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ORIGINAL ARTICLE

Cardiac Toxicity of Chloroquine or Hydroxychloroquine in Patients With COVID-19: A Systematic Review and Meta-regression Analysis

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Abstract

Objective: To systematically review the literature and to estimate the risk of chloroquine (CQ) and hydroxychloroquine (HCQ) cardiac toxicity in patients with coronavirus disease 2019 (COVID-19).

Methods: We searched multiple data sources including PubMed/MEDLINE, Ovid Embase, Ovid EBM Reviews, Scopus, and Web of Science and medrxiv.org from November 2019 through May 27, 2020. We included studies that enrolled patients with COVID-19 treated with CQ or HCQ, with or without azithromycin, and reported on cardiac toxic effects. We performed a meta-analysis using the arcsine transformation of the different incidences.

Results: A total of 19 studies with a total of 5652 patients were included. The pooled incidence of torsades de pointes arrhythmia, ventricular tachycardia, or cardiac arrest was 3 per 1000 (95% CI, 0-21; I^2=96%) in 18 studies with 3725 patients. Among 13 studies of 4334 patients, the pooled incidence of discontinuation of CQ or HCQ due to prolonged QTc or arrhythmias was 5% (95% CI, 1-11; I^2=98%). The pooled incidence of change in QTc from baseline of 60 milliseconds or more or QTc of 500 milliseconds or more was 9% (95% CI, 3-17; I^2=97%). Mean or median age, coronary artery disease, hypertension, diabetes, concomitant QT-prolonging medications, intensive care unit admission, and severity of illness in the study populations explained between-studies heterogeneity.

Conclusion: Treatment of patients with COVID-19 with CQ or HCQ is associated with an important risk of drug-induced QT prolongation and relatively higher incidence of torsades de pointes, ventricular tachycardia, or cardiac arrest. Therefore, these agents should not be used routinely in the management of COVID-19 disease. Patients with COVID-19 who are treated with antimalarials for other indications should be adequately monitored.

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes the coronavirus disease 2019 (COVID-19) has spread across the globe, claiming hundreds of thousands of lives and causing enormous economic losses. Repurposing of approved drugs for the treatment of COVID-19 was a logical approach before the availability of an effective vaccine.

Among the drugs that received early attention were the antimalarial medications chloroquine (CQ) and hydroxychloroquine (HCQ). CQ and HCQ are weak bases that increase the pH of the intracellular vesicles like endosomes.[1] These changes could affect several stages of viral life cycles from cell entry, viral replication, and viral particle assembly to viral particle release from the host cells.[1]

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In addition, these vesicle pH changes interfere with antigen processing and presentation and consequently immune cell activation and production of proinflammatory cytokines.[1] This effect is favorable in the management of autoimmune diseases like systemic lupus erythematosus and may have a favorable impact in patients with COVID-19 with cytokine storm. HCQ was also reported to improve endothelial function and to reverse prothrombotic state,[2] which is relevant to patients with COVID-19 because they manifest pulmonary vascular endothelialitis and microvascular thrombosis.[3]

The successful demonstration of in vitro antiviral properties of CQ and HCQ against SARS-CoV-2 led to initiation of several clinical studies testing the therapeutic potential of CQ and HCQ in COVID-19.[4,5] The early encouraging experience of CQ therapy in 100 patients from China led to its recommendation by the National Health Commission of China.[6,7] Another nonrandomized study of 20 patients with COVID-19 treated with HCQ alone or in combination with azithromycin in France showed reduced nasopharyngeal viral carrier sate at 6 days after the initiation of treatment.[8] Despite its serious methodologic limitations, this report received exceptional attention by media and politicians and triggered a widespread off-label use of CQ and HCQ for COVID-19, with subsequent reports of CQ-related deaths.[9]

Whereas CQ and HCQ are generally considered safe, QT prolongation and torsades de pointes (TdP), ventricular tachycardia as well as other arrhythmias, myocarditis, and cardiomyopathy have been reported with chronic HCQ use.[10-13] Recent reports confirmed the increased risk of QT prolongation among patients with COVID-19.[14,15]

The indiscriminate use of the antimalarial medications for the treatment of COVID-19 in the absence of robust clinical evidence for their efficacy coupled with associated potential harm calls for rigorously conducted systematic reviews and meta-analyses of the available clinical data to present a clearer picture about their safety and efficacy and to provide a data-informed view regarding their utility in the treatment of COVID-19. In this study, we set to systematically review the literature regarding the cardiac toxicity of CQ or HCQ in patients with COVID-19.

METHODS

Inclusion and Exclusion Criteria

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses[16] and Meta-analysis Of Observational Studies in Epidemiology[17] guidelines for reporting systematic review and meta-analysis of observational studies. Studies that reported electrocardiographic changes or cardiac arrhythmias in patients with COVID-19 treated with CQ or HCQ with and without azithromycin were included using prespecified inclusion criteria, as follows: population of patients with COVID-19; the study included more than 10 patients receiving either one of the agents; and electrocardiographic changes or cardiac arrhythmias were reported. To avoid introducing nonindependence by including patients in the analysis more than once, we included results from the same study with the larger sample size if more than one study reported data of overlapping populations of patients.[14]

Literature Search

The literature was searched by a medical librarian for the concepts of CQ or HCQ combined with COVID-19 on several databases including PubMed/MEDLINE, Ovid Embase, Ovid EBM Reviews, Scopus, and Web of Science. The search strategies were created using a combination of keywords and standardized index terms and were run up to May 27, 2020 (Supplement, available online at http://mcpiqojournal.org). We also searched for unpublished manuscripts using the medRxiv in addition to Google Scholar and the references of eligible studies and review articles.

Data Collection and Quality Assessment

Two authors (Z.K., O.A.) independently identified eligible studies, and 4 authors (Z.K., M.G., O.A., H.T.) extracted the data into a prespecified data collection form. We collected data about the study's population and characteristics and different cardiac toxicity end points. A senior author verified all data included in the analyses thrice (T.K.).

The eligible studies were assessed by the Newcastle-Ottawa quality assessment scale according to only 4 parameters relevant to our single-arm meta-analysis (by H.T., O.A., Z.K.): exposure assessment, outcome

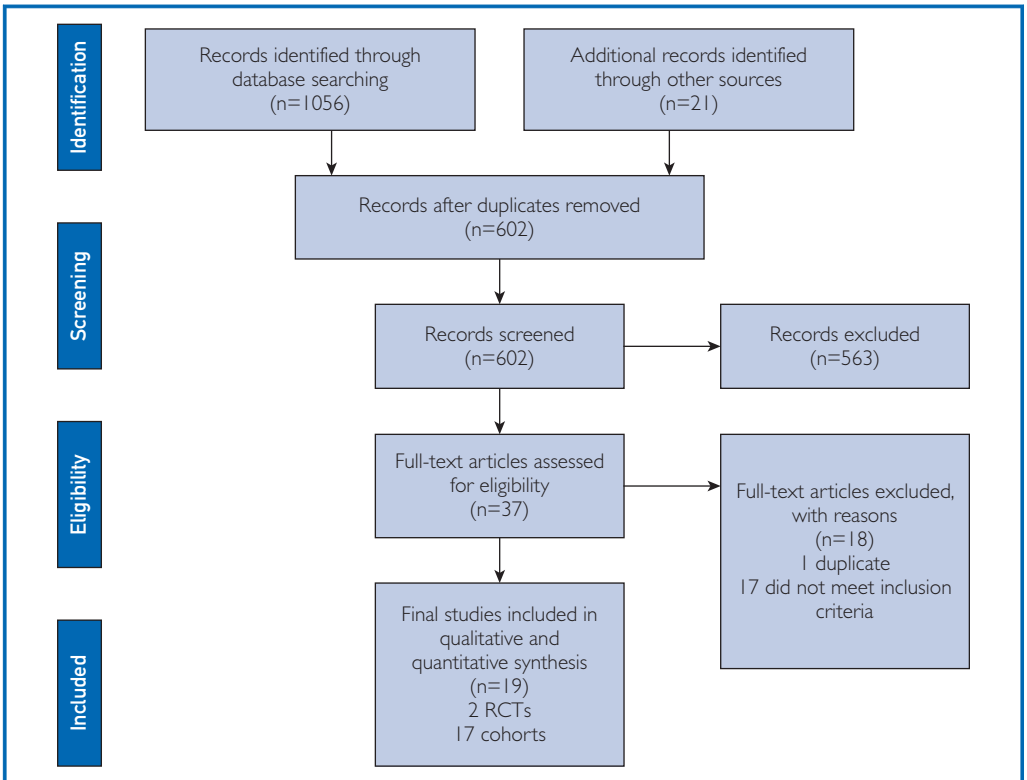

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of eligible studies. RCTs = randomized controlled trials.

assessment, length of follow-up, and loss to follow-up rate.[18]

Study End Points

End points included the incidence of the following: change in QTc interval from baseline of 60 milliseconds or more; QTc of 500 milliseconds or more; composite of change in QTc interval from baseline of 60 milliseconds or more and QTc of 500 milliseconds or more; TdP arrhythmia, ventricular tachycardia, or cardiac arrest; and discontinuation of treatment due to prolonged QT or arrhythmias.

Statistical Analyses

The number and percentage of patients experiencing different end points were extracted from each study. Because of the very low incidence of TdP and other end points (rare events), the arcsine transformation was used to obtain a pooled estimate of the different incidences. For meta-analyses of rare events, this transformation is more appropriate than the commonly used logit transformation as it can accommodate studies with no observed events, without requiring a continuity correction.[19-21] The random effect DerSimonian and Laird model with inverse variance method was used to pool the effect estimates.[22] We evaluated between-studies heterogeneity using the I^2 statistic, which estimates the variability percentage in effect estimates that is due to heterogeneity rather than to chance.

Multiple meta-regression analyses were used to assess whether the incidence of different end points significantly varied by multiple variables specified a priori. These variables were chosen on the basis of risk factors that are known to potentially increase the risk of cardiac arrhythmias (age, sex, coronary artery disease [CAD], congestive heart failure, diabetes mellitus [DM], disease severity, chronic kidney disease, intensive care unit [ICU] admission, and mortality as another surrogate of disease severity).

TABLE 1. Characteristics of Included Studies

Study	Country	Study population	Drugs used	Cardiac toxicity	Monitoring method
Tang et al[24]	China	Hospitalized adult patients with mild to moderate or severe COVID-19 infection based on the fifth version of Chinese guidelines	HCQ 1200 mg daily for 3 days, then 800 mg daily for 2 weeks or 3 weeks	QTc prolongation Cardiac arrhythmia during therapy course	NR
Borba et al[25]	Brazil	Hospitalized adult patients with suspected COVID-19 and respiratory rate >24, heart rate >125, Spo_2 <90% on room air, or shock state	High-dose (total dose, 12 g) or low-dose (total dose, 2.7 g) HCQ for 10 days Azithromycin 500 mg for 5 days	QTc >500 milliseconds or ventricular arrhythmia for 28 days	ECG on days 13 and 28 ECG obtained at clinician's discretion
Perinel et al[26]	France	Hospitalized critically ill patients	HCQ 200 mg 3 times daily for 5 days	NR	NR
Ramireddy et al[38]	United States	Hospitalized patients with COVID-19 who were treated with azithromycin or HCQ	Azithromycin or HCQ	QT prolongation Cardiac arrhythmia during therapy course	Daily ECG
Mahévas et al[27]	France	Hospitalized patients with COVID-19 who received oxygen therapy	HCQ 600 mg daily Duration NR	QTc prolongation Arrhythmia	Daily ECG until 5 days after drug discontinuation
Cipriani et al[39]	France	Hospitalized patients with COVID-19 who were treated with azithromycin and HCQ	HCQ 200 mg twice daily for at least 3 days Azithromycin 500 mg daily	QTc prolongation Arrhythmia	Basal ECG and ECG on day 3 Or 24-hour cardiac monitor for duration of therapy
Chorin et al[14]	United States/Italy	Hospitalized patients with COVID-19 who were treated with azithromycin and HCQ	HCQ 400 mg twice daily on day 1, then 200 mg twice daily for 4 days Azithromycin 500 mg daily	QTc prolongation	Baseline ECG and at least one ECG after drug administration
van den Broek et al[28]	The Netherland	Hospitalized patients with COVID-19 who received respiratory support	Chloroquine 600 mg daily for 5 days	QTc prolongation	Baseline ECG and at least one ECG after drug administration
Saleh et al[29]	United States	Hospitalized patients with COVID-19 who were treated with HCQ ± azithromycin	HCQ ± azithromycin Dose and duration NR	QTc prolongation Arrhythmia	Baseline ECG, then twice-daily ECG or mobile cardiac monitoring
Bessière et al[30]	France	Hospitalized patients with COVID-19 who were admitted to intensive care unit	HCQ 200 mg twice daily for 10 days ± azithromycin 250 mg for 3 days	QTc prolongation	Daily ECG Continuous cardiac monitor

Continued on next page

TABLE 1. Continued

Study	Country	Study population	Drugs used	Cardiac toxicity	Monitoring method
Chang et al[40]	United States	Hospitalized patients with COVID-19 who were treated with HCQ ± azithromycin	HCQ 400 mg twice daily on day 1, then 200 mg twice daily for 4 days ± Azithromycin 500 mg daily	QTc prolongation	Mobile cardiac monitor
Mercuro et al[15]	United States	Hospitalized patients with COVID-19 who were treated with HCQ ± azithromycin	HCQ 400 mg twice daily on day 1, then 200 mg twice daily for 4 days	QTc prolongation	ECG in electronic health records
Ip et al[31]	United States	Hospitalized patients with COVID-19 who were treated with HCQ ± azithromycin	HCQ, azithromycin, or combination Dose and duration NR	QTc prolongation Arrhythmia	ECG in electronic health records
Jain et al[32]	United States	Hospitalized patients with COVID-19	HCQ, dose and duration NR	QTc prolongation	ECG or telemetry monitoring
Million et al[33]	France	Inpatients and outpatients with COVID-19	HCQ 600 mg daily for 10 days Azithromycin 500 mg on day 1, then 250 mg for 4 days	QTc prolongation	Baseline ECG, then ECG on day 2 of treatment
Molina et al[34]	France	Hospitalized patients with COVID-19	HCQ 600 mg daily for 10 days Azithromycin 500 mg on day 1, then 250 mg for 4 days	QTc prolongation	NR
Pereira et al[37]	United States	Hospitalized solid organ transplant patients with COVID-19	HCQ 600 mg twice daily on day 1, then 200 mg twice daily for 4 days Azithromycin 500 mg on day 1, then 250 mg for 4 days	QTc prolongation	Baseline ECG ECG on day 2 or 3 of therapy
Rosenberg et al[35]	United States	Hospitalized patients with COVID-19	HCQ and azithromycin alone or as combination Dose and duration NR	Abnormal ECG (arrhythmia or QT prolongation)	Random ECG screening
Fernández-Ruiz et al[36]	Spain	Hospitalized solid organ transplant patients with COVID-19	HCQ 400 mg twice daily on day 1, then 200 mg twice daily for 4 days	NR	NR

COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; HCQ = hydroxychloroquine; NR = not reported.

TABLE 2. Modified Newcastle-Ottawa Quality Assessment Score[a]

Study	Ascertainment of exposure	Assessment of outcome	Follow-up length	Loss to follow-up rate
Tang et al[24]	1	1	1	1
Borba et al[25]	1	1	1	1
Perinel et al[26]	1	0	0	0
Ramireddy et al[38]	1	1	1	1
Mahévas et al[27]	1	1	1	1
Cipriani et al[39]	1	1	1	1
Chorin et al[14]	1	1	1	1
van den Broek et al[28]	1	1	1	1
Saleh et al[29]	1	1	1	1
Bessière et al[30]	1	1	1	1
Chang et al[40]	1	1	1	1
Mercuro et al[15]	1	1	1	1
Ip et al[31]	1	1	1	1
Jain et al[32]	1	1	1	1
Million et al[33]	1	1	1	1
Molina et al[34]	1	0	1	1
Pereira et al[37]	1	1	1	1
Rosenberg et al[35]	1	1	1	1
Fernández-Ruiz et al[36]	1	0	1	1

[a]A score of 1 means a low risk of bias per the original score of 1 star.

We then performed sensitivity analyses by repeating these analyses after excluding 2 studies that used high-dose CQ or HCQ. Two-tailed *P* values less than .05 were considered to be statistically significant. All statistical analyses were performed using meta and metafor packages in R statistical software, version 3.6.3 (R Foundation for Statistical Computing).[23]

RESULTS

Included Studies

A total of 19 studies with a total of 5652 patients, including single-center and multicenter studies, were included in our systematic review.[14,15,24-40] Figure 1 shows the result of our search strategy. A total of 1077 records were identified; 475 were excluded because they were duplicates, and 565 records were further excluded because they were irrelevant (reviews, letters, basic science). The remaining 37 studies were fully reviewed, of which 18 studies were excluded (1 duplicate and 17 did not meet inclusion criteria). Table 1 illustrates the general characteristics of the included studies. All included studies were of high methodologic quality in terms of exposure ascertainment or outcome assessment (Table 2). Several important cardiovascular adverse events have been observed in our meta-analysis. However, reported cardiovascular adverse events varied among the included studies; therefore, we were able to include some events in the quantitative meta-analysis, whereas other events were included only in the synthesized systematic review because of insufficient data.

Rosenberg et al[35] reported the incidence of any arrhythmia (unspecified) in 19.3% and cardiac arrest in 15% of their cohort of 1006 patients who received HCQ alone or in combination with azithromycin. Nonsustained ventricular tachycardia was reported by 6 studies and was encountered in 0% to 5% of patients treated with CQ or HCQ. On the other hand, sustained ventricular tachycardia was described by 9 studies in 0% to 2.7% of patients. Only two investigators reported about new-onset atrial fibrillation; it was detected

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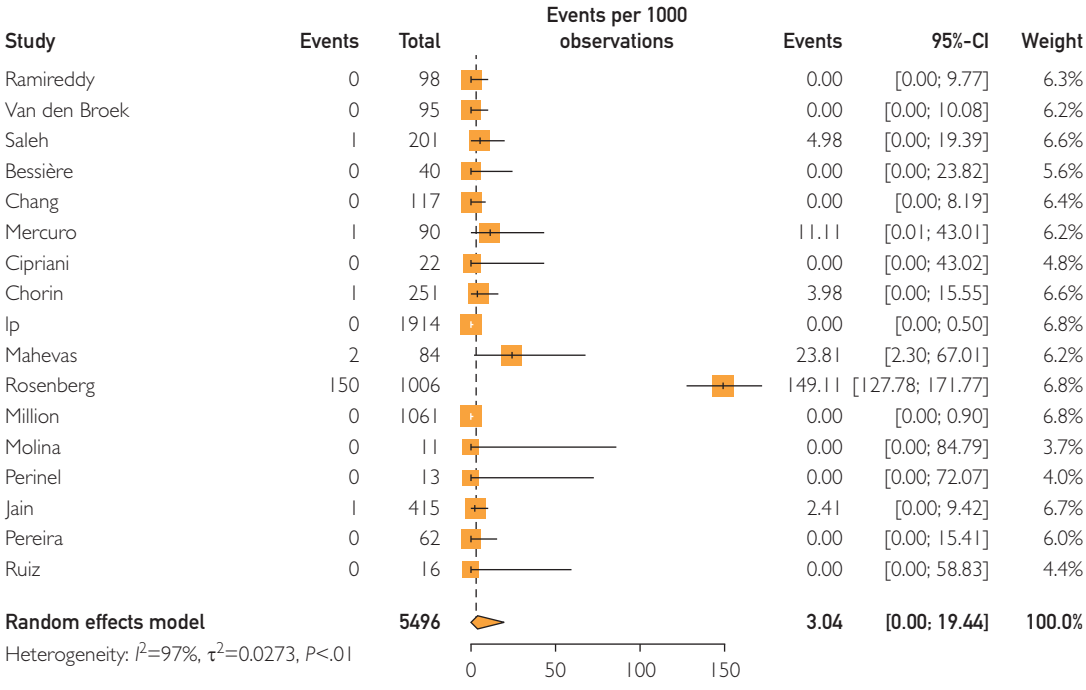

FIGURE 2. Forest plot of the pooled incidence of torsades de pointes, ventricular tachycardia, or cardiac arrest.

in 12.8% of patients by Chang et al[40] and in 8.5% by Saleh et al.[29]

Four studies reported on conduction abnormalities, which developed in 1% to 3.4% of their patients. Moreover, 2 studies observed acute cardiac injury, defined as elevated troponin levels in 27.8%[15] and as elevated cardiac-specific creatine kinase (CK-MB isoenzyme) in 31.8%.[25] In the last study, it was noted that the CK-MB elevation was higher in the high CQ dose in comparison with the lower dose (50% vs 31.6%).[25] Acute myocardial infarction (MI) was reported by 2 studies. Ramireddy et al[38] observed acute MI in 17% of their patients, and Mercuro et al[15] identified acute MI in 1 patient of their cohort of 90 patients. Acute myocarditis was observed by Saleh et al[29] in 1 patient (0.5%) and by Borba et al[25] in 2 patients (8.6%).

Meta-analysis Results

TdP tachycardia, ventricular tachycardia, and cardiac arrest events were observed in 156 patients in 17 studies with a total of 3725 patients. The pooled incidence of these events was 3 per 1000 (95% CI, 0-21; I^2=96%; Figure 2). However, only 2 episodes of TdP tachycardia were reported among 2719 patients. The pooled incidence of discontinuation of CQ or HCQ due to prolonged QTc or arrhythmias was 5% (95% CI, 1-11; I^2=98%) among 4334 patients from 13 studies (Figure 3). Among 11 studies with 3127 patients, the pooled incidence of change in QTc from baseline of 60 milliseconds or more or QTc of 500 milliseconds or more was 9% (95% CI, 3-17; I^2=97%; Figure 4). In 12 studies of 2008 patients, the pooled incidence of change in QTc from baseline of 60 milliseconds or more was 7% (95% CI, 3-14; I^2=94%; Figure 5). Furthermore, the pooled incidence of QTc of 500 milliseconds or more was 6% (95% CI, 2-12; I^2=95%) from 16 studies with 2317 patients (Figure 6). Visual inspection of all funnel plots did not show asymmetry consistent with absence of publication bias (Supplemental Figures 1 to 3, available online at http://mcpiqojournal.org).

Exploring Heterogeneity

We performed multiple meta-regression analyses to identify factors associated with the

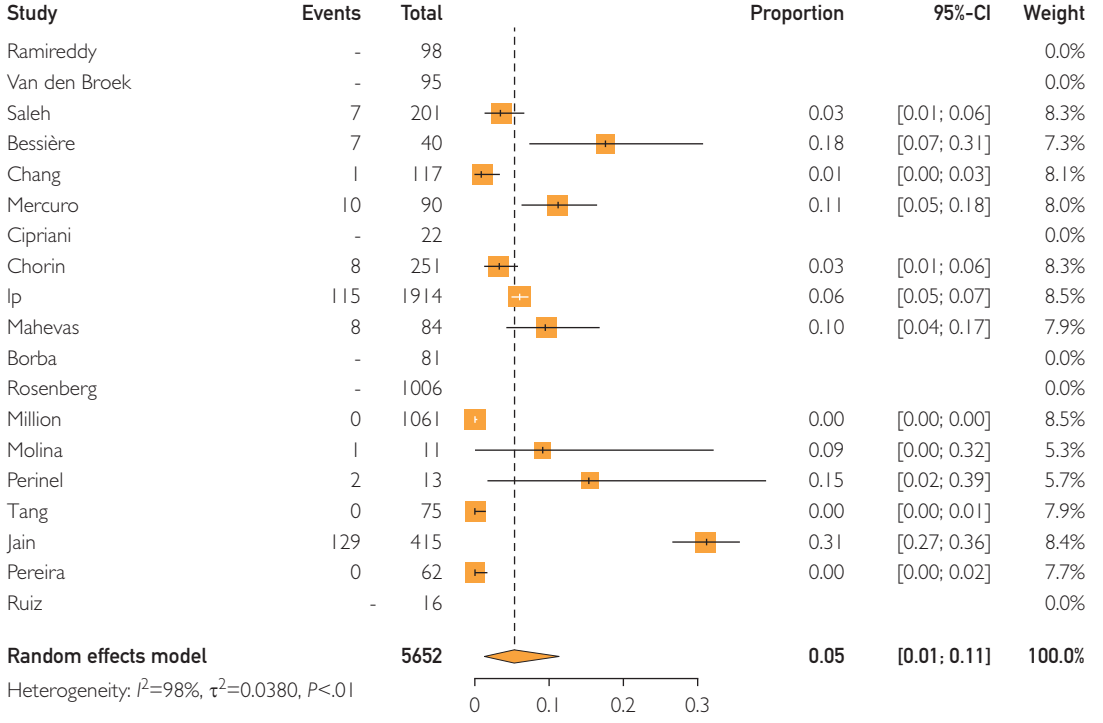

FIGURE 3. Forest plot of the pooled incidence of discontinuation of chloroquine or hydroxychloroquine due to prolonged QTc or arrhythmias.

observed heterogeneity. For TdP arrhythmia, ventricular tachycardia, or cardiac arrest, the prevalence of concomitant QT-prolonging medication use in the included studies was associated with the observed heterogeneity. Regarding discontinuation due to prolonged QTc or arrhythmias, age, CAD, and DM were associated with heterogeneity. For the change in QTc from baseline of 60 milliseconds or more and QTc of 500 milliseconds or more, age, CAD, and hypertension and ICU admission or illness severity were associated with heterogeneity. Finally, age, CAD, hypertension, concomitant QT-prolonging medications, ICU care, and severity of illness were associated with the observed heterogeneity for the change in QTc from baseline of 60 milliseconds or more or QTc of 500 milliseconds or more.

Sensitivity Analysis

After excluding the 2 studies that used high-dose CQ or HCQ,[24,25] we did not observe an important change in pooled estimates or associated heterogeneity.

DISCUSSION

In this meta-analysis, we systematically examined the risk of QTc prolongation and its associated complications in patients with COVID-19 treated with the antimalarial medications CQ and HCQ. The majority of studies included in this analysis used HCQ alone or in combination with azithromycin. Our analysis revealed treatment with CQ or HCQ to be associated with a clinically important increased risk of QTc prolongation and discontinuation of drug due to this risk. In addition, CQ or HCQ was associated with a clinically important risk of TdP, ventricular tachycardia, or cardiac arrest of 3 per 1000 (95% CI, 0.0-21).

The incidence of critical QTc prolongation, defined as QTc of 500 milliseconds or more or change in QTc of 60 milliseconds or more, ranged from 0% to 36%. One of the most remarkable findings is that in the study by Bessière et al,[30] 93% of the studied 40 patients exhibited an increase in QTc prolongation and 36% had critical QTc prolongation.

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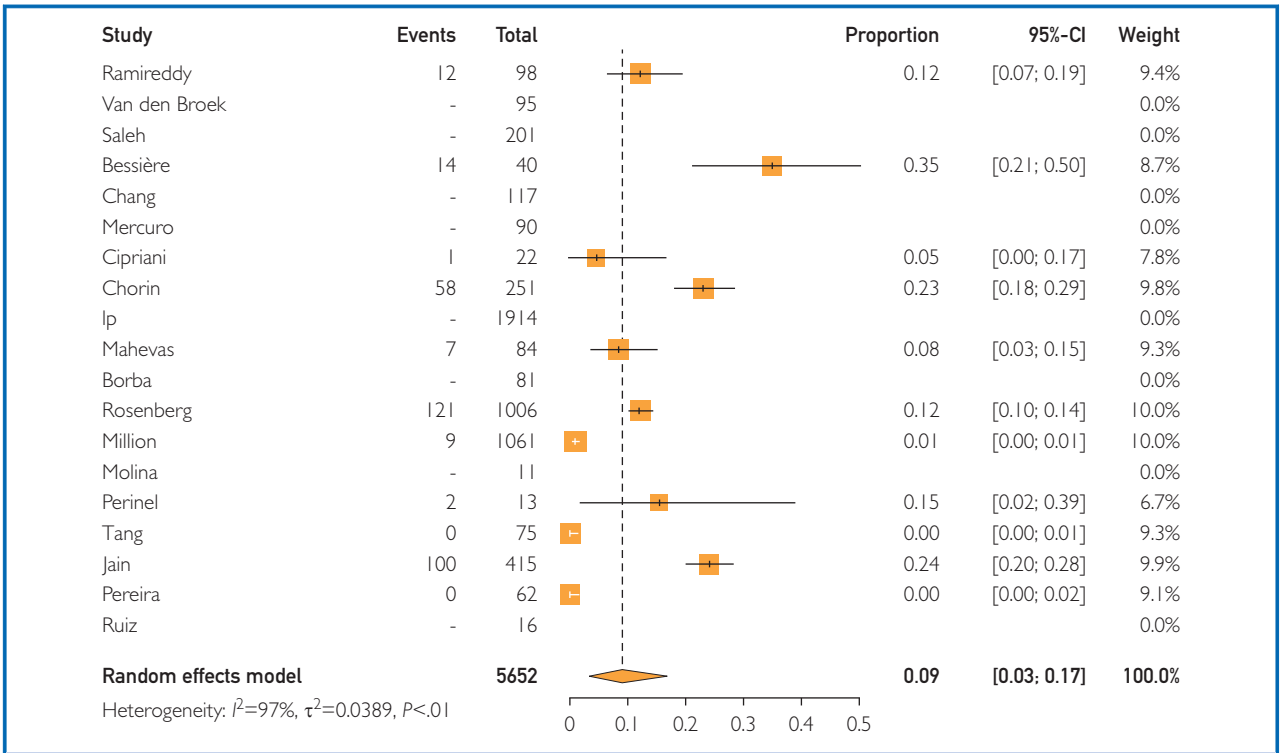

FIGURE 4. Forest plot of the pooled incidence of change in QTc from baseline of 60 milliseconds or more or QTc of 500 milliseconds or more.

In our pooled analysis, critical QTc prolongation ranged between 6% and 9% with marked heterogeneity among the studies (I^2 of up to 98%). Several factors that contributed to the observed heterogeneity were identified by the meta-regression analysis. These include age, hypertension, CAD, ICU admission, DM, use of other QTc-prolonging agents, and COVID-19 disease severity. These factors are concordant with the biologic explanation for the observed differences as it is well known that underlying cardiac conditions, comorbidities, and inflammatory states increase the risk of drug-induced QTc prolongation.[41,42]

This meta-analysis revealed low but clinically important risk of the combined end point of TdP, ventricular tachycardia, and cardiac arrest. However, we could not perform a meta-analysis on TdP separately because there were only 2 reported cases of TdP among 2719 patients from 16 studies (0.073%). The low incidence of TdP is probably an underestimate. A number of factors can explain this low incidence of TdP; most important are the precautionary discontinuation of the drugs when QTc reaches a certain threshold (QTc ≥500 milliseconds or ΔQTc ≥60 milliseconds), short duration of therapy, and, in certain instances, the therapeutic intervention for long QT using QT-shortening agents as reported by Saleh et al,[29] for example. Indeed, in our pooled analysis, 5% of patients had their medication discontinued because of QTc prolongation, and in the study by Jain et al,[32] 30% of patients had CQ or HCQ discontinued because of QTc prolongation. Moreover, some TdP cases could have been missed because of underreporting or misclassification. In fact, the 2 largest studies in this meta-analysis did not specifically include TdP as a separate end point but grouped all arrhythmias under 1 category. The study by Rosenberg et al[35] observed arrhythmias in 19.3% and cardiac arrest in 15% of patients, and it is possible that some of these arrhythmias were TdP or some of the cardiac arrests were preceded by TdP.

Nonetheless, the incidence of TdP reported here is consistent with the published data on the drug-induced TdP. The risk for development of TdP in association with

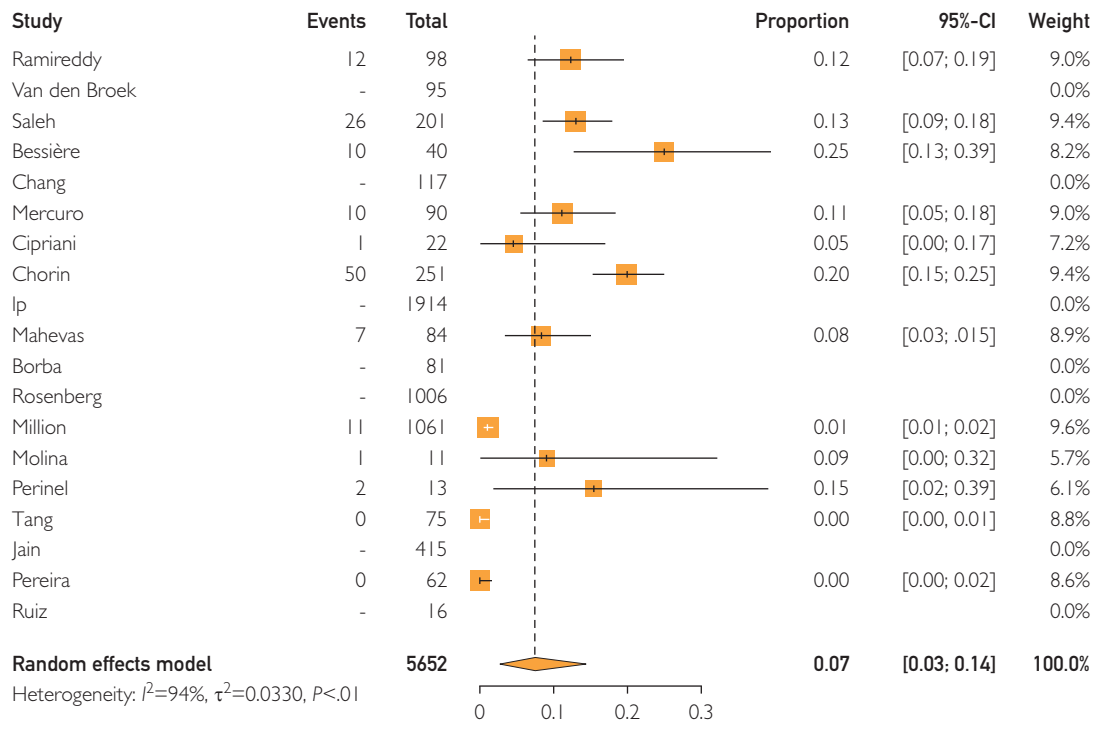

FIGURE 5. Forest plot of the pooled incidence of change in QTc from baseline of 60 milliseconds or more.

non-antiarrhythmic drugs is relatively low; for instance, the risk for cisapride, which has been removed from the market, was 0.001%.[43] The risk of TdP with other non-antiarrhythmic drugs is in the range of that reported with cisapride. The incidence of TdP observed in this meta-analysis (0.073%) is 73-fold higher than that of cisapride. Cisapride and terfenadine (a nonsedating antihistamine) were taken off the market because of the risk of TdP, even though the risk of TdP associated with their use in absolute terms was very low. This underscores the importance of taking into account the total number of potential lethal events rather than the expressed ratios in assessing the risk of drug-induced arrhythmias. It is also well known that the highest risk for drug-induced QT prolongation and TdP is associated with class III antiarrhythmic drugs, which ranges between 1% and 3% during 1 to 2 years.[44] The risk of TdP with sotalol therapy at a low daily dose of 80 mg is only 0.3%.[45] This risk is much higher than the observed risk with CQ and HCQ in this study; however, the estimated risk reported for the antiarrhythmic drugs was during long-term use of 1 to 2 years as opposed to the risk reported here for CQ and HCQ during a short-term use. In fact, this further increases the concern about the cardiac risk associated with CQ and HCQ treatment in COVID-19 disease.

A number of other cardiac adverse events documented in the included studies were not negligible and include myocardial injury, acute MI, myocarditis, and others. Notwithstanding, a cause and effect relationship between CQ or HCQ exposure and these complications cannot be inferred from these studies. However, in the study by Borba et al,[25] the incidence of acute cardiac injury was higher in the high-dose CQ group in comparison with low-dose CQ (50% vs 31.6%), and the 2 patients with sustained ventricular tachycardia also were in the high-dose CQ group, which could imply a dose-response relationship and probable cause and effect link. In a meta-analysis of HCQ effects on the cardiovascular system, ventricular hypertrophy was noted in 22% of patients, whereas heart failure was noted in 26.8% of patients.[46]

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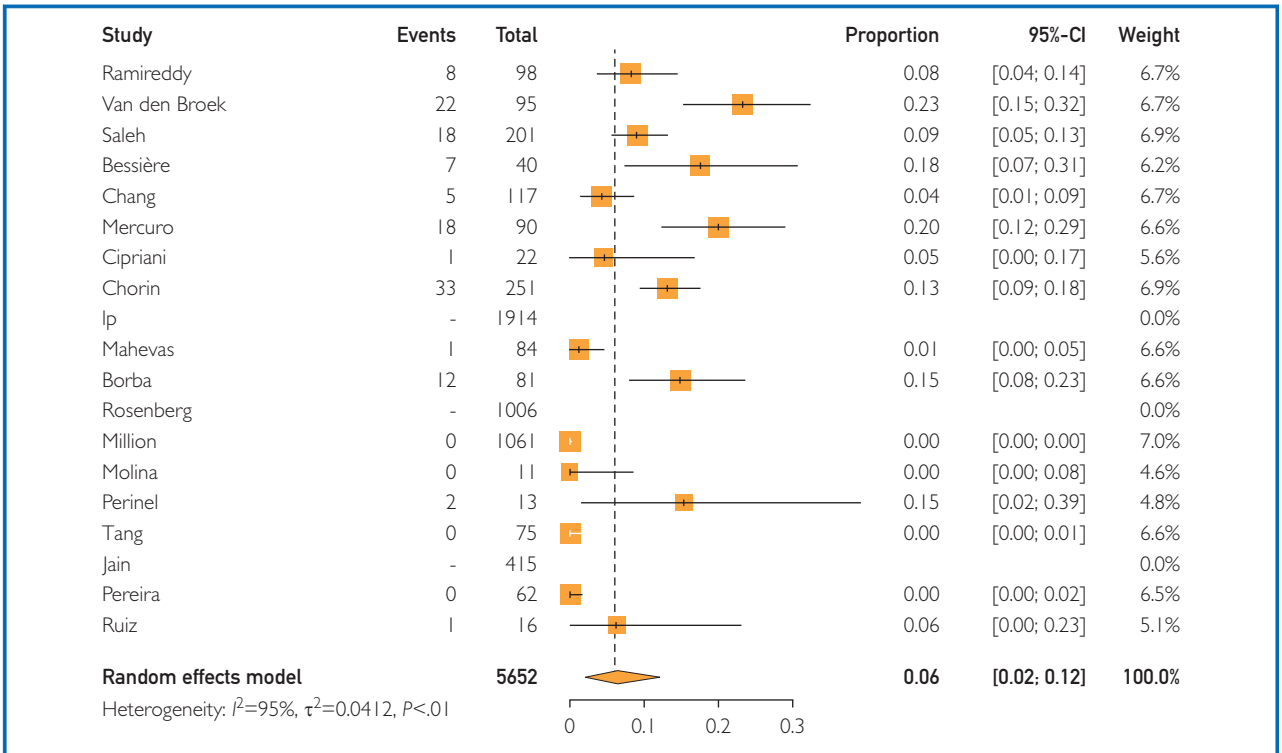

FIGURE 6. Forest plot of the pooled incidence of QTc of 500 milliseconds or more.

It has been a common practice to use HCQ in combination with azithromycin for COVID-19 during the current pandemic. Azithromycin has been identified as a potential cause of serious cardiac arrhythmias through mechanisms dependent on and independent of QT prolongation and has been linked to increased risk of sudden cardiac death.[47,48] Hence, the concomitant use of CQ or HCQ and azithromycin or other QT-prolonging agents could potentially increase the risk of serious cardiac arrhythmias and death, particularly in critically ill patients or those with risk factors for QT prolongation.

Our findings indicate that the cardiac risk imposed by CQ or HCQ use in COVID-19 disease is not trivial and support the need for close monitoring of patients with COVID-19 who are treated with CQ or HCQ alone or in combination with azithromycin. Because their efficacy in improving the outcomes of patients with COVID-19 is lacking, these agents should be used only in the context of randomized clinical trials, given the potential harm that could be associated with their widespread use. This position is supported by the recent Food and Drug Administration statement.[49]

Strength and Limitations

Our meta-analysis is the first comprehensive systematic review examining the risk of QT prolongation and its associated adverse events in patients with COVID-19 treated with CQ or HCQ. However, like any meta-analysis, it has several limitations. First, because of the retrospective nature of most of the included studies, they are likely to have incomplete or missing data. Second, there were variations in the variables collected by individual studies particularly related to reporting of QTc parameters and adverse events and differences in the populations of patients enrolled by these studies. Third, there was marked heterogeneity in our pooled estimates; however, we performed a meta-regression that allowed us to identify contributors to the observed heterogeneity and to determine populations at risk for CQ- or HCQ-induced QT prolongation, which further strengthens our study and its conclusions.

Conclusion

Our meta-analysis indicates that the treatment of patients with COVID-19 with CQ or HCQ alone or in combination with azithromycin is associated with an important risk of drug-induced QT prolongation. CQ or HCQ use resulted in a relatively higher incidence of TdP compared with drugs withdrawn from the market for this particular adverse effect. Therefore, these agents should not be used routinely in the treatment of COVID-19 disease. Patients with COVID-19 who are treated with antimalarials for other indications should be adequately monitored.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CAD** = coronary artery disease; **COVID-19** = coronavirus disease 2019; **CQ** = chloroquine; **DM** = diabetes mellitus; **HCQ** = hydroxychloroquine; **ICU** = intensive care unit; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **TdP** = torsades de pointes

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