

Hydroxychloroquine is protective to the heart, not harmful: a systematic review

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Abstract

Hydroxychloroquine (HCQ) has been shown to be at least somewhat effective in treating patients with coronavirus disease 2019 (COVID-19). Recently the US Food and Drug Administration and Centers for Disease Control and Prevention warnings of fatal cardiac toxicity from torsades de pointes (TDP) arrhythmia from HCQ receipt have been made, notwithstanding the long safe provision of HCQ to treat lupus and rheumatoid arthritis. This has resulted in restricted access of HCQ for COVID-19 treatment. We hypothesized that HCQ and azithromycin have not been reported to cause significant acute cardiac arrhythmic mortality. We performed a literature search for the effects of HCQ and azithromycin on the heart. No TDP or related deaths were found to have been reported as a result of HCQ and azithromycin receipt in the peer-reviewed literature. On the contrary, HCQ and azithromycin were both found to substantially reduce cardiac mortality and also decrease thrombosis, arrhythmia and cholesterol in treated patients in recent peer-reviewed studies and meeting presentations. HCQ and azithromycin do not cause TDP cardiac mortality; rather, HCQ decreases cardiac events. HCQ should not be restricted in COVID-19 patients out of fear of cardiac mortality.

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Keywords: Azithromycin, COVID-19, hydroxychloroquine, SARS-CoV-2

Original Submission: 24 June 2020; **Revised Submission:** 13 August 2020; **Accepted:** 17 August 2020

Article published online: 20 August 2020

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Introduction

Several clinical studies, which by now have assessed thousands of patients [1–4], have shown apparent substantial clinical benefit from the receipt of hydroxychloroquine (HCQ) in coronavirus disease 2019 (COVID-19) patients and have not reported adverse cardiac events. A number of meta-analyses [5–7] have also shown overall good results, although with limited quality studies. Provision of HCQ by physicians who were so inclined is therefore warranted to treat COVID-19 unless there are significant clinical risks to offset the apparent benefits.

However, recently numerous warnings have been issued from the US Food and Drug Administration (FDA) [8], the

Centers for Disease Control and Prevention [9], the American Heart Association [10] and elsewhere about potential fatal cardiac toxicity from torsades de pointes (TDP) or other ventricular arrhythmias from HCQ receipt. These warnings state that such fatalities could occur as a result of the increase in QTc that is sometimes seen with the receipt of HCQ as well as with azithromycin, which is often used in combination with HCQ. The FDA warning, released on 15 June 2020 along with a revocation of its prior emergency use authorization, states, ‘Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and HCQ no longer outweigh the known and potential risks for the authorized use’ [11]. However, this warning does not reference any specific study or note whether any related deaths had occurred.

These warnings seemed odd to us because HCQ has been provided to millions of patients with lupus or rheumatoid arthritis (RA) for more than 50 years with a general reputation for safety [12]. Practicing rheumatologists generally prescribe it without ordering a baseline electrocardiogram (EKG) unless the patient has a history of cardiac disease. The 2019 HCQ

recommendations for the European League Against Rheumatology (EULAR) only mention screening for retinal toxicity in patients receiving HCQ for extended periods of time [12]. Furthermore, azithromycin is also regularly prescribed without a baseline EKG, and is not generally thought to be cardiotoxic to patients with an otherwise normal heart.

These warnings have had the effect of restricting HCQ provision in the hospital setting in some locales. This may not be consistent with good patient care because HCQ is known to be best applied earlier in the patient course, before hospitalization. It has also resulted in some pharmacists or entire pharmacy boards [13] refusing to fill HCQ prescriptions for COVID-19, thus restricting access to a potentially beneficial drug.

Thus, it would be of great benefit to know whether there is in fact significant cardiac risk from the receipt of HCQ. We hypothesized that the scientific literature would not show clinical evidence of increased cardiac mortality from HCQ or HCQ plus azithromycin from TDP. That is, we thought that the reported putative potential cardiac risk [9] of cardiac mortality would not be accompanied by reports of actual TDP or other QTc-related cardiac mortality.

Materials and methods

We limited this study to HCQ and not chloroquine (CQ) because CQ is more toxic than HCQ, such that we do not believe CQ has a place in the treatment of COVID-19, particularly given the wide availability and low cost of HCQ.

We also excluded reports of HCQ cardiomyopathy. This is a rare condition that is only seen after many years (usually decades) of receipt of HCQ, and thus it is not relevant to the brief periods of time that HCQ is used to treat COVID-19. This cardiomyopathic damage is also not what is referenced by agencies that warn of HCQ cardiotoxicity, instead referring to QTc prolongation and the risk of TDP.

We conducted a search of the PubMed, Medline, Cochrane, Embase and Google Scholar databases. Search terms included 'hydroxychloroquine' and 'azithromycin' as well as the following cosearch terms: cardiac, heart, arrhythmia, ventricular arrhythmia, torsades de pointes, COVID-19, treatment for COVID-19, mortality and death. We identified relevant articles. We included only clinical series including case reports, prospective and retrospective cohort studies and meta-analyses. Because of the emerging nature of the COVID-19 pandemic, we included preprint papers in our analysis, including papers published on medRxiv (which are indexed in Google Scholar). The last day of this search consultation was 1 June 2020. We identified four case reports of HCQ cardiomyopathy after long-term receipt [14,15]; these studies were excluded, as explained

above. The remaining articles were individually analysed for evidence of cardiac morbidity and mortality.

Results

Overall, our literature search found that except for a few case reports of nonfatal adverse events, HCQ is actually consistently associated with a decreased incidence of cardiac adverse events and no cardiac mortality from TDP. Table 1 lists the relevant studies.

Nonfatal cardiac adverse event case reports

We found three case reports of patients with increased QTc or other conduction block arrhythmia in patients with lupus [16–18] and one in a patient with COVID-19 [19]. However, in all cases, the patients were successfully treated without any deaths occurring.

Nonfatal cardiac adverse event clinical series

We found one case series describing 251 COVID-19 patients treated with HCQ and azithromycin [36]. A total of 23% developed extreme QTc prolongation. However, HCQ was discontinued in patients with QTc prolongation, and no deaths occurred.

Cardiac mortality from HCQ-induced TDP or other arrhythmia

We found no reports of cardiac death from TDP or other arrhythmia due to receipt of HCQ.

Decreased incidence of cardiac events with HCQ

Eight articles showed a decreased incidence of cardiovascular disease (CVD) in patients receiving HCQ. Hung et al. [23] in 2018 found a decrease in risk of coronary artery disease in RA patients receiving HCQ. Liu et al. [37] found this protective effect of HCQ on coronary artery disease was applicable across a range of ages, the two genders and multiple comorbidities as well as a lower risk of CVD in patients with rheumatic diseases treated with HCQ or CQ. Rempenault et al. [38] in 2018 found that CQ and HCQ lowered CVD in rheumatic disease. Mathieu et al. [39] also in 2018 found that RA patients receiving HCQ had an improved cardiovascular risk profile compared to other RA patients.

Sharma et al. [30] in 2016 found that HCQ receipt was associated with a 72% decrease in the risk of incident CVD in RA patients. Van Halm et al. [29] in 2006 found that HCQ reduced cardiac events in RA patients. Yang et al. [31] in 2019 found a decreased risk for coronary artery disease in patients

TABLE 1. Literature review results on HCQ and cardiac events

Study	Study type	No. of patients	HCQ dosage	HCQ duration	Associated medications	Comorbidities of patients and cardiac background	Study findings
Morgan 2013 [16]	Case report	1	200 mg twice daily	3 years	NA	41-year-old woman with CHF and left ventricular dysfunction and with SLE and hypertension; received renal transplant 3 years before	QTc prolongation
O'Laughlin 2016 [17]	Case report	1	200 mg daily	2 years	NA	50-year-old woman with history of SLE, ESRD treated with dialysis and Afib receiving anticoagulation therapy	QTc prolongation
Chen 2006 [18]	Case report	1	200 mg daily	1 year	15 mg prednisolone daily, 200 mg theophylline daily	67-year-old woman with history of SLE, liver cirrhosis and portal vein thrombosis, asthma and old myocardial infarct with ventricular septal defect	Prolonged QTc leading to TDP
Asli 2020 [19]	Case report	1	400 mg stat dose, then 200 mg twice daily	3 days	Initially amoxicillin/clavulanic acid; switched to meropenem 1000 mg three times daily	60-year-old woman with history of hypertension hyperlipidaemia and overweight	Right bundle branch block and prolonged QTc
Erkan 2002 [20]	Cross-sectional study	133 patients with antiphospholipid syndrome	NA	NA	NA	All patients with history of antiphospholipid syndrome	Found lower rate of thrombosis in aPL-positive patients receiving therapy with either aspirin or HCQ
Izmirly 2012 [21]	Historical cohort study	40 neonates whose mothers received HCQ before delivery	At least 200 mg daily	At least before 10 weeks' gestation	NA	Neonates whose mothers previously gave birth to a child with cardiac neonatal lupus or whose mother had anti-SSA/Ro and/or SSB/La antibodies	Infants with mothers receiving HCQ had 64% lower chance of developing cardiac neonatal lupus
Petri 1994 [22]	Longitudinal cohort study	264 total patients, 125 patients receiving HCQ	NA	NA	80% of all patients in study receiving prednisone	All patients with SLE	HCQ receipt was associated with lower serum cholesterol levels
Hung [23]	Population-based retrospective cohort study	173 in HCQ group	NA	>180 days	NA	Rheumatoid arthritis patients	Showed decreased risk of coronary artery disease in RA patients receiving HCQ
Konig 2019 [24]	Prospective cohort study	812 patients	NA	NA	NA	All patients with SLE	HCQ blood levels inversely associated with risk of any thrombotic event
Ruiz-Irastorza 2006 [25]	Prospective cohort study	104 patients receiving HCQ	NA	average 52 months	NA	232 patients with SLE	Patients receiving either HCQ or CQ were less likely to experience a thrombotic event
Rho 2009 [26]	Prospective cohort study	169 total patients, 42 currently receiving either HCQ or CQ	NA	NA	71% of all patients in study receiving methotrexate	All patients with RA	Diastolic blood pressure, serum LDL and triglyceride levels were all lower in patients currently receiving HCQ or CQ
Million 2020 [2]	Prospective cohort study	1061 patients	200 mg HCQ three times daily	10 days	500 mg azithromycin day		9 patients had QTc prolongation

Continued

TABLE 1. Continued

Study	Study type	No. of patients	HCQ dosage	HCQ duration	Associated medications	Comorbidities of patients and cardiac background	Study findings
Bun 2020 [27]	Prospective cohort study	71 patients receiving HCQ	200 mg three times daily	10 days	1, followed by 250 mg daily days 2–5 Azithromycin 500 mg day 1, 250 mg days 2–5	Patients with PCR-confirmed COVID-19 All PCR-confirmed COVID-19 patients	of >60 ms from baseline, although no patient exceeded 500 ms QTc; no incidents of TDP reported Significant QTc prolongation leading to therapy withdrawal in 2 patients; no incidences of drug-induced life-threatening arrhythmias or death observed Patients receiving azithromycin had greater rates of QTc prolongation; only discontinued in 3.5% of patients; no instances of TDP RA patients receiving DMARDs (including HCQ) reduce risk for CVD
Saleh 2020 [28]	Prospective observational study	201 total patients, 191 receiving HCQ	400 mg twice on day 1, then 200 mg twice daily for days 2–5	5 days	119 patients also receiving azithromycin 500 mg daily for 5 days	All PCR-confirmed COVID-19 patients	Rheumatoid arthritis patients receiving HCQ showed 72% reduction in all CVD events Risk for coronary artery disease decreased in patients with high cumulative doses of HCQ (>100 267) Patients receiving HCQ had lower risk of arterial and venous CVD events Lower risk of atrial fibrillation in patients receiving HCQ
Van Halm 2006 [29]	Retrospective case control study	613 total patients receiving DMARDs, 244 of these receiving HCQ	NA	NA	NA	NA	
Sharma 2016 [30]	Retrospective cohort study	547 patients receiving HCQ	NA	Average 2.3 years	NA	NA	
Yang 2019 [31]	Retrospective cohort study	795 patients receiving HCQ	NA	Variable; grouped as <105, 105–318 and > 318	NA	Patients with history of CVD excluded from study	
Shapiro 2017 [32]	Retrospective cohort study	241 patients receiving HCQ	Either 400 mg daily or 200 mg daily	NA	Most patients also receiving prednisone or methotrexate	NA	
Gupta 2018 [33]	Retrospective cohort study	754 patients receiving HCQ	NA	NA	NA	NA	
Mercurio 2020 [34]	Retrospective cohort study	90	400 mg twice on day 1, then 400 mg daily for days 2–5	5 days	53 patients also receiving azithromycin	Patients with PCR-confirmed COVID-19; most patients had at least one cardiovascular comorbidity	7 patients developed prolonged QTc of over 500 ms; 3 patients had increase in QTc of 50 ms or more; 1 case of TDP reported
Hooks 2020 [35]	Retrospective cohort study	819 patients receiving HCQ	Median dose 400 mg daily	Median duration 1006 days	NA	All patients with rheumatic disease	12 patients with QTc over 500 ms; average patient increased QTc by 7.6 ms while receiving treatment; average on-treatment QTc was 430.9 ms QTc >500 ms in 23% of patients; one patient developed polymorphic ventricular tachycardia (suspected to be TDP) HCQ or CQ receipt was
Chorin 2020 [36]	Retrospective study	251	Loading dose of 400 mg twice for 1 day, then 200 mg twice daily	5 days	Azithromycin 500 mg daily for 5 days	NA	
Liu 2018 [37]	Systematic review and meta-analysis	19 679 total patients	NA	NA	NA	NA	

TABLE 1. Continued

Study	Study type	No. of patients	HCQ dosage	HCQ duration	Associated medications	Comorbidities of patients and cardiac background	Study findings
Rempenault 2018 [38]	Systematic review and meta-analysis	12 245 patients receiving HCQ	NA	NA	NA	NA	associated with 30% reduction in risk of CVD in patients with rheumatic disease Rheumatoid arthritis patients receiving HCQ showed modifiable risk factors for CVD, including improved lipid profile, diabetes incidence, HBA1C and fewer cardiovascular events
Mathieu 2018 [39]	Systematic review and meta-analysis	24 923 patients receiving HCQ	NA	NA	NA	NA	Rheumatic disease patients treated with HCQ had better CVD risk profile and fewer cardiovascular events

Afib, atrial fibrillation; aPL, antiphospholipid antibody; CHF, congestive heart failure; COVID-19, coronavirus disease 2019; CQ, chloroquine; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drug; ESRD, end-stage renal disease; HCQ, hydroxychloroquine; LDL, low-density lipoprotein; NA, not applicable; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSA/Ro, anti-Sjögren syndrome-related antigen A, also called anti-Ro; SSB/La, anti-Sjögren syndrome-related antigen B, also called anti-La; TDP, torsades de pointes.

with systemic lupus erythematosus receiving high doses of HCQ for at least 318 days. Shapiro and Levy [32] in 2017 found decreased mortality with HCQ. In 514 RA patients (241 patients receiving HCQ and 273 controls), the mortality rate for HCQ was 22.4%, versus 38.5% in the control arm. A total of 13.3% of HCQ patients receiving 400 mg per day experienced cardiovascular events compared to 38.1% in the control group. The authors concluded that HCQ receipt in RA patients was associated with decreased cardiovascular morbidity, especially in higher-dosage HCQ, at 400 mg per day.

Neonatal cardiac lupus

Izmirly et al. [21] in 2012 showed the recurrence rate of cardiac neonatal lupus in fetuses exposed to HCQ was 7.5% (3/40) compared to 21.2% (46/217) in the unexposed group (p 0.050). While there were no deaths in the exposed group, the overall case fatality rate of the cardiac neonatal lupus fetuses in the unexposed group was 22%.

Atrial fibrillation

Gupta et al. [33] in 2018 showed a 67% decreased risk of atrial fibrillation in patients receiving HCQ.

Thrombosis

Three articles reported a decreased incidence of thrombosis in patients who received HCQ [20,24,25]. König et al. [24], in a

2019 presentation, found a lower incidence of thrombosis with a higher level of HCQ in the blood.

Cholesterol and lipid profile

Two articles showed lower cholesterol or lipid profile in patients receiving HCQ [22,26].

Clinical series providing HCQ in COVID-19

A clinical series of 1061 COVID-19 patients treated with HCQ and azithromycin reported eight deaths [2]. However, all of these deaths were caused by respiratory failure from COVID-19; no patients showed TDP. The authors obtained a baseline EKG in all patients and discontinued HCQ when necessary. They have now treated over 4000 patients with no cardiac mortality.

Azithromycin

We found five reports addressing the cardiotoxicity of HCQ in COVID-19 patients [27,28,34–36]. All articles described an increased risk of TDP or related ventricular arrhythmia. However, none of the five articles reported an actual death attributed to HCQ.

A report by Farkas [40] explained that HCQ is actually an antiarrhythmic drug and that it has never been shown to pre-dispose its recipients to TDP. Ohara et al. [41] further described azithromycin as never having been shown to cause TDP. In addition, azithromycin has been shown to improve

cardiac remodeling and decrease heart failure after myocardial infarction in animal models [42].

Discussion

The most important finding of this review is that evidence shows HCQ to be overall significantly cardioprotective and apparently not cardiotoxic in short-term receipt. This supports our hypothesis that prudent HCQ therapy would not cause significant mortality from TDP or related cardiac causes. This finding of cardioprotection, which was surprising to us, goes well beyond our hypothesis. Perhaps because many of the studies showing cardioprotection are relatively recent, the cardioprotective effect seems to be generally unknown to both the general population and the medical community. The cardioprotection includes a decrease in cardiac events, in thrombosis in general, in arrhythmia, in lipid profile and even in foetal disease. With HCQ generally beneficial to the heart in patients with rheumatic disease, there would be no reason to think that it would be cardiotoxic in COVID-19 patients, unless these patients were late in the disease course with established viral cardiac damage. Even then, this would be only a theoretical risk, because it is also possible that HCQ might be protective of further damage in this circumstance.

The second major finding of this study is that we were unable to find any reports of death due to HCQ-induced TDP in the peer-reviewed literature. This suggests that in fact no actual significant risk of TDP exists if HCQ is provided prudently and in accordance with established guidelines. In this regard, the protocol used by Raoult's group is instructive [2]. They obtained a baseline EKG and serum electrolyte analysis before initiating HCQ. The EKG was repeated 48 hours after the start of treatment, and HCQ was discontinued when the corrected QT interval was >500 ms. Using this commonsense protocol, they have now treated over 4000 patients without a single cardiac mortality. TDP may occasionally occur in association with HCQ therapy. But on the basis of our finding of not a single death being reported in the peer-reviewed literature, we believe that the frequency of HCQ associated TDP is extremely low, and the incidence of subsequent TDP induced mortality caused by HCQ is rare, if it exists at all. Anecdotally, the Department of Health and Human Services' pharmacovigilance memorandum [43], which publishes self-reported adverse events from providers and patients, reported four cases of TDP with one death in their entire database. This report is not peer reviewed. There is no way to verify the report itself, or causality or whether appropriate procedures were followed. However, at worst, this would still represent only a single TDP mortality despite widespread HCQ therapy for COVID-19.

The cardioprotective properties of HCQ should not be surprising. Cardiac events, including thrombosis, are caused in part by inflammation [44]. HCQ is an anti-inflammatory drug [45]. Furthermore, its separately described antithrombotic properties [46] would also be expected to be cardioprotective.

Limitations of this study include the possibility that cardiac deaths have occurred but not been reported. However, even if a small number of TDP deaths have occurred, it would not change the finding that HCQ is overall safe and generally beneficial for the heart.

In fact, the finding of an antithrombotic effect, an antiarrhythmic effect and a reduction in CVD events raises the possibility that HCQ should be considered in well-controlled clinical trials as a treatment for COVID-19 patients who have sustained cardiac damage as a possible mitigant of these effects.

Conclusions

HCQ is apparently not dangerous to the heart and indeed is cardioprotective. It results in a lower incidence of cardiac events as well as lower levels of arrhythmia, cholesterol and thrombosis. No TDP deaths from HCQ were reported in the peer-reviewed literature. The potential risk of fatal arrhythmia—for example, TDP—from HCQ appears to be merely theoretical. It appears to occur only rarely in clinical practice if HCQ is provided according to standard treatment protocols. Azithromycin provided in combination with HCQ also appears to be safe; it also does not appear to cause TDP mortality and is also apparently cardioprotective. As a result of its ability to decrease CVD events, decrease arrhythmia, decrease thrombosis and decrease cholesterol, HCQ should be considered as an agent for study to potentially treat patients who have developed cardiac damage from COVID-19.

Conflict of interest

None declared.

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