special communication

Saudi Heart Rhythm Society Task Force on Management of Potential Arrhythmogenicity Associated with Pharmacotherapy for COVID-19

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Evidence of cardiovascular complications associated with the COVID-19 global pandemic continues to evolve. These include direct and indirect myocardial injury with subsequent acute myocardial ischemia, and cardiac arrhythmia. Some results from a limited number of trials of antiviral medications, along with chloroquine/hydroxychloroquine and azithromycin, have been beneficial. However, these pharmacotherapies may cause drug-induced QT prolongation leading to ventricular arrhythmias and sudden cardiac death. Mitigation of the potential risk in these susceptible patients may prove exceptionally challenging. The Saudi Heart Rhythm Society established a task force to perform a review of this subject based on has recently published reports, and studies and recommendations from major medical organizations. The objective of this review is to identify high-risk patients, and to set clear guidelines for management of patients receiving these pharmacotherapies.

On March 11th, 2020, the World Health Organization (WHO) declared that the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was a global pandemic. No pharmacological agents have yet been proven to be safe and effective for the treatment of COVID-19, the disease caused by SARS-CoV-2. However, a number of off-label therapeutic regimens have been tried and have shown potential efficacy in treating high-risk patients diagnosed with COVID-19. While no proven effective intervention exists, it is appropriate ethically to offer these experimental interventions to COVID-19 patients after taking into account all legal considerations. As it is not possible to initiate well-controlled clinical studies during an emerging pandemic, the experimental intervention should be documented, and the efficacy and safety should be monitored.[1]

Some of these off-label regimens can potentially cause serious adverse events such as ventricular arrhythmias causing sudden cardiac arrest and sudden cardiac death. For this reason, we decided to establish national guidelines on early recognition and management of the potential arrhythmogenic risks of some pharmacological therapy used in treatment of COVID-19.

COVID-19 and cardiovascular diseases

The majority of patients who have COVID-19 are asymptomatic or have minor symptoms that occur with a variety of clinical presentations. Fever is the most common presentation; other symptoms include cough, shortness of breath, myalgia, headache, and diarrhea. Severely affected patients may present with acute respiratory distress, septic shock or multiorgan failure that requires invasive mechanical ventilation and other supportive measures.[2]

COVID-19 may affect the cardiovascular (CV) system directly or can exacerbate pre-existing cardiovascular diseases (CVD). Patients with CVD are at a higher risk of adverse events.[3-5] The prevalence of CVD in COVID-19 was studied in a meta-analysis of 1527 patients;[3] the study showed that 17.1% had hypertension, 16.4% had CVD, and 9.7% had diabetes. Four studies showed a wide range of CV diseases due to COVID-19 infection, including myocarditis (7-17%), coronary artery disease (5.8%) heart failure (23%), cardiac arrhythmias (16.7%), and cardiogenic shock.[1,5-7]

A multifactorial mechanism of cardiac injury in COVID-19 infection is suggested by previous studies on MERS and SARS epidemics and the ongoing COVID-19 pandemic.[8] As a part of an acute systemic inflammatory response, there is a surge of cytokine levels, which can result in direct injury to multiple organs, including cardiac myocytes. Studies show elevated levels of proinflammatory cytokines in patients with severe COVID-19 disease.[9] SARS-CoV-2 uses ACE2 receptors as an entry point to the cell. ACE2 receptors are expressed in both type 1 and type 2 pneumocytes as well as other types of cells, including endothelial cells. Acute injury to the heart, lung, and endothelium results from the interaction of SARS-CoV-2 with ACE2 receptors.[9] Additionally, patients with COVID-19 infection are known to have a hypercoagulable state that in turn may trigger acute coronary syndromes, resulting in further myocardial injury.[10]

Drug therapy for COVID-19 and potential arrhythmogenicity

Lopinavir/ritonavir (a potent CYP3A4-inhibiting drug) is used to treat human immunodeficiency virus (HIV) infection and is now under investigation for use in COVID-19 patients. Lopinavir/ritonavir may cause PR and QT-interval prolongation especially in patients taking other QT-prolonging drugs or those with prolonged QT at baseline.[11]

Azithromycin (a weak CYP3A4-inhibiting drug) is a macrolide antibiotic that has been used in some of the COVID-19 treatment regimens for its antiviral effect. This agent is well known to cause QT prolongation and needs special attention with proper ECG surveillance.[12] The effect of azithromycin on cardiac repolarization is especially enhanced when used in combination with other QT-prolonging medications.[12]

Chloroquine/hydroxychloroquine (a CYP2D6-inhibiting agent) has been widely used as an anti-malarial drug. It also interferes with virus-receptor binding and shows potential effectiveness as anti-viral therapy. Chloroquine is well known for its modest effect on prolonging the QT interval due to its hERG (coded by the **h**uman ***E**ther-à-go-go-**R**elated **G**ene) potassium channel blocking capabilities. Chloroquine may also increase the concentration of beta-blockers that are metabolized by the liver enzyme CYP2D6 (such as metoprolol, carvedilol, propranolol, or labetalol), and for this reason, heart rate and blood pressure should be monitored carefully.[13,14]

Hydroxychloroquine sulfate, a derivative of chloroquine, is known to be used as an immunomodulating agent for autoimmune diseases with less significant effects on the QT interval compared to chloroquine. It has been used experimentally in the treatment of COVID-19 in combination with azithromycin and antiviral agents.[15] Chloroquine and hydroxychloroquine are metabolised by CYP3A4, and beside the arrhythmic risks, both have the potential of causing direct myocardial injury. The major arrhythmic risk is attributed to torsade de pointes (TdP), especially in patients at risk of QT prolongation.[10,16]

QT prolongation has been reported in cohorts of patients treated with these COVID-19 drugs, with a prevalence of up to 90% in some reports.[17,18] Individual cases of QT prolongation-induced TdP in COVID-19 patients have also been reported.[17,19] A recent meta-analysis showed that although there was no significant benefit of hydroxychloroquine on viral clearance, a significant increase in mortality was observed in patients with COVID-19 treated with hydroxychloroquine, compared to the control group.[20] Rosenberg et al reported that cardiac arrest occurred more likely in patients receiving a combination of hydroxychloroquine and azithromycin (adjusted OR, 2.13 [95% CI, 1.12-4.05]), while the risk was lower when hydroxychloroquine or azithromycin were used alone.[21]

How to accurately measure the QT interval

As the current pandemic continues and these drugs are prescribed "off-label" as treatment or as prophylaxis, correct QTc (heart rate-corrected QT interval) interpretation becomes a fundamental clinical skill for all physi-

cians involved in the care of these patients. The end of the T wave is not always easy to define; therefore measuring the QT interval can be subjective.[22] The method that is being used for baseline QT measurement should be documented and used in all following ECGs to limit subjective variabilities. The QT interval can be measured manually by different methods, such as the tangent (QTTan) and threshold (QTThres) methods.[23] If the T wave is notched, the second component of the T wave (T2) is always included in the QT interval. If, however, the U wave is less than one-half the height of the T wave, it should be ignored. The end of the T wave by the tangent method is defined as the point where the tangent on the steepest point of the terminal limb of the T wave intersects with the isoelectric baseline (**Figure 1**). For the threshold method, the end of the T wave was defined as the intersection of the terminal limb of the T wave with the isoelectric baseline (**Figure 1**). The tangent and threshold methods both have high diagnostic accuracy and validity.[24] The lead with the longest QT interval should be used for QT measurement to avoid underestimation of QT interval. Lead II and V5 in the 12-lead ECG is most commonly used to evaluate the QT accurately when compared to other leads.[25]

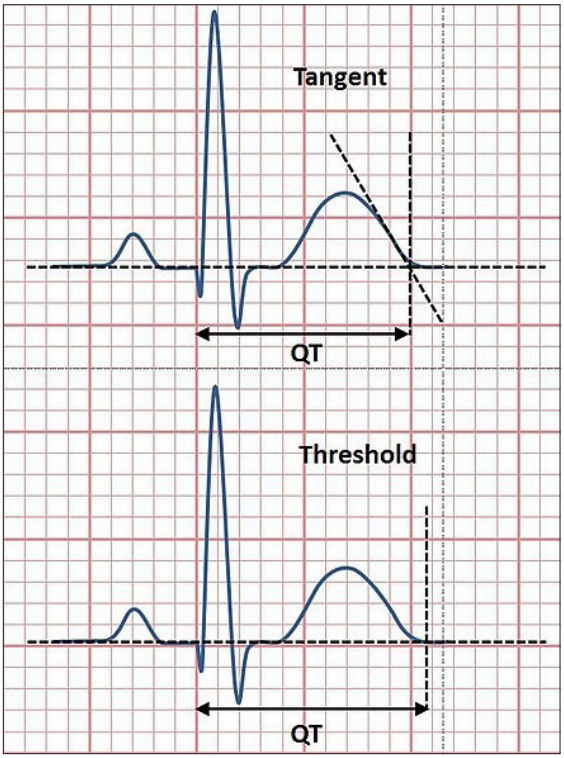

Figure 1. The tangent and the threshold methods. The second component of the T wave (T2) is included, while the U wave is excluded, from QT interval analysis (illustration from Wikipedia).

Manual vs electronic QT interval measurement by the ECG machine

The automated machine measurements of the QTc value are always higher than the manual measurement, and that because ECG machines often overestimates the end of the T wave.[26] Therefore, manual measurements are always recommended.[27]

One lead continuous monitor

As part of infection control mechanisms for patients with established or suspected COVID-19 infection, continuous ECG monitoring is often used to monitor patients. This reduces the number of clinical staff interacting with the patient, thereby reducing the risk to health care workers and preserving personal protective equipment. The QT interval can be manually calculated from lead II in the continuous monitor as a replacement of the 12-lead ECG in such conditions.

Heart rate correction of the QT interval

The heart rate is the most common parameter that can truly affect measurement of the QT interval. The slower the heart rate, the longer the QT interval. To measure the QT interval correctly, Bazett's formula is used for heart rate correction.[28] The Bazett's formula uses the manually calculated QT and RR interval to calculate the QTc:

$$QT_c = \frac{QT}{\sqrt{RR}}$$

Where the RR is calculated in seconds and QT in msec. An example of the QTc calculation is shown in **Figure 2**.

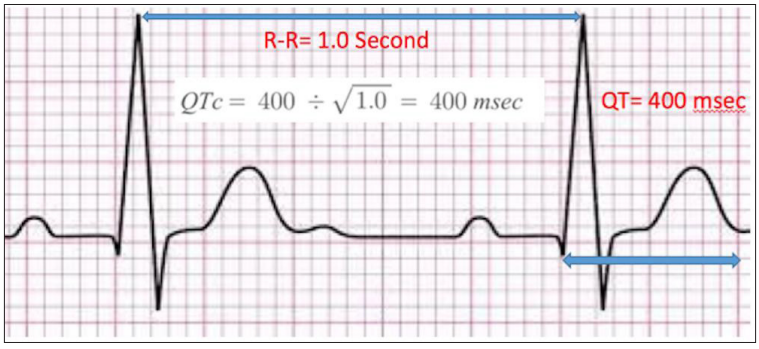

Figure 2. The QTc calculation.

Mitigating the potential risk of drug-induced *torsade de pointes* in COVID-19 patients

While there is a real, albeit low risk of drug-induced TdP with the use of hydroxychloroquine, azithromycin, and lopinavir/ritonavir, small uncontrolled trials suggest a reduction in viral load and potential clinical benefit.[29-31] The COVID-19 pandemic has caused a high demand on healthcare systems and shortage of personal protective equipment and even healthcare providers. If these medications reduce the morbidity and mortality even slightly, this would represent a significant net benefit when compared to the risk of drug-induced life-threatening arrhythmia, especially if measures to mitigate this risk are undertaken. This eventually comes down to identifying high-risk groups and implementing QT surveillance during therapy.

Identifying high-risk groups

Drug-induced QT prolongation occurs more commonly in females than in males and is seen more frequently in older patients (>65 years of age).[32] Patients with long QT syndrome (LQTS) are known to be high risk. Electrolyte abnormalities are known to cause QT prolongation, especially hypokalemia, hypomagnesemia, and hypocalcemia.[33] Patients with underlying cardiac disease such as myocardial ischemia, dysfunction or bradycardia are also at risk. These effects are more pronounced in hospitalized patients who have renal or hepatic dysfunction, hypoglycemia, hypothermia or those already on QT-prolonging medications.[34] Hence, TdP is more likely to be induced with administration of a given drug in a hospitalized patient than in an outpatient setting.[35] It is also safe to assume that severe cases of COVID-19, especially those with cardiac involvement, would be more predisposed to QT prolongation. Several clinical stratification tools that may be used to determine QT-prolongation risks are published in the literature.[36,37]

QTc surveillance during therapy

The goal of QT surveillance is to identify patients who have abnormal repolarization at baseline or on therapy in whom serial ECGs and QT prolongation countermeasures may be needed. A baseline QT interval measurement via a 12-lead ECG should be obtained before administration of COVID-19 pharmacotherapies, particularly in hospitalized patients. A QT interval above the 99th percentile value for healthy individuals (i.e., 460 milliseconds in pre-pubertal females and males, 470 milliseconds in post-pubertal males, and 480 milliseconds in post-pubertal females) may signal an individual at increased risk for TdP.[38] In patients with a QT interval less than the 99th percentile, the risk of TdP is low and COVID-19 pharmacotherapies may be initiated at once. Patients with QT intervals >500 millisecond (and narrow QRS) are at risk of drug-induced TdP and sudden death, and every effort should be done to mitigate this risk (check and correct any electrolyte derangement and discontinue unnecessary QT prolonging medications).[39,40] In patients with wide QRS (QRS >120 ms) secondary to bundle branch block or pacing, a QTc of 550 ms is used as a cut-off for normal QTc. The decision to start QT-prolonging COVID-19 pharmacotherapies in these patients lies with the treating clinician. When the benefit of treatment outweighs the risk of arrhythmias, it would be prudent to start with single therapy rather than combination therapy, along with close monitoring (**Figure 3**).

COVID-19 treatment in patients with inherited channelopathies

In patients with known inherited LQTS or Brugada syndrome, treatment should be undertaken only after consultation with a heart rhythm specialist. Potential measures to reduce pro-arrhythmic risk in this population may include aggressive treatment of fever, frequent QTc interval checks, cardiac pacing, or infusions of lidocaine, magnesium, or dexmedetomidine.[41,42]

Frequency of QTc Surveillance

On-therapy QT assessment for high risk patients (QT ≥500 ms) should include a QT interval obtained 2-4 hours after the first dose, then again after 48 hours, then 96 hours. In low-risk patients, on-therapy assessment should be obtained at 48 and 96 hours.[43] If on-therapy QT increases by ≥60 ms or is ≥500 ms, then the QTc prolongation countermeasures need to be reviewed, and the medications possibly stopped.

Infection control aspects of QT monitoring

If measures to mitigate QT prolongation are necessary they should not increase the risk of exposure to healthcare staff or other patients to SARS-CoV-2.[44] When it is necessary to obtain a 12-lead ECG approach, one ECG machine should be designated for suspected COVID-19 patients and the number of personnel limited to minimize the exposure risk and protective equipment consumption. We encourage the use of real-time QTc monitoring if the telemetry system is equipped with this feature and using lead II for QT measurement.[27] This will not only eliminate exposure risk and protective equipment use, but also allow for more fre-

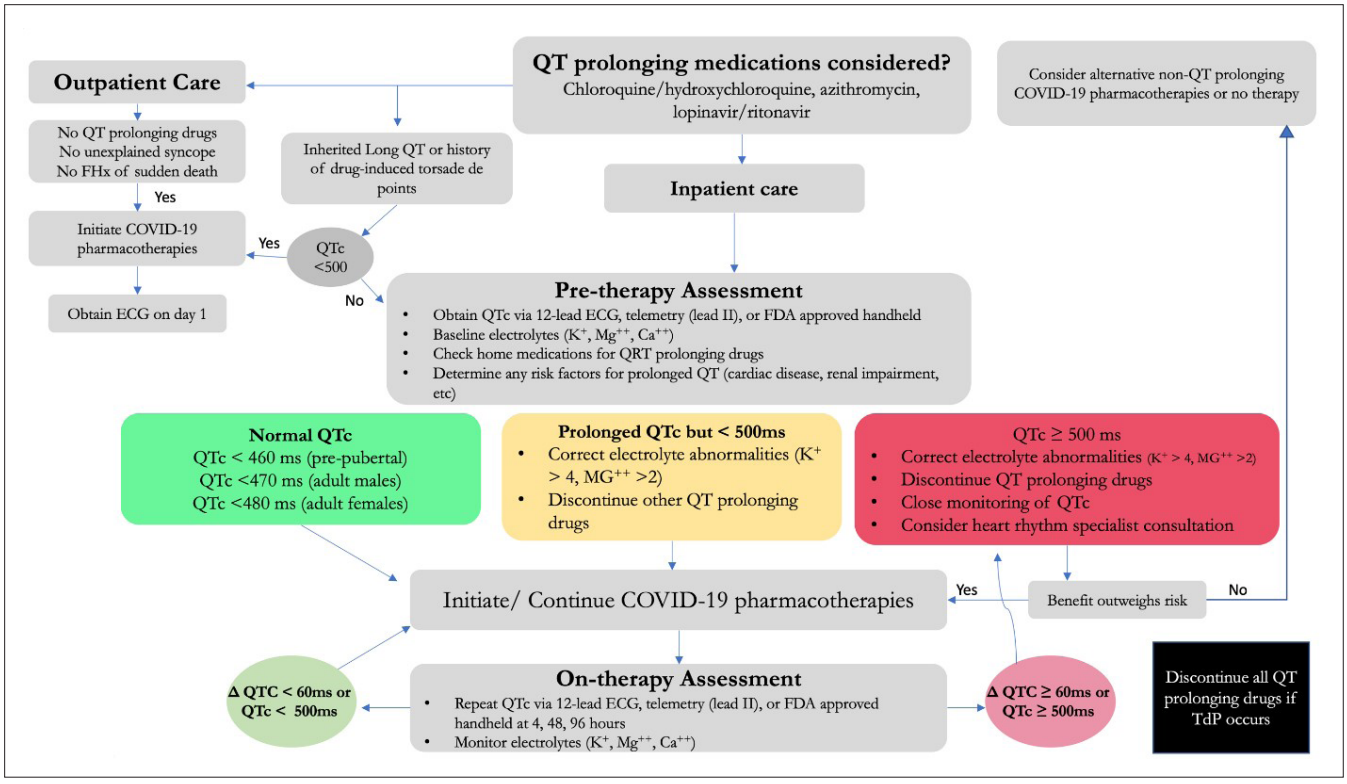

Figure 3. Flow chart to manage effects on QTc with COVID-19 pharmacotherapies. (ECG: electrocardiogram; K: serum potassium; Mg: serum magnesium; TdP: torsade de pointes).

quent QT assessments (e.g. once per shift) thereby allowing early detection of QT prolongation and earlier implementation of countermeasures.

Management of long QT interval

The management of drug-induced long QT syndrome focuses on the identification of patients at risk of developing long QT, the monitoring QT duration during treatment, the early recognition of QT prolongation, and the correction of reversible causes and treatment of life-threatening arrhythmia, namely TdP. Before starting a new treatment with a potential risk of QT prolongation, the patient's medical profile should be reviewed carefully to avoid concomitant use of other QT prolonging therapy. There are more than 50 FDA approved medications with a risk of QT prolongation (a comprehensive list can be found on *https://www.crediblemeds.org*). Special attention is needed to those commonly used non-cardiac medications that can potentially prolong QT duration such as antiemetic drugs.[45] It is not uncommon to have electrolyte imbalances during an acute illness such as COVID-19 infection so careful electrolyte monitoring is recommended.

The most fearful outcome of drug-induced long QT is sudden death due to polymorphic ventricular tachycardia. While on such therapy, patients should be advised to report any new symptoms, especially palpitations and syncope. Patients presenting with hemodynamically unstable TdP should be treated according to the Advanced Cardiovascular Life Support (ACLS) protocol. Infusion of magnesium is the only antiarrhythmic therapy proven to stabilize TdP (**Figure 4**).[46] Patients with short runs of polymorphic VT that is hemodynamically stable can be closely monitored. In those patients, correction of underlying electrolyte imbalances and elimination of drugs with potential QT prolongation may be sufficient. Polymorphic VT is more likely to occur in the setting of bradycardia or frequent pauses; therefore, discontinuing medications causing bradycardia is important. Patient with AV nodal block or significant sinus node disease may require temporary pacing or isoproterenol infusion.[47]

Conclusion

The COVID-19 pandemic poses a major impact on health care systems around the globe. Multiple treatment strategies have been published, but results have been variable. Some of the pharmacological agents

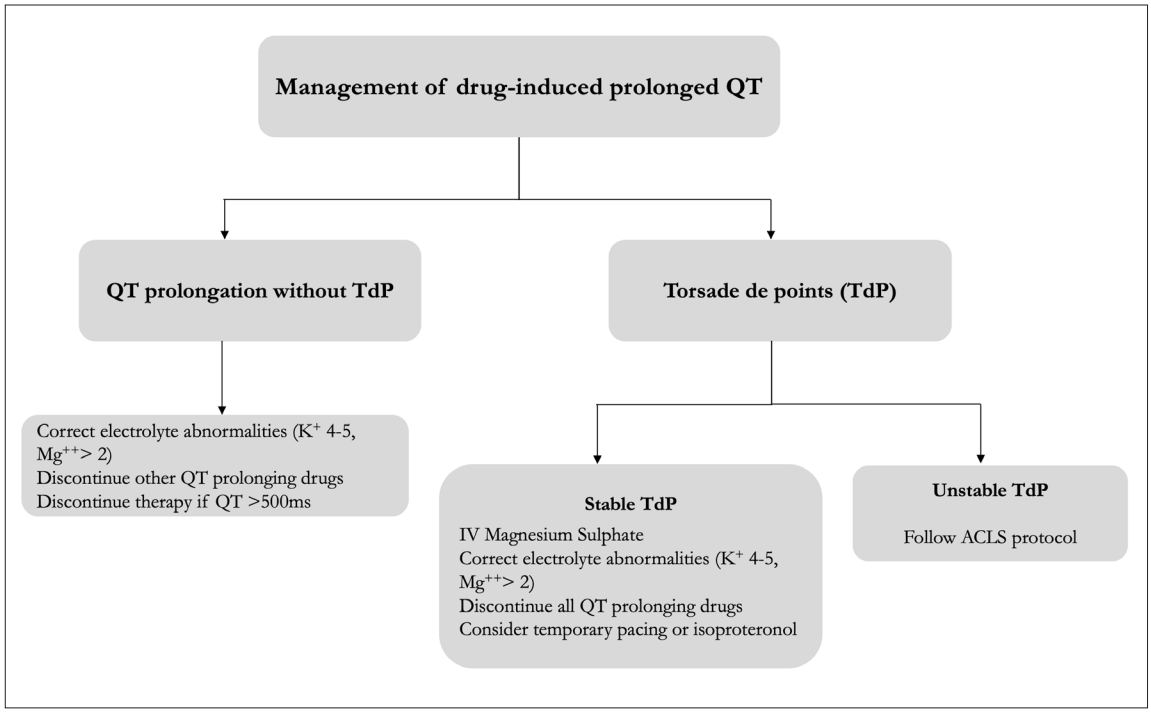

Figure 4. Algorithm for drug-induced QT prolongation management. ACLS: Advanced Cardiovascular Life Support.

- Review other medications for other QT prolonging drugs.
- Check for and correct any electrolyte disturbances.
- Once on therapy, monitor QT interval 2-4 hours after initial dose then 48- and 96-hours interval.
- If the QT interval prolongs >=60ms or QT>=500ms, then consider therapy cessation or countermeasures.
- In patients with a known inherited channelopathy, consult heart rhythm specialist before starting treatment.

Figure 5. Recommended management of patients receiving COVID-19 pharmacotherapies.

used in COVID-19 treatment carry arrhythmogenic risks and can cause malignant ventricular arrhythmias and sudden cardiac death. In patients receiving these pharmacotherapies, the QT interval should be assessed and monitored closely throughout the treatment period. Timely management of QT prolongation and ventricular arrhythmias is important to reduce the morbidities associated with these pharmacotherapies (**Figure 5**).

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