

Safety of antiviral and anti-inflammatory drugs prolonging QT interval in patients with coronavirus disease 2019: an opinion of the Heart Rhythm Section of the Polish Cardiac Society

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KEY WORDS

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Introduction The purpose of this document is neither to evaluate the efficiency of treatment with antiviral and antimalarial drugs in patients with coronavirus disease 2019 (COVID-19), nor to influence the decision on the kind of treatment. The aim of the paper is to draw the attention to the possibility of reducing the risk of sudden cardiac death involving the use of these drugs as well as to ensure the utmost safety for patients requiring such treatment.

Some drugs used in the treatment of COVID-19 (chloroquine, hydroxychloroquine, lopinavir / ritonavir, and azithromycin) may prolong QT / corrected QT (QTc) and cause serious arrhythmias such as torsade de pointes (TdP), an atypical ventricular tachycardia. The induction of such arrhythmias may lead to the loss of consciousness and possibly the cause of sudden cardiac death. Azithromycin can additionally cause polymorphic tachycardia and atrioventricular conduction disturbances (TABLE 1). In order to minimize the risk associated with

the above-mentioned drugs, risk factors of arrhythmia should be taken into account prior to treatment administration (TABLE 2) and, if possible, eradicated. Electrolyte imbalance ought to be corrected, other drugs causing QT prolongation should be discontinued. Lists of QT prolonging drugs is available at www.qt-drugs.org and www.crediblemeds.org. Throughout the treatment of high-risk patients, monitoring of the QTc interval and arrhythmia is necessary (management algorithm is presented in FIGURE 1).

In order to calculate the QTc interval, the Bazett formula is most commonly used. In case of problems when measuring QT (measuring the end of the T wave), a tangent to descending portion of the T wave should be drawn. The result should be an average of at least 3 heart evolutions (FIGURE 3). The upper limit of a QTc interval for men is 450 ms and for women, 460 ms. QTc between 460 ms and 500 ms requires attention.

TABLE 1 Drugs used in the treatment of coronavirus disease 2019 that have proarrhythmic effect (based on Giudicessi et al)¹

| Drug | Risk of TdP/VF/CA | Mechanism |
|-----------------------|-------------------|---|
| Antimalarial drugs | | |
| Chloroquine | Confirmed | Blocking of potassium channel Kv11.1 |
| Hydroxychloroquine | Confirmed | Blocking of potassium channel Kv11.1 |
| Antiviral drugs | | |
| Lopinavir / ritonavir | Possible | Blocking of potassium channel Kv11.1, although its proarrhythmic effect was not proven |
| Supportive drugs | | |
| Azithromycin | Confirmed | QT prolongation in unknown mechanism (rarely TdP) Polymorphic tachycardia in the mechanism of enhanced channel Nav1.5 Bradycardia, atrioventricular conduction disturbances |

Abbreviations: CA, cardiac arrest; TdP, torsade de pointes; VF, ventricular fibrillation

TABLE 2 Risk factors for a prolonged QT interval and serious arrhythmias (modified from Behr et al)²

| | |
|---------------------------------------|---|
| Female sex | |
| Age >68 y | |
| Heart diseases | Myocardial infarction Heart failure Left ventricular hypertrophy First hours after atrial fibrillation cardioversion to sinus rhythm Prolonged QT syndrome and genetic factors predisposing to QT prolongation Bradycardia and atrioventricular disturbances |
| Sepsis | |
| Increased bioavailability of the drug | Genetic versions of P450 cytochrome Other drugs metabolized by cytochrome P450 used simultaneously Liver disease Kidney disease |
| Electrolytic disturbances | Hypokalemia Hypomagnesemia Hypocalcemia |

A simple method of evaluating QTc prolongation is checking whether the QT interval does not exceed half of the preceding R-R interval. In such case, QTc does not exceed 460 ms, which means that the patient has a low risk of TdP.

Monitoring of treatment safety in given clinical cases

- Restricted availability of personal protective equipment: it is advisable to perform electrocardiography (ECG) within 2 to 4 hours after drug administration. QTc measurements by means of telemetry or mobile devices, for example, Apple Watch, AliveCor, KardiaMobile, or others, are acceptable. Proper protection of the phone and leads for ECG ensures sterility and minimizes the risk of virus transmission.
- Restricted availability of telemetry: patients undergoing treatment in which QTc values assessed after the treatment administration are acceptable can be monitored telemetrically, similarly to patients at low risk. Patients at a higher risk should be monitored. If the hospital telemetry is unavailable, mobile methods of monitoring are acceptable. Every syncope should be treated as potentially caused by polymorphic ventricular tachycardia.
- Limiting contact: in patients staying in house care with a low risk of arrhythmia, baseline ECG can be omitted. QTc monitoring should be performed according to the proposed outlines, additional, unnecessary ECG registration should not be performed as it increases the infection risk of personnel and involves the use of additional protective equipment.

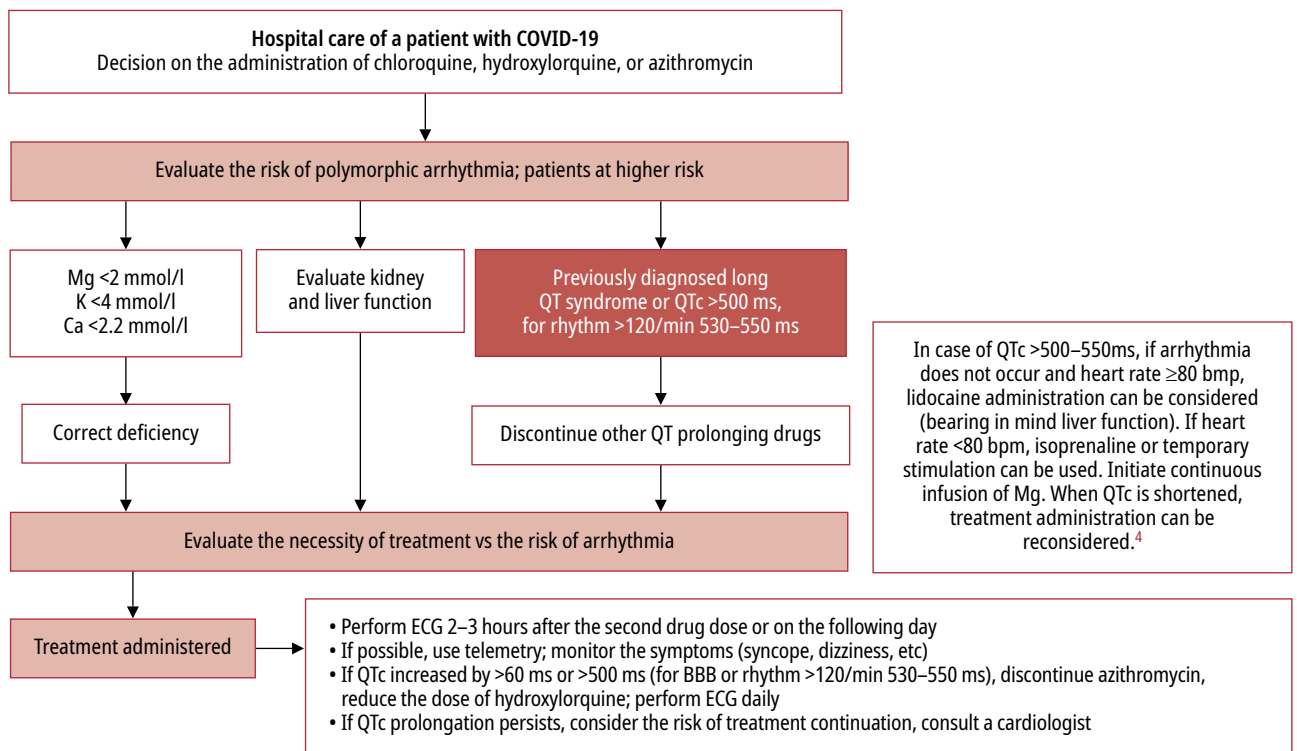


FIGURE 1 Management algorithm in hospitalized patients with coronavirus disease 2019 treated with QT/QTc prolonging drugs (based on Simpson et al,³ Mitra et al)⁴
Abbreviations: BBB, bundle branch block; Ca, calcium; COVID-19, coronavirus disease 2019; ECG, electrocardiography; K, potassium; Mg, magnesium; QTc, corrected QT

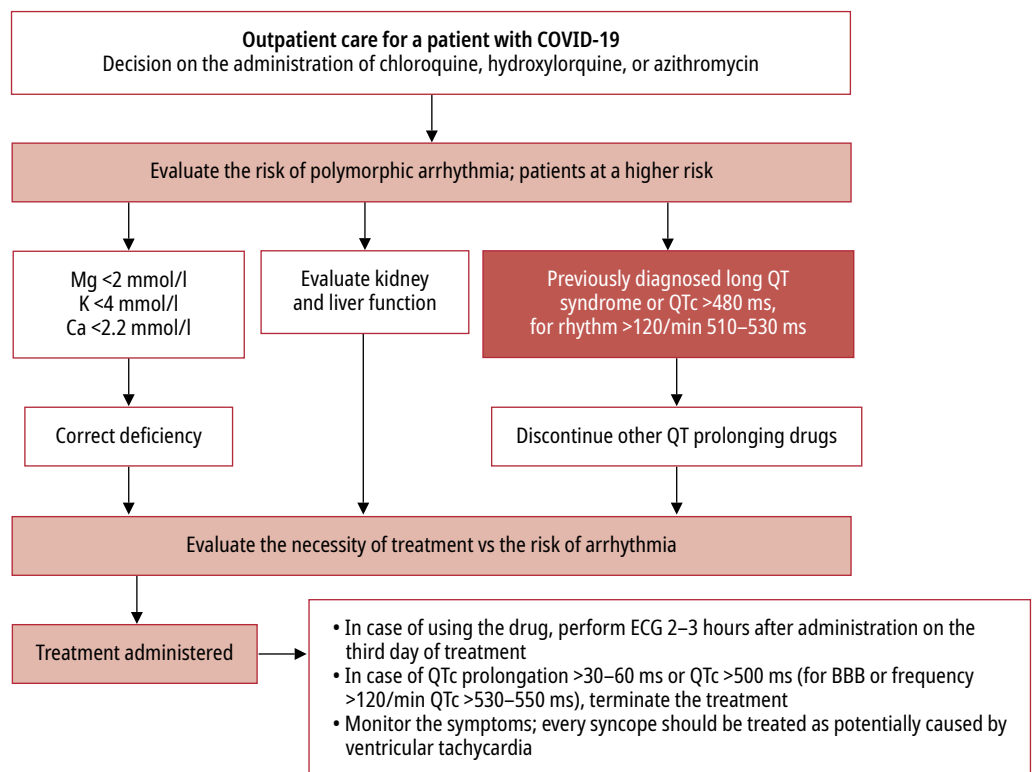


FIGURE 2 Management algorithm in patients with coronavirus disease 2019 treated with QT/QTc prolonging drugs in the outpatient setting (based on Simpson et al,³ Mitra et al)⁴
Abbreviations: see FIGURE 1



FIGURE 3 A formula for corrected QT (online calculator: <http://zwr.cmj.org.pl/biblioteka-wiedzy/qt-c-skorygowany-odstep-qt-wzor-bazetta/>)

Abbreviations: see **FIGURE 1**

- Ensuring safe monitoring: all patients with the following symptoms should be monitored: syncope, dehydration, ion disturbances. Monitoring can be in a form of a phone call. Every syncope should be treated as potentially caused by polymorphic ventricular tachycardia.³

The procedure in case of torsade de pointes tachycardia Sustained tachycardia of the TdP type causing hemodynamic instability, loss

of consciousness, or cardiac arrest requires immediate cardiopulmonary resuscitation, including defibrillation. In case of good tolerance of arrhythmia (single or multiple self-terminating tachycardia), every patient requires monitoring and treatment due to a substantial risk of sudden deterioration. It is recommended to administer magnesium sulfate intravenously in a 2-g dose and to correct potassium and calcium deficiency (up to the upper limit). In case of subsequent recurrence of TdP, temporary heart stimulation can be applied with a frequency of 70 to 80 per minute or intravenous infusion of izoproterenol in a dose of 1 to 5 µg per minute (**FIGURE 4**).^{5,6} In every case of TdP, urgent cardiology consultation is advised.

SUPPLEMENTARY MATERIAL

The Polish version of the paper is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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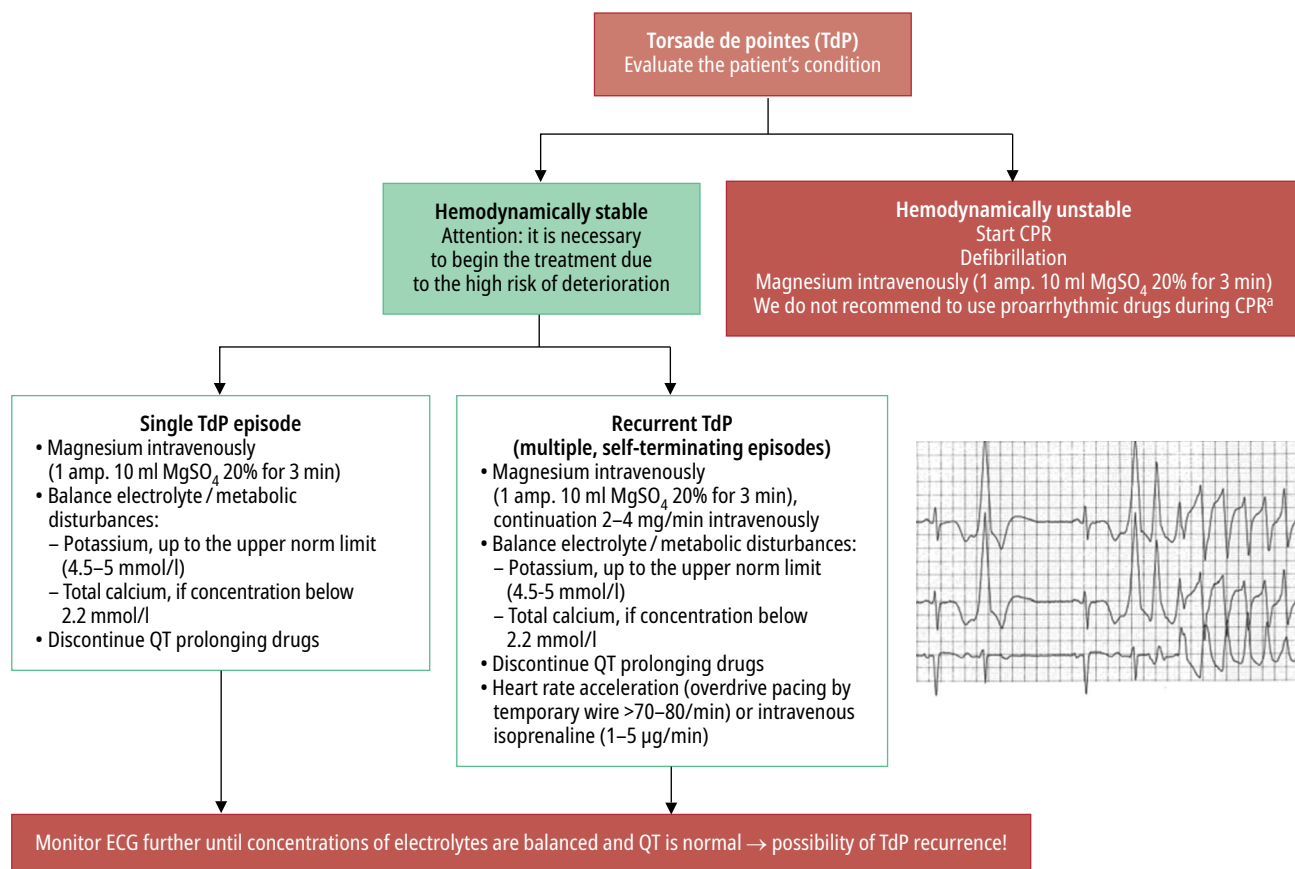


FIGURE 4 Procedure in case of torsade de pointes tachycardia.

a It does not apply to possible use of lidocaine at a later stage

Abbreviations: CPR, cardiopulmonary resuscitation; others, see **TABLE 1** and **FIGURE 1**

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