Targeted Update: Safety and efficacy of hydroxychloroquine or chloroquine for treatment of COVID-19

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Included studies

Search date: 23rd May 2020

This targeted update includes data from three randomised controlled trials and three quasi-experimental studies comparing the use of hydroxychloroquine or chloroquine (with or without a macrolide) with standard care as a treatment for COVID-19.

Key findings

Hydroxychloroquine (with or without a macrolide):

➢ Showed little to no difference in all-cause mortality at day 7 compared with standard care (very low certainty evidence)
➢ May result in a shorter time to intubation/mechanical ventilation or death than standard care (low certainty evidence)
➢ May result in an increased risk of adverse events during days 14-28 compared to standard care (low certainty evidence)
➢ May result in a shorter time to ventricular arrhythmia (low certainty evidence)

Chloroquine (with or without a macrolide):

➢ May result in a shorter time to intubation/mechanical ventilation or death than standard care (low certainty evidence)
➢ May result in a shorter time to ventricular arrhythmia (low certainty evidence)

Main conclusions

Hydroxychloroquine and chloroquine were not associated with a difference in overall mortality when compared to standard care for COVID-19 but may result in a shorter time to intubation, death, and ventricular arrhythmia.
Summary

Background

In December 2019, a novel coronavirus outbreak was documented in Wuhan, Hubei Province, China. Over the first six weeks of the new decade, this novel coronavirus, known as SARS-CoV-2, had spread from China to 20 other countries and on March 11, 2020 the World Health Organization (WHO) declared a pandemic. To overcome this pandemic, researchers are actively working to accelerate the development of diagnostics, preventive interventions, therapeutics, and vaccines.

This emerging situation requires an optimum planning and conduct of research as well as strategies for the appropriate transposition of research into practice. Therefore, decision-makers and researchers urgently need a complete, high-quality, and up-to-date synthesis of data from all ongoing research studies as soon as they are available.

To this end, the following work is being conducted: 1) a living mapping of registered randomised controlled trials (RCTs) and 2) a living systematic review and network meta-analysis of RCTs and quasi-experimental studies.

Objective

The objective of this targeted update is to review the safety and efficacy of hydroxychloroquine or chloroquine for treatment of COVID-19.

Methods

The protocol and data for this targeted updated comes from the COVID-NMA project led by Cochrane France in collaboration with Cochrane Germany, Cochrane Ireland, the Centre for Evidence-Based Medicine Odense, the Centre for Research Epidemiology and Statistics (Université de Paris, Inserm). This project receives some funding from the ANR (Agence Nationale de la Recherche, France).

Search methods

The WHO International Clinical Trials Registry Platform and electronic bibliographic databases (PubMed, MedRxiv, Chinaxiv) are searched weekly. Systematic review and meta-analyses of COVID-19 treatments are being retrieved and the references screened. No language restrictions are used.

The most recent search was conducted on May 23, 2020.

Selection criteria

RCTs and quasi-experimental studies are eligible for inclusion. Early-phase clinical trials, single arm trials, observational studies, and modelling studies of interventions for COVID-19 are also identified but are not formally included in the review.

Studies including patients with suspected, probable, or confirmed COVID-19, evaluating effectiveness of interventions for treating COVID-19, are considered for inclusion. The efficacy of these treatments is evaluated according to the severity of the disease (i.e., mild, moderate, severe, and critical).

The focus of this targeted update is on the efficacy and safety of hydroxychloroquine or chloroquine with or without a macrolide, compared to standard care.

The outcome selection is based on the core outcome sets (COS) developed by the WHO and on the meta-COS for research in COVID-19 hospitalised patients identified through the COMET initiative (www.comet-initiative.org/Studies/Details/1538). We consider viral negative conversion, clinical improvement, the WHO Clinical Progression Score level 5 or above; 6 or above; 7 or above; adverse events; serious adverse events; and all-cause mortality.

For this targeted update we have also evaluated adverse events that have previously been associated with hydroxychloroquine and chloroquine (i.e. QT interval prolongation, arrhythmia, and ventricular fibrillation sudden death)

Data collection and analysis

Screening, data extraction and risk of bias assessment was performed in duplicate by two independent reviewers.

The risk of bias assessment was conducted using the Cochrane Risk of Bias tool—version 2 (RoB 2) (Sterne 2019) and the ROBINS-I tool for observational studies (Sterne 2016).

For dichotomous outcomes from RCTs, risk ratios (RR) or hazard ratios (HR) with 95% confidence intervals (CI) were calculated for each study and pooled using a random effects model (DerSimonian & Laird 1986).

Findings were interpreted using the GRADE approach (Schünemann 2019). See Appendix 1 for details.
Main Results

The comparisons reported here focus on data from RCTs and quasi-experimental studies. In addition, Appendix 2 lists the details and results of observational studies and case series that reported on hydroxychloroquine or chloroquine as a treatment for COVID-19.

Comparison 1. Hydroxychloroquine compared to Standard Care for mild, moderate, and severe COVID-19

See Summary of Findings table 1 and Forest plots 1.

Three RCTs (J Chen 2020, Z Chen 2020, Tang 2020) and three quasi-experimental studies (Geleris 2020, Mahevas 2020, Mehra 2020) were included in this comparison. Three studies were carried out in China, one in France, one in the USA, and one was multinational.

Three studies included patients with moderate or severe COVID-19 (Mahevas 2020, Chen 2020, Tang 2020) and one study included patients with mild, moderate, or severe COVID-19 (Mehra 2020). One study did not report information on severity of the disease (Geleris 2020).

Mortality

Two RCTs reported on all-cause mortality. There were no deaths in either group at 7 days (1 RCT, N=150, very low certainty evidence) and at 14-28 days (2 RCTs, N=180, very low certainty evidence).

In addition, two quasi-experimental studies reported on all-cause mortality and time to death. One study reported little or no difference in all-cause mortality at 7 days between the group of patients with moderate/severe COVID-19 treated with hydroxychloroquine and those receiving standard care (RR 0.93, 95% CI 0.48 to 1.81, N=173, very low certainty evidence). The same study also reported little or no difference in time to death between both groups (HR 1.20, 95% CI 0.42 to 3.45, N=173, very low certainty evidence). The other study reported that hydroxychloroquine may shorten time to death compared to standard care in patients with mild, moderate, or severe COVID-19 (HR 1.34, 95% CI 1.22 to 1.47, N=84,160, low-certainty evidence).

Safety

There were little or no difference in adverse events at 7 days between hydroxychloroquine and standard care (RR 5.00, 95% CI 0.25 to 100.08, 1 RCT, N=150: very low certainty evidence). However, hydroxychloroquine may increase the incidence of adverse events at 14-28 days (RR 2.49, 95% CI 1.04 to 5.98, 2 RCTs, N=180, low certainty evidence).

No serious adverse events were reported in either group at 7 days (1 RCT, N=62), and little or no difference was seen at 14-28 days between groups (RR 5.70, 95% CI 0.28 to 116.84, 1 RCT, N=150: very low certainty evidence).

One RCT reported no cases of QT interval prolongation or ventricular arrhythmia in the group of patients receiving hydroxychloroquine (N=150, very low certainty evidence).

One quasi-experimental study reported on QT interval prolongation in the intervention group only. Of 84 patients who received hydroxychloroquine within the first 48 hours, seven (8.3%) patients had a corrected QT interval prolongation of more than 60 milliseconds (very low certainty evidence).

Comparison 2. Chloroquine versus Standard Care for mild, moderate, and severe COVID-19

See Summary of Findings table 2 and Forest plots 2.

One large multinational quasi-experimental study compared chloroquine to standard care and reported that chloroquine may result in a shorter time to intubation/mechanical ventilation or death (HR 1.58, 95% CI 1.45 to 1.73, N=83,012, low certainty evidence) and death (HR 1.37, 95% CI 1.22 to 1.53, N=83,012, low certainty evidence).

The same study reported that compared to standard care, chloroquine may result in a shorter time to ventricular arrhythmia (HR 3.56, 95% CI 2.76 to 4.60, N=83,012, low certainty evidence).

Comparison 3. Hydroxychloroquine with a macrolide compared to Standard Care for mild, moderate, and severe COVID-19

See Summary of Findings table 3 and Forest plots 3.

One large multinational quasi-experimental study compared hydroxychloroquine with a macrolide to standard care and reported that the use of hydroxychloroquine plus a macrolide may result in a...
shorter time to intubation/mechanical ventilation or death (HR 1.45, 95% CI 1.39 to 1.52, N=87,365, low certainty evidence) and death (HR 1.45, 95% CI 1.37 to 1.53, N=87,365, low certainty evidence).

The same study reported that compared to standard care, hydroxychloroquine plus a macrolide may result in a shorter time to ventricular arrhythmia (HR 5.11, 95% CI 4.36 to 5.98, N=87,365, low certainty evidence).

**Comparison 4. Chloroquine with a macrolide compared to Standard Care for mild, moderate, and severe COVID-19**

See Summary of Findings table 4 and Forest plots 4.

One large multinational quasi-experimental study compared chloroquine with a macrolide to standard care and reported that the use of chloroquine plus a macrolide may result in a shorter time to intubation/mechanical ventilation or death (HR 1.48, 95% CI 1.40 to 1.57, N=85,107, low certainty evidence) and death (HR 1.37, 95% CI 1.27 to 1.47, N=85,017, low certainty evidence).

The same study reported that compared to standard care, hydroxychloroquine plus a macrolide may result in a shorter time to ventricular arrhythmia (HR 4.01, 95% CI 3.34 to 4.81, N=85,017, low certainty evidence).

**Implications and conclusions**

This targeted update reports on all available evidence on the treatment of COVID-19 with hydroxychloroquine or chloroquine (with or without a macrolide) compared to standard care and is current to 23rd May 2020.

The evidence from both RCTs and quasi-experimental studies show little or no benefit of hydroxychloroquine or chloroquine (both with and without a macrolide) over standard care for COVID-19, however this evidence is of very low certainty.

There was also little to no difference in overall mortality between hydroxychloroquine and standard care, though this evidence was also of very low certainty.

With regards to adverse events, hydroxychloroquine may result in more adverse events than standard care, as well as a shorter time to intubation/mechanical ventilation, death, and ventricular arrhythmia than standard care.

Chloroquine, hydroxychloroquine with a macrolide, and chloroquine with a macrolide, may all result in a shorter time to intubation/mechanical ventilation, death, and ventricular arrhythmia than standard care when used in patients with COVID-19.
Summary of Findings 1: Hydroxychloroquine compared to Standard Care for Mild/Moderate/Severe COVID-19

Patients: Mild/Moderate/Severe COVID-19
Setting: Worldwide
Comparison: Hydroxychloroquine vs Standard Care
Study design: randomised controlled trials (RCTs) and quasi-experimental studies

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>N° of participants &amp; studies</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality D7</td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine</td>
<td>RR 0.93 (0.48 to 1.81)</td>
<td>150 (1 RCT)</td>
<td>☑️ ☑️ ☑️anova VERY LOWm</td>
</tr>
<tr>
<td>Time to death</td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine</td>
<td>HR 1.34 (1.22 to 1.47)</td>
<td>84,160 (1 quasi-experimental study)</td>
<td>☑️ ☑️ ☑️anst LOWm</td>
</tr>
<tr>
<td>Time to intubation/mechanical ventilation or death</td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine</td>
<td>HR 0.98 (0.73 to 1.31)</td>
<td>1085 (1 quasi-experimental study)</td>
<td>☑️ ☑️ ☑️anst LOWm</td>
</tr>
<tr>
<td>Incidence of viral negative conversion D7</td>
<td>933 per 1.000</td>
<td>868 per 1.000 (681 to 1.000)</td>
<td>RR 0.93 (0.73 to 1.18)</td>
<td>30 (1 RCT)</td>
<td>☑️ ☑️ ☑️anst LOWm</td>
</tr>
<tr>
<td>Time to 2019-nCoV RT-PCR negativity</td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine</td>
<td>HR 0.85 (0.58 to 1.23)</td>
<td>150 (1 RCT)</td>
<td>☑️ ☑️ ☑️anst LOWm</td>
</tr>
<tr>
<td>WHO Clinical Progression Score (decrease in 1 point) (i.e., improvement)</td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission in ICU or death</td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of WHO progression score (level 6 or above)</td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of WHO progression score (level 7 or above)</td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events D7</td>
<td>0 per 1.000</td>
<td>0 per 1.000 (0 to 0)</td>
<td>RR 5.00 (0.25 to 100.08)</td>
<td>62 (1 RCT)</td>
<td>☑️ ☑️ ☑️anst LOWm</td>
</tr>
</tbody>
</table>
### Adverse events D14-D28

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate/G1</th>
<th>Rate/G2</th>
<th>RR</th>
<th>CI</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events D14-D28</td>
<td>105 per 1.000 (109 to 629)</td>
<td>262 per 1.000 (1.04 to 5.98)</td>
<td>RR 2.49 (1 RCT)</td>
<td>180 (2 RCTs)</td>
<td>⬤⬤⬤⬤ LOW d,i,k</td>
</tr>
<tr>
<td>Serious adverse events D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>62</td>
<td>⬤⬤⬤⬤ VERY LOW d,i,j</td>
</tr>
<tr>
<td>Serious adverse events D14-D28</td>
<td>0 per 1.000 (0 to 0)</td>
<td>0 per 1.000 (0.28 to 116.84)</td>
<td>RR 5.70 (1RCT)</td>
<td>150 (1 RCT)</td>
<td>⬤⬤⬤⬤ VERY LOW d,i,j</td>
</tr>
</tbody>
</table>

#### QT interval prolongation

- One RCT (Tang 2020) reported no cases of QT interval prolongation (0/150) (Moderate/severe cases)
- One quasi-experimental study (Mahevas 2020) reported on QT interval prolongation in the intervention group only. Of 84 patients who received hydroxychloroquine within the first 48 hours, seven (8.3%) patients had a corrected QT interval prolongation of more than 60 ms. (Moderate/severe cases)

#### Time to ventricular arrhythmia

- One RCT (Tang 2020) reported no cases of cardiac arrhythmia (0/150) (Moderate/severe cases)

#### Ventricular fibrillation sudden death

- Outcome not yet measured or reported

---

CI = confidence interval, RR = risk ratio

*The risk in the intervention group* (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

### Explanations

- a. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and selection of the reported results
- b. Indirectness downgraded by 1 level: single study from a single institution, therefore results in this population might not be generalizable to other settings
- c. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants
- d. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended interventions and selection of the reported results
- e. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings
- f. Imprecision downgraded by 2 levels: no events in both groups and low number of participants
- g. Indirectness downgraded by 1 level: studies from a single country, therefore results in this population might not be generalizable to other settings
- h. Risk of bias downgraded by 1 level: high risk of bias and some concerns regarding adequate randomization, deviations from intended interventions and selection of the reported results
- i. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness
- j. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
- k. Imprecision downgraded by 1 level: due to low number of participants
- l. Risk of bias downgraded by 1 level: moderate risk of bias due to confounding, selection of participants into study, and selection of the reported result. No information about deviations from intended interventions.
m. Risk of bias downgraded by 2 levels: moderate risk of bias due to confounding and selection of the reported result; serious risk of bias due to selection of participants and classification of interventions. No information about deviations from intended interventions.

n. Risk of bias downgraded by 2 levels: moderate risk of bias due to confounding and selection of the reported result; serious risk of bias due to selection of participants. No information about deviations from intended interventions.

o. Only non-comparative estimates (i.e. no control group) reported which are of very low certainty.
### Forest plots 1: Hydroxychloroquine versus Standard Care for Mild/Moderate/Severe COVID-19

**Patients:** Moderate/Severe COVID-19  
**Setting:** Worldwide  
**Comparison:** Hydroxychloroquine vs Standard Care

#### Forest plot

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Forest plot</th>
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</thead>
<tbody>
<tr>
<td>All-cause mortality D7</td>
<td><img src="image" alt="Forest plot" /></td>
</tr>
</tbody>
</table>

#### All-cause mortality D7 (RCTs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>dose T, duration T</th>
<th>RR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang et al., 2020</td>
<td>21</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>1200mg for 3 days, then 600mg, 14 to 21 days</td>
<td>0.75</td>
<td>0.75</td>
<td>(excluded)</td>
<td><img src="image" alt="Risk of bias" /></td>
</tr>
</tbody>
</table>

#### Risk of bias ratings

- **□**: low risk of bias  
- **◯**: some concerns  
- **■**: high risk of bias

#### Risk of bias domains

- A: Bias arising from the randomization process  
- B: Bias due to deviations from intended interventions  
- C: Bias due to missing outcome data  
- D: Bias in measurement of the outcome  
- E: Bias in selection of the reported results

**Certainty of the evidence (GRADE)**

- VERY LOW
### All-cause mortality D7

**Quasi-experimental study**

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>dose of</th>
<th>duration of</th>
<th>RR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahvas M, medRev, 2020</td>
<td>7</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>600mg</td>
<td></td>
<td>0.93 [0.48, 1.81]</td>
<td>100.00</td>
<td>F G ? ? ? ? ?</td>
</tr>
</tbody>
</table>

#### Risk of bias ratings
- ⬤ = low risk of bias
- ◯ = moderate risk of bias
- X = serious risk of bias
- ? = No information

#### Risk of bias domains
- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias in selection of the reported result

#### Treatment vs Control
- Treatment better
- Control better

#### All-cause mortality D14-D28

**RCTs**

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>dose of</th>
<th>duration of</th>
<th>tINT</th>
<th>tC/N</th>
<th>RR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen J, J Zhejiang Univ, 2020</td>
<td>14</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>400mg</td>
<td>5 days</td>
<td>0/15</td>
<td>0/15</td>
<td>(excluded)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang W, medRev, 2020</td>
<td>21</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>600mg</td>
<td>3 days, then 600mg</td>
<td>0/75</td>
<td>0/75</td>
<td>(excluded)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Risk of bias ratings
- ⬤ = low risk of bias
- X = some concerns
- □ = high risk of bias

#### Risk of bias domains
- A: Bias arising from the randomization process
- B: Bias due to deviations from intended interventions
- C: Bias due to missing outcome data
- D: Bias in measurement of the outcome
- E: Bias in selection of the reported results

#### Treatment vs Control
- Treatment better
- Control better

### Risk of bias

- VERY LOW

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### Time to death

#### (quasi-experimental studies)

#### Risk of bias ratings

- 🟢 = low risk of bias
- 🟡 = moderate risk of bias
- 🟠 = serious risk of bias
- ✂ = critical risk of bias
- 🟥 = No information

#### Risk of bias domains

- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias in selection of the reported result

#### Time to death

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>doseT</th>
<th>HR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehran, MR, Lancet, 2020</td>
<td>-</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>-</td>
<td>1.34 [1.22, 1.47]</td>
<td>100.00</td>
<td>✠ BDGGBG</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>21</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>600mg</td>
<td>1.20 [0.42, 3.45]</td>
<td>100.00</td>
<td>⬤ ⬤ ⬤</td>
</tr>
</tbody>
</table>

#### Risk of bias summaries

- Treatment better: 1/2
- Control better: 1

### Time to intubation or death

#### (quasi-experimental study)

#### Risk of bias ratings

- 🟢 = low risk of bias
- 🟡 = moderate risk of bias
- 🟠 = serious risk of bias
- ✂ = critical risk of bias
- 🟥 = No information

#### Risk of bias domains

- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias in selection of the reported result

#### Time to intubation or death

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>doseT, durationT</th>
<th>HR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geleris J, N Engl J Med, 2020</td>
<td>22.5</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>600mg initial 400mg maintenance, 5 days</td>
<td>0.68 [0.73, 1.31]</td>
<td>0.68</td>
<td>BDGGBG</td>
</tr>
</tbody>
</table>

#### Risk of bias summaries

- Treatment better: 0.73
- Control better: 1.31
Time to mechanical intubation or death

(quasi-experimental study)

Incidence of viral negative conversion D7

(RCTs)
Time to 2019-nCoV RT-PCR negativity

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>doseT, durationT</th>
<th>HR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/severe</td>
<td>28</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>1200mg for 3 days, then 800mg, 14 to 21 days</td>
<td>0.65 [0.58, 1.23]</td>
<td>100.00</td>
<td>✔️</td>
</tr>
</tbody>
</table>

Control better: Treatment better

Risk of bias ratings:

- ⋁ = low risk of bias,
- ◯ = some concerns,
- ☠ = high risk of bias

Risk of bias domains:

- A: Bias arising from the randomization process
- B: Bias due to deviations from intended interventions
- C: Bias due to missing outcome data
- D: Bias in measurement of the outcome
- E: Bias in selection of the reported results

Adverse events D7

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>doseT, durationT</th>
<th>rT/NT rCANC</th>
<th>RR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/severe</td>
<td>6</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>400mg, 5 days</td>
<td>2/31 0/31</td>
<td>5.00 [0.25, 100.08]</td>
<td>100.00</td>
<td>✔️</td>
</tr>
</tbody>
</table>

Treatment better: Control better

Risk of bias ratings:

- ⋁ = low risk of bias,
- ◯ = some concerns,
- ☠ = high risk of bias

Risk of bias domains:

- A: Bias arising from the randomization process
- B: Bias due to deviations from intended interventions
- C: Bias due to missing outcome data
- D: Bias in measurement of the outcome
- E: Bias in selection of the reported results

Very Low Risk
## Adverse events D14-D28 (RCTs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>doseT, durationT</th>
<th>rT/NT</th>
<th>rC/NC</th>
<th>RR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen J, J Zhejiang Univ, 2020</td>
<td>14</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>400mg, 5 days</td>
<td>4/15</td>
<td>3/15</td>
<td>1.33 [0.36, 4.97]</td>
<td>33.95</td>
<td>E E E E E VERY LOW</td>
</tr>
<tr>
<td>Tang W, medRxiv, 2020</td>
<td>21</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>1200mg for 3 days, then 800mg, 14 to 21 days</td>
<td>21/70</td>
<td>7/80</td>
<td>3.43 [1.55, 7.58]</td>
<td>66.05</td>
<td>E E E E E VERY LOW</td>
</tr>
</tbody>
</table>

### Risk of bias ratings
- □ = low risk of bias
- □ = some concerns
- ■ = high risk of bias

### Risk of bias domains
- A: Bias arising from the randomization process
- B: Bias due to deviations from intended interventions
- C: Bias due to missing outcome data
- D: Bias in measurement of the outcome
- E: Bias in selection of the reported results

## Serious adverse events D7 (RCTs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>doseT, durationT</th>
<th>rT/NT</th>
<th>rC/NC</th>
<th>RR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen Z, medRxiv, 2020</td>
<td>6</td>
<td>Hydroxychloroquine</td>
<td>Standard care</td>
<td>400mg, 5 days</td>
<td>0/31</td>
<td>0/31</td>
<td>(excluded)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias ratings
- □ = low risk of bias
- □ = some concerns
- ■ = high risk of bias

### Risk of bias domains
- A: Bias arising from the randomization process
- B: Bias due to deviations from intended interventions
- C: Bias due to missing outcome data
- D: Bias in measurement of the outcome
- E: Bias in selection of the reported results

---

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### Serious adverse events D14-D28 (RCTs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>dose T</th>
<th>duration T</th>
<th>rT/NT</th>
<th>rC/NC</th>
<th>RR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang W, medRxiv, 2020</td>
<td>28</td>
<td>Hydroxychloroquine, Standard care</td>
<td>1200mg for 3 days, then 800mg, 14 to 21 days</td>
<td>2/70</td>
<td>0/80</td>
<td>5.70</td>
<td>[0.28, 116.84]</td>
<td>100.00</td>
<td>5.70</td>
<td>[0.28, 116.84]</td>
</tr>
</tbody>
</table>

**Risk of bias ratings**
- ✮ = low risk of bias
- ☐ = some concerns
- ☐☐ = high risk of bias

**Risk of bias domains**
- A: Bias arising from the randomization process
- B: Bias due to deviations from intended interventions
- C: Bias due to missing outcome data
- D: Bias in measurement of the outcome
- E: Bias in selection of the reported results

**Overall risk of bias:** VERY LOW
## Summary of Findings 2: Chloroquine compared to Standard Care for Mild/Moderate/Severe COVID-19

**Patients:** Mild/Moderate/Severe COVID-19  
**Setting:** Worldwide  
**Comparison:** Chloroquine vs Standard Care  
**Study design:** Quasi-experimental studies

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect</th>
<th>Nº of participants &amp; studies</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with Standard Care</td>
<td>Risk with Chloroquine</td>
<td>(95% CI)</td>
<td>Nº of participants &amp; studies</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>All-cause mortality D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time to death</td>
<td>-</td>
<td>-</td>
<td><strong>HR 1.37</strong> (1.22 to 1.53)</td>
<td>83,012 (1 quasi-experimental study)</td>
<td>⬤upiter ⬤upiter LOW²</td>
</tr>
<tr>
<td>Time to intubation/mechanical ventilation or death</td>
<td>-</td>
<td>-</td>
<td><strong>HR 1.58</strong> (1.45 to 1.73)</td>
<td>83,012 (1 quasi-experimental study)</td>
<td>⬤upiter ⬤upiter LOW²</td>
</tr>
<tr>
<td>Incidence of viral negative conversion D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WHO Clinical Progression Score (decrease in 1 point) (i.e., improvement)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Admission in ICU or death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Incidence of WHO progression score (level 6 or above)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Incidence of WHO progression score (level 7 or above)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adverse events D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adverse events D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serious adverse events D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serious adverse events D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Outcome</td>
<td>RR</td>
<td>CI</td>
<td>Event rate</td>
<td>Number of events</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------</td>
<td>--------</td>
<td>------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>QT interval prolongation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time to ventricular arrhythmia</td>
<td>-</td>
<td>-</td>
<td>HR 3.56</td>
<td>83,012</td>
<td>☢☢○○ LOW</td>
</tr>
<tr>
<td>Time to ventricular arrhythmia</td>
<td>-</td>
<td>-</td>
<td>(2.76 to 4.60)</td>
<td>(1 quasi-experimental study)</td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation sudden death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>CI=confidence interval, RR=risk ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group* (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**Explanations**

a. Risk of bias downgraded by 2 levels: moderate risk of bias due to confounding and selection of the reported result; serious risk of bias due to selection of participants and classification of interventions. No information about deviations from intended interventions.
### Forest plots 2: Chloroquine compared to Standard Care for Mild/Moderate/Severe COVID-19

Patients: Mild/Moderate/Severe COVID-19  
Setting: Worldwide  
Comparison: Chloroquine vs Standard Care  
Study design: Quasi-experimental studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Forest plot</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to intubation/mechanical ventilation or death</strong> (quasi-experimental study)</td>
<td></td>
<td>![GRADE Icon] LOW</td>
</tr>
</tbody>
</table>

#### Time to intubation/mechanical ventilation or death

**Forest plot**

**Study** | **Follow-up days** | **Treatment** | **Control** | **HR with 95% CI** | **Weight (%)** | **Risk of bias** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate/severe</td>
<td>-</td>
<td>Chloroquine</td>
<td>Standard care</td>
<td>1.58 [1.45, 1.73]</td>
<td>100.00</td>
<td>![GRADE Icon] ![GRADE Icon] ![GRADE Icon] ![GRADE Icon] ![GRADE Icon] ![GRADE Icon] ![GRADE Icon] ![GRADE Icon]</td>
</tr>
</tbody>
</table>

**Risk of bias ratings**

- ✓ = low risk of bias, ✗ = moderate risk of bias, ☹ = serious risk of bias, ★ = critical risk of bias, ? = No information

**Risk of bias domains**

A: Bias due to confounding  
B: Bias in selection of participants into the study  
C: Bias in classification of interventions  
D: Bias due to deviations from intended interventions  
E: Bias due to missing data  
F: Bias due to measurement of outcomes  
G: Bias in selection of the reported result
Time to death

(quasi-experimental study)

### Risk of bias ratings
- = low risk of bias, = moderate risk of bias, = serious risk of bias, = critical risk of bias, ? = No information

### Risk of bias domains
- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias in selection of the reported result

### Study
Mehra, MR, Lancet, 2020 - Chloroquine Standard care

### Time to death

- Treatment better
- Control better

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>HR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate/severe</td>
<td></td>
<td>Chloroquine</td>
<td>Standard care</td>
<td>1.37 [1.22, 1.63]</td>
<td>100.00</td>
<td>LOW</td>
</tr>
</tbody>
</table>
### Summary of Findings 3: Hydroxychloroquine with a macrolide compared to Standard Care for Mild/Moderate/Severe COVID-19

Patients: Mild/Moderate/Severe COVID-19  
Setting: Worldwide  
Comparison: Hydroxychloroquine with a second-generation macrolide (azithromycin or clarithromycin) vs Standard Care  
Study design: Quasi-experimental studies

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Nº of participants &amp; studies</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with Standard Care</td>
<td>Risk with Hydroxychloroquine + macrolide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>All-cause mortality D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Time to death</td>
<td>-</td>
<td>-</td>
<td><strong>HR 1.45</strong> (1.37 to 1.53)</td>
<td>87,365 (1 quasi-experimental study)</td>
<td><img src="#" alt="GRADE LOW" /> <img src="#" alt="GRADE LOW" /></td>
</tr>
<tr>
<td>Time to intubation/mechanical ventilation or death</td>
<td>-</td>
<td>-</td>
<td><strong>HR 1.45</strong> (1.39 to 1.52)</td>
<td>87,365 (1 quasi-experimental study)</td>
<td><img src="#" alt="GRADE LOW" /> <img src="#" alt="GRADE LOW" /></td>
</tr>
<tr>
<td>Incidence of viral negative conversion D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>WHO Clinical Progression Score (decrease in 1 point) (i.e., improvement)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Admission in ICU or death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Incidence of WHO progression score (level 6 or above)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Incidence of WHO progression score (level 7 or above)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Adverse events D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Adverse events D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Serious adverse events D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Serious adverse events D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>outcome not yet measured or reported</td>
</tr>
<tr>
<td>Outcome</td>
<td>RR (95% CI)</td>
<td>Study Design</td>
<td>Risk of Bias</td>
<td>Outcome Status</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>--------------</td>
<td>-----------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>QT interval prolongation</td>
<td></td>
<td></td>
<td></td>
<td>outcome not yet measured or reported</td>
<td></td>
</tr>
<tr>
<td>Time to ventricular arrhythmia</td>
<td>HR 5.11 (4.36 to 5.98)</td>
<td>1 quasi-experimental study</td>
<td>✰✰✰</td>
<td>Mild/moderate/severe cases Forest plot not shown</td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation sudden death</td>
<td></td>
<td></td>
<td></td>
<td>outcome not yet measured or reported</td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence interval, RR=risk ratio

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations

a. Risk of bias downgraded by 2 levels: moderate risk of bias due to confounding and selection of the reported result; serious risk of bias due to selection of participants and classification of interventions. No information about deviations from intended interventions.
## Forest plots 3: Hydroxychloroquine with a macrolide compared to Standard Care for Mild/Moderate/Severe COVID-19

**Patients:** Mild/Moderate/Severe COVID-19  
**Setting:** Worldwide  
**Comparison:** Hydroxychloroquine with a second-generation macrolide (azithromycin or clarithromycin) vs Standard Care  
**Study design:** Quasi-experimental studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Forest plot</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to intubation/mechanical ventilation or death</strong> (quasi-experimental study)</td>
<td></td>
<td>⬤ ⬤ ⬤ ⬤</td>
</tr>
</tbody>
</table>

**Time to intubation/mechanical ventilation or death**

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>HR with 95% CI</th>
<th>Weight (%)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate/severe</td>
<td>-</td>
<td>Hydroxychloroquine + Azithromycin/Clarithromycin</td>
<td>Standard care</td>
<td>1.45 [1.39, 1.52]</td>
<td>100.00</td>
<td>⬤ ⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
</tbody>
</table>

**Risk of bias ratings**

- green = low risk of bias, yellow = moderate risk of bias, red = serious risk of bias
- yellow = critical risk of bias, grey = no information

**Risk of bias domains**

- A: Bias due to confounding  
- B: Bias in selection of participants into the study  
- C: Bias in classification of interventions  
- D: Bias due to deviations from intended interventions  
- E: Bias due to missing data  
- F: Bias due to measurement of outcomes  
- G: Bias in selection of the reported result  

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### Time to death

A quasi-experimental study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>HR with 95% CI</th>
<th>Weight (%)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehra, MR, Lancet, 2020</td>
<td>-</td>
<td>Hydroxychloroquine + Azithromycin/Clarithromycin</td>
<td>Standard care</td>
<td>1.45 (1.37, 1.53)</td>
<td>100.00</td>
<td>⬤ ⬤ ☠ ☠ ☠ ☠ ☠</td>
</tr>
</tbody>
</table>

**Risk of bias ratings**

- ✡ = low risk of bias
- ✡ = moderate risk of bias
- ☠ = serious risk of bias
- ☠ = critical risk of bias
- ☠ = No information

**Risk of bias domains**

- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias in selection of the reported result

**Overall risk of bias:** LOW
### Summary of Findings 4: Chloroquine with a macrolide compared to Standard Care for Mild/Moderate/Severe COVID-19

**Patients:** Mild/Moderate/Severe COVID-19  
**Setting:** Worldwide  
**Comparison:** Chloroquine with a second-generation macrolide (azithromycin or clarithromycin) vs Standard Care  
**Study design:** Quasi-experimental studies

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Nº of participants &amp; studies</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality D7</td>
<td>Risk with Standard Care</td>
<td>Risk with Chloroquine + macrolide</td>
<td>Relative effect (95% CI)</td>
<td>Nº of participants &amp; studies</td>
<td>Certainty of the evidence (GRADE)</td>
</tr>
<tr>
<td>All-cause mortality D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time to death</td>
<td>-</td>
<td>-</td>
<td>HR 1.37 (1.27 to 1.47)</td>
<td>85,017 (1 quasi-experimental study)</td>
<td>☀ ☀ ☀ ☀ LOW^a</td>
</tr>
<tr>
<td>Time to intubation/mechanical ventilation or death</td>
<td>-</td>
<td>-</td>
<td>HR 1.48 (1.40 to 1.57)</td>
<td>85,017 (1 quasi-experimental study)</td>
<td>☀ ☀ ☀ ☀ LOW^a</td>
</tr>
<tr>
<td>Incidence of viral negative conversion D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WHO Clinical Progression Score (decrease in 1 point)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Admission in ICU or death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Incidence of WHO progression score (level 6 or above)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Incidence of WHO progression score (level 7 or above)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adverse events D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adverse events D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serious adverse events D7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serious adverse events D14-D28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Outcome</td>
<td>RR</td>
<td>95% CI</td>
<td>n</td>
<td>GRADE</td>
<td>Risk of Bias</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------</td>
<td>--------------</td>
<td>-----</td>
<td>-------</td>
<td>--------------</td>
</tr>
<tr>
<td>QT interval prolongation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time to ventricular arrhythmia</td>
<td>-</td>
<td>HR 4.01 (3.34 to 4.81)</td>
<td>85,017</td>
<td>LOW³</td>
<td>Mild/moderate/severe cases Forest plot not shown</td>
</tr>
<tr>
<td>Ventricular fibrillation sudden death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CI=confidence interval, RR=risk ratio

*The risk in the intervention group* (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations

a. Risk of bias downgraded by 2 levels: moderate risk of bias due to confounding and selection of the reported result; serious risk of bias due to selection of participants and classification of interventions. No information about deviations from intended interventions.
### Forest plots 4: Chloroquine with a macrolide compared to Standard Care for Mild/Moderate/Severe COVID-19

Patients: Mild/Moderate/Severe COVID-19  
Setting: Worldwide  
Comparison: Chloroquine with a second-generation macrolide (azithromycin or clarithromycin) vs Standard Care  
Study design: Quasi-experimental studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Forest plot</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to intubation/mechanical ventilation or death (quasi-experimental study)</td>
<td><img src="image" alt="Forest plot" /></td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Forest Plot Details

**Outcome:** Time to intubation/mechanical ventilation or death  
**Follow-up days:** 90  
**Study:** Mild/moderate/severe

#### Risk of Bias Ratings
- A: Bias due to confounding  
- B: Bias in selection of participants into the study  
- C: Bias in classification of interventions  
- D: Bias due to deviations from intended interventions  
- E: Bias due to missing data  
- F: Bias due to measurement of outcomes  
- G: Bias in selection of the reported result

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>HR with 95% CI</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate/severe</td>
<td>Chloroquine + Azithromycin/Clarithromycin</td>
<td>Standard care</td>
<td>1.48 [1.40, 1.57]</td>
<td>100.00</td>
</tr>
</tbody>
</table>

#### Certainty of the Evidence (GRADE)
- ⨁◯◯◯ LOW
### Time to death

(Quasi-experimental study)

#### Risk of bias ratings
- ✭ = low risk of bias
- ★ = moderate risk of bias
- ☢ = serious risk of bias
- ☐ = high risk of bias
- ☐ = No information

#### Risk of bias domains
- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias in selection of the reported result

#### Table: Treatment vs Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up days</th>
<th>Treatment</th>
<th>Control</th>
<th>HR with 95% CI</th>
<th>Weight (%)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate/severe</td>
<td>0</td>
<td>Chloroquine + Azithromycin</td>
<td>Standard care</td>
<td>1.37 [1.27, 1.47]</td>
<td>100.00</td>
<td>⭕</td>
<td>✭</td>
<td>☢</td>
<td>☢</td>
<td>☢</td>
<td>☢</td>
<td>☢</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Graph: Time to death

- Treatment better: 1.27
- Control better: 1.47

- Low risk of bias overall
References

Included RCTs

ChiCTR2000029868


NCT04261517

ChiCTR2000029559

Included quasi-experimental studies


Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. doi:https://doi.org/10.1016/S0140-6736(20)31180-6

Other references


Report Contributors

The protocol and data for this targeted updated comes from the COVID-NMA project led by Cochrane France in collaboration with Cochrane Germany, Cochrane Ireland, the Centre for Evidence-Based Medicine Odense, the Centre of Research Epidemiology and Statistics (Université de Paris, Inserm). This project receives some funding from the ANR (Agence Nationale de la Recherche, France). This report was completed by Cochrane Response (Nicholas Henschke, Gemma Villanueva, Hanna Bergman) with the assistance of Isabelle Boutron (Cochrane France), Anna Chaimani, Theodora Oikonomidi, Nivantha Naidoo, Van Nguyen Thu and the living mapping and living systematic review of COVID-19 studies team (http://covid-nma.com).
Appendix 1. GRADE Working Group grades of evidence

In GRADE, a body of evidence from randomised trials begins with a high-certainty rating while a body of evidence from non-randomised studies of interventions (NRSI) begins with a low-certainty rating. The lower rating with NRSI is the result of the potential bias induced by the lack of randomization (i.e. confounding and selection bias).

However, when using the new Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne 2016), an assessment tool that covers the risk of bias due to lack of randomization, all studies may start as high certainty of evidence (Schünemann 2018). The approach of starting all study designs (including NRSI) as high certainty does not conflict with the initial GRADE approach of starting the rating of NRSI as low certainty evidence. This is because a body of evidence from NRSI should generally be downgraded by two levels due to the inherent risk of bias associated with the lack of randomisation, namely confounding and selection bias.

GRADE assessments of certainty are determined through consideration of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias (see table below).

The overall certainty of the evidence for each outcome can be:

- High certainty: further research is very unlikely to change our confidence in the estimate of effect
- Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: we are very uncertain about the estimate.

<table>
<thead>
<tr>
<th>Reasons for considering downgrading the certainty of the evidence:</th>
<th>Reasons for considering upgrading the certainty of the evidence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations in study design or execution (risk of bias)</td>
<td>If the pooled estimates reveal a large magnitude of effect</td>
</tr>
<tr>
<td>Inconsistency of results</td>
<td>Dose-response gradient</td>
</tr>
<tr>
<td>Indirectness of evidence</td>
<td></td>
</tr>
<tr>
<td>Imprecision</td>
<td></td>
</tr>
<tr>
<td>Publication bias</td>
<td></td>
</tr>
</tbody>
</table>

For further details, see the GRADE handbook and the Cochrane Handbook, Chapter 14. Chapter 14: Completing ‘Summary of findings’ tables and grading the certainty of the evidence.
Appendix 2. Observational studies

Below we provide a narrative summary of observational studies reporting on treatment of COVID-19 with hydroxychloroquine or chloroquine. Only information related to outcomes of mortality, arrhythmia, QT interval prolongation, and ventricular fibrillation sudden death are tabulated. Links to these studies are available from the living systematic review website [http://covid-nma.com](http://covid-nma.com).

<table>
<thead>
<tr>
<th>Study, design, country</th>
<th>Intervention(s)</th>
<th>Participants</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlucci 2020</td>
<td>hydroxychloroquine and azithromycin plus zinc versus hydroxychloroquine and azithromycin alone</td>
<td>932 patients with COVID-19</td>
<td>Expired/Hospice</td>
<td>54/411 (13.1%) in hydroxychloroquine and azithromycin plus zinc group; 119/521 (22.8%) in hydroxychloroquine and azithromycin alone group.</td>
</tr>
<tr>
<td>Chorin 2020</td>
<td>hydroxychloroquine/azithromycin combination</td>
<td>84 adult patients with SARS-CoV-2 infection</td>
<td>Mortality</td>
<td>Four patients died from multi-organ failure, without evidence of arrhythmia and without severe QTc prolongation. 64 patients remained admitted and 16 patients were discharged.</td>
</tr>
<tr>
<td>Gautret 2020</td>
<td>hydroxychloroquine, 600mg, with or without azithromycin vs. controls</td>
<td>42 patients with COVID-19</td>
<td>Mortality</td>
<td>One patient treated with hydroxychloroquine died on day 3</td>
</tr>
<tr>
<td>Kim 2020</td>
<td>hydroxychloroquine plus antibiotics (n = 22), lopinavir-ritonavir plus antibiotics (n = 35), or conservative treatment (n = 40)</td>
<td>270 patients with COVID-19</td>
<td>Mortality</td>
<td>None in the hydroxychloroquine group, none in the other groups</td>
</tr>
<tr>
<td>Million 2020</td>
<td>hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days)</td>
<td>1061 patients with COVID-19</td>
<td>Mortality</td>
<td>8 died (0.75%) (74-95 years old). All deaths resulted from respiratory failure and not from cardiac toxicity.</td>
</tr>
<tr>
<td>Molina 2020</td>
<td>hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2 to 5)</td>
<td>11 patients with severe COVID-19</td>
<td>Mortality</td>
<td>Within 5 days, one patient died</td>
</tr>
</tbody>
</table>
### Rosenberg 2020
**Retrospective cohort**
**USA**
- **Exposures:** both hydroxychloroquine and azithromycin (n=735), hydroxychloroquine alone (n=271), azithromycin alone (n=211), or neither (n=221)
- **Participants:** 1438 patients with COVID-19
- **Outcome:** In-hospital mortality
- **Results:** The probability of death for patients receiving hydroxychloroquine + azithromycin was 189/735 (25.7% [95% CI, 22.3%-28.9%]), hydroxychloroquine alone, 54/271 (19.9% [95% CI, 15.2%-24.7%]), azithromycin alone, 21/211 (10.0% [95% CI, 5.9%-14.0%]), and neither drug, 28/221 (12.7% [95% CI, 8.3%-17.1%]). In adjusted Cox proportional hazards models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving hydroxychloroquine + azithromycin (HR, 1.35 [95% CI, 0.76-2.40]), hydroxychloroquine alone (HR, 1.08 [95% CI, 0.63-1.85]), or azithromycin alone (HR, 0.56 [95% CI, 0.26-1.21]).

### Yu 2020
**Retrospective cohort**
**China**
- **Intervention(s):** hydroxychloroquine (200 mg twice a day for 7–10 days) + basic treatments including antiviral drugs and antibiotics (n=48) vs. basic treatments including antiviral drugs and antibiotics (n=502)
- **Participants:** 550 critically ill COVID-19 patients (on mechanical ventilation)
- **Outcome:** Fatalities
- **Results:** Fatalities are 18.8% (9/48) in HCQ group, which is significantly lower than 47.4% (238/502) in the NHCQ group (P<0.001).

### Arrhythmia

<table>
<thead>
<tr>
<th>Study, design, country</th>
<th>Intervention(s)</th>
<th>Participants</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
</table>
| Kim 2020
Retrospective cohort
South Korea | hydroxychloroquine plus antibiotics (n = 22), lopinavir-ritonavir plus antibiotics (n = 35), or conservative treatment (n = 40) | 270 patients with COVID-19 | tachycardia | One event in the hydroxychloroquine group, none in the other groups |
| Million 2020
Retrospective cohort
France | hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days) | 1061 patients with COVID-19 | rhythmic cardiac events | No rhythmic cardiac events or sudden deaths were observed. |
| Rosenberg 2020
Retrospective cohort
USA | exposures: both hydroxychloroquine and azithromycin (n=735), hydroxychloroquine alone (n=271), azithromycin alone (n=211), or neither (n=221) | 1438 patients with COVID-19 | abnormal electrocardiogram findings, arrhythmia | Abnormal ECG findings were more common among patients receiving hydroxychloroquine + azithromycin and hydroxychloroquine alone, both overall and among those with a record of ECG screening. However, in logistic regression models of abnormal ECG findings, there were no significant differences between the groups. |
## QT interval prolongation

<table>
<thead>
<tr>
<th>Study, design, country</th>
<th>Intervention(s)</th>
<th>Participants</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chorin 2020</strong>&lt;br&gt;Retrospective cohort&lt;br&gt;USA</td>
<td>Hydroxychloroquine/Azithromycin combination</td>
<td>84 adult patients with SARS-CoV-2 infection</td>
<td>change in the QT interval; prolongation of the QTc</td>
<td>In 30% of patients QTc increased by greater than 40ms. In 11% of patients QTc increased to &gt;500 ms, representing high risk group for arrhythmia.</td>
</tr>
<tr>
<td><strong>Mercuro 2020</strong>&lt;br&gt;Retrospective cohort&lt;br&gt;USA</td>
<td>hydroxychloroquine with (n=53) or without azithromycin</td>
<td>90 patients with COVID-19</td>
<td>QTc prolongation</td>
<td>Those receiving concomitant azithromycin had a greater median (interquartile range) change in QT interval (23 [10-40] milliseconds) compared with those receiving hydroxychloroquine alone (5.5 [-15.5 to 34.25] milliseconds; P = .03). Seven patients (19%) who received hydroxychloroquine monotherapy developed prolonged QTc of 500 milliseconds or more, and 3 patients (3%) had a change in QTc of 60 milliseconds or more. Of those who received concomitant azithromycin, 11 of 53 (21%) had prolonged QTc of 500 milliseconds or more and 7 of 53 (13 %) had a change in QTc of 60 milliseconds or more.</td>
</tr>
<tr>
<td><strong>Million 2020</strong>&lt;br&gt;Retrospective cohort&lt;br&gt;France</td>
<td>hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days)</td>
<td>1061 patients with COVID-19</td>
<td>QTc prolongation</td>
<td>Nine patients had a QTc prolongation of more than 60 ms from baseline but no patient exceeded 500 ms, which corresponds to the threshold contraindicating treatment.</td>
</tr>
<tr>
<td><strong>Molina 2020</strong>&lt;br&gt;Case series, consecutive&lt;br&gt;France</td>
<td>hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2 to 5)</td>
<td>11 patients with severe COVID-19</td>
<td>prolongation of the QT interval</td>
<td>In one patient, hydroxychloroquine and azithromycin were discontinued after 4 days because of a prolongation of the QT interval from 405 ms before treatment to 460 and470 ms under the combination.</td>
</tr>
<tr>
<td><strong>Ramireddy 2020</strong>&lt;br&gt;Case series&lt;br&gt;USA</td>
<td>Azithromycin (28%), hydroxychloroquine (10%) or a combination (62%)</td>
<td>490 COVID-19 positive/suspected patients</td>
<td>Critical QTc prolongation (a) maximum QTc ≥500 ms (if QRS &lt;120 ms) or QTc ≥550 (if QRS ≥120 ms) and b) increased QTc of ≥60 ms</td>
<td>Significant prolongation was observed only in men (18±43 ms vs -0.2±28 ms in women, p=0.02). 12% of patients reached critical QTc prolongation. Changes in QTc were highest with the combination compared to either drug, with many-fold greater prolongation with the combination vs. azithromycin alone (17±39 vs. 0.5±40 ms, p=0.07).</td>
</tr>
<tr>
<td><strong>Rosenberg 2020</strong>&lt;br&gt;Retrospective cohort</td>
<td>exposures: both hydroxychloroquine and azithromycin (n=735), hydroxychloroquine</td>
<td>1438 patients with COVID-19</td>
<td>abnormal electrocardiogram findings, QT prolongation)</td>
<td>Abnormal ECG findings were more common among patients receiving hydroxychloroquine + azithromycin and hydroxychloroquine alone, both</td>
</tr>
</tbody>
</table>
Ventricular fibrillation sudden death

<table>
<thead>
<tr>
<th>Study, design, country</th>
<th>Intervention(s)</th>
<th>Participants</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Million 2020 Retrospective cohort France</td>
<td>hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days)</td>
<td>1061 patients with COVID-19</td>
<td>sudden deaths</td>
<td>No rhythmic cardiac events or sudden deaths were observed.</td>
</tr>
<tr>
<td>Rosenberg 2020 Retrospective cohort USA</td>
<td>exposures: both hydroxychloroquine and azithromycin (n=735), hydroxychloroquine alone (n=271), azithromycin alone (n=211), or neither (n=221)</td>
<td>1438 patients with COVID-19</td>
<td>death due to cardiac arrest</td>
<td>Of participants with a known cause of death: 35/118 (29.7%) in hydroxychloroquine + azithromycin group; 14/38 (36.8%) in hydroxychloroquine group; 5/17 (29.4%) in azithromycin group.</td>
</tr>
</tbody>
</table>