The European Research Journal 2022;8(5):732-741 Review

DOI: 10.18621/eurj.1102545 *Emergency Medicine*

Clinical update of medications associated with QT prolongation among COVID-19 patients

Ernest Herbert, Dominique Fournier

Erdomo LLP, England and Wales, United Kingdom

ABSTRACT

In the struggle against COVID-19 pandemic, chloroquine (CQ) (a 4-aminoquinoline) and its derivative hydroxychloroquine (HCQ) have both been used as a potential form of treatment among infected patients. Originally known as an antimalarial quinolone, many countries have adopted their use as an option to treat COVID-19 patients. In humans, dose-dependent chloroquine induces QT interval prolongation. It also blocks the human ether-a-go-go-related gene (hERG), which encodes the rapidly activating delayed rectifier K+ channel. The action potential duration is then prolonged, as the eventual QTc interval of the electrocardiogram (ECG), resulting in torsade de pointes and cardiac arrhythmias that could lead to sudden death. It is yet unknown whether COVID-19 itself has any effect on the QTc interval. The current review established what is new and different from other studies involving the use of chloroquine and hydroxychloroquine among COVID-19 patients plus the corresponding QT interval prolongation in affected individuals.

Keywords: Long QT prolongation, hERG, ionic channels, drug repurposing, mobile devices, SARS-CoV-2

Up until now, there is no end in sight despite the recent vaccines produced; some are yet to get each their regulatory approval. The irony of this pandemic is the paralysis of businesses/economies that is catastrophic, fatalities, change in our ways of living and the huge price still being paid with increasing numbers of lives lost (6.14M) and 487M cases in 220 countries/areas worldwide as of March 31, 2022 [1]. The associated consequences have also dehumanized human beings, as people are left to die in self-isolation without loved ones and its sudden change in normality [2].

T he panic and the rush for measures in tackling the pandemic on a global scale have resulted, for a few cases, in the use of various drugs without proven efficacy, for instance, hydroxychloroquine, favipiravir, remdesivir, azithromycin or lopinavir/ritonavir [3]. The affinity of these medications in blocking the rapid component of the delayed rectifier current (IKr) encoding the human ether-a-go-go-related gene (hERG) as well as their propensity to prolong cardiac repolarization (QTc interval) and to cause torsades de pointes (TdP) (Fig. 1) were reported [4]. The quantification of drug-induced long QT syndrome (LQTS) through the use of six indices has been carried out by querying the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database with particular key words, according to Michaud *et al*. [5].

As of March 31, 2022, there are 6,274 studies on COVID-19 in the World Health Organization database, available at https://clinicaltrials.gov/ct2/who_table. Based upon their modes of action, some repurposed drugs were selected for the therapeutic management of COVID-19 [6]. If one of these is administered, it

***Received:** April 12, 2022; **Accepted:** July 29, 2022; **Published Online:** August 3, 2022*

***How to cite this article:** Herbert E, Fournier D. Clinical update of medications associated with QT prolongation among COVID-19 patients. Eur Res J 2022;8(5):732-741. DOI: 10.18621/eurj.1102545*

e-ISSN: 2149-3189

***Address for correspondence:** Ernest Herbert, PhD., Erdomo LLP, 22 Appletree Gardens, Whitley Bay, England and Wales, United Kingdom. E-mail: eherbertdoc@gmail.com, Phone: +44 793 326 81 73*

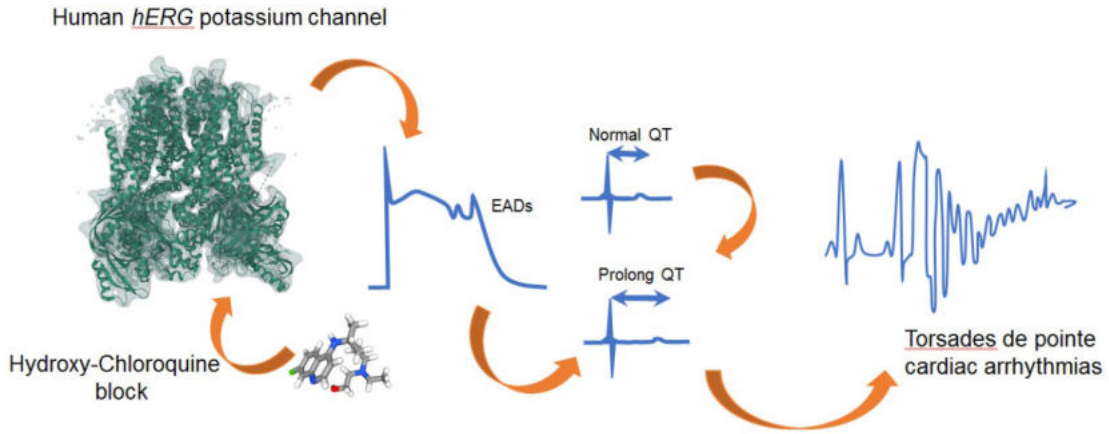

Fig. 1. Hydroxychloroquine and chloroquine have the affinity of these medications in blocking the rapid component of the delayed rectifier current encoding the human ether-a-go-go-related gene (hERG) as well as opensity to prolong cardiac repolarization (QTc interval) and to cause torsades de pointes.

could lead to serious, even fatal consequences, depending on its appropriate and safe use. Drugs such as hydroxychloroquine and chloroquine (Fig. 2) prolong the QTc interval and may result in ventricular arrhythmia and sudden cardiac arrest [7]. As a consequence, direct impacts of COVID-19 infection may include ventricular arrhythmias, harmful side effects of systemic illness and adverse events to medications applied in treating it [8].

COVID-19 was rapidly evolving right from the onset, and it is now a global battle to treat and be contained. There are variations from one population to the other with regard to prevalence of arrhythmia episodes and conduction system disorders, along with cardiovascular diseases in patients with COVID-19 [9]. The particular causes for palpitations, or even the types of arrhythmia, have not been specified in most available reports [10, 11]. Electrolyte abnormalities and hypoxia, both known to be associated with the development of acute arrhythmias are observed in the acute phase of severe COVID-19, however, it is unclear yet the exact contribution of an infection to arrhythmia in asymptomatic, mildly ill, critically ill and recovered patients [12].

Interestingly, gender was compared in terms of QT prolongation among COVID-19 patients undergoing chloroquine and hydroxychloroquine with/without azithromycin treatment. In women, it is identified as a risk factor, being one of the highest pro-arrhythmic [13-15]. It is significant, the greater one for developing the potentially fatal torsades de pointes (TdP) ventricular tachycardia, which is related to certain medications that prolong the repolarization of ventricles, being more prominent in women than men. The female gender is considered an independent risk factor for the incidence of syncope and sudden death in the inherited long QT syndrome, knowing that TdP is three times more commonly in women if compared to men [16].

According to Rosenberg *et al*. [17], the sex disproportionality in hospitalizations is precluded as being a distinct risk factor in association with the female

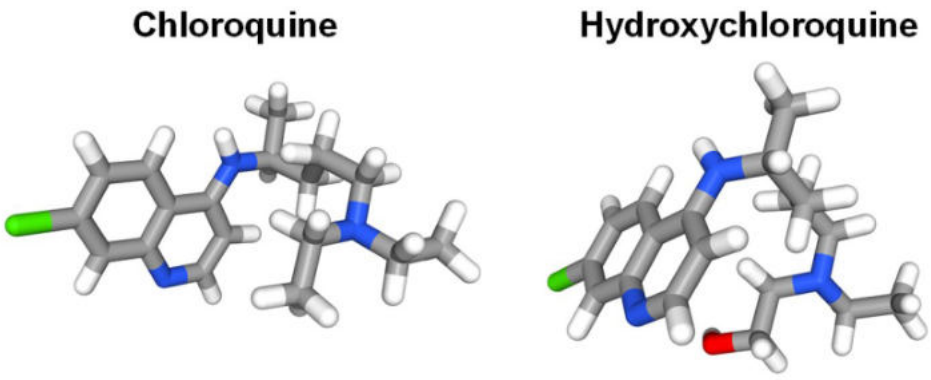

Fig. 2. Drugs such as hydroxychloroquine and chloroquine prolong the QTc interval.

COVID-19 patients, as a greater proportion that are admitted to hospitals are males. hERG channel is responsible for controlling the movement of potassium ions going out of the myocytes, and for conducting the rapid IKr component that is critical in phase 3, the repolarization phase of the cardiac action potential (AP) [18]. The higher susceptibility of women to drug-induced LQTS is believed to be attributed to the estrogen-mediated reduced repolarization [19].

Congenital LQTS is described as the hereditary form linked with mutations in several genes, the most significant being KCNQ1, KCNH2 two potassium channels, and SCN5A (specific to INa sodium current). LQTS could also be acquired, the most prevalent form having an incidence rate of 0.8 to 1.2 per million people per year [20]. Many wide-ranging pharmacological agents, from different therapeutic categories, block IKr and induce QT prolongation, they include class III antiarrhythmics and medications that are prescribed for non-cardiovascular indications like antibiotics, antidepressants, antipsychotics and antimalarial drugs (Table 1).

Pharmacodynamics and QTc-Prolonging Chloroquine/Hydroxychloroquine

The synthetic analog of quinine, namely chloroquine, is a muscle relaxant extracted from the bark of the cinchona tree (Cinchona officinalis). The synthesis of chloroquine was first conducted in 1934, and marketed as Resochin® by Bayer following the isolation of quinine in 1820. It was initially used in the West to treat malaria in 1631, in Rome. As for hydroxychloroquine, it was synthesized in 1946, and clinically introduced in 1955 under the brand name of Plaquenil®, while the introduction of chloroquine was, on the other hand, in 1947 as a prophylactic treatment of malaria [21].

Treating COVID-19 patients with the administration of hydroxychloroquine, chloroquine and/or azithromycin led to statistically significant increases in QT prolongation, as even after controlling a proportion of patients for electrolyte abnormalities [22]. The prolongation of QTc interval seemed consistent, irrespective of race or ethnicity [23].

It is perceived that chloroquine and hydroxychloroquine can have in vitro antiviral characteristics [24]. The entry and post-entry stages of SARS-CoV-2 infection are believed to be acted upon by CQ and HCQ through effects on endosomal pH and ensuing under-glycosylation of angiotensin-converting enzyme 2 (ACE2) receptors needed for viral entry. It has been hypothesized that the therapeutic effects of chloroquine and hydroxychloroquine involve (a) prevention of SARS-CoV-2 infection via inhibition of ACE2 mediated viral entries and (b) attenuation of the cytokine storm induced by the virus and experienced in severe COVID-19 cases [25].

If multiple medications are administered in combination, the risk of drug-induced sudden cardiac death (DI-SCD) could be amplified, each of which has its own QTc-prolonging and torsadogenic potential [26]. There has been scrambling for solutions and treatment options in the battle against COVID-19, such that little or no adequate time for precautionary measures.

A decision rested with the treating clinician and patient implied the risk-benefit calculus and navigating around a QTc value of 500 ms or more. Among younger COVID-19 patients (less than 40 years of age) who may have mild symptoms with above value, it could be appropriate to avoid treatment completely as the risk of arrhythmia may outweigh that of developing COVID-19-related acute respiratory distress syndrome [26]. On the other hand, patients more than 65 with a QTc of 500 ms or more, immunocompromised, underlying health conditions, and/or gradually worsening breathing problems, the potential benefit of a possible QTc-prolonging pharmacotherapy for COVID-19 may exceed the risk of arrhythmia.

For more than two decades, the inclination of using old drugs has intensified based on costs and reduction of time frames with the approval of regulatory agencies, considering that their safety profile is already known. There is no defined clarity to use the term “repurposing” here, except for the fact that off-patented drugs are being indicated as new therapeutic medications. The successes associated with repurposed drugs are few, but many have failed expectations from non-clinical investigations and observational studies [21].

By taking safety concerns into consideration, many advocates for chloroquine are based on data from patients with rheumatic diseases, but applying these facts for COVID-19 is implausible biologically. The infection process of COVID-19 and its metabolic consequences promote a pro-arrhythmic milieu, and

Table 1. QTc-prolonging drugs and arrhythmogenic adverse drug events for repurposed medications used for COVID-19.

Drug Name	VT/VF/TdP/LQTS	VT/VF/VA/VFL/VT	TdP/LQTS
Azithromycin			
Chloroquine			
Chlorpromazine	0		0
Cilostazol			
Cisapride			
Clarithromycin			
Clozapine			
Dasatinib			
Domperidone			1
Donepezil			
Droperidol			2
Escitalopram			
Halofantrine	4	1	1
Haloperidol			
Hydroxychloroquine			
Lapatinib			3
Lopinavir/Ritonavir			
Methadone			
Ondansetron			
Pentamidine	0	0	0
Pimozide	7	6	4
Propofol			
Risperidone			
Ritonavir			
Thioridazine	6	9	1
Vandetanib	1	1	1

VT = Ventricular tachycardia, VF = Ventricular fibrillation, TdP = Torsade de pointes, LQTS = Long QT syndrome, VA = Ventricular arrhythmia, VFL = Ventricular flutter (*Modified from* Michaud *et al.* [5])

added adverse events of medication could generate a devastating blow [27].

In terms of practice guidelines, the American College of Physicians do not recommend either chloroquine or hydroxychloroquine for prophylaxis or treatment. The pursuit and investment toward the use of 4-aminoquinolines in COVID-19 are not prudent and it is high time to bring to an end [27].

Portable ECG Measurements for QTc-monitoring of COVID-19 Patients

An interesting fact is that some FDA-approved mobile consumer ECG devices are capable of generating accurate QTc measurements [28]. AliveCor Inc., the manufacturer of the Kardia-Mobile 6L device that was approved for atrial fibrillation detection received in March 2020 an emergency clearance from the FDA for its use in monitoring COVID-19 patients prescribed with QTc-prolonging medications. The next-generation algorithm determines whether two or more ventricular ectopic beats are detected, if narrow complexes are noticed, and if there are QRS intervals of

120 ms or longer [29].

For COVID-19 patients who are about to be treated with drug-inducing torsade de pointes/sudden cardiac death, baseline QTc values could be obtained either through a conventional 12-lead ECG or the use of a smartphone-enabled mobile QTc meter to minimize personnel exposures [26]. Patients having QTc intervals of ≥ 500 ms (with QRS ≤ 120 ms) present an increased risk of QT prolongation and polymorphic VT [30]. The electrolyte abnormalities (for instance, hypocalcemia, hypokalemia, and/or hypomagnesemia) in such patients could be corrected with a potassium level close to 5 mEq/L.

Generally, patients with the following QTc intervals are perceived to be at low risk of significant QT prolongation and polymorphic VT [31].

–Prepubertal male/female ratio = QTc < 460 ms

–Postpubertal males = < 470 ms

–Postpubertal females = < 480 ms

There are concerns of cardiovascular toxicity associated with chloroquine and hydroxychloroquine, especially because of their relationship with electrical instability, characterized by QT interval prolongation. The mechanism relates to block the hERG potassium channel, which lengthens ventricular repolarization and duration of its AP. Throughout the course of COVID-19, malignant arrhythmia episodes that involve multifocal ventricular tachycardia/ventricular fibrillation develop and were linked with higher troponin T levels. Myocardial injury defined as troponin elevation could be because of target organ damage by hypoxemia, Takotsubo cardiomyopathy, or myocarditis, indicating that myocardial injury may play a role in the fatality of some COVID-19 infected patients [32, 33]. The characteristic features of patients treated with CQ and HCQ are shown in Table 2.

The risk of optimization and the benefit ratio when exploratory drugs are being given should be taken into consideration before resorting to electrocardiographic/QTc monitoring plus associated decisional guidance. The patients with COVID-19 who are severely ill are frequently disturbed by underlying comorbidities especially electrolyte imbalances, consequential QTc-prolonging medications and systemic inflammatory reactions resulting to torsades de pointes.

With the chaos and confusion surrounding the search for effective COVID-19 treatment, there has been a lack of systematic strategy, hence the rush toward CQ and HCQ. The repurposing of both for COVID-19 has been carried out without any formal determination of antiviral safety, effectiveness and dosing. Also, the global scientific community spirit has been collaborative but it seems to be fragmented and disoriented as well.

When the level of interleukin-6 (IL-6) is ≥ 10 pg/mL along with QTc > 500 ms, it is advisable to administer anti-IL-6 targeted drugs such as tocilizumab and sarilumab. The risk of inflammation-driven QTc changes could be minimized through blockage of IL-6, thereby reducing the need or even withdrawal of COVID-19 repurposed pharmacological treatments. It is not a sure thing if benefits are associated with the use of chloroquine or hydroxychloroquine to treat patients with COVID-19; rather, these drugs have links to ventricular arrhythmias and show a higher risk of in-hospital death [34]. In consequence, their usage should be prevented outside clinical and other emergency randomized trials.

Despite a widespread use of both medications in treating malaria and autoimmune disorders, even for a short-term duration, the undesirable effects associated with such drugs cannot be ignored. These adverse drug reactions are involving, but are not limited to, gastrointestinal and cutaneous manifestations, hypoglycemia, neuropsychiatric effects, and drug-drug interactions to name some. The cardiac-related complications are prevalent among 85% of affected patients while other non-specific events include ventricular hypertrophy, heart failure, hypokinesia, pulmonary arterial hypertension and valvular dysfunction. The RECOVERY trial that is the world's largest for COVID-19 concluded that hydroxychloroquine had no beneficial effect in COVID-19 hospitalized patients, and stopped the enrolment to that arm of the trial immediately.

Since the inception of the pandemic, both chloroquine/hydroxychloroquine have significantly gained scientific and political attention, however, evidence from large epidemiological studies and clinical trials have shown that CQ/HCQ have no significant mortality benefits among hospitalized COVID-19 patients. There are equivocations and inconsistencies surrounding their roles during the early phases of the outbreak, resulting in unsubstantiated support benefits for outpatients with COVID-19. Additionally, cardiotoxicity

Table 2. Summary of chloroquine or hydroxychloroquine and the cardiotoxicity among COVID-19 treated patients

Drug used	Cardiac toxicity	Beta blockers	Ca^{2+}channel blockers
HCQ 1,200 mg daily for 3 days, then 800 mg daily for 2 or 3 weeks	QT prolongation Cardiac arrhythmia during therapy course	Potential interaction	Potential interaction
High-dose (12 g) or low-dose (2.7 g) HCQ for 10 days	QTc > 500 ms or ventricular arrhythmia for 28 days	Potential interaction	Potential interaction
HCQ 200 mg 3 times daily for 5 days	Not reported		
Azithromycin or HCQ	QT prolongation Cardiac arrhythmia during therapy course		
HCQ 600 mg daily Duration not reported	QT prolongation Arrhythmia		
HCQ 200 mg twice daily for at least 3 days	QT prolongation Arrhythmia		
HCQ 400 mg twice daily on day 1, then 200 mg twice daily for 4 days	QT prolongation		
Chloroquine 600 mg daily for 5 days	QT prolongation		
HCQ 200 mg twice daily for 10 days	QT prolongation		
HCQ dose and duration, not reported	QT prolongation		
HCQ 600 mg daily for 10 days	QT prolongation		
HCQ 600 mg twice daily on day 1, then 200 mg twice daily for 4 days	QT prolongation		
HCQ 400 mg twice daily on day 1, then 200 mg twice daily for 4 days	Not reported		

(*Adapted from* Tleyjeh *et al.* [41] and Levett *et al.* [47])

particularly prolongation of QTc is the major concerns raised.

Other treatment agents applied in COVID-19 beyond therapies targeting cytokines, alias the cytokine release syndrome (CRS), include antivirals, antibacterial drugs, immunomodulators, angiotensin II receptor blockers, bradykinin B2 receptor antagonists, corticosteroids, anthelmintics, antiprotozoal drugs, H2 blockers and anticoagulants. Remdesivir, which is a broad-spectrum antiviral agent, was given approval in October 2020 by the FDA in the USA for the treatment of hospitalized patients with COVID-19. These were adult and pediatric subjects (over 12 years of age and weighing at least 40 kg or more) with severe disease. The limitations and controversial efficacy of remdesivir make it difficult to be used widely in hospital patients [35].

The first oral antiviral drug molnupiravir (Lagevrio; Merck, NJ, USA) approved in the UK for the treatment of COVID-19 was on November 4, 2021, for adults who tested positive with at least a risk factor for developing severe illness [36]. Its role is still limited for moderate to severe COVID-19 patients despite the fact that it prevents SARS-COV-2 to replicate by causing multiple mutations in the genome, and led to a significant reduction in hospitalization or death among mild cases. Like all developments in repositioning, COVID-19 drug repurposing research requires to pass through three stages before it can be assumed for advancement into the product portfolio:

the recognition of candidates, the mechanistic evaluation of effects in preclinical models, and the assessment of its efficacy in phase II clinical trials.

A protease inhibitor by the name of Paxlovid (Pfizer, NY, USA) undergoing phase III trials for testing its safety and effectiveness in order to treat non-hospitalized adults having COVID-19, but who are not at risk of developing serious illness, is a nirmatrelvir and ritonavir combination. While Paxlovid is being explored in post-exposure prophylaxis among patients with previous SARS-CoV-2 infection [37], it was able to reduce hospitalization by 80% based on its clinical efficacy.

In another development, angiotensin II receptor antagonist, a sartan derivative, an antihypertensive drug is also under study for COVID-19 treatment. From the onset of the pandemic, it has been reported that coronaviruses transfer their genetic material to the host cell, binding the ACE2 receptors. The physiological effects of angiotensin II are counteracting when losartan blocks binding between ACE2 and SARS-CoV-2 through the AT1 receptor.

The glucocorticoids are indicated for COVID-19 pneumonia, except in the event of specific comorbid conditions such as COPD exacerbations, according to a general advice from World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC), however, there are still controversies surrounding the use of corticosteroids.

Recent results published in The Lancet Respiratory Medicine support benefits of Evusheld in the outpatient treatment of mild to moderate COVID-19. Results from the TACKLE Phase III outpatient treatment trial showed that AstraZeneca's Evusheld (tixagevimab and cilgavimab, formerly AZD7442) provided clinically and statistically significant protection against COVID-19, from progressing to severe disease or death for any cause compared to placebo. Earlier treatment with Evusheld in the course of the disease led to favorable outcomes [38]. TACKLE is the phase III study of AZD7442 for treatment of COVID-19, which is a randomized, double-blind, placebo-controlled, multi-centre trial assessing the safety and efficacy of a single Evusheld 600 mg IM dose compared to a placebo in the outpatient treatment of mild-to-moderate disease. The study was conducted in 95 sites in the USA, Latin America, Europe and Japan. The sample comprised of 903 participants being randomized (1:1) to receive either Evusheld (n = 452) or saline placebo (n = 451), administered in two separate consecutive intramuscular (IM) injections.

The enthusiasm surrounding the use of hydroxychloroquine as a potential therapy for COVID-19 was based on a combination of factors, such as broad availability, oral administration, and its history in treating malaria. However, as reported recently by Self *et al*. [39] and White *et al*. [40], recent findings are consistently showing hydroxychloroquine as ineffective for treating COVID-19 patients. Furthermore, the risks of chloroquine- or hydroxychloroquine-induced QT prolongation and relatively higher events of torsade de pointes, ventricular tachycardia, or cardiac arrest are likely to be encountered among COVID-19 patients under treatment with these antimalarial drugs (see Fig. 1). It is therefore not advisable to use these agents in the routine management of people affected with COVID-19. There should be adequate monitoring of those who could be treated with chloroquine or hydroxychloroquine and for other indications. QT interval prolongation and torsade de pointes that are provoked have also been implicated in occasional case reports of systematic treatment in patients with systemic lupus erythematosus [41].

There are multiple risk factors associated with COVID-19 syndrome. For instance, hypokalemia, in the range of 3.0–3.4 mol/L is common, drug-induced Ikr blockade is amplified by fever; an increase in the levels of IL-6 has been experienced in COVID-19 infection, so this could be a mechanism for prolonging the QTc interval that is linked with inflammation [42]. Some practical measures have been highlighted to be considered when using CQ or HCQ alone or along with azithromycin. These include ECG recording before initiation of treatment where possible, avoidance of concomitant non-essential drugs known to prolong QT, potassium supplementation to > 4 mmol/L, if QTc is long (> 480 ms) at the baseline, obtaining an ECG within 2–4 hours after the first dose and to refrain from further treatment if QTc is documented to be above 520 ms [43]. And noteworthy, in the meta-analysis study by Fiolet *et al*. [44] reaffirmed that hydroxychloroquine alone does not have any therapeutic effect on patients with COVID-19, but the risk of mortality is enhanced if it is combined with azithromycin.

CONCLUSION

Summarily, from all indications, the use of CQ or HCQ for treating COVID-19 infected patients has been non-beneficial and resulted in the risk of ventricular arrhythmias with a greater chance of in-hospital death among the affected individuals. Also, the combination of azithromycin and hydroxychloroquine did not increase the likelihood of survival or discharge in hospitalized patients with COVID-19. This inference tallies with European Respiratory guidelines, which indicated no clinical benefits in relation to the use of hydroxychloroquine and/or azithromycin to treat infected COVID-19 patients [45]. The optimal approach in managing COVID-19 is yet to be established and the evidence for suggesting repurposing HCQ is purely based on the reduction of in vitro viral replication whereas the clinical data are in contradiction. From the RECOVERY trial, no mortality benefit is found associated with HCQ in treating COVID-19 patients, with longer hospital stays, and higher risk of disease progression toward invasive mechanical ventilation and/or death. In a similar fashion, the WHO SOLIDARITY trial also indicated no advantage either [46]. In RECOVERY and WHO SOLIDARITY trials, HCQ was used in comparative higher doses, with the exception of REMAP-CAP trial.

Interestingly, Evusheld has marketing authorization by the European Union and had granted a conditional status by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK for pre-exposure prophylaxis of COVID-19, likewise in the USA. Evusheld is gaining authorization for use and being supplied in many countries around the globe with regulatory filings increasing for both prevention and treatment worldwide. These are encouraging developments and an alternative solution especially among those individuals that were reluctant or did not want to be vaccinated for COVID-19.

Authors' Contribution

Study Conception: EH, DF; Study Design: EH, DF; Supervision: EH, DF; Funding: N/A; Materials: N/A; Data Collection and/or Processing: N/A; Statistical Analysis and/or Data Interpretation: EH, DF; Literature Review: EH, DF; Manuscript Preparation: EH, DF and Critical Review: EH, DF.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Worldometer. Reported cases and deaths by country, territory, or conveyance Globally: Worldometer; 2020 [July 5, 2020]. Available from: https://www.worldometers.info/.
2. Bavel JJV, Baicker K, Boggio PS, Capraro V, Cichocka A, Cikara M, et al. Using social and behavioural science to support COVID-19 pandemic response. Nat Hum Behav 2020;4:460-71.
3. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 2020;323:1824-36.
4. Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020;26:808-9.
5. Michaud V, Dow P, Al Rihani SB, Deodhar M, Arwood M, Cicali B, et al. Risk assessment of drug-induced long QT syndrome for some COVID-19 repurposed drugs. Clin Transl Sci 2021;14:20-8.
6. Zhou Y, Wang F, Tang J, Nussinov R, Cheng F. Artificial intelligence in COVID-19 drug repurposing. Lancet Digit Health 2020;2:e667-76.
7. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review. Heart Rhythm 2020;17:1472-9.
8. Manolis AS, Manolis AA, Manolis TA, Apostolopoulos EJ, Papatheou D, Melita H. COVID-19 infection and cardiac arrhythmias. Trends Cardiovasc Med 2020;30:451-60.
9. Wang Y, Wang Z, Tse G, Zhang L, Wan EY, Guo Y, et al. Cardiac arrhythmias in patients with COVID-19. J Arrhythm 2020;36:827-36.
10. Babapoor-Farrokhran S, Rasekhi RT, Gill D, Babapoor S, Amanullah A. Arrhythmia in COVID-19. SN Compr Clin Med 2020;2:1430-5.
11. Kochav SM, Coromilas E, Nalbandian A, Ranard LS, Gupta A, Chung MK, et al. Cardiac arrhythmias in COVID-19 infection. Circ Arrhythm Electrophysiol 2020;13:e008719.
12. Lakkireddy DR, Chung MK, Gopinathannair R, Patton KK, Gluckman TJ, Turagam M, et al. Guidance for cardiac electrophysiology during the COVID-19 pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. Heart Rhythm

2020;17:e233-41.
13. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 1993;270:2590-7.
14. Bednar MM, Harrigan EP, Ruskin JN. Torsades de pointes associated with nonantiarrhythmic drugs and observations on gender and QTc. Am J Cardiol 2002;89:1316-9.
15. Lehmann MH, Hardy S, Archibald D, quart B, MacNeil DJ. Sex difference in risk of torsade de pointes with d,l-sotalol. Circulation 1996;94:2535-41.
16. Darpo B, Karnad DR, Badilini F, Florian J, Garnett CE, Kothari S, et al. Are women more susceptible than men to drug-induced QT prolongation? Concentration-QTc modelling in a phase 1 study with oral rac-sotalol. Br J Clin Pharmacol 2014;77:522-31.
17. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;323:2493-502.
18. Tristani-Firouzi M, Chen J, Mitcheson JS, Sanguinetti MC. Molecular biology of K(+) channels and their role in cardiac arrhythmias. Am J Med 2001;110:50-9.
19. Li G, Cheng G, Wu J, Zhou X, Liu P, Sun C. Drug-induced long QT syndrome in women. Adv Ther 2013;30:793-802.
20. Molokhia M, Pathak A, Lapeyre-Mestre M, Caturla L, Montastruc JL, L'Association Francaise des Centres Regionaux de P, et al. Case ascertainment and estimated incidence of drug-induced long-QT syndrome: study in Southwest France. Br J Clin Pharmacol 2008;66:386-95.
21. Shah RR. Chloroquine and hydroxychloroquine for COVID-19: Perspectives on their failure in repurposing. J Clin Pharm Ther 2021;46:17-27.
22. Saleh M, Gabriels J, Chang D, Soo Kim B, Mansoor A, Mahmood E, et al. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circ Arrhythm Electrophysiol 2020;13:e008662.
23. Shah RR. Drug-induced QT interval prolongation: does ethnicity of the thorough QT study population matter? Br J Clin Pharmacol 2013;75:347-58.
24. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020;71:732-9.
25. Pastick KA, Okafor EC, Wang F, Lofgren SM, Skipper CP, Nicol MR, et al. Review: hydroxychloroquine and chloroquine for treatment of SARS-CoV-2 (COVID-19). Open Forum Infect Dis 2020;7:ofaa130.
26. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc 2020;95:1213-21.
27. Gupta A, Malviya A. Chloroquine and hydroxychloroquine for COVID-19: time to close the chapter. Postgraduate Med J 2021;97:676-7.
28. Varma N, Marrouche NF, Aguinaga L, Albert CM, Arbelo E, Choi JI, et al. HRS/EHRA/APHRS/LAHRS/ACC/AHA Worldwide Practice Update for telehealth and arrhythmia monitoring during and after a pandemic. Circ Arrhythm Electrophysiol 2020;13:e009007.
29. Nair TRG. Advances in Electrocardiogram Information Management. In: Khosrow-Pour M, editor. Encyclopedia of Information Science and Technology. 3rd ed. Pennsylvania: IGI Global, 2015: pp. 3296-304.
30. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for drug interactions on QTc in exploratory COVID-19 treatment. Circulation 2020;141:e906-7.
31. O'Hare M, Maldonado Y, Munro J, Ackerman MJ, Ramakrishna H, Sorajja D. Perioperative management of patients with congenital or acquired disorders of the QT interval. Br J Anaesth 2018;120:629-44.
32. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:811-8.
33. Minhas AS, Scheel P, Garibaldi B, Liu G, Horton M, Jennings M, et al. Takotsubo syndrome in the setting of COVID-19. JACC Case Rep 2020;2:1321-5.
34. Lazzerini PE, Laghi-Pasini F, Acampa M, Boutjdir M, Leopoldo Capecchi P. IL-6 (interleukin 6) blockade and heart rate corrected QT interval prolongation in COVID-19. Circ Arrhythm Electrophysiol 2020;13:e008791.
35. De Clercq E. Remdesivir: Quo vadis? Biochem Pharmacol 2021;193:114800.
36. Cave JA, Phizackerley D. Molnupiravir: evidence by press release. Drug Ther Bull 2022;60:2.
37. Heskin J, Pallett SJC, Mughal N, Davies GW, Moore LSP, Rayment M, et al. Caution required with use of ritonavir-boosted PF-07321332 in COVID-19 management. Lancet 2022;399:21-2.
38. Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, et al. Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2022. doi: 10.1016/S2213-2600(22)00180-1
39. Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. JAMA 2020;324:2165-76.
40. White NJ, Watson JA, Hoglund RM, Chan XHS, Cheah PY, Tarning J. COVID-19 prevention and treatment: A critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. PLoS Med 2020;17:e1003252.
41. Tleyjeh IM, Kashour Z, AlDosary O, Riaz M, Tlayjeh H, Garbati MA, et al. Cardiac toxicity of chloroquine or hydroxychloroquine in patients with COVID-19: a systematic review and meta-regression analysis. Mayo Clin Proc Innov Qual Outcomes. 2021;5:137-50.
42. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet

2020;395:1054-62.
43. Funck-Brentano C, Salem JE, Nguyen LS, Drici MD, Roden DM. Response to the editorial "COVID-19 in patients with cardiovascular diseases": Covid-19 treatment with hydroxychloroquine or chloroquine and azithromycin: A potential risk of Torsades de Pointes. Arch Cardiovasc Dis 2020;113:367-8.
44. Fiolet T, Guihur A, Rebeaud ME, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. Clin Microbiol Infect 2021;27:19-27.
45. Chalmers JD, Crichton ML, Goeminne PC, Cao B, Humbert M, Shteinberg M, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J 2021;57:2100048.
46. WHO Solidarity Trial Consortium; Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Karim QA, et al. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. N Eng J Med 2021;384:497-511.
47. Levett JY, Raparelli V, Mardigyan V, Eisenberg MJ. Cardiovascular pathophysiology, epidemiology, and treatment considerations of coronavirus disease 2019 (COVID-19): a review. CJC Open 2021;3:28-40.