Hydroxychloroquine versus placebo in the treatment of non-hospitalised patients with COVID-19 (COPE — Coalition V): A double-blind, multicentre, randomised, controlled trial

Álvaro Avezum, a* Gustavo B F Oliveira, a Haliton Oliveira, a Rosa C Lucchetta, a Valéria F A Pereira, b André L Dabarian, b Ricardo DO Vieira, c Daniel V Silva, c Adrián P M Kormann, d Alexandre P Tognon, e Ricardo De Gasperi, f Mauro E Hernandes, g Audes D M Feitosa, h Aghnaldo Piscopo, i André S Souza, j Carlos H Miguel, k Vinícius O Noqueira, l César Minelli, m Carlos C Magalhães, n Karen M L Morejon, o Leticia S Bicudo, p Germano E C Souza, q Marco A M Gomes, r José J F Raposo Fo, s Alexandre V Schwarzbald, t Alexandre Zilli, u Roberto B Amazonsas, v Frederico R Moreira, w Lucas B O Alves, x Silvia R L Assis, y Regis G Rosa, z Renato D Lopes, a, z Alexandre B Cavalcanti, a and Otavio Berwanger, a, on behalf of the COPE - COALITION COVID-19 Brazil V Investigators 1

Summary

Background Previous Randomised controlled trials (RCT) evaluating chloroquine and hydroxychloroquine in non-hospitalised COVID-19 patients have found no significant difference in hospitalisation rates. However, low statistical power precluded definitive answers.

DOI of original article: http://dx.doi.org/10.1016/j.lana.2022.100268

*Corresponding author.
E-mail address: aavezum@haoc.com.br (Á. Avezum).

1 COPE - COALITION COVID-19 Brazil V collaborators are listed in the supplementary file.
Methods We conducted a multicenter, double-blind, RCT in 56 Brazilian sites. Adults with suspected or confirmed COVID-19 presenting with mild or moderate symptoms with ≤ 07 days prior to enrollment and at least one risk factor for clinical deterioration were randomised (1:1) to receive hydroxychloroquine 400 mg twice a day (BID) in the first day, 400 mg once daily (OD) thereafter for a total of seven days, or matching placebo. The primary outcome was hospitalisation due to COVID-19 at 30 days, which was assessed by an adjudication committee masked to treatment allocation and following the intention-to-treat (ITT) principle. An additional analysis was performed only in participants with SARS-CoV-2 infection confirmed by molecular or serology testing (modified ITT [mITT] analysis). This trial was registered at ClinicalTrials.gov, NCT04466540.

Findings From May 12, 2020 to July 07, 2021, 1372 patients were randomly allocated to hydroxychloroquine or placebo. There was no significant difference in the risk of hospitalisation between hydroxychloroquine and placebo groups (44/689 [6.4%] and 57/683 [8.3%], RR 0.77 [95% CI 0.52–1.12], respectively, p=0.16), and similar results were found in the mITT analysis with 43/478 [9.0%] and 55/471 [11.7%] events, RR 0.77 [95% CI 0.53–1.12]), respectively, p=0.17. To further complement our data, we conducted a meta-analysis which suggested no significant benefit of hydroxychloroquine in reducing hospitalisation among patients with positive testing (69/1222 [5.6%], and 88/1186 [7.4%]; RR 0.77 [95% CI 0.57–1.04]).

Interpretation In outpatients with mild or moderate forms of COVID-19, the use of hydroxychloroquine did not reduce the risk of hospitalisation compared to the placebo control. Our findings do not support the routine use of hydroxychloroquine for treatment of COVID-19 in the outpatient setting.

Funding COALITION COVID-19 Brazil and EMS.

Copyright © 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Research in context

Evidence before this study

Eight randomised clinical trials evaluated hydroxychloroquine or chloroquine in non-hospitalised patients with mild to moderate COVID-19 for various outcomes. Six randomised controlled trials which evaluated hospitalisation due to COVID-19-related complications found no significant difference in hospitalisation rates between hydroxychloroquine and control/placebo. In addition, no serious adverse events were seen in patients treated with hydroxychloroquine. However, the risk of significant bias and low statistical power from previous studies precluded definitive conclusions. Therefore, the efficacy and safety of hydroxychloroquine or chloroquine in this clinical setting remains unknown.

Added value of this study

To the best of our knowledge, this study is the largest randomised clinical trial assessing the effect of hydroxychloroquine versus placebo added to a standard of care regimen, evaluating hospitalisation due to COVID-19 in suspected and confirmed cases in the outpatient setting. Also, we provided a meta-analysis of the most updated scientific evidence, including the current COPE trial. Our study is the most recent and comprehensive analysis of the use of hydroxychloroquine in outpatients with COVID-19, which may inform clinical practice and international guidelines. Hydroxychloroquine did not reduce hospitalisation due to COVID-19 in this setting.

Furthermore, hydroxychloroquine did not result in higher rates of serious adverse events including sudden death, ventricular arrhythmias, or retinopathy.

Implications of all evidence available

The COPE trial and the related meta-analysis demonstrated that the incidence of hospitalisation due to COVID-19 was similar between treatment groups with no concerns regarding safety. The 95% confidence interval around the effect estimate shows that potential benefits or harms cannot be clearly excluded. Therefore, the definitive answer about the efficacy and safety of hydroxychloroquine in outpatients with COVID-19 remains uncertain and this treatment should not be routinely used in this clinical setting.

Introduction

As of March 2022, SARS-CoV-2 has infected more than 450 million people and caused approximately 6.0 million deaths worldwide since 2019. Furthermore, new therapeutic agents are specially necessary due to the resurgence of COVID-19 on its delta and omicron variants, which have been associated with reduced vaccine efficacy as well as greater transmissivity and the probability of COVID-19 persistence for decades. During the COVID-19 pandemic, drug repurposing has been the subject of intense clinical investigation as
prophylaxis and treatment of COVID-19.\textsuperscript{5,6} Among candidates, the antimalarial drugs chloroquine and hydroxychloroquine initially drew substantial attention after the report of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) \textit{in vitro} activity.\textsuperscript{7,8} Hydroxychloroquine mechanisms of action have been proposed to potentially interfere with viral structure, thus, promoting an antiviral effect.\textsuperscript{9}

Despite the need for effective and safe therapeutic options for COVID-19, there is no robust evidence of effectiveness for any repurposing treatment in the outpatient setting to reduce the burden of hospitalisation due to COVID-19, which would be more relevant in terms of financial resources and hospital beds shortage among low and middle-income countries.

Therefore, it is essential to evaluate safe, inexpensive and widely available therapies against COVID-19, which could lead to reduced risk of clinical deterioration, hospitalisation, mechanical ventilation requirement, and death, specifically in an early phase of COVID-19 infection. When considering outpatient COVID-19 cases, clinical data from previously reported RCTs assessing hydroxychloroquine have found no significant difference in hospitalisation rate.\textsuperscript{10,11} Furthermore, in hospitalised patients the evidence has shown that hydroxychloroquine yields little or no difference to risk of all-cause death (RR 1.09, 95% CI 0.99 to 1.19; 8208 participants; 9 trials; high-certainty evidence).\textsuperscript{12}

We conducted the COPE randomised trial to assess whether an early treatment with hydroxychloroquine, for seven days, in outpatients with mild or moderate COVID-19 decreases the risk of hospitalisation due to COVID-19 at 30 days after randomization.

\section*{Methods}
\subsection*{Study design and participants}

The trial methods have been published previously.\textsuperscript{11} In brief, COPE-COALITION V was an academic-led, multicentre, double-blind, placebo-controlled randomised trial conducted in 56 research centers in Brazil. The trial was approved by national and institutional research ethics committees. Written informed consent was obtained from all patients. The trial protocol and statistical analysis plan are available in the \textit{Supplementary appendix}.

Eligibility criteria included patients ≥18 years old with suspected or confirmed COVID-19, with symptoms duration prior to enrollment ≤7 days, presenting as mild/moderate forms of the disease at primary care centers or emergency departments, without clinical indication of hospitalisation according to the attending physician, and at least one risk factor for clinical deterioration as follows: age >65 years; hypertension; diabetes mellitus; asthma; chronic obstructive pulmonary disease (COPD) or other chronic lung disease; current smoking; immunosuppression; obesity (defined as body mass index [BMI] ≥30 Kg/m\textsuperscript{2}). Detailed definitions of suspected or confirmed cases are provided in the \textit{Supplementary Methods} — Study protocol. Key exclusion criteria were: hospitalisation at the first medical care; positive test for influenza at the first medical care; known hypersensitivity to hydroxychloroquine or chloroquine; previous diagnosis of retinopathy or macular degeneration; previous diagnosis of Long QT-syndrome, history of sudden death in close family members (parents and siblings), decompensated heart failure, unstable coronary artery disease, use of anti-arrhythmic drugs or other treatments that can increase the hydroxychloroquine bioavailability or enhance its effect; evidence of known liver or kidney diseases reported by the patient; diagnoses of pancreatitis; baseline electrocardiogram (ECG) with QTc interval ≥480ms; chronic use of hydroxychloroquine or chloroquine for other reasons; and pregnancy.

\subsection*{Randomization and masking}

Patients were randomly assigned (1:1) to receive hydroxychloroquine (400 mg twice a day [BID] in the first day, followed by 400 mg once daily [OD] thereafter, for seven days) or matching placebo. Randomization was performed in permuted blocks of eight. Concealment of the randomization list was maintained through a 24-h, centralised, automated, internet-based randomisation system. Patients, principal investigators and study coordinators, healthcare providers and outcome adjudicators were unaware of study medication assignments.

\subsection*{COVID-19 tests and trial procedures}

Real-time reverse transcription–polymerase chain reaction assay for SARS-CoV-2 virus detection was preferably collected between the 4\textsuperscript{th} and 7\textsuperscript{th} days of symptoms onset by nasopharyngeal/oropharyngeal swabs, regardless of signs and symptoms. Immunological test (rapid test or classic serology to detect IgM/IgG antibodies) was applied in those patients with seven or more days of symptoms onset. Patients with suspected infection whose test results were negative after recruitment were instructed to stop study drug but completed the planned 30-day follow-up.

Data were collected through an electronic case report form system. The following demographic and clinical data were collected: age, sex, and relevant sociodemographic characteristics; results from molecular or serology tests for COVID-19 (according to the most appropriate time window for diagnosis); co-interventions; and duration of symptoms. Two follow-up visits were scheduled after randomization: at 7 days, to assess study drug adherence and safety, and at 30 days, to assess efficacy and safety endpoints.

This trial was registered at ClinicalTrials.gov, NCT04466540.
Primary and secondary outcomes

The primary outcome was hospitalisation due to COVID-19 at 30 days from randomization. Indication for hospitalisation due to COVID-19 followed the local practice and clinical judgement at each participating site. Key secondary endpoints included: uncontrolled asthma after ≥5 days of starting study medication; pneumonia; otitis media; fever resolution time; time to improve respiratory symptoms (cough, runny nose); hospitalisation in the Intensive Care Unit; need for oro-tracheal intubation; mechanical ventilation time; and all-cause mortality. All patients were followed up to the first clinical event. We were able to retrieve the relevant information from the participating sites whether it was a hospitalisation due to COVID-19 or a fatal event not occurring during hospitalisation. Secondary outcome definition is provided in the Supplementary appendix – Study protocol. The following outcomes were considered rather exploratory: time to hospitalisation after randomisation; and assessment of the patient clinical status at the time of hospitalisation. Safety outcomes were assessed during the 30-day follow-up. Clinical outcomes of primary interest were adjudicated by the Events Adjudication Committee which included two research physicians with experience in pharmacovigilance and clinical events validation in national and international studies. Hospitalisations due to COVID-19 were documented by the local study team and essential data was collected and sent to the adjudicators for a blinded assessment following standardized criteria.

Statistical analysis

Based on initial epidemiological data, we assumed that the primary outcome would occur in 20% of individuals in the placebo group and in 14% of patients in the hydroxychloroquine group, which corresponds to a relative risk reduction of 30%. It is important to state that, in infectious diseases such as COVID-19, in the beginning of the surge throughout the pandemic situation, and based on inherent diagnostic testing limitations, we could end up ruling out a definitive COVID-19 case due to expected false-negative results, which depend on various reasons. The sample size calculation was initially performed based on suspected/probable and confirmed cases, as the time interval to receive the diagnostic results was variable and could be after 4-5 days. Moreover, clinically eligible patients should be randomized within 7 days from symptom onset, therefore, they could be enrolled with diagnostic work-up still ongoing. Statistical assumptions were based on epidemiological data and observations in daily practice. The eligibility criteria provide a good level of understanding regarding the probable and confirmed diagnoses, as described above and in the previously published rationale and design of the trial. We, therefore, estimated a sample size of 1230 (615 per group) to provide 80% statistical power to detect this reduction at a significance level of 5%, using the Chi-square test and assuming a two-sided significance hypothesis and considering a 1:1 allocation. Assuming a dropout rate of 5% in each group, we would require 1296 individuals (648 per group). According to initial estimates, up to 5% of non-positive cases would have no impact on statistical power. By contrast, if ≥5%, it was requested by the National Health Agency (ANVISA) that additional participants should be included according to the impact of non-positive cases in the predicted power. After reaching the initial 1300 target sample size, we estimated nearly 30% of negative tested cases, therefore, additional enrollment was deemed necessary to maintain a statistical power ≥80% for the mITT analysis (please refer to Supplementary Fig. 1). A new sample size was calculated in the first 3-4 months of 2021 to include 320 COVID-19 positive patients. However, from May to July 2021, there was a significant drop in the randomization rates due to a substantial reduction in COVID-19 cases in Brazil. After discussion with ANVISA, Coalition COVID-19 Brazil Executive Committee, EMS, Data and Safety Monitoring Board (DSMB), and with notification to Local and National Ethics Committees and participating sites, we decided to stop recruitment into the COPE trial based upon difficulties to maintain the randomization rates to achieve the new proposed sample size of 1620 cases, finalizing the recruitment phase with 1372 patients. Additional details in terms of protocol amendment, DSMB role and interim analyses, and review by ethics and regulatory agencies are provided in the Supplementary appendix – Study protocol.

Baseline characteristics were reported as counts and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR), whenever appropriate. Normality was assessed by visual inspection of histograms and with application of Shapiro-Wilk normality test when appropriate.

The effect of the hydroxychloroquine intervention on the primary outcome and on binary secondary outcomes were estimated as risk ratios (RRs) and 95% confidence intervals. Absolute difference between two proportions with 95% CI according to Newcombe’s method were also estimated. Chi-squared test or Fisher exact test was applied for hypothesis testing. Sensitivity analyses for the primary outcome were conducted considering effect of the intervention within prespecified subgroups using stratified analyses. Interaction tests were also performed to evaluate whether the treatment effect is influenced by patient characteristics (factor of interest). These subgroups included age, sex, smoking status at baseline, symptom onset to randomization, and prior history of COPD or asthma, hypertension, diabetes, obesity. These interaction tests were conducted using binary logistic regression models that includes the treatment effect, the factor of interest, and an interaction term between the two variables (treatment-by-subgroup interaction.
Results
From May 12, 2020 to July 07, 2021, 3954 patients were screened upon admission, of whom 2582 did not meet full eligibility criteria or were duplicate records, and 1372 were enrolled in the trial (Figure 1). No patients were lost to 30-day follow-up, and 8 patients withdrew informed consent. For the intention-to-treat analysis, we evaluated 1372 patients (68% in the hydroxychloroquine group and 68% in the placebo group). Groups were well balanced with respect to baseline characteristics (Table 1). Median age was 45 (36-56) years, 729 (53%) were women; 752 (54%) were obese, 732 (53%) had hypertension, and 222 (16%) had diabetes. The median time from symptom onset to randomization was 4 (3-5) days. A total of 949 patients (60%) had a positive test for SARS-CoV-2 infection and constituted the mITT population, with similar baseline characteristics between allocation arms (Supplementary Table 2). One-week adherence rates were 87.7% in the hydroxychloroquine group and 85.4% in the placebo group, and partial adherence rates were 9.9% in the hydroxychloroquine group (median 3 days) and 12.0% in the placebo group (median 3 days). Only 35 patients, despite being randomised, did not take any study drug due to their own decision. Treatment for COVID-19 and other therapies during the 7-day study treatment period were similar between allocation arms in both the ITT and mITT populations (Supplementary Tables 3 and 4).

The primary efficacy outcome was fully ascertained in all patients. In the ITT analysis, there was no significant difference in the risk of 30-day hospitalisation due to COVID-19 between hydroxychloroquine and placebo groups (44/689 [6.4%] and 57/683 [8.3%]; RR 0.77 [95% CI 0.52-1.12]). There was also no significant difference in the primary outcome between hydroxychloroquine and placebo groups in the mITT analysis (43/478 [9.0%] and 55/471 [11.7%]; RR 0.77 [95% CI 0.55-1.12]). Prespecified secondary efficacy outcomes (pneumonia, otitis, worsening of asthma, ICU admission and need of invasive mechanical ventilation) were not significantly different between ITT groups (Table 2). Secondary outcomes in the mITT groups are shown in Supplementary Table 5.

Hospitalisation-free survival curves, due to COVID-19, depicted no clear differences after randomization. In the ITT and mITT analyses, the distribution of the primary outcome events at 30 days between hydroxychloroquine and placebo did not reach significant difference, as shown in Figure 2A and B.
There was no significant interaction detected in any prespecified subgroup for ITT and mITT analyses (Figure 3A and B).

In the ITT population, the total number of adverse events was 24.2% in the hydroxychloroquine group and 22.1% in the placebo group (Supplementary Table 6). The proportions of 30-day serious adverse events were 4.1% in the hydroxychloroquine and 5.1% in the placebo group. In the mITT population, the total number of adverse events was 27.6% in the hydroxychloroquine group and 26.1% in the placebo group (Supplementary Table 6); while proportions of 30-day serious adverse events were 5.7%, and 7.3% in the hydroxychloroquine and in the placebo group, respectively. After a thorough review and blinded adjudication, there were 5 deaths caused by severe acute respiratory syndrome due to COVID-19, per allocation arm, during the 30-day follow-up after randomization (Table 2), and all deaths occurred during hospitalisation due to progressive severity of COVID-19. There were no severe cardiac arrhythmias, sudden death, or retinopathy in both groups.

Additionally, we conducted a meta-analysis, including six published studies which had reported hospitalisation due to COVID-19 complication as an efficacy outcome. The full meta-analysis methodology is registered at PROSPERO CRD42021265427. Since most studies included in the meta-analysis had enrolled
participants with positive diagnostic testing for SARS-CoV-2, the COPE mITT population was selected for inclusion in the metaanalysis. There was no significant benefit of outpatient-administered hydroxychloroquine in reducing hospitalisation due to COVID-19 among patients with confirmed diagnosis of COVID-19 RR 0.77 (95% CI 0.57; 1.04), as shown in Figure 4.

**Table 1**: Baseline characteristics and treatments at the time of randomization in the intention-to-treat analysis.

| Variable                        | Level          | Group          | n/N  | %   | n/N  | %   |
|---------------------------------|----------------|----------------|------|-----|------|-----|
| Age, by median                  |                |                |      |     |      |     |
| <45                             | 329/689        | 47.8           | 326/683 | 47.7 |
| ≥45                             | 360/689        | 52.2           | 357/683 | 52.3 |
| Sex                             |                |                |      |     |      |     |
| Male                            | 329/689        | 47.8           | 314/683 | 46.0 |
| Female                          | 360/689        | 52.2           | 369/683 | 54.0 |
| Ethnicity                       |                |                |      |     |      |     |
| White                           | 495/688        | 71.9           | 465/683 | 68.1 |
| Black                           | 192/688        | 27.9           | 212/683 | 31.0 |
| Others                          | 1/688          | 0.2            | 6/683  | 0.9  |
| Body mass index, kg/m²          |                |                |      |     |      |     |
| Normal (20-24.9)                | 127/689        | 18.4           | 114/683 | 16.7 |
| Overweight (25-29.9)            | 199/689        | 28.9           | 180/683 | 26.3 |
| Obese (≥30)                     | 363/689        | 52.7           | 389/683 | 57.0 |
| Time from symptom onset to randomization by median, days | | | | | |
| <4                              | 267/689        | 38.8           | 255/683 | 37.3 |
| ≥4                              | 422/689        | 61.2           | 428/683 | 62.7 |
| SARS-CoV-2 testing              |                |                |      |     |      |     |
| Positive                        | 478/689        | 69.4           | 471/683 | 69.0 |
| Negative                        | 197/689        | 28.6           | 194/683 | 28.4 |
| Not performed                   | 14/689         | 2.0            | 18/683  | 2.6  |
| Smoking                         |                |                |      |     |      |     |
| Never                           | 561/689        | 81.4           | 569/683 | 83.3 |
| Current/Former                  | 128/689        | 18.6           | 114/683 | 16.7 |
| Treatments at baseline          |                |                |      |     |      |     |
| Azithromycin                    | 375/687        | 54.6           | 379/682 | 55.6 |
| Ivermectin                      | 140/689        | 20.3           | 121/683 | 17.7 |
| Oseltamivir                     | 43/689         | 6.2            | 30/683  | 4.4  |
| Heart disease                   | 3/689          | 0.4            | 6/683   | 0.9  |
| Lung disease                    | 21/689         | 3.0            | 26/683  | 3.8  |
| Diabetes                        | 113/689        | 16.4           | 109/683 | 16.0 |
| Hypertension                    | 377/689        | 54.7           | 355/683 | 52.0 |
| Asthma                          | 87/689         | 12.6           | 91/683  | 13.3 |
| Fever                           | 429/687        | 62.4           | 413/683 | 60.5 |
| Cough                           | 552/688        | 80.2           | 545/683 | 79.8 |
| Sore throat                     | 417/688        | 60.6           | 392/683 | 57.4 |
| Myalgia                         | 461/688        | 67.0           | 450/683 | 65.9 |
| Fatigue                         | 423/688        | 61.5           | 440/683 | 64.4 |
| Dyspnea                         | 190/687        | 27.7           | 190/683 | 27.8 |
| Heart Rate (SD) (N, bpm)        |                |                |      |     |      |     |
| 84.6 (14.2) (N=685)             | -              | 84.6 (15.0) (N=682) | -  |
| Respiratory Rate (SD) (N, rpm)  |                |                |      |     |      |     |
| 19.1 (2.5) (N=673)              | -              | 19.1 (2.5) (N=673) | -  |
| SBP (SD) (N, mmHg)              |                |                |      |     |      |     |
| 131.2 (16.5) (N=674)            | -              | 130.4 (17.7) (N=670) | -  |
| DBP (SD) (N, mmHg)              |                |                |      |     |      |     |
| 82.7 (10.3) (N=674)             | -              | 81.7 (11.7) (N=670) | -  |
| SaO2 (SD) (N, %)                |                |                |      |     |      |     |
| 97.1 (1.6) (N=685)              | -              | 97.1 (1.3) (N=679) | -  |
| Temperature (SD) (N, °C)        |                |                |      |     |      |     |
| 36.6 (0.7) (N=685)              | -              | 36.6 (0.7) (N=683) | -  |

**Discussion**

In this double-blind, multicenter, randomised trial, hydroxychloroquine did not significantly reduce the risk of hospitalisation due to COVID-19 as compared with placebo in symptomatic non-hospitalized patients. Results were consistent in both the ITT and mITT analyses. In addition, there was no significant difference in
the rates of prespecified serious adverse events and, specifically, there were no severe cardiac arrhythmias, sudden death, or retinopathy as per the study dosing and regimen, compared with placebo. The updated meta-analysis of all previous RCTs and the COPE trial found similar results.

Previous RCTs evaluating a similar scientific question in relatively comparable patient populations did not show significant benefit when comparing hydroxychloroquine or chloroquine vs control. Those trials were small and underpowered. Reis and cols. evaluated the effect of early treatment with hydroxychloroquine and did not find any significant benefit in reducing the risk of COVID-19 related hospitalisation. Despite the original sample size of 1,476 patients, the hydroxychloroquine analysis included 441 patients (30% of study population).17 Skipper and cols. enrolled symptomatic, non-hospitalised patients with confirmed or probable COVID-19, and 423 out of 491 patients had primary endpoint data ascertained. They found that hydroxychloroquine did not reduce symptom severity or hospitalisation due to COVID-19 and was associated with higher incidence of side effects. Incidence of hospitalisation was very low (3.0%), making the planned analysis of the ordinal endpoint futile.10 Schwartz and cols. reported results from 148 randomised patients with confirmed COVID-19 from a planned recruitment of 1,446, and 16.2% of those did not take the study drug. There was no evidence that hydroxychloroquine reduced symptom duration or prevented severe outcomes, and the study was terminated early.18 Johnston and cols. evaluated the use of hydroxychloroquine and azithromycin in 231 non-hospitalised patients. Neither hydroxychloroquine alone nor hydroxychloroquine plus azithromycin shortened the clinical course of outpatients with COVID-19, and hydroxychloroquine alone had only a modest effect on SARS-CoV-2 viral shedding. Because of the low event rates, the study was terminated due to operational futility.19 Mitja and cols. evaluated 293 patients in the outpatient clinical setting and found that hydroxychloroquine did not reduce the risk of hospitalization, nor improved the time to complete resolution of symptoms. No relevant treatment-related adverse events were reported.20

There is also evidence that hydroxychloroquine does not work in postexposure prophylaxis, although potential benefits cannot be ruled out by the available studies.20-22 Furthermore, among adults hospitalised with respiratory illness from COVID-19, treatment with hydroxychloroquine did not significantly improve clinical status, mortality rates or need for invasive mechanical ventilation at 14 days compared with placebo or control.23-25 Two trials with larger sample sizes, evaluating hydroxychloroquine in hospitalized patients with mild/moderate COVID-19, consistently confirmed the lack of benefit in the hospital setting. Robust and actionable evidence from large RCT in hospitalised patients has come from the RECOVERY and Coalition I COVID-19 Brazil trials.26,27

Current data differs somewhat from RCTs conducted in hospitalized patients, where the hypothesis that hydroxychloroquine would improve clinical outcomes either by reduction in the symptoms ordinary scale or events was not confirmed, and harmful effect was suggested.26,27 Firstly, patient populations are substantially different in terms of clinical presentation, COVID-19 severity, risk factors, comorbidities, multiorgan complications, polypharmacy, and sample size. Hospital trials evaluated more severe and critically ill patients, i.e., in a more advanced phase of the disease. Additionally, the mechanism of action of

### Table 2: Primary and secondary efficacy outcomes in the intention-to-treat analysis.

| ITT population | 30-day Efficacy Outcomes | HCQ | Placebo | Difference in proportions, % (95% CI) | RR (95% CI) | P-value |
|----------------|--------------------------|-----|---------|--------------------------------------|------------|---------|
| Primary        | Hospitalisation due to COVID-19 | 44/689 (6.4%) | 57/683 (8.3%) | -1.9 (-4.8, 0.8) | 0.77 (0.52,1.12) | 0.1646 |
| Secondary      | Pneumonia | 17/685 (2.5%) | 27/680 (4.0%) | -1.5 (-3.5, 0.4) | 0.63 (0.34, 1.14) | 0.1194 |
|                | Otitis | 1/684 (0.1%) | 4/680 (0.6%) | -0.5 (-1.4, 0.3) | 0.25 (0.03, 2.22) | 0.2167 |
|                | Worsening of Asthma | 19/685 (2.8%) | 23/679 (3.4%) | -0.6 (-2.5, 1.3) | 0.82 (0.45, 1.49) | 0.5119 |
|                | ICU Admission | 16/687 (2.3%) | 19/682 (2.8%) | -0.5 (-2.2, 1.3) | 0.84 (0.43, 1.61) | 0.5922 |
|                | Requirement of invasive mechanical ventilation | 8/687 (1.2%) | 6/682 (0.9%) | 0.3 (-0.9, 1.5) | 1.32 (0.46, 3.79) | 0.6066 |
|                | Death* | 5/687 (0.73%) | 5/682 (0.73%) | - - - - - - - - | 1.56 (0.42-6.72) | 0.540 |

*For death at 30 days, effect measure was HR (Hazard Ratio) and all parameter estimates were computed from Univariate Cox Regression with Firth’s Penalized Likelihood.

P-value from chi-squared test (except for death at 30 days); RR: Relative Risk (except for death at 30 days); ICU: Intensive care unit; HCQ: Hydroxychloroquine.
hydroxychloroquine towards possible benefit is more likely and biologically plausible at the early phase of COVID-19 when acute viral load and increased replication are observed.

The pro-arrhythmic and anti-arrhythmic effects of both hydroxychloroquine and chloroquine have been a matter of much debate. However, the risk of arrhythmia has been frequently inferred based on QT interval prolongation rather than derived from good quality clinical data. In a recent retrospective analysis of nearly one million rheumatoid arthritis patients, starting treatment with hydroxychloroquine was associated with a lower risk of arrhythmia in the first 30 days but showed no effect on mortality. There is no evidence of significant risk of torsade de pointes in acute treatment with doses usually recommended in malaria or rheumatological conditions.

In the COPE trial, safety profile was carefully assessed with appropriate eligibility criteria before randomization. Potential patients who were screened with factors likely to increase the probability of adverse cardiovascular events, along with mandatory baseline ECG where QTc interval was measured and considered to last ≥480 ms were not randomised. There was no difference in total or serious adverse events between hydroxychloroquine and placebo, with very low rates of 30-day serious adverse events. Moreover, we emphasize that there were no severe cardiac arrhythmias, sudden death or retinopathy in this outpatient setting.

Figure 2. Hospitalisation-free survival according to hydroxychloroquine and placebo allocation in: (A) Intention-to-treat analysis; and (B) Modified intention-to-treat analysis.
The totality of scientific evidence available, including the COPE trial, does not provide evidence to support the routine use of hydroxychloroquine in the outpatient setting as a treatment for COVID-19. It should be acknowledged that some uncertainty persists after taking into account the wide 95% CI found in the meta-analysis, which does not completely exclude potential benefits or harms of hydroxychloroquine in this clinical setting.

The following limitations should be considered in the COPE trial: lack of sufficient power to detect meaningful benefit towards lower risk of hospitalisation, as the study sample size and event rates were below the expected figures to reliably detect relative risk reduction of the primary outcome; clear attenuation of eligible cases for randomization into the study due to significant reduction in the number of infected cases in Brazil (as a result of wearing facial masks, washing hands, social distance, and effective vaccination); proportion of negative test results around 30% of the total recruitment leading to lower statistical power.

Figure 3. Subgroup analysis for interaction between clinically relevant variables and treatment effect of Hydroxychloroquine versus placebo in: (A) Intention-to-treat analysis; and (B) Modified intention-to-treat analysis.
Nevertheless, although the COPE study did not reach the intended power, we were able to enroll an adequate number of patients to conduct statistically robust analysis.

In conclusion, based on the COPE trial and on the most updated meta-analysis results, hydroxychloroquine did not reduce the risk of hospitalisation due to COVID-19 in the outpatient setting. Thus, there is no evidence of benefit to support the routinely use of the treatment in the clinical management of COVID-19.

Contributors
AA conceived the trial and wrote the initial proposal, contributed to the literature search, study design, selecting participating sites, data interpretation, obtaining funding and drafting of the manuscript. GBFO contributed to the literature search, study design, selecting participating sites, obtaining funding, data interpretation, and drafting of the manuscript. HOJ contributed to the study design, literature search, data interpretation, obtaining funding and drafting of the manuscript. RCL and JYM contributed to the systematic review and meta-analysis, and critical review of the manuscript. FRM estimated the sample size, drafted the statistical analysis plan and contributed to statistical analyses, including the final data analysis. LBOA and SRLA contributed to statistical analyses, including the final data analysis. ABC, VCV, RGR, LCPA, RDL, and OB contributed to study design, data interpretation, and critical review of the manuscript. VFAP, ALD, RDV, DVS, APMK, APT, RDG, MEH, ADMF, AP, ASS, CHM, VON, CM, CCM, KMLM, LSB, GECS, MAMG, JJFRF, AVS, AZ contributed to data collection and critical review of the manuscript. IB, DGMC and PDMMN contributed to study design and critical review of the manuscript. RBA contributed to critical review of the manuscript. All authors had access to the data, contributed to the manuscript, agreed to submit for publication, and vouch for the integrity, accuracy, and completeness of the data and for the fidelity of the trial to the protocol.

Data sharing statement
Anonymised participant data can be made available upon requests directed to the corresponding author. Proposals will be reviewed on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement.

Declaration of interests
AA reports consultant and lectures fees from Bayer, NovoNordisk and Lilly outside of this submitted work, and research grants from Bayer, EMS Pharma and Population Health Research Institute. GBFO received honoraria for lectures from Novartis and Janssen outside of this submitted work; AD reports lecture fees from Bayer, Libbs, Apsen, and Biolab outside of this submitted work. ASS reports lectures fees from BioLab, Torrents and Servier. AVS reported research grants from AstraZeneca, MSD, Esperion, Clover Biopharm and Enanta Pharmaceutical outside of this submitted work. ABC received honoraria for lectures from EMS Pharma. LCPA reports personal fees from Baxter, Pfizer, and Halex-Istar; and grants from Ache Laboratorios Farmaceuticos, outside of this submitted work. OB reports...
grants from AstraZeneca, Pfizer, Bayer, Boehringer Ingelheim, Servier, and Amgen, and advisory board and personal fees from Novartis, outside of this submitted work. RBA reports to be an EMS employee. RDL reports grants and personal fees from Bristol Myers Squibb, Pfizer, GlaxoSmithKline, Medtronic PLC, and Sanofi; and personal fees from Amgen, Bayer, and Boehringer Ingelheim, outside of this submitted work. RCR received honoraria for lectures from Novartis outside of this submitted work; VCV reports grants from Aspen Pharma, Pfizer, and Cristalia, outside of this submitted work. The other authors have no conflict to declare.

Acknowledgements

The authors are indebted to all collaborating sites and respective teams who worked hard to enroll participants with high data quality, and to all healthcare professionals who provided recommended care for all patients during the study conduction. This trial was funded by the COALITION COVID-19 Brazil Research Institutions. EMS provided partial funding and the study drugs, without any involvement in the study conduction, analysis, or decision to publish these results. All the authors reassure the integrity and completeness of the data and the fidelity of the trial to the study protocol.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lan.2022.100243.

References

1 World Health Organization (WHO). WHO Coronavirus (COVID-19) Dashboard. WHO site; 2022. https://covid19.who.int/. Accessed in March 2022.
2 Grant R, Charmet T, Schaeffer L, et al. Impact of SARS-CoV-2 Delta variant on incubation, transmission settings and vaccine effectiveness: results from a nationwide case-control study in France. Lancet Reg Health Eur. 2021;100278.
3 Kartim SSA, Kartim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. Lancet. 2021;398:2126–2128.
4 Callaway E. Beyond Omicron: what’s next for COVID’s viral evolution. Nature. 2021;580:204–207.
5 Jean SS, Hsieh PR. Old and re-purposed drugs for the treatment of COVID-19. Expert Rev Anti Infect Ther. 2020;18:843–847.
6 Repurposed antiviral drugs for COVID-19-interim WHO solidarity trial results. N Engl J Med. 2021;384:497–511.
7 Yao X, Ye F, Zhang M, et al. In vivo antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71:712–719.
8 Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.
9 Kalra RS, Tomar D, Meena AS, Kandimalla R. SARS-CoV-2, ACE2, and hydroxychloroquine: cardiovascular complications, therapeutics, and clinical readouts in the current settings. Pathogens. 2020;9:546.
10 Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. Ann Intern Med. 2020;173:62–69.
11 Mitja O, Corbacho-Monné M, Ubal M, et al. Hydroxychloroquine for early treatment of adults with mild coronavirus disease 2019: a randomized, controlled trial. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa1009, published online July 16.
12 Singh B, Ryan H, Krede T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database Syst Rev. 2021. https://doi.org/10.1002/14651858.CD013157.pub2.
13 Junior HAO, Ferri CP, Boscozowski I, et al. Rationale and design of the COVID-19 outpatient prevention evaluation (COPE) randomized clinical trial: hydroxychloroquine vs. placebo in non-hospitalized patients. Arq Bras Cardiol. 2022. https://doi.org/10.36669/abc.20218532. e-pub.
14 Liu T, Huang J. Generating Model Based Subgroup Analysis Using SAS Procedures. Proc. Pharm. SAS Users Gr. Conf. (PharmaSUG 2019) - SAS Inst. 2019. https://www.lexjansen.com/pharmasug/2019/?=pharmasug2019. Accessed 17 November 2021.
15 Liu X. Survival Analysis: Models and Applications. Hoboken, NJ: John Wiley & Sons; 2012.
16 Blenkinsop A, Parmar MK, Choohadi-Oskoei B. Assessing the impact of efficacy stopping rules on the error rates under the multi-arm multi-stage framework. Clin Trials. 2019;16:135–147.
17 Reis C, Moreira Silva EA, de S, et al. Effect of early treatment with hydroxychloroquine or lopinavir and ritonavir on risk of hospitalization among patients with COVID-19. JAMA Netw Open. 2021;4: e214568.
18 Schwartz I, Boesen ME, Cerchiaro G, et al. Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial. C Open. 2021;6:E063–E072.
19 Johnston C, Brown ER, Stewart J, et al. Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: a randomized clinical trial. EClinicalMedicine. 2021;33:100737.
20 Mitja O, Corbacho-Monné M, Ubal M, et al. A cluster-randomized trial of hydroxychloroquine for prevention of COVID-19. N Engl J Med. 2020;384:417–427.
21 Boullarde DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med. 2020;383:377–391.
22 Barnabas RV, Brown ER, Berstein A, et al. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection: a randomized trial. Ann Intern Med. 2021;174:144–152.
23 Abd-Elsalam S, Esmail ES, Khalfah M, et al. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. Am J Trop Med Hyg. 2021;105:639–639.
24 Hernandez-Carmonas C, Trizon-Romerio I, Rodriguez-Llamazares S, et al. Hydroxychloroquine for the treatment of severe respiratory infection by COVID-19: a randomized controlled trial. PLoS One. 2021;16: e0237248.
25 Self WH, Seidner MW, Leibher LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19. JAMA. 2020;324:2165.
26 The RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;383:2030–2040.
27 Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. N Engl J Med. 2020;383:2031–2032.
28 White NJ, Watson JA, Hoglund RM, Chan XHS, Cheah PY, Tarning J. COVID-19 prevention and treatment: a critical analysis of emergency use authorization for emergency use of chloroquine phosphate and hydroxychloroquine sulfate. FDA site. 2020. https://www.fda.gov/media/138945/download. Accessed 17 November 2021.
29 Ponticelli C, Moroni G. Hydroxychloroquine in systemic lupus erythematosus (SLE). Expert Opin Drug Saf. 2017;16:419–429.
30 Taylor WRJ, White NJ. Antimalarial drug toxicity. Drug Saf. 2004;27:25–61.