Cardiovascular considerations for patients with COVID-19 and candidate drugs against SARS-CoV-2

Xie Saiyang, MD [1,2], Deng Wei, MD, PhD [1,2#], Tang Qizhu, MD, PhD [1,2#].

Affiliations:

1. Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan 430060, RP China
2. Hubei Key Laboratory of Metabolic and Chronic Diseases, Wuhan 430060, RP China

#Corresponding authors:

Wei Deng; vivideng1982@whu.edu.cn and Qi-Zhu Tang; qztang@whu.edu.cn ,
Address for Correspondence: Department of Cardiology, Renmin Hospital of Wuhan University, Jiefang Road 238, Wuhan 430060, P.R. of China.
Tel.: +86 27 88073385; Fax: +86 27 88042292.

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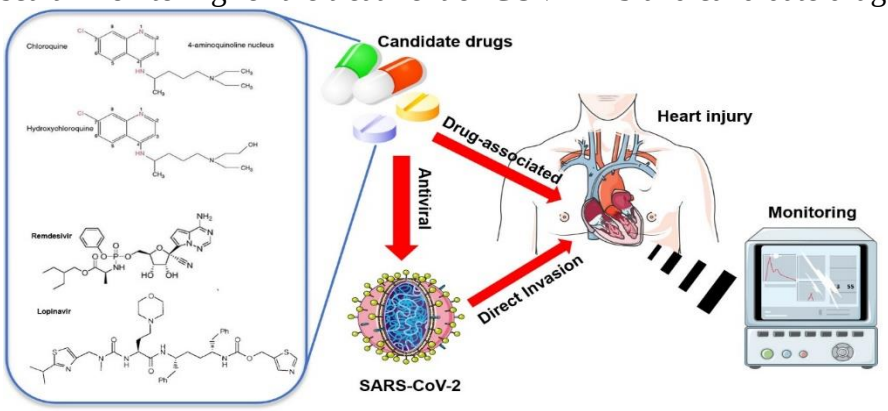
Highlights

- SARS-CoV-2 may infect the host cell by ACE2 pathway and CD147 pathway, and impact on RAS axis.
- Coronavirus disease 2019 (COVID-19) may predispose patients to severe cardiovascular complications.
- The cardiovascular effects of investigational agents, especially in patients with underlying CVD are summarized.
- Drug-drug interactions between cardiovascular agents and investigational COVID-19 agents should be considered.
- A systematic approach on the care of patients with CVD during COVID-19 pandemic is provided.

Graphical Abstract

In addition to myocardial injury caused by SARS-CoV-2 invasion, drug-related cardiac injury is frequently overlooked, in particular candidate drugs against COVID-19. Evidence from prior studies of non-COVID-19 populations has showed that these investigational agents under investigation for COVID-19 may have cardiovascular side Effects and result in drug-associated myocardial injury. And here we underlined the cardiovascular monitoring for the treatment of COVID-19 and candidate drugs.



Abstract
The coronavirus disease-2019 (COVID-19) is an infectious respiratory disease attributed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has rapidly spread globally leading to a pandemic. Frequently, COVID-19 contributes to multiple cardiovascular diseases (CVD) including acute myocardial injury, myocarditis, arrhythmias and thromboembolism, due to excessive inflammation and endothelial dysfunction. Moreover, a large proportion of affected patients, especially for elderly patients have been reported to pre-exist comorbidities such as hypertension, diabetes and CVD. However, although some antiviral drugs targeted SARS-CoV-2 have been applied to clinical trial, a few of these investigational agents are associated with excess risk for cardiovascular events in prior studies of non-COVID-19 populations. The objective of this document is to introduce the cardiovascular complications caused by COVID-19 and related investigational therapies, as well as the potential consequences in patients with antiviral drugs and cardiovascular drugs, and then provide recommendations for a systematic approach on the care of patients with CVD during COVID-19 pandemic.
Keywords: COVID-19; SARS-CoV-2; cardiovascular diseases; Therapy

Abbreviations
ACE2: angiotensin-converting enzyme 2
ACS: acute coronary syndrome
Ang II: angiotensin II
ARDS: acute respiratory distress syndrome
AS: atherosclerosis
COVID-19: coronavirus disease 2019
CPR: cardiopulmonary resuscitation
CYP3A4: cytochrome P450 enzyme 3A4
ECMO: extracorporeal membrane oxygenation
HCQ/CQ: hydroxychloroquine/chloroquine
hs-TnI: high-sensitivity troponin I
IABP: intra-aortic balloon pump
ICU: intensive care unit
LDL: low-density lipoprotein
MACE: major adverse cardiovascular events
NSTEMI: non-ST-elevation myocardial infarction
RAS: renin-angiotensin system
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2
STEMI: ST-elevation myocardial infarction
SVT: sustained ventricular tachycardia
PCI: percutaneous coronary intervention
VTE: venous thromboembolism

Introduction
The coronavirus disease of 2019 (COVID-19)—the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has affected more than 11.6 million patients with more than 500 thousand deaths all around the world as of 6 July 2020 6(World Health Organization. Coronavirus Disease 2019 (COVID-19): Situation Report—161; World Health Organization: Geneva). Given the rapid spread of SARS-CoV-2 with serious consequences worldwide, COVID-19 was deemed a pandemic by the World Health Organization (WHO) on March 11th 2020

(https://www.who.int/dg/speeches/detail/whodirector-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (Accessed on March 12 2020).). Patients infected with the virus may either be asymptomatic or may experience mild to severe clinical symptoms such as pneumonia, respiratory failure and even death (Yang et al., 2020). In terms of mechanism, strong evidences of basic research and clinical pathology support that cytokine storm is considered to be the dominating pathophysiological feature of COVID-19 (Cao, 2020; Mehta et al., 2020).

Apart from impaired respiratory defense, there has been growing recognition that individuals with underlying increased cardiovascular risk may be affected (Guo et al., 2020; Shi et al., 2020). More importantly, older patients and those with pre-existing respiratory or cardiovascular conditions appear to be at the greatest risk for undesirable consequences (Weiss & Murdoch, 2020; Wu et al., 2020). Several studies have noted arrhythmias, cardiomyopathy, acute coronary syndrome (ACS) and cardiac arrest as terminal events in patients with COVID-19 (Arentz et al., 2020; Wu et al., 2020). And the ever-increasing number of infections highlights the need for rapid responses in developing strategies for the emerging diseases. Although several approved drugs and investigational agents have shown antiviral capacity against SARS-CoV-2, therapeutics for COVID-19 have the potential for adverse cardiovascular effects as well.

The current manuscript is to summarize the cardiovascular characteristics in patients with COVID-19, the cardiovascular impact of investigational agents, as well as the potential consequences in patients with antiviral drugs and cardiovascular drugs, as understanding and addressing these issues will be of great significance to optimize outcomes during the current critical period and beyond. Herein, we propose recommendations for a systematic approach for the care of patients with CVD during COVID-19 pandemic.

SARS-CoV-2 and Invasion

Several members of coronavirus family have been reported to be constantly circulated in the human population and frequently contribute to respiratory illness (Geller, Varbanov & Duval, 2012). The severe acute respiratory syndrome (SARS) emerged in the Guangdong Province in southern China in November 2002, which was caused by severe acute respiratory syndrome coronavirus (SARS-CoV) (Berry, Gamieldien & Fielding, 2015; Lau et al., 2005). And the Middle East respiratory syndrome coronavirus (MERS-CoV) epidemic emerged in Saudi Arabia in June 2012, which was shed into the environment and transferred from environmental surfaces to hands (Mohd, Al-Tawfiq & Memish, 2016; Otter, Donskey, Yezli, Douthwaite, Goldenberg & Weber, 2016). In December 2019, a new infectious respiratory disease emerged in Wuhan, Hubei province, China. And a novel coronavirus, SARS-coronavirus 2 (SARS-CoV-2), which is closely related to SARS-CoV, was detected in patients and was officially identified as the cause of an outbreak of COVID-19 (Huang et al., 2020; Zhu et al., 2020b). Transmission of SARS-CoV-2 seems to be primarily from person to person via close contact, with an estimated incubation period to be 14 days (ranges from 2-14 days) (Backer, Klinkenberg & Wallinga, 2020).

SARS-CoV-2, like other members of the coronavirus family, is a single-strand RNA coronavirus, which belongs to the β-CoVs group (Chan et al., 2020). SARS-CoV-2 has 89% nucleotide identity with bat SARS-like CoV-ZXC21 and 82%with that human SARS-CoV, and similar to SARS-CoV, binds to the angiotensin-converting enzyme 2 (ACE2), through which SARS-CoV-2 enters the host cell (Chan et al., 2020; Wan, Shang, Graham, Baric & Li, 2020). The interaction between the receptor binding domain (RBD) of the S1 subunit on the viral spike glycoprotein (S-protein) and the

extracellular domain of ACE2.3 contributes to the binding and entry of SARS-CoV-2 into host cells (Walls, Park, Tortorici, Wall, McGuire & Veesler, 2020). ACE2, widely expressed in a variety of tissues, is highly detected in the cardiovascular system including cardiomyocytes, cardiac fibroblasts, vascular smooth muscle, epicardial adipose tissue and endothelial cells (Zhong et al., 2010). As an endogenous counter-regulator of the renin-angiotensin system (RAS), ACE2 plays critical role in the occurrence and development of CVD, and phase I clinical trials of recombinant human-derived ACE2 (rhACE2) in the treatment of heart failure (HF) and phase II clinical trials of the treatment of pulmonary hypertension (PAH) are in progress (Basu, Poglitsch, Yogasundaram, Thomas, Rowe & Oudit, 2017; Hemnes et al., 2018). At the molecular level, firstly, cleavage of Ang I by ACE produces Ang II, which performs as the pivotal effector peptide of the ACE/Ang II/AT1 receptor axis, triggering undesirable outcomes such as vasoconstriction, inflammation, oxidative stress, cell proliferation, hypertrophy, fibrosis and cardiovascular remodeling (Patel, Zhong, Grant & Oudit, 2016). Subsequently, ACE2, a type I transmembrane protein that functions as a mono-carboxypeptidase, cleaves Ang II into Ang 1-7, which has a protective effect on the heart. Interestingly, Ang 1-7 exerts cardioprotective effect through the Mas receptor to counter the detrimental effects of Ang II signaling (Jiang et al., 2014). In addition, the combination of Ang II and AT1R can activate ADAM17 (ADAM metallopeptidase domain 17, also named as tumor necrosis factor α converting enzyme) that cleaves ACE2 on the membrane of cardiomyocytes to generate soluble ACE2, which results in the loss of ACE2's protection (Patel et al., 2014; Wang, Gheblawi & Oudit, 2020). (Figure 1)

Aside from well-known virus receptor ACE2, the latest study suggested that CD147 might be the second way for SARS-CoV-2 to invade host cells (SARS-CoV-2 invades host cells via a novel route: CD147-spike protein.Ke Wang). As a transmembrane glycoprotein, CD147 is widely expressed in various cells. Moreover, CD147 plays an important role in regulating cell metabolism, multidrug resistance, Alzheimer's disease, the chemotaxis of human peripheral blood leukemia T cells and atherosclerosis (Eichner et al., 2016; Huang et al., 2018). Recently, the researchers have found that S-protein of virus binds to the receptor CD147 on the host cell, thereby mediating the invasion of SARS-CoV-2 (SARS-CoV-2 invades host cells via a novel route: CD147-spike protein.Ke Wang). (Figure 1)

COVID-19 and Cardiovascular Complications

The major clinical symptoms of COVID-19 are fever, cough and shortness of breath. Less common symptoms include muscle pain, anorexia, discomfort, sore throat, stuffy nose, dyspnea and headache. Symptoms may appear with an incubation period ranging from 2 to 14 days after exposure (Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). Accessed February 22). Notably, Large amounts of data showed that aside from the typical respiratory symptoms, SARS-CoV-2 infection affected the cardiovascular system, especially causing severe myocardial injury, which aggravated the condition and prognosis (Zheng, Ma, Zhang & Xie, 2020). Myocardial injury associated with the SARS- CoV-2 is common among patients with COVID-19 and correlates with disease severity. In a primal study of 138 hospitalized COVID-19 patients, 36 (26.1%) were transferred into the intensive care unit (ICU) as a result of complications, including acute respiratory distress syndrome (ARDS) (61%), arrhythmia (44%) and shock (31%). 64 patients (46.4%) had one or more comorbidities, including hypertension (31%), diabetes (10%), cardiovascular disease (14.5%) and malignant tumors (7.2%) (Wang et al., 2020a). In another study of 191 patients with

laboratory-confirmed COVID-19 including 54 died and 137 survived, compared with survivors, the incidence of comorbidities in fatal cases is higher, with hypertension (48% vs 23%), diabetes (31% vs 14%) and coronary heart disease (24% vs 1%) (Zhou et al., 2020). And the incidence of heart failure (52% vs 12%) and acute heart injury (59% vs 1%) among non-survivors is significantly higher than that of survivors (Zhou et al., 2020). Since the beginning of the current outbreak in December 2019, multiple studies have suggested a significant portion of patients with COVID-19 have elevated biomarkers of cardiac injury. Cardiac injury is defined as the serum level of highly sensitive cardiac troponin I (hs-TnI) being above the upper limit of the reference range (>28 pg/mL), which increased in 15% of survivors and 28% of non-survivors (Madjid, Safavi-Naeini, Solomon & Vardeny, 2020). Meanwhile, another small retrospective study revealed that patients died for COVID-19 had higher levels of troponin, creatine kinase-MB (CK-MB), myoglobin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), serum ferritin, and interleukin-6 (IL-6), further suggesting the significance of inflammatory storm and myocarditis in COVID-19 (Hu, Ma, Wei & Fang, 2020). Besides, mild thrombocytopenia and increased D-dimer levels are associated with a higher risk of requiring mechanical ventilation, ICU admission and death (Favaloro & Thachil, 2020; Han et al., 2020; Lippi, Plebani & Henry, 2020). And the severity of COVID-19 is associated with prolongation of the prothrombin time (PT), international normalized ratio (INR), thrombin time (TT) and activated partial thromboplastin time (APTT) (Gao et al., 2020; Lippi, Salvagno, Ippolito, Franchini & Favaloro, 2010; Wu et al., 2020).

SARS-CoV-2 can directly infect host cells and cause inflammatory response so that increases the risk of plaque rupture and thrombus formation, leading to either an ST-elevation myocardial infarction (MI) or non-ST-elevation MI (Mahmud et al., 2020). Furthermore, SARS-CoV-2 infection induced-hypoxemia and vasoconstriction may result in reduced oxygen delivery to myocardium, as well as hemodynamic instability due to sepsis with increased myocardial oxygen demand. The mismatch of supply and demand may lead to persistent myocardial ischemia in patients with underlying coronary artery disease. However, the serum levels of high-sensitivity troponin I (hs-TnI) is not sufficient to ensure the diagnosis of acute myocardial infarction (Kang et al., 2020). In addition, a new case investigation shows that disseminated intravascular coagulation (DIC) is one of the causes in non-survivors with COVID-19, which is associated with coronary thrombosis (extracardiac vessels and microvasculature), focal myocardial necrosis and severe cardiac dysfunction (Connors & Levy, 2020; Tang, Li, Wang & Sun, 2020). Simultaneously, SARS-CoV-2 can facilitate the intense release of multiple cytokines and chemokines by activating the immune system (Mehta et al., 2020). Accumulating evidence suggests that patients with severe COVID-19 frequently develop cytokine storm, which is characterized by increased plasma levels of IL-1β, IL-6, IL-8 and tumor necrosis factor α (TNF-α), and evolved into microcirculation disorder (Mann, 2015; Mehta et al., 2020; Ruan, Yang, Wang, Jiang & Song, 2020). Moreover, Arrhythmia may be the earliest symptom of myocardial injury in COVID-19 patients, especially patients in ICU, and the crude incidence rate is as high as 16.7% (Guo et al., 2020). Because of inflammation, hypercoagulable status and prolonged immobilization, patients with COVID-19 are predisposed to venous thromboembolism (VTE) (Klok et al., 2020; Spyropoulos et al., 2011). A recent study from China reported that 40% of hospitalized patients with COVID-19 were at high risk of VTE, and patients with severe COVID-19 showed a higher D-dimer and fibrin degradation product (FDP) titres than those with milder disease (Wang et al., 2020c). Regrettably, multiple cardiovascular complications of COVID-19 as mentioned above are easily evolved into

life-threatening diseases such as heart failure and cardiogenic shock (Tavazzi et al., 2020). (Figure 2)

Treatment considerations

Although lots of alternative interventions are under investigation, there is currently no proven therapy for COVID-19. Undoubtedly, our priority is to timely assess patients with severe COVID-19, especially for elderly patients, and avoid fatal cardiovascular complications. We summarized the supportive therapies and considerations of potential therapies relevant to cardiovascular emergency in patients with COVID-19. Table 1. However, in many mild COVID-19 cases, properly chosen non-invasive interventions can effectually improve symptoms and alleviate the illness. Hence, we focus our discussion here on the cardiovascular effect of investigational agents, especially in patients with underlying CVD.

Lopinavir/Ritonavir

As a new generation of human immunodeficiency virus (HIV) protease inhibitors, lopinavir/ritonavir was approved for treatment of HIV infection by the US Food and Drug Administration (FDA) in 2000 (Oldfield & Plosker, 2006). In terms of mechanism, lopinavir is a protease inhibitor, while ritonavir inhibits CYP3A4 metabolism and increases level of lopinavir (Croxtall & Perry, 2010). Based on the efficacy of anti-MERS-CoV, lopinavir/ritonavir was examined in several clinical trials after establishing the antiviral susceptibility of the SARS-CoV-2 in vitro to a panel of antiviral agents (Carmona-Bayonas, Jimenez-Fonseca & Castañón, 2020; Sheahan et al., 2020). Table 2. In addition, what needs to be emphasized here is that multiple adverse reactions may be occurred during lopinavir/ritonavir application, especially cardiovascular side-effects. Table 3. Previous clinical studies indicated that lopinavir/ritonavir contributed to dyslipidemia, leading to hypertriglyceridemia, hyperlipemia and increasing the risk of CVD (Dai et al., 2019; Greffrath, du Plessis, Viljoen & Cockeran, 2018; Shaffer et al., 2014). Besides, long-term treatment with lopinavir/ritonavir might increase the level of low-density lipoprotein (LDL) and result in atherosclerosis (AS) (Badiou, Merle De Boever, Dupuy, Baillat, Cristol & Reynes, 2003). More importantly, lopinavir/ritonavir may result in QT and PR interval prolongation, especially in patients who have a baseline abnormality (long QT) or those who are at risk for conduction abnormalities including those taking other QT prolonging drugs (Vicente et al., 2019). In terms of molecular mechanism, lopinavir/ritonavir can regulate cardiomyocytes apoptosis, lysosomal-mediated protein degradation, calcium signaling pathway, and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway (Reyskens et al., 2013).

Hydroxychloroquine (HCQ)/Chloroquine (CQ)

Chloroquine and its analog hydroxychloroquine have been widely used as prophylactic pharmacotherapies for malaria, as well as the management of rheumatoid arthritis and systemic lupus erythematosus with immunomodulatory effects (Bijker et al., 2013; Savarino, Boelaert, Cassone, Majori & Cauda, 2003). Following the emergence of COVID-19, some data suggested that the antimalarials HCQ and CQ possessed in vitro antiviral activity against SARS-CoV-2 (Liu et al., 2020; Wang et al., 2020b). The molecular mechanism of action of CQ and HCQ has not been fully elucidated, previous studies have suggested that CQ and HCQ may inhibit the coronavirus through changing the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus to the cell membrane (Fox, 1993), and block nucleic acid replication, glycosylation of

viral proteins, virus assembly, new virus particle transport, virus release and other processes to achieve its antiviral effects (Fox, 1993). At present, fortunately, multiple clinical trials targeted HCQ/CQ are underway. Table 2. Importantly, the potential adverse effect of HCQ/CQ is something in particular that we should be aware of. HCQ/CQ have been reported to be also extremely toxic in overdose (Juurlink, 2020). Table 4. Along with common adverse effects such as pruritus, nausea, dizziness and headache, HCQ/CQ can predispose patients to life-threatening cardiovascular complications, an effect that may be enhanced by concomitant utilization of azithromycin (AZM) (Juurlink, 2020). Although HCQ and AZM are generally well-tolerated medications used in clinical practice, both can cause corrected QT (QTc) prolongation and an increased risk of torsades de pointes (TdP) in a dose-dependent manner (Mzayek et al., 2007; Ray, Murray, Hall, Arbogast & Stein, 2012; World Health Organization. The cardiotoxicity of antimalarials: Malaria Policy Advisory Committee Meeting. Published March 24). Mechanically, HCQ blocks the rapidly activating delayed rectifier K^+ current, encoded by the human-ether-a-go-go-related gene (hERG) (Pukrittayakamee et al., 2014; Ursing et al., 2020). Meanwhile, CQ has been shown to inhibit the hERG K^+ channels in a concentration- and time-dependent manner (Traebert, Dumotier, Meister, Hoffmann, Dominguez-Estevez & Suter, 2004). And Inhibition of the hERG channel can lead to prolongation of the action potential duration and prolong the QT interval of the electrocardiogram (ECG), which may lead to TdP (Keating & Sanguinetti, 2001). Furthermore, a cohort study revealed that patients who received HCQ for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation, and concurrent treatment with azithromycin was associated with greater changes in QTc (Mercuro et al., 2020). Additionally, in another small study, CQ has been reported to significantly prolong the QTc interval in a clinically relevant matter (van den Broek, Möhlmann, Abeln, Liebregts, van Dijk & van de Garde, 2020). CQ and HCQ are extremely toxic in overdose, which results in rapid onset of central nervous system toxicity (seizures and coma), cardiovascular collapse (including inhibition of cardiac sodium and potassium channels resulting in QRS widening and QT interval prolongation, respectively) and hypokalemia, eventually causing 2.5% - 25% death (de Olano, Howland, Su, Hoffman & Biary, 2019). In an acute poisoning, some emergency measures should be taken: firstly, patients with acute CQ/HCQ poisoning should be immediately given gastric lavage, and simultaneously treated by mechanical ventilation. Furthermore, they are supposed to be administrated with diazepam (2 mg/kg, 30 min as a loading dose, followed by 1-2 mg/kg per day for 2-4 days) and epinephrine (250 ng/kg/min initial dose and 250ng/ kg/min increment until the systolic pressure restored at ≥100mmHg) (Hughes, 2020; Riou, Barriot, Rimailho & Baud, 1988).

Remdesivir

Remdesivir (also GS-5734), a broad-acting antiviral nucleotide prodrug, has been recently recognized as a promising antiviral drug against SARS-CoV-2 infection. In fact, remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases (Sheahan et al., 2017; Sheahan et al., 2020), which has a broad antiviral spectrum including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses (Lo et al., 2017). However, clinical evidence is insufficient to make recommendations of remdesivir on anti- SARS-CoV-2, and it is currently under clinical development for the treatment of SARS-CoV-2 infection. Table 2. In addition, the results which have already announced also have shortage such as limited quantality, inappropriate endpoint and unreasonable

framework of control experiment. Nowadays, the COVID-19 treatment guidelines panel (the panel) recommends the investigational antiviral agent remdesivir for treatment of COVID-19 in hospitalized patients with SpO2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen (AI). The Panel also recommends remdesivir for treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (BI) (https://www.covid19treatmentguidelines.nih.gov). More importantly, the clinical improvement in those treated with remdesivir requires confirmation in larger studies. And on the other hand, fortunately, there is no obvious adverse reactions during the application of remdesivir, at least for the time being.

Tocilizumab

Tocilizumab, an interleukin-6 (IL-6) receptor antibody, has been used to treat several pediatric autoinflammatory diseases, including juvenile idiopathic arthritis (JIA)-associated uveitis and Castleman's disease (Kaneko et al., 2018). As we all known, IL-6 has been proven to be the crucial cytokine in inflammation induced by SARS-CoV-2, and which may correlate with disease severity (Libby & Simon, 2001; Sheppard, Laskou, Stapleton, Hadavi & Dasgupta, 2017). The biopsy samples analysis at autopsy suggested that increased alveolar exudate caused by aberrant host immune response and inflammatory cytokine storm probably blocks alveolar gas exchange and contributes to the high mortality of severe COVID-19 patients (Fu, Xu & Wei, 2020; Michot et al., 2020). Therefore, tocilizumab may be an effective treatment in severe patients of COVID-19 to inhibit the inflammatory storm and reduce mortality. And we hold the brief here that tocilizumab could be used to treat COVID-19 and delay the progression of this illness with huge potential. Admittedly, tocilizumab is known to result in various adverse reactions as listed in table 5, and especially cause a wide spectrum of cardiovascular manifestations, including hypertension, hypercholesterolemia, myocardial amyloidosis and myocardial infarction (MI) (Hellmich et al., 2020). And a previous randomized controlled trial uncovered that tocilizumab increased the risk for occurrence of major adverse cardiovascular events (MACE) in patients with rheumatoid arthritis (RA) (Giles et al., 2020). Furthermore, another monoclonal antibody, bevacizumab has been associated with excess risk as well. Bevacizumab binds to vascular endothelial growth factor (VEGF), and is under investigational utilization for COVID-19, which is associated with increased risk for adverse cardiovascular effects, including MI, cerebrovascular accidents, and VTE (Economopoulou, Kotsakis, Kapiris & Kentepozidis, 2015; Totzeck, Mincu & Rassaf, 2017). And yet there is no denying that tocilizumab can ameliorate pulmonary arterial hypertension (PAH) through inhibiting IL-6/IL-21 signaling axis in endothelial cell (Hashimoto-Kataoka et al., 2015).

Other safety concerns

As one of the most commonly drugs in anti-inflammatory and immunosuppression, glucocorticoid is currently used to reduce the myocardial inflammation and "cytokine storm" caused by SARS-CoV-2 (Li, Lu & Zhang, 2020). However, a large number of studies indicate that glucocorticoid inhibits the removal of viral RNA, and it is not recommended for the treatment of COVID-19, especially in mild patients (Ling et al., 2020; Lv et al., 2017). In addition, glucocorticoid may lead to glucose metabolic disorders, hypertension, obesity, sodium and water retention, hypokalemia, hypokalemia alkalosis and myocardial injury, and eventually increasing the risk of death (Dinsen et al., 2013).

Ribavirin is a purine nucleoside analog with a broad-spectrum of antiviral activity, which can effectively inhibit the proliferation of various respiratory viruses (Feld, Jacobson, Sulkowski, Poordad, Tatsch & Pawlotsky, 2017). At present, like other antiviral drugs, ribavirin is also used for antiviral therapy in patients with COVID-19 (Gordon et al., 2020; Hung et al., 2020). However, ribavirin often results in various adverse effects such as cardiotoxicity, dyspnea and chest pain, especially in patients with chronic obstructive pulmonary disease and bronchial asthma (Lu et al., 2015). Recently, several studies have shown that large dose of ribavirin increases the risk of CVD in patients, especially elderly patients over 65, simultaneously increasing the risk of death in patients with underlying CVD (Beigel et al., 2017). In terms of molecular mechanism, ribavirin exacerbates Ca^{2+} metabolism disorder in mitochondria, which leads to mitochondrial toxicity and disturbs the energy metabolism in cardiomyocytes (Lafeuillade, Hittinger & Chadapaud, 2001).

Drug-drug interactions

Several investigational agents as mentioned above are being tested in the management of COVID-19, especially for patients who develop severe disease. Some of these drugs have clinically important interactions with some cardiovascular drugs. Table 6. Herein, we summarized the possible drug-drug interactions of investigational agents and cardiovascular drugs from the view of drug metabolism. Through which we hope this will be helpful for the design of clinical trials for drugs in COVID-19, as data regarding in vitro virus inhibition and efficacy in preclinical animal studies are still not available for the time being.

Lopinavir/Ritonavir is a protease inhibitor and inhibits CYP3A4 metabolism, which can interact with various anti-arrhythmic drugs such as amiodarone, digoxin and procainamide, increasing the risk of arrhythmia (Pal & Mitra, 2006). Of note, Lopinavir/Ritonavir can also increase the bioavailability of atorvastatin and rosuvastatin (Kiser, Gerber, Predhomme, Wolfe, Flynn & Hoody, 2008), therefore, it is recommended here to refer to the latest safety and adverse reaction guidelines of statin in COVID-19 patients given with these two statins. Ritonavir has been shown to be a potent inhibitor of CYP3A4, an enzyme responsible for warfarin metabolism, it is reasonable to assume that ritonavir inhibits removal of warfarin and changes the international normalized ratio (INR) (Knoell, Young & Cousins, 1998). Moreover, suppression of CYP3A4 may result in reduction in effective dosage of clopidogrel and promote effects of ticagrelor (Holmberg et al., 2019; Jia et al., 2019). Hence, the concomitant utilization of these agents along with lopinavir/ritonavir should be cautioned (Itkonen et al., 2019). While an alternative, in the absence of contraindications, is recommended to use prasugrel, which is not prone to these interactions at present (Marsousi et al., 2018). Furthermore, a previous case report has suggested that the co-administration of ritonavir with nifedipine may significantly increase serum concentration of nifedipine, therefore resulting in toxicity such as headache, peripheral edema, hypotension and tachycardia (Baeza, Merino, Boix & Climent, 2007).

HCQ/CQ has been reported to competitively inhibit CYP2D6 activity, and they possess the potential to influence the fate of other drugs reliant on CYP2D6 for metabolism such as metoprolol (Masimirembwa, Hasler & Johansson, 1995; Somer, Kallio, Pesonen, Pyykkö, Huupponen & Scheinin, 2000). Additionally, HCQ/CQ potentiate other CYP2D6 substrates (including carvedilol), and suppress the effectiveness of prodrugs reliant on CYP2D6 for activation such as codeine and tramadol (Kirchheiner, Keulen, Bauer, Roots & Brockmöller, 2008). Beyond that, accumulate large numbers

of CQ increase the accumulation of digoxin and digitoxin, which increases a risk of poisoning (Griffiths, Lamb & Ogden, 1983).
As a nucleotide-analog inhibitor of RNA-dependent RNA polymerases, remdesivir has been reported to be an inducer of CYP3A4 (Sheahan et al., 2020). Although data is limited, it is reasonable to assume that remdesivir is involved in control of oral antiplatelet agents. Prudently, remdesivir is currently not recommended to co-administrated with oral antiplatelet agents.
Tocilizumab, like the lopinavir/ritonavir, increases expression of CYP3A4 (Sebba, 2008). rivaroxaban and warfarin are frequently used to alleviate hypercoagulability, and both of them are substrates of CYP3A4, while tocilizumab accelerates the removal of them, and eventually increase the risk of VTE (Clarivet et al., 2016). Moreover, a previous research suggested that caution should be exercised when starting tocilizumab in patients who are taking simvastatin (Schmitt, Kuhn, Zhang, Kivitz & Grange, 2011). However, in consideration of prudent, no anticoagulant dose adjustments are currently recommended with concomitant use of tocilizumab at this time.

Conclusions and Respective

The COVID-19 pandemic has affected thousands of patients and contributes to a major health threat on an international scale. Unfortunately, the use of either antivirus or anti-inflammation for treatment or prevention of SARS-CoV-2 infection is currently supported primarily by in vitro data and weak studies involving humans. In the coming months, efforts towards evaluating new therapies will be crucial to the treatment of this virus, and as this process develops. Since the outbreak, a number of clinical investigations have revealed the elevated risk for adverse events for patients with CVD who develop COVID-19. Particularly, better understanding of the relationship between cardiovascular agents and the investigational therapies of COVID-19 will have significant implications for patients with both COVID-19 and CVD. Moreover, physicians should be aware of several potential adverse effects of cardiovascular system before better-designed studies determine their benefit in treating or preventing COVID-19. In addition, special attention should be given to patients with pre-existing CVD who are currently being treated with cardiovascular drugs. For this group of patients, we should focus on the administration of CVD that already existed, and adjust the treatment plan by monitoring rate, blood pressure, blood lipids, electrocardiogram, coagulation function and cardiac function. In particular, we need to be reminded the drug-drug interaction between cardiovascular agents and the investigational therapies of COVID-19, and get rid of the adverse effects due to drug-drug interaction. At present, the co-administration of more than three antiviral agents is not recommended, and it should be more vigilant in elderly COVID-19 patients with underlying CVD. Furthermore, on the basis of drug intervention, mechanical circulatory support (MCS), such as IABP, mechanical ventilation and ECMO should be given in severe and critically ill patients. (Figure 3)
The current manuscript has provided an interim summary and guidance for cardiovascular considerations to promote optimization of COVID-19 investigational therapies during the COVID-19 pandemic. However, we must confess that such guidance should supplement rather than replace clinical decision-making, and a comprehensive assessment should be considered for appropriate patient-centered decisions. Delightfully, there has been a breakthrough in COVID-19 vaccine research currently (Thanh Le et al., 2020; Zhu et al., 2020a), which is of great significance for the prevention and control of COVID-19 epidemic.
In conclusion, CVD may be a potential life-threatening complication in patients with

COVID-19. Apart from the consideration for CVD complication during COVID-19, considerations for use of these investigational therapies in COVID-19 should be kept in mind to refrain from drug-induced myocardial injury. Indeed, more data and higher-quality data are required to learn how COVID-19 and CVD interact.

Conflict of interest

None.

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Figure Legends

Figure 1. Proposed mechanism of entry for SARS-CoV2 and ACE2/Ang1-7/Mas axis in the renin-angiotensin system (RAS) system. ACE2 is a type I transmembrane protein that functions as a monocarboxypeptidase with a catalytically active ectodomain exposed to the circulation that hydrolyzes various peptides, including angiotensin II (Ang II) generating angiotensin 1-7 (Ang 1-7). The discovery of ACE2 introduced an alternative protective arm, ACE2/Ang 1-7/Mas receptor axis, to counterbalance the more renowned pathogenic ACE/Ang II/AT1 receptor axis that predominates in disease states due to RAS overactivation. However, the interaction between the receptor binding domain (RBD) of the S1 subunit on the viral spike glycoprotein (S-protein) and the extracellular domain of ACE2.3 contributes to the binding and entry of SARS-CoV-2 into host cells. A soluble form of ACE2 can be released from the membrane through proteolytic cleavage mediated by ADAM17 resulting in loss of ACE2 protection against tissue RAS. Since then, two major functions have been identified for ACE2 as (1) an endogenous counter-regulator of RAS, (2) a cellular receptor for SARS-CoV-2. In addition, CD147 may be the second way for SARS-CoV-2 to invade host cells. S-protein of virus binds to the receptor CD147 on the host cell, thereby mediating the invasion of SARS-CoV-2.

Figure 2. Possible mechanisms of cardiovascular injury due to COVID-19. SARS-CoV-2 may cause acute coronary syndrome (ACS), heart arrhythmia, Myocarditis and thromboembolism by direct invasion or evoking cytokine storm, hypoxemia,

disseminated intravascular coagulation (DIC) and microcirculation disturbance, and eventually leads to cardiogenic shock and heart failure.

Figure 3. Care pathway for a patient with COVID-19 and CVD in hospital. Patients diagnosed as COVID-19 should be distinguished based on past medical history of cardiovascular diseases (CVD). Patients with CVD who are COVID-19 possible should proceed to monitoring heart rate, blood pressure, blood lipids, coagulation function, echocardiography and electrocardiogram. Then investigational drugs are applied to alleviate COVID-19 including Lopinavir/Ritonavir, HCQ/CQ, remdesivir, ribavirin, IFN-α and tocilizumab. Meanwhile the related-cardiovascular monitoring should be continuing, therefore refraining from drug-induced life-threatening myocardial injury and drug-drug interaction. Furthermore, the mechanical circulatory support (MCS), intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO), should be given to those who are under the condition of hemodynamic instability. In addition, Patients with classic clinical presentation and ECG finding consistent with a STEMI or NSTEMI who are COVID-19 possible should proceed to primary PCI.

Figure 1.

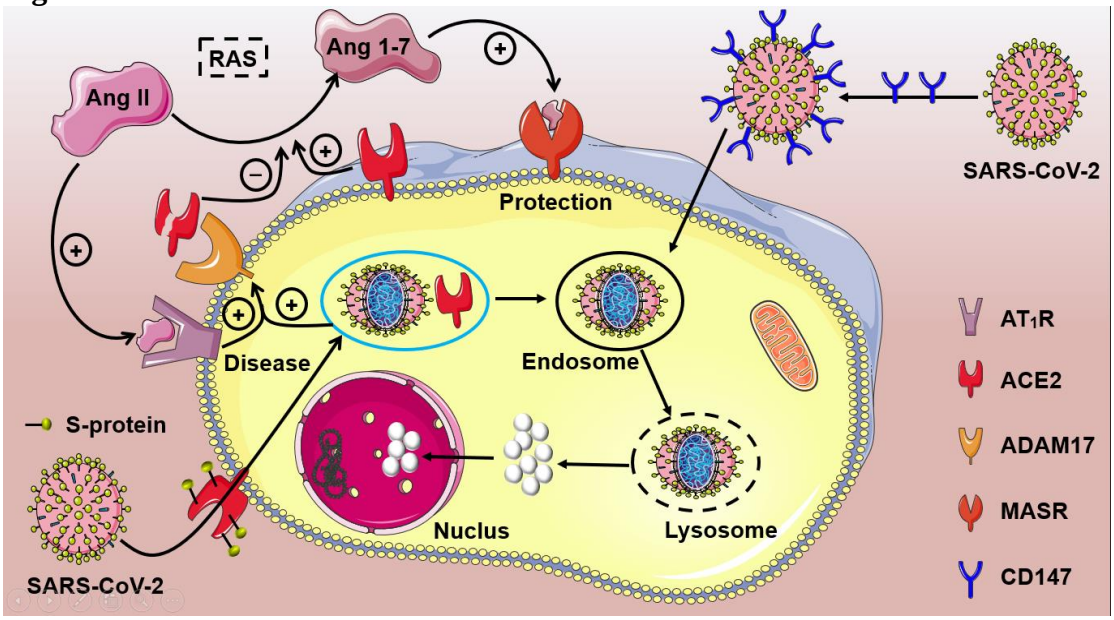

Figure 2.

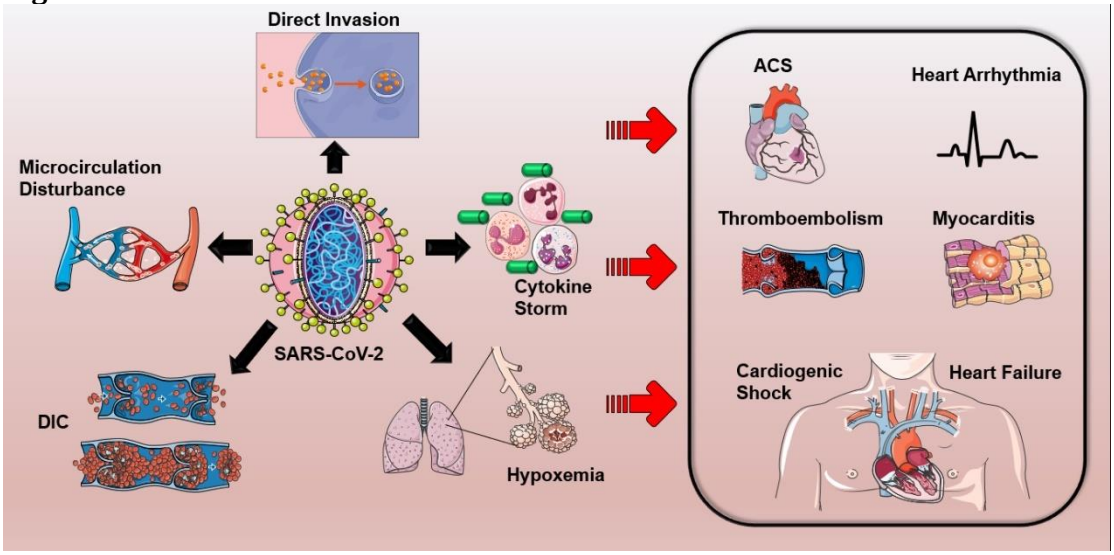

Figure 3.

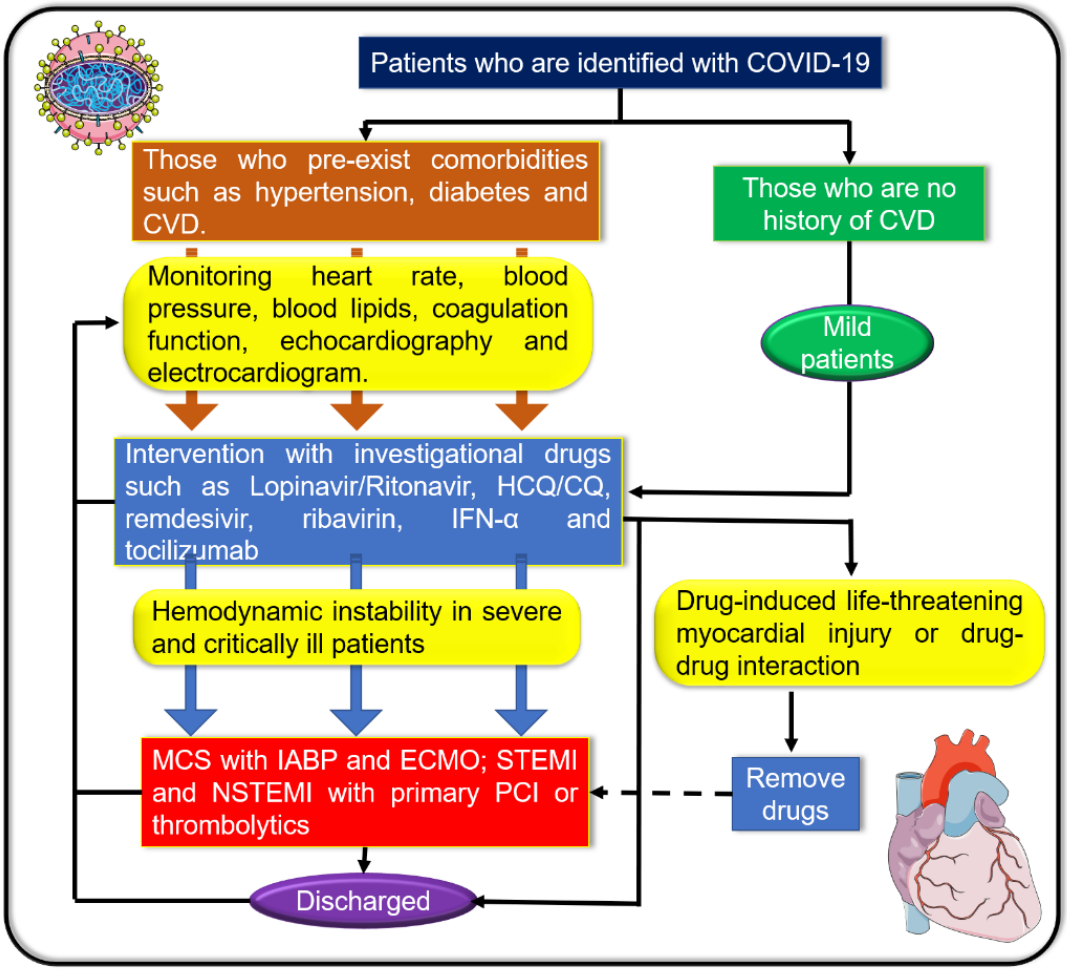

Table 1. Cardiovascular interventions in patients with COVID-19

Cardiovascular concerns	Intervention considerations
Myocardial injury	Monitoring myocardial injury markers and ECG
STEMI and NSTEMI	primary PCI or thrombolytics, antiplatelet
SVT	Amiodarone or cardioversion
VF	Defibrillation and CPR
Hypercoagulable state	Thromboprophylaxis
Hypertension	ACEI or ARB Continue treatment
Cardiogenic shock	MCS with IABP and ECMO

Abbreviations: ECG electrocardiogram; STEMI ST-elevation myocardial infarction; NSTEMI non-ST-elevation myocardial infarction; PCI percutaneous coronary intervention; SVT sustained ventricular tachycardia; VF ventricular fibrillation; CPR cardiopulmonary resuscitation; ACEI angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; MCS mechanical circulatory support; IABP, intra-aortic balloon pump; ECMO extracorporeal membrane oxygenation.

Table 2. List of Selected Registered Antivirus Agents Clinical Trials in COVID-19.

ClinicalTrials.gov identifier	Intervention:	Status	Estimated		
			No. of enrollment	Study start date	Complete date
NCT04340544 (HCQ/CQ)	600mg daily for 7 days	Recruiting	2700	April 22, 2020	September 30, 2022
NCT04351620 (HCQ/CQ)	1200 mg daily administered as 600 mg	Recruiting	20	April 2020	June 2020

	bid for 5 days				
NCT04364815 (HCQ/CQ)	400mg bid on Day 1 then 400 mg qd for Day 2-10	Not yet recruiting	950	May 2020	May 2021
NCT04382625 (HCQ/CQ)	400mg bid then 200mg tid for 14 days	Not yet recruiting	120	May 2020	June 1, 2022
NCT04334382 (HCQ/CQ)	400mg bid for 1 day, then 200mg bid for 4 days	Recruiting	1550	April 2, 2020	December 31, 2021
NCT04323631 (HCQ/CQ)	400mg bid 1 day, followed by 200mg bid on days 2-10	Not yet recruiting	1116	March 2020	December 2020
NCT04307693 (LPV/RTV)	200mg/100mg orally for 7-10 days	Recruiting	150	March 11, 2020	May 2020
NCT04330690 (LPV/RTV)	400 mg/100 mg orally for a 14-day	Recruiting	440	March 18, 2020	May 18, 2022
NCT04328012 (LPV/RTV)	400mg/200mg mg po BID, 5-14 days	Recruiting	4000	April 6, 2020	April 1, 2021
NCT04364022 (LPV/RTV)	200mg/50mg, po twice daily for 5 days	Recruiting	420	April 2020	October 2020
NCT04365725 (Remdesivir)	200 mg on day 1 followed by RDV 100 mg for 4 days	Recruiting	200	May 5, 2020	June 2020
NCT04292899 (Remdesivir)	200 mg on day 1 followed by RDV 100 mg for 4 days	Recruiting	6000	March 6, 2020	May 2021
NCT04292730 (Remdesivir)	200 mg on day 1 followed by RDV 100 mg for 4 days	Recruiting	1600	March 15, 2020	May 2021
NCT04280705 (Remdesivir)	200 mg on day 1, followed by 100 mg qd. for 9 days	Recruiting	800	February 21, 2020	April 1, 2023
NCT04315948 (Remdesivir)	200 mg on day 1 followed by RDV 100 mg for 9 days	Recruiting	3100	March 22, 2020	March 2023
NCT04257656 (Remdesivir)	200 mg on day 1, followed by 100 mg qd. for 9 days	Terminated	237	February 6, 2020	April 10, 2020
NCT04317092 (Tocilizumab)	8 mg/kg i.v. once, with an interval of 12 hours.	Recruiting	400	March 19, 2020	December 19, 2022
NCT04345445 (Tocilizumab)	8 mg/kg i.v. once, with an interval of 60 mins.	Not yet recruiting	310	April 15, 2020	October 31, 2020
NCT04346355 (Tocilizumab)	8 mg/kg i.v. up to a maximum of 800 mg with repetition of the same dosage after 12 hours	Recruiting	398	March 31, 2020	May 30, 2020
NCT04356937 (Tocilizumab)	8 mg/kg i.v. up to a maximum of 800 mg	Not yet recruiting	300	April 27, 2020	August 30, 2020

Abbreviations: HCQ/CQ Hydroxychloroquine/Chloroquine; LPV/RTV Lopinavir/Ritonavir; COVID-19 coronavirus disease 2019; Antivirus agents are administrated with conventional standardized treatment. Complete date is the estimated study completion date. All data of this table is collected from https://clinicaltrials.gov. Terminated: the epidemic of COVID-19 has been controlled well in China; no eligible patients can be enrolled at present.

Table 3. Side effects of Lopinavir/ritonavir

System	Side effects
Cardiovascular system	Hypertriglyceridemia, hyperlipemia, atherosclerosis, long QT, bradycardia, high degree atrioventricular block, torsade de pointes

Digestive system	Nausea, vomiting, constipation, dysphagia, dyspepsia, cholecystitis, pancreatitis
Nervous system	Moderate to severe headache, insomnia and weakness
Metabolic/endocrine system	Centripetal obesity, diabetes, thin limbs
Blood system	Spontaneous skin hematomas and hemarthrosis
Musculoskeletal system	Avascular necrosis of femoral head

Table 4. Side effects of HCQ/CQ

System	Side effects
Cardiovascular system	AVB, myocardiopathy, HF, Tdp, AS-syndrome, long QT, SCD
Eye	Macula lutea, retinal diseases, blindness or vision loss, corneal opacity, macular degenerative diseases, night blind, oculogyric crisis, dark spot
Neuropsychiatric effects	Extrapyramidal diseases, epilepsy (ataxia, dyskinesia neuromyopathy, polyneuritis)
Metabolic/endocrine system	Hypoglycemia
Blood system	G6PD deficiency, lymphopenia, eosinophilia and atypical lymphocytosis, HA
Immune system	Anaphylaxis
Musculoskeletal system	Myasthenia
Genetic variability	CYP2D6 genetic polymorphisms

Abbreviations: AVB atrioventricular block; HF heart failure; Tdp Torsade de Pointe; AS-syndrome Adams-Stokes syndrome; G6PD glucose-6-phosphatedehydrogenase; HA hemolytic anemia; CYP2D6 cytochrome P450 enzyme 2D6

Table 5. Side effects of Tocilizumab

System	Side effects
Cardiovascular system	Hypertension (4-6%), hypercholesterolemia, unstable plaque, myocardial amyloidosis, Thromboembolic events
Digestive system	Diarrhea, abdominal pain, mouth ulcers, chronic gastritis
Nervous system	Headache (5-7% in adults,> 5% in children), dizziness (2-3% in adults)
Metabolic/endocrine system	Hypothyroidism, hypertriglyceridemia, increased total bilirubin
Blood system	Thrombocytopenia (1-4%), neutropenia, leukopenia, neutropenia
Immune system	Rash (2%-4%), itching, urticaria, allergic reactions

Table 6. Potential Drug Interactions Between Cardiovascular Agents and Investigational Therapies for COVID-19

Investigational COVID-19 Therapies	Mechanism of Action of COVID-19 Therapy	Potential Drug Interactions
Lopinavir /Ritonavir	Lopinavir is a protease inhibitor, while ritonavir inhibits CYP3A4 metabolism and increases levels of lopinavir	1.Increase the blood concentration of amiodarone, digoxin and procainamide; 2.Increase the bioavailability of atorvastatin and rosuvastatin; 3.Reduce effective dosage of clopidogrel and promote effects of ticagrelor; 4.Increase serum concentrations of nifedipine resulting in toxicity; 5. Inhibit removal of warfarin, rivaroxaban

		and apixaban;
HCQ/CQ	CQ/HCQ may competitively inhibit CYP2D6 activity; CQ/HCQ may inhibit the coronavirus through changing the pH at the surface of the cell membrane, and thus inhibit virus release;	1.Potentiate other CYP2D6 substrates (including carvedilol); 2.Increase systemic exposure to orally administered metoprolol level; 3.Undermine the effectiveness of prodrugs reliant on CYP2D6 for activation such as codeine and tramadol; 4.Increase the accumulation of digoxin and digitoxin;
Remdesivir	Nucleotide-analog inhibitor of RNA-dependent RNA polymerases	——
Tocilizumab	Inhibits IL-6 receptor, may potentially mitigate cytokine release syndrome symptoms in severely patients	1.Simvastatin reverse the inhibition of IL-6 mediated by tocilizumab 2.Increases the metabolism of rivaroxaban and warfarin, triggering VTE

Abbreviations: HCQ/CQ Hydroxychloroquine/Chloroquine; COVID-19 coronavirus disease 2019; CYP3A4 cytochrome P450 enzyme 3A4; CYP2D6 cytochrome P450 enzyme 2D6; VTE Venous thromboembolism; IL-6 interleukin 6; Other drugs being studied to treat COVID-19 include azithromycin, bevacizumab, eculizumab, fingolimod, interferon, losartan, methylprednisolone, pirfenidone, and ribavirin. Drug-drug interactions between these medications and cardiovascular agents have yet to be identified.