

# Chloroquine and hydroxychloroquine for the prevention and therapy of coronavirus disease 2019: new hopes and old cardiovascular concerns

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## KEY WORDS

chloroquine, hydroxychloroquine, coronavirus disease 2019, QT prolongation, ventricular arrhythmia

## Chloroquine and hydroxychloroquine for the prophylaxis and treatment of COVID-19: what do we now in mid-June?

Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in central China and was identified as an etiological factor of an epidemic pneumonia.<sup>1</sup> In the large urban agglomeration of Wuhan, the virus was easily transmitted via droplets, which resulted in an epidemic outbreak with notable morbidity and mortality rates.<sup>2</sup> Shortly after, SARS-CoV-2 very quickly spread throughout the whole China<sup>3</sup> and further around the world. Currently, the SARS-CoV-2 pandemic is considered “the latest threat to global health”.<sup>4,5</sup>

Important questions arose: how to treat the disease and whether there are therapies improving outcomes, also in the most severe cases of coronavirus disease 2019 (COVID-19) that require intensive care and mechanical ventilation. Furthermore, there are understandable concerns amongst healthcare professionals, police, and military staff, whether they are properly protected from the potentially life-threatening condition in the absence of any evidence-based prophylaxis. Two groups of drugs are still intensively investigated as therapeutic options

in COVID-19: 1) classical antiviral drugs interfering with pathogen dissemination / replication, and 2) compounds inhibiting host inflammatory reactions (cytokine inhibitors and specific antibodies).<sup>6,7</sup> Special hopes were initially placed in quinoline derivatives, such as chloroquine (CQ) and hydroxychloroquine (HCQ), used for decades as antimalarial (CQ) and immunomodulatory (HCQ) drugs.<sup>7-9</sup>

Chloroquine, which is chemically a weak base, exerts anti-coronavirus effects by increasing endosomal pH (which hampers the fusion between the virus and target cells) and interfering with glycosylation of cellular receptors (angiotensin-converting enzyme 2) for the virus.<sup>10</sup> At the beginning of the pandemic, clinical research involving CQ and HCQ in COVID-19 began from a few studies (experimental rather than clinical) that suggested that these drugs may bring clinical benefits in SARS-CoV-2 infection.<sup>9,11</sup> Already 15 years ago, it was demonstrated that CQ exerted a noticeable antiviral activity against SARS-CoV-1 *in vitro*.<sup>12</sup> Importantly, similar observations have been made for SARS-CoV-2 shortly after the virus spread around the world. Wang et al<sup>13</sup> have demonstrated that CQ effectively hampers SARS-CoV-2 infection of Vero

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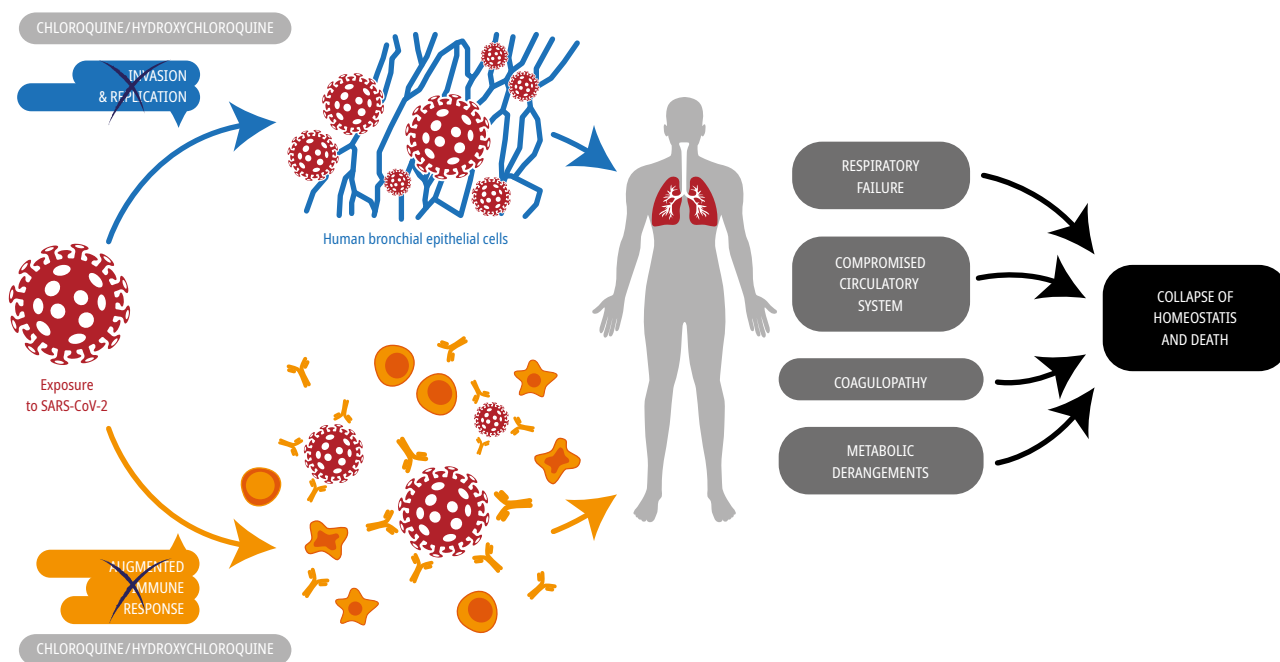
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Received: April 18, 2020.

Revision accepted: July 6, 2020.

Published online: July 14, 2020.

Kardiol Pol. 2020; 78 (7-8): 811-817  
doi:10.33963/KP.15511

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**FIGURE 1** Postulated beneficial effects of the administration of chloroquine and hydroxychloroquine in coronavirus disease 2019 involve both hampering the invasion / replication of the virus (via increasing endosomal pH and affecting the glycosylation of entry receptors for the virus) and preventing the so-called cytokine storm  
Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

cell cultures even in low micromolar concentrations (which are achievable in the human lung tissue). Consistent findings have been reported by Yao et al,<sup>14</sup> who have shown that both CQ and HCQ decrease coronaviral activity and replication in cell cultures in vitro. Another mechanism of how CQ and HCQ can potentially interfere with the course of SARS-CoV-2 infection in humans is related to their anti-inflammatory properties known from the use in rheumatoid disorders such as systemic lupus erythematosus. A decrease in the uncontrolled production and release of different inflammatory cytokines (including interleukin [IL] 1, IL-6, interferon  $\alpha$ , tumor necrosis factor) is considered protective against the so-called cytokine storm which is responsible for rapid disease deterioration with underlying multiorgan injury in some infected patients.<sup>15,16</sup> Postulated (however not yet proven) mechanisms of anti-coronavirus properties of CQ and HCQ are demonstrated in **FIGURE 1**.

Until now (mid-June 2020), there have been published only a few prospective clinical trials regarding the prophylaxis and treatment of COVID-19 with HCQ and CQ, and currently available evidence does not support the routine use of 4-aminoquinolines due to unproven benefits of such therapy. The summary of these trials are presented in **TABLE 1**. The only trial that demonstrated some small benefits was a small non-randomized open-label French study in which the researchers administered HCQ  $\pm$  antibiotic azithromycin (it is worth noting that the latter

medication is also considered to prolong the QT interval as discussed below) for 6 consecutive days in 20 persons infected with SARS-CoV-2 (varying of clinical status, that is, ranging from asymptomatic cases to an overt pneumonia). Then, they evaluated viral RNA using reverse transcriptase-polymerase chain reaction in nasopharyngeal swabs of treated patients and compared them with patients with COVID-19 who did not receive HCQ nor azithromycin.<sup>17</sup> There were more negative tests for SARS-CoV-2 in the treated group as compared with untreated patients as soon as on day 3 and thereafter.<sup>17</sup> The follow-up and side effects of this therapy are supposed to be described in detail in another paper, as stated by the authors.<sup>17</sup> In a study by Borba et al,<sup>18</sup> therapy with a very high dose of CQ (600 mg twice daily for 10 days) in critically ill patients with COVID-19 was associated with increased mortality and prolonged QTc intervals as compared with a group treated with a low dose of CQ. Authors and experts have emphasized that these unfavorable effects were most likely associated with high doses of CQ applied in already extremely ill patients with serious metabolic derangements and several comorbidities and in patients who were concomitantly treated with numerous drugs also known for their cardiac side effects. Importantly, in the largest clinical trial so far performed in 821 adults who had household or occupational high- or moderate-risk exposure to SARS-CoV-2, the most common side effects of prophylactic

**TABLE 1** Prospective clinical trials (alphabetically) on chloroquine and hydroxychloroquine in the prophylaxis and treatment of coronavirus disease 2019 published until mid-June 2020

Trial	Design	Aim of the study: treatment or prophylaxis; drug	Patients	Main outcome analyzed	Results	Safety / AEs / SEs
Borba et al <sup>18</sup>	Parallel, double-masked, randomized, no control group	Treatment, CQ in 2 dosing schemes – high- and low-dose	81 adults with confirmed or only suspected severe COVID-19	All-cause death up to day 13	Increased mortality in the high-dose CQ arm	QTc longer than 500 ms more frequent in the high-dose CQ arm
Boulware et al <sup>19</sup>	Multicenter, randomized, double-blind, placebo-controlled	Post-exposure prophylaxis, HCQ vs placebo	821 adults who had household or occupational high- or moderate-risk exposure to SARS-CoV-2	COVID-19 confirmed or suspected based on typical symptoms within 14 days	No benefits of HCQ-based prophylaxis	SEs more common in the HCQ arm but no serious AEs
Gautret et al <sup>17</sup>	Single center, open label, not randomized	Treatment, HCQ ± azithromycin based on clinical presentation	20 patients with COVID-19 (from asymptomatic to pneumonia) were compared with those who refused to participate and untreated patients from another center	Viral clearance at day 6	Reduction of viral carriage at day 6 in the HCQ +/- azithromycin group	Not described in the paper
Tang et al <sup>44</sup>	Multicenter, open label, randomized 1:1 controlled	Treatment, HCQ	150 inpatients with mainly mild to moderate COVID-19	Negative conversion by day 28	No differences between HCQ vs controls	More AEs in the HCQ arm (mostly gastrointestinal ones)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; CQ, chloroquine; HCQ, hydroxychloroquine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, side effect

administration of HCQ were nausea, loose stools, and abdominal discomfort, and there were no serious intervention-related adverse reactions or cardiac arrhythmias.<sup>19</sup>

There is no doubt that further studies are needed to make unequivocal evidence-based statements regarding both effectiveness and safety of such therapy (see below). Mass-scale therapeutic programs are ongoing, for example, the Solidarity trial initiated by the World Health Organization. Of note, a simultaneous compassionate use of different immunomodulatory and antiviral drugs in critically ill patients with COVID-19 makes it very difficult to clearly evaluate individual effectiveness and safety of particular substances.

#### **Tolerability of chloroquine and hydroxychloroquine and their impact on the cardiovascular system**

Chloroquine is an old antimalarial drug that has been widely used for decades for prevention and therapy of this parasitosis.<sup>20</sup> Similarly, CQ has been used effectively for therapy of amebiasis, including severe cases of pulmonary abscesses and pleural empyema.<sup>21</sup> Chloroquine is cost-effective and constitutes one of key antiparasitic drugs used worldwide. It is considered safe also in pregnant women and children, with few side effects, which are mild or moderate in the majority of cases.<sup>20,22</sup> As

mentioned above, nonspecific anti-inflammatory features of quinoline derivatives such as CQ or HCQ have also been used in rheumatology (in patients with lupus erythematosus or rheumatoid arthritis) due to the inhibition of proinflammatory cytokine production.<sup>23,24</sup>

Chloroquine is considered safe and well-tolerated, with few side effects only, including headache, malaise, nausea and/or vomiting (most frequent side effects), blurred vision, pruritus, dizziness, difficulties in concentrating, and gastric symptoms, to name just a few.<sup>22</sup> Detailed statistical analysis of common side effects of CQ are summarized elsewhere.<sup>22</sup> Serious side effects of CQ such as neuromyopathy, retinopathy, or idiosyncratic reactions are very rare and may occur in the course of a very long therapy with CQ.

Cardiovascular concerns regarding the use of CQ and HCQ are related to their chemical (structural) similarity to quinidine (both substances belong to quinoline derivatives), which is an old antiarrhythmic drug that may prolong the QT interval (the “quinidine effect”) predisposing to life-threatening polymorphic ventricular tachycardia (torsade de pointes).<sup>25</sup> The established arrhythmogenic cardiotoxicity of quinidine should not be extrapolated directly to CQ or HCQ.<sup>20</sup> Indeed, among antimalarial drugs being structurally related to quinoline, only quinidine and halofantrine (but

not CQ) are known to significantly affect ventricular repolarization, and as a consequence, cause clinically relevant QT prolongation (TABLES 2 and 3).<sup>25</sup> In the past, CQ was administered also intravenously (this route of administration was withdrawn as it induced severe hypotension) and even then its effect on QT prolongation was only borderline (TABLE 2).<sup>25</sup> Cardiovascular toxicity of oral CQ in anti-parasite doses is considered negligible, as it rarely induces conduction abnormalities and may only slightly widen the QRS complex and prolong the QT interval (TABLE 3).<sup>25</sup>

Haeusler et al<sup>26</sup> performed a systematic review where they assessed the arrhythmogenic toxicity of different antimalarial drugs using a structured and comprehensive approach. The authors analyzed clinical and electrocardiographic cardiovascular side effects of quinoline derivatives from 177 malaria clinical trials yielding a total number of more than 35 000 patients receiving potentially QT-prolonging medications (including more than 1200 patients treated with CQ).<sup>26</sup> The authors made a very important statement on lack of sudden deaths related to cardiac arrhythmia in these trials.<sup>26</sup> Moreover, experts on long QT syndrome after the comprehensive and structured review of available reliable evidence concluded in a publication from *JAMA* that CQ is a drug of unknown potential for causing QT prolongation, whereas—on the contrary—quinidine and amiodarone were classified as drugs of very probable potential for causing QT prolongation.<sup>27</sup>

Cardiovascular safety of CQ and HCQ has been also the subject of interest in patients with rheumatic disorders, in whom these 2 drugs are administered since many years. Liu et al<sup>28</sup> performed a systematic review and meta-analysis of rheumatology studies on CQ/HCQ in order to estimate the effects of these drugs on cardiovascular risk. They analyzed data from 19 studies (unfortunately none of these studies was a clinical trial) including almost 20 000 patients with rheumatic diseases and demonstrated that the applied therapy with CQ/HCQ reduced the risk of cardiovascular events (pooled relative risk, 0.72; 95% confidence interval, 0.56–0.94;  $P < 0.05$ ).

Relevant data have been included in a recent pharmacovigilance report on CQ phosphate (March 2020) produced by a Polish pharmaceutical company.<sup>29</sup> More than 800 000 packages of CQ phosphate (30 tablets each) were sold in the reporting period (from January 1, 2015 to December 31, 2019). During this period, the responsible entity recorded only 19 adverse drug reactions, including 11 classified as severe, related with the administration of CQ. There were no deaths associated with CQ phosphate during the reporting period.<sup>29</sup> An update of this report did not bring any new conclusions.<sup>30</sup>

With regard to quinoline derivatives, recently, there have been a few reports published that investigated changes in the QTc interval during the combined therapies with antimicrobial drugs, including CQ/HCQ in patients with COVID-19.<sup>31-35</sup> Indeed, after the recent retraction of one paper published in a highly prestigious journal suggesting hazardous cardiovascular toxicity of CQ/HCQ in a meta-analysis of almost 100 000 patients with COVID-19 (with or without azithromycin), the public expectation to deliver unequivocal data has substantially grown.

In a few published reports (mostly retrospective observational studies), therapy with CQ/HCQ has been shown to prolong the QTc interval in some groups of patients with COVID-19—combined with azithromycin in most cases.<sup>31-35</sup> Importantly, clinical relevance, including a causal relationship with arrhythmogenic nonfatal and fatal events as well as an exclusive contribution of CQ/HCQ to these electrophysiological effects beyond azithromycin, have not been clearly elucidated.<sup>31-35</sup> For example, out of 22 patients with COVID-19 treated with HCQ and azithromycin, 4 developed a QTc interval longer than 480 ms, 1 developed a QTc interval longer than 500 ms, and most importantly, in this group only 1 episode of 5-beat nonsustained ventricular tachycardia was recorded, without any case of syncope, fatal arrhythmia, or sudden cardiac death.<sup>34</sup> Out of 98 patients with COVID-19 treated with HCQ and/or azithromycin, 12 (5 treated with azithromycin and 7 treated with azithromycin and HCQ) demonstrated

**TABLE 2** Cardiovascular effects of intravenously administered antimalarial drugs (reprinted from White,<sup>25</sup> with permission from Elsevier)

	Hypotension if injected rapidly	Hypotensive with rate controlled infusion	ECG QRS widening	ECG QT prolongation
Quinine*	+++	0	+	+
Quinidine*	+++	++	+	+++
Chloroquine*	+++	0	+	+/-
Artesunate	0	0	0	0

ECG=electrocardiogram. 0=none. +/-=borderline. +=slight. ++=moderate. +++=severe. \*Potentially lethal if given by intravenous injection.

**TABLE 3** Cardiovascular effects of orally administered antimalarial drugs (reprinted from White,<sup>25</sup> with permission from Elsevier)

	Conduction abnormalities reported	ECG QRS widening	ECG QT prolongation	Cardiovascular toxicity in overdose
Quinine	+	+	+	++
Quinidine	+	+	+++	+++
Chloroquine	+	+	+/-	+++
Amodiaquine	+/-	+/-	+/-	..
Mefloquine	+	0	0	..
Halofantrine	++	+	+++	..
Lumefantrine	0	0	0	..
Piperaquine	0	+	0	..
Primaquine	..	..	..	..
Pyrimethamine	0	0	0	0
(Chlor)proguanil	0	0	0	0
Atovaquone	0	0	0	0
Dihydroartemisinin*	0	0	0	0

ECG=electrocardiogram. ..=no data. 0=none. +/-=borderline. +=slight. ++=moderate. +++=severe. \*Dihydroartemisinin is the active metabolite [sic] of artesunate and artemether.

a critical QTc prolongation (QTc  $\geq 500$  ms if QRS  $< 120$  ms, or QTc  $\geq 550$  ms if QRS  $\geq 120$  ms, or an increase from baseline QTc of  $\geq 60$  ms).<sup>32</sup> In a observational study, Mercurio et al<sup>33</sup> investigated the effects of HCQ therapy (in approximately 60% of cases with adjunctive azithromycin) on the QTc prolongation in 90 patients hospitalized for pneumonia complicating COVID-19.<sup>33</sup> The authors demonstrated that the use of HCQ was related with the risk of QTc prolongation, including cases of QTc  $> 500$  ms, and the concomitant azithromycin administration further potentiated these effects on the QTc interval—the median increase in the QTc interval was 5.5 ms in patients treated only with HCQ as compared with 23 ms in those treated with HCQ and azithromycin ( $P < 0.05$ ).<sup>33</sup> Importantly, only one episode of torsade de pointes was observed in this study group, and—not surprisingly—the longer baseline QTc interval and the administration of loop diuretics (affecting electrolyte balance and most likely indirectly identifying patients with heart failure) were additional risk factors for QTc prolongation.<sup>33</sup> On the contrary, Saleh et al<sup>31</sup> comprehensively analyzed electrocardiography recordings in 200 COVID-19 inpatients treated with HCQ/CQ  $\pm$  azithromycin from 3 United States hospitals in a prospective observational study. Although few patients (7 out of 200) discontinued the therapy due to QTc prolongation, there were no torsade de pointes episodes nor arrhythmogenic deaths reported in the aforementioned study cohort, and the maximum QTc interval in patients receiving both HCQ/CQ

and azithromycin was  $470 \pm 45$  ms.<sup>31</sup> In another observational study including approximately 150 patients with COVID-19,<sup>36</sup> 84% patients receiving HCQ (out of those, 85% were additionally treated with other drugs potentially prolonging the QTc interval) presented with the QTc interval of 460 ms or less, and only in 2%, the QTc interval exceeded 500 ms. There were no arrhythmic events.

There are pre-pandemic reports of severe cardiac arrhythmias attributed to azithromycin or HCQ in the World Health Organization pharmacovigilance database<sup>37</sup> and some experts consider the use of this combination unsafe outside well-supervised clinical trials.<sup>38</sup> Nevertheless, all researchers highlight the need for larger randomized controlled clinical trials evaluating and confronting the safety and efficacy of CQ/HCQ in different populations of patients with COVID-19 (eg, severe versus oligosymptomatic) independently of other confounders.

#### How to minimize the potential risk of proarrhythmia?

Until now (mid-June 2020), evidence derived from clinical trials regarding the effectiveness and safety of CQ and HCQ in SARS-CoV-2 infection in humans is still very limited and more reliable data are still being anticipated to establish any evidence-based recommendations for clinicians all over the world. Regardless of completed or ongoing studies evaluating both the efficacy and safety of CQ and HCQ in COVID-19 (including the potential effect on QTc prolongation and related arrhythmia events), basic electrophysiological and



“common-sense” safety rules are applicable to patients treated with reviewed substances.<sup>39,40</sup>

Experts recommend the following procedures: 1) not initiating CQ/HCQ when QTc exceeds 500 ms (long baseline QTc may be related to inherited arrhythmic disorders in some patients); 2) active screening for and correction of any electrolyte disturbances (especially hypokalemia); 3) frequent control or even remote (continuous?) monitoring of QTc interval when possible and withdrawal of the drug when QTc interval is longer than 500 ms for normal QRS width); and 4) avoiding or discontinuing other medicines known to affect QTc interval.<sup>36,39,40</sup> Obviously, in the setting of an infectious respiratory disease transmitted via droplets, “classic” approaches with a daily meticulous electrocardiography supervision may not be achievable due to logistic reasons (problems with disinfection, etc); however, cardiology experts recommend to do so if baseline QTc is longer than 480 ms due to the fact that these patients are at particular risk for proarrhythmia.<sup>36</sup>

### **Evolving statements from drug agencies in Poland and worldwide**

With regard to CQ, already on March 13, 2020, the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Poland) issued a decision on the amendment to the marketing authorization for the medicinal product Arechin (CQ phosphate), consisting in adding a new therapeutic indication: “Adjunctive therapy in beta coronavirus infections such as SARS-CoV, MERS-CoV and SARS-CoV-2”.<sup>41,42</sup> In the summary of medicinal product characteristics for CQ (Arechin), cardiovascular disease is not considered as a contraindication for therapy with CQ, and electrocardiography is not considered as an obligatory diagnostic test before commencing therapy with CQ. It is emphasized that a combined therapy of CQ and amiodarone is contraindicated, as such a combination increases the risk of arrhythmias, including ventricular tachycardia and conductance disturbances.<sup>41</sup> Moreover, according to the recommendations for SARS-CoV-2 infections of Polish Society of Epidemiologists and Infectious Disease Specialists dated June 8, 2020,<sup>43</sup> CQ/HCQ are accepted as supportive therapy in patients with COVID-19 (in stable condition or with respiratory insufficiency, but not in critical condition).

On April 3, 2020, the United States Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to allow HCQ and CQ donated to the Strategic National Stockpile (SNS) to be distributed and used for certain hospitalized patients with COVID-19. Further, on June 15, the revocation of EUA for CQ and HCQ was released, due to “unlikelihood to produce an antiviral effect,” recommendations not to treat COVID-19 inpatients with these drugs outside clinical

trials, and “no evidence of benefit for mortality or other outcomes” based on published trials. Following the first FDA statement, the initial position of the European Medicines Agency was more conservative, and recommended that patients and healthcare professionals only use CQ and HCQ for their authorized uses or as part of clinical trials or a national emergency use program for the treatment of COVID-19. Consequently, EMA published 2 reminders of potential adverse reactions and side effects of CQ/HCQ, based on emerging data that we summarized above. There is an urgent need to provide more high-quality, secure, clinical evidence.<sup>6</sup> Beyond efficacy, the therapy with CQ or HCQ in COVID-19 should be subject to a meticulous pharmacovigilance supervision in order to comprehensively assess its safety profile in this clinical setting.

### **ARTICLE INFORMATION**

**ACKNOWLEDGMENTS** This research was financially supported by the Medical Research Agency, Warsaw, Poland (grant no. 2020/ABM/SARS/3).

**CONFLICT OF INTEREST** None declared.

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**HOW TO CITE** Jankowska EA, Sierpiński R, Tkaczyszyn M, et al. Chloroquine and hydroxychloroquine for the prevention and therapy of coronavirus disease 2019: new hopes and old cardiovascular concerns. *Kardiol Pol.* 2020; 78: 811-817. doi:10.33963/KP.15511

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