

Cardiovascular Safety of Potential Drugs for the Treatment of Coronavirus Disease 2019



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Coronavirus disease 2019 (COVID-19) has become a global pandemic. It is still uncontrolled in most countries and no therapies are currently available. Various drugs are under investigation for its treatment. The disease is known to have worse outcomes in patients who have underlying cardiovascular disease. Chloroquine/hydroxychloroquine, azithromycin, remdesivir and lopinavir/ritonavir are currently being studied in trials and show some promise. Conduction disorders, heart failure, and mortality have been reported with the use of these drugs. It is important to have knowledge of potential cardiotoxic effects of these drugs before using them for COVID-19 patients for better allocation of healthcare resources and improvement in clinical outcomes. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;128:147–150)

The current outbreak of coronavirus disease 2019 (COVID-19) has been declared as a global pandemic. It is caused by the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) and has thus far infected >1.5 million people with >500,000 cases in the United States alone.¹ Physicians and scientists are working tirelessly to find a potential drug or vaccine for its treatment. Increased disease severity and mortality have been noted in those with cardiovascular disease who develop COVID-19.^{2,3} Moreover, a decreased potassium level has also been reported in patients with COVID-19, which can cause electrocardiographic changes like prolonged QT interval and may increase the risk of adverse reactions with pharmacotherapies. Hence, understanding the cardiovascular risks of potential pharmacotherapies being investigated for COVID-19 is of utmost importance. Numerous drugs are currently under investigation, some in early phase clinical trials. The drugs of highest interest to-date include chloroquine/hydroxychloroquine (CQ/HCQ) alone or in combination with azithromycin, remdesivir, lopinavir/ritonavir, and interferon alpha-2b.⁴ This article reviews the potential cardiovascular risks associated with these drugs.

Chloroquine/Hydroxychloroquine

CQ/HCQ are quinoline medications widely used in treatment of malaria, rheumatoid arthritis (RA) and discoid or systemic lupus erythematosus (SLE). However, they have been shown to be cardiotoxic due to lysosomal dysfunction and accumulation of glycogen and phospholipids.⁵

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See page 149 for disclosure information.

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The cardiotoxic effects of CQ/HCQ appear to be related to the cumulative dose. High cumulative doses of CQ/HC have been shown to be associated with atrioventricular blocks and cardiac arrest.⁶ Sick sinus syndrome and QT prolongation have also been reported with high doses.^{7,8} In some of these cases, baseline QT interval was found to be mildly prolonged and hence QT interval in such patients should be closely monitored to prevent risk of ventricular arrhythmias. Given the fact that hypokalemia causes prolongation of QTc interval, low potassium levels in patients with severe COVID-19 may further exacerbate the arrhythmogenic potential of CQ/HCQ. CQ has been found to be more associated with conduction defects compared to HCQ. In a study of 85 patients treated with HCQ for a minimum of 1 year and who had no underlying cardiac disease, HCQ was found to be safe with only 2 patients developing right bundle branch block and 1 patient developing left bundle branch block.⁹ There were no instances of atrioventricular blocks or QT prolongation.

Echocardiographic abnormalities have also been reported in patients exposed to high cumulative doses of CQ/HCQ. In a robust systematic review, Chatre et al found that patients with cardiac complications attributed to CQ/HCQ were mainly female (65%) and had a median age of 56 years.¹⁰ Conduction disorders accounted for almost 85% of the reported cardiac complications. Other reported toxicities included left ventricular hypertrophy (22%), heart failure (27%), valvular dysfunction (7%), and pulmonary hypertension (4%).

Cardiac magnetic resonance imaging (cMRI) in such patients has shown patchy delayed contrast enhancement.^{7,11} Endomyocardial biopsy in such patients shows no evidence of inflammation or vasculitis.¹¹ Instead, the important findings are swollen myocytes with vacuolated cytoplasm filled with numerous curvilinear bodies, myeloid bodies and large secondary lysosomes. The curvilinear bodies are membrane bound and closely associated with lysosomes and contain partially digested lipids. After discontinuation of the drug, complete recovery of cardiac function has been reported in <half of the patients.¹⁰ Irreversible damage including death and need for pacemaker and heart transplantation has been described in literature.¹⁰

A recent small randomized study has shown beneficial effects of HCQ treatment on time to clinical recovery and pneumonia resolution.¹² For patients infected with COVID-19, CQ/HCQ are currently recommended for a 10- to 14-day course. The cumulative dose for this duration may not be high, but the prolonged recovery time and uncertainty about the best duration of treatment may potentially lead to cardiotoxicity. Moreover, as noted, the cardiotoxic effects may still occur even with low cumulative doses.

Azithromycin

Azithromycin is a semisynthetic macrolide antibiotic and is the most common prescribed antibiotic in the United States. It works against gram positive, gram negative, and atypical pathogens. It has been postulated as a possible cure for COVID-19 in combination with CQ/HCQ.⁴ Initially thought to be free of cardiotoxic effects, it was later found to cause QT prolongation and higher risk of cardiovascular morbidity and mortality. Multiple studies have shown the risk of QT prolongation and ventricular tachycardia with azithromycin. Its use has also been linked to risk of atrial fibrillation and cardiac arrest. In a large multinational case-control study, azithromycin use was found to be associated with an increased risk of ventricular tachycardia (adjusted odds ratio [OR] 1.97, 95% confidence interval [CI] 1.35 to 2.86).¹³ However, other studies have not revealed similar findings. In a large Canadian cohort, azithromycin use was not associated with risk of ventricular arrhythmia (relative risk [RR] 1.06, 95% CI 0.83 to 1.36).¹⁴ The mechanism by which azithromycin causes arrhythmias is still under investigation. QT prolongation and ventricular arrhythmias have been postulated to be due to increased Na⁺ current and inhibition of outward flow of K⁺ ions from ventricular myocytes.¹⁵ QT interval usually returns to baseline once the drug is stopped. However, this could be clinically significant especially when taken for prolonged period or in those patients who are on other QT prolonging drugs. Taking into account the published literature, FDA released a statement in 2013 cautioning the use of azithromycin in patients with underlying cardiovascular disease due to risk of fatal arrhythmias.¹⁶ Again, as discussed before, hypokalemia seen in COVID-19 patients can further prolong the QTc interval and cause ventricular arrhythmias.

Multiple studies have been performed to evaluate risk of all-cause and cardiovascular mortality with use of azithromycin. In a large cohort study, Ray et al found a 5-day course of azithromycin to be associated with a significantly higher risk of cardiovascular death (hazard ratio HR 2.88, 95% CI 1.79 to 4.63, $p < 0.001$) and all-cause death (HR 1.85, 95% CI 1.25 to 2.75, $p = 0.002$) compared with those on no antibiotics.¹⁷ However, other studies have found no association between azithromycin and cardiovascular disease or mortality. In a large observational study, Svanstrom et al found increased risk of cardiovascular death with use of azithromycin compared with no antibiotic use (rate ratio 2.85, 95% CI 1.13 to 7.24).¹⁸ However, no difference was found between those on azithromycin versus those on penicillin V (rate ratio 0.93, 95% CI 0.56 to 1.55). The authors concluded that excess mortality in patients on azithromycin when compared to those not on antibiotics was most likely

due to the mortality risk of the underlying infection itself. An interesting finding among some studies is a trend toward higher mortality in first 5 days of azithromycin use compared with other antibiotics, but no difference from day 6.¹⁹

A large meta-analysis of 33 randomized and observational studies found azithromycin use to be associated with higher risk of cardiovascular death but not with all-cause death.²⁰ In this meta-analysis, authors also found a higher risk of ventricular arrhythmias and sudden death (RR 3.40, 95% CI 1.68 to 6.90) with the use of azithromycin. As evident from the above, the cardiovascular risks associated with azithromycin have yet to be fully elucidated, and further prospective studies are needed.

We suggest clinicians be careful in patients who are elderly, have underlying cardiovascular disease, those who are on drugs known to prolong QT interval and those with renal failure. We recommend electrocardiography (EKG) before starting HCQ or azithromycin for all patients, and then serially monitoring QT interval in patients at risk for torsade de pointes.

Remdesivir

Remdesivir is 1'-cyano-substituted adenosine nucleotide prodrug which inhibits viral RNA synthesis which was first studied in treatment for ebolavirus. The data are scant on potential efficacy and risks with remdesivir. The only study evaluating effects of remdesivir in humans randomized 681 patients infected with ebolavirus to 4 different treatment strategies, out of which 175 patients received remdesivir. Only 1 patient who received remdesivir had hypotension and subsequently died due to cardiac arrest.²¹ However, the authors could not exclude the death in this patient was related to underlying ebolavirus itself. If this drug does show therapeutic efficacy in treatment of COVID-19, then ongoing surveillance would be needed to study its potential cardiovascular adverse effects.

Lopinavir-Ritonavir

Lopinavir/ritonavir are protease-inhibitors frequently used in the treatment of human immunodeficiency virus (HIV) infection. This combination has been studied for treatment of SARS and MERS. However, a randomized comparison between this combination and standard care showed no difference in mortality in patients with severe COVID-19 illness, though there was a trend toward shortened median time to clinical improvement.²² In this study, only 1 patient in the lopinavir/ritonavir group was found to have prolongation of QT interval. More studies are ongoing evaluating its efficacy in patients with COVID-19.

The main cardiac risk associated with lopinavir/ritonavir is progression of atherosclerosis. Elevation in plasma levels of total cholesterol, low-density lipoprotein (LDL) and total cholesterol to high-density lipoprotein (HDL) ratio, and decrease in HDL levels has been reported with the use of lopinavir/ritonavir therapy.²³ Cardiac conduction defects have also been reported with the use of lopinavir/ritonavir. Sinus arrest, first, and second degree atrioventricular blocks have been documented with its use.²⁴

Table 1

Cardiotoxic effects of potential drugs or treatment of coronavirus 2019

Drug name	Cardiotoxic effects
Chloroquine/ Hydroxychloroquine	Atrio-ventricular block, ⁶ Ventricular arrhythmias, ⁶ Sinus arrest, ⁷ Prolonged QTc interval, ⁸ Bundle branch block, ⁹ Biventricular hypertrophy, ¹⁰ Systolic dysfunction, ¹⁰ Valvular regurgitation, ¹⁰ Congestive heart failure, ¹⁰ Pulmonary hypertension ¹⁰
Azithromycin	Prolonged QTc interval, ¹³ Ventricular arrhythmias, ^{13,14} Myocardial infarction, ²⁰ Cardiovascular death ^{17,18}
Remdesivir	Cardiac arrest ²¹
Lopinavir/ Ritonavir	Elevated total cholesterol and low-density lipoprotein, ²³ Prolonged QTc interval, ²⁴ Atrioventricular blocks ²⁴
Interferon-alpha	Cardiogenic shock, ²⁵ Cardiomyopathy, ²⁶ Arrhythmias, ¹⁴ Ischemic heart disease, ²⁸ Pericardial effusion ²⁷
Favipiravir	Prolonged QTc interval ²⁸
Vitamin C	Cardiovascular mortality ²⁹
Monoclonal antibodies	Elevated total cholesterol and LDL levels ³⁰

Interferon-Alpha

Pegylated interferon-alpha (α) has been also studied for treatment of SARS and MERS. However, it has been linked to cardiovascular adverse effects in previous studies. In a study of 295 patients who were treated with interferon- α for hepatitis C, cardiac complications were noted in 6 patients during treatment and 4 more within 1 year after end of treatment.²⁵ A total of 4 patients had arrhythmias, 4 patients had ischemic heart disease, and 2 patients developed cardiomyopathy in this study. The increase in tumor necrosis factor-alpha levels during interferon- α therapy may be the underlying mechanism mediating its cardiotoxic effects, though this same mechanism may be beneficial in inhibiting viral replication in patients with COVID-19.²⁶ Pericardial effusion has been reported to occur with interferon- α therapy.²⁷

Other Potential Therapies

Some other therapies being studied for treatment of COVID-19 are favipiravir and high-dose vitamin C. Data are scant on potential cardiovascular risks with these drugs. Favipiravir was reported to be associated with mild prolongation of QT interval in a young patient treated for ebolavirus.²⁸ High dose of vitamin C was found to be associated with higher cardiovascular mortality in patients with diabetes.²⁹ Human monoclonal antibodies that inhibit interleukin-6 (IL-6) pathway by binding and blocking IL-6 receptor are also being currently studied for treatment of COVID-19. They have been shown to cause increases in total cholesterol and LDL levels.³⁰ A phase 3 trial evaluating colchicine is ongoing for treatment of patients with COVID-19 that plans to enroll 6,000 participants [clinicaltrials.gov NCT04322682]; colchicine has not been linked to cardiovascular side effects but may worsen bleeding. Finally, ACE inhibitors and ARBs are also under investigation for the treatment of COVID. SAR-CoV-2 may directly interact with the Renin-Angiotensin-Aldosterone System, with the virus using the angiotensin converting enzyme 2 (ACE2) as its host receptor on type II pneumocytes. As such, a link between angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and COVID has been proposed. However, there is little, if any,

convincing evidence to suggest discontinuation of such drugs and ARBs are currently undergoing a clinical trial as a treatment for severe COVID-19.

Conclusion

COVID-19 is a pandemic with high morbidity and mortality burden. The patients who have underlying cardiovascular disease or those who develop cardiac dysfunction during infection with COVID-19 are at higher risk of mortality. Various drugs currently under investigation for treatment of the novel coronavirus have been associated with cardiotoxic effects (Table 1). Though cumulative dose effects impact toxicity, conduction defects, prolongation of QTc interval, cardiomyopathy, and ischemic heart disease have been shown to occur with use of hydroxychloroquine, chloroquine, azithromycin, remdesivir, interferon-alpha, and lopinavir/ritonavir therapies. Caution and careful monitoring should be exercised when prescribing these therapies in patients at risk for cardiac disease.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. WHO. *Coronavirus Disease 2019 (COVID-19) Pandemic*. 2020.
2. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46:846–848.
3. Aggarwal G, Cheruiyot I, Aggarwal S, et al. Association of cardiovascular disease with coronavirus disease 2019 (COVID-19) Severity: A Meta-Analysis [published online ahead of print, 2020 Apr 28]. *Curr Probl Cardiol* 2020:100617.
4. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honoré S, Colson P, Chabrière E, La Scola B, Rolain J-M, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agon* 2020. 105949.
5. Thome R, Lopes SC, Costa FT, Verinaud L. Chloroquine: modes of action of an undervalued drug. *Immunol Lett* 2013;153:50–57.
6. Ladipo GO, Essien EE, Andy JJ. Complete heart block in chronic chloroquine poisoning. *Int J Cardiol* 1983;4:198–200.
7. Lee JH, Chung WB, Kang JH, Kim HW, Kim JJ, Kim JH, Hwang HJ, Lee JB, Chung JW, Kim HL, Choi YS, Park CS, Youn HJ, Lee MY. A

- case of chloroquine-induced cardiomyopathy that presented as sick sinus syndrome. *Korean Circ J* 2010;40:604–608.
8. 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.
 9. Costedoat-Chalumeau N, Hulot JS, Amoura Z, Leroux G, Lechat P, Funck-Brentano C, Piette JC. Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases. *Rheumatol (Oxford)* 2007;46:808–810.
 10. 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.
 11. Reffelmann T, Naami A, Spuentrup E, Kuhl HP. Images in cardiovascular medicine. Contrast-enhanced magnetic resonance imaging of a patient with chloroquine-induced cardiomyopathy confirmed by endomyocardial biopsy. *Circulation* 2006;114:e357–e358.
 12. 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. <https://doi.org/10.1101/2020.03.22.20040758>.
 13. Trifiro G, de Ridder M, Sultana J, Oteri A, Rijnbeek P, Pecchioli S, Mazzaglia G, Bezemer I, Garbe E, Schink T, Poluzzi E, Froslev T, Molokhia M, Diemberger I, Sturkenboom M. Use of azithromycin and risk of ventricular arrhythmia. *CMAJ* 2017;189:E560–E568.
 14. Trac MH, McArthur E, Jandoc R, Dixon SN, Nash DM, Hackam DG, Garg AX. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. *CMAJ* 2016;188:E120–E129.
 15. Yang Z, Prinsen JK, Bersell KR, Shen W, Yermalitskaya L, Sidorova T, Luis PB, Hall L, Zhang W, Du L, Milne G, Tucker P, George AL Jr., Campbell CM, Pickett RA, Shaffer CM, Chopra N, Yang T, Knollmann BC, Roden DM, Murray KT. Azithromycin causes a novel proarrhythmic syndrome. *Circ Arrhythm Electrophysiol* 2017;10:e003560.
 16. FDA. In brief: FDA azithromycin warning. *Med Lett Drugs Ther* 2013;55:28.
 17. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881–1890.
 18. Svanstrom H, Pasternak B, Hviid A. Use of azithromycin and death from cardiovascular causes. *N Engl J Med* 2013;368:1704–1712.
 19. Rao GA, Mann JR, Shoaibi A, Bennett CL, Nahhas G, Sutton SS, Jacob S, Strayer SM. Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. *Ann Fam Med* 2014;12:121–127.
 20. Cheng YJ, Nie XY, Chen XM, Lin XX, Tang K, Zeng WT, Mei WY, Liu LJ, Long M, Yao FJ, Liu J, Liao XX, Du ZM, Dong YG, Ma H, Xiao HP, Wu SH. The role of macrolide antibiotics in increasing cardiovascular risk. *J Am Coll Cardiol* 2015;66:2173–2184.
 21. Mulangu S, Dodd LE, Davey RT Jr., Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, Ali R, Coulilaly S, Levine AC, Grais R, Diaz J, Lane HC, Muyembe-Tamfum JJ, Group PW, Sivahera B, Camara M, Kojan R, Walker R, Digheo-Kemp B, Cao H, Mukumbayi P, Mbala-Kingebeni P, Ahuka S, Albert S, Bonnett T, Crozier I, Duvenhage M, Proffitt C, Teitelbaum M, Moench T, Aboulhab J, Barrett K, Cahill K, Cone K, Eckes R, Hensley L, Herpin B, Higgs E, Ledgerwood J, Pierson J, Smolskis M, Sow Y, Tierney J, Sivapalasingam S, Holman W, Gettinger N, Vallee D, Nordwall J, Team PCS. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019;381:2293–2303.
 22. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382:1787–1799.
 23. Limsreng S, Marcy O, Ly S, Ouk V, Chanroern H, Thavary S, Boroath B, Canestri A, Viretto G, Delfraissy JF, Segal O. Dyslipidemias and elevated cardiovascular risk on lopinavir-based antiretroviral therapy in Cambodia. *PLoS One* 2016;11:e0160306.
 24. Chaubey SK, Sinha AK, Phillips E, Russell DB, Falhammar H. Transient cardiac arrhythmias related to lopinavir/ritonavir in two patients with HIV infection. *Sex Health* 2009;6:254–257.
 25. Teragawa H, Hondo T, Amano H, Hino F, Ohbayashi M. Adverse effects of interferon on the cardiovascular system in patients with chronic hepatitis C. *Jpn Heart J* 1996;37:905–915.
 26. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res* 2020;7:11.
 27. El-Dosouky II, El Hawari SA-M, Emara MH, Hamed EF. Types and predictors of interferon/ribavirin induced cardiac complications in the Egyptian patients with chronic hepatitis C virus. *J Indian Coll Cardiol* 2016;6:16–21.
 28. Chinello P, Petrosillo N, Pittalis S, Biava G, Ippolito G, Nicastri E, Team IE. QTc interval prolongation during favipiravir therapy in an Ebolavirus-infected patient. *PLoS Negl Trop Dis* 2017;11:e0006034.
 29. Lee D-H, Folsom AR, Harnack L, Halliwell B, Jacobs DR Jr. Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? *Am J Clin Nutr* 2004;80:1194–1200.
 30. Bacchiaga BC, Bacchiaga AB, Usnayo MJG, Bedirian R, Singh G, Pinheiro GdRC. Interleukin 6 inhibition and coronary artery disease in a high-risk population: a prospective community-based clinical study. *J Am Heart Assoc* 2017;6:e005038.