Circulation: Arrhythmia and Electrophysiology

PERSPECTIVE

Use of Chloroquine and Hydroxychloroquine in COVID-19 and Cardiovascular Implications

Understanding Safety Discrepancies to Improve Interpretation and Design of Clinical Trials

Ohad Oren, MD; Eric H. Yang, MD; Ty J. Gluckman, MD; Erin D. Michos, MD, MHS; Roger S. Blumenthal, MD; Bernard J. Gersh, MB, ChB, DPhil, MACC

The public health burden imposed by coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been substantial. As of May 5, 2020, >3.6 million individuals have been infected globally and >250 000 have died.[1] Mounting research efforts are under way to test and develop effective prophylactics and therapeutics. Among the compounds under investigation are chloroquine and hydroxychloroquine, 2 widely used antimalarial drugs with additional indications for use in patients with connective tissue diseases and autoimmune disorders.

Guided by in vitro evidence of antiviral activity and early clinical studies demonstrating improvements in surrogate end points, in the early weeks of the outbreak some prominent politicians, journalists, and physicians have advocated for the routine empirical use of these medications in patients with COVID-19 and for prophylaxis to prevent infection. While such an approach may seem reasonable given the current pandemic, it strongly contrasts with the standard modus operandi that demands supportive data from well-designed clinical trials before widespread medication use. In this article, we discuss the cardiovascular impact of chloroquine and hydroxychloroquine and provide our scientific opinion regarding the safety of these medications in patients with COVID-19 before formal regulatory review.

Chloroquine and hydroxychloroquine are commonly prescribed worldwide. When used for malaria prophylaxis, chloroquine is generally administered at a dose of 500 mg per week starting 2 weeks before and continuing for up to 8 weeks following endemic exposure. Long-term use can be considered for the treatment of chronic autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine is typically prescribed as a 400 mg weekly dose when used for malaria chemoprophylaxis and as a 200 to 400 mg daily dose in patients with systemic lupus erythematosus or with rheumatoid arthritis.

MECHANISMS OF ACTION

Chloroquine and hydroxychloroquine alkalinize phagolysosomes, leading to impairment of cellular fusion and viral uncoating.[2] The drug-mediated pH elevation also increases protease activity and decreases intracellular processing of secretory proteins, such as tumor necrosis factor α and interleukin-6, which are proinflammatory cytokines. This has prompted clinical investigation of tocilizumab, a humanized monoclonal antibody targeting interleukin-6, for which results are eagerly awaited. Specific antiparasitic mechanisms include inhibition of hemoglobin degradation in intraerythrocytic trophozoites, culminating in the accumulation of cytoxic heme and lysosome toxicity.[3] Antiautoimmune activity stems from its activation of transcription factor FOXP3 (forkhead/winged helix transcription factor) and the promotion of regulatory T cells.

Chloroquine and hydroxychloroquine have broad in vitro antiviral properties, prompting previous evaluation

Key Words: chloroquine ■ COVID-19 ■ hydroxychloroquine ■ pandemic ■ trophozoites

Correspondence to: Bernard J. Gersh, MB, ChB, DPhil, MACC, Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, 200 First Street SW, Rochester MN 55905. Email Gersh.Bernard@mayo.edu

For Sources of Funding and Disclosures, see page 590.

Circulation: Arrhythmia and Electrophysiology is available at www.ahajournals.org/journal/circep

Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
COVID-19	coronavirus disease 2019
FOXP3	forkhead/winged helix transcription factor
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

in HIV and the severe acute respiratory syndrome. In a primate cell model of the severe acute respiratory syndrome, both drugs inhibit terminal glycosylation of the cellular receptor, ACE2 (angiotensin-converting enzyme 2).[4] Because blockade of ACE2 attenuates virus receptor binding pre- and post-infection, chloroquine and hydroxychloroquine are thought to be potentially effective options for viral prophylaxis and treatment.

In SARS-CoV-2 cells, chloroquine suppresses viral entry and postentry stages, while promoting immune-modulating activity thought to be synergistic with its direct antiviral effects. In an in vitro pharmacokinetic model of SARS-CoV-2 infected cells, hydroxychloroquine appears to be more potent than chloroquine, with a significantly lower half maximal effective concentration (EC50=0.72 μmol/L, EC50=5.47 μmol/L).[5] Azithromycin, whose combination with hydroxychloroquine is currently being evaluated in several trials, has multiple direct antiviral properties, with the most established mechanism being inhibition of interferon-stimulated gene expression and protein production.

CLINICAL STUDIES

While a number of clinical trials are seeking to evaluate the effect of chloroquine and hydroxychloroquine in COVID-19, several have already been published. A summary of the most important studies with available results is included in Table.[6,7,9–11] Although a few trials have demonstrated improvement in various surrogate end points (ie, viral clearance), these investigations are limited by small sample size. Importantly, this precludes adequate evaluation of safety and efficacy among diverse populations, including those with underlying cardiovascular disease.

Based predominantly on preclinical data, the US Food and Drug Administration issued an emergency use authorization of chloroquine phosphate in adults hospitalized with COVID-19 for whom clinical trial participation is not possible.[12] The authorization statement recognizes that optimal dosing and treatment durations are currently unknown, and that high-quality clinical trial data are essential to understanding any therapeutic benefits. To date, only few clinical trials evaluating chloroquine and hydroxychloroquine have reported the cardiovascular safety of these medications when used to treat COVID-19. This is particularly important given the adverse cardiovascular effects, including cardiomyopathy, that have been reported previously. Both medications can induce cardiotoxicity via inhibition of lysosomal enzymes in cardiomyocytes, including α-galactosidase A, β-galactosidase, and arylsulfatase.[13] These changes are reminiscent of the cardiomyopathy associated with Fabry disease, with biventricular concentric hypertrophy and diastolic dysfunction. At the ultrastructural level, hydroxychloroquine toxicity is associated with intracellular accumulation of myelin and formation of curvilinear bodies.[14]

Chloroquine blocks the cardiac inward rectifier K^+ current, I_{K1}, and to a lesser degree the rapidly activating delayed rectifier, I_{Kr}, resulting in prolongation of the action potential. This increases the likelihood of ventricular ectopy and lethal ventricular arrhythmias. Hydroxychloroquine prolongs spontaneous action potential firing via inhibition of multiple cardiac channels, including that of I_{CaL} and I_f.

Chloroquine and hydroxychloroquine are also characterized by a number of additional adverse effects, including cutaneous (hyperpigmentation of skin), neuromuscular (weakness), and ophthalmologic (retinopathy) manifestations (Figure).

To a large degree, the incidence and spectrum of adverse cardiovascular effects with chloroquine and hydroxychloroquine are not well described. Existing reports show that undifferentiated cardiac toxicity from these drugs appears to be more frequent in women (65%), typically following a long treatment duration (median of 7 years) and high cumulative dose.[14] According to a systematic review of published cardiac complications with chloroquine and hydroxychloroquine (median duration of 7 years [range: 3 days–35 years]), conduction disorders were reported most commonly (85% of cases). Less frequently encountered cardiovascular effects included left ventricular hypertrophy, left ventricular hypokinesis and heart failure, QTc prolongation (especially in patients with preexisting QT prolongation and in combination with macrolide antibiotics), valvular heart disease, and pulmonary arterial hypertension.[15] Interestingly, complete atrioventricular block was more commonly associated with chloroquine; whereas, left ventricular hypokinesis was more commonly encountered with hydroxychloroquine.

A great deal of cardiovascular uncertainty exists when considering use of chloroquine or hydroxychloroquine in patients with COVID-19. First, historical trials that established the value of these medications in rheumatoid arthritis and systemic lupus erythematosus did not systematically collect cardiovascular safety data.[16] Since electrocardiograms and cardiac imaging were not routinely performed, the incidence, risk factors, and clinical outcomes of cardiac arrhythmias or heart failure among patients receiving chloroquine or hydroxychloroquine are not known. In addition, the likelihood of recovery or

Table. Major Clinical Trials of Chloroquine or Hydroxychloroquine in Patients With COVID-19

Author	Country	Study Population	Study Sample	Medications	End Points	Results
Gautret et al[6]	France	Hospitalized patients, age>12 y, SARS-CoV-2 positive PCR	36	HCQ±azithromycin	Viral clearance, nasopharyngeal swab, PCR	Viral-free: HCQ, 57%; HCQ+azithromycin: 100%
						Control: 12.5% (day 6)
Chen et al[7]	China	Hospitalized patients, SARS-CoV-2 positive PCR	30	Arm A: HCQ	Viral clearance, nasopharyngeal swab, PCR	Viral-free: HCQ, 87%
				Arm B: control		Control: 93% (P>0.05; day 7)
Borba et al[9]	Brazil	Hospitalized patients with clinically suspected COVID-19	81	Arm A: high-dose (600 mg twice daily for 10 days) chloroquine	All-cause mortality; QTc >500 msec	Mortality: high-dose, 39%; low-dose, 15%
				Arm B: low-dose (450 mg twice daily on day 1 and once daily for 4 days) chloroquine diphosphate.z		QTc >500 msec: high-dose, 19%; low-dose, 11%
Mahevas et al[10]	France	Hospitalized adult patients, SARS-CoV-2 positive PCR, requiring oxygen	181	Arm A: HCQ	Transfer to ICU, all-cause mortality, within 7 days	All-cause mortality: HCQ, 2.8%; control, 4.6% (nonsignificant)
				Arm B: control		Transfer to ICU or death: HCQ, 20%; control, 22% (nonsignificant)
Chen et al[11]	China	Hospitalized adult patients, SARS-CoV-2 positive PCR	62	Arm A: HCQ	Time to clinical recovery	Improvement in pneumonia: HCQ, 81%; control, 55%
				Arm B: control		

COVID-19 indicates coronavirus disease 2019; HCQ, hydroxychloroquine; ICU, intensive care unit; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

response to neurohumoral blockade has also not been studied. Finally, while the potential for QTc prolongation is well known to occur with these medications, its incidence has not been established.

This point is particularly relevant in patients with COVID-19, as both arrhythmias and cardiomyopathy have been described in those with more severe manifestations of the disease. Moreover, acutely ill patients with COVID-19 may be more likely to receive empirical antimicrobial regimens that include other QTc-prolonging drugs, such as azithromycin, levofloxacin, and azole antifungals. Azithromycin, in particular, has been recognized as a cause of QT prolongation and a higher risk of sudden cardiac death, which is more likely in women and in the elderly. Patients with severe COVID-19 also commonly manifest biochemical changes such as hypokalemia, hypomagnesemia, as well as fever, which can potentiate QT prolongation. In addition, although a recent randomized controlled trial showed no benefit with lopinavir/ritonavir compared with standard of care in patients with severe COVID-19,[17] this combination therapy can interact with chloroquine, and may further prolong the QT interval.

Collectively, these findings underscore the urgent need for additional studies formally assessing the arrhythmic potential of these agents through double-blind trial design and rigorous electrocardiographic monitoring protocols. Such an approach is feasible in the outpatient setting and in those already on telemetry. This is likely to be more challenging for those admitted to floors without telemetry services, as repeated electrocardiographic assessment increases exposure risk to healthcare workers. Therefore, a more pragmatic approach leveraging electrocardiographic assessment in permissive scenarios or in those at higher arrhythmia risk (concomitant proarrhythmic medications, underling cardiac disease). While preliminary data has been published evaluating the use of mobile cardiac telemetry for QTc and arrhythmia monitoring in patients with COVID-19 receiving medications with torsadogenic potential,[18] additional studies are needed.

A recent review from the Mayo Clinic outlines an approach to mitigating the torsadogenic potential of investigated pharmacotherapies for COVID-19.[19] The article endorses the performance of a baseline ECG with QTc measurement for all patients with COVID-19 slated for treatment with medications which may lead to torsades des pointes. QTc intervals longer than the 99th percentile (470 msec in adult males, 480 msec in adult females) should be considered higher risk for ventricular arrhythmias and those with QTc intervals exceeding 500 ms should be regarded as higher risk for torsades des pointes as well as sudden cardiac death. In both groups, careful investigation of modifiable co-contributors to QTc prolongation should be mandated,

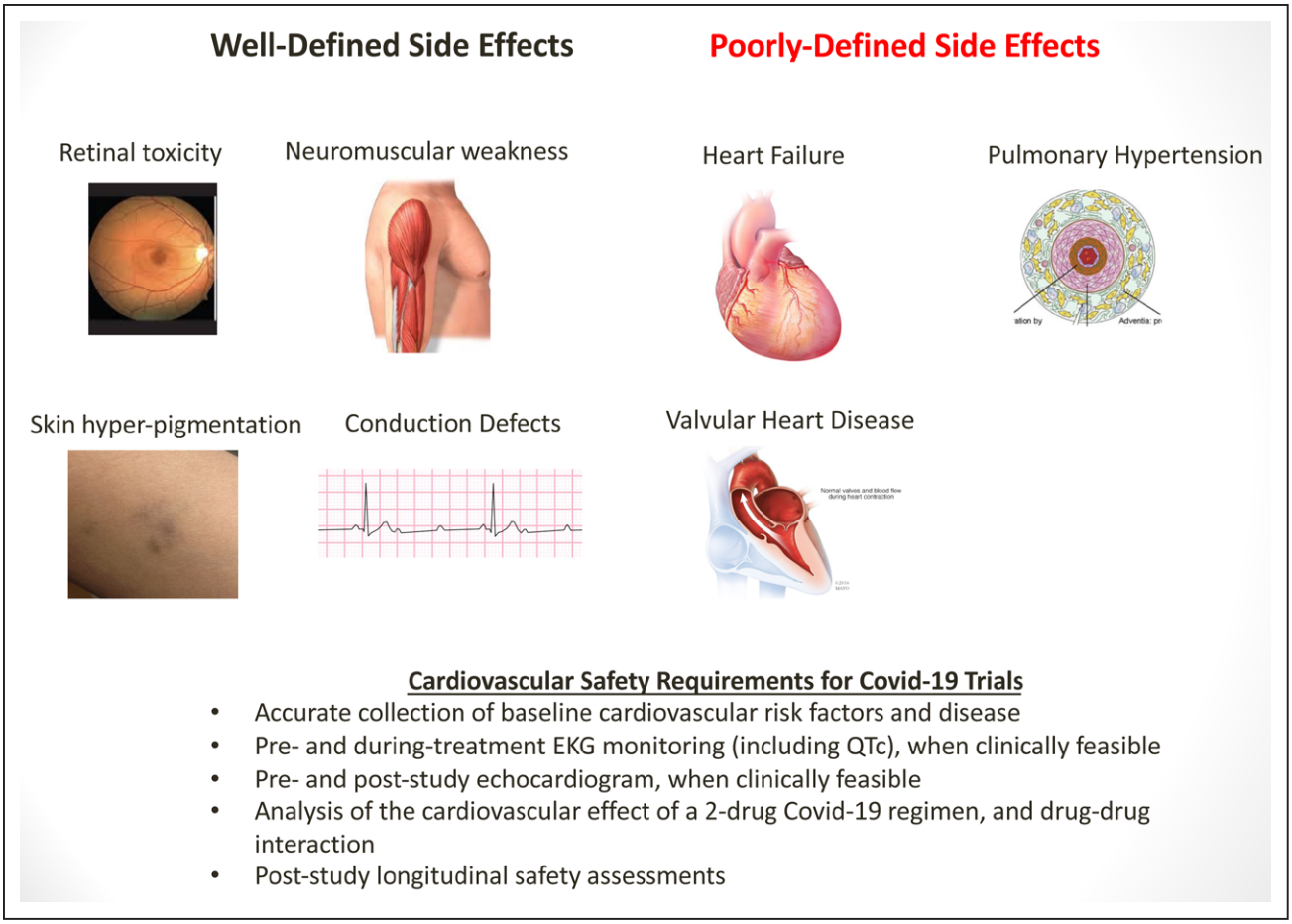

Figure. Systemic adverse effects of chloroquine and hydroxychloroquine.

with discontinuation of nonessential medications and close monitoring with telemetry.

In late April, the Food and Drug Administration released a safety communication in which it cautioned against the use of chloroquine or hydroxychloroquine in patients with COVID-19 in a nonhospital, nontrial setting, due to the risk of serious arrhythmias. The Food and Drug Administration's safety statement followed reports of QT prolongation, ventricular tachycardia, and ventricular fibrillation in patients with COVID-19 treated with chloroquine or hydroxychloroquine with or without azithromycin.

EFFECT ON LEFT VENTRICULAR FUNCTION

The incidence of cardiomyopathy with chloroquine and hydroxychloroquine is currently unknown, with most available data derived from case reports. Both medications, however, have been implicated as a cause and exacerbator of left ventricular diastolic dysfunction—a finding largely believed to be reversible upon drug discontinuation.[20] There exists an important need to improve our understanding of the potential for cardiomyopathy in the midst of the COVID-19 pandemic. This is challenged by (1) the lack of pharmacovigilance and adverse event-focused studies to date, (2) marked differences between patients historically treated with these agents from those likely to be treated in the midst of an acute symptomatic viral infection, and (3) the added effect of the SARS-CoV-2 infection on the cardiovascular system. The potential for drug-induced valvular abnormalities, alterations to the conduction system, and left ventricular dysfunction, underscore the urgent need for dedicated studies to determine the prevalence, predisposing factors, and short- as well as long-term consequences.

PRUDENT RECOMMENDATIONS

In light of the potential for serious cardiovascular effects with chloroquine and hydroxychloroquine, we believe their use in COVID-19 should be limited to randomized controlled trials. For critically ill patients unable to enroll in a trial, selective in-hospital use could be considered, with careful clinical monitoring in keeping with the Food and Drug Administration's emergency use authorization.

Empirically administering these drugs outside of a clinical trial risks exposing patients to serious adverse effects beyond those associated with COVID-19. Non

evidence-based use may also limit their availability for patients with approved clinical indications (eg, systemic lupus erythematosus, rheumatoid arthritis). Of key importance is the need for condition-specific pharmacotoxicity analyses and trial safety reporting (Figure).

In summary, findings regarding the benefit of chloroquine/hydrochloquine have not been encouraging to date, but larger trials are underway to assess the efficacy, and in particular the efficacy related to timing of drug administration. There exists an urgent need to enroll patients in clinical trials that are able to identify rare, but important adverse cardiovascular events. Studies evaluating chloroquine and hydroxychloroquine should systematically collect baseline demographic data, results from electrocardiographic and echocardiographic monitoring before and during treatment, and rates of adverse cardiovascular events in both the short- and long-term. Only with such an approach will the safety of these agents be truly understood.

ARTICLE INFORMATION

Affiliations

Division of Hematology and Oncology, Mayo Clinic, Rochester, MN (O.O.). Division of Cardiology, Department of Medicine, University of California at Los Angeles (E.H.Y.). Center for Cardiovascular Analytics, Research and Data Science (CARDS), Providence Heart Institute, Providence St Joseph Health, Portland, OR (T.J.G.). The Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD (E.D.M., R.S.B.). Department of Cardiovascular Medicine, Mayo Clinic & Mayo Clinic College of Medicine, Rochester, MN (B.J.G.).

Sources of Funding

None.

Disclosures

B.J. Gersh is CRO for Trials involving Edwards Percutaneous Valve Devices: Baim Institute; DSMB—REPRISE Study: Boston Scientific Corporation, DSMB—RELIEVE-HF & SPYRAL Trials: Cardiovascular Research Foundation, DSMB—Pioneer HCM: Duke Clinical Research Institute, DSMB: Duke University, ENVISAGE-TAVI DSMB: Icahn School of Medicine at Mount Sinai, Executive Committee ORBIT Registries; Chairman DSMB; Steering Committee & Writing Committee (REVEAL Trial): Janssen Scientific Affairs (DSMB—PROMINENT Trial Medtronic Inc); Kowa Research Institute, Inc, DSMB— General Consulting: MyoKardia, Steering Committee—Garfield Study: Thrombosis Research Institute. The other authors report no conflicts.

REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20:533–534. doi: 10.1016/S1473-3099(20)30120-1
2. Rolain JM, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents*. 2007;30:297–308. doi: 10.1016/j.ijantimicag.2007.05.015
3. Sullivan DJ Jr, Gluzman IY, Russell DG, Goldberg DE. On the molecular mechanism of chloroquine's antimalarial action. *Proc Natl Acad Sci U S A*. 1996;93:11865–11870. doi: 10.1073/pnas.93.21.11865
4. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, Seidah NG, Nichol ST. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:69. doi: 10.1186/1743-422X-2-69
5. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, 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;ciaa237. doi: 10.1093/cid/ciaa237
6. Gautret P, Lagier JC, Parola P, Honag VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial[published online ahead of print, 2020 Mar 20]. *Int J Antimicrob Agents*. 2020;105949. doi: 10.1016/j.ijantimicag.2020.105949
7. Chen J, Liu D, Liu L, Ping L, Qingnian XU, Lu X, Yun L, Dan H, Shuli S, Dandan Z, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J XheJiang Univ*. 2020;49:215–219.
8. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14:72–73. doi: 10.5582/bst.2020.01047
9. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, Mourão MPG, Brito-Sousa JD, Baía-da-Silva D, Guerra MVF, et al; CloroCovid-19 Team. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a Randomized Clinical Trial. *JAMA Netw Open*. 2020;3:e208857. doi: 10.1001/jamanetworkopen.2020.8857
10. Mahevas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, Gallien S, Lepeule R, Szwebel T, Lescure X, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. *medRxiv*. 2020;04.10.20060699. doi: 10.1101/2020.04.10.20060699
11. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, Zhuang R, Hu B, Zhang Z. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv*. 2020;03.22.20040758. doi: 10.1101/2020.03.22.20040758
12. Fact Sheet for health care providers. Emergency use authorization (EUA) of chloroquine phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. U.S Food and Drug Administration (FDA). https://www.fda.gov/media/136535/download. Accessed April 3, 2020
13. Frustaci A, Morgante E, Antuzzi D, Russo MA, Chimenti C. Inhibition of cardiomyocyte lysosomal activity in hydroxychloroquine cardiomyopathy. *Int J Cardiol*. 2012;157:117–119. doi: 10.1016/j.ijcard.2012.03.112
14. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. *Drug Saf*. 2018;41:919–931. doi: 10.1007/s40264-018-0689-4
15. Stas P, Faes D, Noyens P. Conduction disorder and QT prolongation secondary to long-term treatment with chloroquine. *Int J Cardiol*. 2008;127:e80–e82. doi: 10.1016/j.ijcard.2007.04.055
16. Tye MJ, White H, Appel B, Ansell HB. Lupus erythematosus treated with a combination of quinacrine, hydroxychloroquine and chloroquine. *N Engl J Med*. 1959;260:63–66. doi: 10.1056/NEJM195901082600203
17. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Son B, Cai Y, Wei M, et al. A yrial of lopinavir-ritonavir in adults hospitalized with severe Covid-19.[published online ahead of print, 2020 Mar 18]*N Engl J Med*. 2020;382:1787–1799. doi: 10.1056/NEJMoa2001282
18. Chang D, Saleh M, Gabriels J, Ismail H, Goldber B, Willner J, Beldner S, Mitra R, John R, Epstein LM. Inpatient use of ambulatory telemetry monitors for COVID-19 patients treated with hydroxychloroquine and/or azithromycin.[published online ahead of print, 2020 Apr 18]*J Am Coll Cardiol*. 2020;S0735-1097(20)35009-9. doi: 10.1016/j.jacc.2020.04.032
19. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for COVID-19. Mayo Clinic Proceedings. 2020;95. https://www.mayoclinicproceedings.org/article/S0025-6196(20)30313-X/pdf. Accessed May 29, 2020.
20. Yogasundaram H, Hung W, Paterson ID, Sergi C, Oudit GY. Chloroquine-induced cardiomyopathy: a reversible cause of heart failure. *ESC Heart Fail*. 2018;5:372–375. doi: 10.1002/ehf2.12276