Review Article

Cardiovascular implications of the COVID-19: Management of complications and drug safety concerns

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has rapidly spread worldwide and has been infected more than 219 million individuals with 4.55 million deaths worldwide as of September 2021, causing a pandemic. Preexisting cardiovascular (CV) comorbidities such as hypertension, diabetes, and coronary artery disease seem to be associated with greater severity of infection, worse prognosis, and higher mortality. Moreover, COVID-19 can contribute to CV complications, including acute myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism, emphasizing the importance of precocious detection and implementation of optimal therapeutic strategies. This review provides an overview of evidence-based data of CV complications of COVID-19, focusing on their management strategies, as well as potential cardiac adverse effects and drug interactions, due to off-label and investigational drugs used for the treatment of COVID-19.

Key words: Adverse effects, coronavirus disease 2019, complications, disease management, heart

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INTRODUCTION

The first cluster of pneumonia patients infected with coronavirus appeared in China from December 2019 and rapidly expanded all over the world as a global concern, and the World Health Organization (WHO) announced coronavirus disease 2019 (COVID-19) outbreak as a public health emergency since that time. Respiratory droplets and human contact are the two main factors responsible for virus transmission.[1] Mucosal epithelium of the nasal cavity and pharynx are the first cites that the virus replicates and after that expands to the lower respiratory tract, gastrointestinal mucosa, and blood.[2] Therefore, clinical manifestations of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) differ with the severity of disease, but most patients experience fever, cough, sputum production, dyspnea, diarrhea, fatigue, nausea or vomiting, and myalgia or arthralgia throughout the disease.[1] Although the primary symptoms of COVID-19 influence the respiratory system, the cardiovascular (CV) complications associated with COVID-19 infection should not be ignored. COVID-19 may lead to CV complications such as pulmonary embolism (PE), coagulation, arrhythmia, and acute myocardial injury and dysfunction, which can increase the risk of shock and multisystem organ failure.[3] On the other hand, the presence of preexisting cardiac conditions places this population at higher risk of complications, such as possible drug–drug interactions, adverse drug events, severe illness, and death.[4,5] A study revealed that 30%–35% of COVID-related deaths had underlying CV disease. Moreover, the fatality rate in patients with CV disease was reported to be 10.5% compared with a case-fatality rate of 0.9% in those with

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no comorbidities.[6] The goal of this study is to summarize the prophylactic/therapeutic approaches to minimize these complications as well as CV adverse effects of drugs used for the management of COVID-19.

METHODOLOGY

We searched through databases such as Scopus and PubMed for relevant literature with the keywords: COVID-19, Cardiovascular, Complications, Management, Adverse effects, and Interactions from the beginning to September 30, 2021. Nearly 65 relevant papers dealing with the therapeutic strategies of CV complications associated with COVID-19 and CV side effects of these approaches applied in COVID-19 were selected.

THE CARDIOVASCULAR IMPLICATION OF THERAPEUTIC APPROACHES USED IN CORONAVIRUS DISEASE 2019: SAFETY CONCERNS AND INTERACTIONS

The potential therapies for COVID-19 being under investigation in different clinical trials are mainly based on repurposing the available therapeutic drugs. These medications can be categorized into two therapeutic approaches: antivirals and immunomodulators. We focus here on their potential CV side effects and toxicities and drug interactions with other CV medications as summarized in Table 1.

Antiviral agents

Remdesivir

Remdesivir is an investigational nucleoside analog prodrug that inhibits viral RNA polymerases and has a broad-spectrum antiviral activity against several viruses. It was originally developed for the treatment of Ebola virus disease and is a potential drug for the treatment of COVID-19, currently available through compassionate use in clinical trials. Intravenous (IV) administration of remdesivir has shown promising efficacy in both *in vitro* and *in vivo* models against coronaviruses.[7] It was associated with clinical benefit in patients with severe COVID-19[8] and also in noncritically ill patients. According to trials, it just resulted in faster time to clinical improvement than in patients who received standard care.[9] Although remdesivir has been regarded as a drug with an optimal safety profile, several CV adverse events such as hypotension and bradycardia (8%), cardiopulmonary failure (5%), cardiac arrest (1%), and deep vein thrombosis (1%) have been reported so far. The most serious adverse events were hypotension and bradycardia, which were more common in patients undergoing invasive ventilation.[8] The mechanism of abovementioned CV adverse effects is unknown; however, similarity of the active metabolite of remdesivir (a nucleotide triphosphate derivative) with adenosine triphosphate may slow sinoatrial node automaticity.[10]

Ribavirin

Ribavirin is another agent that inserts its broad-spectrum antiviral activity among inhibition of viral RNA replication and is a part of standard care against the hepatitis C virus. Ribavirin, in combination with other agents such as lopinavir/ritonavir, interferon-beta, and interferon-a2b,[11] is under investigation in numerous clinical trials for COVID-19. Ribavirin is generally considered a safe drug from the perspective of CV adverse effects. However, it has the potential to cause QT interval prolongation, especially in patients with baseline QTc abnormality; moreover, thrombocytopenia and hemolytic anemia are common complications of ribavirin therapy which may result in the worsening of coronary artery disease, leading to myocardial infarction, and should be avoided in patients with significant/unstable cardiac disease. Regarding the possible interactions with CV medications, ribavirin has the potential to diminish the anticoagulant effect of Vitamin K antagonists; therefore, more closely monitoring of the coagulation status of warfarin may be needed.[12]

Lopinavir/ritonavir

Lopinavir and ritonavir, usually used as a fixed-dose drug combination (Kaletra®) in the treatment for human immunodeficiency virus, are protease inhibitors that inhibit replication of RNA virus. Several clinical trials had examined the efficacy of lopinavir and ritonavir against coronavirus disease, but no clinical benefit was observed;[13] however, its combination with interferon beta-1b and ribavirin had been beneficial in suppressing high viral load, shortening the quantity of virus shedding, improving clinical parameters, and expediting hospital discharge in patients with mild-to-moderate COVID-19. This drug combination is generally safe, and its adverse effects are mild and self-limiting.[14] Regarding CV side effects, lopinavir and ritonavir are associated with sinus bradycardia (3%), hypotension, atrioventricular conduction disturbances, and QT and PR-interval prolongation, especially in patients taking other QT-prolonging drugs.[13] Hyperlipidemia is another CV concern among patients taking lopinavir and ritonavir; therefore, baseline lipid measurements should be recommended in individuals starting treatment with this combination, and routine follow-up should be conducted in the case of borderline high lipids, especially triglycerides and total cholesterol. With regard to pharmacokinetics, lopinavir–ritonavir should be used with caution in patients with COVID-19 due to its inhibitory effect on cytochrome 3A4 (CYP3A4) and its potential to interact with other substrates of this enzyme, including antiplatelet drugs, anticoagulants, antiarrhythmic agents, and statins.[15]

Table 1: Therapies currently studied for the management of coronavirus disease 2019; potential cardiovascular toxicities and interactions

Therapy	Mechanism of action	CV adverse effects	Precautions	CV drug interactions	Interaction management
Remdesivir	Nucleotide-analog inhibitor of RNA-dependent RNA polymerases	Limited clinical data reported cardiopulmonary failure, cardiac arrest, deep vein thrombosis, and hypotension but not common	N/A	N/A It is a potential inducer of CYP1A2, CYP2B6, and CYP3A4	-
Ribavirin	Inhibition of viral RNA-dependent RNA polymerases	Drug-induced thrombocytopenia and hemolytic anemia QT interval prolongation	May result in worsening of CAD leading to MI Concomitant administration of QT-prolonging agents Concomitant electrolyte imbalances	Vitamin K antagonists: Warfarin	Monitor coagulation status and INR more closely (increased dose of warfarin may be needed)
Lopinavir/ ritonavir	Lopinavir: Protease inhibitors Ritonavir: CYP3A4 inhibitor increasing levels of lopinavir	Hypotension Sinus bradycardia Atrioventricular conduction disturbances: QT and PR-interval prolongation Hyperlipidemia	Conduction system disease Ischemic heart disease Cardiomyopathy or structural heart disease Uncorrected hypokalemia or hypomagnesemia Concomitant administration of QT-prolonging agents Baseline lipid measurements	Antiplatelets Anticoagulants Antiarrhythmics Statin	Prasugrel is recommended among P2Y12 inhibitors Apixaban should be administered at 50% of the usual dose but should not be administered if the dosage requirement is 2.5 mg twice daily) Rivaroxaban administration is contraindicated Dabigatran and warfarin can be administered with caution Monitor INR with warfarin Monitor ECG with antiarrhythmics Start at the lowest possible dose of rosuvastatin and atorvastatin and titrate up to a maximum dose of 10 mg/day and 20 mg/day, respectively Lovastatin and simvastatin: Do not co-administer Can consider pitavastatin and fluvastatin
Favipiravir	Inhibition of viral RNA-dependent RNA polymerases	QT interval prolongation	Concomitant administration of QT-prolonging agents Concomitant electrolyte imbalances	Calcium channel blockers antiarrhythmics: Propafenone	-
Hydroxy - chloroquine	Blocking ACE2-mediated viral entry by altering the endosomal PH Interfering with the glycosylation of cellular receptors	Conduction disorders: Bundle-branch block, incomplete or complete atrioventricular block, QT prolongation, and subsequent torsade de pointes Cardiomyopathy: HF, ventricular hypertrophy, valvular dysfunction, and pulmonary arterial hypertension	Cardiomyopathy Ventricular arrhythmias (avoid in patients with preexisting QT prolongation or torsades de pointes, baseline and serial ECG recordings is needed) Uncorrected hypokalemia or hypomagnesemia Bradycardia (<50 b.p.m.) Concomitant administration of QT-prolonging agents renal insufficiency	Beta-blockers: Metoprolol, carvedilol, propranolol, labetalol Antiarrhythmics: QT-prolonging Digoxin	Dose reduction for beta-blockers may be required Monitor ECG due to intensified QTc prolongation Monitor digoxin levels (dose reduction for digoxin may be needed)

Contd...

Table 1: Contd...

Therapy	Mechanism of action	CV adverse effects	Precautions	CV drug interactions	Interaction management
Azithromycin	Antibacterial effect: A macrolide antibiotic which prevents bacterial growth through inhibiting mRNA translation Immunomodulatory and anti-inflammatory effect: Reduction of lung leukocytes, inflammatory cytokines, myeloperoxidase, tumor necrosis factor, and interleukin-1β	QT interval prolongation and subsequent torsade de pointes	Cardiac-related comorbidities Concomitant administration of QT-prolonging agents Concomitant electrolyte imbalances Renal insufficiency	Anticoagulants: Edoxaban, rivaroxaban, warfarin	Dose reduction may be required Monitor INR more closely
Tocilizumab	IL-6 inhibition	Hypertension Hyperlipidemia	Hyperlipidemia (increases in total cholesterol, triglycerides, LDL and/or HDL) Monitor 4 to 8 weeks after initiation and manage abnormalities accordingly	Anticoagulants Antiplatelets Statins Antiarrhythmics Beta-blockers Calcium channel blockers	No recommendation for dose adjustment Monitor INR Monitor ECG
Baricitinib	Janus-associated kinase inhibitor	Pulmonary embolism Deep vein thrombosis	Dose-dependent increase in lipid parameters (e.g., total, LDL, and HDL cholesterol) Assess lipids 12 weeks after initiation and manage abnormalities accordingly	-	-
Glucocorticoids	Alters gene expression to reduce inflammation	Fluid retention Edema Weight gain Hypertension Arrhythmias Atherosclerosis	Should be administered for a short duration	Anticoagulants: Warfarin	Monitor INR Dose reduction for warfarin may be needed

N/A: Not available, ACE: Angiotensin-converting enzyme, CAD: Coronary artery disease, CV: Cardiovascular, CYP450: Cytochrome P450, ECG: Electrocardiogram, IL: Interleukin, INR: International normalized ratio, HF: Heart failure, MI: Myocardial infarction, RNA: Ribonucleic acid, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, PR: Time from the start of the P wave to the end of the R wave

Favipiravir

Favipiravir (Avigan®), a prodrug, has a broad spectrum of activity against RNA viruses, such as influenza, Ebola, and norovirus. It acts via interfering with viral replication by inhibiting RNA polymerase. It has been studied for the treatment of SARS-CoV-2 since the COVID-19 pandemic and demonstrated the potential for partially controlling inflammatory mediators, faster resolution of fever and cough, and better treatment outcomes, but it did not affect respiratory failure.[16] The CV concern of favipiravir includes its potential to prolong QT interval mainly reported in Ebola virus-infected patients who have received higher drug doses than usual dosage administered for the treatment of influenza. The malignant ventricular arrhythmia is more likely to happen when favipiravir is administered in high doses, with other QT-prolonging drugs or concomitant electrolyte imbalances.[17] Favipiravir metabolism is via aldehyde oxidase in the liver, and drug interactions are possible when it is coadministered with aldehyde oxidase inhibitors such as calcium channel blockers (felodipine, amlodipine, and verapamil) and the antiarrhythmic drug propafenone.[18]

Antimalarial agents

Hydroxychloroquine

Chloroquine and hydroxychloroquine are aminoquinolines known as antimalarial agents with the dual aspect of clinical use; they (a) act as anti-inflammatory and immunomodulatory agents in chronic inflammatory diseases such as rheumatoid arthritis (RA) and (b) act as antimalarial agents; besides, they process *in vitro* antiviral activity against DNA and RNA viruses such as SARS-CoV, middle east respiratory syndrome coronavirus (MERSCoV), and SARS-CoV-2 within two mechanisms: (1) by altering endosomal pH via inhibiting acidification that eventually results in blocking angiotensin-converting enzyme 2-mediated viral entry and (2) by inhibiting glycosylation of cellular receptors. Despite the effectiveness of hydroxychloroquine

in inhibiting SARS-CoV-2 infection in *in vitro* studies and the Food and Drug Administration (FDA) emergency authorization for hydroxychloroquine for the management of COVID-19 according to initial positive findings, evidence from *in vivo* studies is still tentative and conflicting. Moderate certainty evidence from several recent systematic reviews and meta-analyses suggests that hydroxychloroquine lacks beneficial effect in patients with COVID-19; moreover, there is growing concern about the safety profile of chloroquine and hydroxychloroquine and their potential to have fatal cardiac effects; therefore, the FDA repealed the emergency use authorization of these drugs for the management of COVID-19 patients.[19] Further randomized controlled clinical trials are needed, and until then, risk–benefit balance should guide hydroxychloroquine administration in this setting.[20] According to a systematic review, adverse cardiac events associated with chloroquine and hydroxychloroquine are conduction disorders (85%), including bundle branch block, incomplete or complete atrioventricular block, QT prolongation and subsequent torsade de pointes (TdP), plus cardiomyopathy, including heart failure (HF) (26.8%), ventricular hypertrophy (22%), valvular dysfunction (7.1%), as well as pulmonary arterial hypertension (3.9%). These drugs may cause QT prolongation and consequently torsade des pointes through inducing sodium, potassium, and calcium channel blockage and alter membrane-stabilization. Considering the pharmacokinetic area, chloroquine and hydroxychloroquine are metabolized by CYP2C8 and CYP3A4. These medications are predisposed to drug interactions with CYP3A4 inhibitors that may be used for the treatment of COVID-19, like lopinavir/ritonavir, umifenovir, and azithromycin. These drugs enhance the possibility of significant QT prolongation; therefore, it is highly discouraged to coadminister other drugs with QT prolongation properties with these drugs.[21] Another concern owing to the inhibitory effect of these drugs on CYP2D6 is the increment of blood concentration of cardiac drugs metabolized via CYP2D6, such as beta-blockers (e.g., metoprolol, carvedilol, propranolol, or labetalol) and digoxin. This interaction requires attentive observation for heart rate and blood pressure.[22]

Antimicrobial agents

Azithromycin

Azithromycin, a macrolide antibiotic, prevents bacterial growth; moreover, it exerts immunomodulatory and anti-inflammatory effects that makes it an active agent against viral respiratory tract infections including Zika, Ebola, and influenza viruses.[23] Since the COVID-19 pandemic, many trials have been assessed the effectiveness of azithromycin in conjunction with hydroxychloroquine; however, results are yet insufficient to evaluate its clinical benefits versus adverse effects.[24] Azithromycin can cause QT interval prolongation, and its coadministration with chloroquine/hydroxychloroquine is associated with an extreme increase in the risk of TdP as reported in different studies.[25] Drug interactions of azithromycin with cardiovascular medications include minimally interference with the CYP450 system resulting in increasing plasma concentration of edoxaban and less strongly rivaroxaban, and increasing international normalized ratio (INR) in patients taking warfarin.[26]

Immunomodulatory agents

Tocilizumab

Tocilizumab (Actemra®) is a humanized monoclonal antibody against interleukin-6 (IL-6) receptor approved for the management of RA, systemic juvenile idiopathic arthritis, and relapsing or refractory giant cell arteritis. It has been proposed to mitigate the hyperinflammatory state in severe COVID-19 which is associated with elevated levels of inflammatory cytokines such as IL-6, leading to adult respiratory distress syndrome (ARDS) and cytokine storm syndrome.[27] According to a retrospective case–control study, tocilizumab exerted a significant reduction in the mortality of patients with COVID-19 ARDS undergoing noninvasive ventilation.[28] In another retrospective observational cohort study which was performed at 13 hospitals on 764 COVID-19 patients in ICU, 210 (27%) cases who received tocilizumab had a reduction in hospital-related mortality.[29] CV adverse effects such as alterations in lipid profile and hypertension have been reported. In an observational study comparing COVID-19 patients who received tocilizumab to those who did not receive tocilizumab, 8% of patients in the drug group developed hypertension.[30] In view of the pharmacokinetic properties, it has been demonstrated that CYP450s are generally downregulated by infection and inflammation stimuli such as IL-6; therefore, tocilizumab may act as an indirect inducer that increases the metabolism of CYP450 substrates. A single dose of tocilizumab may exert its induction effect up to 1-week postinjection. Concomitant use of tocilizumab with CV drugs metabolized by CYP3A4, 1A2, 2C9, and P-glycoprotein (e.g., atorvastatin, simvastatin, calcium channel blockers, warfarin, rivaroxaban, and dabigatran) could result in decreased concentration of these medications; therefore, it is necessary to monitor patients with these combinations.[31]

Baricitinib

Baricitinib is a Janus-associated kinase 1/2 inhibitor, approved for treating RA. It had shown to interrupt the signaling of multiple cytokines and control of exaggerated inflammatory responses implicated in COVID-19 immunopathology.[32] It has been demonstrated that baricitinib could prevent the progression to severe, extreme form of the COVID-19. Moreover, its combination with remdesivir was superior to remdesivir alone in improving

the clinical status and reducing recovery time in patients with COVID-19, leading to its emergency use authorization in COVID-19–hospitalized patients requiring supplemental oxygen or invasive mechanical ventilation.[33,34] However, despite overall encouraging results, it may carry the risk of increased probability of PE and deep vein thrombosis, which is concerning given the proclivity toward a hypercoagulable state in COVID-19 patients. Baricitinib is metabolized by the CYP450 3A4 enzyme without any inhibition or induction effect or specific interaction with CV drugs.[35]

Glucocorticoids

Glucocorticoids have anti-inflammatory, immunosuppressive, and antiproliferative properties. Their administration in the early stages of cytokine storm and macrophage activation syndrome during an overwhelming inflammatory response to an infectious trigger is of great advantage.[36] In the COVID-19 era, according to the RECOVERY study, a 28-day mortality was reduced in hospitalized patients (risk ratio [RR] = 0.83; 95% confidence interval [CI] [0.75, 0.93]), particularly in mechanically ventilated patients (RR = 0.64; 95% CI [0.51, 0.81]) who received dexamethasone.[37] In another retrospective analysis, methylprednisolone has also been associated with decreased mortality in patients with COVID-19 who developed ARDS;[38] moreover, the administration of systemic corticosteroids in comparison with usual care or placebo was associated with lower 28-day all-cause mortality, according to a prospective meta-analysis of clinical trials of critically ill patients with COVID-19.[39] In view of side effects, glucocorticoids have direct CV effects due to their mineralocorticoid effects, leading to fluid retention, edema, weight gain, and hypertension albeit only with higher doses; besides, they may cause arrhythmias through increasing renal excretion of potassium, calcium, and phosphate. Premature atherosclerosis was also reported with the long-term use of a medium-high dose of glucocorticoids. According to the WHO and National Institute of Health, dexamethasone is recommended as a vital medicine for the treatment of COVID-19 infected patients.[40] To minimize the aforementioned adverse effects, a short-term glucocorticoids therapy and then a progressive de-escalation are recommended. The primary metabolic pathway for the degradation of glucocorticoids is through CYP3A4 isoenzyme. Hence, co-administration of CYP 3A4 modulators increase the bioavailability of synthetic steroids. This may lead to iatrogenic cushing syndrome and inhibition of the hypothalamic pituitary adrenal axis. Another concern is that glucocorticoids themselves can influence metabolizing enzymes of the CYP450 superfamily, leading to interaction with warfarin via an undescribed mechanism (developing supratherapeutic INR values of patients on warfarin).[36]

MANAGEMENT OF CARDIOVASCULAR COMPLICATIONS RESULTING FROM CORONAVIRUS DISEASE 2019

The management of COVID-19 CV complications is summarized in Figure 1.

Management of thrombosis

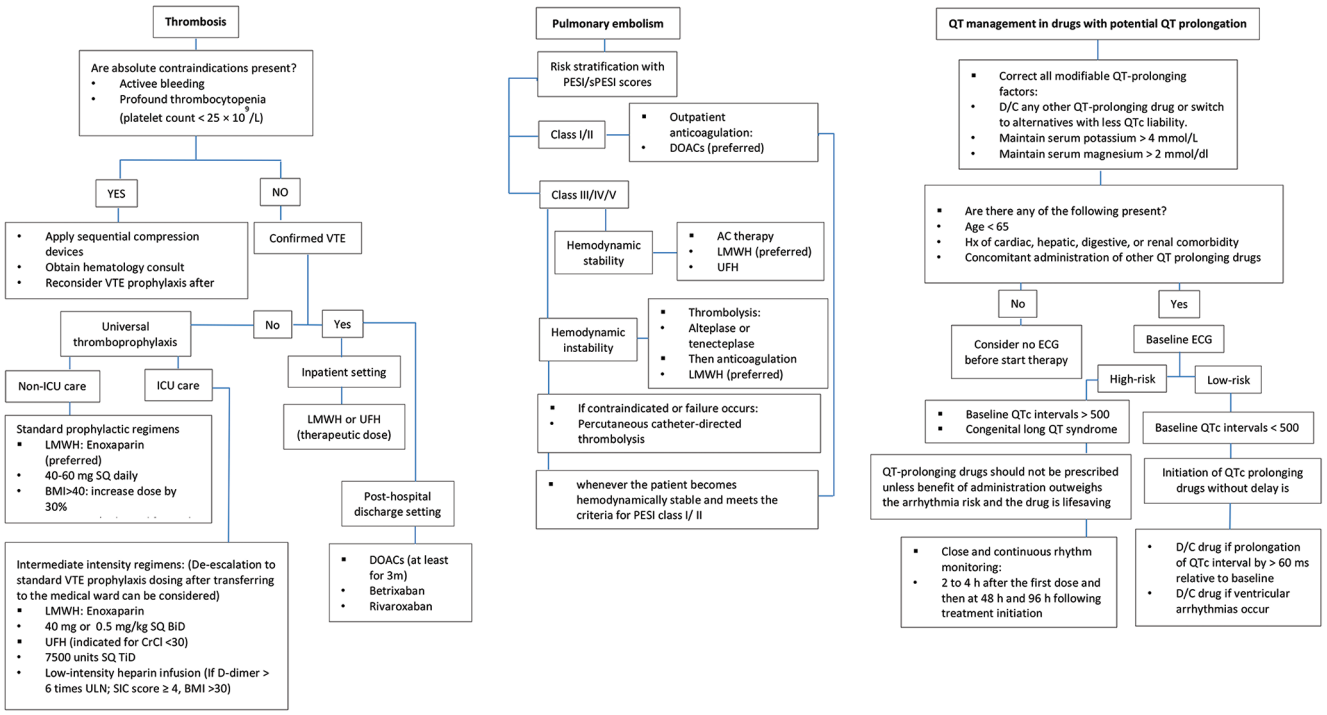
A serious aspect of coronavirus disease pathogenesis that raised too much concerns is coagulopathic manifestations of this virus. This includes increased rate of thrombotic and microvascular complications due to inflammatory response to SARS-CoV-2 infection;[41] however, the use of antithrombotic drugs such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), direct oral anticoagulants (DOACs), warfarin, and antiplatelet remains to be evaluated in these patients.

Heparins possess pharmacologic properties beyond their well-known anticoagulant effects including anti-inflammatory effects, endothelial protection, and antiviral (by inhibiting viral cell entry) effects, which all are potentially beneficial in patients with COVID-19.[42]

A Dutch study on 184 ICU patients with proven COVID-19 pneumonia demonstrated that despite standard thromboprophylaxis, about 31% of cases experienced thrombotic complications and were at high risk of all-cause death [hazard ratio (HR) = 5.4; 95% CI (2.4, 12)]. The study revealed that anticoagulation with therapeutic doses was not associated with all-cause death (HR = 0.79; 95% CI [0.35, 1.8]); therefore, it is strongly recommended to administer thrombosis prophylaxis in all COVID-19 patients admitted to the ICU and even suggested high-prophylactic doses for further coagulation prevention.[43]

In an early study evaluated heparin on 449 severe COVID-19 patients in China, 99 patients received heparin (mainly LMWH). It was indicated that the 28-day mortality of patients with sepsis-induced coagulopathy (SIC) score ≥4 or D-dimer >6-fold of the upper limit of normal (ULN) was lower among heparin users in comparison to nonusers (40.0% vs. 64.2%; $P = 0.029$; and 32.8% vs. 52.4%; $P = 0.017$, respectively).[44] Despite the results of the latter study, inferences from the first meta-analysis including eight studies on the efficacy of heparin prophylaxis suggest that there is insufficient evidence to support the role of prophylactic heparin in reducing mortality among COVID-19 patients; however, patients with moderate symptoms (e.g., D-dimer >3 μg/L, a platelet count >100 × 10^9/L, and a prothrombin time (PT) <14 s) seem to be favored with thromboprophylaxis.[45]

Results from a retrospective study of 450 laboratory-confirmed COVID-19 patients have reported a lower incidence of



AC, anticoagulant; BMI, body mass index, DOAC, direct oral anticoagulants; ECG, electrocardiogram; Hx, history; LMWH, low molecular weight heparin; PESI, pulmonary embolism severity index, SIC, sepsis-induced coagulopathy; Spesi, simplified pulmonary embolism severity index; SQ, subcutaneous; UFH, unfractionated heparin; ULN , upper limit normal; VTE, venous thromboembolism

Figure 1: Management of cardiovascular complications

in-hospital mortality with intermediate LMWH prophylaxis dosing (40–60 mg twice daily) in comparison to standard LMWH prophylaxis dosing (40–60 mg daily) for the same time (18.8% vs. 5.8%, $P = 0.02$).[46] In favor of the previous study, another retrospective study demonstrated that using intermediate doses of LMWH is both safe and effective in hospitalized COVID-19 patients.[47]

In the era of DOACs, there is little evidence regarding their safety and efficacy in COVID-19–related hypercoagulopathy. According to a retrospective study of 1583 COVID-19 patients, 38 patients (0.82%) suffered from venous thromboembolism (VTE). Among them, 27 patients received UFH/LMWH as initial anticoagulant therapy while 10 were treated with DOACs. Most patients (83%) were discharged on DOACs, and there were no reports of VTE recurrence or bleeding postdischarge, which is suggestive of the safety and efficacy of these drugs in selected hemodynamically stable VTE patients.[48] The important issue to worry about is the possible interaction of these agents with antiviral drugs, which is evaluated in the Cremona experience. According to their results, among patients who were on anticoagulant therapy with DOACs before admission, concentration-trough levels of DOACs were 6.14 times higher during hospitalization compared to prehospitalization level in patients treated with antiviral medications.[49] With this in mind, it is recommended to withhold DOACs and replace parenteral antithrombotic agents as long as antiviral agents are applied for patients.

A practical guide discussing the use of warfarin in the COVID-19 pandemic recommends clinicians to switch warfarin to DOACs or in the case of contraindication to LMWHs or fondaparinux for outpatient anticoagulation to minimize the frequent INR monitoring and healthcare contact. Self-monitoring of INR is the last recommendation if both DOACs and LMWH/fondaparinux are not appropriate or inaccessible.[50] In conclusion, the use of anticoagulants (prophylactically or therapeutically) in COVID-19 patients has been emerged according to the patients' characteristics such as setting of hospitalization, risk assessment scores (e.g. IMPROVE, Padua, Caprini), and VTE risk factors including prior history of VTE, active cancer, obesity, pregnancy, or congestive HF, advanced age (e.g., > 65 years) and immobility.[51]

Recommendations for anticoagulation are as follows:

1. Universal thromboprophylaxis strategy is recommended for all hospitalized patients with confirmed or suspected COVID-19 based on the recommendations of the International Society on Thrombosis and Hemostasis and also the results of early studies which have been reported a 60% reduction in the incidence of VTE[41] unless there are absolute

contraindications (e.g., active bleeding, profound thrombocytopenia [platelet count <25 × 10^9/L]).[52]

2. Considering the potential for drug interactions with antiviral agents or investigational COVID-19 therapies, UFH or LMWH is the preferred agent for thromboprophylaxis in these patients.[41,53] LMWH may have further advantages over UFH including once daily versus twice or thrice daily dosing, no need for frequent laboratory monitoring, less incidence of heparin-induced thrombocytopenia, and lack of resistance. DOACs, despite having approval for in-hospital prophylaxis, have several disadvantages in hospitalized COVID-19 patients because of potential drug interactions when coadministered with immunomodulatory agents and antivirals (i.e., lopinavir/ritonavir)[41]
3. For non-ICU hospitalized patients, standard prophylactic regimens with LMWH (e.g., enoxaparin, 40–60 mg daily) or UFH (e.g., 5000 IU twice or thrice daily) are favorable and are associated with improved outcomes and better prognosis[41]
4. For critically ill patients hospitalized in ICU, increased VTE risk is expected due to hemostatic derangements, immobility, systemic inflammatory state, mechanical ventilation, and central venous catheters; moreover, nutritional deficiencies and liver dysfunction may also deteriorate coagulation factors production.[54] Emerging clinical data suggest increased doses of VTE prophylaxis to "intermediate-intensity" regimens (e.g., enoxaparin 40 mg subcutaneous twice daily, enoxaparin 0.5 mg/kg subcutaneous twice daily, heparin 7500 units subcutaneous three times daily, or low-intensity heparin infusion targeted to an anti-factor Xa level of 0.30–0.70 IU/mL), especially in patients with D-dimer >6 times ULN; SIC score ≥4, and body mass index (BMI) >30 kg/m^2. Studies from the Netherlands and France revealed an increased incidence of VTE among ICU patients even after standard VTE prophylaxis. Deescalating to standard VTE prophylaxis dosing can be considered when patients are improving and transferring from the ICU to the medical ward[52]
5. LMWH dose recommendations should be modified regarding obesity, pregnancy, and renal function.
   i. In obesity (BMI >40 kg/m^2) and during pregnancy and the postpartum period, the risk of VTE is increased, especially in the setting of COVID-19, and intermediate-dose thromboprophylaxis with LMWH is recommended among these high-risk patients[41,53]
   ii. It is recommended to use UFH over LMWH in renal insufficiency (creatinine clearance <15–30 mL/min) and the setting of anticipated procedures[54]
6. In the setting of posthospital discharge, DOACs such as betrixaban or rivaroxaban and enoxaparin are preferred agents over warfarin, considering no need for routine monitoring which minimizes patient exposure with the health-care system. A treatment course of at least 3 months is an acceptable duration[53]
7. For patients with confirmed VTE due to conditions such as atrial fibrillation (AF), mechanical cardiac valves, or long-term secondary VTE prevention, established guidelines recommend continuing anticoagulation with shorter-acting agents (e.g., LMWH or UFH) in the inpatient setting and DOACs in the posthospital discharge setting (with attention to the administration of therapeutic doses of these drugs)[41,53]
8. In case of contraindication to pharmacologic VTE prophylaxis (e.g., active bleeding, profound thrombocytopenia), consistent application of mechanical thromboprophylaxis such as intermittent pneumatic compression should be utilized until the pertinent state for conversion to pharmacologic prophylaxis is achieved.[41]

Management of pulmonary embolism in coronavirus disease 2019

Another life-threatening complication associated with COVID-19 infection is PE with a prevalence of 23% according to French experience.[55] A case series presented six patients with documented PE without any hypercoagulable risk factors. As a therapeutic approach, two of them with intermediate risk defined by PE Severity Index (PESI) score according to the 2019 European Society of Cardiology (ESC) guidelines received systemic thrombolysis using tissue plasminogen activator (t-PA) followed by therapeutic enoxaparin (1 mg/kg subcutaneously twice daily) or heparin infusion. Other patients were treated with therapeutic enoxaparin or heparin without t-PA. All patients discharged on anticoagulation with DOACs (apixaban 10 mg twice daily for 7 days followed by apixaban 5 mg twice daily or rivaroxaban 15 mg twice daily for 21 days followed by rivaroxaban 20 mg daily) for a minimum duration of 3 months.[56]

There are two case reports from the UK described patients with the diagnosis of SARS-CoV-2 who have received prophylactic dose of LMWH during hospitalizations. Both were readmitted to hospital 1 week after discharge with the diagnosis of PE. They were treated with recombinant t-PA and long-term anticoagulation therapy that were prescribed for both.[55,57] The presentations of PE within a week from discharge despite prophylactic anticoagulation during hospitalization raise concerns about enhanced thromboembolic complications even in moderate infections of COVID-19 and necessitate determining the importance and exact role of extended thromboprophylaxis.

Results from a cohort study on 12 patients with COVID-19 treated with alteplase for severe hypoxia, which is thought to contribute significantly to PE, had been shown improvement in the pulmonary function (PF) ratio and

preserved fibrinogen levels 24 h postthrombolysis, which may reflect both improvement in alveolar perfusion and ventilation without significant bleeding.[58]

In a case series including three patients with COVID-19 suffering from ARDS and respiratory failure who received IV t-PA, improvement in PaO_2/FiO_2 ratio from 38% to 100% was reported; nevertheless, this effect was not durable in two of the patients after discontinuation of the infusion. The study also suggests evaluating larger bolus doses of t-PA (50 mg or 100 mg bolus) in COVID-19 ARDS while continuing anticoagulation with heparins in submassive PE due to high effectiveness in reducing mortality, while the bleeding risk increases only 1.2%.[59]

To reach an applicable therapeutic approach in patients presenting with acute PE and identifying its severity, risk stratification with the validated PESI/simplified PESI scores is recommended according to the ESC and British Thoracic Society (BTS) guidelines. In PESI Class I (very low-risk), II (low-risk), III (intermediate-risk), IV (high-risk), and V (very high-risk), the risk of 30-day mortality ranged from 0% to 1.6%, 1.7% to 3.5%, 3.2% to 7.1%, 4% to 10.4%, and 10.0% to 24.5%, respectively.[60,61]

For patients categorized in Class I/II, outpatient anticoagulant therapy is possible with Vitamin K antagonists or DOACs with similar efficacy and significantly lower risk of bleeding complications. Both the ESC and BTS guidelines state that patients with intermediate-risk to very high-risk PESI score should be managed in the hospital, and anticoagulation therapy should be initiated immediately with LMWH. In the case of hemodynamic instability or risk of further decompensation, UFH is superior to LMWH. ESC recommends systemic thrombolysis in patients with hemodynamic instability in the absence of contraindications.[60,61]

The preferred thrombolytic agents are alteplase and tenecteplase, demonstrated to diminish mortality and recurrent PE, besides limiting the severity and improving PF.[62] After thrombolysis, anticoagulation with UFH or LMWH should be continued. An early discharge may be considered followed by warfarin or novel oral anticoagulants for an extended period, whenever the patient becomes hemodynamically stable and meets the criteria for PESI Class I/II.[60,61]

In the case of contraindication or failure (continued oxygen dependence) with thrombolysis, alternative therapies including percutaneous catheter-directed thrombolysis or surgical embolectomy should be considered if local facilities exist which also minimize the risk of bleeding, particularly intracranial hemorrhage.

Management of arrhythmia in coronavirus disease 2019

Arrhythmia is a challenging and concerning issue in the COVID-19 era. Administration of QT-prolonging drugs in addition to other predisposing risk conditions due to COVID-19 infection including electrolyte abnormalities, fever, and inflammatory state could result in ventricular arrhythmias, conduction blockade, and CV collapse that may increase the risk of sudden cardiac death (SCD) by an almost threefold.[63]

The incidence of QT prolongation, in particular TdP, depends on a set of several factors categorized as modifiable and nonmodifiable risk factors. Modifiable risk factors include concomitant use of drugs that prolong the QT interval, serum potassium concentration <3.5 mmol/L, serum calcium concentration <90 mg/L (2.2 mmol/L), serum magnesium concentration <15 mg/L (<0.6 mmol/L), and bradycardia (heart rate <50 bpm). Nonmodifiable risk factors include female sex, age >65 years, inherited long QT syndrome, intrinsic baseline QTc >460 ms, and comorbidities (ACS, HF, kidney or liver disease, and sepsis).[64] To minimize arrhythmia risk, it is recommended to obtain a baseline 12-lead electrocardiogram (ECG) as a tool for risk stratification before initiating QT-prolonging medications to approximately estimate the patient's risk of TdP and SCD.[63] In the absence of other QT-prolonging drugs, if a patient is younger than 65 years old without any cardiac, hepatic, digestive, or renal comorbidity, it is not necessary to obtain a baseline ECG.[21]

Recommendations for medical therapy considering QT-prolongation risk in COVID-19 cases are as follows:

1. In high-risk patients with baseline QTc intervals >500 ms and those with known congenital long QT syndrome, QT-prolonging drugs should not be prescribed or should be stopped in case of prolongation of QTc interval by >60 ms relative to baseline or if ventricular arrhythmias occur; moreover, any other QT-prolonging drug needs to be discontinued. Despite the aforementioned precautions, if the patient has been presenting with severe and progressively worsening respiratory symptoms or if the patient is in the high-risk group for developing respiratory complications (e.g., >65 years of age, immunosuppressed, and/or high-risk comorbid conditions), the benefit of administration of QTc-prolonging COVID-19 medications may outweigh the arrhythmia risk and may be lifesaving. The latter situation is advisable only in circumstances of close and continuous rhythm monitoring (around 2–4 h after the first dose and then at 48 h and 96 h following treatment initiation) besides maintaining serum potassium >4 mmol/L.[21,65] It is also recommended to give magnesium prophylaxis as an antitorsadogenic agent regardless of its baseline level. High-risk patients

are defined as QT intervals above the upper limit of 500 ms, while patients with a QT interval below 460 ms are categorized as low risk[21]
2. In low-risk patients, the initiation of QTc-prolonging COVID-19 pharmacotherapies without delay is advisable according to the QTc monitoring algorithm[66]
3. In all patients, modifying the underlying risk factors should be on the agenda including the correction of electrolyte abnormalities (e.g., repleting potassium and magnesium to levels >4 mmol/L and >2 mg/dL, respectively), discontinuation of other unnecessary QTc-prolonging drugs, or switching to alternatives with less QTc liability
4. Regarding the potassium level, the initiation of QT-prolonging drugs when serum potassium level is below 3.5 mmol/L is discouraged until its correction to reach at least level of 3.5 mmol/L. If the potassium level is between 3.5 and 4.0 mmol/L, the administration of QT-prolonging drugs is feasible if concurrent potassium supplementation is given.[21]

CONCLUSION

The COVID-19 pandemic, the most critical public health issue of the century, has been emerged with cardiac involvement as one of the prominent features of the disease, leading to worse outcomes and increased risk of in-hospital death. Our review has discussed the best management strategies of CV manifestations compatible with specific therapies used in the treatment of SARS-CoV-2 infection, as well as considering potential drug–drug interactions and dose adjustment requirements. To meet the urgent need for discovering safe and practical therapeutic and preventive strategies for this infection, researchers and physicians must be vigilant about the various clinical presentations and potential drug–drug interactions related to COVID-19.

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Conflicts of interest

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