Telemedicine-based early rule out electrocardiography algorithm: Hydroxychloroquine in COVID-19 patients

HİDROKSİKLOROKİN TEDAVİSİ A ŁACAK COVID-19 HASTALARINDA ELEKTROKARDİYOGRAFİ TAKİBİNİ ERKEN SONLANDIRAN TELETIP TEMELLİ ALGORİTMA

Oğuzhan Ekrem TURAN1, Reşit Yiğit YILANCIOĞLU1, Çetin ALAK1, Ahmet Anıl BAŞKURT1, Burak HÜNÜK2, Esra DUĞRAL3, Aylin ÖZGEN ALPAYDIN3, Figen COŞKUN4, Mehmet Birhan YILMAZ1, Asım Oktay ERGENE1, Emin Evren OZCAN1

1Department of Cardiology, Dokuz Eylül University, Faculty of Medicine, İzmir, TURKEY
2Department of Cardiology, Yeditepe University School of Medicine, Istanbul, TURKEY
3Department of Pulmonar Diseases, Dokuz Eylül University, Faculty of Medicine, İzmir, TURKEY
4Department of Emergency Medicine, Dokuz Eylül University, Faculty of Medicine, İzmir, TURKEY

ABSTRACT

Objective: Drugs with the potential to prolong QT are used in the treatment of coronavirus 19 (COVID-19) pneumonia. We have developed a telemedicine-based corrected QT (QTc) follow-up algorithm that allows early rule out for follow up. In this study, we investigated the availability and safety of the algorithm.

Materials and Methods: Consecutive patients; administered hydroxychloroquine (HCQ) for COVID-19 pneumonia were enrolled into digital ECG recording program which includes QTc follow-up algorithm.

Results: Patients were classified into three groups as follows: Those excluded promptly from the QTc follow-up based on two consecutive ECG findings (early rule out, n=92) and those for whom the follow-up was continued (n=12) and the usual care group (n=68). Of note, 237 ECG tracings were performed in our algorithm population contrary to standard practice of daily-recommended ECG monitoring which could have yielded 975 ECG tracings along with accompanied risks of exposure. This way; we ended in 738 (75.7%) fewer ECG tracings. Sustained ventricular arrhythmia or sudden cardiac death was not observed in the entire patient population.

Conclusion: It is safe to rely on telemedicine-based early rule out algorithm in COVID-19 patients, receiving hydroxychloroquine treatment. This algorithm abolished the need for further ECG in majority of patients without increased risk during follow up. These algorithms can significantly reduce the healthcare worker exposures by eliminating the need for ECG follow-up promptly.

Keywords: COVID-19, QT, hydroxychloroquine, telemedicine, early rule out
The global pandemic associated with coronavirus disease (COVID-19) has led to the use of potentially QT-prolonging drugs such as hydroxychloroquine (HCQ) and azithromycin in the prophylaxis and treatment (1). Particularly, a combination of these drugs pose a potential risk for the development of torsades de pointes (TdP) and sudden cardiac death (SCD) via the summation of their effects of prolonging the corrected QT interval (QTc) (2-10).

As the short and long-term untoward effects of the virus on the myocardium have not been established yet; the use of these drugs, which pose an increased risk for the development of TdP, may be a concern for clinicians (11). For this reason, various algorithms have been developed to predict and prevent arrhythmic complications in COVID-19 patients receiving treatment with hydroxychloroquine-based regimens (12-18). The main purpose of these algorithms is to stratify the patients into risk categories and to ensure that treatment should be given to appropriate patients along with maintained continuity. Essentially, the majority of patients to start treatment is expected to have QTc values within the normal range (males ≤470, females ≤480 ms) and the majority of them have a low risk for TdP or SCD (13). It may be appropriate to identify high-risk patients that should be followed up and to promptly exclude others from QTc follow-up via electrocardiography (ECG) tracings to reduce their contact with healthcare professionals. However, many algorithms still recommend QTc follow-up with daily ECG or telemetric methods for COVID-19 patients under treatment (13, 18).

Just at the beginning of the pandemic, we have developed a basic lean QTc follow-up algorithm for COVID-19 patients in our hospital by developing a digital platform, in which each ECG is evaluated online by a cardiologist and early rule out for ECG monitoring is allowed. In this study, we aimed to investigate the usability and safety of this algorithm.

MATERIALS and METHODS

Patients diagnosed with COVID-19 related pneumonia (n=174) and receiving at least two doses of HCQ were included in the study during the period between 18 March 2020 and 5 May 2020. Pre-treatment and follow-
up ECGs were recorded and uploaded to the digital QTc platform by blinded healthcare technicians, and were assessed online by a cardiologist who responded 24/7 and provided consultation about initiation of treatment by correcting the QT interval according to the Bazett’s formula. The Tisdale score of each patient was calculated to assess the risk of QTc prolongation (19). Of note, before initiation of treatment, each patient with serum potassium levels lower than 4 mEq/L or magnesium levels lower than 0.6 mmol/L received replacement therapy. The concurrent use of other QT-prolonging drugs was not allowed. Two patients (1.2%) with pre-treatment QTc of > 550 ms could not receive HCQ treatment and were excluded from the study (one patient had congenital heart disease and one had a basal QTc value of more than 600 ms). After the second dose of HCQ, ECG was consulted again via the same platform and the consultant cardiologist decided whether to continue the follow-up. In the absence of algorithm-based requirements, no further ECG was obtained and these patients were classified as early rule out group (n=92) (no QTc interval prolongation of more than 500 ms or prolongation of the QTc interval by no more than 50 ms after the second dose of treatment compared to the pretreatment value) during treatment. Patients were then classified into two more groups as those, for whom the follow-up was continued (n=12) (a QTc interval of more than 500 ms or prolongation of the QTc interval by more than 50 ms after the second dose of treatment compared to the pretreatment value) and usual care no follow-up group (n=68) (had baseline ECG and then the treatment was continued without ECG follow-up due to pandemic conditions and/or follow-up ECGs and clinical data were not or late consulted via the system). Primary physician interface of the algorithm is shown in Figure 1 and the consulting cardiologist interface of the algorithm is shown in Figure 2. Data regarding sustained ventricular arrhythmia, sudden cardiac death, and all-cause death occurring during hospitalization for all patients were recorded. Our study was approved by local ethical committee (approval date: 18/01/2021 and number: 2021/02-54).

Figure 1. Primary physician interface of the algorithm on the digital QTc portal.
Figure 2. Consulting cardiologist interface of the algorithm on the digital platform.

*If pretreatment QRS ≥ 120 msec apply QTc value according to 550 msec

Delta (Δ) QTc= After second dose of HCQ QTc minus pretreatment QTc value

Statistical analysis

Statistical analyses were performed by using the SPSS software (Version 14.0, SPSS, Inc., Chicago, IL). Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk’s test) to determine whether they were normally distributed or not. Continuous variables were presented using means and standard deviations. All continuous variables were normally distributed; Student’s t-test was used to compare the differences between variables. One-way ANOVA was used to compare among the “no follow-up”, “early rule out” and “continue to follow-up” groups. P-values less than 0.017 were considered statistically significant. When an overall significance was observed, pairwise post-hoc tests were performed using Tukey’s test. Chi-square test was used to compare categorical variables. P-values less than 0.05 were considered statistically significant.

RESULTS

Although the baseline ECGs of 172 patients were consulted via the platform before the treatment, follow-up ECGs of only 104 (60.5%) patients were consulted via the system. All patients mean age was 68.9±18.9 and 95 (55.2%) of them were female. There were 107 (62.2%) confirmed cases with COVID-19 based on the results of molecular tests and 65 (37.8%) possible cases diagnosed based on clinical and radiological findings. An HCQ-based treatment regimen was started within 2.8 ± 1.9 days from the onset of symptoms. HCQ was started with a loading dose (400 mg bid on the first day followed by 200 mg bid maintenance therapy for 4 days) in 156 (90.7%) of the patients and maintenance doses of HCQ (200 days bid on 5 days) were administered to 16 patients. The most common co-morbidity in all patients was hypertension (63.4%) and diabetes mellitus (29.7%). Demographic data of the patients are given in Table 1. At the time of diagnosis, 44 (25.6%) patients had SIRS and 17 (9.9%) patients required mechanical ventilation.
Table 1. Baseline clinical characteristics and in hospital follow-up findings of study population

| Variables                                          | All patients (n=172) | Continue Follow-up group (n=12) | Early Rule out group (n=92) | No follow-up group (n=68) | p-value |
|----------------------------------------------------|----------------------|--------------------------------|----------------------------|---------------------------|---------|
| Age (years)                                        | 68.9±18.9            | 76.4±7.4                       | 70±19.9                    | 66.1±18.6                 | 0.156   |
| Female, n (%)                                      | 95 (55.2)            | 6 (50)                         | 57 (60)                    | 32 (33.7)                 | 0.161   |
| HT, n (%)                                          | 109 (63.4)           | 11 (91.7)                      | 61 (66.3)                  | 37 (54.4)                 | 0.033   |
| DM, n (%)                                          | 51 (29.7)            | 5 (41.7)                       | 25 (27.2)                  | 21 (30.9)                 | 0.563   |
| CAD, n (%)                                         | 42 (24.4)            | 3 (25)                         | 23 (25)                    | 16 (23.5)                 | 0.976   |
| CHF, n (%)                                         | 28 (16.3)            | 3 (25)                         | 8 (8.7)                    | 17 (25)                   | 0.015   |
| COPD, n (%)                                        | 32 (18.6)            | 3 (25)                         | 15 (16.3)                  | 14 (20.6)                 | 0.663   |
| CKD, n (%)                                         | 39 (22.7)            | 4 (33.3)                       | 17 (18.5)                  | 18 (26.5)                 | 0.323   |
| AF, n (%)                                          | 18 (10.5)            | 5 (41.7)                       | 8 (8.7)                    | 5 (7.4)                   | 0.001   |
| ACE inh. or ARB, n (%)                             | 46 (26.7)            | 6 (50)                         | 27 (29.3)                  | 13 (19.1)                 | 0.059   |
| Loop diuretic before hospital, n (%)               | 12 (7)               | 2 (16.7)                       | 5 (5.4)                    | 5 (7.4)                   | 0.352   |
| Beta-blocker, n (%)                                | 61 (35.5)            | 8 (66.7)                       | 29 (31.5)                  | 24 (35.3)                 | 0.057   |
| Loop diuretic in hospital, n (%)                   | 30 (17.4)            | 3 (33.3)                       | 13 (14.1)                  | 13 (19.1)                 | 0.230   |
| HCQ loading, n (%)                                 | 156 (90.7)           | 11 (91.7)                      | 83 (90.2)                  | 62 (91.2)                 | 0.972   |
| Symptom presence prior to hospitalization, days    | 2.8±1.9              | 2.9±1.3                        | 2.8±1.5                    | 2.7±2.3                   | 0.943   |
| Length of stay, days                               | 7.9±6.2              | 11.6±7                         | 8±6.2                      | 7.2±6                     | 0.074   |
| Temperature on day of treatment initiation, °C     | 37.2±0.8             | 37.4±0.9                       | 37.2±0.8                   | 37.1±0.7                  | 0.333   |
| Supplemental oxygen required, n (%)                | 58 (33.7)            | 5 (41.6)                       | 31 (33.7)                  | 22 (32.4)                 | 0.820   |
| Radiographic findings of pneumonia, n (%)          | 126 (73.3)           | 9 (75)                         | 60 (65.2)                  | 57 (83.8)                 | 0.031   |
| Patients transferred to ICU during the follow up, n (%) | 25 (14.5)          | 3 (25)                         | 10 (10.9)                  | 12 (17.6)                 | 0.275   |
| Mechanically ventilated at time of initiation of therapy, n (%) | 17 (9.9)          | 1 (8.3)                         | 5 (5.4)                    | 11 (16.2)                 | 0.078   |
| Vasopressor support, n (%)                         | 16 (9.3)             | 1 (6.3)                        | 5 (5.4)                    | 10 (14.7)                 | 0.135   |
| SIRS, n (%)                                        | 44 (25.6)            | 7 (58.3)                       | 18 (26.5)                  | 19 (20.7)                 | 0.019   |
| AML, n (%)                                         | 68 (39.5)            | 7 (58.3)                       | 38 (40.2)                  | 24 (35.3)                 | 0.316   |
| Mortality, n (%)                                   | 20 (11.9)            | 2 (16.7)                       | 9 (9.8)                    | 9 (14.1)                  | 0.625   |
| Tisdale Score                                      | 64±3.3               | 8.2±3.6                        | 5.9±4                      | 5.7±4.8                   | 0.196   |
| Tisdale Score > 11, n (%)                          | 55 (33.5)            | 7 (58.3)                       | 29 (31.5)                  | 19 (31.7)                 | 0.168   |
| Obtained ECG count                                 | 1.7±0.9              | 3.1±1                          | 2.2±0.4*                   | 0.9±0.3*                  | <0.001  |

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, AF: Atrial fibrillation, ACE: Angiotensinogen converting enzyme, ARB: Angiotensin receptor blocker, HCQ: Hydroxychloroquine, HR: Heart rate, ICU: Intensive care unit, SIRS: systemic inflammatory respiratory syndrome, AML: Acute myocardial injury, ECG: Electrocardiography. Data are given as mean ± SD, number of patients and percentages.* p value less than 0.05 for binary groups.
Ninety-two patients; who received treatment and had a delta QTc of <50 ms, or whose QTc did not exceed 50 ms according to the pretreatment value, constituted the group of patients of early termination to follow-up. In this group of patient congestive heart failure incidence was lower than the other groups. Other demographics and clinical status variables were similar to other groups. In this patient group QTc value decreased (mean 6.8±27 ms) after second dose of HCQ. New ECG tracings were obtained from only 18 of these patients after the start of another QTc prolonging medication (azithromycin in 5 patients and haloperidol in 13 patients) and these patients were excluded from the follow-up after a total number of 3 follow-up ECGs for each patient with QTc values in the normal range.

The group of patients; for whom the follow-up was continued, comprised 12 patients (7%). The follow-up was continued in 6 patients because of a delta QTc value of ≥50 ms in the follow-up ECG, and in 6 patients because of a QTc value of ≥500 ms in the follow-up ECG. Of this group of patients, 6 were excluded from the ECG follow-up when the follow-up delta QTc was <50 ms after the fourth dose (48th hour) (a total of three ECG tracings were obtained). The remaining 6 patients with QTc over 500 ms received treatment with daily ECG monitoring, although QTc values decreased. Continue to follow-up group had more SIRS rate than the others. However, fever, supplemental oxygen requirement, the need for mechanical ventilation, and the need for vasopressor support were similar across the three groups. The incidence of hypertension (HT) and atrial fibrillation (AF) was higher in the continued to follow-up group compared to the other group of patients. The Tisdale score, which predicts the potential for QTc prolongation, was at a mean of 6±4.3 in all patients and this value was similar to that found between three groups. Also pretreatment serum creatine level was higher than the other groups (Table 2). The mean QTc values of all patients changed from the pretreatment value of 437±6.9 ms to 435.8±35.7 ms (p=0.696) after the second dose of medication. All patients pre-treatment and after second dose of therapy QTc values change were given in Figure 3.

Table 2. Baseline laboratory findings of the study population.

| Variables                  | All patients (n=172) | Continue Follow-up group (n=12) | Early Rule out group (n=92) | No follow-up group (n=68) | p-value |
|----------------------------|----------------------|--------------------------------|-----------------------------|---------------------------|---------|
| Creatinine, mg/dL          | 1.2±1.1              | 2.1±2.1*                       | 1±0.8                       | 1.2±1.2                   | 0.009   |
| Sodium, mEq/L              | 136.9±4.8            | 134.1±3.9                      | 137.2±4                     | 136.9±5.8                 | 0.108   |
| Potassium, mEq/L           | 4.4±2.9              | 3.96±0.4                       | 4.2±0.7                     | 4.7±4.6                   | 0.471   |
| Hypokalemia, n (%)         | 19 (11)              | 1 (8.3)                        | 11 (12)                     | 7 (10.3)                  | 0.902   |
| Magnesium, mmol/L          | 0.77±0.15            | 0.82±0.12                      | 0.79±0.12                   | 0.72±0.2                  | 0.440   |
| WBC <4 and >12, 10³ cells/mm³, n (%) | 35 (20.3) | 4 (33.3)                       | 17 (18.5)                   | 14 (20.6)                 | 0.485   |
| C-reactive protein, mg/L   | 68.4±78.8            | 110.3±114.2                    | 66.7±76.7                   | 63.1±73.2                 | 0.155   |
| Procalcitonin, ng/mL       | 1.2±6.8              | 1.5±3.3                        | 1.5±9                       | 0.7±2.2                   | 0.737   |

WBC: White blood cell. Data are given as mean ± SD, number of patients and percentages.
* p value less than 0.05 for binary groups
**DISCUSSION**

In usual care group (n=68) there were 6 patients with a pretreatment QTc value above 500 ms. They did receive HCQ therapy without QTc follow-up. This group of patients had lower AF hypertension and SIRS rate. Their total hospital stay duration tend to be lower than the other groups.

Sustained ventricular arrhythmia or sudden cardiac death was not observed within all patients’ group. During the follow-up period in the inpatient unit, 20 (14.5%) patients were transferred to the intensive care unit because of clinical deterioration. Mortality due to acute respiratory distress syndrome and multiorgan failure occurred in 20 (11.9%) patients during the intensive care monitorization. TdP was not observed in these patients. Early termination of the need for ECG follow-up was not associated with mortality compare to continue and no follow-up (9.8, 16.7 vs 14.1%, respectively, p = 0.625).

**Figure 3.** The individual QTc values change from the pre-treatment and after the second dose of HCQ therapy.

*Orange lines are expressed continue to follow-up and black lines are expressed early rule out group.

HCQ, used for the treatment of COVID-19, has also been used safety for a long time for the treatment of autoimmune diseases after its established use for the treatment of malaria (20). It has been demonstrated that 600 milligrams of HCQ cause QTc prolongation of 9-23 ms in healthy adults, most commonly occurring four hours after the second dose (21). QTc monitoring with ECG is not a part of standard care when used in the treatment of malaria or rheumatic diseases as monotherapy (22). However, because of the prolonged half-life of the drug, its use in COVID-19 patients, especially in COVID-19 patients in a critical clinical condition, may differ from the use in malaria and rheumatic disorders. Moreover, the combined use of potentially QTc prolonging medications (such as HCQ, Azithromycin, favipiravir) in these patients may cause further prolongation (2-10). Based on these observations, the need for regular QTc monitoring becomes reasonable during the treatment process. Therefore, QTc follow-up algorithms have been developed right at the beginning of the pandemic, usually recommending strict follow-up to avoid TdP (12-18). However; along with the accumulation of clinical data and many studies reporting no or very few patients developing drug-related TdP, the strict follow-up recommendation in current meticulous follow-up algorithms has become questionable (23, 24). Short-term (5-10 days) treatment of COVID-19-associated pneumonia may have a low risk of developing arrhythmias because of low levels of drug accumulation compared to long-term treatments. This suggests that evaluating QTc once at a time before and after the treatment may be sufficient alone and that there may be no need for close QTc monitoring. Furthermore, only 3-10% of COVID-19 patients receiving HCQ treatment develop QTc prolongation of 60 ms or more on the first day (2, 23) and QTc remains stable throughout the treatment (25). In our study, only two patients (1.2%) with pre-treatment QTc of >550 ms could not receive HCQ treatment. Moreover, QTc interval prolongation of more than 50 ms was observed only in 6 (5.8%) patients. Arrhythmic events or sudden cardiac death was not observed in any of the patients, including these 6 patients.

Physicians, who are at the forefront in the treatment of COVID-19 related pneumonia, are mostly from different fields of medicine other than cardiology such as pulmonary diseases, internal medicine and intensive care; therefore, they need a simple and easy-to-apply algorithm for QTc follow-up. With the emergence of the first case in our
country in March 2020, we created the simple and easily applicable QTc portal algorithm for QTc monitoring. We ensured a holistic cardiac assessment with QTc analysis on ECG tracings as performed by cardiologists on the online sharing platform. In our study, while the QTc values of 172 patients were measured before the treatment, the follow-up ECGs of only 60.5% of the patients were consulted via the system. Because of the healthcare workers’ concerns about the exposure to COVID-19 and the intensity of work during the pandemic, follow-up ECGs after the second dose of the medication could not be either traced or transferred to the system in 39.5% of the patients. This ratio highlights the importance of telemetric measurements. Telemetric QTc monitoring may reduce healthcare worker exposure but the scarcity of proven methods and difficulties in their availability is a considerable issue globally. Moreover, even when QTc prolongation is detected via telemetry, there will be a need to confirm the findings with ECG.25 Therefore, algorithms allowing for digital assessments for the early termination of the need for ECG follow-up may help reduce healthcare worker exposure. Our study has shown that early termination of the need for follow-up is safe and usable based on the absence of an increase of more than 50 ms between the pretreatment QTc value and the QTc value calculated after the administration of the second dose of the medication. Only 237 ECG tracings were obtained in our follow-up patient population. If the standard daily ECG follow-up schedule had to be performed, 975 ECGs would have been traced (in our study; the average number of ECGs traced per patient is 1.7±0.9 and the estimated average total number of ECG tracings per patient during the total hospitalization period is 7.9±6.2, p<0.001). So, only 738 (75.7%) ECGs were traced. This provides benefits beyond its economic advantages. Our study shows that early termination to follow-up practices can reduce the risk of contamination of healthcare workers without risking patients. In addition, the absence of any arrhythmic events or SCD in the no follow-up group also questioned that the necessity of QTc monitoring in COVID-19 patients who will receive only HCQ.

Ventricular arrhythmias may occur during the course of COVID-19 in association with several factors including direct myocardial injury, ion channel (K+ and Ca++) blockage resulting from hypoxia-induced apoptosis or cytokine storm, and pharmacological treatment-related QT prolongation (26). Aminoquinolones, including HCQ, inhibit the fast component of the delayed rectifier potassium channel (IKr) synthesized by the protein expressed by the KCNH2 gene (also known as hERG). The consequent delayed repolarisation may allow for early after depolarisations (EADs), which may cause torsades de pointes (27-28). In our study, no ventricular arrhythmias were observed in 172 COVID-19 patients receiving treatment with HCQ-based regimens. Moreover, no ventricular arrhythmias or sudden death occurred in our study although the study population consisted of both elderly patients with co-morbid diseases (mean age 68.9±18.9 years) and 55 (33.5%) patients with a pre-treatment Tisdale score above 11. The important issue is to prevent drug-related ventricular arrhythmias before the start of the treatment by the effective management of modifiable factors causing QT prolongation.

In conclusion, telemedicine-based early termination algorithms involving cardiologist support significantly reduce the number of ECG tracings and prevent the exposure of healthcare professionals to COVID-19 patients. The QTc follow-up algorithm based on the early rule out to follow-up principle seems to be usable and safe.

Limitations

This is a single center study from a tertiary care center. Hence, such a digital platform might not be practical in every hospital. Secondly, the number of patients in all subgroups were low and hence definitive conclusions cannot be withdrawn from this study, though, a hypothesis about safety of this timesaving early rule out approach might be generated. However, the value remains to be validated in larger prospective cohorts.

REFERENCES

1. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: What to expect for COVID-19? Int J Antimicrob Agents. 2020;105938.

2. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy ZM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of
hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(9):1036-41. doi:10.1001/jamacardio.2020.1834

3. Chorin E, Wadhwani L, Magnani S, Dai M, Shulman E, Nadeau-Routhier C, et al. QT Interval Prolongation and Torsade de Pointes in Patients with COVID-19 treated with Hydroxychloroquine/Azithromycin. Ann Emerg Med. 2020;7(9):1036-41. doi:10.1016/j.annemergmed.2020.08.016

4. Saleh M, Gabriels J, Chang D, Soo Kim B, Mansoor A, Mahmood E, et al. The Effect of Chloroquine, Hydroxychloroquine and Azithromycin on the Corrected QT Interval in Patients with SARS-CoV-2 Infection. Circ Arrhythm Electrophysiol. 2020;13(6):e008662. doi:10.1161/CIRCEP.120.008662

5. van den Broek MPH, Möhlmann JE, Abeln BGS, Liebregts M, van Dijk VF, van de Garde EMW. Chloroquine-induced QTc prolongation in COVID-19 patients. Neth Heart J. 2020;28(7-8):406-9. doi:10.1007/s12471-020-01429-7

6. Bessière F, Roccia H, Delinière A, Charrière R, Chevalier P, Argaud L, et al. Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit. JAMA Cardiol. 2020;5(9):1067-9. doi:10.1001/jamacardio.2020.1787

7. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol. 2020;31(5):1003-8. doi:10.1111/jce.14479

8. Sarayani A, Cicali B, Henriksen CH, Brown JD. Safety signals for QT prolongation or Torsades de Pointes associated with azithromycin with or without chloroquine or hydroxychloroquine. Res Social Adm Pharm. 2021;17(2):483-6. doi:10.1016/j.sapharm.2020.04.016

9. Carpenter A, Chambers OJ, EI Harchi A, Bond R, Hanington O, Harmer SC, et al. COVID-19 Management and Arrhythmia: Risks and Challenges for Clinicians Treating Patients Affected by SARS-CoV-2. Front Cardiovasc Med. 2020;7:85. doi:10.3389/fcvm.2020.00085

10. Rosenberg ES, Dufort EM, Udo T, Wilderschild 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(24):2493-502. doi:10.1001/jama.2020.8630

11. Javelot H, El-Hage W, Meyer G, Becker G, Michel B, Hingray C. COVID-19 and (hydroxy)chloroquine-Azithromycin combination: Should we take the risk for our patients? Br J Clin Pharmacol. 2020;86(6):1176-7. doi:10.1111/bcp.14335

12. Naksuk N, Lazar S, Peeraphatdit TB. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. Eur Heart J Acute Cardiovasc Care. 2020;9(3):215-21. doi:10.1177/2048876219822784

13. 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(6):1213-21. doi:10.1016/j.mayocp.2020.03.024

14. Wu CI, Postema PG, Arbelo E, Behr ER, Bezzina CR, Napolitano C, et al. SARS-CoV-2, COVID-19, and inherited arrhythmia syndromes. Heart Rhythm. 2020;17(9):1456-62. doi:10.1016/j.hrthm.2020.03.024

15. Mitra RL, Greenstein SA, Epstein LM. An algorithm for managing QT prolongation in coronavirus disease 2019 (COVID-19) patients.
treated with either chloroquine or hydroxychloroquine in conjunction with azithromycin: Possible benefits of intravenous lidocaine. HeartRhythm Case Rep. 2020; 6(5):244-8. doi:10.1016/j.hrcr.2020.03.016

16. Sapp JL, Alqarawi W, MacIntyre CJ, Todros R, Steinberg C, Roberts JD, et al. Guidance on Minimizing Risk of Drug-Induced Ventricular Arrhythmia During Treatment of COVID-19: A Statement from the Canadian Heart Rhythm Society. Can J Cardiol. 2020;36(6):948-51. doi:10.1016/j.cjca.2020.04.003

17. Biernacka EK, Kosior DA, Zieniuk-Krajka A, Miszczak-Knecht M, Kempa M, Przybylski A. An opinion of the Heart Rhythm Section of the Polish Cardiac Society on safety of using antiviral and anti-inflammatory drugs prolonging QT interval in patients with COVID-19. Kardiol Pol. 2020;78(5):493-7. doi:10.33963/KP.15354

18. Asensio E, Acunzo R, Uribe W, Saad EB, Sáenz LC. Recommendations for the measurement of the QT interval during the use of drugs for COVID-19 infection treatment. Updatable in accordance with the availability of new evidence. J Interv Card Electrophysiol.2020;59(2):315-20. doi:10.1007/s10840-020-00765-3

19. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovascular Qual Outcomes. 2013;6(4):479-87.

20. Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. Clin Rev Allergy Immunol 2012; 42: 145-53.

21. Mzayek F, Deng H, Mather FJ, Wasilevich EC, Liu H, Hadi CM, et al. Randomized dose-ranging controlled trial of AQ-13, a candidate antimalarial, and chloroquine in healthy volunteers. PLoS Clin Trials 2007;2(1):e6

22. 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(4):ofaa130. doi:10.1093/ofid/ofaa130

23. 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(9):1472-9. doi:10.1016/j.hrthm.2020.05.008

24. Cipriani A, Zorzi A, Ceccato D, Capone F, Parolin M, Donato F, et al. Arrhythmic profile and 24-hour QT interval variability in COVID-19 patients treated with Hydroxychloroquine and azithromycin. Int J Cardiol. 2020;316:280-4. doi:10.1016/j.ijcard.2020.05.036

25. Jain S, Workman V, Ganeshan R, Obasare ER, Burr A, DeBiasi RM, et al. Enhanced electrocardiographic monitoring of patients with Coronavirus Disease 2019. Heart Rhythm. 2020;17(9):1417-1422. doi:10.1016/j.hrthm.2020.04.047.

26. Lazzerini PE, Boutjdir M, Capecchi PL. COVID-19, Arrhythmic Risk and Inflammation: Mind the Gap! Circulation. 2020;142(1):7-9. doi:10.1161/CIRCULATIONAHA.120.047293.

27. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004;350:1013-22.

28. Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. J Physiol. 2016;594:2459-68.