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Hydroxychloroquine for the treatment of COVID-19 and its potential cardiovascular toxicity: Hero or villain?

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A B S T R A C T

A variety of treatment modalities have been investigated since the beginning of the Coronavirus Disease-19 (COVID-19) pandemic. The use of antimalarials (hydroxychloroquine and chloroquine) for COVID-19 treatment and prevention has proven to be a cautionary tale for widespread, off-label use of a medication during a crisis. The investigation of antimalarials for COVID-19 has also been a driver for a deluge of scientific output in a short amount of time. In this narrative review, we detail the evidence for and against antimalarial use in COVID-19, starting with the early small observational studies that influenced strategies worldwide. We then contrast these findings to later published larger observational studies and randomized controlled trials. We detail the emerging possible cardiovascular risks associated with antimalarial use in COVID-19 and whether COVID-19-related outcomes and cardiovascular risks may differ for antimalarials used in rheumatic diseases.

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has disrupted all aspects of society. In the midst of a global health disaster, there has been a sprint to find safe and effective treatments. There was early *in vitro* evidence for antimalarial drugs such as hydroxychloroquine (HCQ) or chloroquine (CQ) for use against SARS-CoV-2 which is the virus that causes COVID-19 [1–3]. As the pandemic spread around the world, so did the off-label use of antimalarials. This led to many retrospective and prospective observational studies and multiple randomized controlled trials (RCTs). With the dissemination of knowledge about HCQ in COVID-19 treatment, issues arose of scientific communication, research ethics, and the conduct of medical research. By the end of June 2020, the enthusiasm for HCQ in treating COVID-19 seemed to wane as evidence pointed toward its inefficacy for this indication. In this review, we examine the evidence for the efficacy of antimalarials for COVID-19 treatment and prevention, as well as the safety of antimalarial use in COVID-19. We then discuss the efficacy of antimalarials for COVID-19-related outcomes in patients with rheumatic diseases, as well as the evidence for associated cardiovascular risks in this population.

Efficacy of antimalarials for COVID-19

The initial studies for the efficacy of antimalarials for the treatment of COVID-19 were small studies that were mostly performed in France and China [4–7]. Most of these were not controlled and those that did often did not have adequate comparison groups. With time, larger observational studies were published [8,9]. Overall, these did not show a beneficial effect on mortality or the need for mechanical ventilation in hospitalized patients with COVID-19. Later RCT data did not demonstrate efficacy among this population of patients who were hospitalized for COVID-19. In this section, we review the evidence for antimalarials for COVID-19 treatment in the general population using observational studies (Table 1) and RCTs (Table 2).

Smaller observational studies

Huang et al. reported the results of their multicenter prospective observational study from 12 hospitals in the Guangdong and Hubei Provinces [10]. A group of 197 patients was treated with CQ 500 mg daily for up to 10 days, whereas the comparator group of 176 patients did not receive any CQ treatment, according to the decision-making of the clinician and patient (i.e., not randomized). The primary outcome was time to negative polymerase chain reaction (PCR) conversion, and the secondary outcomes were the proportion of the patients with PCR conversion at days 10 and 14, hospital length of stay, duration of fever, and adverse events. The time to undetectable viral PCR was significantly shorter in the CQ group as were the duration of fever and the length of the hospital stay. There was also a significant difference in seroconversion at day 14 between the CQ group (96%) and the control (80%).

In the first single-center series from Marseilles, France, the authors reported 42 inpatients who had received HCQ [11]. These were compared to patients who were treated at other hospitals in the same region or patients who had contraindications to HCQ or had declined its use. The outcome was viral clearance at six days, which was seen in 70% of those on HCQ versus 13% of those receiving standard of care. However, this first study was complicated by many design flaws which have previously been discussed in prior publications [12,13]. These design flaws include the lack of an adequate comparator group, the removal of those who had been lost to follow-up who had the primary outcome of death, and the use of a surrogate outcome of viral clearance rather than in outcomes such as death or worsening symptoms.

In the second study from the same group in Marseilles, 80 patients receiving HCQ and azithromycin (including six reported by the authors previously) were assessed for a favorable outcome, as defined by negative viral load, length of stay, and negative viral cultures [14]. The authors reported that 81% of participants in this case series had a favorable outcome.

In the third study from the same group, 1061 patients receiving HCQ 200 mg twice daily for ten days and azithromycin 500 mg on day one followed by 250 mg daily were investigated [15]. The outcomes of interest included death, worsening of disease (intensive care unit [ICU] transfer or length of stay

Table 1
Observational studies evaluating antimalarials ± azithromycin for the treatment of COVID-19.

Study	Design	Country	Sample size, population	Antimalarial dosing	Comparator	Primary Outcome	Secondary Outcomes	Main Results
Huang et al.	Cohort	China	373 hospitalized	CQ 500 mg for maximum of 10 days	No CQ	Conversion to negative PCR in two consecutive samples	- Proportion who had conversion to negative PCR by days 10 and 14 - Length of hospitalization - Duration of fever - Adverse events	There was a significant difference in the time of conversion to negative PCR between the CQ group (3) and the control (9) ($p < 0.0001$) There was a significant difference in conversion to negative PCR at day 14 between The CQ group (96%) and the control (80%) ($p < 0.0001$)
Gautret. et al.	Case series	France	36 hospitalized	HCQ 200 mg thrice daily for 10 days (6 patients received AZT [500 mg first day, then 250 mg daily for 4 days])	Supportive treatment	Conversion to negative PCR of respiratory tract specimens at day 6	- Clinical status - Conversion to negative PCR period - Side effects	There was a significant difference in conversion to negative PCR at 6 days between the HCQ group (70%) and the control (12.5%) ($p < 0.001$)
Gautret et al.	Case series	France	80 hospitalized	HCQ 200 mg thrice daily for 10 days AND AZT 500 mg on day 1, then 250 mg for 4 days	N/A	- At least 3 days of supplemental oxygen or ICU level of care	- PCR and culture - Length of stay in the infectious diseases unit	Conversion to negative PCR at day 5: 83%; At day 7: 93%; At day 8: 98%
Million et al.	Case series	France	1061 hospitalized	HCQ 200 mg thrice daily for 10 days AND AZT 500 mg on day 1, then 250 mg for 4 days	N/A	- Death - Clinical worsening (ICU or >10-day hospitalization - Conversion to negative PCR at day 10		- Clinical worsening: 4.3% - Death: 0.75% - Conversion to negative PCR at day 10: 95.6%
Membrillo et al.	Cohort	Spain	166 hospitalized	Loading dose of HCQ 1200 mg, Maintenance dose of HCQ 400 mg; Unknown duration	No HCQ	- Death		There was a significant difference in mortality between the HCQ group (22%) and the control (48.8%) ($p = 0.002$)

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Table 1 (*continued*)

Study	Design	Country	Sample size, population	Antimalarial dosing	Comparator	Primary Outcome	Secondary Outcomes	Main Results
Mallat et al.	Cohort	UAE	34 hospitalized	HCQ 400 mg twice daily for 1 day, then 400 mg daily for 10 days	No HCQ	Conversion to negative PCR	- Hospital length of stay - Conversion to negative PCR at day 14 - Admission to ICU - Required high flow O2 and ventilation - Pneumonia	There was a significant difference in conversion to negative PCR at day 14 between the HCQ group (47.8%) and the control (90.9%) ($p = 0.016$)
Mahévas et al.	Cohort	France	181 hospitalized with pneumonia	HCQ 600 mg daily for 7 days	Supportive care	Transfer to the ICU within 21 days	- All cause mortality - ARDS	There was not a significant difference in ICU transfers at 21 days between the HCQ group (76%) and the control (75%) ($p > 0.05$)
Molina et al.	Case series	France	11 hospitalized	HCQ 600 mg for 10 days AND AZT 500 mg on day 1, then 250 mg for 4 days	N/A	- Virological status - Clinical status		Conversion to negative PCR at day 6: 20% Mortality: 9%
Chen et al.	Cohort	China	284 hospitalized; 25 received CQ (8%)	CQ duration and dose unknown	Supportive treatment No CQ ($n = 121$)	Conversion to negative PCR at 7, 14, 21 days		There was not a significant difference in conversion to negative PCR at 14 days between the CQ group (64.7) and the control (71.7%); OR 0.98, 95% CI 0.58−1.67
Yu et al.	Cohort	China	568 hospitalized patients requiring the ICU (48 HCQ, 520 control)	HCQ 200 mg twice daily for 7−10 days	Supportive treatment+ antiviral/antibiotic	- Death	- Cytokine levels - Hospital stay duration	There was a significant difference in mortality between the HCQ group (18.8%) and the control (47.4%) ($p < 0.001$)
Rosenberg et al.	Cohort	USA	1438 hospitalized	HCQ + AZT/HCQ alone/AZT alone; Dose and duration unknown	Supportive	- In-hospital mortality	- Cardiac arrest - QTc prolongation	There was no significant association with in-hospital mortality for HCQ alone (HR 1.08, 95% CI 0.63−1.85), AZT alone (HR 1.35, 95% CI 0.76−2.40), or combination HCQ + AZT (HR 0.56, 95% CI 0.26−1.26) groups

Geleris et al.	Cohort	USA	1376 hospitalized with respiratory distress	HCQ 600 mg twice daily on day 1, then 400 mg daily for 4 days AND AZT 500 mg on day 1, then 250 mg daily for 4 days	Supportive treatment/No HCQ	Death or intubation		There was no significant association between HCQ use and the primary outcome of death or intubation (HR 1.04, 95% CI 0.82−1.32)
Magagnoli et al.	Cohort	USA	368 hospitalized	HCQ + AZT or HCQ alone; Dose and duration Unknown	Supportive treatment +AZT	- Mortality - Need for mechanical ventilation	- Hospitalization among patients requiring mechanical ventilation	There was a significant difference in mortality between the HCQ group (19.2%), HCQ + AZT group (22.9%), and the control (9.4%) ($p < 0.001$). There was no significant difference in need for mechanical ventilation between the HCQ + AZT group (6.9%) and the control (14.11%) ($p > 0.05$)
Arshad et al.	Cohort	USA	2541 patients	HCQ 400 mg twice daily on day 1, then 200 mg twice daily on days 2−5. 500 mg AZT daily on day 1 followed by 250 mg daily for 4 days.	Supportive treatment	Mortality		Compared to those receiving neither treatment, those receiving either HCQ alone or in combination with azithromycin had a lower risk of in-hospital mortality in multivariable models (HR 0.34, 95% CI 02.5−0.46; HR 0.29, 95% CI 0.22−0.40).

Abbreviations: HCQ: Hydroxychloroquine; CQ: Chloroquine; AZT: Azithromycin; RR: Relative Risk; OR: Odds Ratio; HR: Hazard Ratio; CI: Confidence Interval; ICU: intensive care unit; PCR: polymerase chain reaction; ARDS: acute respiratory distress syndrome.

Table 2
Randomized controlled trials evaluating antimalarials ± azithromycin for the treatment of COVID-19.

Study	Country	Sample size, population	Antimalarial dosing	Comparator	Primary Outcome	Secondary Outcomes	Main Results
Zhaowei Chen et al.	China	62 hospitalized with pneumonia on chest CT	HCQ 200 mg twice daily for 5 days	Supportive treatment	Time to clinical recovery[a] - Clinical status	Radiological demonstration of pulmonary recovery on chest CT	There was a significant difference in time to clinical recovery between the HCQ group (80.6%) and the control (54.8%) ($p = 0.05$)
Huang et al.	China	22 hospitalized	CQ 500 mg twice daily for 10 days	Antiviral and supportive therapy (Placebo-controlled)	Conversion to negative PCR	- Chest imaging - Length of hospitalization	There was no significant difference in conversion to negative PCR at 10 days between the CQ group (90%) and the control (75%) ($p > 0.05$)
Lan Chen et al.	China	48 patients with moderate severity	CQ 1000 mg for one day, then 500 mg daily for nine days OR HCQ 200 mg twice daily for ten days	Supportive treatment	Clinical recovery	Negative PCR conversion	There was a significant difference in time to clinical recovery between CQ group and the control (CQ shorter, $p = 0.019$). (HCQ $p = 0.049$)
Tang et al.	China	150 hospitalized	HCQ 1200 mg for 3 days then 800 mg daily	Unknown	Conversion to negative PCR of respiratory tract specimens at day 28	- Negative PCR conversion at 4, 7,10, 14, and 21 days - Clinical status - Laboratory examinations (CRP and lymphocyte count) - Chest imaging	There was not a significant difference in conversion to negative PCR at 23 days between the HCQ group (70.7%) and the control (74%) ($p > 0.05$)
Jun Chen et al.	China	30 hospitalized	HCQ 400 mg daily for 5 days	Supportive treatment	Conversion to negative PCR on day 7 - Death within 2 weeks	- Serious adverse drug event - Clinical status within 2 weeks	There was not a significant difference in conversion to PCR negativity at 7 days between the HCQ group (86.7%) and the control (93.3%) ($p > 0.05$)
Borba et al.	Brazil	81 (62 with confirmed COVID-19 infection)	600 mg HCQ twice daily for 10 days (AZT 500 mg daily for 5 days in ARDS)	450 mg HCQ twice on day 1 followed by 450 mg daily for 4 days (AZT 500 mg daily for 5 days in ARDS)	Reduction in mortality by at least 50%	- Mortality on day 13 - Clinical status - Laboratory examinations - ECG on days 13 and 28 - Duration of mechanical ventilation	There was not a significant difference in mortality at 13 days between the high dose CQ group (39%) and the low dose CQ group (18.9%) ($p = 0.03$)

Horby et al.	UK	1561 hospitalized	HCQ 1600 mg twice first day, then 400 mg twice daily for 9 days	Supportive treatment	Mortality at 28 days	- Duration of hospital stay - Intubation	There was not a significant difference in mortality at 28 days between the HCQ group and the control (RR 1.09, 95% CI 0.96−1.23)
Mitja et al.	Spain	293 non-hospitalized	HCQ 800 mg first day, then 400 mg daily for 6 days	No treatment	Conversion to negative PCR at 7 days	- Disease progression - Time to symptom resolution	There was not a significant difference in conversion to negative PCR at 7 days between the HCQ group and the no treatment group
Skipper et al.	USA and Canada	491 non-hospitalized	HCQ 800 mg once, then 600 mg daily for 4 days	Supportive treatment (Placebo-controlled)	Change in symptom severity over 14 days		There was not a significant difference in change in symptom severity at 14 days between the HCQ group and the control ($p = 0.21$)
Cavalcanti et al.	Brazil	504 hospitalized	HCQ 400 mg twice daily for 7 days OR HCQ 400 mg twice daily for 7 days + AZT 500 mg daily for 7 days	Supportive treatment	- Clinical status at 15 days	- Clinical status at 7 days - Intubation - Oxygen requirement - Hospital stay duration - Death	There was not a significant difference in clinical status at 10 days between the HCQ group and the control (OR 1.21, 95% CI 0.69−2.11; $p > 0.05$)
Boulware. et al.	USA and Canada	821 asymptomatic participants with exposure to sick contacts with COVID-19	HCQ 1200 mg twice daily on day 1, then 600 mg daily for 4 days	Supportive treatment	PCR confirmed COVID-19 or COVID-19-like illness within 14 days	- Hospitalization - Mortality	There was not a significant difference in COVID-19 with PCR positivity between HCQ group and the control (11.8% vs. 14.3%) ($p = 0.35$)
Mitja et al.	Spain	2314 asymptomatic participants with exposure to sick contacts with COVID-19	HCQ 800 mg daily then 400 mg daily for 6 days	No specific treatment	PCR positivity in 14 days		There was not a significant difference in COVID-19 with PCR positivity between HCQ group and the control (5.7% vs. 6.2%; RR 0.89) (95% CI: 0.54−1.46)

Abbreviations: HCQ: Hydroxychloroquine; CQ: Chloroquine; AZT: Azithromycin; RR: Relative Risk; OR: Odds Ratio; HR: Hazard Ratio; CI: Confidence Interval; ICU: intensive care unit; PCR: polymerase chain reaction; ARDS: acute respiratory distress syndrome.

[a] The definition of clinical recovery in this study is the resolution of fever and cough that is maintained for at least 72 h.

greater than ten days), viral shedding that persisted for more than ten days. A poor outcome was based on a composite of these events and was seen in 46 (4.3%) patients. Eight patients (0.75%) died in this study.

A Spanish single-center study of 166 patients presented results on a reduction in mortality associated with an initial HCQ loading dose of 800 mg [16]. There was a significant difference in mortality between the HCQ group (22%) and the comparator group (48.8%) ($p = 0.002$). However, the inclusion criteria of the study did not require PCR positivity, so patients were included if they had a probable clinical picture and the presence of bilateral interstitial pneumonia on imaging. The duration of the symptoms prior to admission was reported in the HCQ group, but not in the non-HCQ group, which may be an important confounding factor. These two points hinder the interpretation of the results of the study. A small retrospective study from the UAE showed an association of HCQ with longer time to negative PCR conversion in 34 hospitalized patients when compared to no HCQ use [17].

Seemingly counter to this evidence, a small French case series of 11 patients with the primary outcome of viral load at six days demonstrated negative results [18]. These authors found that there was a persistent viral load in eight out of ten patients who had received HCQ. This series was followed by the publication of a larger observational study by Mahevas et al. [19]. This study included a total of 181 patients from four French sites who required supplemental oxygen for COVID-19 that were included in these analyses. HCQ was given within 48 h of admission in the main analysis. The primary outcome of interest was survival without ICU transfer within 21 days. This study did not find a significant association between use of HCQ versus no HCQ on this primary outcome. Secondary outcomes of interest included overall survival, survival without acute respiratory distress syndrome, ability to wean supplemental oxygen, and discharge from the hospital. There were no significant associations with HCQ use in any of these secondary outcomes.

Finally, in a retrospective study from a single center in China, 284 hospitalized patients were assessed for outcomes of viral clearance and length of stay [20]. Overall, 65% of patients were on supplemental oxygen, 8.5% required an ICU level of care, and 1.4% required mechanical ventilation. Twenty-five patients received CQ. The authors assessed the association of antiviral therapy and the outcome of clearance at 14 days. Therapies assessed included CQ, lopinavir/ritonavir, and oseltamivir. Overall, 89% had viral clearance by 21 days, and this was not significantly shortened by any antiviral therapy including CQ.

Larger observational studies

These small studies were followed by the publication of larger observational studies. Some of these studies leveraged electronic health records as data sources, providing higher power to evaluate relatively rare outcomes among a large sample of individuals. However, this comes with the tradeoff of being less able to ascertain important confounding or outcome variables.

One of the larger retrospective studies from China included 568 patients in critical conditions with acute respiratory distress syndrome (ARDS) [21]. Of these patients, 48 were treated with HCQ at a dose of 200 mg twice a day for 7–10 days. The authors found a lower mortality rate in the group that received HCQ compared to the patients who did not (18.8%–45.8%, $p < 0.001$). Interleukin-6 level was a secondary outcome of the study, which was significantly lower in the HCQ group at the end of the treatment.

In a random sample of patients admitted for COVID-19 in the New York Metropolitan area, Rosenberg, et al. found no association between the use of HCQ with or without azithromycin on the outcome of in-hospital mortality [8]. Geleris et al. investigated the impact of HCQ treatment on the outcomes of intubation or death using observational data from 1446 hospitalized patients with COVID-19 in New York City [9]. Their study also found no significant association with the primary outcome. Methodologically, the authors accounted for confounding by indication using inverse probability weighting. Although doing so does not reproduce the results of an RCT, using these methods, one can better approximate the causal effects of treatment, given a set of certain assumptions. These assumptions include a well-designed study, having appropriate and well-measured data, and correctly identifying potential confounders.

The study by Magagnoli et al. used national US data from the Veterans Health Administration to assess the risk of death comparing those treated with HCQ versus not, or HCQ with azithromycin versus neither, among patients admitted for COVID-19 [22]. Although they found a nonsignificant association of HCQ and azithromycin treatment and the outcome of death, there was a statistically higher risk of death for those on HCQ alone versus standard of care. There was no association for the secondary outcome of mechanical ventilation for both those receiving HCQ alone and those receiving HCQ with azithromycin. The interpretation of these results is difficult. The combination of HCQ and azithromycin may have been expected to have similar or even worse outcomes as was observed in HCQ monotherapy vs. standard of care given possible interaction for QTc prolongation. Enhanced efficacy of combination therapy for COVID-19 could possibly have dampened the excess mortality of HCQ monotherapy. However, it is most likely that these results may have been biased due to issues with study validity, particularly unmeasured and residual confounding.

Another controversial observational study, from the Henry Ford Health System in Michigan, evaluated 2541 patients admitted for COVID-19 from March through the beginning of May 2020 [23]. The authors evaluated exposures of HCQ alone, azithromycin alone, combination of HCQ and azithromycin, and neither (reference group). Compared to those receiving neither treatment, those receiving either HCQ alone or in combination with azithromycin had a lower risk of in-hospital mortality in multivariable models (hazard ratio [HR] 0.34, 95% confidence interval [CI] 0.25–0.46; HR 0.29, 95% CI 0.22–0.40, respectively). The limitations of the statistical analysis warrant further comment. Although the authors adjusted for important known confounders such as age, cardiovascular and pulmonary comorbidities, and markers of COVID-19 disease severity, there remains a concern that their results of a protective association may be due to residual and unmeasured confounding, particularly the concomitant use of steroids that appear to be effective in severe COVID-19 [24]. Further, there may be strong temporal trends over calendar time for HCQ use during the early period of the pandemic. These issues limit the inference that can be drawn from these results.

By June 2020, the data from large, well-designed observational studies and emerging evidence from RCTs pointed toward a lack of efficacy for antimalarials in the treatment of COVID-19. The systematic review and meta-analysis by Putman et al. reported data from 45 studies up until May 2020, which included hospitalized COVID-19 patients who were treated with medications commonly used as antirheumatic therapies medication [25]. When pooled, the three included cohort studies assessing HCQ did not demonstrate an association with COVID-19 mortality. A later systematic review and meta-analysis by Fiolet et al. included 29 studies until the end of July 2020 [26]. This review only included studies with the primary outcome of mortality. The results of the study were in agreement with the earlier meta-analysis, with no benefit seen for HCQ on COVID-19 mortality.

RCTs

In the early stages of the pandemic, multiple small RCTs were initiated to study the effect of HCQ on COVID-19-related outcomes (Table 2). These trials were later followed by larger, multi-national RCTs; however, many of these were terminated early due to inefficacy of the intervention under study.

Chen et al. conducted a single center RCT in Wuhan [5] with 62 participants randomized to HCQ 400 mg daily for four days compared to standard of care. The primary outcome was recovery (return to normal body temperature for in 72 h or the resolution of cough 72 h). Both outcomes were significantly reduced in the intervention group compared to controls. In another small trial conducted by Huang et al., 22 hospitalized patients were randomized into two groups based on the treatment modality: CQ 500 mg twice daily for ten days compared to standard of care [7]. The primary outcome was seroconversion at 10 days which was not found to be statistically significant. An open-label study was conducted in China of 48 patients with moderate-severity COVID-19 randomized patients to CQ (dosed 1000 mg for one day, then 500 mg daily for nine days), HCQ (200 mg twice daily for ten days), or control, with a primary outcome of time to clinical recovery and a secondary outcome of viral RNA seroconversion [27]. Both outcomes were significantly shorter in the CQ group, and the HCQ group had quicker seroconversion compared to controls.

In a larger open-label controlled trial comprising 16 centers in China that enrolled 150 patients, the findings were negative [28]. Participants were randomized to HCQ 1200 mg for three days and subsequently 800 mg daily versus standard of care, assessing the outcome of seroconversion at 28 days.

Chlorocovid was a phase IIb RCT comparing two doses of CQ among patients in Brazil hospitalized with COVID-19 compared to historical controls from Wuhan [29]. In this study, there was a possible safety signal of QTC prolongation seen for CQ, but no clinical benefit was detected. High dose CQ at 600 mg twice daily for ten days was associated with higher risk of mortality versus low dose of CQ at 450 mg twice a day for one day followed by 450 mg daily for four days.

Several large, multinational RCTs were stopped in late May/early June 2020 due to inefficacy, including the HCQ arm of RECOVERY (Randomised Evaluation of COVID-19 Therapy), the WHO-sponsored Solidarity, and the NIH-sponsored ORCHID (Outcomes Related to COVID-19 Treated with HCQ Among Patients with Symptomatic Disease). The HCQ arm of the RECOVERY trial was reported in mid-July [30]. A total of 1561 participants hospitalized with COVID-19 from the UK were randomized to HCQ (800 mg followed by 800 mg six h later, and subsequently 400 mg twice daily for nine days) versus usual care. The primary outcome of this well-powered study was mortality at 28 days, which was not significantly different between the two groups (rate ratio [RR] 1.09, 95% CI 0.96–1.23). Subgroup analyses, including by age, sex, level of respiratory support, and days since symptom onset, did not show meaningful differences in the primary outcome in any subgroup. Two of the secondary outcomes favored usual care – the HCQ intervention group had a significantly longer length of stay and were more likely to progress to mechanical ventilator or death. This was the first large-scale RCT reported for HCQ in hospitalized patients with COVID-19, although it did not provide data on those with early or less severe infection.

Two other RCTs were reported in mid-July 2020, both evaluating the use of HCQ in non-hospitalized participants with early COVID-19 infections [31,32] Skipper et al. randomized 491 non-hospitalized participants with COVID-19 within four days of symptom onset from sites in the US and Canada to HCQ (800 mg followed by 600 mg in six to eight h, and subsequently 600 mg daily for four days) versus placebo. The primary outcome of change in symptom severity over 14 days was not statistically significant. The limitations of the study included the inclusion of participants who did not have PCR confirmation of infection (although 81% overall were either PCR positive or had high risk exposure to a contact that was PCR positive) as well as the modification of the initial primary outcome of hospitalization or death to change in symptom severity as there were too few events. (2% vs 3% hospitalized, 0.4% vs 0.4% died).

Mitja et al. performed an open label study in 293 Spanish patients with COVID-19 with symptom onset less than five days and who were not hospitalized [32]. The dosing of HCQ was 800 mg followed by 400 mg daily for six days. The primary outcome of reduction in RNA viral load at seven days after treatment initiation was not statistically significant comparing the two groups, nor were the secondary outcomes of disease progression or time to symptom resolution. Limitations of this study included its lack of a placebo and the use of a surrogate outcome.

A Brazilian placebo-controlled RCT by Cavalcanti et al. has further disproven the efficacy of HCQ, either alone or with azithromycin in mild-to-moderate hospitalized COVID-19 patients [34]. Patients were randomized and equally distributed to either receive standard treatment, an additional 400 mg twice daily HCQ to the standard treatment, or standard care with the same HCQ regimen as the prior group plus daily azithromycin at a dose of 500 mg. Neither of the treatment groups had a statistically significant benefit over the negative control group in terms of the primary and the secondary outcomes. Furthermore, HCQ treatment was associated with a higher frequency of adverse events, such as elevation of liver enzymes and QTc interval prolongation.

Efficacy of antimalarials for COVID-19 post-exposure prophylaxis/prevention

Boulware et al. conducted a multicenter RCT at sites in the US and Canada [33]. They randomized 821 participants who were asymptomatic but had had household or occupational exposure to a confirmed COVID-19 case. Overall, 66.4% were healthcare workers; the median age was 40 years, and 27.4% cases were with at least one chronic condition. Participants were further stratified by high risk (<6 feet, >10-minute contact without facemask or eye shield) and moderate risk (<6 feet, >10-minute contact with face mask but no eye shield). They were randomized to either HCQ 800 mg once, then 600 mg in 6–8 h, and then 600 mg daily for 4 days or placebo. The primary outcome was laboratory-confirmed COVID-19 or COVID-19-like illness within 14 days assessed by follow-up surveys online or by phone. The outcome occurred in 11.8% in the HCQ group versus 14.3% in the placebo group and was not statistically different. The secondary outcomes, COVID-19 hospitalization or death, were also not statistically significant. Side effects were more common with HCQ than with placebo (40.1% vs 16.8%). The limitations of this study included the inclusion of a younger, healthier population rather than a more at-risk population and limited access to confirmatory testing of COVID-19, especially for participants in the US.

An open-label, cluster-randomized trial conducted in Catalonia, Spain, also assessed the use of HCQ as a post-exposure prevention [35]. The intervention arm (n = 1116) was treated with 800 mg once and then 400 mg daily for six days, while the control group (n = 1198) received no specific treatment. The primary outcome of confirmed COVID-19 infection within 14 days was not statistically significant (6.2% control group vs. 5.7% HCQ, RR 0.89, 95% CI 0.54–1.46). Adverse event frequency was higher in the treatment arm (51.6% vs. 5.9%) ($p < 0.001$) mostly consisting of mild gastrointestinal symptoms, but cardiac side effects consisting of palpitations were only seen in 0.4% of the treatment arm (vs. 0.1% in the control arm).

The importance of these last several RCTs [31–35] were that they were published at a time when the RCTs of hospitalized COVID-19 patients were criticized for assessing the efficacy of HCQ in a subset of patients who had higher disease severity. The RCTs in early, non-hospitalized COVID-19 and the multiple RCTs in hospitalized COVID-19 have emphasized the lack of efficacy of HCQ in COVID-19.

Antimalarials and COVID-19 outcomes in patients with rheumatic disease

In April 2020, hypotheses that patients with systemic lupus erythematosus (SLE) were protected against COVID-19, possibly through their use of HCQ, began to spread. Initial case series of SLE patients were mixed, with some including patients with severe diseases [36] and others including only patients with mild or moderate courses [37]. Ramirez et al. systematically reviewed SLE- and COVID-19 related publications through the end of June 2020, concluding that the data did not support a protective association between HCQ and COVID-19 among subjects with SLE [38].

The COVID-19 Global Rheumatology Alliance registry published an analysis with 600 patients with COVID-19 disease from 40 countries with rheumatic conditions including rheumatoid arthritis (RA) (38%), SLE (14%), and psoriatic arthritis (12%) [39,40]. Among these, 22% were on antimalarials prior to COVID-19 diagnosis. The use of antimalarials was not significantly associated with hospitalization following COVID-19 diagnosis. This study was limited by the method of data collection (i.e., voluntary entry by physicians into an online registry), and there was potential selection bias toward more severe cases.

D'Silva et al. performed a matched cohort study of 52 patients with rheumatic conditions and confirmed COVID-19 compared with 104 patients without rheumatic disease from the greater Boston area [41]. Among the patients with a rheumatic disease, nine patients (17%) were treated with HCQ. The only primary outcome showing a significant difference was intensive care admission and mechanical ventilation, which was higher in the rheumatic disease group (48%–18%) ($p = 0.01$). The admission and mortality rates were similar in both groups. In the group of patients with rheumatic disease, there was no significant difference between hospitalized and non-hospitalized patients regarding the use of antimalarial therapy. This study was not powered to evaluate the association of antimalarial use and any of these outcomes.

Antimalarials and cardiovascular safety in COVID-19

The evidence for possible cardiovascular toxicity with antimalarial treatment in COVID-19 has come from small studies from the US and Europe. These data are presented in Table 3.

Four observational studies from the US evaluated the cardiovascular safety of antimalarial treatment with or without concomitant azithromycin [42–45]. One study was prospective, and the others were retrospective. All compared the post-antimalarial treatment QTc interval with the baseline.

Table 3
Antimalarial treatment for COVID-19 and cardiovascular-related safety outcomes.

Study	Design	Country	Sample size, Population	Antimalarial dosing	Comparator	Cardiovascular-related Safety Outcomes	Main Results
Borba et al.	RCT	Brazil	81 (62/81 with confirmed COVID-19 infection)	HCQ 600 mg twice daily for 10 days (AND AZT 500 mg daily for 5 days in ARDS)	HCQ 450 mg twice daily on day 1, then daily for 4 days (AND AZT 500 mg daily for 5 days in ARDS)	ECG on day 13 and 28	QTc was greater than 500 msec in 18.9% of the high-dosage group and in 11.1% of the low-dosage group ($p = 0.51$)
Mercuro et al.	Cohort	USA	90 hospitalized with pneumonia	HCQ 400 mg twice on day 1, then 400 mg daily for 4 days AND AZT (dose and duration unknown)	Only HCQ	QTc prolongation	Combination HCQ + AZT therapy was associated with a greater change in QTc compared with HCQ alone ($p = 0.03$) QTc was greater than 500 msec in 19% of the HCQ group and in 21% of the HCQ+AZT group
Rosenberg et al.	Cohort	USA	1438 hospitalized	HCQ + AZT/HCQ alone/AZT alone; Dose and duration unknown	Supportive treatment	- Cardiac arrest (secondary outcome) - QTc prolongation (secondary outcome)	There was a significant association with cardiac arrest in the HCQ + AZT group (OR 2.13, 95% CI 1.12–4.05) but not in the HCQ-alone group (OR 1.91, 95% CI 0.96–3.81) There was no significant difference in abnormal ECG findings (27.1% in the HCQ + AZT group, 27.3% in the HCQ-alone group, 16.1% in the AZT-alone group, and 15% in the supportive treatment group)
Ramireddy et al.	Case series	USA	98 hospitalized with confirmed COVID-19 or clinical suspicion for COVID-19	HCQ 400 mg twice on day 1, then 200 mg twice daily for 4 days + AZT 500 mg for 5 days	ECGs prior to CQ treatment	Prolonged QTc	Critical QTc prolongation was observed in 12% of the patients
Chorin et al.	Case series	USA	84 hospitalized	HCQ and AZT; Dose and duration unknown	ECGs prior to CQ treatment	Prolonged QTc	QTc prolongation was observed in 11% of the patients

Saleh et al.	Cohort	USA	201 hospitalized	CQ 500 mg twice on day 1, then 500 mg daily for 4 days AND/OR HCQ 400 mg twice daily on day 1, then 200 mg twice daily for 4 days + AZT 500 mg daily for 5 days	ECGs prior to CQ treatment	- QTc prolongation - Torsades de pointes	QTc prolongation was observed in 9% of the patients; Torsades de pointes was not observed
Bessiere et al.	Case series	France	40 ICU patients	HCQ 200 mg twice daily for 10 days	ECGs prior to CQ treatment	Prolonged QTc	QTc prolongation was observed in 36% of the patients
van den Broek et al.	Case series	The Netherlands	95 suspected hospitalized	CQ 600 mg loading dose, then 300 mg twice daily for 4 days	ECGs prior to CQ treatment	Prolonged QTc	QTc prolongation was observed in 23% of the patients
Cipriani et al.	Case series	Italy	126 hospitalized	HCQ 200 mg twice daily for 3 or more days AND AZT 500 mg daily for 3 or more days	ECGs prior to CQ treatment	Prolonged QTc	There was no significant difference in QTc interval duration between post-treatment results (450 msec) and pre-treatment results (426 msec) ($p = 0.02$)

Abbreviations: HCQ: Hydroxychloroquine; CQ: Chloroquine; AZT: Azithromycin; RR: Relative Risk; OR: Odds Ratio; HR: Hazard Ratio; CI: Confidence Interval; ICU: intensive care unit; PCR: polymerase chain reaction; QTc: QT corrected; ECG: electrocardiogram.

Mercuro et al. reported that of the 90 who received HCQ, 19% had prolonged QTc [42]. Of the 53 who received HCQ and concomitant azithromycin, this frequency was 21%. Compared to baseline values, on average, those receiving HCQ alone had an increase of 5.5 ms, while those who received combination therapy had an increase of 23 ms. In the study by Ramireddy et al., the overall QTc increase was observed with the greatest mean change in patients receiving both of the treatments [45]. Critical QTc prolongation was observed in 12% of the patients. The cohort of 84 patients reported by Chorin et al. demonstrated a statistically significant difference when comparing the QTc from baseline to treatment values [43]. Finally, in the prospective study by Saleh et al., the QT interval during the combination treatment was significantly longer than that of the monotherapy group, although the QTc intervals in the CQ/HCQ monotherapy group versus the combination of either one with azithromycin were similar at baseline [44]. Overall, torsades de pointes or arrhythmogenic cardiac mortality were not observed in any of these studies.

Three similar studies were published from France, Italy, and the Netherlands [46–48]. The study by Bessiere et al. had a unique criterion of including only severely affected patients; 75% required mechanical ventilation [46]. All 40 patients had normal QTc intervals at baseline. HCQ alone was given to 18 patients (45%) and in combination with azithromycin to 22 patients (55%). The QTc interval was prolonged in 14 (36%) after therapy initiation. Cipriani et al. included 126 hospitalized patients who all received HCQ with azithromycin [47]. Their subjects had significantly longer QTc intervals compared to before treatment (450 vs 426 msec). Finally, van den Broek et al. evaluated CQ-related QTc prolongation in 95 hospitalized patients [48]. There was a mean prolongation of 35 ms comparing the follow-up and baseline QTc intervals. QTc prolongation exceeding 500 ms was observed in 23% of the patients. There were no cases of torsades in all three of the studies.

A later-retracted large observational study using purported international registry data on nearly 100,000 patients with COVID-19 found an increased risk of mortality and new arrhythmias for HCQ or CQ alone and either antimalarial in combination with a macrolide versus comparators receiving neither an antimalarial nor a macrolide [49,50]. The issues with the integrity of the data source have been discussed at length [51].

Although both CQ and HCQ are known to have potentially serious cardiovascular side effects, the data and clinical experience so far demonstrate their general tolerability as treatment for COVID-19 in the general population. These treatment modalities have been mostly analyzed using QTc prolongation as a surrogate outcome. Despite the primary mechanism of drug-induced arrhythmogenicity being QTc prolongation, fatal arrhythmias can also occur in patients with a normal QTc interval [52].

The studies described above demonstrate a potentially clinically relevant prolongation of the QTc interval (>500 ms) in at least 10% of the patients. The addition of azithromycin to antimalarial treatment was found to be associated with a longer QTc duration. However, the majority of the studies reached a conclusion that cardiovascular side effects rarely warrant the discontinuation of the treatment as there were no incidents of ventricular arrhythmia or torsades de pointes. Overall, these studies in COVID-19 were limited by small sample sizes and surrogate outcomes.

Safety of antimalarials in patients with rheumatic disease

The concerns about cardiovascular safety with the use of antimalarials for COVID-19 led to a renewed interest in the same toxicity concerns among long-term users with rheumatic disease such as SLE or RA. Due to the need for large numbers to investigate rare outcomes, this question was primarily studied using administrative databases.

Lane et al. used claims data from 14 sources and spanning six countries in three continents to study HCQ with or without azithromycin versus active comparators (sulfasalazine and amoxicillin, respectively) [53]. They performed two separate studies: one in patients with RA using an active comparator design and one in the general population using a self-controlled case series design. Although their study did not find a difference in short-term outcomes with 30-day follow-up, they did detect a concerning safety signal; HCQ combined with azithromycin was associated with increased risk of three separate outcomes: cardiovascular death, chest/pain angina, and heart failure.

Hooks et al. performed an analysis of veterans in the Minneapolis Veterans Affairs system who were prescribed HCQ from the years 2000–2020 [54]. The majority of these patients had underlying SLE as the indication for treatment with HCQ. They evaluated characteristics associated with prolonged QTc intervals. However, comparing those with prolonged QTc intervals greater than or equal to 470 ms to those with normal QTc intervals, they did not find a statistically significant association with mortality. These data suggest that HCQ use, while associated with elevated QTc intervals in patients with SLE, were not associated with increased mortality in such patients.

Lo et al. investigated the safety of HCQ in patients with RA by analyzing the arrhythmia history from the National Health Insurance Research Database in Taiwan from 1999 to 2013 [55]. The study included 8564 patients with newly diagnosed RA. The authors reported that the cumulative risk of arrhythmia was not significantly higher in patients treated with HCQ regardless of the daily dose. In addition, the addition of a macrolide to HCQ treatment did not cause a significant increase in the incidence of arrhythmias.

The studies from larger databases concluded that the use of HCQ as maintenance therapy in rheumatic diseases appeared to be safe with regards to cardiovascular safety. The combination treatment of HCQ with azithromycin is concerning and may require additional monitoring.

Summary

The rapid uptake of antimalarials for the treatment of COVID-19 has prompted both a fervor to publish and a flurry of criticism. By September 2020, the data from large RCTs and well-designed observational studies demonstrated the lack of efficacy of antimalarials for the treatment of mild, moderate, or severe COVID-19 or as post-exposure prophylaxis. In addition, there are concerns about cardiovascular adverse events, particularly if used in combination with azithromycin. Studies have not shown a protective association for COVID-18 infection or COVD-19 related outcomes for those with rheumatic disease who use HCQ as maintenance therapy. The data thus far do not point toward increased cardiovascular adverse events in this population when used for non-COVID-19 indications.

Practice points

- Based on the current randomized controlled trials and high-quality evidence from large, observational studies, the use of antimalarials, especially hydroxychloroquine (HCQ), for the treatment of mild, moderate, or severe COVID-19 is not efficacious.
- Based on a similar level of current evidence, the use of HCQ as post-exposure prophylaxis for COVID-19 is not efficacious.
- There is no current evidence that chronic therapy with HCQ is protective against COVID-19 among those with rheumatic disease such as lupus or rheumatoid arthritis.
- The risk of developing new arrhythmias on antimalarials, particularly when used in conjunction with azithromycin, may be heightened in those with COVID-19 who receive this treatment regimen. However, there is limited evidence for a similar cardiovascular risk among those with rheumatic disease on maintenance therapy with hydroxychloroquine who do not have COVID-19.

Research agenda

- Further studies are needed to investigate the cardiovascular risks of long-term HCQ use among those with rheumatic disease who do not have COVID-19 in order to help determine the utility of baseline cardiac testing and follow-up monitoring.

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Declaration of competing interest

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