Drugs - Real World Outcomes (2022) 9:231–241
https://doi.org/10.1007/s40801-022-00300-y

ORIGINAL RESEARCH ARTICLE

Serious Cardiovascular Adverse Events Associated with Hydroxychloroquine/Chloroquine Alone or with Azithromycin in Patients with COVID-19: A Pharmacovigilance Analysis of the FDA Adverse Event Reporting System (FAERS)

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Accepted: 12 March 2022 / Published online: 6 April 2022

Abstract

Background The use of hydroxychloroquine or chloroquine (HCQ/CQ) as monotherapy or combined with azithromycin for the treatment of coronavirus disease 2019 (COVID-19) may increase the risk of serious cardiovascular adverse events (SCAEs).

Objective Our objective was to describe and evaluate the risk of SCAEs with HCQ/CQ as monotherapy or combined with azithromycin compared with that for therapeutic alternatives.

Methods We performed a disproportionality analysis and descriptive case series using the US FDA Adverse Event Reporting System.

Results Compared with remdesivir, HCQ/CQ was associated with increased reporting of SCAEs (reporting odds ratio [ROR] 2.1; 95% confidence interval [CI] 1.8–2.5), torsade de pointes (TdP)/QTc prolongation (ROR 35.4; 95% CI 19.4–64.5), and ventricular arrhythmia (ROR 2.5; 95% CI 1.6–3.9); similar results were found in comparison with other therapeutic alternatives. Compared with lopinavir/ritonavir, HCQ/CQ was associated with increased reporting of ventricular arrhythmia (ROR 10.5; 95% CI 3.3–33.4); RORs were larger when HCQ/CQ was used in combination with azithromycin. In 2020, 312 of the 575 reports of SCAEs listed concomitant use of HCQ/CQ and azithromycin, including QTc prolongation (61.4%), ventricular arrhythmia (12.0%), atrial fibrillation (8.2%), TdP (4.9%), and cardiac arrest (4.4%); 88 (15.3%) cases resulted in hospitalization and 79 (13.7%) resulted in death. In total, 122 fatal QTc prolongation-related cardiovascular reports were associated with 1.4 times higher odds of reported death than those induced by SCAEs; 87 patients received more than one QTc-prolonging agent.

Conclusions Patients treated with HCQ/CQ monotherapy or HCQ/CQ + azithromycin may be at increased risk of SCAEs, TdP/QTc prolongation, and ventricular arrhythmia. Cardiovascular risks need to be considered when evaluating the benefit/harm balance of treatment with HCQ/CQ, especially with the concurrent use of QTc-prolonging agents and cytochrome P450 3A4 inhibitors when treating COVID-19.

1 Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; coronavirus disease 2019 [COVID-19]) pandemic has lasted for more than 2 years, and the number of cumulative confirmed cases continues to grow, with an increasing trend that has led to the worst modern global emergency [1]. As of early March 2022, a total of 435,501,000 confirmed COVID-19 cases had been diagnosed and more than 5,950,000 deaths had occurred worldwide [1]. Since the publication of an uncontrolled French study suggesting the combination of hydroxychloroquine (HCQ) and azithromycin may be effective for COVID-19, this regimen has been widely used despite controversy over its efficacy and safety [2]. The US FDA issued an Emergency Use Authorization (EUA) for the use of HCQ and

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Key Points

Hydroxychloroquine or chloroquine (HCQ/CQ) as monotherapy or in combination with azithromycin was associated with increased reporting of serious cardiovascular adverse events, TdP/QTc prolongation, and ventricular arrhythmia. HCQ/CQ–azithromycin combination therapy was associated with higher reporting odds of cardiovascular events than was HCQ/CQ monotherapy.

Concurrent use of HCQ/CQ and QTc-prolonging agents or cytochrome P450 3A4 inhibitors may increase the odds of serious cardiovascular adverse events.

Cardiovascular risks need to be considered when evaluating the benefit/harm balance of the use of HCQ/CQ as monotherapy or in combination with azithromycin, especially when treating vulnerable patients with coronavirus disease 2019.

chloroquine (CQ) for the treatment of COVID-19 on the basis of limited results, which partly contributed to the substantial use of these drugs during the early months of the pandemic in March and April 2020 [3, 4]. Randomized trials [5, 6] and observational studies [7–9] have reported that HCQ/CQ monotherapy or HCQ/CQ–azithromycin combination therapy was not associated with improved clinical outcomes for COVID-19 and that it posed serious cardiovascular safety risks, especially QTc prolongation and torsade de pointes (TdP) [10]. Although the FDA issued an alert in April 2020 cautioning against the use of HCQ outside hospital or clinical trial settings [11], revoked the EUA on June 15, 2020 [12], and issued COVID-19 treatment guidelines recommending against the use of HCQ/CQ with or without azithromycin to treat COVID-19 [13], prescribing of these agents remained elevated through October 2020 [4]. Although the evidence for patient benefit remain inconsistent [14–16], HCQ/CQ and azithromycin use in COVID-19 may persist because of a lack of identified treatments.

Similarly, current evidence regarding cardiovascular adverse effects is conflicting across studies [14, 15]. Because randomized trials assessing rare drug adverse events, such as serious cardiovascular adverse events (SCAEs), may be underpowered, pharmacovigilance studies may be valuable for early evidence generation in large, real-world populations [17]. One pharmacovigilance study using the US FDA Event Reporting System (FAERS) and disproportionality analysis evaluated the safety of HCQ/CQ + azithromycin in case reports from before the COVID-19 pandemic through the first quarter of 2020 [18]. In this study, case reports of HCQ-induced SCAEs before and during COVID-19 were found to be significantly different because of the changes in patient characteristics, comorbid conditions, effects of drug interactions, and possible modifications to drug pharmacokinetics in patients with COVID-19 [19, 20]. Another disproportionality analysis, conducted by Diaby et al. [21], evaluated QTc prolongation and TdP with HCQ/CQ monotherapy or HCQ/CQ + azithromycin for COVID-19 from December 2019 to the second quarter of 2020 [21]; however, the sample size of patients with COVID-19 was relatively limited. Considering the increased use of HCQ, CQ, and azithromycin, even after revocation of the HCQ EUA and after the reporting of new safety profiles for these agents in patients with COVID-19, reevaluation of SCAE risk is needed.

In this study, we reviewed the reported cases of serious cardiovascular events associated with HCQ/CQ and azithromycin in the FAERS database to summarize case characteristics and to evaluate SCAE reporting associated with combination therapy for COVID-19.

2 Methods

2.1 Data Sources and Study Design

We used the FAERS data files from Q1/2020 through Q4/2020, using both brand and generic names (Table S1 in the electronic supplementary material [ESM]) to identify intervention and comparator drugs. We included only case reports with a COVID-19 diagnosis. The primary outcome was SCAEs, which were defined as a composite endpoint based on previous literature [22–24], including cardiac arrest, ventricular arrhythmia, atrial fibrillation, bradyarrhythmia, QTc prolongation, myocardial infarction, stroke, cardiac failure, coronary ischemia, and TdP. COVID-19 and SCAEs were identified using Medical Dictionary for Regulatory Activities (MedDRA version 23.0) preferred terms (Table S2 in the ESM). We included all types of reporting (primary suspect, secondary suspect, concomitant, and interacting) in our analysis and excluded duplicates.

We designed eight comparison groups to estimate the SCAEs associated with HCQ in patients with COVID-19:

1. HCQ/CQ + azithromycin versus HCQ/CQ + amoxicillin
2. HCQ/CQ + azithromycin versus HCQ/CQ
3. HCQ/CQ + azithromycin versus lopinavir/ritonavir
4. HCQ/CQ + azithromycin versus remdesivir
5. HCQ/CQ + azithromycin versus all other drugs except for HCQ/CQ, azithromycin, lopinavir/ritonavir, and remdesivir (e.g., insulin, simvastatin, etc.)
6. HCQ/CQ versus lopinavir/ritonavir
7. HCQ/CQ versus remdesivir
8. HCQ/CQ versus all other drugs.

Therapeutic alternatives were selected as comparison drugs. Amoxicillin was chosen as a comparator antibiotic because of its shared indications with azithromycin and because it has not been shown to have adverse cardiovascular effects [25]. Lopinavir/ritonavir and remdesivir were chosen as comparators as they are likely used to treat patients with COVID-19 [13]. Comparison 2 and comparisons 6–8 were designed to evaluate the hypothesis that combined therapy is associated with increased SCAE reporting compared with monotherapy of HCQ/CQ.

Secondary outcomes included SCAE components related to QTc prolongation: TdP/QTc prolongation, ventricular arrhythmia, and cardiac arrest. We also assessed TdP/QTc prolongation events using the broad standardized MedDRA queries (SMQ) preferred terms (Table S3 in the ESM) to reduce the probability of missing potential TdP events (i.e., exclude the possibility that clinicians may report a more serious, final outcome, e.g., death, rather than TdP/QTc prolongation).

We performed subgroup analyses for (1) a subpopulation aged > 65 years and (2) a subpopulation with other concomitant QTc-prolonging drugs (as shown in Table 1) for two comparisons: (1) HCQ/CQ + azithromycin versus remdesivir and (2) HCQ/CQ + azithromycin versus lopinavir/ritonavir.

2.2 Case Extraction

Because recent literature and guidelines [26–28] have shown that HCQ/CQ + azithromycin combination therapy is more likely to be associated with increased SCAEs, we further retrieved each case report of SCAE listing the use of HCQ/CQ + azithromycin. The following details were extracted: age, sex, weight, dose and frequency, duration of therapy, concurrent QTc-prolonging medications that may induce SCAEs, other comedications, precipitating factors [29], type of SCAE, and outcome. MedDRA terms used to identify diseases are provided in Table S4 in the ESM, and generic/brand names to identify concomitant QTc-prolonging medications that may induce SCAEs are provided in Table S5 in the ESM. Additionally, we extracted case reports of fatal QTc prolongation-related cardiovascular events (TdP, cardiac arrest, and ventricular arrhythmia) from January 1, 2020, to December 31, 2020, related to HCQ/CQ use with or without azithromycin in patients with COVID-19 [2].

2.3 Statistical Analysis

We performed a disproportionality analysis using the reporting odds ratio (ROR) to assess whether the combined use of HCQ/CQ monotherapy or HCQ/CQ + azithromycin was associated with an increased reporting frequency of SCAEs. The ROR is calculated by dividing the odds of a SCAE reported for the drug of interest by the odds of a SCAE reported for the comparison drugs using two-by-two contingency tables of unique event counts [30]. A detailed description of the method is shown in Table S6 in the ESM. We defined a significant signal of increased SCAE reporting as having a ROR ≥ 2, Chi-squared test statistic ≥ 4, and five or more cases [30, 31]. Data management and analysis were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3 Results

3.1 Disproportionality Analysis

A total of 575 SCAE cases were reported with HCQ or CQ from Q1/2020 through Q4/2020; 312 were reports involving HCQ/CQ + azithromycin. For primary analyses, the RORs (95% confidence interval [CI]) were > 2 when comparing case reports listing HCQ/CQ ± azithromycin with those listing remdesivir or other medications for treating COVID-19 (Fig. 1; Table S7 in the ESM); therefore, SCAEs were reported more often in case reports listing HCQ/CQ ± azithromycin than in reports listing these comparators. When comparing case reports listing HCQ/CQ and those listing lopinavir/ritonavir—another medication with a potential risk of SCAE—there was a weak signal of increased SCAE reporting (ROR 1.6; 95% CI 1.3–2.0). For combination therapy of HCQ/CQ + azithromycin versus HCQ/CQ monotherapy, a weak signal for SCAE was observed (ROR 1.7; 95% CI 1.4–2.0). Additionally, when we only included case reports identified by HCQ/CQ + azithromycin, the RORs were larger than comparisons without combination use (Fig. 1; Table S7 in the ESM).

For TdP/QTc prolongation, the RORs for each comparison were greater than those for primary analyses. Notably, RORs for HCQ/CQ versus remdesivir and HCQ/CQ + azithromycin versus remdesivir were more than ten times larger than those in the primary analysis (Fig. 1; Table S7 in the ESM). When using the broad SMQ terms, results were similar to those observed in primary analyses. For ventricular arrhythmia, a strong signal for increased risk was observed for both HCQ/CQ monotherapy and HCQ/CQ + azithromycin, especially when compared with lopinavir/ritonavir (ROR 10.5 [95% CI 3.3–33.4] for HCQ/CQ monotherapy; ROR 15.0 [95% CI 6.4–35.2] for HCQ/CQ + azithromycin) and other medications treating COVID-19. Adverse event reports with HCQ/CQ monotherapy and HCQ/CQ + azithromycin were not associated with increased reporting of cardiac arrest. Analysis results are summarized in Fig. 1 and in Table S7 in the ESM.

In the older subpopulation (aged >65 years), the ROR (1.7 [95% CI 1.3–2.2]) for HCQ/CQ + azithromycin versus lopinavir/ritonavir were similar to those in the primary

Table 1 Descriptive characteristics of serious cardiovascular adverse events case reports listing the use of hydroxychloroquine/chloroquine monotherapy and hydroxychloroquine/chloroquine + azithromycin combination therapy in COVID-19 cases reported to FAERS from January 1, 2020, to December 31, 2020

Characteristics	HCQ/CQ + azithromycin ($N = 312$)	HCQ/CQ monotherapy ($N = 263$)	Total ($N = 575$)
Age, years	229 reported	208 reported	437 reported
Mean ± SD	64.1 ± 14.7	63.7 ± 20.1	63.9 ± 17.7
Sex	230 reported	213 reported	443 reported
Female	65 (28.3)	70 (32.9)	135 (30.5)
Weight, kg	70 reported	78 reported	148 reported
Mean ± SD	84.15 ± 16.8	85.93 ± 19.7	85.09 ± 17.5
Precipitating factors[a]			
Hypertension	13 (4.2)	23 (8.8)	36 (6.3)
Heart failure	2 (0.6)	6 (2.3)	8 (1.4)
Diabetes	4 (1.3)	13 (4.9)	17 (3.0)
Sepsis	0	1 (0.4)	1 (0.2)
Female sex	65 (28.3)	70 (32.9)	135 (30.5)
Advanced age >65 years	135/229 (58.0)	132/208 (63.5)	267 (61.1)
Concurrent QTc-prolonging medications that may induce SCAEs[b]			
Lopinavir/ritonavir	67 (21.5)	44 (16.7)	111 (19.3)
Quinolones	5 (1.6)	12 (4.6)	17 (3.0)
Macrolides	0	2 (0.7)	2 (0.4)
Azole antifungals	0	5 (1.9)	5 (0.9)
Tricyclics	0	7 (2.7)	7 (1.2)
SSRIs	5 (1.6)	1 (0.4)	6 (1.0)
5-HT3 antagonist	0	6 (2.28)	6 (1.04)
Antipsychotics	4 (1.3)	3 (1.1)	7 (1.2)
Loop diuretics	15 (4.8)	19 (7.2)	34 (5.9)
Class III antiarrhythmics	15 (4.8)	7 (2.7)	22 (3.8)
Donepezil	0	1 (0.4)	1 (0.2)
Serious cardiac adverse events[c]			
QTc prolongation	195 (62.5)	158 (60.1)	353 (61.4)
Ventricular arrhythmia	48 (15.4)	21 (8.0)	69 (12.0)
Atrial fibrillation	24 (7.7)	23 (8.8)	47 (8.2)
Torsade de pointes	14 (4.5)	14 (5.3)	28 (4.9)
Cardiac arrest	12 (3.9)	13 (4.9)	25 (4.4)
Heart failure	9 (2.9)	13 (4.9)	22 (3.8)
Stroke	3 (1.0)	8 (1.0)	11 (1.9)
Myocardial infarction	2 (0.6)	8 (3.0)	10 (1.7)
Bradyarrhythmia	5 (1.6)	5 (1.9)	10 (1.7)
Serious outcomes			
Number reported	312 reported	256 reported	568 reported
Hospitalization	46 (14.7)	42 (16.0)	88 (15.3)
Life threatening	46 (14.7)	37 (14.1)	87 (15.1)
Death	46 (14.7)	33 (12.6)	79 (13.7)
Other serious events	177 (56.7)	144 (54.8)	321 (55.8)

Data are presented as n (%) of events or mean ± standard deviation unless otherwise noted

COVID-19 coronavirus disease 2019, *CQ* chloroquine, *HCQ* hydroxychloroquine, *SCAE* serious cardiovascular adverse event, *SD* standard deviation, *SSRIs* selective serotonin reuptake inhibitors

[a]Precipitating factors included heart failure, hypertension, hyperlipidemia, left ventricular hypertrophy, severe renal disease, diabetes, female sex, advanced age >65 years, sepsis, hypokalemia, hypomagnesemia, hypocalcemia, and obesity. Those with zero or missing values were not listed

[b]The individual drugs of each group are shown in Table S5 in the electronic supplementary material

[c]SCAEs was predefined as a composite endpoint including cardiac arrest, ventricular arrhythmia, atrial fibrillation, bradyarrhythmia, QTc prolongation, myocardial infarction, stroke, cardiac failure, coronary ischemia, and torsade de pointes. Those with zero or missing values were not listed

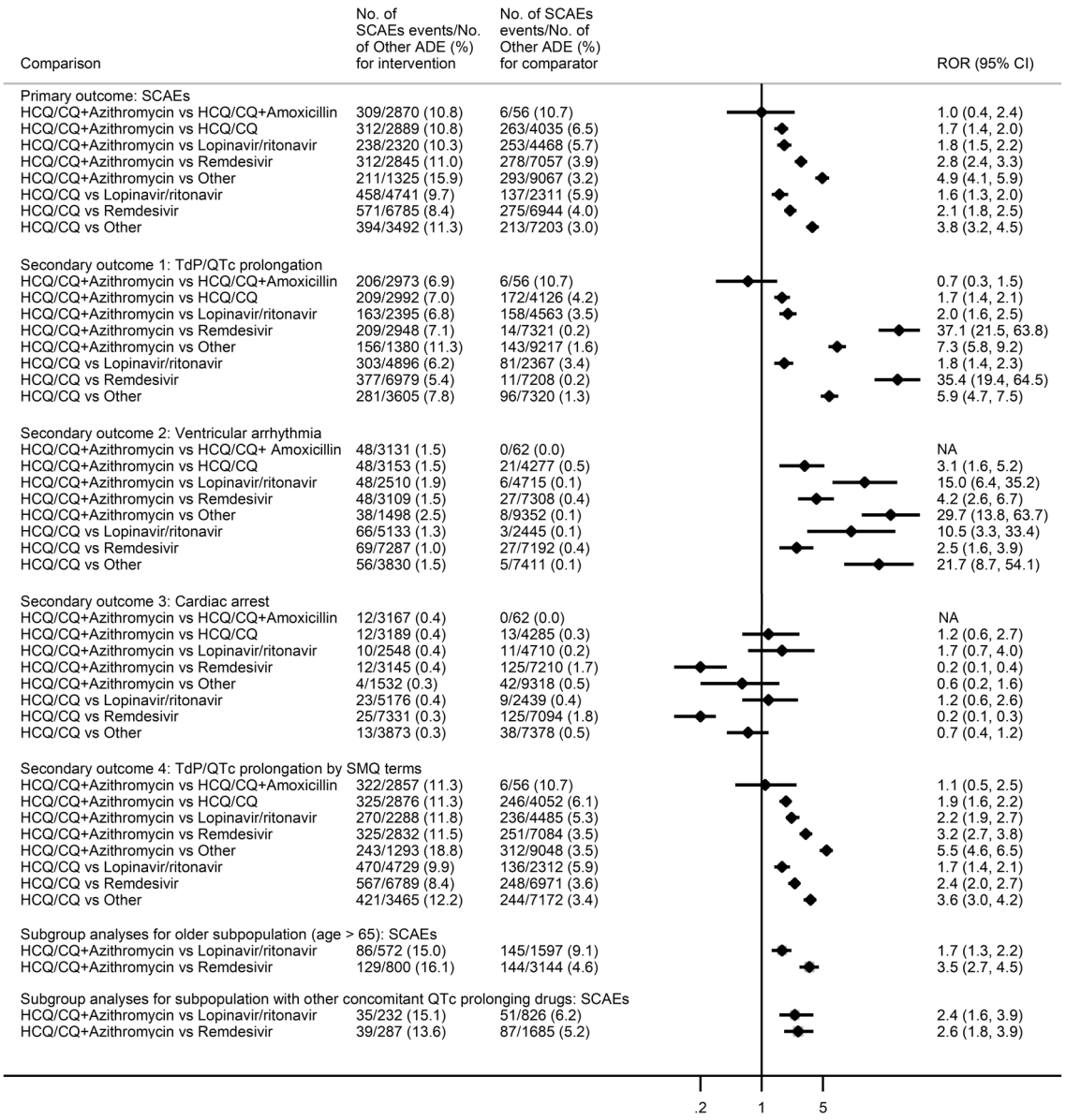

Fig. 1 Primary and sensitivity analyses for serious cardiovascular adverse events. Numbers of events were counted unless otherwise noted. The details of SMQ preferred terms are shown in Table S3 in the electronic supplementary material. *ADE* adverse drug event, *CI* confidence interval, *CQ* chloroquine, *HCQ* hydroxychloroquine, *ROR* reporting odds ratio, *SCAE* serious cardiovascular adverse event, *SMQ* standardized MedDRA queries, *TdP* torsade de pointes. "Other" indicates other medications used by patients with COVID-19 except for HCQ/CQ, azithromycin, lopinavir/ritonavir, and remdesivir (e.g., insulin, simvastatin, etc.)

analysis (ROR 1.8 [95% CI 1.5–2.2]). For the comparison of HCQ/CQ + azithromycin versus remdesivir, a stronger signal for increased risk of SCAEs was observed compared with the primary analysis (ROR 3.5 [95% CI 2.7–4.5] vs. ROR 2.8 [95% CI 2.4–3.3]). In the subpopulation with other concomitant QTc-prolonging drugs, HCQ/CQ + azithromycin versus lopinavir/ritonavir had a larger ROR (2.6 [95% CI 1.8–3.9]) than the primary analysis, whereas the ROR for HCQ/CQ + azithromycin versus remdesivir comparison was similar to the primary analysis (Fig. 1).

3.2 Case Series

3.2.1 Serious Cardiovascular Adverse Event Case Reports Listing the Use of Hydroxychloroquine or Chloroquine (HCQ/CQ) Monotherapy and HCQ/CQ + Azithromycin

Table 1 summarizes the clinical characteristics of the 575 SCAE case reports listing the use of HCQ/CQ monotherapy and HCQ/CQ + azithromycin in patients with COVID-19.

For all reports listing the use of HCQ/CQ therapy, the majority were male (69.5%), and the mean age was 63.9 years. Of the reports listing comorbidities of interest, 36 (6.3%) had hypertension, 17 (3.0%) had diabetes, and eight (1.4%) had heart failure. Of the reports received, cases with concomitant QTc-prolonging medications that may induce SCAEs included 111 (19.3%) with lopinavir/ritonavir, 34 (5.9%) with loop diuretics, 22 (3.8%) with class III antiarrhythmic agents, and 17 (3.0%) with quinolone antibiotics.

The most common SCAEs in our analysis were QTc prolongation (61.4%), followed by ventricular arrhythmia (12.0%), atrial fibrillation (8.2%), TdP (4.9%), and cardiac arrest (4.4%). Among 312 reports listing the use of HCQ/CQ + azithromycin, 158 (60.1%) experienced QTc prolongation, 23 (8.8%) experienced atrial fibrillation, 14 (5.3%) experienced TdP, and 13 (4.9%) experienced cardiac arrest. Overall, 88 (15.3%) cases were hospitalized with SCAEs, and 79 (13.7%) died.

Compared with HCQ/CQ users, remdesivir users were more likely to be female and to receive loop diuretics, and lopinavir/ritonavir users were more likely to have heart failure, to receive quinolones, and to be older (Tables S8–S10 in the ESM).

3.2.2 Fatal QTc Prolongation-Related Cardiovascular Events (Torsade de Pointes, Cardiac Arrest, and Ventricular Arrhythmia)

Of 575 SCAE case reports listing the use of HCQ/CQ monotherapy and HCQ/CQ + azithromycin, 122 were reports of fatal QTc prolongation-related cardiovascular events. Table 2 summarizes the clinical characteristics. Among these, 74 (60.7%) listed the use of HCQ/CQ + azithromycin. The percentage of females (31.8%) was similar to that in the SCAE case reports. Of the reports listing comorbidities of interest, ten (8.2%) had hypertension, four (3.3%) had diabetes, and four (3.3%) had heart failure, which were all higher than in the SCAE case reports.

Of note, in reports listing concurrent additional agents that could further extend the QTc interval, 87 received more than one QTc-prolonging agent and eight received three QTc-prolonging agents. Loop diuretics, quinolone, and lopinavir/ritonavir were the top three concurrently used agents. Overall, 40 (32.8%) fatal QTc prolongation-induced deaths were reported, 2.4 times the number induced by SCAEs.

Dosing of HCQ varied from 200 mg twice daily to 600 mg twice daily; 400 mg with or without a loading dose once daily was the most preferred regimen.

4 Discussion

This study found that composite SCAEs, TdP/QTc prolongation, and ventricular arrhythmia were reported more often in adverse event reports listing HCQ/CQ than in reports listing alternative therapies. RORs for cardiac arrest included a number of estimates close to or on the other side of the null value, suggesting no signals; however, these analyses were imprecise compared with other outcome analyses, largely because of the small number of events. Overall, our findings are partly consistent with previous evidence [9] and the FDA warning [11]. Further, increases in adverse event reports listing the combination use of HCQ/CQ and azithromycin may be associated with increased reporting of SCAE compared with events reported with HCQ/CQ monotherapy, and the potential signal (or association) was stronger among reports in older adults. This is the largest and most extensive pharmacovigilance study to assess associations between HCQ/CQ with or without azithromycin and SCAEs in patients with COVID-19. Our study thus provides additional information for the safety profiles of HCQ/CQ in patients with COVID-19.

Our findings regarding HCQ/CQ monotherapy and HCQ/CQ + azithromycin combination therapy are consistent with both the most recent analysis [32] of the World Health Organization's pharmacovigilance database and previous studies [9, 21, 33, 34] suggesting that HCQ/CQ monotherapy is associated with an increased risk of QTc prolongation and cardiovascular events and that concurrent use may increase this risk. A case series report of 84 patients with COVID-19 treated with 5 days of HCQ + azithromycin found that QTc increased significantly from a mean ± standard deviation of 435 ± 24 ms to a maximum of 463 ± 32 ms ($P < 0.001$) on day 3.6 ± 1.6 of therapy [10]. Nine of 84 (11%) patients recorded a QTc > 500 ms (five of the nine patients had a normal QTc at baseline), although none of them developed TdP or cardiovascular death. Considering that both HCQ/CQ and azithromycin have a long half-life (approximately 40 days [33, 34] and 68 h [35], respectively), cardiovascular events could occur after discharge. If such an increased risk associated with HCQ/CQ + azithromycin combination therapy truly exists, it could be explained by the hypothesis that HCQ/CQ and azithromycin used concurrently may simultaneously block the hERG/Kv11.1 potassium channel [36–39], thereby increasing the risk of QTc prolongation, TdP, and other SCAEs.

Similarly, the concomitant use of medications that induce QTc prolongation may have a synergistic or additive effect in QTc prolongation risk, and almost one-third of the reports of HCQ/CQ monotherapy or HCQ/CQ + azithromycin included the concomitant use of other QTc-prolonging agents in our study. In addition, another mechanism worth considering is the pharmacokinetic interaction between HCQ/CQ and these concomitant agents, which may inhibit drug metabolism and further increase the systemic exposure of HCQ/CQ, increasing the cardiotoxicity [40]. Both HCQ and CQ are metabolized by cytochrome P450 (CYP) enzymes, and the concomitant use of CYP3A4 inhibitors,

Table 2 Descriptive characteristics of fatal QTc prolongation-related case reports listing use of hydroxychloroquine/chloroquine monotherapy and hydroxychloroquine/chloroquine + azithromycin combination therapy in COVID-19 cases reported to FAERS from January 1, 2020, to December 31, 2020

Characteristics	HCQ/CQ + azithromycin ($N = 74$)	HCQ/CQ monotherapy ($N = 48$)	Total ($N = 122$)
Age, years	39 reported	26 reported	65 reported
Median (IQR)	66 (43–69)	70 (47–75)	67 (44–74)
Sex	38 reported	28 reported	66 reported
Female	12 (31.6)	9 (32.1)	21 (31.8)
Precipitating factors[a]			
Hypertension	5 (6.8)	5 (10.4)	10 (8.2)
Heart failure	1 (1.4)	3 (6.3)	4 (3.3)
Diabetes	1 (1.4)	3 (6.3)	4 (3.3)
Sepsis	0 (0)	1 (2.1)	1 (0.8)
Female sex	12/38 (31.6)	9/28 (32.1)	21/66 (31.8)
Advanced age >65 years	22/39 (56.4)	16/26 (61.5)	38/65 (58.5)
Concurrent QTc-prolonging medications may induce QTs[b]			
Lopinavir/ritonavir	2 (2.7)	3 (6.3)	5 (4.1)
Loop diuretics	4 (5.4)	6 (12.5)	10 (8.2)
Quinolones	1 (1.4)	0	1 (0.8)
Azole antifungals	0	4 (8.3)	4 (3.3)
Macrolide	0	1 (0.8)	1 (0.8)
HCQ/CQ alone	NA	35 (72.9)	35 (28.7)
Two QTc-prolonging agents	67 (90.5)	12 (25.0)	79 (64.8)
Three QTc-prolonging agents	7 (9.5)	1 (2.1)	8 (6.6)
Serious outcomes	74 reported	46 reported	120 reported
Hospitalization	29 (39.2)	25 (52.08)	54 (44.3)
Life threatening	25 (33.8)	9 (18.8)	34 (27.9)
Death	22 (29.7)	18 (37.5)	40 (32.8)
Other serious events	54 (73.0)	32 (66.7)	86 (70.5)
Dosing of HCQ/CQ	23 reported	25 reported	48 reported
400 mg qd, with or without a loading dose	9	5	14
600 mg bid	0	1	1
800 mg qd	0	3	3
600 mg qd	7	1	8
400 mg bid	4	2	6
200 mg bid	3	6	9
1000 mg qd or 500 mg bid (CQ)	0	4	4
500 mg qd (CQ)	1	1	2
200 mg tid	0	1	1
Duration, days	24 reported	24 reported	48 reported
Median (IQR)	4 (2–5)	4 (1–9.5)	4 (2–5)

Data are presented as n (%) of events unless otherwise noted

bid twice daily, *COVID-19* coronavirus disease 2019, *CQ* chloroquine, *HCQ* hydroxychloroquine, *IQR* interquartile range, *NA* not applicable, *qd* once daily, *SCAE* serious cardiovascular adverse event, *tid* three times daily

[a]Precipitating factors included heart failure, hypertension, hyperlipidemia, left ventricular hypertrophy, severe renal disease, diabetes, female sex, advanced age >65 years, sepsis, hypokalemia, hypomagnesemia, hypocalcemia, and obesity. Those with zero or missing values were not listed

[b]The individual drugs for each group are shown in Table S5 in the electronic supplementary material

including lopinavir/ritonavir, antifungals (e.g., itraconazole and ketoconazole), and macrolides (e.g., clarithromycin and erythromycin) may increase the risk of SCAEs [40]. Azithromycin, a new-generation macrolide, is a weaker CYP3A4 inhibitor, and the risk of QTc prolongation might increase when used in combination with HCQ/CQ to treat COVID-19. This may further explain why HCQ/CQ + azithromycin combination therapy has a more significant

QT prolongation effect [40]. Moreover, this may explain why cases reporting the concomitant use of other QTc-prolonging agents and HCQ/CQ + azithromycin were more likely to report SCAEs than were cases reporting the use of lopinavir/ritonavir. Notably, 111 (19.30%) case reports with COVID-19 listed HCQ/CQ ± azithromycin combined with lopinavir/ritonavir, suggesting it is important to monitor QTc prolongation and ventricular arrhythmia in this setting. Our finding that HCQ/CQ + azithromycin was associated with increased relative reporting of SCAEs in older patients is consistent with a retrospective cohort study that found that age > 65 years was an independent risk factor associated with QTc prolongation ≥ 500 ms in hospitalized patients with COVID-19 [41]. Special attention must be paid in this regard since age has been proven to be a key risk factor of mortality in such patients [41].

HCQ/CQ monotherapy and HCQ/CQ + azithromycin combination therapies are likely associated with an increased risk of SCAEs, specifically TdP and ventricular arrhythmia. A previous study found that baseline cardiovascular diseases, including coronary artery disease and congestive heart disease, were associated with an increased risk of fatal cardiac complications, such as TdP, cardiac arrest, and ventricular arrhythmia, in patients receiving HCQ + azithromycin [42]. Although the use of HCQ and azithromycin has been proven to have little impact on QTc duration in most patients with COVID-19, and does not induce any substrate prone to arrhythmia [9], patients with COVID-19 and primary moderate hypokalemia, tachycardia, and subclinical-to-mild long QT syndrome still have a higher risk of developing drug-induced arrhythmias than patients without these comorbidities [43]. More importantly, when treating patients with COVID-19, such therapy may be associated with a higher risk of cardiovascular events as such patients are prone to QTc prolongation [44, 45]. The American College of Cardiology has recommended close monitoring for QTc prolongation and arrhythmia in patients with COVID-19 treated with HCQ + azithromycin [26]. Extra caution is recommended in patients with QTc > 480 ms at baseline. Atrial fibrillation was also an observed serious cardiac adverse event in our study, although we did not perform a disproportionality analysis because of the relatively low number of events. One recent cohort study with 416 patients hospitalized with COVID-19 found that high-sensitivity troponin I was elevated in 82 (19.7%) patients [49]. Another similar study reported 52 cases (27.8%) of troponin T elevation out of 187 patients hospitalized with COVID-19 [47]. Both studies reported a staggering increase in mortality of more than 50% among patients with myocardial injury [44, 47]. It should be noted that concurrent QTc agents listed on case reports of QTc prolongation events included quinolones and azole antifungals; this is especially worrisome for severe COVID-19 cases as they may develop nosocomial infection after prolonged hospitalization and broad-spectrum antibiotic coverage. Also, patients under intensive care often develop electrolyte disturbances, such as hypokalemia and hypomagnesemia, which would increase even further the risk of QTc prolongation/TdP [48]. The results of this study support an increased cardiovascular risk in patients treated with HCQ/CQ and azithromycin and reinforce the need for following treatment guidance, particularly when treating patients with COVID-19.

Our study has several strengths. First, we assessed the cardiovascular safety of HCQ/CQ + azithromycin in patients with COVID-19. The availability and lag time of FAERS data updates meant that previous studies were primarily based in patients with rheumatoid arthritis, lupus, or malaria. However, when treating rheumatoid arthritis or lupus, HCQ/CQ is used for much longer than the typical 5-day course used for the treatment of COVID-19. Given that patients with COVID-19 are prone to QTc prolongation and myocardial injuries [46, 47], our results are more generalizable to the COVID-19 patient population than were those prior studies [7, 9]. Second, we used therapeutic alternatives as comparators to reduce unmeasured confounding (by indication) [17]. Third, we performed multiple comparisons to assess both HCQ/CQ combination and monotherapy, and we examined both composite and individual endpoints to explore the drivers of cardiovascular risk. We also performed multiple sensitivity analyses to increase the internal validity of our exposure and outcome definitions. Additionally, we extracted detailed information for cases by mining FAERS data, and we summarized clinical features associated with SCAEs.

Our study also has notable limitations. As we only included case reports with a confirmed diagnosis of COVID-19 (by treatment with explicit indication for COVID-19), we may have missed some COVID-19 cases (e.g., a true COVID-19 case receiving HCQ with an indication for "pneumonia"). The extracted case reports often had missing data on comorbidities, previous treatments, or dose and duration of treatment. The FAERS database, like other spontaneous reporting data sources, is also prone to channeling bias and reporting bias and lacks a "true" treatment denominator for estimating adverse event risks. In addition, a patient who experienced multiple SCAEs (e.g., both cardiac arrest and myocardial infarction) could be counted multiple times in our analyses, which may have introduced bias. Furthermore, when assessing signals, we were unable to fully control for confounding and do not have appropriate denominators to calculate incidence [49]. Thus, further high-quality cohort studies are needed to confirm our findings.

5 Conclusions

This study assessed the potential cardiovascular adverse events associated with the use of HCQ/CQ, with or without azithromycin, in patients with COVID-19 by analyzing adverse events reported in the FAERS database. Compared with case reports listing comparison drugs, case reports of patients treated with HCQ/CQ were associated with increased reporting of the composite endpoint SCAEs and fatal QTc prolongation-related cardiovascular events (mainly TdP and ventricular arrhythmia), especially when azithromycin was also listed. Thus, these patients should be monitored closely. When treatment calls for concomitant use of both other QTc-prolonging agents and CYP3A4 inhibitors, the potential benefits need to be weighed against the potential harms. Given the scarcity of evidence demonstrating benefits from HCQ/CQ treatment for patients with COVID-19, the evidence for harm is crucial for clinical decision making. Together with prior evidence, our data provide further evidence to caution against the widespread use of the combination regimen in preventing or treating COVID-19, especially in vulnerable populations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-022-00300-y.

Acknowledgements The authors thank Dr. Huilin Tang for preparing the figure used in the article.

Declarations

Funding No sources of funding were used to conduct this study or prepare this manuscript.

Conflicts of interest J.B.B. has received consulting fees and travel support for contracted activities, paid to the University of North Carolina (UNC), by Adocia, AstraZeneca, Dance Biopharm, Dexcom, Eli Lilly, Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, MannKind, Metavention, NovaTarg, Novo Nordisk, Orexigen, PhaseBio, Sanofi, Senseonics, vTv Therapeutics, and Zafgen; has received grant support from AstraZeneca, Eli Lilly, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, NovaTarg, Novo Nordisk, Sanofi, Theracos, Tolerion, and vTv Therapeutics; is a consultant to Cirius Therapeutics Inc, CSL Behring, Mellitus Health, Neurimmune AG, Pendulum Therapeutics, and Stability Health; holds stock/options in Mellitus Health, Pendulum Therapeutics, PhaseBio, and Stability Health; and is supported by grants from the National Institutes of Health (NIH; UL1TR002489, U01DK098246, UC4DK108612, U54DK118612, P30DK124723), the Patient-Centered Outcomes Research Institute, and ADA. T.S. has received investigator-initiated research funding and support from the National Institute on Aging as a principal investigator (R01 AG056479) and from the NIH as co-investigator (R01 CA174453, R01 HL118255, and R21-HD080214); has received salary support as co-director of the Biostatistics, Epidemiology, and Research Design (BERD), North Carolina Translational and Clinical Sciences Institute (UL1TR002489) and from the Center for Pharmacoepidemiology (current members are GlaxoSmithKline, UCB BioSciences, Merck, and Takeda); has received research support from Amgen, AstraZeneca, and Novo Nordisk to the Department of Epidemiology, UNC; and owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk. T.S. does not accept personal compensation of any kind from any pharmaceutical company. Ying Zhao, Jingru Zhang, Kai Zheng, Sydney Thai, Ross J Simpson Jr, Alan C. Kinlaw, Yang Xu, Jingkai Wei, Xiangli Cui, and Tiansheng Wang have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval This research does not involve human subjects. It is not required to obtain institutional review board approval.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data are available upon reasonable request.

Code availability SAS codes are available upon reasonable request.

Authors' contributions YZ and KZ wrote the first draft of the manuscript. JZ did the statistical analysis. TW oversaw and supported programing. LZ prepared the data. YZ, JZ, KZ, TW, RJSJ, ST, JBB and TS were involved in data review and interpretation. All authors contributed to critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. TW, KZ, YZ, and JZ designed the study. YZ and KZ developed the protocol. JZ, YZ, and TW are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Patient consent Not applicable as the data are publicly available from FAERS.

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