Withdrawals due to adverse events, n (%)	NR	NR	NR	NR	NR	NR	NR

AZ = azithromycin; HCQ = hydroxychloroquine; NR = not reported; SoC = standard of care.

[a] Adverse events reported by day 5.

Table 24: Summary of Harms – Treatment Trials (Horby et al., Lyngbakken et al., and Mitjà et al.)

	Horby et al.[7]		Lyngbakken et al.[8]		Mitjà et al.[9]	
	HCQ N = 1,561	UC N = 3,155	HCQ plus SoC N = 27	SoC N = 26	HCQ N = 169	Control N = 184
Adverse events, n (%)	NR	NR	125	112	121 (72.0)	16 (8.7)
Serious adverse events, n (%)	1	0	5 (18.5)	6 (23.1)	8 (4.8)	12 (6.6)
Withdrawals due to adverse events, n (%)	NR	NR	NR	NR	NR	NR

HCQ = hydroxychloroquine; NR = not reported; SoC = standard of care; UC = usual care.

Table 25: Summary of Harms – Treatment Trials (WHO Solidarity Trial Consortium, Ulrich et al., and Khamis et al.)

	WHO Solidarity Trial Consortium[10]		Ulrich et al.[11]		Khamis et al.[12]	
	Hydroxychloroquine N = 947	Control N = 906	Hydroxychloroquine N = 67	Placebo N = 61	Favipiravir N = 45	Hydroxychloroquine N = 44
Adverse events, n (%)	NR	NR	63	59	NR	NR
Serious adverse events, n (%)	NR	NR	14	13	NR	NR
Withdrawals due to adverse events, n (%)	NR	NR	NR	NR	NR	NR

NR = not reported.

Table 26: Summary of Harms – Treatment Trials (Self et al. and Brown et al.)

	Self et al.[13]		Brown et al.[14]	
	Hydroxychloroquine N = 242	Placebo N = 237	Hydroxychloroquine N = 42	Azithromycin N = 43
Adverse events, n (%)	50	39	39	42
Serious adverse events, n (%)	18	12	6	0
Withdrawals due to adverse events, n (%)	NR	NR	NR	NR

NR = not reported.

Evidence Results for the Prevention Trials

Patient Disposition

The patient disposition table for the prevention trials is provided in Appendix 1.

Boulware et al.

Of 6,926 patients screened, 4,687 patients were asymptomatic and eligible for inclusion in the trial. After the further exclusion of those who did not meet the inclusion criteria, 921 patients were randomized into the trial. A breakdown of which inclusion and exclusion criteria were violated was not provided. By day 1 of the trial, an additional 100 patients no longer met the inclusion criteria, as they had developed symptoms of COVID-19. This meant that 414 patients were assigned to the hydroxychloroquine group and 407 patients were assigned to the placebo group, for a total of 821 patients. Four patients in each treatment group withdrew from the trial and 46 patients in the hydroxychloroquine groups and 42 patients in the placebo group were lost to follow-up.[15]

Abella et al.

Of the 139 patients who were screened, 7 participants were excluded because of ineligibility. This left 132 patients who were randomized to either the hydroxychloroquine group (n = 66) or placebo group (n = 66). Among the patients in the placebo group, 5 were excluded. These 5 participants included 2 patients with a positive COVID-19 test result at baseline, 1 patient who never took the study medication, and 2 patients who withdrew early. Among the patients in the hydroxychloroquine group, 2 were excluded. These 2 participants included 1 patient who never took the study medication and 1 who withdrew early. Therefore, 61 patients were assigned to the placebo group, and 64 patients in the hydroxychloroquine group were evaluable for the primary objective.[16]

Rajasingham et al.

Of the 2,271 participants screened, 2,254 were from the US and 17 were from Canada. After 390 declined enrolment and 385 did not meet the criteria to be included, 1,496 were randomized (1,493 in the US and 3 in Canada). An additional 13 patients were excluded due to having reached the primary end point by the start of the study drug administration. Therefore, 1,483 participants were included in the analysis (1,480 in the US and 3 in Canada). A total of 494 patients were assigned to the once-weekly hydroxychloroquine group, 495 patients were assigned to the twice-weekly hydroxychloroquine group, and 494 patients were assigned to the placebo group.[17]

Baseline Characteristics

Boulware et al.

The baseline demographic and clinical characteristics of patients included in the Boulware et al. study are presented in Appendix 2. The median age in the hydroxychloroquine group was 41 years (IQR, 33 to 51), whereas the median age in the placebo group was 40 years (IQR, 32 to 50). Of the comorbidity data collected, hypertension was most common (12.3% in the hydroxychloroquine group and 11.8% in the placebo group), followed by asthma (7.5% in the hydroxychloroquine group and 7.6% in the placebo group) and diabetes (2.9% in the hydroxychloroquine group and 3.9% in the placebo group). The majority of

patients included in the study were health care workers (66.4% in the hydroxychloroquine group and 66.3% in the placebo group).

Abella et al.

The baseline demographic and clinical characteristics of patients included in the Abella et al. study are presented in Appendix 2. The median age in the hydroxychloroquine group was 31 years (range, 20 to 66), whereas the median age in the placebo group was 34 years (range, 23 to 62). Females comprised 82% of the hydroxychloroquine group and 56% of the placebo group. The majority of patients in the hydroxychloroquine group (82%) and the placebo group (61%) reported no comorbidities. Asthma, hypertension, and diabetes were the only comorbidities recorded, with 14%, 5%, 2% of patients in the hydroxychloroquine group, respectively, and 21%, 21%, and 5% of patients in the placebo group, respectively. The majority of participants included in the study were nurses (70% in the hydroxychloroquine group and 64% in the placebo group), followed by physicians (17% in the hydroxychloroquine group and 24% in the placebo group), and certified nursing assistants (3% in the hydroxychloroquine group and 3% in the placebo group).[16]

Rajasingham et al.

The baseline demographic and clinical characteristics of the patients included in Rajasingham et al. are presented in Appendix 2. The mean age in the once-weekly hydroxychloroquine group was 42 years, whereas the mean age in the twice-weekly hydroxychloroquine group was 41 years, and 40 years in the placebo group. Females comprised 52.8%, 52.1%, and 48.8% of the participants in the once-weekly hydroxychloroquine group, twice-weekly hydroxychloroquine group, and placebo group, respectively. High blood pressure and asthma were the only comorbid conditions recorded among participants and were present among 16.0% and 9.3% of the once-weekly hydroxychloroquine group, respectively; 13.3% and 9.1% of the twice-weekly hydroxychloroquine group, respectively; and 12.1%, and 11.9% of the placebo group, respectively. A majority of participants from all groups reported having no comorbid conditions, i.e., 63.0% in the hydroxychloroquine once-weekly group, 67.7% in the hydroxychloroquine twice-weekly group, and 68% in the placebo group.[17]

Efficacy

Boulware et al.

The clinical efficacy results for Boulware et al. are reported in Table 27.[15]

- **Incidence of laboratory-confirmed COVID-19 or illness compatible with COVID-19 at day 14:** There was no difference between the 2 groups in the number of patients with confirmed or probable COVID-19 (11.8% in the hydroxychloroquine group versus 14.3% in the placebo group; absolute difference = –2.4%; 95% CI, –7.0 to 2.2).
- **Symptoms:** There was no difference in the median symptom severity score between the 2 groups (P = 0.34).
- **Hospitalization:** 1 patient in each group required hospitalization.
- **Mortality:** There were no deaths reported in either group.

Table 27: Clinical Outcomes for Boulware et al.

	Boulware et al.[15]	
	Hydroxychloroquine N = 414	Placebo N = 407
New diagnosis at day 14		
Patients with confirmed or probable COVID-19, n (%)	49 (11.8)	58 (14.3)
Absolute difference, % (95%)	−2.4 (−7.0 to 2.2)	
P value	0.35	
Patients with laboratory-confirmed diagnosis, n (%)	11 (2.7)	9 (2.2)
P value	0.82	
Patients with symptoms compatible with COVID-19, n (%)	48 (11.6)	55 (13.5)
P value	0.46	
Symptoms		
Symptom severity score,[a] median (IQR)	2.8 (1.6 to 5.0)	2.7 (1.4 to 4.8)
P value	0.34	
Any hospitalization		
Patients requiring hospitalization, n (%)	1 (0.2)	1 (0.2)
P value	0.99	
Mortality		
Deaths, n (%)	0	0

COVID-19 = coronavirus disease 2019; IQR = interquartile range.

[a] Scale of 0 to 10, with higher scores indicating greater severity.

Abella et al.

The clinical efficacy results for Abella et al. are reported in Table 28.[16]

- **COVID-19 positivity at 8 weeks:** There was no significant difference in the proportion of COVID-19 positivity when comparing the hydroxychloroquine group with the placebo group (P > 0.99).
- **Presence of immunoglobulin G (IgG) antibody against SARS-CoV-2:** There was no significant difference in the presence of the IgG antibody against SARS-CoV-2 when comparing the hydroxychloroquine group with the placebo group (P = 0.4).
- **Treatment discontinuation:** There was no significant difference in the total number of patients discontinuing treatment at 8 weeks when comparing the hydroxychloroquine group with the placebo group (P = 0.81).
- **Adverse events:** There was a significant difference in the total number of patients experiencing adverse events at 8 weeks when comparing the hydroxychloroquine group (45%) with the placebo group (26%; P = 0.03).
- **Mean QTc interval:** There was no significant difference in the median change in QTc interval at 8 weeks when comparing the hydroxychloroquine group with the placebo group (P = 0.98).

Table 28: Clinical Outcomes for Abella et al.

	Hydroxychloroquine (N = 64)	Placebo (N = 61)
COVID-19 positivity		
Patients with confirmed RT-PCR COVID-19 at 8 weeks, n (%)	4 (6.3)	4 (6.6)
Absolute difference, % (95% CI)	−0.3 (−8.9 to 8.3)	
P value	> 0.99	
Presence of IgG antibody against SARS-CoV-2, n (%)	4 (7.4%)	2 (3.7%)
P value	0.40	
Treatment discontinuation		
Total discontinuing treatment at 8 weeks, (%)	19	16
P value	0.81	
Adverse events		
Total experiencing adverse events at 8 weeks, (%)	45	26
P value	0.03	
Diarrhea, (%)	32	12
P value	0.01	
Cardiac events		
Total experiencing adverse events at 8 weeks, (%)	0	0
P value	NA	
Change in QTc		
Median change at 8 weeks, milliseconds (95% CI)	4 (−9 to 7)	3 (−5 to 11)
P value	0.98	

CI = confidence interval; COVID-19 = coronavirus disease 2019; IgG = immunoglobulin G; NA = not applicable; RT-PCR = reverse transcription–polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; QTc = corrected QT interval.

Rajasingham et al.

The clinical efficacy results for Rajasingham et al. are reported in Table 25.[17]

Primary Outcome

- The incidence of COVID-19 or compatible illness was 0.27 events per person-year among the treatment group receiving once-weekly hydroxychloroquine, 0.28 events per person-year among the group receiving twice-weekly hydroxychloroquine, and 0.38 events per person-year among the treatment group receiving the placebo.
- The hazard ratio for confirmed COVID-19 or compatible illness in participants among the treatment group receiving once-weekly hydroxychloroquine was 0.72 (95% CI, 0.44 to 1.16; P = 0.18), whereas the hazard ratio for participants among the treatment group receiving twice-weekly hydroxychloroquine was 0.74 (95% CI, 0.46 to 1.19; P = 0.22) compared with participants in the placebo group.
- The combined hazard ratio for participants in both the once-weekly and twice-weekly hydroxychloroquine treatment groups was 0.73 (95% CI, 0.48 to 1.09; P = 0.12) compared with placebo.
- Among individuals with PCR-confirmed COVID-19, the hazard ratio for participants in the treatment group receiving once-weekly hydroxychloroquine was 0.65 (95% CI, 0.18 to 2.32; P = 0.51), whereas the hazard ratio for participants in the treatment group receiving twice-weekly hydroxychloroquine was 1.18 (95% CI, 0.40 to 3.51; P = 0.77).

- Among individuals with 80% or greater adherence to study medication, the hazard ratio for participants in the treatment group receiving once-weekly hydroxychloroquine was 0.66 (95% CI, 0.37 to 1.17; P = 0.16), whereas the hazard ratio for participants in the treatment group receiving twice-weekly hydroxychloroquine was 0.68 (95% CI, 0.37 to 1.22; P = 0.19).

Secondary Outcomes

- There were 3 hospitalizations in the treatment group receiving once-weekly hydroxychloroquine, 8 hospitalizations in the treatment group receiving twice-weekly hydroxychloroquine, and 9 hospitalizations in the treatment group receiving placebo.
- There were no patients in the study who required intensive care or who died.
- The median hydroxychloroquine drug concentration was 98 ng/mL (IQR, 82 ng/mL to 120 ng/mL) among patients in the treatment group receiving once-weekly hydroxychloroquine, and 200 ng/mL (IQR, 159 ng/mL to 258 ng/mL) in the treatment group receiving twice-weekly hydroxychloroquine (P < 0.0001).
- The median hydroxychloroquine drug concentration was 154 ng/mL (IQR, 119 ng/mL to 231 ng/mL) among those who developed COVID-19 (confirmed, probable, and possible cases), and 133 ng/mL (IQR, 93 ng/mL to 198 ng/mL) among those who did not develop COVID-19 (P = 0.08).

Table 29: Clinical Outcomes for Rajasingham et al.

	Rajasingham et al.[17]		
	HCQ once weekly N = 494	HCQ twice weekly N = 495	Placebo N = 494
Primary outcomes			
Incidence of COVID-19 (confirmed and compatible illness cases)			
Frequency of COVID-19 diagnosis, n (%)	29 (5.9)	29 (5.9)	39 (7.9)
Incidence of COVID-19, events per person-year	0.27	0.28	0.38
Hazard ratios of COVID-19 (compared with placebo)			
Hazard ratio, (95% CI)	0.72 (0.44 to 1.16)	0.74 (0.46 to 1.19)	NA
P value	0.18	0.22	NA
Combined hazard ratio of both treatment groups, (95% CI)	0.73 (0.48 to 1.09)		NA
P value	0.12		NA
Subgroup analysis: hazard ratio for individuals with PCR-confirmed COVID-19 (95% CI)	0.65 (0.18 to 2.32)	1.18 (0.40 to 3.51)	NA
P value	0.51	0.77	NA
Subgroup analysis: hazard ratio for individuals with ≥ 80% adherence to study medication, (95% CI)	0.66 (0.37 to 1.17)	0.68 (0.37 to 1.22)	NA
P value	0.16	0.19	NA
Secondary outcomes			
Hospitalizations, n	3	8	9
Intensive care unit stays, n	0	0	0
Deaths, n	0	0	0
HCQ drug concentrations, median ng/mL (IQR)	98 (82 to 120)	200 (159 to 258)	NA
P value	< 0.0001		NA

	Rajasingham et al.[17]		
	HCQ once weekly N = 494	HCQ twice weekly N = 495	Placebo N = 494
HCQ drug concentrations subgroup analysis			
HCQ drug concentrations among those who developed COVID-19, median ng/mL (IQR)	154 (119 to 231)		NA
HCQ drug concentrations among those who did not develop COVID-19, median ng/mL (IQR)	133 (93 to 198)		NA
P value	0.08		NA

CI = confidence interval; COVID-19 = coronavirus disease 2019; HCQ = hydroxychloroquine; IQR = interquartile range; NA = not applicable; ng = nanogram.

Harms

A summary of harms is provided in Table 22, Table 23, Table 24, Table 25, and Table 26. Detailed harms outcomes for the prevention trials are reported in Appendix 3.

Boulware et al.

A total of 40.1% and 16.8% of patients in the hydroxychloroquine group and in the placebo group, respectively, experienced an adverse event. The most frequently reported adverse events in the hydroxychloroquine group were diarrhea, abdominal discomfort, or vomiting (23.2%); nausea or upset stomach (22.9%); neurologic reaction, such as irritability, dizziness, or vertigo (5.4%); and headache (3.7%). The placebo group reported nausea or upset stomach (7.7%); diarrhea, abdominal discomfort, or vomiting (4.3%); neurologic reaction (3.7%); and headache (2.3%).[15]

No patients were reported to have experienced a serious adverse event. Adverse events leading to drug discontinuation were reported in 4.1% of the patients in the hydroxychloroquine group compared with 2.0% of patients in the placebo group.[15]

Abella et al.

A total of 45% and 26% of patients in the hydroxychloroquine group and in the placebo group, respectively, experienced an adverse event. The most frequently reported adverse events in the hydroxychloroquine group were diarrhea (20% grade 1, 12% grade 2), anorexia (11% grade 1, 0% grade 2), and nausea (9% grade 1, 0% grade 2). The most frequently reported adverse events in the placebo group were diarrhea (11% grade 1, 1% grade 2), nausea (8% grade 1, 0% grade 2), and headache (3% grade 1, 3% grade 2). No patients were reported to have experienced a serious adverse event consisting of a grade 3 or 4 adverse event. It is unknown to what extent adverse events led to drug discontinuation in either treatment group.[16]

Rajasingham et al.

Adverse events were reported in 21% of patients (100 of 469) in the placebo group, 31% of patients (148 of 473) in the once-weekly hydroxychloroquine group, and 36% of patients (168 of 463) in the twice-weekly hydroxychloroquine group. The most common adverse events were stomach upset and nausea (placebo, 12.2%; hydroxychloroquine once weekly, 17.5%; and hydroxychloroquine twice weekly, 19.4%), as well as gastrointestinal disturbance and diarrhea (placebo, 7.5%; hydroxychloroquine once weekly, 12.9%; and hydroxychloroquine twice weekly, 17.1%). Of note, 1 person in the hydroxychloroquine twice-weekly group was hospitalized for syncope and new supraventricular tachycardia; the

authors indicated this could have been a possible hydroxychloroquine-related serious adverse event.[17]

Table 30: Summary of Harms – Boulware et al. Trial

	Boulware et al.[15]	
	Hydroxychloroquine N = 414	Placebo N = 407
Adverse events, n/N (%)	140/349 (40.1)	59/351 (16.8)
Serious adverse events, n/N (%)	0	0
Patients not taking all the assigned intervention due to adverse events, n (%)	17 (4.1)	8 (2.0)

Table 31: Summary of Harms – Abella et al. Prevention Trial

	Abella et al.[16]	
	Hydroxychloroquine N = 65	Placebo N = 65
Adverse events, n (%)[a]	29 (45)	17 (26)
Serious adverse events, n (%)[b]	0	0
Withdrawals due to adverse events, n (%)	NR	NR

NR = not reported.

[a] Grade 1 or 2 adverse event on the Common Terminology Criteria for Adverse Events scale.

[b] Grade 3 or 4 adverse event on the Common Terminology Criteria for Adverse Events scale.

Table 32: Summary of Harms – Rajasingham et al. Prevention Trial

	Rajasingham et al.[17]		
	Hydroxychloroquine once weekly N = 473	Hydroxychloroquine twice weekly N = 463	Placebo N = 469
Adverse events, n (%)	148 (31)	168 (36)	100 (21) NR
Serious adverse events, n (%)	NR	1	NR
Withdrawals due to adverse events, n (%)	NR	NR	NR

NR = not reported.

Critical Appraisal of the Treatment Trials

CloroCovid-19[1]

Internal Validity

With the CloroCovid-19 trial being double blinded, allocation was concealed from both the patients and the researchers. Despite interventions being based on different regimens using chloroquine 150 mg tablets, both the chloroquine and placebo tablets were produced by the Farmanguinhos pharmaceutical laboratory to standardize the treatment and masking of the research team and participants.

Randomization was conducted by means of an electronically generated randomization list with 110 blocks and 4 patients per block developed by a statistician independent to the study. This list was accessible only to an unblinded pharmacist and, in the case of serious

adverse events, unblinding was available to DSMB members. Despite best intentions for randomization to yield similar populations in each treatment group, the low sample size resulting from the early termination of the study may have caused the imbalance of covariates among treatment groups. Most notably, the high-dosage group included patients with a higher mean age (54.7 years in the high-dosage group compared with 47.4 years in the low-dosage group) and more heart disease (17.9% in the high-dosage group compared with 0% in the low-dosage group), hypertension, diabetes, and asthma compared with the low-dosage group. Given the imbalances in comorbidities that could influence cardiac adverse events, it is difficult to distinguish whether the toxic effects noted in the study are primarily attributable to chloroquine.

Some of the patient characteristics were missing at baseline due to some patients being unconscious, which did not allow for complete data collection. There is no indication whether the patients for whom baseline characteristics were not collected were expected to be representative of the broader population of patients in each treatment group. In the absence of this information, it is challenging to assess the overall proportion of comorbidities in each treatment group.

External Validity

A total of 131 patients were screened for trial eligibility and 48 people did not meet the study inclusion criteria. The reasons for the exclusion of these patients at the time of recruitment were not reported. This information would have been useful for assessing the generalizability of the study population.

All patients enrolled in the study were considered to have severe COVID-19. This included patients with "clinical suspicion of COVID-19 (i.e., history of fever and any respiratory symptom, e.g., cough or rhinorrhea)…with respiratory rate higher than 24 rpm and/or heart rate higher than 125 bpm (in the absence of fever) and/or peripheral oxygen saturation lower than 90% in ambient air and/or shock (i.e., arterial pressure lower than 65 mm Hg, with the need for vasopressor medicines, oliguria, or a lower level of consciousness)."[1]

By comparison, US National Institutes of Health (NIH) guidelines define severe disease as follows: "Severe illness: individuals who have respiratory frequency greater than 30 breaths per minute, $SaO_2 \leq 93\%$ on room air at sea level, ratio of arterial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) less than 300, or lung infiltrates greater than 50%."[25] Given that the criteria the investigators used to identify severe COVID-19 cases were less restrictive for the respiratory rate than the NIH guidelines, were more restrictive for peripheral oxygen saturation, and included additional criteria (e.g., shock, the need for vasopressor medicines, oliguria, or a lower level of consciousness), the generalizability to other studies using the NIH guidelines should be interpreted with caution.

Given that laboratory confirmation of COVID-19 may have delayed randomization, patients were enrolled in the study prior to virologic confirmation of COVID-19. In sum, 31 of the 40 patients in the low-dosage group had virologic confirmation of COVID-19 by means of RT-PCR testing, whereas 9 were diagnosed on the premise of clinical-epidemiological suspicion in the absence of virologic confirmation. In comparison, 31 of the 41 patients in the high-dosage group had virologic confirmation of COVID-19 by RT-PCR testing, whereas 10 were diagnosed on the premise of clinical-epidemiological suspicion in the absence of virologic confirmation.

The following comorbidities were reported: hypertension (45.5%), diabetes (25.5%), and alcohol use disorder (27.5%), which are known risk factors for more severe COVID-19.

This trial was conducted in a single country. Therefore, it is unclear whether results would be generalizable to patients in Canada who are hospitalized with COVID-19.

The original health care providers' fact sheet on the emergency use authorization (EUA) for the chloroquine phosphate supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients indicated that the optimal dosage and duration of treatment for COVID-19 is unknown; however, the suggested dosage to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 is 1 g of chloroquine phosphate on day 1 followed by 500 mg daily for 4 days to 7 days of total treatment, based on clinical evaluation.[26] This fact sheet has since been revoked as of June 15, 2020. The revocation was based on the FDA's continued review that hydroxychloroquine sulphate and chloroquine phosphate no longer met the statutory criteria for the EUA. Despite the FDA chloroquine fact sheet being revoked after the CloroCovid-19 trial was published on April 24, 2020, the treatment regimens for CloroCovid-19 were between 2.7 g total dose for the low-dosage group and 12 g total dose for the high-dosage group. Given that the FDA recommendations for total dosage would have ranged from 2.5 g to 4.0 g, depending on the duration of treatment, the dosage in the CloroCovid-19 trial ranges from 1 g to 2 g below FDA recommendations in the low-dosage group to 3 to 4 times higher than the recommended dose in the high-dosage group.

Tang et al.[2]

Internal Validity

The randomization method used for this study was a stratified sampling according to disease severity, followed by random assignment in each stratum to ensure balanced disease severity in each treatment group. A computer was used to generate equal numbers of cards, with each group assignment number administered to patients sequentially as they were enrolled in the study. In contrast with the CloroCovid-19 trial, patients, investigators, and statisticians were not masked or blinded to the treatment assignment, as this was an open-label study where information was not withheld from the trial patients. This has the possibility to introduce bias, particularly with subjective outcomes.

While participation in the study was restricted to patients with mild and moderate illness confirmed by respiratory tract specimens with RT-PCR, the authors expanded the inclusion criteria to also include patients with severe COVID-19 (approved by the ethics committee on February 17, 2020). However, the authors noted that only 2 patients with severe COVID-19 were enrolled in the study.

Despite the study being terminated early by an independent data and safety monitoring committee due to a rapid decline in eligible new cases of COVID-19 in China, randomization appears to have balanced the baseline characteristics and comorbidities among the treatment groups. Initial intentions were to have 180 patients per group (360 total) provide a power of 80% and detect a hazard ratio of 0.7. However, with the reduced statistical power resulting from an undersized sample size, the investigators could not analyze patients with severe illness and therefore could not evaluate the planned primary outcome of symptom alleviation in patients with severe COVID-19.

Upon randomization, 60% of patients received concomitant drug treatment, with the most common being antiviral drugs (52%).

Despite the lack of control for type I error in the original protocol, both type I and type II error were considered when the sample size was recalculated in the updated protocol.

Specifically, the O'Brien-Fleming cumulative alpha and Lan-DeMets algorithm were used to control for type I error. Also related to the statistical analysis, it is important to note that the Kaplan-Meier curves crossed over time, which suggests that the proportional hazards assumption was violated for the time-to-event analyses.

External Validity

A total of 191 patients were assessed for study eligibility, with 41 patients not meeting eligibility criteria and therefore not enrolled in the study. It is unclear what eligibility criteria were not met.

The definition of COVID-19 disease severity used in this study was based on the fifth version of the Chinese guideline for the management of COVID-19. The authors note that "mild disease includes patients with mild symptoms but no manifestation of pneumonia on imaging. Moderate disease includes patients with fever, cough, sputum production, and other respiratory tract or non-specific symptoms along with manifestation of pneumonia on imaging but no signs of severe pneumonia defined as the presence of SaO_2/SpO_2 below 94% on room air or a PaO_2 to FiO_2 ratio of 300 or lower."

In comparison, the NIH guidelines define mild illness as "individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging," and moderate illness is defined as "individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥ 94% on room air at sea level."[25] While the NIH guidelines do not exactly match those of the fifth version of the Chinese guideline for the management of COVID-19, there is similarity between both guidelines for the definition of mild and moderate illness/disease. Therefore, there is reason to believe that the classifications may be generalizable; however, caution is advised, given that the definitions are not identical.

This trial was conducted in 16 COVID-19 treatment centres spanning 3 provinces in China. While the increased recruitment sites may increase the generalizability to a Chinese population, it is unclear whether the results would be generalizable to a more diverse demographic population, including patients with COVID-19 in Canada.

The dosage of hydroxychloroquine administered to patients in the treatment group was 1,200 mg daily for 3 days within 24 hours of randomization, followed by 800 mg daily for a total treatment duration of 2 weeks for patients with mild-to-moderate illness, and 3 weeks for those with severe illness. The total treatment dose was therefore 12.4 g for mild-to-moderate illness and 18 g for severe illness. The original health care providers' fact sheet, on the EUA for hydroxychloroquine sulphate supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, indicated that the optimal dosing and duration of treatment for COVID-19 is unknown; however, the suggested dose to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 is 800 mg of hydroxychloroquine phosphate on day 1, followed by 400 mg daily for 4 to 7 days of total treatment based on clinical evaluation.[27] This would yield a total treatment dose of 2.0 g to 3.2 g, depending on treatment duration. Similar to the FDA fact sheet on chloroquine, this FDA EUA has since been revoked on June 15, 2020. That was based on the FDA's continued review that hydroxychloroquine sulphate and chloroquine sulphate no longer met the statutory criteria for the EAU. Despite the FDA chloroquine fact sheet being revoked after the Tang et al. trial was published on May 6, 2020, the total dosage of hydroxychloroquine in this trial is 4 to 9 times greater than the

recommended dosage for the mild-to-moderate illness group, and 4 to 6 times greater in the severe illness group.

Davoodi et al.[3]

Internal Validity

With this study referred to by the authors as an open-label clinical trial, there is the assumption that both the researchers and patients were aware of what treatment was being administered. However, the authors indicated that "both patients and physicians did not know the contents of the tables [tablets]," and the outcome assessment was blinded. Because of the discrepancies regarding the blinding of the trial, caution is advised when interpreting the findings as those of either a blinded or open-label trial, as there are contradictions in the body of the article.

Randomization was conducted using a balanced block method to achieve 30 patients in each treatment group. Sample size calculations to arrive at the 30 patients in each group were based on an effect size of 0.3, 80% power, and an alpha of 0.05. A total of 6 patients (1 patient in the febuxostat group and 5 patients in the hydroxychloroquine group) withdrew from the study. Therefore, further sample size restraints on a study that already has a low sample size may have influenced the power to detect a statistically significant difference between the 2 groups; thus, the findings should be interpreted with caution. Despite the low sample size, patients in each treatment group were relatively balanced in terms of demographics and comorbidities. The only notable difference between the treatment groups was the higher prevalence of fever (temperature greater than 37.8°C) in the hydroxychloroquine group (80.0%) compared with the febuxostat group (55.2%).

In addition to the medications under study, patients enrolled in the study were prescribed 325 mg of acetaminophen, as needed, to control fever. It is unknown whether this dosage of acetaminophen was equal between the febuxostat and hydroxychloroquine groups, which may have influenced the likelihood of fever. To mitigate potential drug interactions, patients were excluded from entry into the study if concurrent use of azathioprine, didanosine, mercaptopurine, or pegloticase was present. The authors did not mention whether patients had concomitant use of other common medications, including ceftriaxone, azithromycin, and oseltamivir, which may have influenced the outcomes of the study.

While the authors concluded that the effects of febuxostat did not differ from hydroxychloroquine regarding the need for hospitalization and improvement in clinical symptoms, there is no mention of any control for type I error. However, statistical differences were not found between groups for any of the outcomes that were evaluated; therefore, type I error is not an issue, given the findings of this study.

External Validity

The study authors did not report the number of people screened for inclusion in the study; therefore, the generalizability of the population included in the study relative to the overall COVID-19 population cannot be assessed.

Patients with a moderate illness enrolled in the study were required to have a chest CT finding compatible with a COVID-19 infection and other associated symptoms of an active infection (e.g., cough, dyspnea). Patients also were required to have contact with a known case of COVID-19 and a creatinine clearance above 60 mL per minute. The authors made the decision to base the diagnosis on a combination of clinical symptoms, laboratory

findings, and history of exposure in order to avoid the additional time that would be required for the RT-PCR test. In comparison with the aforementioned NIH guidelines for moderate illness, there are incongruencies between the 2 definitions.[25] While there is similarity in how the authors and the NIH refer to respiratory impairment, with the authors requiring a chest CT finding and the NIH guideline requiring evidence of lower respiratory disease by clinical assessment or imaging, the difference between the 2 definitions of moderate illness surrounds the saturation of oxygen. The authors make no reference to saturation of oxygen and instead have a condition of creatinine clearance. Therefore, the generalizability of the moderate-illness patients to the other studies that use the NIH guidelines is uncertain. Furthermore, the authors' conclusion of the beneficial effect of administering febuxostat in patients with suspected mild-to-moderate COVID-19 is problematic for 2 reasons. First, in the absence of the enrolment of patients with mild COVID-19, it is uncertain whether findings from a moderate-illness population can be generalized to a mild-illness population. Second, in the absence of a standard of care for the placebo comparator group, there are insufficient grounds for a conclusion that febuxostat is beneficial.

Patients in the treatment group were administered a total daily dosage of 400 mg of hydroxychloroquine for 5 days, whereas patients in the treatment group were administered 80 mg of febuxostat daily, also for 5 days.

In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA for hydroxychloroquine sulphate supplied from the strategic national stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 2 g of hydroxychloroquine is within the range of the 2.0 g to 3.2 g, depending on treatment duration recommended in the guideline.[27]

This trial was conducted at a single fever clinic in Iran. It is unclear whether the results would be generalizable to patients in Canada diagnosed with COVID-19.

Cavalcanti et al.[4]

Internal Validity

Cavalcanti et al. reported the findings of a multi-centre, randomized, open-label, controlled trial conducted in Brazil. As this study was classified as open-label, both the patients and the investigators were aware of the trial group assignments. This has the possibility to introduce bias in the investigator-determined assessments. Furthermore, this study did not have any adjudication of trial outcomes, which may have influenced the validity of the trial results.

In terms of randomization, a trial statistician who was neither involved with patient enrolment nor medical care used blocks of 6 and stratified according to the use or non-use of supplemental oxygen at the time of randomization. Randomization was performed with both R software and REDCap, an electronic case-reporting system. While the study had originally planned to include a total of 630 patients with an ITT analysis population and a 6-level ordinal outcome to measure clinical status, the investigators amended the outcome to a 7-level ordinal outcome and used a modified ITT population of patients with RT-PCR–confirmed COVID-19. As a result, the sample size was reassessed to accommodate the revised distribution of clinical status over 7 ordinal levels. With 630 patients already having undergone randomization and 510 included in the modified ITT analysis with the revised outcome, the investigators determined they had sufficient power (80%) to detect an odds ratio of 0.5 between groups with an alpha significance level of 0.05 and accounting for

multiple comparisons. To address the issue of multiple comparisons for assessments across 3 groups, Bonferroni adjustments were conducted to reduce the significance level for between-group comparisons; however, this was for the primary outcome only.

Patients in each treatment group were relatively balanced in terms of demographics and comorbidities. When comparing patients in the modified ITT analysis with those without a confirmed diagnosis of COVID-19 (n = 161), patients without a confirmed diagnosis of COVID-19 had a higher prevalence of chronic obstructive pulmonary disease, lower prevalence of diabetes, and were less likely to receive supplemental oxygen. Despite differences between the populations with and without a confirmed diagnosis, the sensitivity analyses for the primary outcome did not demonstrate a significant effect of the treatments between groups.

External Validity

The authors described the patients included in this study as being hospitalized with mild-to-moderate COVID-19 and receiving no more than 4 litres per minute of supplemental oxygen. Aside from this, the supplemental oxygen descriptor and the additional inclusion criteria, which were more a function of the study inclusion as opposed to characteristics of mild-to-moderate illness, there is no mention of what definition was used to characterize mild-to-moderate COVID-19. In comparison, the NIH guidelines define mild illness as "individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging," and moderate illness is defined as "individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥ 94% on room air at sea level." While the authors did use RT-PCR testing to confirm the diagnosis of COVID-19, the authors make no mention of the symptoms of COVID-19 used to identify disease severity. Therefore, the generalizability of the patients with mild-to-moderate illness in this study to other studies making use of the NIH guidelines is uncertain.

This trial was conducted in 55 hospitals in Brazil. While the increased number of recruitment sites may increase the generalizability to a Brazilian population, it is unclear whether results would be generalizable to a more diverse demographic population, including patients with COVID-19 in Canada.

The dosage of hydroxychloroquine administered to patients in both the hydroxychloroquine plus azithromycin and the hydroxychloroquine-alone treatment groups was 400 mg twice daily for 7 days for a total treatment dosage of 5.6 g, irrespective of disease severity. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 5.6 g is 2 to 3 times the recommended dosage from the EAU of hydroxychloroquine sulphate, depending on treatment duration, recommended in the guideline.

Skipper et al.[5]

Internal Validity

Skipper et al. reported the findings of a randomized, double-blind, placebo-controlled trial conducted in the US and Canada (40 states and 3 provinces). With a double-blinded study design, allocation assignment was concealed from both investigators and participants.

Furthermore, the hydroxychloroquine and placebo tablets were similar in appearance with both being white and oblong in shape to better maintain the allocation masking.

Sequential randomization was conducted at 2 research pharmacies in the US (Minneapolis, Minnesota), and 1 research pharmacy in Canada (Montreal). A permutated-block randomization sequence was generated by the trial statistician using different-sized blocks and a 1:1 allocation, which was stratified by country. Asymptomatic patients initially enrolled in the parallel prophylaxis trial were randomized through a separate randomization stratum. Patients in each treatment group were relatively balanced in terms of demographics and comorbidities.

To assess the success of the masking, the authors surveyed the participants in both groups at day 14 to identify whether they believed they were receiving the placebo or the treatment. Of the participants in the hydroxychloroquine group, 49% correctly identified they received hydroxychloroquine, 7% incorrectly believed they receive the placebo, and 44% were unsure. In comparison, 30% of the participants in the placebo group correctly identified they had received the placebo, 25% incorrectly believed they received the hydroxychloroquine, and 42% were unsure. Due to the low percentages of participants correctly identifying their treatment groups, the authors concluded the masking was generally effective.

The original primary outcome of this study was a 4-level ordinal patient clinical status outcome, which was assessed at day 14. However, an interim analysis conducted on April 24, 2020 identified power concerns surrounding the low frequency of patients in the hospitalized and death categories. Accordingly, a DSMB approved modifying the primary outcome to the change in overall symptom severity over 14 days as measured by a 10-point scale visual analogue scale, which was originally a secondary outcome.

External Validity

The authors utilized the US Council of State and Territorial Epidemiologists COVID-19 case definition. According to the case definition, the clinical criteria for reporting a COVID-19 case requires at least 2 of the following symptoms in outpatient or telehealth settings: fever (measured or subjective), chills, rigours, myalgia, headache, sore throat, or new olfactory and taste disorder(s). Alternatively, clinical criteria could include 1 of the following symptoms: cough, shortness of breath, or difficulty breathing. To be diagnosed with severe respiratory illness, the case definition requires at least 1 of the following: clinical or radiographic evidence of pneumonia or acute respiratory distress syndrome. Lastly, for all clinical COVID-19 diagnoses, it was required that there be no alternative, more likely diagnosis.

While the authors included symptomatic non-hospitalized adults with probable or confirmed early COVID-19 and made inferences to a population of patients with early, mild COVID-19, there are concerns surrounding the generalizability of findings, since the authors did not provide a definition for illness severity. Granted that many of the symptoms identified in the US Council of State and Territorial Epidemiologists COVID-19 case definition also parallel the NIH guidelines for mild illness, the challenge is that the case definition used by the authors includes a range of clinical diagnostic symptoms appearing to encompass all cases from mild to severe in symptom presentation. By designing the trial to solely recruit an outpatient population, this study excludes severely critically ill patients; however, it is still unknown to what extent the included patients exhibited mild or moderate COVID-19.

Therefore, caution is advised when inferring to a population of mild COVID-19 as defined by the NIH guidelines.

Recruitment for this trial was conducted in 40 states in the US and 3 Canadian provinces (Quebec, Manitoba, and Alberta). While the increased recruitment sites may increase the generalizability to a North American population, the population of patients included in the study were noted to be young, with few comorbid conditions, and unrepresentative of persons identifying as Black or African. As such, it is unclear the extent to which findings from this study can be extrapolated beyond the study population.

The dosage of hydroxychloroquine administered to patients in the hydroxychloroquine group was 800 mg of hydroxychloroquine (four 200 mg tablets) on entry on day 1, followed by 600 mg (three 200 mg tablets) 6 to 8 hours after the loading dose and then once daily for 4 additional days for a total treatment duration of 5 days. This yielded a total treatment dosage of 3.2 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 3.2 g of hydroxychloroquine is within the range of the 2.0 g to 3.2 g dosage, depending on treatment duration, recommended in the guideline.[27]

Abd-Elsalam et al.[6]

Internal Validity

This study was referred to as a multi-centre, randomized, open-label controlled study. If efforts were not made to conceal the allocation assignment from the participants and/or investigators, this may have the potential to bias the findings of the study. In addition, the open-label nature of the trial may have imparted bias in the investigator assessment of the primary end point of recovery, which was not clearly defined in the publication.

Randomization was conducted using a random number generator using simple randomization with an equal allocation ratio. A post hoc power analysis concluded that a sample size of 97 individuals per treatment group was required to achieve a power of 80.6% and a precision of alpha of 0.05. While the simple randomization method is not as robust as randomization methods that make use of block randomization sequences, patients in each treatment group were matched on age and sex and relatively balanced in terms of baseline demographic data. However, there is no indication of whether the 2 groups were balanced in terms of disease severity at entry into the study. While the investigators stratified all participants into mild, moderate, and severe COVID-19, the authors did not specify whether there was an equal proportion of patients with differing disease severities among the 2 treatment groups.

In addition to hydroxychloroquine administered to the patients in the treatment group, the patients under study in both treatment groups were administered standard of care, which included “paracetamol, oxygen, fluids (according to assessment), empiric antibiotics (cephalosporins), oseltamivir if needed (75 mg/12 hours for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO_2 < 60 mm Hg, O_2 saturation < 90% despite oxygen or non-invasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock.” Given the concomitant use of various drug treatments, this study was unable to assess the harms of hydroxychloroquine alone. Furthermore, the authors do not mention whether patients had

concomitant use of other common medications, including ceftriaxone and azithromycin, which may have influenced the outcomes of the study.

Another issue regarding the internal validity for Abd-Elsalam et al. concerns the inconsistencies in the reporting of the statistical findings. Throughout the paper, there are various instances where the reported results do not match how those results are reported in a different location of the paper. For instance, the statistical significance for the difference in mortality rate between 2 groups is identified to be P = 0.77 in the abstract, yet P = 0.76 is reported in the results of the paper. The second inconsistency involves the reporting of the statistical significance comparing the disease severity after 28 days between the 2 groups where a P value of 0.07 was reported in the body of the results and a P value of 0.06 was reported in Table 3 of the results. While these inconsistencies do not substantially change the interpretation, since neither value is significant, this inattention to detail by the authors and publisher may be cause for concern regarding the level accuracy of the remainder of the paper.

External Validity

The study authors did not report the number of people screened for inclusion in the study; therefore, the generalizability of the population included in the study relative to the overall COVID-19 population cannot be assessed.

Patients with a mild, moderate, and severe illness were enrolled in the study using the WHO interim guidelines published on March 13, 2020. Specifically, “mild cases represented patients with uncomplicated upper respiratory tract viral infection, moderate cases represented patients with pneumonia but without need for supplemental oxygen, whereas severe disease represented cases with fever or suspected respiratory infection, plus 1 of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or $SpO_2 \leq 93\%$ on room air.” While the NIH guidelines provide more depth in the definitions for disease severity, there is reason to believe that the classifications may be generalizable; however, caution is advised, given that the definitions are not identical.

The dosage of hydroxychloroquine administered to patients in the hydroxychloroquine group was 400 mg twice daily (on day 1), followed by 200 mg tablets twice daily for 15 days, for a total treatment dosage of 6.4 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 6.4 g of hydroxychloroquine is double the range of the 2.0 g to 3.2 g dosage, depending on treatment duration, recommended in the guideline.[27]

This trial was conducted at 3 treatment centres in Egypt. It is unclear whether the results would be generalizable to patients in Canada diagnosed with COVID-19.

Horby et al.[7]

Internal Validity

Horby et al. reported the findings of a multi-centre, randomized, open-label, controlled trial involving 4,716 hospitalized patients. This study was part of the larger RECOVERY study assessing the effect of various treatments on patients with COVID-19. The part of the trial that included the hydroxychloroquine group was conducted from March 25 to June 5, 2020 at 176 hospitals in the UK. This study was classified as open-label, with both the patients

and the investigators aware of the trial group assignments. This has the possibility to introduce biased investigator-determined assessments. Furthermore, this study did not have any adjudication of trial outcomes, which may have influenced the validity of the trial results.

In terms of randomization, patients were assigned to receive either hydroxychloroquine plus the usual standard of care, or standard of care alone using a web-based unstratified randomization method. Patients were assigned in a 2:1 ratio in favour of the usual care group. While the study investigators noted the inability to estimate sample sizes when the trial was being planned, the steering committee identified that a sample size of 2,000 patients allocated to the active drug group and 4,000 patients allocated to the usual care group would be required to yield a power of 90% and a 2-sided alpha of 0.01 to detect a proportional reduction of 4 percentage points in the primary outcome of 28-day mortality between the 2 groups. However, on June 4, 2020, the independent data monitoring committee recommended the closure of the enrolment of patients to hydroxychloroquine, due to concerns that the premature termination of the study yielded insufficient power to detect a statistically significant association, had such an association been present. Also related to the statistical modelling, the authors noted a lack of control for multiple comparisons. While this would not greatly influence the main outcome of mortality at 28 days, given that no statistically significant difference between the 2 groups was found, the lack of control and multiple comparisons may have influenced the findings of other statistically significant comparisons. Despite the reduction in sample size due to the early termination of this part of the trial, patients in each treatment group were relatively balanced in terms of demographics and comorbidities.

With respect to the usual standard of care, an important point of consideration is that the authors did not specify what the usual standard of care consisted of. If the concomitant use of other drugs was a permitted form of standard of care, as it has been for other COVID-19 studies, the study may be unable to assess the toxic role of hydroxychloroquine alone. Furthermore, since patients in both groups received the usual standard of care, if the concomitant use of other drugs differed between the 2 treatment groups, this may have resulted in biased effect estimates.

External Validity

The authors described the patients included in this study as being hospitalized with clinically suspected or laboratory-confirmed SARS-CoV-2 infection; however, there is no indication of how the enrolled patients fit within the COVID-19 treatment guidelines for the clinical presentation of people with SARS-CoV-2. While hospitalized patients may represent a more severe classification of COVID-19, in the absence of any disease severity specification, the generalizability to patients in similar taxonomies may be limited.

This trial was conducted across 176 hospitals in the UK. While the increased recruitment sites may increase the generalizability to a European population, it is unclear whether results would be generalizable to a Canadian population.

The dosage of hydroxychloroquine administered to patients in the hydroxychloroquine group was a loading dose of 4 tablets (total dose, 800 mg) at baseline and again at 6 hours. This was followed by 2 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 first. This yielded a total dosage of 8.8 g in the event that hospitalized patients were not discharged prior to receiving the total dosage. In comparison with the total dosage outlined

in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID 19 in certain hospitalized patients, the total dosage of 8.8 g is 4 to 5 times the recommended dosage from the EAU for hydroxychloroquine sulphate, depending on treatment duration, recommended in the guideline.[27]

Lyngbakken et al.[8]

Internal Validity

Lyngbakken et al. reported the findings of a pragmatic, single-site, open-label RCT with 53 patients with confirmed COVID-19 infections recruited from March to May 2020 at Akershus University Hospital in Norway. As this study was classified as open-label, both the patients and the investigators were aware of the trial group assignments. This has the possibility to introduce biased investigator-determined assessments. Furthermore, there was no blinded adjudication of the trial outcomes for this study, which may have influenced the validity of the trial results.

In terms of randomization, while the authors note that a "computer randomization procedure" was utilized, there was no form of stratification, nor were there further details about the specific randomization procedures. Furthermore, with the trial being terminated prematurely due to the decreasing incidence of COVID-19 in Norway, the authors noted that the sample size was less than what was planned and resulted in lower power. However, it is unclear what the original sample size estimations were, given that they were not mentioned in either the article or the supplementary appendix. The only mention of a sample size was where the authors noted that a future clinical trial consisting of 464 patients in each arm would be required, given the exact effect estimates and SDs observed in this report. Considering the sample size in this publication is approximately 17-fold less than the required minimum sample size when considering exact effect estimates, there are further concerns in the ability of the authors to detect a statistically significant difference between the 2 treatment arms, if such a difference truly exists, given the power concerns. Also related to the statistical modelling, there was no mention of the control for multiple comparisons. While this would not influence the primary or secondary outcomes, since there were no statistically significant associations, there should have been control for multiple comparisons, given the multiple statistical methods explored by the authors.

As a result of the reduction in sample size due to early termination of the study, there are concerns this may have caused imbalances among the treatment groups. Specifically, the hydroxychloroquine plus standard of care group was younger, with an average age of 56 years compared with 69 years in the standard of care group, and there was a higher percentage of males: 70.4% versus 61.5%, respectively. Furthermore, several coexisting conditions, including hypertension, obstructive pulmonary disease and obesity, were 10% to 20% more prevalent among the standard of care group. Given the imbalances among the treatment groups, caution is advised when interpreting the findings from this study.

With respect to the standard of care, the authors specified that standard of care consisted of an appropriate level and intensity of medical treatment in accordance with local and national guidelines; however, no further information was provided on the types of treatment offered to the patients. If the concomitant use of other drugs was a permitted form of standard of care, as it has been for other COVID-19 studies, the study may be unable to assess the toxic role of hydroxychloroquine alone. Furthermore, since patients in both

groups received the usual standard of care, if the concomitant use of other drugs differed between the 2 treatment groups, this may have resulted in biased effect estimates.

External Validity

The authors described the patients included in this study as being hospitalized with moderately severe COVID-19; however, there is no indication of how the enrolled patients fit within the COVID-19 treatment guidelines for the clinical presentation of people with SARS-CoV-2. As the NIH guidelines identify specific criteria for either moderate or severe COVID-19, it is unclear what classification criteria were used to diagnose patients in this study as having moderately severe COVID-19. While hospitalized patients may represent a more severe classification of COVID-19, in the absence of any disease severity specification, the generalizability to patients in similar taxonomies may be limited.

This trial was conducted at a single site in Norway. As a result, it is unclear whether results would be generalizable to a Canadian population.

The dosage of hydroxychloroquine administered to patients in the hydroxychloroquine plus standard of care group was 400 mg twice daily for 7 days. This yielded a total dosage of 5.6 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 5.6 g is 2 to 3 times the recommended dosage from the EAU of hydroxychloroquine sulphate of 2.0 g to 3.2 g.

Mitjà et al.[9]

Internal Validity

Mitjà et al. reported the findings of a multi-centre, randomized, open-label, controlled study involving 293 non-hospitalized patients in 3 health administrative regions in Catalonia, Spain. As this study was classified as open-label, both the patients and the investigators were aware of the trial group assignments, and blinded adjudication of the trial end points did not occur. As a result, this could have introduced biased investigator-determined assessments.

In terms of randomization, participants were randomized in a 1:1 ratio to either the intervention or the comparator group through a random number generator. The sample size calculated to identify a 0.5 $\log_{10}$ mean reduction in viral load with 80% power, an alpha of 0.05, and an expected SD of 1.5 was 280 patients. Given that 293 patients were included in the ITT sample and 270 patients were included in the per-protocol sample, there are minimal concerns regarding insufficient power. Patients in each treatment and comparator group were relatively balanced in terms of demographics and comorbidities as a result of the randomization.

Primary efficacy analyses were completed on the ITT population, and sensitivity analyses were performed on the per-protocol population. Sensitivity analyses for the primary outcome did not demonstrate a statistically significant effect of the treatments between groups.

With respect to the usual standard of care, no further information was provided on the types of treatment offered to patients receiving standard of care. If the concomitant use of other drugs was a permitted form of standard of care, as it has been for other COVID-19 studies, the study may be unable to assess the toxic role of hydroxychloroquine alone. Furthermore,

since patients in both groups received the usual standard of care, if the concomitant use of other drugs differed between the 2 treatment groups, this may have resulted in biased effect estimates. Furthermore, it should be noted that an unreported number of participants who were enrolled in the hydroxychloroquine group early in the study were also administered cobicistat-boosted darunavir combined treatment, but the protocols were later adapted to limit treatment to hydroxychloroquine alone. There is the potential that the concomitant use of cobicistat-boosted darunavir may have increased the plasma levels of hydroxychloroquine.

External Validity

The authors described the patients included in this study as being non-hospitalized with mild symptoms of COVID-19, which may include "fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, or influenza-like illness for fewer than 5 days before enrolment." While the NIH guidelines provide more depth in the definitions for mild disease severity, there is reason to believe that the classifications may be generalizable; however, caution is advised, given that the definitions are not identical.

This trial was conducted in 3 health administrative regions in Catalonia (Spain) covering 60% of the Catalan population (4,206,440 residents). Given the large catchment area, there are minimal concerns about whether the findings of this study can be extended to a Catalan population; however, it is unclear whether results would be generalizable to a North American population, including patients with COVID-19 in Canada.

The dosage of hydroxychloroquine administered to patients in the group was 800 mg on day 1, followed by 400 mg daily for 6 days. This yielded a total dosage of 3.2 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 3.2 g is within the recommended dosage from the EAU of hydroxychloroquine sulphate of 2.0 g to 3.2 g.

WHO Solidarity Trial Consortium[10]

Internal Validity

The WHO Solidarity Trial Consortium reported the interim findings of a multi-centre, randomized, open-label, controlled study involving 11,330 hospital inpatients, of which 954 received hydroxychloroquine and 909 served as controls to the hydroxychloroquine group. This study was conducted in 405 hospitals in 30 countries with the objective to evaluate the effectiveness of 4 drugs on in-hospital mortality. While there were 4 treatment groups, only the results of the hydroxychloroquine group and associated control groups are pertinent to this report. This trial was adaptive in design and hydroxychloroquine was dropped from the trial on the basis of futility on June 19, 2020. As this study was classified as open-label, both the patients and investigators were aware of the trial group assignments. This has the possibility to introduce biased investigator-determined assessments.

In terms of randomization, patients were randomized twice, with the first identifying which of the 4 treatment groups they would be assigned to, and the second identifying whether they would be part of the treatment or control group. Randomization procedures were conducted in real time over the internet, following which patients were randomly allocated to a treatment group immediately following consent. While the study investigators noted the

inability to estimate sample sizes in the trial protocol, the study did not provide post hoc power calculations to verify the significance of the findings. This is an important consideration, given that the hydroxychloroquine arm of the trial was deemed futile at an interim analysis and recruitment was subsequently terminated on June 19, 2020. With the study recruiting only 954 patients to the hydroxychloroquine group and 909 patients to the control group, and with no indication of a target sample size, there may be concerns that the premature termination of the study yielded insufficient power to detect a statistically significant association, had one been present. Also, despite the reduction in sample size due to early termination of the study, patients in each treatment group were relatively balanced in terms of demographics and comorbidities.

External Validity

The authors described the patients included in this study as being hospitalized with a diagnosis of COVID-19; however, there is no indication of how the enrolled patients fit within the COVID-19 treatment guidelines for the clinical presentation of people with SARS-CoV-2. While hospitalized patients may represent a more severe classification of COVID-19, in the absence of any disease severity specification, the generalizability to patients in similar taxonomies may be limited.

This trial was conducted across 405 hospitals in 30 countries, making this trial one of the most comprehensive RCTs to date in terms of geographical representation. The external validity of this trial to a Canadian population is further reinforced, given that Canada was included as one of the participating countries. However, caution should be advised when directly inferring findings from this study to a Canadian population, since the interim findings do not indicate the proportion of the patients who were recruited from Canada.

Patients in the hydroxychloroquine intervention group were administered four 200 mg tablets of hydroxychloroquine at hour 0, four 200 mg tablets at hour 6, and, starting at hour 12, two 200 mg tablets twice daily for 10 days. This yielded a total dosage of 5.6 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 5.6 g is double the recommended dosage from the EAU of hydroxychloroquine sulphate, depending on treatment duration recommended in the guideline. The dosage used in the Solidarity trial could possibly increase the risk of hydroxychloroquine-related adverse events.

Ulrich et al.[11]

Internal Validity

Ulrich et al. reported the findings of a double-blind, multi-centre, randomized, controlled study involving 128 patients that was conducted between April 17 and May 12, 2020 at various hospitals in New York City. With a double-blinded study design, allocation assignment was concealed from both investigators and participants.

In terms of randomization, patients were randomized in a 1:1 ratio to receive either hydroxychloroquine or the placebo. While the initial sample size was calculated to be 626 patients in order to provide an error rate of 0.05, a power of 80%, and detect a 10% to 20% reduction in the end point rate in the hydroxychloroquine group, recruitment for this study was terminated early due to decreased COVID-19 admissions at the recruitment sites. Consequently, the premature cessation of recruitment resulted in the study yielding

128 participants, which is less than 25% of the target. The low sample size may not only have been underpowered to detect a statistically significant difference between the 2 groups, if such a difference truly existed, but also may have led to imbalances in randomization between the 2 groups; however, the only notable imbalance was that there was a higher proportion of patients with a body mass index of 20 kg/m^2 to less than 30 kg/m^2 in the hydroxychloroquine group.

Given that multiple statistical tests were conducted to identify the presence of differences between the 2 groups, there was no mention of the control for multiple comparisons. While this would not influence the primary or secondary outcomes, given that there were minimal statistically significant associations, there should have been control for multiple comparisons, given the multiple statistical methods conducted by the authors.

External Validity

The authors described the patients included in this study as being hospitalized with a diagnosis of COVID-19; however, there is no indication of how the enrolled patients fit within the COVID-19 treatment guidelines for the clinical presentation of people with SARS-CoV-2. While hospitalized patients may represent a more severe classification of COVID-19, in the absence of any disease severity specification, the generalizability to patients in similar taxonomies may be limited.

This trial was conducted across various hospitals in New York City. While the increased recruitment sites may increase the generalizability to a population from New York City, it is unclear whether results would be generalizable to a Canadian population.

Patients in the hydroxychloroquine intervention group were prescribed 400 mg (2 tablets) twice daily on day 1 followed by 200 mg (1 tablet) twice daily for days 2 through 5 for a total dosage of 2.4 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 2.4 g is within the recommended dosage from the EAU of hydroxychloroquine sulphate, depending on treatment duration recommended in the guideline.

Khamis et al.[12]

Internal Validity

Khamis et al. reported the findings of a randomized, open-label, controlled study involving 89 patients recruited at the Royal Hospital in Muscat, Oman. As this study was classified as open-label, both the patients and the investigators were aware of the trial group assignments. This has the possibility to introduce biased investigator-determined assessments. Furthermore, there was no blinded adjudication of trial outcomes for this study, which may have influenced the validity of the trial results.

In terms of randomization, participants were randomized by an investigator external to the study using block randomization and a computer-generated random number list. Originally, 190 patients were required to achieve 90% power to detect a 50% improvement in either clinical recovery or normalization of inflammatory markers; however, the reported sample size was only 89 patients. The authors cited logistical and financial constraints as the reasons for the low recruitment. The small sample size may have resulted not only in a lack of power to detect a statistically significant difference between the 2 groups but may also

have created imbalances in randomization between the 2 groups. While the authors assessed for the presence of imbalances between the 2 groups for each baseline demographic characteristic, there were imbalances between the treatment and control groups for chronic kidney disease and for baseline symptoms, including sore throat and diarrhea.

External Validity

The authors described the patients included in this study as being hospitalized with moderate-to-severe COVID-19, as defined by the WHO interim guideline case definitions. According to these definitions, moderate disease is defined as follows:

- "Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥ 90% on room air.
- Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40.
- While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications (p.19)."[28]

In comparison, severe disease is defined by the WHO interim guideline case definitions as follows:

- "Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus 1 of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 < 90% on room air.
- Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following:
  - Central cyanosis or SpO_2 < 90%; severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.
  - Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40.
- While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications (p. 20).[28]

Given the similarities between the case definitions depicted in the WHO interim guidelines and the NIH guidelines, there are minimal concerns regarding the external validity of the study in terms of the use of case definitions.

Similar to the critique of Davoodi et al., in the absence of a standard of care for the placebo comparator group, there are insufficient grounds to conclude that either hydroxychloroquine or favipiravir is beneficial in the treatment of COVID-19.

This trial was conducted at a single site in Oman. Therefore, it is unclear whether the results would be generalizable to a Canadian population.

The dosage of hydroxychloroquine administered to patients in the comparator group was 400 mg twice daily on day 1 followed by 200 mg twice daily for 7 days. This yielded a total dosage of 3.6 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients,

the total dosage of 3.6 g is above the recommended dosage from the EAU of hydroxychloroquine sulphate of 2.0 g to 3.2 g.

Self et al.[13]

Internal Validity

Self et al. reported the findings of a blinded, multi-centre, randomized, controlled study involving 479 patients that was conducted between April 2 and June 19, 2020 at 34 hospitals in the US. In this blinded study design, allocation assignment was concealed from the patients, treating clinicians, trial personnel, and outcome assessors.

Patients were randomized in a 1:1 ratio stratified by the enrolling hospital using randomization block sizes of 2 and 4. While the initial sample size was identified to be 510 patients in order to provide 90% power to detect an adjusted odds ratio of 1.82 for the primary outcome of difference in clinical status at 14 days, recruitment for this study was terminated at the fourth interim analysis on June 19, 2020 after the DSMB determined that it would be futile for the study to continue. Post hoc analyses identified a power of less than 1% probability of reaching the threshold of efficacy, which was defined as a greater than 95% probability of an adjusted odds ratio greater than 1.0. The low sample size may have been underpowered to detect a statistically significant difference between the 2 groups.

In terms of statistical modelling, this is one of the only studies to include a modelling strategy inclusive of interaction terms within the multi-variable proportional odds model. The inclusion of interaction/effect modification terms in the model serves to better represent a priori associations between independent variables to improve model fit. Findings were further confirmed by a sensitivity analysis among a subset of patients with laboratory-confirmed SARS-CoV-2 infection (n = 477).

The authors noted that some patients enrolled in the study were treated with open-label remdesivir (21.7%), azithromycin (19.0%), and corticosteroids (18.4%). When further stratified by treatment group, there were similarities in the use of concomitant medications between the 2 groups. Given the concomitant use of these drugs among study participants, there is a concern that the study may be unable to determine which adverse events were associated with hydroxychloroquine treatment alone. Aside from this concern, the trial investigators conducted multiple post hoc sensitivity analyses among patients treated with these medications, which further demonstrated null findings.

External Validity

The authors described the patients included in this study as being hospitalized with a diagnosis of COVID-19; however, there is no indication of how the enrolled patients fit within the COVID-19 treatment guidelines for the clinical presentation of people with SARS-CoV-2. Various inclusion criteria for the symptoms, such as cough, fever, and shortness of breath, may align with a mild illness on the clinical spectrum, whereas other symptoms, including hypoxemia or increased supplemental oxygen to maintain an SPO_2 of 92% or higher, may better align with moderate-to-severe illness on the clinical spectrum. While hospitalized patients may represent a more severe classification of COVID-19, in the absence of any disease severity specification, the generalizability to patients in similar taxonomies may be limited.

This trial was conducted across 34 hospitals in the US; however, the distribution of these treatment facilities across the US remains unknown. Generalizability may be hindered if certain locales are under-represented. Furthermore, it is unclear whether results would be generalizable to a Canadian population.

Patients in the hydroxychloroquine intervention group were prescribed 400 mg twice daily on day 1 followed by 200 mg twice daily for days 2 through 5 for a total dosage of 2.4 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 2.4 g is within the recommended dosage from the EAU of hydroxychloroquine sulphate, depending on treatment duration recommended in the guideline.

Brown et al.[14]

Internal Validity

Brown et al. reported the findings of a randomized, open-label, multi-centre, controlled study involving 85 patients recruited at 13 hospitals in Utah between April 3 and June 19, 2020. As this study was classified as open-label, both the patients and the investigators were aware of the trial group assignments. This has the possibility to introduce biased investigator-determined assessments. Furthermore, there was no blinded adjudication of the trial outcomes for this study, which may have influenced the validity of the trial results.

In terms of randomization, participants were randomized through permutated blocks with concealed allocation in a 1:1 ratio to either the hydroxychloroquine or azithromycin group. Originally, 300 patients were required to detect an odds ratio of 0.55 with 80% power; however, the DSMB providing oversight to this study recommended that the study cease enrolment based on findings from the interim analysis on the first 60 patients with 14-day follow-up on June 19, 2020. The low sample size may have been underpowered to detect a statistically significant difference between the 2 groups.

With Bayesian analyses, the posterior probabilities are dependent on the choice of prior probabilities and the likelihood. Because the authors chose to use relatively non-informative priors, this study would have benefited from a sensitivity analysis with other priors to identify the degree to which the posterior probability is influenced by the prior. This is especially important considering that the dataset was underpowered and may be heavily influenced by the prior probability.

External Validity

The authors described the patients included in this study as being hospitalized with a diagnosis of COVID-19; however, there is no indication of how the enrolled patients fit within the COVID-19 treatment guidelines for the clinical presentation of people with SARS-CoV-2. While hospitalized patients may represent a more severe classification of COVID-19, in the absence of any disease severity specification, the generalizability to patients in similar taxonomies may be limited.

This trial was conducted across 13 hospitals in Utah. While the increased recruitment sites may increase the generalizability to a population from Utah, it is unclear whether results would be generalizable to a Canadian population.

The dosage of hydroxychloroquine administered to patients in the intervention group was 400 mg twice daily on day 1 followed by 200 mg twice daily for 4 days. This yielded a total dosage of 2.4 g. In comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 3.4 g is within the recommended dosage from the EAU of hydroxychloroquine sulphate of 2.0 g to 3.2 g.

Critical Appraisal of the Prevention Trial

Boulware et al.[15]

Internal Validity

With the trial being randomized, double blind, and placebo controlled, allocation was concealed from both the participants and the researchers. Regarding randomization, statisticians for the trial generated a permutated-block randomization sequence using variably sized blocks and stratification according to country. A research pharmacist sequentially assigned patients and neither investigators nor participants were aware of the assignments.

While a sample size of 750 participants per group was initially calculated and based on the premise of a 50% relative effect size, 90% power, and an alpha of 0.05, the conditional power analysis conducted at the third interim analysis (May 6, 2020) deemed the study futile to continue, as conditional power was less than 1%. Recruitment for the study was subsequently terminated. Despite the reduction in sample size, the randomization resulted in baseline characteristics and comorbidities that were similar between treatment groups.

To assess the success of the blinding, the authors surveyed the participants in both groups at day 14 to identify whether they believed they were receiving the placebo or the treatment. Of the participants in the hydroxychloroquine group, 45.5% correctly identified they received hydroxychloroquine, and 35.7% of the participants in the control group correctly identified they received the placebo. The investigators indicated that if a participant experienced side effects, they were more likely to guess correctly that they were receiving hydroxychloroquine. This may have impacted the reporting of symptoms.

All analyses were conducted according to “the ITT principle, with 2-sided type I error with an alpha of 0.05.”

External Validity

A total of 3,528 patients out of the 6,924 patients assessed for eligibility were excluded from the trial because they did not meet eligibility criteria. The study authors did not report which eligibility criteria were not met. Therefore, the generalizability of the inclusion and exclusion criteria relative to the overall population of patients exposed to COVID-19 cannot be assessed.

Patients in the treatment group were administered an initial dose of 800 mg of hydroxychloroquine, followed by 600 mg 6 to 8 hours later, then 600 mg daily for 4 additional days, for a total dosage of 3.8 g. Placebo folate tablets that were similar to the hydroxychloroquine tablets were prescribed to patients in the control group at the same regimen.

As previously mentioned, in comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 3.8 g of hydroxychloroquine is above the acceptable range of 2.0 g to 3.2 g, depending on the treatment duration recommended in the guideline.[27]

With this trial being conducted across the US and in parts of Canada, the challenges associated with generalizing the findings to a North American population are minimal. Generalizability could have been further increased had the authors conducted weighted sampling across the US and Canada. Aside from the geographic generalizability of the findings, the online-based recruitment resulted in a generally younger and healthier population than would normally be at risk for severe COVID-19. In addition, the majority of patients enrolled in the study were health care workers. Therefore, the findings from the study may not be equally generalizable to older populations.

Abella et al.[16]

Internal Validity

Abella et al. reported the findings of a randomized, double-blind, placebo-controlled trial conducted in the US. With a double-blinded study design, allocation assignment was concealed from both investigators and participants until the second interim analysis. Furthermore, the hydroxychloroquine and placebo tablets were similar in appearance to better maintain the allocation masking. Regarding randomization, statisticians at the University of Pennsylvania Investigational Drug Service randomized participants in a 1:1 ratio to receive either hydroxychloroquine or placebo.

A sample size of 100 participants per group was initially based on the premise of a 10% infection rate in the health care worker population, a 1-sided z test alpha of 0.05, and 80% power to detect a significant difference when the difference in the population rates was at least 9%. However, for the second interim analysis, the DSMB recommended early termination of the study, given that only 4 patients in the hydroxychloroquine group and 3 patients in the placebo group had converted to positive SARS-CoV-2 status. The few positive SARS-CoV-2 conversions yielded a z score of −0.42, which was below the futility threshold of −0.27. Consequently, 3 of the recently recruited patients were advised to immediately discontinue study procedures, while 32 participants near completion were allowed to finish study procedures. As a result of the early termination of the study, the sample size was reduced to 132 between the 2 groups. There were concerns noted by the authors that the limited sample size may have reduced the power to detect a statistically significant difference between the 2 groups. Given these constraints, the study may have been underpowered to detect a modest prophylactic benefit for hydroxychloroquine.

Statistical analyses were conducted to assess the difference in baseline characteristics and comorbidities between the 2 treatment groups. Despite the reduction in sample size, the randomization resulted in baseline characteristics and comorbidities that were similar between the treatment groups. The only notable differences were that females were more prevalent in the hydroxychloroquine group (82%) compared with the placebo group (56%), and hypertension was more common among the placebo group (21%) compared with the hydroxychloroquine group (5%). These imbalances between the 2 groups may be the result of the low sample size due to the early termination of the study. The authors did not mention if blinding was assessed over the course of the treatment. While other studies that have utilized double-blind procedures have assessed the success of the blinding, the

reason why the authors did not assess the success of the blinding in the present study is unknown, given the propensity for biased results when patients are aware of the treatment group allocation.

Control for type I and II error rates was accomplished at each interim analysis.

External Validity

A total of 7 patients out of the 139 patients assessed for eligibility were excluded from the trial because they did not meet eligibility criteria. The study authors did not report which eligibility criteria were not met. Therefore, the generalizability of the inclusion and exclusion criteria relative to the overall population of patients exposed to COVID-19 cannot be assessed.

Patients in the treatment group were administered a total daily dosage of 600 mg of hydroxychloroquine daily for 8 weeks, for a total dosage of 33.6 g. Placebo microcrystalline cellulose tablets that were similar in appearance to the hydroxychloroquine tablets were prescribed to the control group at the same regimen. As previously mentioned, in comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 33.6 g of hydroxychloroquine far exceeds the acceptable range of 2.0 g to 3.2 g, depending on the treatment duration recommended in the guideline.

With this trial being conducted solely in Philadelphia, Pennsylvania, there may be challenges generalizing the findings to a broader American or Canadian population. Aside from the geographic generalizability of findings, the recruitment resulted in a generally younger population of health care workers who may have been healthier than those who would normally be at risk for severe COVID-19. In addition, the majority of patients enrolled in the study were health care workers. Therefore, the findings from the study may not be equally generalizable to older populations.

Rajasingham et al.[17]

Internal Validity

Rajasingham et al. reported the findings of a randomized, double-blind, placebo-controlled trial with 1,483 patients recruited through online recruitment in the US and Manitoba, Canada. With a double-blinded study design, allocation assignment was concealed from both investigators and participants.

Regarding randomization, participants were randomized in a 2:2:1:1 ratio to receive either 1 of the 2 hydroxychloroquine dosages or a placebo that matched each of the hydroxychloroquine doses. While it was originally planned that the study would include a total of 4,200 participants (1,050 per treatment group), the interim analysis conducted once 100 patients had completed the observation period identified z scores lower than the threshold (−0.27). With insufficient power, it was determined to be futile to continue recruiting patients and so study recruitment was terminated. Given the potential inability to detect a statistically significant association arising from the sample size limitations, caution is warranted when interpreting the findings from this study.

Patients in each treatment group were relatively balanced in terms of demographics and comorbidities.

External Validity

A total of 7 patients out of 1,483 patients included in the analysis were excluded from the trial because they did not meet eligibility criteria. The study authors did not report which eligibility criteria were not met. Therefore, the generalizability of the inclusion and exclusion criteria relative to the overall population of patients exposed to COVID-19 cannot be assessed.

Patients in the first treatment group were administered a loading dose of 400 mg of hydroxychloroquine (two 200 mg tablets) two times separated by 6 to 8 hours, followed by 400 mg (two 200 mg tablets) once weekly for 12 weeks for a total dosage of 5.6 g. In contrast, patients in the second treatment group were administered the same loading dose followed by 400 mg (two 200 mg tablets) twice weekly for the same duration for a total dosage of 10.4 g. Placebo tablets were prescribed to the patients in the control groups at the same regimens. As previously mentioned, in comparison with the total dosage outlined in the revoked fact sheet for health care providers on the EUA of hydroxychloroquine sulphate, supplied from the US Strategic National Stockpile for the treatment of COVID-19 in certain hospitalized patients, the total dosage of 5.6 g of hydroxychloroquine in the once-weekly group to 10.4 g of hydroxychloroquine in the twice-weekly group exceeds the acceptable range of 2.0 g to 3.2 g, depending on the treatment regimen. This higher treatment dosage could potentially expose patients to higher risk of serious adverse events. This may therefore limit the generalizability of these findings.

With this trial being conducted primarily in the US, there may be challenges generalizing the findings to a Canadian health care worker population. Furthermore, with this study targeting health care workers, the findings may not be equally generalizable to a more diverse population of first responders, such as paramedics, police officers, and fire fighters.

Ongoing Trials

As of November 20, 2020, there were a total of 75 ongoing clinical trials that had reached at least their phase II/III clinical development stage (Appendix 4) and had a primary completion date on or before July 2021. Among these, there were 52 ongoing COVID-19 treatment clinical studies, including 13 phase II/III, 22 phase III, and 17 phase IV trials (Table 79). There were also 23 COVID-19 prevention clinical studies. Among these, there were 10 phase III and 1 phase IV pre-exposure trials, as well as 3 phase II/III and 9 phase III post-exposure trials (Table 80). The sample sizes of included trials ranged from 30 patients to 6,400 patients. Based on the dates included in the tables, 58 trials had estimated primary completion dates of December 2020. Four trials with Canadian study sites were identified.

Discussion

Summary of Available Evidence

Seventeen RCTs had been published as of November 20, 2020. At that time, there were close to 100 ongoing trials (Appendix 4), which highlights the interest in assessing chloroquine and hydroxychloroquine to prevent or treat SARS-CoV-2 infection.

Treatment

Fourteen trials evaluated chloroquine or hydroxychloroquine as treatments for COVID-19.

Borba et al. (CloroCovid-19) was a phase IIb, single-centre, double-blind RCT of 81 patients with severe COVID-19 conducted in Brazil.[1] Patients were randomized to low-dosage chloroquine (40 patients) or high-dosage chloroquine (41 patients). Originally, the trial planned to enrol 440 patients; however, the trial was terminated early by the DSMB when a preliminary analysis showed a high number of deaths in the high-dosage chloroquine group. The original primary outcome was lethality by day 28; however, the study reported lethality by day 13. The mean age of the patients was 47.4 years and 54.7 years for the low-dosage and high-dosage chloroquine groups, respectively. All patients received concomitant therapy of ceftriaxone and azithromycin. Oseltamivir was also administered if influenza was suspected.[1]

Tang et al. was a phase IV, multi-centre, open-label RCT conducted in China that included 150 patients with mild-to-moderate COVID-19.[2] The original sample size of 200 was not reached because of a lack of eligible patients to enroll. A total of 75 patients were randomized to hydroxychloroquine and standard of care, and 75 patients were randomized to standard of care alone. Standard of care was not defined. The primary outcome was a negative conversion of SARS-CoV-2 infection by day 28 and whether patients with severe COVID-19 had clinical improvement by day 28; however, only 2 patients with severe COVID-19 were enrolled in the study. Therefore, the latter primary outcome was not evaluated. The mean age of the hydroxychloroquine plus standard of care group was 48.0 years, and 44.1 years for the standard of care group. Most patients (84%) had moderate disease and 30% of patients had a coexisting condition. During the trial, more than 60% of patients received an antiviral treatment after randomization, with the most common being Arbidol.[2]

Davoodi et al. conducted a phase III, single-centre (in Iran), open-label RCT of 60 outpatients with moderate respiratory illness due to COVID-19.[3] Patients were allocated to receive either febuxostat (30 patients) or hydroxychloroquine (30 patients) for 5 days. The primary end point was the frequency of hospitalization. Patients in the febuxostat group had a mean age of 58.0 years and those in the hydroxychloroquine group had a mean age of 57.7 years. Approximately 28% of the patients had diabetes.[3]

Cavalcanti et al. reported the findings of a multi-centre, randomized, open-label, 3-group, controlled study involving 667 patients with suspected or confirmed COVID-19. This trial included 2 intervention groups and 1 control group. Patients in the first intervention group were administered hydroxychloroquine, whereas patients in the second intervention group were administered the same dosage and frequency of hydroxychloroquine plus azithromycin. The primary outcome was clinical status at 15 days post-hospitalization evaluated by a 7-level ordinal scale, with a higher score indicating a worse condition. The

mean age in the hydroxychloroquine plus azithromycin group was 49.6 years, whereas the mean age in the hydroxychloroquine group was 51.3 years, and 49.9 years in the control group.[4]

Skipper et al. reported the findings of a randomized, double-blind, placebo-controlled trial involving 491 participants conducted in the US and Canada (40 states and 3 provinces). Patients enrolled into the trial were randomized to either the treatment group (hydroxychloroquine) or the placebo group. American patients in the placebo group received folic acid prescribed at the same frequency and duration as the intervention group, whereas Canadian patients in the placebo group received lactose tablets in place of folic acid. The initial primary outcome for this study was the assessment of patient clinical status at day 14 using an ordinal scale comprising 4 categories: not hospitalized, hospitalized, ICU, or death. However, an interim analysis identified power concerns surrounding the low frequency of patients in the hospitalized and death categories. Accordingly, a DSMB approved changing the primary outcome to the change in overall symptom severity over 14 days, as measured by a 10-point scale. The mean age in the hydroxychloroquine group was 41 years, whereas the mean age in the placebo group was 39 years.[5]

Abd-Elsalam et al. reported the findings of a multi-centre open-label RCT with 194 patients with confirmed COVID-19 infections recruited from 3 tertiary referral centres in Egypt. Patients in the treatment group (n = 97) were administered hydroxychloroquine for 15 days, which was added to the standard of care treatment adopted by the Egyptian medical officer of health. In contrast, patients in the comparator (n = 97) group received standard of care alone for 15 days. Standard of care included paracetamol, oxygen, fluids, empiric antibiotics (cephalosporins), oseltamivir, and invasive mechanical ventilation with hydrocortisone for severe cases. The primary outcome of this study was the percentage of patients recovered within 28 days. The mean age in the hydroxychloroquine plus standard of care group was 40.4 years, whereas the mean age in the standard of care alone group was 41.1 years.[6]

Horby et al. reported the findings of a multi-centre, randomized, open-label, controlled study involving 4,716 hospitalized patients. This study was part of the larger RECOVERY trial assessing the effect of various treatments on patients with COVID-19 at 176 hospitals in the UK. Enrolment was terminated early after an interim analysis by an independent data monitoring committee determined there was a lack of efficacy, as hydroxychloroquine had no apparent beneficial effect in patients hospitalized with COVID-19. The primary outcome was all-cause mortality within 28 days after randomization. The mean age in the hydroxychloroquine group was 65.2 years, whereas the mean age in the usual care group was 65.4 years.[7]

Lyngbakken et al. reported the findings of a pragmatic, single-site, open-label RCT with 53 patients with confirmed COVID-19 infections recruited from March to May 2020 at Akershus University Hospital in Norway. Patients in the treatment group (n = 27) were administered hydroxychloroquine, whereas patients in the comparator group (n = 26) received the standard of care. Standard of care included an appropriate level and intensity of medical treatment in accordance with local and national guidelines. The trial was terminated prematurely due to the decreasing incidence of COVID-19 in Norway. The primary outcome of this study was the rate of decline in SARS-CoV-2 viral load in the oropharynx from baseline through the first 96 hours after randomization. The mean age in the hydroxychloroquine plus standard of care group was 56 years, whereas the mean age in the standard of care group was 69 years.[8]

Mitjà et al. reported the findings of a multi-centre, randomized, open-label, controlled study involving 293 non-hospitalized patients recruited in 3 health administrative regions in Catalonia, Spain. Patients in the intervention group (n = 157) were administered hydroxychloroquine, whereas patients in the comparator group (n = 136) were provided with the usual standard of care, which was not directly specified in the publication. The protocol was adapted to hydroxychloroquine alone, mainly due to lack of data supporting the efficacy of darunavir to treat COVID-19. The primary outcome was the reduction of viral RNA load in nasopharyngeal swabs at days 3 and 7 after treatment start. The mean age in the hydroxychloroquine group was 41.6 years, whereas the mean age in the standard of care group was 41.7 years.[9]

The WHO Solidarity Trial Consortium reported the interim findings of a multi-centre, randomized, open-label, controlled study involving 11,330 hospital inpatients conducted in 405 hospitals in 30 countries. While there were 4 treatment groups, only the results of the hydroxychloroquine group (n = 954) and associated control group (n = 909) are pertinent to this report. This trial included 4 intervention groups and a non-mutually exclusive comparator (standard of care) group for each intervention group. Patients in the 4 intervention groups were assigned either remdesivir, hydroxychloroquine, lopinavir, or interferon. Patients in the comparator groups were provided with the standard of care that was defined in each local hospital for the same duration. Recruitment was terminated for hydroxychloroquine due to futility. The primary outcome was in-hospital mortality before or after day 28. There were 335 patients less than 50 years old in the hydroxychloroquine group, and 317 patients in the same age stratification in the control group. There were 410 patients in the 50 to 69 years old stratification in the hydroxychloroquine group, and 396 patients in the same age stratification in the control group. Lastly, there were 202 patients in the 70 years old age stratification in the hydroxychloroquine group, and 193 patients in the same age stratification in the control group.[10]

Ulrich et al. reported the findings of a double-blind, multi-centre, randomized, controlled study involving 128 patients recruited at various hospitals in the New York City metropolitan area. Patients in the intervention group (n = 67) were administered hydroxychloroquine, whereas patients in the comparator groups (n = 61) were provided with placebo calcium citrate tablets prescribed at an identical regimen as hydroxychloroquine in the intervention group. Recruitment for this study was terminated early due to decreased COVID-19 admissions at the recruitment sites. The primary outcome was the proportion of patients meeting a severe COVID-19 progression composite end point at day 14, whereas the primary safety outcome was the cumulative incidence of serious adverse events, grade 3 or 4 adverse events, and/or discontinuation of therapy at day 30. The mean age in the hydroxychloroquine group was 66.5 years, whereas the mean age in the placebo group was 65.8 years.[11]

Khamis et al. reported the findings of a randomized, open-label, controlled study involving 89 patients recruited at the Royal Hospital in Muscat, Oman. The objective of this study was to evaluate the therapeutic effectiveness of favipiravir combined with inhaled interferon beta-1b versus hydroxychloroquine in adult patients hospitalized with moderate-to-severe COVID-19 pneumonia. Patients in the intervention group (n = 45) were administered favipiravir and interferon beta-1b, whereas patients in the comparator group (n = 44) were prescribed hydroxychloroquine. The primary outcomes were the time from assignment to clinical recovery, the normalization of inflammatory markers, and an improvement in oxygen saturation that is maintained for at least 72 hours. The mean age in the favipiravir group was 54 years, whereas the mean age in the hydroxychloroquine group was 56 years.[12]

Self et al. reported the findings of a blinded, multi-centre, randomized, placebo-controlled clinical trial involving 479 patients recruited at 34 hospitals in the US. Patients in the intervention group (n = 242) were administered hydroxychloroquine sulphate, whereas patients assigned to the placebo group (n = 237) received matching placebo in the same dosing frequency. Recruitment for this study was terminated at the fourth interim analysis after the DSMB determined it would be futile for the study to continue. The primary outcome was clinical status 14 days after randomization, assessed using a 7-category ordinal scale (the COVID Outcomes Scale) recommended by the World Health Organization. The mean age in the hydroxychloroquine group was 58 years, whereas the mean age in the placebo group was 57 years.[13]

Brown et al. reported the findings of a randomized, open-label, multi-centre, controlled study involving 85 patients recruited at 13 hospitals in Utah, US. Patients in the intervention group (n = 42) were administered hydroxychloroquine sulphate, whereas patients in the comparator groups (n = 43) were prescribed azithromycin for the same duration. The DSMB providing oversight to this study recommended that the study cease enrolment based on findings from the interim analysis on the first 60 patients with 14-day follow-up. The primary outcome was the day 14 COVID Ordinal Scale for Clinical Improvement score. The mean age in the hydroxychloroquine group was 51 years, whereas the mean age in the azithromycin group was 58 years.[14]

Prevention

Three trials assessed hydroxychloroquine as a prophylactic treatment post–COVID-19 exposure.

Boulware et al. was a phase III, double-blind, placebo-controlled RCT conducted in the US and Canada.[15] Adults with moderate- or high-risk exposure to COVID-19 received hydroxychloroquine (n = 414) or placebo (n = 407) within 4 days of exposure. The initial sample size was 1,500 participants, with pre-planned interim analyses. At the third interim analysis, the trial was stopped for futility. The primary outcome was the incidence of laboratory-confirmed COVID-19 or illness compatible with COVID-19 within 14 days. The median age of patients in the hydroxychloroquine group was 41.0 years, and 40.0 years in the placebo group. A total of 66% of participants were health care workers and 87% of participants were in a high-risk exposure group. More than 70% of participants did not have a coexisting condition.[15]

Abella et al. reported the findings of a randomized, double-blind, placebo-controlled trial with 132 patients in 2 tertiary urban hospitals, part of a single health system, in Philadelphia, Pennsylvania. Patients assigned to the treatment group received hydroxychloroquine, whereas patients in the placebo group received a size-matched placebo prescribed at the same frequency and duration as the intervention group. For the second interim analysis, the DSMB recommended early termination of the study, given that only 4 patients in the hydroxychloroquine group and 3 patients in the placebo group had converted to positive SARS-C0V-2 status. The primary outcome of this study was the rate of conversion to SARS-CoV-2–positive status via nasopharyngeal swab in enrolled participants during the 8 weeks of study participation. The median age in the hydroxychloroquine group was 31 years, whereas the median age in the placebo group was 34 years.[16]

Rajasingham et al. reported the findings of a randomized, double-blind, placebo-controlled trial with 1,483 patients recruited through online recruitment in the US and Manitoba, Canada. Patients enrolled into the trial were randomized in a 2:2:1 ratio to receive either a high dosage of hydroxychloroquine (n = 463), a low dosage of hydroxychloroquine (n = 473), or the placebo (n = 469). An interim analysis conducted once 100 patients had completed the observation period determined it was futile to continue recruiting patients and study recruitment was terminated. The primary outcome of this study was COVID-19–free survival time by laboratory-confirmed or probable compatible illness. The mean age in the once-weekly hydroxychloroquine group was 42 years, whereas the mean age in the twice-weekly hydroxychloroquine group was 41 years, and 40 years in the placebo group.[17]

Interpretation of Results

Treatment

Efficacy

In Borba et al. (CloroCovid-19), statistically significantly more patients in the high-dosage chloroquine group (39%) died compared with the low-dosage chloroquine group (15%) (odds ratio = 3.6; 95% CI, 1.2 to 10.6; P = 0.03).[1] One limitation of the trial is the lack of a placebo or standard of care group.[1]

In Tang et al., no statistically significant differences were observed between hydroxychloroquine plus standard of care and standard of care alone for several clinical outcomes in patients with mild or moderate disease, including negative conversion by day 28 and median time to alleviation of clinical symptoms of COVID-19.[2] This may be attributed to the early termination of the study and a smaller sample size than anticipated. There was also a delay between symptom onset and the administration of treatment (median 16 days).[2]

Davoodi et al. reported no statistically significant differences between hydroxychloroquine and febuxostat for the outcomes of mortality, ICU care, the reduction in lung involvement, and the number of patients with a negative lung CT at day 14.[3] The trial was not blinded and lacked a placebo or standard of care group.[3]

Cavalcanti et al. reported there was no statistically significant difference in the proportion of patients having a higher score measured with a 7-level ordinal scale at 15 days when comparing the hydroxychloroquine plus azithromycin group with the control group (odds ratio = 0.99; 95% CI, 0.57 to 1.73; P = 1.00). There was no statistically significant difference in the proportion of patients having a higher score when comparing the hydroxychloroquine-alone group with the control group (odds ratio = 1.21; 95% CI, 0.69 to 2.11; P = 1.00). Lastly, there was no statistically significant difference in the proportion of patients having a higher score when comparing the hydroxychloroquine plus azithromycin group with the hydroxychloroquine-alone group (odds ratio = 0.82; 95% CI, 0.47 to 1.43; P = 1.00).[4]

Skipper et al. reported there was no statistically significant difference in the change in symptom severity score over 14 days between the hydroxychloroquine and placebo groups (absolute difference = −0.27; 95% CI, −0.61 to 0.07 points; P = 0.117).[5]

Abd-Elsalam et al. reported there was no significant difference in the disease severity after 28 days when comparing the hydroxychloroquine plus standard of care group with the standard of care group (P = 0.06). There was also no significant difference in the proportion of participants that died when comparing the hydroxychloroquine plus standard of care

group (6.1%) with the standard of care alone group (5.1%; P = 0.76), and no significant difference in the proportion of participants requiring mechanical ventilation when comparing the hydroxychloroquine plus standard of care group (4.1%) with the standard of care alone group (5.2%; P = 0.75).[6]

Horby et al. reported there was no significant difference in 28-day mortality when comparing the hydroxychloroquine plus standard of care group with the standard of care group (27.0% vs. 25.0%; rate ratio = 1.09; 95% CI, 0.97 to 1.23, P = 0.15). Results were consistent across all pre-specified subgroups, including age, sex, race or ethnic group, days since symptom onset, respiratory support at randomization, and baseline risk.[7]

Lyngbakken et al. reported there was no significant difference in rate of reduction in SARS-CoV-2 viral load at 24 hours when comparing the hydroxychloroquine plus standard of care group (0.24; 95% CI, 0.03 to 0.46) with the standard of care group (0.14; 95% CI, −0.10 to 0.37).[8]

Mitjà et al. reported there was no significant difference in the reduction in viral load in nasopharyngeal swabs when comparing the hydroxychloroquine group with the standard of care group at day 3 or 7. There was a mean difference of 0.01 (95% CI, −0.28 to 0.29) in the hydroxychloroquine group at day 3, and a mean difference of −0.07 (95% CI, −0.44 to 0.29) in the hydroxychloroquine group at day 7.[9]

The WHO Solidarity Trial Consortium reported there was no statistically significant differences in the likelihood of mortality between the treatment group and the control group among stratified subgroup analyses (less than 50 years old, 50 to 69 years old, 70 years old or older, no mechanical ventilation at entry, and mechanical ventilation at entry). The clinical outcome of the need for initiating ventilation was similar in the hydroxychloroquine group (8.7%) and the control group (8.0%). Lastly, the percentage of patients ever reported as discharged who were still in the hospital at various times was similar in the hydroxychloroquine group and the control group at 7 days (n = 64 and n = 54, respectively), 14 days (n = 23 and n = 20, respectively), and 21 days (n = 11 and n = 10, respectively).[10]

Ulrich et al. reported there was no statistically significant difference in the likelihood of severe disease progression at day 14 between the hydroxychloroquine group (16.4%) and the placebo group (9.8%; P = 0.350).[11]

Khamis et al. reported there was no statistical difference in any of the inflammatory markers between the favipiravir and the hydroxychloroquine group. There was no statistically significant difference in the length of hospital stay between the favipiravir group (median = 7 days; IQR, 4 to 12) and the hydroxychloroquine group (median = 7 days; IQR, 3 to 11; P = 0.948), and there was no statistically significant difference in the oxygen saturation between the favipiravir group (median = 94%; IQR, 93 to 96) and the hydroxychloroquine group (median = 95%; IQR, 93 to 96; P = 0.324). [12]

Self et al. reported there was no statistically significant difference in the COVID Outcomes Scale score at 14 days between the hydroxychloroquine group and the placebo group (odds ratio = 1.02; 95% CI, 0.73 to 1.42).[13]

Brown et al. reported that the posterior median odds ratio for a less favourable COVID Ordinal Scale for Clinical Improvement score at 14 days was 1.07 (95% CrI, 0.63 to 1.83) for the hydroxychloroquine arm compared with the azithromycin arm. The odds ratio is consistent with azithromycin having a small benefit over hydroxychloroquine, given there is a 60% probability of hydroxychloroquine being worse than azithromycin.[14]

Harms

Overall adverse events, serious adverse events, and withdrawals due to adverse events were not reported in CloroCovid-19, Davoodi et al., Abd-Elsalam et al., or the WHO Solidarity Trial Consortium. Borba et al. reported a higher incidence of cardiac adverse events with high-dosage chloroquine compared with low-dosage chloroquine.[1]

In Tang et al., there were more patients with an adverse event in the hydroxychloroquine (plus standard of care) group compared with standard of care (27.1% versus 8.8%, respectively).[2] The most frequently reported adverse events with hydroxychloroquine were gastrointestinal adverse events (diarrhea or vomiting). Two patients reported a serious adverse event with hydroxychloroquine (disease progression and upper respiratory tract infection).[2]

In Cavalcanti et al., there were more patients with an adverse event in the hydroxychloroquine plus azithromycin group compared with the standard of care group (33.7% versus 22.6%, respectively). QTc interval prolongation was more common in both the hydroxychloroquine plus azithromycin group (14.7%) and the hydroxychloroquine-alone group (14.6%) when compared with the standard of care group (1.7%).[4]

In Skipper et al., there were more adverse events reported in the hydroxychloroquine group (43.4%) compared with the placebo group (21.8%). Upset stomach, diarrhea, and neurologic side effects were the most common adverse events with 31.1%, 23.6%, and 9.4% of the patients in the hydroxychloroquine group experiencing these symptoms, respectively, and 12.3%, 9.5%, and 6.2% of the patients in the placebo group experiencing these symptoms, respectively.[5]

In Horby et al., 8.2% of the patients in the hydroxychloroquine group reported a major cardiac arrythmia, whereas 6.3% of the patients in the usual care group reported a major cardiac arrythmia. Only 1 patient in the hydroxychloroquine group experienced a serious adverse event, a case of torsades de pointes.[7]

In Lyngbakken et al., there were more adverse events reported in the hydroxychloroquine plus standard of care group (n = 125), compared with the standard of care alone group (n = 112). Adverse events included visual disturbances, gastrointestinal discomfort, diarrhea, headache, nausea, and dizziness; however, the authors did not discern which categories of adverse events were most prevalent. In terms of serious adverse events, 18.5% (n = 5) of patients in the hydroxychloroquine plus standard of care group experienced a serious adverse event, and 23.1% (n = 6) of patients in the standard of care alone group experienced a serious adverse event.[8]

In Mitjà et al., there were more adverse events reported in the hydroxychloroquine group (72.0%), compared with the standard of care group (8.7%). Also, 4.8% and 6.6% of patients in the hydroxychloroquine group and the standard of care group experienced a serious adverse event, respectively, although none of the serious adverse events were adjudicated by the pharmacovigilance group as being related to hydroxychloroquine. Diarrhea, nausea, and abdominal pain were the most frequent adverse events in the hydroxychloroquine group.[9]

In Ulrich et al., the frequency of adverse events was similar between the patients in the hydroxychloroquine group (56.7%) compared with patients in the placebo group (59.0%). Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, constipation), rash, and headaches were the most common adverse events with 25.4%, 1.5%, and 1.5% of the patients in the hydroxychloroquine group experiencing these symptoms, respectively, and

16.4%, 6.6%, and 3.3% of the patients in the placebo group experiencing these symptoms, respectively. There were 14 severe adverse events among the hydroxychloroquine group, and 13 among the placebo group.[11]

In Khamis et al. the authors noted there were no major side effects, such as hyperuricemia, increased liver enzymes, or QTc interval prolongation, experienced in either group.[12]

In Self et al., there were more adverse events reported in the hydroxychloroquine group (5.8%), compared with the placebo group (4.6%). Cytopenia, aspartate aminotransferase, or alanine aminotransferase greater than or equal to twice the normal limit, and cardiac arrest treated with CPR were the most common adverse events, with 38.0%, 20.7%, and 4.1% of the patients in the hydroxychloroquine group experiencing these symptoms, respectively, and 36.7%, 27.4%, and 1.7% of the patients in the placebo group experiencing these symptoms, respectively. There were 18 serious adverse events in the hydroxychloroquine group and 12 serious adverse events in the placebo group.[13]

In Brown et al., adverse events and safety outcomes within the first 5 days were both common and similar between the hydroxychloroquine group (95%) compared with the azithromycin group (100%).[14]

Prevention

Efficacy

Hydroxychloroquine was not effective at preventing COVID-19 after disease exposure compared with placebo in Boulware et al.[15] There were no statistically significant differences in patients with confirmed or probable COVID-19 at day 14 or in symptom severity score. As laboratory testing to confirm infection was not available to most participants, a symptomatic case definition was used to identify cases of probable COVID-19. This could have led to participants with non–SARS-CoV-2 viral infection to be labelled as having COVID-19.[15]

Abella et al. reported there was no significant difference in the proportion of patients with COVID-19 positivity when comparing the hydroxychloroquine group with the placebo group ($P > 0.99$). In addition, there was no significant difference in the presence of the IgG antibody against SARS-CoV-2 when comparing the hydroxychloroquine group with the placebo group ($P = 0.4$), and there was no significant difference in the total discontinuing treatment at 8 weeks when comparing the hydroxychloroquine group with the placebo group ($P = 0.81$).[16]

Rajasingham et al. reported that the incidence of COVID-19 or compatible illness was 0.27 events per person-year among the treatment group receiving once-weekly hydroxychloroquine treatment, 0.28 events per person-year among the treatment group receiving twice-weekly hydroxychloroquine treatment, and 0.38 events per person-year among the treatment group receiving the placebo. The hazard ratio for confirmed COVID-19 or compatible illness in participants among the treatment group receiving once-weekly hydroxychloroquine treatment was 0.72 (95% CI, 0.44 to 1.16; $P = 0.18$), whereas the hazard ratio for participants among the treatment group receiving twice-weekly hydroxychloroquine treatment was 0.74 (95% CI, 0.46 to 1.19; $P = 0.22$), compared with participants in the placebo group.[17]

Harms

In Boulware et al., more patients had an adverse event with hydroxychloroquine than with placebo (40.1% versus 16.8%, respectively).[15] While there were no serious adverse events reported in either group, 4.1% of patients in the hydroxychloroquine group reported not taking all of their assigned medication due to an adverse event compared with 2.0% of the patients in the placebo group. The most commonly reported adverse events in the hydroxychloroquine group were nausea or upset stomach; diarrhea, abdominal discomfort, or vomiting; irritability, dizziness, or vertigo; and headache.[15]

In Abella et al., there were more adverse events reported in the hydroxychloroquine group (45%) compared with the placebo group (26%). The most frequently reported adverse events in the hydroxychloroquine group were diarrhea, anorexia, and nausea, whereas the most frequently reported adverse events in the placebo group were diarrhea, nausea, and headache. No patients were reported to have experienced a serious adverse event consisting of a grade 3 or 4 adverse event.[16]

In Rajasingham et al., there were more adverse events reported in the twice-weekly hydroxychloroquine group (36%) compared with the once-weekly hydroxychloroquine group (31%) and the placebo group (21%). The most common adverse events were stomach upset and nausea, as well as gastrointestinal disturbance and diarrhea. Of note, 1 person in the hydroxychloroquine twice-weekly group was hospitalized for syncope and new supraventricular tachycardia.[17]

Conclusions

The included RCTs differed in important aspects of their design, including trial location; countries; single-centre versus multi-centre; inclusion criteria; populations, doses, and duration of treatment; comparators; and primary outcomes; which precludes the direct comparison of results across studies. Various limitations of the trials were noted, which affects their internal validity. The trials often included adult patients with few comorbidities. The current evidence does not support the use of high-dosage chloroquine because of concerns of cardiac toxicity and increased lethality relative to low-dosage chloroquine. The results of the included studies also do not support the use of hydroxychloroquine for treating patients with mild, moderate, or severe COVID-19, nor does hydroxychloroquine appear to prevent COVID-19 post-exposure.

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Appendix 1: Patient Disposition

Table 33: Patient Disposition for Borba et al. (CloroCovid-19)[1]

	Chloroquine low dosage	Chloroquine high dosage
Screened, N	131	
Excluded, N	50	
Did not meet inclusion criteria	48	
Declined to participate	2	
Randomized, N	40	41

Table 34: Patient Disposition for Tang et al.[2]

	Hydroxychloroquine plus standard of care	Standard of care
Screened, N	191	
Did not meet eligibility criteria, N	41	
Randomized, N	75	75
Did not received hydroxychloroquine, N	6	NA
Withdrew consent	3	NA
Refused treatment	3	NA
Received hydroxychloroquine in error, N	NA	1
ITT population,[a] N	75	75
Safety population,[b] N	70	80

NA = not applicable; ITT = intention to treat.

[a] ITT population: Patients who were randomly assigned to the treatment group or control group. Analyses of efficacy were to be based on this population. The ITT analyses grouping was to be according to the treatment planned.

[b] Safety population: Patients who had received at least 1 administration of any study treatment (partial or complete). This population was to be used for all safety analyses. The safety analyses grouping was to be according to the treatment actually received.

Table 35: Patient Disposition for Davoodi et al.[3]

	Febuxostat	Hydroxychloroquine
Screened, N	NR	
Did not meet eligibility criteria, N	NR	
Randomized, N	30	30
Withdrawals, N	1	5
Did not take laboratory tests	1	3
Changed physician	0	1
Other	0	1
Population analyzed, N	29	25

NR = not reported.

Table 36: Patient Disposition for Cavalcanti et al.[4]

	Hydroxychloroquine plus azithromycin	Hydroxychloroquine	Control
Screened, N	760		
Did not meet eligibility criteria, N	57		
Were eligible but not randomized, N	36		
Randomized, N	217	221	229
Withdrawals, N			
Withdrew consent after randomization	1		
Enrolled twice	1		
ITT population at baseline, N	217	221	227
Modified ITT population at baseline[a]	172	159	173
Population analyzed, N	172	159	173

ITT = intention to treat.

[a] The upper limit of normal for D dimer is 500 ng/mL. Information on comorbidities was obtained from the medical records.

Table 37: Patient Disposition for Skipper et al.[5]

	Hydroxychloroquine	Placebo
Screened, N	6,924	
Did not meet eligibility criteria, N	6,433	
Randomized, N	244	247
Withdrawals, N		
Lost to follow-up	13	13
Had vital status data (removed from population analyzed, but contributed to secondary end points)	19	23
Population analyzed, N	212	211

Table 38: Patient Disposition for Abd-Elsalam et al.[6]

	Hydroxychloroquine	Placebo
Screened, N	NR	
Did not meet eligibility criteria, N	NR	
Randomized, N	97	97
Withdrawals, N	NR	NR
Population analyzed, N	97	97

NR = not reported.

Table 39: Patient Disposition for Horby et al.[7]

	Hydroxychloroquine	Usual care
Screened, N	11,197	
Did not meet eligibility criteria, N		
Did not have access to hydroxychloroquine at their hospital	639	
Were considered unsuitable for receiving hydroxychloroquine	3,199	
Randomized to receive hydroxychloroquine or other treatments	7,513	
Assigned to another active treatment	2,797	
Assigned to lopinavir plus ritonavir	1,010	
Assigned to dexamethasone	1,170	
Assigned to azithromycin	617	
Randomized to receive hydroxychloroquine or usual care alone	4,716	
Assigned to group	1,561	3,155
Received hydroxychloroquine	1,430	12
Withdrew consent	3	5
Proceeded to second randomization	75	178
Included in 28-day intention-to-treat analysis	1,561	3,155

Table 40: Patient Disposition for Lyngbakken et al.[8]

	Hydroxychloroquine plus standard of care	Standard of care
Screened, N	NR	
Did not meet eligibility criteria, N	NR	
Randomized to receive hydroxychloroquine or standard of care alone	53	
Assigned to group	27	26
Received allocated intervention	27	26
Loss to follow-up	0	1
Excluded from analyses due to missing baseline data	1	0
Analyzed	26	25

NR = not reported.

Table 41: Patient Disposition for Mitjà et al.[9]

	Hydroxychloroquine	Control
Screened, N	753	
Not considered for inclusion at initial assessment, N	400	
More than 5 days since the start of symptoms	29	
Severely ill or hospital admission	76	
Predefined exclusion disease	5	
Death before enrolment	14	
Contraindicated concomitant medication	24	
Pregnant or breastfeeding	7	
Dementia or mental illness (not able to consent)	133	
Consent not signed	84	

	Hydroxychloroquine	Control
Previous hydroxychloroquine treatment	28	
Enrolled and randomized	353	
Assigned to group	169	184
Consent withdrew	0	2
RT-PCR negative at baseline	32	25
Did not have any follow-up PCR	1	0
Cases eligible for ITT sample	136	157
Excluded during follow-up	14	9
More than 5 days since start of symptoms	4	4
Lost to follow-up	3	5
Severely ill	1	0
Contraindicated concomitant medication	3	0
Treatment compliance under 80%	3	0
Cases completed follow-up (PP sample)	122	148

ITT = intention to treat; PCR = polymerase chain reaction; PP = per protocol; RT-PCR = reverse transcription–polymerase chain reaction.

Table 42: Patient Disposition for WHO Solidarity Trial Consortium et al.[10]

	Hydroxychloroquine	Control
Screened, N	NR	
Randomized,[a] N	11,330	
Randomized to hydroxychloroquine and control group, N	1,863	
Assigned to group	954	909
No or unknown consent to follow-up	7	3
Included in the ITT analysis	947	906
Died or left the hospital	932	891
Entered trial before or on June 19; still an inpatient in late September	12	13
Entered trial before or on June 19; not reported on in late September	3	2

ITT = intention to treat.

[a] The Solidarity trial had 4 different treatment groups (remdesivir, hydroxychloroquine, lopinavir, and interferon) and a control group. Only the patient disposition for hydroxychloroquine and the corresponding controls are reported beyond initial randomization.

Table 43: Patient Disposition for Ulrich et al.[11]

	Hydroxychloroquine	Placebo
Screened, N	764	
Excluded, N	633	
Prior hydroxychloroquine	170	
No symptoms	87	
PCR > 72 hours	81	
QT prolonged	76	
Patient refused	49	
ICU status	37	
Provider refused	37	
No capacity or LAR	34	

	Hydroxychloroquine	Placebo
Retinopathy	14	
Antiarrhythmic	11	
Other	37	
Enrolled, N	131	
Excluded pre-randomization, N	3	
Repeat PCR negative	1	
QT prolonged	1	
Enrolled in plasma trial prior to allowing co-enrolment	1	
Randomized, ITT analysis, N	128	
Assigned to group, N	67	61
Loss to follow-up, N		
Lost to follow-up on day 14	7	4
Lost to follow-up on day 30	14	11
Analysis, N		
Safety analysis	63	59
Per-protocol analysis	50	50

ICU = intensive care unit; ITT = intention to treat; LAR = legally authorized representative; PCR = polymerase chain reaction.

Table 44: Patient Disposition for Khamis et al.[12]

	Favipiravir	Hydroxychloroquine
Screened, N	NR	
Did not meet eligibility criteria, N	NR	
Randomized, N	89	
Randomized to favipiravir	44	
Randomized to hydroxychloroquine	45	
Excluded, N	NR	NR

NR = not reported.

Table 45: Patient Disposition for Self et al.[13]

	Hydroxychloroquine	Placebo
Screened, N	1,889	
Excluded for incomplete screening data, N	11	
Screened with complete screening data, N	1,878	
Screened patients with exclusion criteria, N	837	
Symptoms of acute respiratory infection for > 10 days	291	
> 48 hours from hospitalization	210	
QTc interval > 500 milliseconds	117	
Other	288	
Eligible, N	1,041	
Eligible patients not randomized, N	562	
Patient/legally authorized representative refusal	337	
Language barrier	47	

	Hydroxychloroquine	Placebo
Enrolled in another clinical trial	46	
Legally authorized representative or research staff unavailable	45	
Other	88	
Randomized, N	479	
Randomized to hydroxychloroquine	242	
Randomized to placebo	237	
Included in primary analysis, N	242	237

QTc = corrected QT.

Table 46: Patient Disposition for Boulware et al. (COVID-19 PEP)

	Hydroxychloroquine	Placebo
Screened, N	6,924	
Did not meet eligibility criteria, N (symptomatic or tested positive for SARS-CoV-2)	2,237	
Asymptomatic, N	4,687	
Excluded, N		
Did not complete enrolment survey	238	
Did not meet inclusion criteria	3,210	
Did not meet inclusion criteria and met exclusion criteria	303	
Met inclusion and exclusion criteria	15	
Randomized, N	921	
No longer meet inclusion criteria (initially asymptomatic but symptomatic by day 1)	100	
Treatment assignment, N	414	407
Discontinuations, N (%)		
Withdrawal from trial	4 (1.0)	4 (1.0)
Lost to follow-up	46 (11.1)	42 (10.3)

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 47: Patient Disposition for Brown et al.[14]

	Hydroxychloroquine	Azithromycin
Screened, N	829	
Did not meet inclusion criteria, N	195	
Met at least 1 exclusion criterion, N	423	
Recovered/discharged	122	
Prolonged QTc interval at baseline	55	
Dialysis/GFR	53	
> 2 days hydroxychloroquine or azithromycin	27	
Outpatient	19	
Attending declined	43	
Seizure disorder	18	
Contraindicated medications	20	
Competing study	30	

	Hydroxychloroquine	Azithromycin
Severe liver disease	9	
Language barrier	12	
Pregnant	21	
Psoriasis	6	
Prisoner	4	
Allergy to study drug	3	
LAR unavailable	8	
History of bone marrow transplant	2	
Prior enrolment	2	
Porphyria	1	
Weight < 35 kg	2	
Approached	211	
Declined to participate	126	
Patient declined	110	
LAR declined	16	
Randomized, N	85	
Randomized, N	42	43

GFR = glomerular filtration rate; LAR = legally authorized representative; QTc = corrected QT.

Table 48: Patient Disposition for Abella et al.[16]

	Hydroxychloroquine	Placebo
Screened, N	139	
Did not meet eligibility criteria, N	7	
Randomized, N	132	
Randomized to hydroxychloroquine	66	
Randomized to placebo	66	
Excluded, N	2	25
Positive COVID-19 test result at baseline	0	2
Never took study medication	1	1
Early termination of study	1	2
Evaluable for primary objective	64	61
Evaluable for adverse events	65	65

COVID-19 = coronavirus disease 2019.

Table 49: Patient Disposition for Rajasingham et al.[17]

	Hydroxychloroquine (once or twice weekly) or placebo		
Screened, N	2,271		
US	2,254		
Canada	17		
Excluded, N			
Declined enrolment	390		
Did not meet inclusion criteria	385		
Randomized, N	1,496		
US	1,493		
Canada	3		
Reached primary end point by start of study, N (excluded)	13		
Included in analysis, N	1,483		
US	1,480		
Canada	3		
	Hydroxychloroquine		**Placebo**
	Once weekly	**Twice weekly**	
Assigned to group, N	494	495	494
Did not meet inclusion or exclusion criteria	4	2	1

Appendix 2: Baseline Characteristics

Table 50: Demographic and Clinical Characteristics at Baseline for Borba et al. (CloroCovid-19)[1]

Characteristics[a]	Chloroquine low dosage (N = 40)	Chloroquine high dosage (N = 41)
Age (years), mean (SD)	47.4 (13.3)	54.7 (13.7)
Men, n/N (%)	30/40 (75.5)	31/41 (24.4)
Race, n/N (%)		
White	10/40 (25.0)	7/41(17.1)
Mixed	28/40 (70.0)	30/41 (73.2)
Black	2/40 (5.0)	4/41 (9.8)
Pregnant, n/N (%)	1/10 (10.0)	1/10 (10.0)
History of smoking, n/N (%)		
Never	18/24 (75.0)	15/24 (62.5)
Current	3/24 (12.5)	1/24 (4.2)
Former	3/24 (12.5)	8/24 (33.3)
Comorbidities, n/N (%)		
Hypertension	10/27 (37)	15/28 (53.6)
Diabetes	5/27 (18.5)	9/28 (32.1)
Alcohol use disorder	8/26 (30.8)	6/25 (24)
Heart disease	0/27	5/28 (17.9)
Asthma	1/26 (3.8)	3/28 (10.7)
Chronic kidney disease	1/26 (3.8)	3/28 (10.7)
Rheumatic diseases	3/27 (11.1)	0/28
Liver diseases	2/27 (7.4)	0/28
Tuberculosis	2/27 (7.4)	0/28
HIV/AIDS	0/27	1/28 (3.6)
Oxygen therapy on admission, n/N (%)	36/40 (90.0)	36/41 (87.8)
Respiratory rate (rpm), median (IQR)	25.0 (22.0 to 30.0)	28.0 (20.0 to 31.0)
BMI (kg/m^2), median (IQR)	28.9 (26.1 to 32.7)	27.1 (25.7 to 31.2)
Oxygen saturation (%), median (IQR)	96 (93.0 to 98.0)	95 (94.0 to 98.2)
Creatine (U/L), median (IQR)		
Kinase	82.8 (55.8 to 177.4)	96.8 (70.8 to 279.0)
Kinase MB isoenzyme	18.6 (15.8 to 24.5)	20.9 (15.8 to 27.3)
C-reactive protein (mg/dL), median (IQR)	8.09 (6.19 to 9.51)	8.61 (7.73 to 9.19)
QTc interval (ms), mean (SD)	421.9 (24.0)	427.8 (31.0)
Lung radiologic findings, n/N (%)		
Ground-glass opacity infiltration		
Unilateral	20/40 (50.0)	21/41 (51.2)
Bilateral	6/40 (15.0)	2/41 (4.9)
Consolidation, n/N (%)		

Characteristics[a]	Chloroquine low dosage (N = 40)	Chloroquine high dosage (N = 41)
Unilateral	15/40 (37.5)	10/41 (24.4)
Bilateral	7/40 (17.5)	8/41 (19.5)
Pleural effusion	3/40 (7.5)	2/41 (4.9)

BMI = body mass index; IQR = interquartile range; MB = myocardial band; QTc = corrected QT; rpm = respirations per minute; SD = standard deviation; U = units.

[a] For some variables, patients' unconsciousness did not allow for complete personal history data collection.

Table 51: Demographic and Clinical Characteristics at Baseline for Tang et al.[2]

Characteristics	Hydroxychloroquine plus standard of care N = 75	Standard of care N = 75
Age (years), mean (SD)	48.0 (14.1)	44.1 (15.0)
Male sex, n (%)	42 (56)	40 (53)
Body mass index, mean (SD)	23.9 (3.24) (n = 74)	23.2 (3.0) (n = 71)
Disease onset to randomization (days), mean (SD)	16.0 (9.9) (n = 73)	17.1 (11.1) (n = 74)
Drug treatment before randomization, n (%)	47 (63)	43 (57.3)
Antiviral drugs	28 (37)	24 (32.0)
Arbidol	12 (16)	8 (11)
Lopinavir plus ritonavir	18 (24)	14 (19)
Oseltamivir	3 (4)	3 (4)
Entecavir	1 (1)	0
Virazole	3 (4)	6 (8)
Ganciclovir	0	2 (3)
Disease severity, n (%)		
Mild	15 (20)	7 (9)
Moderate	59 (79)	67 (89)
Severe	1 (1)	1 (1)
Coexisting conditions, n (%)	28 (37)	17 (23)
Diabetes	12 (16)	9 (12)
Hypertension	6 (8)	3 (4)
Others	21 (28)	10 (13)
Respiratory rate (breaths per minute), mean (SD) (n)	19.6 (1.3) (n = 73)	19.7 (1.7) (n = 70)
Pulse oximetry (%), mean (SD) (n)	97.4 (1.6)	97.3 (1.6) (n = 73)
Creatine kinase (U/L), mean (SD) (n)	74.4 (110.1) (n = 67)	71.0 (52.6) (n = 68)
Creatine kinase MB isoenzyme (U/L), mean (SD) (n)	8.0 (4.2) (n = 46)	6.8 (3.9) (n = 44)
C-reactive protein (mg/L), mean (SD) (n)	9.9 (13.3) (n = 73)	7.4 (12.8) (n = 74)

MB = myocardial band; SD = standard deviation; U = units.

Table 52: Demographic and Clinical Characteristics at Baseline for Davoodi et al.[3]

Characteristics	Hydroxychloroquine N = 25	Febuxostat N = 29
Age (years), mean (SE)	57.3 (2.2)	58 (1.47)
Male sex, n (%)	16 (64)	16 (55.2)
Current smoking, n (%)	0 (0)	1 (3.6)
Coexisting conditions, n (%)		
Diabetes	7 (28)	8 (27.6)
Lung disease	1 (4)	0 (0)
Respiratory rate, mean (SE)	19.6 (0.37)	19.8 (0.32)
Elevated CRP, n (%)	23 (92)	28 (96.6)
Lung CT (% involvement), mean (SE)	19.2 (2.6)	16 (1.2)

CRP = C-reactive protein; SE = standard error.

Table 53: Demographic and Clinical Characteristics at Baseline for Cavalcanti et al.[4]

Characteristics[a]	Hydroxychloroquine plus azithromycin plus standard of care N = 217	Hydroxychloroquine plus standard of care N = 221	Control (standard of care) N = 227
Age (years), mean (SD)	49.6 (14.2)	51.3 (14.5)	49.9 (15.1)
Men, n/N (%)	123 (56.7)	142 (64.3)	123 (54.2)
Coexisting condition, n (%)			
Hypertension	81 (37.3)	94 (42.5)	83 (36.6)
Diabetes	40 (18.4)	47 (21.3)	40 (17.6)
Current or former smoking	17 (7.8)	12 (5.4)	15 (6.6)
Obesity	29 (13.4)	37 (16.7)	37 (16.3)
Cancer	7 (3.2)	4 (1.8)	8 (3.5)
Heart failure	4 (1.8)	3 (1.4)	3 (1.3)
COPD	4 (1.8)	4 (1.8)	4 (1.8)
AIDS	1 (0.5)	0	3 (1.3)
Chronic renal failure	2 (0.9)	1 (0.5)	2 (0.9)
Asthma	16 (7.4)	9 (4.1)	15 (6.6)
Previous medication use, n (%)			
Glucocorticoid	4 (1.8)	1 (0.5)	3 (1.3)
ACE inhibitor	16 (7.4)	19 (8.6)	13 (5.7)
Angiotensin II-receptor antagonist	39 (18.0)	36 (16.3)	41 (18.1)
NSAID	8 (3.7)	12 (5.4)	9 (4.0)
Randomization location			
Emergency department or ward	187 (86.2)	189 (85.5)	197 (86.8)
ICU	30 (13.8)	32 (14.5)	30 (13.2)
Testing for COVID-19, n (%)			
Positive on RT-PCR	172 (79.3)	159 (71.9)	173 (76.2)
Negative on RT-PCR or unavailable	45 (20.7)	62 (28.1)	54 (23.8)

Characteristics[a]	Hydroxychloroquine plus azithromycin plus standard of care N = 217	Hydroxychloroquine plus standard of care N = 221	Control (standard of care) N = 227
Score on 7-level ordinal scale, n (%)[b]			
3 (hospitalized and not receiving supplemental oxygen)	125 (57.6)	132 (59.7)	130 (57.3)
4 (hospitalized and receiving supplemental oxygen)	92 (42.4)	89 (40.3)	97 (42.7)
Use of trial medication[c]			
Hydroxychloroquine, n (%)	23 (10.6)	20 (9.0)	19 (8.4)
Azithromycin, n/N (%)	74/217 (34.1)	76/221 (34.4)	90/226 (39.8)
Time from admission to randomization (days), median (IQR)	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)
Time from symptom onset to randomization (days), median (IQR)	7 (5 to 9)	7 (5 to 8)	7 (4 to 9)

ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; RT-PCR = reverse transcription–polymerase chain reaction; SD = standard deviation.

[a] Intention-to-treat population included all patients who had undergone randomization. Information on coexisting conditions was obtained from the medical records. The values shown are based on available data. Percentages may not total 100 because of rounding.

[b] Only hospitalized patients who were not receiving supplemental oxygen or who were receiving up to 4 litres per minute of supplemental oxygen were eligible for the trial. Patients who had scores on other than level 3 or 4 of the 7-level ordinal scale were not eligible.

[c] Use of trial medication was defined as the use of hydroxychloroquine or azithromycin during the 24-hour period before randomization.

Table 54: Demographic and Clinical Characteristics at Baseline for Skipper et al.[5]

Characteristics	Hydroxychloroquine N = 212	Placebo N = 211
Age (years), median (IQR)	41 (33 to 49)	39 (31 to 50)
Weight (kg), median (IQR)	73 (61 to 85)	74 (64 to 86)
Female sex, n (%)[a]	123 (58.0)	115 (54.5)
Health care worker, n (%)	124 (58.5)	117 (55.5)
Canadian, n (%)	20 (9.4)	18 (8.5)
Asymptomatic at time of consent, n (%)	47 (22.2)	52 (24.6)
Comorbid conditions, n (%)		
None	140 (66.0)	147 (69.7)
Hypertension	23 (10.8)	23 (10.9)
Diabetes	8 (3.8)	7 (3.3)
Asthma	28 (13.2)	20 (9.5)
Current smoker	8 (3.8)	9 (4.3)
Duration of antecedent symptoms, n (%)		
< 1 day	86 (40.6)	83 (39.3)
1 to 2 days	67 (31.6)	78 (37.0)
3 to 4 days[b]	59 (27.8)	50 (23.7)
Symptoms at baseline, n (%)		
Cough	138 (65.1)	137 (64.9)
Fever	84 (39.6)	78 (37.0)
Shortness of breath	65 (30.7)	74 (35.1)

Characteristics	Hydroxychloroquine N = 212	Placebo N = 211
Headache	116 (54.7)	98 (46.4)
Sore throat	90 (42.5)	85 (40.3)
Fatigue	116 (54.7)	102 (48.3)
Muscle aches	100 (47.2)	85 (40.3)
Lack of smell	29 (13.7)	30 (14.2)
Number of COVID-19 symptoms, median (IQR)	4 (2 to 6)	4 (2 to 5)
Mean symptom severity score, mean (SD)[c]	4.1 (2.2)	4.2 (2.3)
COVID-19 diagnostic classification, n (%)[d]		
Participant PCR positive	73 (34.4)	72 (34.1)
Exposure contact PCR positive	134 (63.2)	146 (69.2)

COVID-19 = coronavirus disease 2019; IQR = interquartile range; PCR = polymerase chain reaction; SD = standard deviation.

[a] Three women were breastfeeding, zero were pregnant.

[b] Six participants had greater than 4 days of symptoms by the time of randomization.

[c] Assessed using a 0- to 10-point visual analogue scale with 0.1-point increments.

[d] Not mutually exclusive.

Table 55: Demographic and Clinical Characteristics at Baseline for Abd-Elsalam et al.[6]

Characteristics	Hydroxychloroquine plus standard of care (N = 75)	Standard of care (N = 75)
Age (years), mean (SD)	40.35 (18.65)	41.09 (20.07)
Male sex, n (%)	56 (57.7)	58 (59.8)
Body mass index, n (%)		
Normal	4 (4.1)	9 (9.3)
Overweight	32 (33.0)	29 (29.9)
Obese	40 (41.2)	35 (36.1)
Morbid obesity	21 (21.6)	24 (24.7)
Residence		
Rural	54 (55.7)	46 (37.4)
Urban	43 (44.3)	51 (52.6)
Smoking, n (%)	35 (36.1)	25 (25.8)
Comorbidities, n (%)	15 (15.5)	12 (12.4)
Liver diseases, n (%)	0 (0.0)	2 (2.1)
Renal impairment, n (%)	2 (2.1)	4 (4.1)

SD = standard deviation.

Table 56: Demographic and Clinical Characteristics at Baseline for Horby et al.[7]

Characteristics	Hydroxychloroquine (N = 1,561)	Usual care (N = 3,155)
Age (years), mean (SD)	65.2 (15.2)	65.4 (15.4)
Male sex, n (%)	960 (61.5)	1,974 (62.6)
Race or ethnic group, n (%)[a]		
White	1,181 (75.7)	2,298 (72.8)
Black, Asian, or minority ethnic group	264 (16.9)	593 (18.8)
Unknown	116 (7.4)	264 (8.4)
Number of days since symptom onset, median (IQR)[b]	9 (5 to 14)	9 (5 to 13)
Number of days since hospitalization, median (IQR)	3 (1 to 6)	3 (1 to 5)
Respiratory support, n (%)		
No oxygen received	362 (23.2)	750 (23.8)
Oxygen only	938 (60.1)	1,873 (59.4)
Invasive mechanical ventilation	261 (16.7)	532 (16.9)
Previous disease, n (%)		
Any of the listed conditions	882 (56.5)	1,807 (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[c]	18 (1.2)	46 (1.5)
Severe kidney impairment[d]	111 (7.1)	261 (8.3)
SARS-CoV-2 test result, n (%)		
Positive	1,399 (89.6)	2,867 (90.9)
Negative	156 (10.0)	275 (8.7)
Unknown	6 (0.4)	13 (0.4)

IQR = interquartile range; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

[a] Race or ethnic group is reported as it was recorded in the patient's electronic health record.

[b] 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.

[c] Severe liver disease was defined as a diagnosis that resulted in ongoing specialist care.

[d] 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.

Table 57: Demographic and Clinical Characteristics at Baseline for Lyngbakken et al.[8]

Characteristics	Hydroxychloroquine (N = 27)	Usual care (N = 26)
Age (years), mean (IQR),	56 (41 to 72)	69 (51 to 74)
Male sex, n (%)	19 (70.4)	16 (61.5)
Body mass index (kg/m^2), median (IQR)	25.6 (23.9 to 29.4)	27.6 (24.2 to 33.0)
Current smoker, n (%)	1 (3.7)	1 (3.8)
Time from symptom onset to randomization (days), median (IQR)	8 (7 to 13)	8 (6 to 11)
Coexisting conditions, n (%)		
Hypertension	6 (22.2)	11 (42.3)
Diabetes mellitus	4 (14.8)	5 (19.2)
Coronary heart disease	3 (11.1)	2 (7.7)
Obstructive pulmonary disease	5 (18.5)	9 (34.6)
Obesity	5 (19.2)	11 (42.3)
≥ 1 coexisting condition	14 (51.9)	19 (73.1)
On admission		
Systolic blood pressure (mm Hg), median (IQR)	129 (120 to 142)	137 (130 to 145)
Diastolic blood pressure (mm Hg), median (IQR)	75 (70 to 87)	74 (71 to 79)
Heart rate (beats per minute), median (IQR)	88 (76 to 98)	86 (80 to 100)
Respiratory rate (breaths per minute), median (IQR)	22 (20 to 30)	26 (20 to 32)
Oxygen saturation (%),median (IQR)	95 (94 to 96)	95 (92 to 96)
NEWS2, median (IQR)	4 (2 to 6)	5 (3 to 7)
Body temperature (°C), median (IQR)	38.2 (37.3 to 38.7)	38.2 (37.5 to 38.6)
Body temperature > 37.8°C, n (%)	17 (63.0)	18 (69.2)
Supplemental oxygen, n (%)	8 (29.6)	12 (46.2)

IQR = interquartile range; NEWS2 = National Early Warning Score 2.

Table 58: Demographic and Clinical Characteristics at Baseline for Mitjà et al.[9]

Characteristics	Hydroxychloroquine N = 136	Control N = 157
Age (years), mean (SD)	41.6 (12.4)	41.7 (12.6)
Female sex, n (%)	98 (72.1)	103 (65.6)
Coexisting disease, n (%)		
Any coexisting disease	71 (52.2)	85 (54.1)
Cardiovascular disease	20 (14.7)	15 (9.6)
Respiratory disease	7 (5.1)	10 (6.4)
Metabolic disease	9 (6.6)	11 (9.0)
Nervous system disease	19 (14.0)	21 (13.4)
Symptoms at baseline, n (%)		
Dyspnea	21 (15.4)	22 (14.1)
Fever	91 (66.9)	96 (61.5)

Characteristics	Hydroxychloroquine N = 136	Control N = 157
Cough	85 (62.5)	104 (66.7)
Sudden olfactory or gustatory loss	58 (42.6)	67 (42.9)
Rhinitis	15 (11.0)	13 (8.3)
Main risk factor of exposure to COVID-19, n (%)		
Health care worker	106 (77.9)	132 (84.1)
Nursing home worker	8 (5.9)	8 (5.1)
Household contact of a case	4 (2.9)	1 (0.6)
Unknown	18 (13.2)	16 (10.2)

SD = standard deviation.

Table 59: Demographic and Clinical Characteristics at Baseline for WHO Solidarity Trial Consortium[10]

Characteristics	Hydroxychloroquine N = 947	Control N = 906
Age (years), n		
< 50	335	317
50 to 69	410	396
≥ 70	202	193
Respiratory support, n		
No supplemental oxygen at entry	345	341
Supplemental oxygen at entry	517	483
Already receiving ventilation	85	82
Lesions in both lungs, n		
No	154	170
Yes	656	618
No images taken at entry	137	118
Previous days in the hospital, n		
0	296	281
1	317	312
≥ 2	334	313
Geographic region, n		
Europe and Canada[a]	286	267
Latin America[b]	97	96
Asia and Africa[c]	564	543
Other characteristics, n		
Male sex	574	535
Current smoker	92	82
Coexisting conditions, n		
Diabetes	199	205
Heart disease	193	194
Chronic lung disease	62	66

Characteristics	Hydroxychloroquine N = 947	Control N = 906
Asthma	41	46
Chronic liver disease	15	14

[a] Countries in Europe were Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, North Macedonia, Norway, Spain, and Switzerland.

[b] Countries included Argentina, Brazil, Colombia, Honduras, and Peru.

[c] Countries included Egypt, India, Indonesia, Iran, Kuwait, Lebanon, Malaysia, Pakistan, the Philippines, Saudi Arabia, and South Africa.

Table 60: Demographic and Clinical Characteristics at Baseline for Ulrich et al.[11]

Characteristics	Hydroxychloroquine N = 67	Placebo N = 61	P value
Age (years), mean (SD)	66.5 (16.4)	65.8 (16.0)	0.804
Male sex, n (%)	45 (67.2)	31 (50.8)	0.089
Race/ethnicity, n (%)			
Hispanic	25 (37.3)	25 (41.0)	0.807
Non-Hispanic African American	15 (22.4)	11 (18.0)	0.695
Non-Hispanic Asian	3 (4.5)	7 (11.5)	0.253
Non-Hispanic White	23 (34.3)	18 (29.5)	0.694
Unknown	1 (1.5)	0 (0)	1.000
Temperature (°F), n (%)			
Afebrile (< 100.4)	46 (68.7)	40 (65.6)	0.855
Febrile (≥ 100.4)	21 (31.3)	21 (34.4)	
Oxygen supplementation, n (%)			
Nasal cannula	28 (41.8)	34 (55.7)	0.162
O_2 (L[a]), mean (SD)	2.96 (1.79)	3.34 (1.36)	0.355
High-flow nasal cannula	1 (1.5)	0 (0.0)	1.000
Non-invasive ventilation (CPAP or BiPAP)	1 (1.5)	0 (0.0)	1.000
Non-rebreather	11 (16.4)	7 (11.5)	0.583
Body mass index (kg/m^2),[b] n (%)			0.023
< 20	56 (7.5)	3 (4.9)	
≥ 20 to < 30	45 (67.2)	29 (47.5)	
≥ 30 to ≤ 40	15 (22.4)	19 (31.3)	
> 40	2 (3.0)	10 (16.4)	
COVID-19 symptoms, n (%)			
Cough	42 (62.7)	44 (72.1)	0.343
Dyspnea/shortness of breath	41 (61.2)	42 (68.9)	0.471
Fever	36 (53.7)	36 (59.0)	0.672
Fatigue	33 (49.3)	26 (42.6)	0.566
Myalgia	13 (19.4)	20 (32.8)	0.127
Diarrhea	17 (25.4)	17 (27.9)	0.905
Nausea/vomiting	11 (16.4)	11 (18.0)	0.994
Abdominal pain	7 (10.4)	11 (18.0)	0.328
Chest pain	7 (10.4)	10 (16.4)	0.466
Headache	9 (13.4)	8 (13.1)	1.000

Characteristics	Hydroxychloroquine N = 67	Placebo N = 61	P value
Loss of sense of smell	6 (9.0)	7 (11.5)	0.858
Loss of sense of taste	9 (13.4)	7 (11.5)	0.947
Anorexia	6 (9.0)	10 (16.4)	0.316
Sore throat	5 (7.5)	7 (11.5)	0.635
Rhinorrhea	5 (7.5)	2 (3.3)	0.515
Nasal congestion	4 (6.0)	2 (3.3)	0.763
Other	21 (31.3)	16 (26.2)	0.658
Symptom duration, median (IQR)			
Days since symptom onset	6.50 (6.00)	7.00 (10.0)	0.091
Comorbidities, n (%)			
Hypertension	36 (53.7)	38 (62.3)	0.423
Diabetes	19 (28.4)	22 (36.1)	0.457
Cardiovascular disease (non-hypertension)	21 (31.3)	13 (21.3)	0.279
Asthma	9 (13.4)	11 (18.0)	0.637
Cancer	8 (11.9)	7 (11.5)	1.000
Hyperlipidemia	8 (11.9)	5 (8.2)	0.684
Chronic renal disease (non-dialysis)	7 (10.4)	3 (4.9)	0.404
COPD	5 (7.5)	4 (6.6)	1.000
Cerebrovascular disease	7 (10.4)	1 (1.6)	0.091
HIV	5 (7.5)	2 (3.3)	0.515
Chronic renal disease (dialysis)	2 (3.0)	2 (3.3)	1.000
History of solid organ transplant	2 (3.0)	0 (0)	0.518
Other	19 (28.4)	26 (42.6)	0.133
None of the above	8 (11.9)	8 (13.1)	1.000
Smoking, n (%)			
Active smoking	5 (7.5)	3 (4.9)	0.819
Past smoking	16 (23.9)	20 (32.8)	0.356
Vaporizer use	1 (1.5)	0 (0)	1.000
Inhaler use, n (%)			0.199
No inhaler	54 (80.6)	42 (68.9)	–
Yes; albuterol only	7 (10.4)	7 (11.5)	–
Yes; albuterol and other long-acting inhalers	6 (9.0)	12 (19.7)	–
Electrocardiogram, n (%)			
Corrected QT interval, Bazett formula (ms), mean (SD)	439 (23.2)	443 (22.6)	0.354
Radiography, n (%)			
Chest X-ray	64 (95.5)	58 (95.1)	1.000
Chest CT	6 (9.0)	5 (8.2)	1.000
Radiography results, n (%)			
Opacities	41 (61.2)	42 (68.9)	0.471
Consolidations	10 (14.9)	11 (18.0)	0.814
Bilateral	47 (70.1)	48 (78.7)	0.368

Characteristics	Hydroxychloroquine N = 67	Placebo N = 61	P value
Unilateral	6 (9.0)	5 (8.2)	1.000
None of the above	14 (20.9)	10 (16.4)	0.671
COVID-19 severity score[c]			0.777
3: Hospitalized, on non-invasive ventilation or high-flow nasal cannula	14 (20.9)	7 (11.5)	–
4: Hospitalized, on supplemental oxygen	26 (38.8)	36 (59.0)	–
5: Hospitalized, not on O_2, requiring ongoing medical care	26 (38.8)	17 (27.9)	–
6: Hospitalized, not on O_2, not requiring ongoing care	1 (1.5)	1 (1.6)	–

BiPAP = bi-level or 2-level positive airway pressure; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; CPAP = continuous positive airway pressure; IQR = interquartile range; O_2 = oxygen; SD = standard deviation.

[a] Litres of oxygen calculated for n = 62 patients on nasal cannula.

[b] Body mass index categories differ between treatment groups using the chi-square test (P = 0.023).

[c] Wilcoxon rank sum test is used for COVID-19 score.

Table 61: Demographic and Clinical Characteristics at Baseline for Khamis et al.[12]

Characteristics	Favipiravir N = 44	Hydroxychloroquine N = 45	P value
Age (years), mean (SD)	54 (15)	56 (16)	0.426
Male gender, n (%)	28 (64)	24 (53)	0.324
Omani, n (%)	37 (84)	40 (89)	0.508
Comorbidity, n (%)			
Diabetes mellitus	17 (39)	23 (51)	0.237
Hypertension	24 (55)	24 (53)	0.909
Heart disease	7 (16)	6 (13)	0.772
Lung disease	3 (6.8)	2 (2.4)	0.677
CKD, n (%)			
Stage 1: eGFR > 90	7 (16)	15 (33)	0.009
Stage 2: Mild CKD	32 (73)	17 (38)	
Stage 3: Moderate CKD	4 (9.1)	6 (13)	
Stage 4: Severe CKD	0	2 (4.4)	
Stage 5: End-stage CKD	1 (2.3)	5 (11)	
Signs and symptoms, n (%)			
Fever	37 (84)	36 (80)	0.784
Sore throat	23 (52)	12 (27)	0.017
Shortness of breath	33 (75)	37 (82)	0.447
Diarrhea	16 (36)	8 (18)	0.048
Fatigue	8 (18)	6 (13)	0.573

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; SD = standard deviation.

Table 62: Demographic and Clinical Characteristics at Baseline for Self et al.[13]

Characteristics	Hydroxychloroquine N = 242	Placebo N = 237
Age (years), median (IQR)	58 (45 to 69)	57 (43 to 68)
Female sex, n (%)	107 (44.2)	105 (44.3)
Race/ethnicity, n/N (%)		
Hispanic/Latinx	91/232 (39.2)	87/227 (38.3)
White	72/232 (31.0)	65/227 (28.6)
Black	57/232 (24.6)	55/227 (24.2)
American Indian or Alaska Native	5/232 (2.2)	8/227 (3.5)
Asian	4/232 (1.7)	7/227 (3.1)
Native Hawaiian or Other Pacific Islander	2/232 (0.9)	4/227 (1.8)
Multi-race	1/232 (0.4)	1/227 (0.4)
Living at home in the community prior to hospitalization	190 (78.5)	183 (77.2)
Body mass index, median/N (IQR)[a]	31.3/226 (26.4 to 37.2)	31.1/219 (27.2 to 36.5)
Chronic conditions, n (%)		
Hypertension	136 (56.2)	117 (49.4)
Diabetes	88 (36.4)	78 (32.9)
Chronic kidney disease	28 (11.6)	14 (5.9)
Coronary artery disease	19 (7.9)	23 (9.7)
Chronic obstructive pulmonary disease	18 (7.4)	21 (8.9)
Location at time of randomization, n/N (%)		
Hospital ward	157/228 (68.9)	132/224 (58.9)
Intensive care unit	37/228 (16.2)	54/224 (24.1)
Emergency department	34/228 (14.9)	38/224 (17.0)
Symptoms of acute respiratory infection, n (%)		
Shortness of breath	175 (72.3)	168 (70.9)
Cough	143 (59.1)	140 (59.1)
Fever (temperature > 37.5°C)	138 (57.0)	132 (55.7)
Duration of symptoms prior to randomization (days), median (IQR)	5 (3 to 7)	5 (3 to 7)
Time between hospital presentation and randomization (hours[b]), median (IQR)	22.2 (14.6 to 33.1)	22.7 (14.1 to 29.9)
COVID Outcomes Scale category at randomization[c]		
2: Hospitalized, receiving ECMO or invasive mechanical ventilation	13 (5.4)	19 (8.0)
3: Hospitalized, receiving non-invasive ventilation or nasal high-flow oxygen	28 (11.6)	27 (11.4)
4: Hospitalized, receiving supplemental oxygen without positive pressure or high flow	116 (47.9)	108 (45.6)
5: Hospitalized, not receiving supplemental oxygen	85 (35.1)	83 (35.0)
Vasopressor use at enrolment, n (%)	8 (3.3)	20 (8.4)

Characteristics	Hydroxychloroquine N = 242	Placebo N = 237
Total SOFA score at enrolment, median (IQR)[d]	2 (1 to 4)	2 (1 to 4)

ECMO = extracorporeal membrane oxygenation; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment.

[a] Calculated as weight in kilograms divided by height in metres squared.

[b] Defined as the time of the first contact with an acute care hospital during the health care episode that resulted in the hospitalization during which the patient was enrolled. For patients who initially presented to the emergency department, time of hospital presentation was the time of emergency department arrival. For patients directly hospitalized without presenting to the emergency department, time of hospital presentation was the time of arrival at the admission unit.

[c] The COVID Outcomes Scale is a 7-category ordinal scale that classifies a patient's clinical status. Lower scores indicate more severely ill clinical status. Patients in the following categories at baseline were not eligible for enrolment: category 1 (death); category 6 (not hospitalized and unable to perform normal activities); and category 7 (not hospitalized and able to perform normal activities).

[d] The SOFA score categorizes illness severity based on organ dysfunction across 6 organ systems: respiratory, coagulation, liver, cardiovascular, central nervous system, and kidney. SOFA scores range from 0 to 24, with higher scores indicating greater illness severity. A SOFA score of 2 indicates moderate dysfunction in 1 organ system or mild dysfunction in 2 organ systems.

Table 63: Demographic and Clinical Characteristics at Baseline for Brown et al.[14]

Characteristics	Hydroxychloroquine N = 42	Azithromycin N = 43
Age (years), median (IQR)	51 (42 to 60)	58 (43 to 68)
Female sex, n (%)	19 (44)	14 (33)
Latinx ethnicity, n (%)	17 (40)	15 (36)
Race/ethnicity, n (%)		
Black/African American	1 (2)	0 (0)
Native Hawaiian/Pacific Islander	6 (14)	4 (10)
American Indian/Alaska Native	3 (7)	5 (12)
White	26 (60)	28 (67)
Non-White race or Latinx ethnicity	29 (67)	23 (55)
Other or multiple	7 (16)	5 (12)
Admission SOFA score, median (IQR)	3 (2 to 3)	3 (2 to 4)
Comorbidities, n (%)		
Total Charlson count, median (IQR)	1 (0 to 2)	0 (0 to 2)
No comorbidities, n (%)	18 (42)	23 (55)
Baseline ordinal scale, n (%)		
3: Hospitalized, no oxygen	6 (14)	6 (14)
4: Hospitalized, some oxygen	24 (56)	23 (55)
5: HFNC or NIV	7 (16)	6 (14)
6: Mechanical ventilation	4 (9)	5 (12)
7: Mechanical ventilation and other organ support	2 (5)	2 (5)
Duration of symptoms (days), median (IQR)	9 (7 to 11)	8 (5 to 12)

HFNC = high-flow nasal cannula oxygen; IQR = interquartile range; NIV = non-invasive ventilation; SOFA = Sequential Organ Failure Assessment.

Table 64: Demographic and Clinical Characteristics at Baseline for Boulware et al.[15]

Characteristics	Hydroxychloroquine N = 414	Placebo N = 407
Age (years), median (IQR)	41 (33 to 51)	40 (32 to 50)
Weight (kg), median (IQR)	75 (64 to 86)	76 (64 to 91)
Female sex, n (%)[a]	218 (52.7)	206 (50.6)
Current smoker, n (%)	15 (3.6)	12 (2.9)
Health care worker, n (%)	275 (66.4)	270 (66.3)
High-risk exposure, n (%)[b]	365 (88.2)	354 (87.0)
No PPE worn, n (%)	258 (62.3)	237 (58.2)
Time from exposure to enrolment, n/N (%)		
1 day	77/413 (18.6)	63/407 (15.5)
2 days	100/413 (24.2)	106/407 (26.0)
3 days	98/413 (23.7)	117/407 (28.7)
4 days	138/413 (33.4)	121/407 (29.7)
Coexisting conditions, n (%)		
None	306 (73.9)	290 (71.3)
Hypertension	51 (12.3)	48 (11.8)
Asthma	31 (7.5)	31 (7.6)
Diabetes	12 (2.9)	16 (3.9)

COVID-19 = coronavirus disease 2019; IQR = interquartile range; PPE = personal protective equipment.

[a] total of 0.2% of the women (1 out of 424) were pregnant and 1.4% (6 out of 424) were breastfeeding at the time of enrolment. One woman (0.2%) reported a new pregnancy at day 14.

[b] High-risk exposure was defined as exposure to a person with confirmed COVID-19 at a distance of less than 6 feet for more than 10 minutes while wearing neither a face mask nor eye shield.

Table 65: Demographic and Clinical Characteristics at Baseline for Abella et al.[16]

Characteristics	Hydroxychloroquine N = 54 to 66[a]		Placebo N = 62 to 66[a]	
	n (%)	N	n (%)	N
Age (years), median (range)	31 (20 to 66)	66	34 (23 to 62)	66
Weight (kg), median (range)	75 (53 to 190)	54	75 (50 to 145)	63
BMI, median (range)	26 (19 to 37)	54	26 (20 to 50)	62
Women, n (%)	54 (82)	66	37 (56)	66
Current smoker, n (%)	0	66	0	66
Coexisting conditions		66		66
Asthma	9 (14)		14 (21)	
Diabetes	1 (2)		3 (5)	
Hypertension	3 (5)		14 (21)	
None	54 (82)		40 (61)	
Practice location, n (%)		66		66
Emergency department	38 (58)		36 (55)	
Internal medicine ward	17 (26)		18 (27)	
Intensive care unit and/or on anesthesia	6 (9)		6 (9)	

Characteristics	Hydroxychloroquine N = 54 to 66[a]		Placebo N = 62 to 66[a]	
	n (%)	N	n (%)	N
Labour and delivery	5 (7)		6 (9)	
Occupation, n (%)		66		66
Nurse	46 (70)		42 (64)	
Physician	11 (17)		16 (24)	
Certified nursing assistant	2 (3)		2 (3)	
Emergency department technician	3 (4)		1 (2)	
Physician assistant	1 (2)		0	
Respiratory therapist	3 (4)		5 (7)	
Race, n (%)		66		66
White	55 (83)		54 (82)	
Asian	7 (11)		7 (11)	
Black or African American	3 (4)		1 (2)	
Latinx	0		2 (3)	
Mixed heritage	1(2)		2 (3)	

BMI = body mass index.

[a] Denominators for percentage calculations varied by baseline demographic of interest.

Table 66: Demographic and Clinical Characteristics at Baseline for Rajasingham et al.[17]

Characteristics[a]	Hydroxychloroquine once weekly N = 494	Hydroxychloroquine twice weekly N = 495	Placebo N = 494
Age (years), median (IQR)	42 (35 to 49)	41 (35 to 49)	40 (34 to 48)
Weight (kg), median (IQR)	79 (67,93)	82 (68 to 95)	80 (68 to 95)
Female, n (%)	261 (52.8)	258 (52.1)	241 (48.8)
Ethnicity, n (%)			
White or Caucasian	431 (87.2)	421 (85.1)	419 (84.8)
Black or African	5 (1.0)	5 (1.0)	10 (2.0)
Asian	23 (4.7)	23 (4.6)	29 (5.9)
Native Hawaiian or Pacific Islander	0 (0.0)	1 (0.2)	1 (0.2)
Hispanic or Latino	18 (3.6)	22 (4.4)	18 (3.6)
Native American or Alaska Native	4 (0.8)	7 (1.4)	8 (1.6)
Middle Eastern	6 (1.2)	5 (1.0)	4 (0.8)
South Asian	17 (3.4)	18 (3.6)	12 (2.4)
Other	3 (0.6)	1 (0.2)	4 (0.8)
Current smoker, n (%)	17 (3.4)	21 (4.2)	13 (2.6)
Chronic health conditions			
High blood pressure	79 (16.0)	66 (13.3)	60 (12.1)
Asthma	46 (9.3)	45 (9.1)	59 (11.9)
None	311 (63.0)	335 (67.7)	336 (68.0)
Risk factors for acquisition of SARS-CoV-2 at screening			

Characteristics[a]	Hydroxychloroquine once weekly N = 494	Hydroxychloroquine twice weekly N = 495	Placebo N = 494
Perform aerosol-generating procedures, n (%)	378 (77)	377 (76.3)	410 (83)
Setting of occupational exposure, n (%)			
Emergency department	210 (42.5)	207 (40.8)	190 (38.5)
Intensive care unit	82 (16.6)	102 (20.6)	85 (17.2)
Operating room	61 (12.3)	42 (8.5)	75 (15.2)
COVID-19 ward	51 (10.3)	47 (9.5)	56 (11.3)
Ambulance	40 (8.1)	33 (6.7)	45 (9.1)
Congregate care setting	19 (3.8)	27 (5.5)	20 (4.0)

COVID-19 = coronavirus disease 2019; IQR = interquartile range; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

Appendix 3: Harms Data

Table 67: Harms Outcomes for Borba et al. (CloroCovid-19)[1]

	Chloroquine low dosage N = 40	Chloroquine high dosage N = 41
Laboratory outcomes until day 13, n/N (%)[a]		
Hemoglobin decreased[b]	4/18 (22.2)	7/24 (19.2)
Creatinine increased[c]	7/15 (46.7)	9/23 (39.1)
CK increased	6/19 (31.6)	7/14 (50.0)
CK-MB increased	3/13 (23.1)	7/13 (53.8)
QTcF > 500 milliseconds	4/36 (11.1)	7/37 (18.9)
Ventricular tachycardia	0/36	2/37 (2.7)

CK = creatine kinase; CK-MB = creatine kinase myocardial band; QTcF = QT interval corrected by the Fridericia method.

[a] Not all patients completed the day 13 visit.

[b] Decreases in hemoglobin level > 3 g/dL or ≥ 30% from baseline.

[c] Increases in creatinine serum levels of ≥ 30% from baseline.

Table 68: Harms Outcomes for Tang et al.[2]

	Safety population	
	Hydroxychloroquine plus standard of care N = 70	Standard of care N = 80
Adverse events, n (%)		
Adverse events	21 (30.0)	7 (8.8)
Diarrhea	7 (10.0)	0
Vomiting	2 (2.8)	0
Nausea	1 (1.4)	0
Abdominal discomfort	1 (1.4)	0
Thirst	1 (1.4)	0
Abdominal bloating	0	1 (1.2)
Sinus bradycardia	1 (1.4)	0
Hypertension	1 (1.4)	0
Orthostatic hypotension	1 (1.4)	0
Hypertriglyceridemia	1 (1.4)	0
Decreased appetite	1 (1.4)	0
Fatigue	1 (1.4)	0
Fever	0	1 (1.2)
Dyspnea	1 (1.4)	0
Flush	1 (1.4)	0
Liver abnormality	0	1 (1.2)
Kidney injury	1 (1.4)	0
Coagulation dysfunction	1 (1.4)	0
Hepatic steatosis	0	1 (1.2)

	Safety population	
	Hydroxychloroquine plus standard of care N = 70	Standard of care N = 80
Otitis externa	0	1 (1.2)
Blurred vision	1 (1.4)	0
Decreased white blood cells	1 (1.4)	0
Increased alanine aminotransferase	1 (1.4)	1 (1.2)
Increased serum amylase	1 (1.4)	0
Decreased neutrophil count	1 (1.4)	0
Increased serum amyloid A	0	1 (1.2)
Serious adverse events, n (%)		
Serious adverse event	2 (2.8)	0
Disease progression	1 (1.4)	0
Upper respiratory tract infection	1 (1.4)	0

Table 69: Harms Outcomes for Cavalcanti et al.[4]

	Safety population[a]			
	Hydroxychloroquine plus azithromycin (N = 239)	Hydroxychloroquine (N = 199)	Azithromycin (N = 50)	Neither hydroxychloroquine nor azithromycin (N = 177)
Reported serious adverse event, according to classification[b]	5 (2.1)	2 (1.0)	0	2 (1.1)
Risk to life, n (%)	1 (0.4)	1 (0.5)	0	0
Extension of hospitalization, n (%)	2 (0.8)	0	0	1 (0.6)
Clinically significant event, n (%)	0	1 (0.5)	0	1 (0.6)
Death, n (%)	2 (0.8)	0	0	0
Other adverse events				0
Any adverse event, n (%)	94 (39.3)	67 (33.7)	9 (18.0)	40 (22.6)
QTc interval > 480 milliseconds within 7 days, n/N (%)	17/116 (14.7)	13/89 (14.6)	0/6	1/58 (1.7)
Arrhythmia, n (%)	3 (1.3)	3 (1.5)	0	1 (0.6)
Bradycardia, n (%)	2 (0.8)	1 (0.5)	0	1 (0.6)
Supraventricular tachycardia, n (%)	1 (0.4)	2 (1.0)	0	0
Ventricular tachycardia, n (%)	0	0	0	0
Myocardial infarction, n (%)	1 (0.4)	0	0	0
Abdominal-wall hemorrhage, n (%)	1 (0.4)	0	0	0
Pulmonary embolism, n (%)	2 (0.8)	0	0	0
Pneumothorax, n (%)	0	1 (0.5)	0	0
Bronchospasm, n (%)	0	0	0	1 (0.6)
Epistaxis, n (%)	2 (0.8)	0	0	0
Bloodstream infection, n (%)	0	1 (0.5)	0	0
Itching, n (%)	0	1 (0.5)	0	0

	Safety population[a]			
	Hydroxychloroquine plus azithromycin (N = 239)	Hydroxychloroquine (N = 199)	Azithromycin (N = 50)	Neither hydroxychloroquine nor azithromycin (N = 177)
Nausea, n (%)	6 (2.5)	9 (4.5)	0	2 (1.1)
Vomiting, n (%)	0	0	0	1 (0.6)
Anemia, n (%)[c]	23 (9.6)	14 (7.0)	5 (10.0)	11 (6.2)
Elevated ALT or AST level, n (%)[d]	26 (10.9)	17 (8.5)	2 (4.0)	6 (3.4)
Hypoglycemia, n (%)[e]	0	1 (0.5)	0	0
Elevated bilirubin level, n (%)	1 (0.4)	5 (2.5)	0	2 (1.1)
Leukopenia, n (%)[f]	6 (2.5)	3 (1.5)	2 (4.0)	3 (1.7)
Low lymphocyte level, n (%)[g]	29 (12.1)	17 (8.5)	2 (4.0)	16 (9.0)
Thrombocytopenia, n (%)[h]	17 (7.1)	14 (7.0)	1 (2.0)	18 (10.2)
Hypoacusis, n (%)	0	0	0	0

ALT = alanine aminotransferase; AST = aminotransferase; QTc = corrected QT.

[a] The safety population included patients according to the medications received (as treated). P < 0.001 for the occurrence of any adverse events (pairwise comparisons: P < 0.001 for hydroxychloroquine plus azithromycin versus control, P = 0.01 for hydroxychloroquine alone versus control). P = 0.02 for the occurrence of a QTc interval of more than 480 milliseconds within 7 days (pairwise comparisons: P = 0.04 for hydroxychloroquine plus azithromycin versus control, P = 0.01 for hydroxychloroquine alone versus control). P = 0.02 for the occurrence of an elevated ALT or AST level (pairwise comparisons: P = 0.01 for hydroxychloroquine plus azithromycin versus control, P = 0.09 for hydroxychloroquine alone versus control).

[b] Among patients who received hydroxychloroquine plus azithromycin, the serious adverse events were pulmonary embolism (in 2 patients), QTc interval prolongation (in 1; considered to be clinically important), myocardial infarction (in 1), and abdominal-wall hemorrhage (in 1). Among patients who received hydroxychloroquine only, the serious adverse events were bradycardia (in 1) and pneumothorax (in 1). Among patients who received neither hydroxychloroquine nor azithromycin, the serious adverse events were bradycardia (in 1) and severe vomiting (in 1). The 2 serious adverse events leading to death were myocardial infarction and abdominal-wall hemorrhage with shock, both of which occurred in patients receiving hydroxychloroquine and azithromycin.

[c] Anemia was defined as a hemoglobin level lower than 11 g per decilitre for men and lower than 10.5 g per decilitre for women.

[d] An elevated ALT or AST level was defined as a level that was more than 3 times the upper limit of the normal range.

[e] Hypoglycemia was defined as a glucose level below 40 mg per decilitre (2.2 mmol per litre).

[f] Leukopenia was defined as fewer than 2,500 leukocytes per cubic millimetre.

[g] A low lymphocyte level was defined as fewer than 650 lymphocytes per cubic millimetre.

[h] Thrombocytopenia was defined as a platelet count below 125,000 per cubic millimetre.

Table 70: Harms Outcomes for Skipper et al.[5]

	Safety population	
	Hydroxychloroquine N = 212	Placebo N = 211
Adverse events, n (%)		
Any side effects	92 (43.4)	46 (21.8)
Upset stomach or nausea	66 (31.1)	26 (12.3)
Diarrhea, other GI symptoms, vomiting	50 (23.6)	20 (9.5)
Neurologic (nervousness, irritability, dizziness, or vertigo)	20 (9.4)	13 (6.2)
Skin reaction, rash	6 (2.8)	2 (1.0)
Ringing in ears	8 (3.8)	5 (2.4)
Allergic reaction, self-reported	5 (2.4)	0 (0)
Changes in vision	4 (1.9)	5 (2.4)

	Safety population	
	Hydroxychloroquine N = 212	Placebo N = 211
Warmth, hot flashes, night sweats	2 (0.9)	0 (0)
Headache	2 (0.9)	0 (0)
Taste, dry mouth	0 (0)	1 (0.5)
Heart racing, anxiety, panic attack	0 (0)	1 (0.5)
Cardiac arrhythmia	0 (0)	0 (0)

GI = gastrointestinal.

Table 71: Harms Outcomes for Horby et al.[7]

	Safety population	
	Hydroxychloroquine N = 1,561	Usual care N = 3,155
Intensive mechanical ventilation or death, n/N (%)	399/1,300 (30.7)	705/2,623 (26.9)
Intensive mechanical ventilation, n/N (%)	128/1,300 (9.8)	225/2,623 (8.6)
Death, n/N (%)	311/1,300 (23.9)	574/2,623 (21.9)

CI = confidence interval.

Table 72: Harms Outcomes for Mitjà et al.[9]

	Safety population	
	Hydroxychloroquine N = 169	Control N = 184
Adverse events, n (%)		
Cardiac disorders	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	5 (3.0)	0 (0.0)
Eye disorders	5 (3.0)	0 (0.0)
Gastrointestinal disorders	148 (88.1)	7 (3.8)
General disorders	30 (17.9)	1 (0.5)
Infections and infestations	9 (5.4)	12 (6.6)
Injury, poisoning, and procedural complications	1 (0.6)	0 (0.0)
Metabolism and nutrition disorders	2 (1.2)	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (0.6)	0 (0.0)
Nervous system disorders	63 (37.5)	3 (1.6)
Psychiatric disorders	2 (1.2)	0 (0.0)
Renal and urinary disorders	1 (0.6)	0 (0.0)
Reproductive system and breast disorders	1 (0.6)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (1.2)	0 (0.0)
Skin and subcutaneous tissue disorders	11 (6.5)	0 (0.0)
Vascular disorders	1 (0.6)	0 (0.0)

Table 73: Harms Outcomes for Ulrich et al.[11]

	Safety population		
	Hydroxychloroquine N = 67	Placebo N = 61	P value
Total patients with AEs, n (%)	38 (56.7)	36 (59.0)	0.933
Total events, n (%)	63	59	
AE severity, n (%)			
Mild	22 (32.8)	27 (44.3)	0.252
Mild, number of events	30	38	
Moderate	14 (20.9)	7 (11.5)	0.231
Moderate, number of events	18	8	
Severe	9 (13.4)	8 (13.1)	1.000
Severe, number of events	14	13	
Relatedness to study treatment, n (%)			
Possibly related	7 (10.4)	4 (6.6)	0.639
Possibly related, number of events	9	7	
AEs of interest, n (%)			
GI symptoms[a]	17 (25.4)	10 (16.4)	0.305
GI number of events	18	11	
Rash	1 (1.5)	4 (6.6)	0.308
Rash, number of events	2	5	
Headaches	1 (1.5)	2 (3.3)	0.934
Headaches, number of events	1	3	
Vision number of events	0	0	
Arrhythmia	0	0	
Cardiac arrest	0	0	

AE = adverse event; GI = gastrointestinal.

[a] Nausea, vomiting, diarrhea, and/or constipation.

Table 74: Harms Outcomes for Self et al.[13]

	Safety population	
	Hydroxychloroquine N = 242	Placebo N = 237
Adverse events,[a] n (%)		
Cytopenia[b]	92 (38.0)	87 (36.7)
AST or ALT ≥ 2 times upper limit of normal	50 (20.7)	65 (27.4)
Cardiac arrest treated with CPR[c]	10 (4.1)	4 (1.7)
Symptomatic hypoglycemia[d]	10 (4.1)	8 (3.4)
Ventricular tachyarrhythmia[e]	5 (2.1)	6 (2.5)
Seizure	1 (0.4)	0
Patients with ≥ 1 SAEs reported	14 (5.8)	11 (4.6)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPR = cardiopulmonary resuscitation; SAE = serious adverse event.

[a] Variables based on the known potential toxicities of hydroxychloroquine were collected for every participant. Adverse event and SAE reporting was based on the judgment of site investigators.

[b] Defined as any of the following values on a clinically obtained laboratory test between randomization and 28 days later: an absolute neutrophil count of less than 1,000 cells/μL, an absolute lymphocyte count of less than 1,000 cells/μL, a hemoglobin of less than 12.0 g/dL, and a platelet count of less than 50,000/μL.

[c] Defined as loss of a palpable pulse and treated as a cardiac arrest with resuscitative efforts between randomization and 28 days later. An expected cardiac arrest that occurred as part of the dying process for patients on comfort measures was not classified as cardiac arrest treated with CPR.

[d] Defined as a clinically reported low blood glucose level (no specific threshold provided) that led to treatment for reversal of hypoglycemia between randomization and 28 days later.

[e] Ventricular tachyarrhythmia was defined as ventricular fibrillation or ventricular tachycardia treated with a medication or electrical cardioversion or defibrillation between randomization and 28 days later.

Table 75: Harms Outcomes for Brown et al.[14]

	Safety population		
	Hydroxychloroquine N = 42	Azithromycin N = 43	P value
Any safety outcome, n (%)	39 (95)	42 (100)	0.241
Death unrelated to study drug or procedures	2 (5)	1 (2)	0.616
Seizure	0 (0)	0 (0)	0.999
Receipt of vasopressors	11 (27)	7 (17)	0.297
Atrial or ventricular arrythmia	1 (2)	2 (5)	0.999
Cardiomyopathy	0 (0)	0 (0)	0.999
Cardiac arrest	0 (0)	0 (0)	0.999
Hypoxemia requiring supplemental oxygen	39 (95)	42 (100)	0.241
ARDS	9 (22)	14 (33)	0.328
Mechanical ventilation	15 (37)	13 (31)	0.647
ECMO	0 (0)	0 (0)	0.999
Elevated LFTs	19 (46)	22 (52)	0.663
Pancreatitis	0 (0)	0 (0)	0.999
Acute kidney injury	6 (17)	0 (0)	0.01
Renal replacement therapy	0 (0)	0 (0)	0.999
Symptomatic hypoglycemia	1 (2)	0 (0)	0.494
Hematologic or coagulation events	1 (2)	0 (0)	0.494

	Safety population		
	Hydroxychloroquine N = 42	Azithromycin N = 43	P value
Cytopenia	3 (7)	7 (17)	0.313
Severe dermatologic reaction	0 (0)	0 (0)	0.999
Nausea/vomiting	6 (15)	11 (26)	0.277
Visual changes	0 (0)	0 (0)	0.999
Clostridium difficile infection	0 (0)	0 (0)	0.999

ARDS = acute respiratory distress syndrome; LFT = liver function test.

Table 76: Harm Outcomes for Boulware et al.[15]

	Hydroxychloroquine N = 414	Placebo N = 407
Adverse events[a]		
Any adverse events, n/N (%)	140/349 (40.1)	59/351 (16.8)
Nausea or upset stomach	80/349 (22.9)	27/351 (7.7)
Diarrhea, abdominal discomfort, or vomiting	81/349 (23.2)	15/351 (4.3)
Neurologic reaction: irritability, dizziness, or vertigo	19/349 (5.4)	13/351 (3.7)
Headache	13/349 (3.7)	8/351 (2.3)
Tinnitus	8/349 (2.3)	3/351 (0.9)
Visual changes	3/349 (0.9)	0/351
Skin reaction	4/349 (1.1)	2/351 (0.6)
Allergic reaction	1/349 (0.3)	1/351 (0.3)
Fatigue	1/349 (0.3)	1/351 (0.3)
Change in taste or dry mouth	3/349 (0.9)	2/351 (0.6)
Hot flashes, night sweats, or palpitations	0/349	1/351 (0.3)
Reasons for not taking all of the assigned hydroxychloroquine or placebo, n (%)		
Adverse events	17 (4.1)	8 (2.0)
Advised not to take hydroxychloroquine	6 (1.4)	2 (0.5)
Intervention not received from courier	9 (2.2)	2 (0.5)
Took non-trial hydroxychloroquine	4 (1.0)	0
Felt no longer at risk	5 (1.2)	3 (0.7)
Other reason	12 (2.9)	10 (2.5)

[a] Values are through day 5, the date of the scheduled completion of the trial intervention (more than 1 adverse event could occur).

Table 77: Harms outcomes for Abella et al.[16]

	Abella et al.			
	Hydroxychloroquine (N = 65)		Placebo (N = 65)	
Adverse events, n (%)	**Grade 1**	**Grade 2**	**Grade 1**	**Grade 2**
Abdominal pain	2 (3)	2 (3)	0	0
Anorexia	7 (11)	0	2 (3)	0
Chest pain	1 (2)	0	1 (2)	0
Constipation	0	0	1 (2)	0
Diarrhea	13 (20)	8 (12)	7 (11)	1 (2)
Dizziness	1 (2)	0	0	0
Fatigue	2 (3)	0	0	0
Gastroesophageal reflux	2 (3)	0	0	0
Headache	0	0	2 (3)	2 (3)
Nausea	6 (9)	0	5 (8)	0
Paresthesia	1 (2)	0	0	0
Rash	2 (3)	1 (2)	1 (2)	0
Throat tightness	0	0	0	1 (2)

Table 78: Harms Outcomes for Rajasingham et al.[17]

	Rajasingham et al.		
	Hydroxychloroquine once weekly N = 473	Hydroxychloroquine twice weekly N = 463	Placebo N = 469
Adverse events, %			
Upset stomach and nausea	17.5	19.4	12.2
Gastrointestinal disturbance and diarrhea	12.9	17.1	7.5

Appendix 4: Ongoing Randomized Controlled Trials

Table 79: Chloroquine or Hydroxychloroquine to Treat COVID-19 – Ongoing Randomized Controlled Trials, 2020 Estimated Primary Completion Date[29]

Experimental arm	Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
Phase IV					
Interferon beta-1a and lopinavir plus ritonavir and single dose of hydroxychloroquine	IB1aIC	DB, PC Iran N = 40	April 20, 2020	Adults (≥ 50 years) with COVID-19	NCT04350671
Umifenovir and combination of interferon beta-1a, lopinavir plus ritonavir and single dose of hydroxychloroquine	UAIIC	DB, PC Iran N = 40	April 22, 2020	Hospitalized adults (≥ 18 years) with COVID-19	NCT04350684
Favipiravir and hydroxychloroquine	FIC	DB, PC Iran N = 40	May 3, 2020	Hospitalized adults (≥ 18 years) with moderate-to-severe COVID-19	NCT04359615
Azithromycin and hydroxychloroquine	AIC	DB, PC Iran N = 40	May 3, 2020	Adults (≥ 18 years) with moderate-to-severe COVID-19	NCT04359316
Hydroxychloroquine	NO COVID-19	OL Norway N = 53	May 25, 2020	Adults (≥ 18 years) with moderate-to-severe SARS-CoV-2 infection	NCT04316377
Hydroxychloroquine at various doses or chloroquine	PRECISE	DB Pakistan N = 400	May 30, 2020	Adults (20 to 50 years) with RT-PCR–positive test and symptomatic for COVID-19	NCT04351191
Hydroxychloroquine at various doses or chloroquine	PEACE	DB Pakistan N = 400	May 30, 2020	Adults (20 to 50 years) with nasopharyngeal RT-PCR–positive test for SARS-CoV-2	NCT04346667
Bromhexine and hydroxychloroquine	NA	OL Slovenia N = 90	June 30, 2020	Hospitalized adults (≥ 19 years old) with COVID-19	NCT04355026

Experimental arm	Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
Hydroxychloroquine	COALITION-V	DB, PC Brazil N = 1,300	August 30, 2020	Non-hospitalized adults (≥ 18 years) with confirmed or probable COVID-19	NCT04466540
Nitazoxanide and hydroxychloroquine	NA	SB Mexico N = 86	August 30, 2020	Hospitalized children (≥ 5 years) and adults with COVID-19	NCT04341493
Hydroxychloroquine and zinc with azithromycin or doxycycline	NA	OL US N = 750	September 30, 2020	Adults (≥ 30 years) with COVID-19 in outpatient setting	NCT04370782
Chloroquine and telemedicine	NA	MC, OL Poland N = 400	September 30, 2020	Adults (≥ 18 years) with SARS-CoV-2 infection, hospitalization not required	NCT04331600
Hydroxychloroquine	NA	DB, PC US N = 700	December 7, 2020	Hospitalized adults (≥ 18 years) with COVID-19	NCT04429867
NEW Carrimycin or lopinavir plus ritonavir or Arbidol or chloroquine	NA	MC, OL China N = 520	February 28, 2021	Adults (18 to 75 years) with 2019-nCoV pneumonia	NCT04286503
NEW Hydroxychloroquine, azithromycin, and zinc	NA	DB, PC US N = 750	May 2021	Adults (≥ 30 years) with COVID-19 in outpatient setting	NCT04621461
NEW Ivermectin or hydroxychloroquine and darunavir plus ritonavir	IDRA-COVID19	OL Thailand N = 80	June 2021	Adults (≥ 18 years) with asymptomatic or afebrile COVID-19 infection	NCT04435587
NEW Camostat mesylate and/or hydroxychloroquine	CLOCC	DB Germany N = 334	June 01, 2021	Hospitalized adults (≥ 18 years) with moderate COVID-19 infection	NCT04338906
Phase III					
Hydroxychloroquine with or without azithromycin	NA	SB Pakistan N = 75	May 28, 2020	Adults (18 to 50 years) with mild to severe COVID-19	NCT04328272

Experimental arm	Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
Dexamethasone and hydroxychloroquine	DHYSCO	MC France N = 122	June 2020	Adults (18 to 80 years) with ARDS due to COVID-19	NCT04347980
Hydroxychloroquine	HYDRA	DB, PC Mexico N = 500	July 1, 2020	Adults (≥ 18 years) with COVID-19	NCT04315896
Favipiravir or favipiravir and hydroxychloroquine or favipiravir and azithromycin or hydroxychloroquine or hydroxychloroquine and azithromycin	NA	MC, OL Turkey N = 1,000	July 30, 2020	Adults (18 to 70 years) with mild-to-moderate COVID-19	NCT04411433
NEW Favipiravir or oseltamivir and standard therapy (includes hydroxychloroquine)	NA	MC, OL Russian Federation N = 168	August 06, 2020	Adults (18 to 60 years) with mild-to-moderate COVID 2019	NCT04501783
Hydroxychloroquine with or without azithromycin	Coalition-I	MC, OL Brazil N = 630	August 30, 2020	Hospitalized adults (≥ 18 years) with suspected or confirmed COVID-19	NCT04322123
Levamisole and isoprinosine or hydroxychloroquine and azithromycin	NA	DB Egypt N = 60	August 30, 2020	Patients (≥ 6 years) with COVID-19	NCT04383717
Hydroxychloroquine or azithromycin or oseltamivir or in combination	PROTECT	Adaptive, MC, DB Pakistan N = 500	September 1, 2020	Adults (≥ 18 years) with SARS-CoV2	NCT04338698
Lopinavir plus ritonavir or hydroxychloroquine or combination	The Hope Coalition - 1	MC, DB, PC Brazil N = 1,968	September 3, 2020	Adults (≥ 18 years) with mild symptoms of COVID-19	NCT04403100
NEW Favipiravir or oseltamivir and standard therapy (includes hydroxychloroquine)	NA	OL Indonesia N = 100	September 30, 2020	Adults (18 to 75 years old) with COVID-19	NCT04558463
Chloroquine or chloroquine and zinc	NA	DB Egypt N = 200	October 1, 2020	Adults (≥ 18 years) with COVID-19	NCT04447534

Experimental arm	Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
Hydroxychloroquine in combination with camostat mesylate or hydroxychloroquine in combination of azithromycin	COSTA	OL, PC Israel N = 250	October 11, 2020	Hospitalized adults (18 to 120 years) with mild or moderate COVID-19	NCT04355052
Various formulations of isotretinoin (13-*cis*-retinoic acid) compared with SoC (includes hydroxychloroquine)	NA	OL Egypt N = 1,000	November 2020	Adults (18 to 80 years) with COVID-19	NCT04353180
Various formulations of dalargin and standard therapy (includes hydroxychloroquine)	NA	OL Russian Federation N = 320	December 2020	Hospitalized adults (≥ 18 years) with COVID-19	NCT04346693
Hydroxychloroquine with or without azithromycin	PACTT	DB Tunisia N = 200	December 2020	Hospitalized adults (≥ 18 years) with SARS-CoV2 infection	NCT04405921
Hydroxychloroquine or azithromycin	HyAzOUT	OL US N = 1,550	December 31, 2020	Adult outpatients (≥ 45 years) with COVID-19	NCT04334382
NEW Nafamostat mesylate and standard therapy (includes hydroxychloroquine)	SEN-CoV-Fadj	OL Senegal N = 186	February 12, 2021	Hospitalized adults (≥ 18 years) with SARS-CoV2 infection	NCT04390594
NEW Hydroxychloroquine	COV-HCQ	DB, PC Germany N = 220	March 2021	Hospitalized adults (18 to 99 years) with SARS-CoV2 infection	NCT04342221
NEW Hydroxychloroquine and/or azithromycin	NA	OL US N = 600	April 10, 2021	Adults (18 to 100 years) with early moderate-to-severe COVID-19	NCT04344444
NEW Hydroxychloroquine	COVID-Preg	MC, DB, PC Spain N = 714	May 13, 2021	Pregnant women (of any age) with symptom suggestive of COVID-19 or contact of a SARS-CoV-2 confirmed or suspected case in the past 14 days	NCT04410562

Experimental arm	Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
NEW Hydroxychloroquine or azithromycin or telmisartan	COVID-Aging	MC, OL France N = 1,600	June 01, 2021	Hospitalized adults (≥ 60 years) with SARS-CoV2 infection	NCT04359953
NEW Lopinavir plus ritonavir and/or hydroxychloroquine or convalescent plasma	ASCOT	MC, OL Australia N = 2,400	June 12, 2021	Hospitalized adults (≥ 18 years) with SARS-CoV2 infection	NCT04483960
Phase II/III					
Levamisole and budesonide plus formoterol inhaler or lopinavir plus ritonavir and hydroxychloroquine	NA	DB Iran N = 30	April 20, 2020	Children and adults (15- to 100 years) with COVID-19	NCT04331470
Favipiravir at various doses, and SoC (may include hydroxychloroquine)	NA	MC, OL Russian Federation N = 330	July 2020	Hospitalized adults (≥ 18 years old) with COVID-19	NCT04434248
Mefloquine alone or hydroxychloroquine alone or either drug in combination with azithromycin and tocilizumab	NA	MC, OL Russian Federation N = 320	August 1, 2020	Hospitalized adult (18 to 60 years) patients with COVID-19	NCT04347031
Hydroxychloroquine	#StayHome	DB, PC Switzerland N = 800	August 2020	Adults (≥ 18 years) with SARS-CoV2 infection, and able to self-isolate at home, at risk of COVID-19 complication	NCT04385264
Hydroxychloroquine or remdesivir and SoC	NA	MC, OL Norway N = 700	August 2020	Hospitalized adults (≥ 18 years) with SARS-CoV2 infection	NCT04321616
Chloroquine or hydroxychloroquine	NA	OL Egypt N = 200	September 23, 2020	Children and adults with COVID-19	NCT04353336
Hydroxychloroquine and nitazoxanide	NA	DB Egypt N = 100	October 2020	Adult patients (18 to 65 years) with COVID-19	NCT04361318

Experimental arm	Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
Hydroxychloroquine, sofosbuvir, and daclatasvir	NA	OL Egypt N = 100	October 2020	Adult patients (18 to 65 years) with SARS-CoV-2 infection	NCT04443725
Hydroxychloroquine, folic acid, lopinavir plus ritonavir, ascorbic acid, and azithromycin	NA	MC, DB, PC US N = 300	December 2020	Adults (18 to 80 years) with SARS-CoV2 infection at high risk of developing COVID-19 disease	NCT04354428
Hydroxychloroquine or chloroquine, or lopinavir plus ritonavir combined with 1 of 3 treatments: rivaroxaban or candesartan or clazakizumab	ACOVACT	MC, OL Austria N = 500	December 1, 2020	Hospitalized adults (18 to 99 years) with SARS-CoV-2 infection	NCT04351724
Hydroxychloroquine	COVID65plus	DB, PC Germany N = 350	December 31, 2020	Older adults (≥ 65 years) with mild-to-moderate COVID-19 not requiring hospitalization	NCT04351516
COVID-19 convalescent plasma or anti-COVID-19 human immunoglobulin or standard (specific) therapy for COVID-19 (may include chloroquine or hydroxychloroquine)	NA	MC, OL Colombia N = 75	December 2020	Hospitalized adults (≥ 18 years) with COVID-19	NCT04395170
NEW Hydroxychloroquine and metabolic cofactor supplementation	NA	MC, OL Turkey N = 400	January 31, 2021	Adults (≥ 18 years) with COVID-19	NCT04573153

ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; DB = double blind; HC = Health Canada; MC = multi-centre; NA = not applicable; OL = open label; PC = placebo controlled; RT-PCR = reverse transcription–polymerase chain reaction; SARS-CoV2 = severe acute respiratory syndrome coronavirus 2; SB = single-blind; SoC = standard of care.

[a] The date on which the data collection was completed for all primary outcome measures.

Table 80: Chloroquine or Hydroxychloroquine to Prevent COVID-19 – Ongoing Randomized Controlled Trials, 2020 Estimated Primary Completion Date[29]

Experimental arm	Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
Pre-exposure prophylaxis and prevention treatments					
Phase IV					
Hydroxychloroquine	NA	DB, PC Spain N = 800	November 6, 2020	Adults (18 to 75 years) receiving a biological treatment and/or a JAK inhibitor	NCT04330495
Phase III					
Hydroxychloroquine	HERO	DB, PC US N = 374	June 24, 2020	Health care workers (≥ 18 years) in a hospital setting	NCT04352946
Hydroxychloroquine at different dosing regimens	WHIP COVID-19	MC, DB US N = 3,000	June 30, 2020	Adults (18 to 75 years), including health care workers, nursing home workers, first responders, and public bus drivers	NCT04341441
Hydroxychloroquine	PROVIDE	MC, DB Canada N = 1,100	July 31, 2020	Health care workers (≥ 18 years) with primary practice in intensive care unit, general internal medicine; and at testing centres, emergency rooms, and nursing homes	NCT04371523
Hydroxychloroquine at different dosing regimens	NA	DB, PC US N = 1,500	August 2020	Health care workers (≥ 18 years) at high risk of COVID-19 exposure	NCT04328467 HC control number: 238396[30]
Hydroxychloroquine	HEROs	MC, DB, PC Canada N = 988	August 27, 2020	Health care workers (≥ 18 years) in emergency departments	NCT04374942 HC control number: 237851[31]
Hydroxychloroquine	NA	OL Peru N = 320	September 2020	Health care workers (≥ 18 years) in service during COVID-19 outbreak	NCT04414241
Hydroxychloroquine at different dosing regimens	PROLIFIC	DB, PC, UK N = 1,000	October 31, 2020	Health care workers (18 to 70 years) who work in high-risk secondary or tertiary hospital settings with direct patient-facing care	NCT04352933

Experimental arm	Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
Hydroxychloroquine	HERO-HCQ	DB, PC US N = 1,363	December 2020	Health care worker (≥ 18 years) at risk of COVID-19 infection through work exposure	NCT04334148
Emtricitabine-tenofovir disoproxil fumarate or hydroxychloroquine or in combination	EPICOS	MC, DB, PC Spain N = 4,000	December 31, 2020	Health care workers (18 to 70 years) at risk of SARS-CoV-2	NCT04334928
Hydroxychloroquine	HCQPreP	DB, PC US N = 1,700	March 31, 2021	Health care or hospital workers (≥ 18 years) who have direct patient contact	NCT04363450
Post-exposure prophylaxis					
Phase III					
Hydroxychloroquine with or without zinc	COVID-Milit	DB, MC, PC Tunisia N = 660	May 24, 2020	Military health care professionals (18 to 65 years) exposed to SARS-CoV-2 but with a COVID-19 negative diagnosis	NCT04377646
Hydroxychloroquine	Chloroquine UN	DB, PC Colombia N = 86	June 1, 2020	Health care professionals (≥ 18 years) highly exposed to SARS-CoV-2	NCT04346329
Hydroxychloroquine and vitamin D	NA	DB US N = 1[c]	June 4, 2020	Health care professionals (≥ 18 years) exposed to persons with COVID-19	NCT04372017
Hydroxychloroquine (low dose)	NA	DB, PC Austria N = 440	July 2020	Health care workers (≥ 18 years) with frequent contact with confirmed COVID-19 patients	NCT04336748
Hydroxychloroquine or lopinavir plus ritonavir	COVIDAXIS	MC, DB, PC France N = 1,200	November 30, 2020	Health care workers (≥ 18 years) treating suspected or confirmed COVID-19 cases	NCT04328285
Hydroxychloroquine	PHYDRA	DB, PC Mexico N = 400	December 31, 2020	Health care workers (≥ 18 years) exposed to patients with COVID-19 (including high-risk and low-risk groups)	NCT04318015

Experimental arm		Trial name	Study design, country, sample size	Estimated trial primary completion date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)
NEW	Hydroxychloroquine	HOPE Trial	OL Korea N = 2,486	March 30, 2021	Adults (≥ 18 years), including medical staff exposed to confirmed case of SARS-CoV-2 infection	NCT04330144
NEW	Hydroxychloroquine	NA	DB, PC Canada N = 336	April 30, 2021	High-risk older adults (≥ 40 years) in long-term and specialized care	NCT04397328 HC control number: 238857
NEW	Lopinavir plus ritonavir or hydroxychloroquine	PROTECT-Surg	OL UK N = 6,400	May 14, 2021	Adult patients (≥ 16 years) undergoing any type of elective or emergency surgery in a COVID-19–exposed environment	NCT04386070
Phase II/III						
Hydroxychloroquine		PREVICHARM	DB Spain N = 1,930	December 15, 2020	Adults (≥ 18 years), including institutionalized persons in nursing homes since the beginning of the COVID-19 pandemic who do not have the infection present at the time of entering into the study and health care workers in nursing homes providing care to institutionalized older persons with confirmed COVID-19 cases during the past 2 weeks	NCT04400019
NEW	Hydroxychloroquine	APCC-19	MC, OL Tunisia N = 93	January 15, 2021	Adults (18 to 65 years old) exposed to a COVID-19 case	NCT04597775
NEW	Hydroxychloroquine	NA	DB, PC US N = 1,600	March 2021	Adults (≥ 18 years) exposed to a COVID-19 case through household contact	NCT04318444

COVID-19 = coronavirus disease 2019; DB = double blind; HC = Health Canada; JAK = Janus kinase; MC = multi-centre; NA = not applicable; OL = open label; PC = placebo controlled; SARS-CoV2 = severe acute respiratory syndrome coronavirus 2.

[a] The date on which the data collection was completed for all primary outcome measures.

[b] Study suspended as of July 15, 2020, until new epidemic curve occurs.

[c] Anticipated sample size was 1,739; however, the currently reported sample size is 1.

Table 81: Chloroquine or Hydroxychloroquine to Treat or Prevent COVID-19 – Unpublished Completed Randomized Controlled Trials[29]

Treatment groups (treatment or prophylaxis)	Trial name	Study design, country, sample size	Trial end date[a]	Population	ClinicalTrials.gov reference and HC control number (if available)	Publication status
Phase III						
Treatment and prophylaxis (hydroxychloroquine) or standard public health measures (treatment and chemoprophylaxis)	HCQ4COV19	Open label Spain N = 2,300	June 15, 2020	• Adults (≥ 18 years). Study 1 (prevention): asymptomatic individuals (health care worker or household contact) with exposure to confirmed COVID-19 cases • Study 2 (treatment): Patients with mild COVID-19	NCT04304053	Not yet published
Favipiravir or oseltamivir with hydroxychloroquine (treatment)	FAV-001	Open label Egypt N = 100	June 20, 2020	Adult (18 to 80 years old) patients with mild-to-moderate (confirmed) COVID-19	NCT04349241	Not yet published

COVID-19 = coronavirus disease 2019; HC = Health Canada.

[a] Actual trial completion date as indicated at ClinicalTrials.gov.