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Hydroxychloroquine for pre-exposure prophylaxis of COVID-19 in health care workers: a randomized, multicenter, placebo-controlled trial Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine (HERO-HCQ)

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ABSTRACT

Objectives: To determine whether hydroxychloroquine (HCQ) is safe and effective at preventing COVID-19 infections among health care workers (HCWs).

Methods: In a 1: 1 randomized, placebo-controlled, double-blind, parallel-group, superiority trial at 34 US clinical centers, 1360 HCWs at risk for COVID-19 infection were enrolled between April and November 2020. Participants were randomized to HCQ or matched placebo. The HCQ dosing included a loading dose of HCQ 600 mg twice on day 1, followed by 400 mg daily for 29 days. The primary outcome was a composite of confirmed or suspected COVID-19 clinical infection by day 30, defined as new-onset fever, cough, or dyspnea and either a positive SARS-CoV-2 polymerase chain reaction test (confirmed) or a lack of confirmatory testing due to local restrictions (suspected).

Results: Study enrollment closed before full accrual due to recruitment challenges. The primary end point occurred in 41 (6.0%) participants receiving HCQ and 53 (7.8%) participants receiving placebo. No difference in the proportion of participants experiencing clinical infection (estimated difference of -1.8%, 95% confidence interval -4.6-0.9%, $P = 0.20$) was identified nor any significant safety issues.

Conclusion: Oral HCQ taken as prescribed appeared safe among HCWs. No significant clinical benefits were observed. The study was not powered to detect a small but potentially important reduction in infection.

Trial registration: NCT04334148.

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INTRODUCTION

After the emergence of SARS-CoV-2 in late 2019, the virus spread rapidly, resulting in the worst pandemic in nearly a century. Early in the pandemic, health care systems struggled with maintaining adequate supply of personal protective equipment, and infections in health care workers (HCWs) were reported worldwide [1]. Without the availability of protective vaccines, there was a need to identify therapies that might prevent infection and could be taken regularly by HCWs who were at a high risk for frequent exposures, such as approaches taken with malaria and HIV pre-exposure prophylaxis. As is common with new diseases, repurposed drugs offered immediate options for therapeutics and usually with a well-known safety profile, allowing a more rapid introduction into clinical trials and thereafter into clinical practice.

Chloroquine had been previously reported to have *in vitro* antiviral activity against SARS-CoV-1 and Middle East respiratory syndrome-CoV, and both chloroquine and hydroxychloroquine (HCQ) showed similar *in vitro* activity against SARS-CoV-2 [2–4]. Thus, clinicians turned to HCQ early in the pandemic as a therapy that might have clinical benefit for treating COVID-19, the disease associated with SARS-CoV-2 infection, as investigators began testing the drug's safety and efficacy in the treatment and prevention of COVID-19. Although vaccines are now available for the prevention of SARS-CoV-2 infection, access to sufficient quantities of vaccine remains challenging in some areas, and hesitancy toward vaccines and treatments further complicates the public health response. Thus, preventive therapies for SARS-CoV-2 infection remain relevant.

The Healthcare Worker Exposure Response and Outcomes (HERO) Registry (NCT04342806) was created as a community of HCWs from across the United States to learn about issues impacting frontline workers and to offer opportunities to participate in research studies [5]. The HERO-HCQ trial was one of the first studies in the United States to test the safety and efficacy of HCQ as pre-exposure prophylaxis among frontline HCWs. HERO-HCQ leveraged both the HERO Registry as well as its relationship with PCORnet®, the National Patient-Centered Clinical Research Network, as a pragmatic and largely remote clinical trial, using a patient-facing online portal to capture frequent patient-reported outcomes [6]. The primary objective of HERO-HCQ was to evaluate the efficacy of HCQ in preventing SARS-CoV-2 clinical infection in HCWs when taken daily. The secondary objectives of the study were to assess the efficacy of HCQ in preventing asymptomatic viral shedding of SARS-CoV-2 among HCWs and to assess the safety and tolerability of HCQ in this study population. The protocol is available at https://heroesresearch.org/hero-hcq/.

METHODS

Study design

HERO-HCQ was a multicenter, double-blind, randomized, parallel-group study designed to evaluate the superiority of HCQ versus placebo for COVID-19 pre-exposure prophylaxis among HCWs.

The HERO-HCQ trial was reviewed by the Duke University School of Medicine Institutional Review Board and approved by the Western Institutional Review Board (Pro00105274). Additional details on the HERO-HCQ design can be accessed at Friedland *et al.* [7].

Participants

Eligible participants were aged 18 years or older, working in a health care setting with potential exposure to patients with COVID-19, and provided written informed consent. The main exclusions were previous diagnosis of COVID-19 infection or contraindications to HCQ [7].

Randomization and masking

Participants were randomized in a 1: 1 ratio to receive HCQ or placebo at the level of the individual participant using the study portal. Randomization was stratified by clinical site using a permuted block design with varying block sizes. In the intervention arm, participants received an oral loading dose of the study drug at 600 mg twice on the first day, followed by 400 mg daily for 29 days. Because of a lack of phase IIb data at the time, the dose was selected based on available *in vitro* studies that reported a wide range of 50% effective concentration of chloroquine and HCQ for SARS-CoV-2, as well as known variability of absorption and of tissue distribution into the lung [8–14]. In the control arm, placebo tablets were administered using the same dosage schedule and number of tablets as the intervention arm. The placebo was similar in appearance to the study drug and packaged and labeled in a masked manner in compliance with regulatory requirements. All study drug doses were oral self-administrations. The study drug was supplied as 200-mg tablets, and each eligible participant was provided a quantity sufficient for 30 days.

Procedures

Participants were prescreened through the HERO Registry, and eligibility was confirmed by the site by phone or in person [5]. Participants were able to electronically consent through the portal, which was done at the time of the site visit or in advance. There were two on-site visits—one at baseline and another at 30 days. Baseline assessments included a nasopharyngeal swab for SARS-CoV-2 and a blood sample to assess baseline SARS-CoV-2 nucleocapsid immunoglobulin (Ig)G antibody status. Weekly follow-up was performed remotely using standardized questionnaires using the online portal. These questionnaires included screening for COVID-19 clinical signs/symptoms and self-reporting of COVID-19 testing and diagnosis. In addition, participants were able to self-report medication changes, hospitalizations, clinical events, and adverse events. A call center provided support for missed visits to re-engage and remind participants to complete the questionnaires.

The second on-site visit at approximately 30 days was completed to assess study drug adherence and any subsequent clinical or safety events. A nasopharyngeal swab for SARS-CoV-2 polymerase chain reaction (PCR) and a blood sample for SARS-CoV-2 nucleocapsid IgG antibody were obtained. Individual participants received the study drug for 30 days and were followed up for an additional 30 days for clinical events and patient-reported outcomes. An end-of-study virtual visit was conducted approximately 60 days after the randomization using the direct-to-participant portal or call center to assess for any subsequent clinical or safety events.

Outcomes

The primary outcome was a composite of confirmed or suspected clinical infection with COVID-19 through 30 days, which was defined as new-onset fever, cough, or dyspnea and confirmed SARS-CoV-2 PCR-positive test result through local testing or suspected COVID-19 disease without confirmation testing due to local restrictions or policies. Participants who developed symptoms of COVID-19 were expected to follow local clinical and/or employee health protocols for testing and management. The secondary outcomes were (i) viral shedding of SARS-CoV-2 at 30 days and (ii) safety and tolerability as determined by subject-reported adverse

events that met criteria per protocol for serious adverse events and HCQ-associated events of special interest; this latter group comprised fever, arrhythmia (ventricular), psychosis, angioedema, prolonged QT interval, secondary bacterial infection, and suicidal ideation.

The exploratory outcomes were (i) SARS-CoV-2 nucleocapsid IgG seroconversion at 30 days; (ii) COVID-19 complications, including hospitalization, intensive care unit level care, or need for invasive ventilation; (iii) days sick or lost work time; (iv) self-reported health and well-being obtained from the Patient-Reported Outcomes Measurement Information System Emotional Distress-Anxiety Short Form [15], a single-item burnout measure [16–19], and the patient health questionnaire [20,21]; and (v) patient-reported clinical infections among household contacts and other impacts on the HCW's household.

Statistical analysis

The original sample size of approximately 15,000 randomized participants was selected to yield high power for testing the primary outcome of clinical infection with SARS-CoV-2, assuming that the usual risk of SARS-CoV-2 infection is 5%. This sample size was expected to provide greater than 80% power to detect a 1% absolute decrease (20% relative decrease) in COVID-19 infection rates between treatment arms. These calculations assumed a two-sided type I error rate of 0.05 with 1: 1 randomization. In October 2020, due to slower-than-expected enrollment and changing community attitudes about HCQ effectiveness, the study protocol was amended to reduce the total sample size to 2000, which provided 80% power to detect a 50% relative decrease in the risk of COVID-19 infections, assuming a placebo group risk of 5%.

The primary analyses were conducted in the modified intention-to-treat population, which included participants with negative nasal swab at baseline (1359 of the 1360 subjects randomized). Statistical comparisons were performed using two-sided significance tests. The primary end point was clinical infection with SARS-CoV-2 through the 30-day period. Data collected during the 60-day follow-up were included for the safety analyses. For the primary outcome of the clinical infection with SARS-CoV-2, comparisons between treatment arms were presented as differences in proportions with 95% confidence intervals (CIs) using the Miettinen-Nurminen method and a *P*-value calculated using Fisher's exact test. A secondary analysis was based on a logistic regression model with an indicator variable for the treatment group. Supplemental analyses were conducted to (i) examine the differences using other methods for constructing the CIs [22] and (ii) compute the common odds ratio using the Mantel-Haenszel test, stratifying by enrolling site [23].

Subgroup analyses were planned for age, sex, race, and ethnicity. For each subgroup analysis, a logistic regression model was estimated, with additional terms identifying subgroup membership and intervention by subgroup interaction. The statistical comparisons of serious adverse events and events of special interest were based on chi-square tests and Fisher's exact test. All analyses were conducted using SAS Version 9.4 software. The Duke Clinical Research Institute served as the statistical and data coordinating center.

Patient and public involvement

HCWs were engaged in the HERO program and trial through membership in HERO governance, including participation in the steering committee and subcommittees. HCW stakeholders reviewed the enrollment materials and the study protocol and advised on trial conduct throughout the study. An independent data safety monitoring board, which included an HCW representative, met regularly and monitored participant safety and study performance. The protocol was publicly shared and is available on heroesresearch.org.

RESULTS

The HERO-HCQ trial start-up timeline was 4 weeks from concept to first participant randomized (Supplemental Figure 1). Between April 2020 and November 2020, a total of 1360 participants were enrolled and randomized from 34 US sites participating in PCORnet (Figure 1, see Supplemental Table 1). One participant had a positive SARS-CoV-2 PCR test at the time of the baseline visit and was excluded from the primary analysis population. Overall, 92.9% and 92.3% of the randomized participants completed their PCR and serology tests, respectively, at their day 30 visit with no significant difference by treatment group. The day 60 visit was completed by 89.0% of the total participants.

Baseline participant characteristics

The mean age of the HCWs in the study population was 43.6 years, 65.3% were female, 90.8% reported being White race, and 5.8% self-reported as Hispanic or Latino ethnicity (Table 1). The median body mass index was 27.1 kg/m^2, and 33.2% of the population was considered obese (body mass index $\geq$30 kg/m^2). The most common comorbidities were hypertension (14.6%), asthma (9.9%), and diabetes (4.0%). Among the most common HCW locations were the emergency department (14.0%), ambulatory or outpatient care (9.5%), inpatient medical unit (8.5%), emergency medical services (8.1%), intensive care unit (7.9%), inpatient surgical unit (6.8%), and dedicated COVID-19 unit (5.7%). Among the enrolled participants, the most common occupation/employment characteristics were registered nurse (26.2%), physician (21.3%), nurse practitioner (5.2%), and paramedic (5.2%). A total of 12 (0.9%) participants were positive for SARS-CoV-2 nucleocapsid IgG at study enrollment.

Primary end point

There was a total of 94 primary end point events during the 30-day follow-up period. Most of these end points were suspected clinical infection (n = 85) rather than confirmed clinical infection with COVID-19 (n = 9; Table 2). The most common presenting symptoms were cough (86.2%), fatigue (68.1%), headache (66.0%), and muscle aches/joint pain (51.1%). There were numerically fewer primary end point events in the HCQ group (41 [6.0%]) than in the placebo group (53 [7.8%]); however, this difference of -1.8% (95% CI -4.6-0.9%) was not significant (Fisher's exact P = 0.20; Supplemental Table 2). A secondary analysis based on a logistic regression model yielded similar results (OR 0.75, 95% CI 0.49-1.15, P = 0.18). Among the participants with confirmed clinical infection, there were numerically fewer in the HCQ group (three events [0.4%]) than in the placebo group (6 events [0.9%]), and the difference was not significant (0.45%, 95% CI -1.54% to 0.50%; Figure 2a,b). The supplemental analyses using the Mantel-Haenszel method, which stratified by enrolling site, yielded a similar estimate of the common OR (0.69, 95% CI 0.45-1.05). However, there was evidence of heterogeneity at the site level for the primary end point (P = 0.011).

Subgroup analyses

The prespecified subgroups for the primary end point are shown in Figure 3. All subgroups except for the youngest age group (18-35 years) showed estimated odds ratios <1.0, favoring HCQ, but none were significant, with CIs overlapping 1.0. In addition,

Table 1
Baseline participant characteristics.

Characteristics	Hydroxychloroquine (n = 683)	Placebo (n = 676)
Mean age (SD) (years)	44.2 (11.9)	43.1 (11.2)
Women	442 (64.7%)	446 (66.0%)
Race or ethnicity		
Black or African American	18 (2.6%)	23 (3.4%)
White	624 (91.4%)	610 (90.2%)
Other	41 (6.0%)	43 (6.4%)
Hispanic or Latino	39 (5.7%)	40 (5.9%)
Mean Weight (SD) (kg)	82.5 (21.4)	83.1 (21.8)
Median body mass index (SD) (kg/m^2)	28.3 (6.3)	28.6 (6.7)
Obesity	226 (33.1%)	225 (33.3%)
Hypertension	99 (14.5%)	99 (14.6%)
Asthma	58 (8.5%)	77 (11.4%)
Diabetes	20 (2.9%)	35 (5.2%)
Chronic obstructive pulmonary disease	1 (0.1%)	2 (0.3%)
Coronary artery disease	5 (0.7%)	6 (0.9%)
Occupation characteristics[a]		
Registered nurse	186/ 677 (27.5%)	167/668 (25.0%)
Physician	143/ 677 (21.1%)	144/ 668 (21.6%)
Nurse practitioner	33/ 677 (4.9%)	37/ 668 (5.5%)
Paramedic	30/ 677 (4.4%)	40/ 668 (6.0%)
Qualifying hospital location[a]		
Emergency department	96 (14.1%)	94 (13.9%)
Ambulatory care unit	66 (9.7%)	63 (9.3%)
Medical unit	52 (7.6%)	63 (9.3%)
Emergency medical services	57 (8.3%)	53 (7.9%)
Intensive care unit	48 (7.0%)	59 (8.7%)
Surgical unit	50 (7.3%)	43 (6.4%)
COVID-19 hospital unit	38 (5.6%)	39 (5.8%)
Positive SARS-CoV-2 nucleocapsid immunoglobulin G at study entry	4/671 (0.6%)	8/668 (1.2%)
Mean number of people living in the home of the participant (SD)	2.5 (1.4)	2.5 (1.4)

[a] Only characteristics with >5% are presented.

Table 2
Key outcomes.

Endpoint	Hydroxychloroquine (N = 683)	Placebo (N = 676)	% Difference (95% confidence interval)
Primary			
Clinical infection with COVID-19 by day 30	41 (6.0%)	53 (7.8%)	-1.84 (-4.60, 0.87), $P = 0.20$
Confirmed: Fever, cough or dyspnea with COVID-19 positive test results via local or central polymerase chain reaction testing	3 (0.4%)	6 (0.9%)	-0.45 (-1.54, 0.50), $P = 0.34$
Suspected: Fever, cough or dyspnea without negative local or central testing within 7 days[a]	38 (5.6%)	47 (7.0%)	-1.39 (-4.03, 1.21), $P = 0.31$
Secondary			
SARS-CoV-2 detection at day 30 via Covance swab polymerase chain reaction testing	2 / 635 (0.3%)	2 / 628 (0.3%)	-0.00 (-0.87, 0.86)
Other			
Seroconversion[b]	2 / 619 (0.3%)	5 / 612 (0.8%)	-0.49 (-1.61, 0.45)
Worst postrandomization burnout level			
i. I enjoy my work. I have no symptoms of burnout.	144 / 667 (21.6%)	118 / 655 (18.0%)	0.065
ii. Occasionally I am under stress, and I don't always have as much energy as I once did, but I don't feel burned out.	361 / 667 (54.1%)	363 / 655 (55.4%)	
iii. I am definitely burning out and have one or more symptoms of burnout, such as physical and emotional exhaustion.	122 / 667 (18.3%)	115 / 655 (17.6%)	
iv. The symptoms of burnout that I'm experiencing won't go away. I think about frustration at work a lot.	28 / 667 (4.2%)	48 / 655 (7.3%)	
v. I feel completely burned out and often wonder if I can go on. I am at the point where I may need some changes or may need to seek some sort of help.	12 / 667 (1.8%)	11 / 655 (1.7%)	
Highest postrandomization PROMIS Emotional Distress-Anxiety Short Form T-Score[c]	49.8 +/- 8.7	51.1 +/- 8.8	-1.3 (-2.2, -0.04), $P = 0.007$
Personal Health Questionnaire-2 score ≥3 during follow-up[d]	40 / 667 (6.0%)	46 / 654 (7.0%)	-1.0% (-3.8%, 1.7%), $P = 0.50$

PROMIS, Patient-Reported Outcomes Measurement Information System.
[a] Of the 85 suspected cases, 80 completed the 30 day test; all 80 tests were negative.
[b] Participants were required to have a negative serology test at baseline, and both baseline and 30 day tests to be included in the analysis. Seroconversion is defined as having a negative serology test at baseline and a positive serology test at day 30.
[c] A higher PROMIS T-score represents more anxiety. A T-score of 60 is one SD worse than average. By comparison, an anxiety T-score of 40 is one SD better than average. The value of 50 represents the average for the United States general population.
[d] Higher values indicate increased likelihood of major depressive disorder (https://www.hiv.uw.edu/page/mental-health-screening/phq-2).

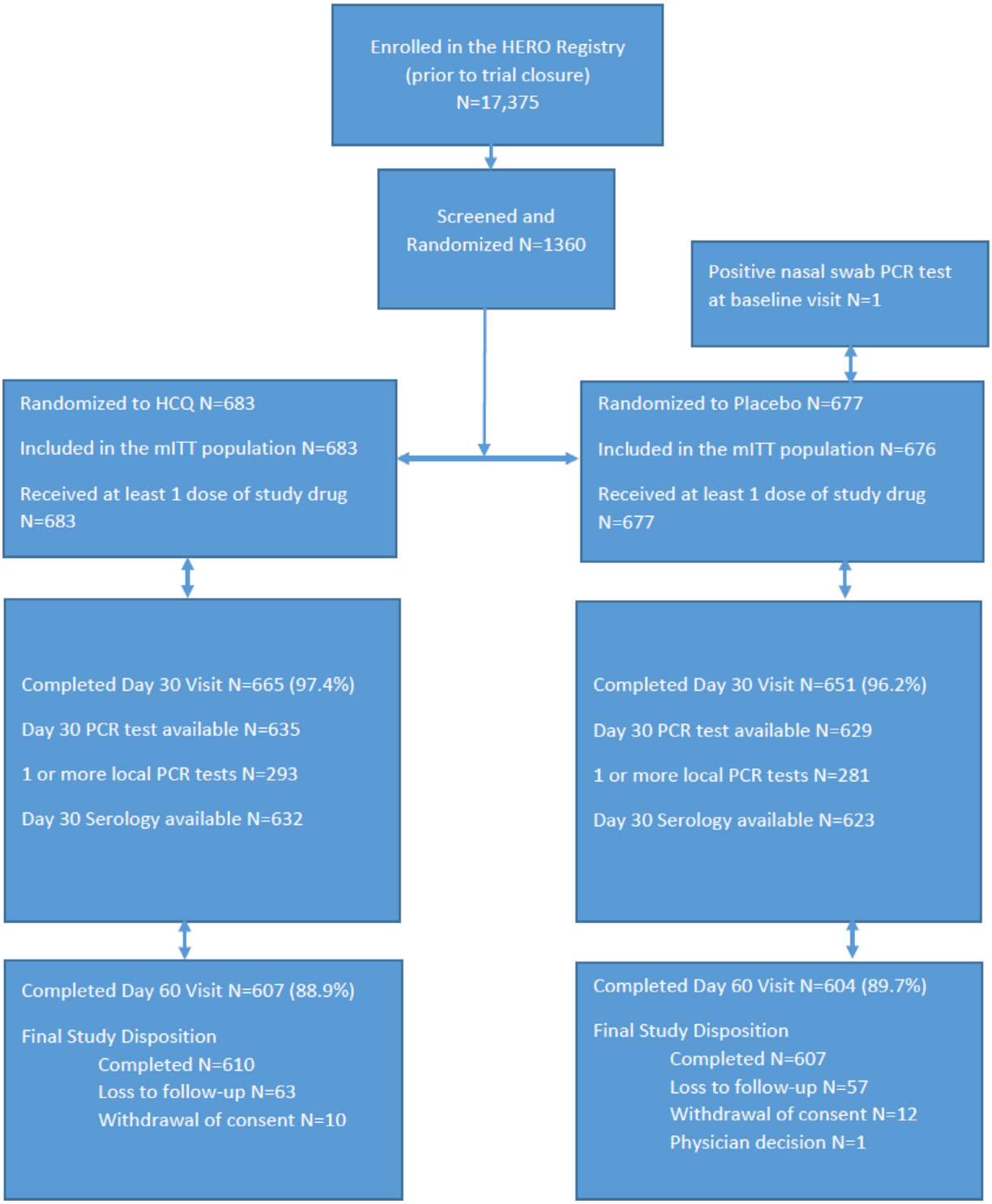

Figure 1. Enrollment, randomization, and follow-up.
HERO, Healthcare Worker Exposure Response and Outcomes; HCQ, hydroxychloroquine; mITT, modified intention-to-treat; PCR, polymerase chain reaction.

there were no statistically significant findings for the subgroup interaction tests, suggesting a lack of evidence for heterogeneous treatment effects."

Secondary end points

Four participants had a positive SARS-CoV-2 PCR test at the day 30 visit, with each treatment arm having two positive cases (0.3% viral shedding rate at 30 days for both groups, $P = 1.00$). Similarly, there were few seroconversions, defined as having a negative SARS-CoV-2 nucleocapsid IgG at entry and a positive IgG at day 30, with two (0.3%) participants in the HCQ arm and five (0.8%) in the placebo arm having evidence of seroconversion. There were no deaths reported during the study period.

Participants in the HCQ arm reported lower levels of emotional distress and anxiety during the 30-day treatment period based on

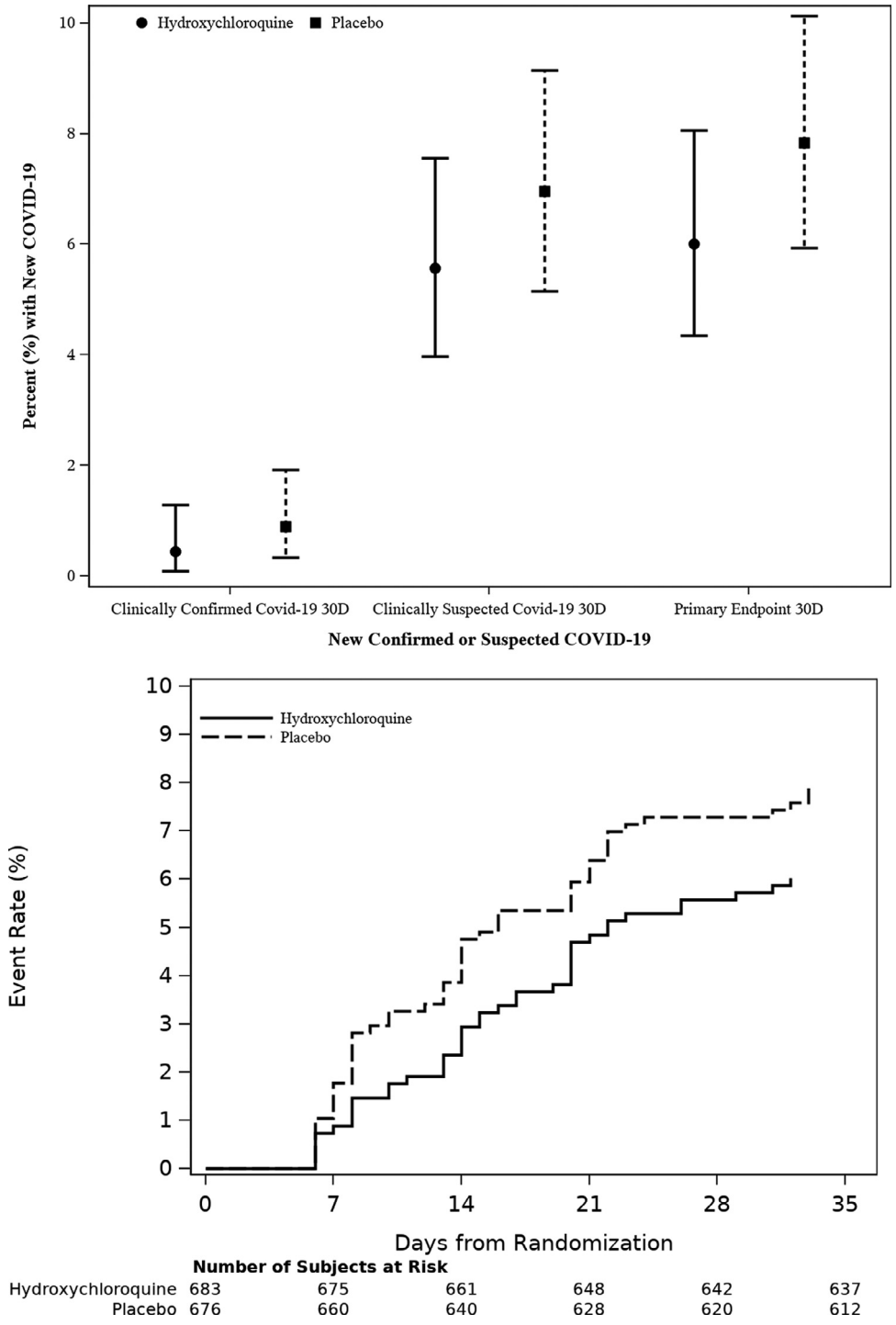

Figure 2. Primary Outcome, Overall and by Component
A, Confirmed, suspected, and overall primary endpoint by treatment group. B, Time-to-primary endpoint by treatment group.

the worst recorded Patient-Reported Outcomes Measurement Information System Short Form T-scores (49.8 vs 51.1 for a difference of -1.3 points, 95% CI -2.2–0.4, $P = 0.007$). The percentage of participants reporting the patient health questionnaire-2 score ≥3 was not different between the two treatments (6.0% for HCQ vs 7.0% for placebo; $P = 0.50$). The levels of burnout were not different between groups over the treatment period ($P = 0.065$); however, numerically more participants in the HCQ arm reported no symptoms of burnout (21.6% vs 18.0%) than placebo.

Adherence to treatment and study drug discontinuation

At day 30, self-reported adherence (*i.e.,* taking the drug for 29 days) was 94.4% for HCQ and 95.7% for placebo ($P = 0.32$). Permanent discontinuation rates were 4.1% for HCQ and 2.7% for placebo. Permanent discontinuation due to adverse events was more common in the HCQ group (12 of 28 discontinuations) than in the placebo group (3 of 18 discontinuations).

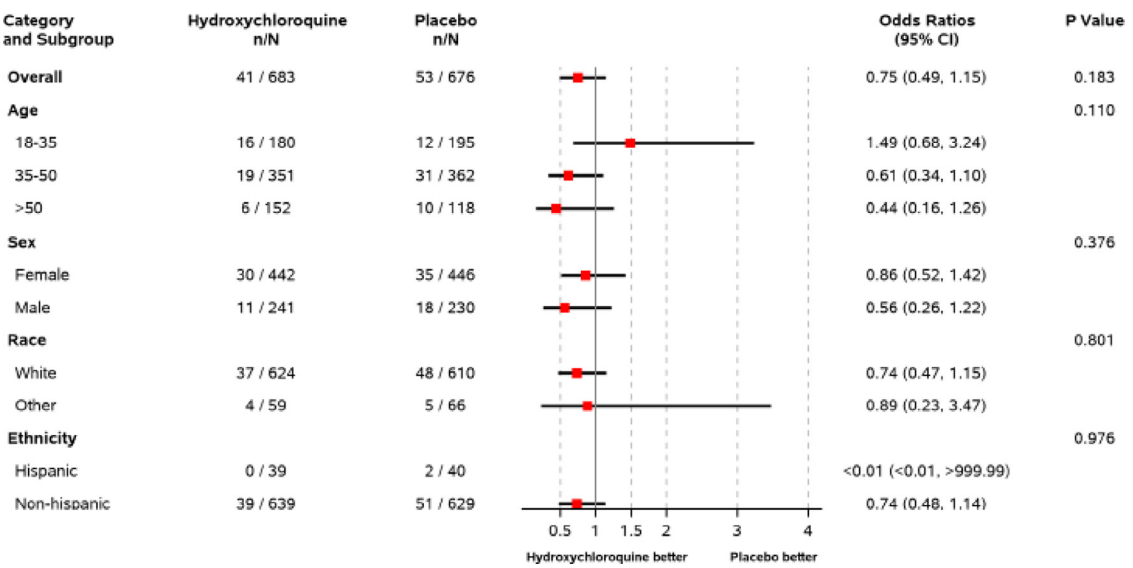

Figure 3. Prespecified subgroup analyses (point estimates for the treatment effect on the odds ratio scale 95% CI). CI, confidence interval.

Adverse events and safety

Adverse events of special interest (fever, ventricular arrhythmia, psychosis, angioedema, prolonged QT interval, secondary bacterial infection, and suicidal ideation) over the 60 days of follow-up were similar across groups (seven subjects in HCQ arm and eight in placebo). At 60 days, serious adverse events were reported for three participants (0.4%) in the HCQ group and two (0.3%) in the placebo group. Of those serious adverse events, two for the HCQ group and one for the placebo group resulted in hospitalizations (Table 3).

DISCUSSION

Statement of principal findings

The study was not powered to detect a small beneficial effect and the test of the primary end point does not provide evidence of a benefit for HCQ for pre-exposure prophylaxis in a high-risk HCW population.

Strengths and weaknesses in context

The original study design was powered to show a 20% relative treatment effect, assuming a 5% event rate in the placebo arm. However, due to slowed enrollment early in the study, the study was amended to decrease the sample size and hence the power, increasing the detectable relative treatment effect to 50%. Thus, the study was not powered to detect a small treatment effect. This outcome was not unique to this randomized trial; a 2021 analysis concluded that among the early COVID-19 studies, only 5% were both randomized and adequately powered [24].

Although the partially remote nature of the trial was novel and improved feasibility during a pandemic, it also resulted in the limitation that we did not have laboratory confirmation for COVID-19-like illness. Early in the pandemic, in some regions, testing was not performed per local policies in HCWs with suspected infection and mild or moderate symptoms. Per the study protocol, these events were defined as suspected cases and were combined with the confirmed cases in the primary composite outcome. This resulted in few confirmed COVID-19 infections; thus, our primary outcome was primarily comprised of suspected COVID-19 clinical infections. Although the study did not have frequent PCR testing, testing at entry and end-of-study showed low cross-sectional asymptomatic rates of viral shedding in the study population. Similarly, the seroconversion rate was low (0.6%) over the 30-day intervention period. These low rates of asymptomatic shedding and seroconversion suggest that SARS-CoV-2 infection was lower than expected in the study population and may be overestimated by our composite primary outcome definition.

Furthermore, the trial was designed to evaluate the clinical efficacy of HCQ for the prevention of SARS-CoV-2, with dosing based on previous *in vitro* data on activity against SARS-CoV-2, smaller trials, or observational data and dosing strategies already used safely in medical practice. As such, we did not perform a dose-finding study nor incorporate testing of HCQ plasma concentrations. There are strengths to highlight in the HERO-HCQ trial that might inform future clinical trials. As with many trials, there was a need for rapid development and execution; HERO-HCQ went from initial discussions with the funder to first participant enrolled in 1 month. Although there was a need to move expeditiously, HERO-HCQ did not trade speed for validity. Many studies during the pandemic have had limited impact due to significant study design limitations, particularly the lack of randomization and blinding to the intervention arm. HERO-HCQ is a randomized, double-blind, placebo-controlled trial. In part, to respond to the need to limit in-person activities and to design a trial that was patient-centered and pragmatic, HERO-HCQ used direct-to-participant recruitment and a participant-facing portal to capture patient-reported outcomes. Because recruitment and retention remain significant challenges for many clinical trials, we believe these strategies should be considered more frequently in trial design across more disease states.

Worldwide, there remains a role for preventive therapeutics against SARS-CoV-2 infection, particularly in regions where access to or acceptance of preventive vaccines remains low [25,26]. Furthermore, additional preventive options may become more relevant as novel variants or subvariants emerge with vaccine immune escape. In addition to HERO-HCQ, other similar randomized clinical trials investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs have been completed and were not able to demonstrate that HCQ significantly reduces the risk of confirmed or clinically suspected SARS-CoV-2 infection [27–31]. Therefore, although this study was not powered to detect a large effect size,

Table 3
Serious adverse events, adverse events of special interest, adverse events, self-reported adherence, and self-reported symptoms.

	Hydroxychloroquine (N = 683)	Placebo (N = 676)	*P*-value
Number of participants with serious adverse events (to day 60)	3 (0.4%)	2 (0.3%)	1.00
Serious adverse event resulted in initial or prolonged hospitalization for the participant	2 (0.3%)	1 (0.1%)	1.00
Adverse events of special interest	7 (1.0%)	8 (1.2%)[a]	0.80
Fever	6 (0.9%)	1 (0.1%)	
Arrhythmias (ventricular)	1 (0.1%)	1 (0.1%)	
Psychosis	0	2 (0.3%)	
Angioedema	0	1 (0.1%)	
Prolonged QT interval	0	1 (0.1%)	
Secondary bacterial	0	1 (0.1%)	
Suicidal ideation	1 (0.1%)	0	
Adverse events (to day 60)	16 (2.3%)	13 (1.9%)	0.71
Adherence (self-reported at 100%)	645 (94.4%)	647 (95.7%)	0.32
COVID-related symptoms			
Fatigue	29 (4.2%)	35 (5.2%)	
Muscle aches / joint pain	22 (3.2%)	26 (3.8%)	
Cough	35 (5.1%)	46 (6.8%)	
Dyspnea	13 (1.9%)	15 (2.2%)	
Headache	29 (4.2%)	33 (4.9%)	
Sore throat	14 (2.0%)	20 (3.0%)	
Fever	5 (0.7%)	4 (0.6%)	
Loss of smell	5 (0.7%)	4 (0.6%)	
Loss of taste	4 (0.6%)	3 (0.4%)	
Number of COVID-related symptoms			
0	642 (94.0%)	623 (92.2%)	
1	7 (1.0%)	10 (1.5%)	
2	6 (0.9%)	9 (1.3%)	
3	5 (0.7%)	4 (0.6%)	
4	8 (1.2%)	12 (1.8%)	
5	8 (1.2%)	13 (1.9%)	
≥6	7 (1.0%)	5 (0.7%)	
Symptoms caused participant to miss work (between randomization and day 30 visit)	41/673 (6.1%)	49 (7.4%)	0.38
Other people in the participant's household had a positive COVID-19 test (between randomization and day 30)	13/594 (2.2%)	17/584 (2.9%)	0.46
Other nonspecific symptoms			
Nausea/vomiting	17 (2.5%)	12 (1.8%)	
Diarrhea	26 (3.8%)	16 (2.4%)	
Abdominal pain	9 (1.3%)	12 (1.8%)	
Chills	6 (0.9%)	4 (0.6%)	
Poor appetite	13 (1.9%)	7 (1.0%)	
Wheezing	6 (0.9%)	10 (1.5%)	
Sinus congestion	26 (3.8%)	35 (5.2%)	
Runny nose	25 (3.7%)	29 (4.3%)	

[a] One participant indicated that an event of special interest occurred but did not specify which one.

taken together, these studies do not support a role for HCQ for pre-exposure prophylaxis for COVID-19 among HCWs.

Conclusion and future research

The prophylactic use of HCQ by HCWs was safe but not effective to prevent COVID-19 clinical infection. This is one of several negative studies assessing HCQ for the prevention of COVID-19, all of which were not powered for <50% efficacy. Due to ongoing interest in HCQ worldwide, a meta-analysis of all published randomized, placebo-controlled trials could provide more definitive evidence through a pooled analysis.

Declaration of competing interest

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Ethical approval

The HERO-HCQ trial was reviewed by the Duke University School of Medicine Institutional Review Board and approved by the Western Institutional Review Board (Pro00105274).

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Author contributions

The senior author (AH) obtained funding from the PCORI to conduct the study (Contract Number COVID-19-2020-001). AH and the lead author (SN) affirm the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained. SN, LC, EF, AF, RO, CW, KA, and AH conceived, designed, and oversaw the study and led the manuscript development. JG, HM, JS, and KA were responsible for data management and statistical analysis. All of the authors participated in data collection and acquisition; reviewed the manuscript for important intellectual content; and gave administrative, technical, or material support. The lead author had full access to all the data in the study and takes responsibility for the integrity, transparency of the data, and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing

Data will be made available upon reasonable request and per the PCORI guidelines for open science and transparency.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.01.019.

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