

# Cardiovascular Considerations in Treating Patients With Coronavirus Disease 2019 (COVID-19)

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**Abstract:** A novel betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly across the globe since December 2019. Coronavirus disease 2019 (COVID-19) has a significantly higher mortality rate than seasonal influenza and has disproportionately affected older adults, especially those with cardiovascular disease and related risk factors. Adverse cardiovascular sequelae, such as myocarditis, acute myocardial infarction, and heart failure, have been reported in patients with COVID-19. No established treatment is currently available; however, several therapies, including remdesivir, hydroxychloroquine and chloroquine, and interleukin (IL)-6 inhibitors, are being used off-label and evaluated in ongoing clinical trials. Considering these therapies are not familiar to cardiovascular clinicians managing these patients, this review describes the pharmacology of these therapies in the context of their use in patients with cardiovascular-related conditions.

**Key Words:** coronavirus, COVID-19, cardiovascular, drug interaction

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## BACKGROUND

The first cases of pneumonia due to a novel betacoronavirus were first identified in December 2019 in Wuhan, China.<sup>1</sup> Later named, severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), has infected hundreds of thousands across 6 continents.<sup>1</sup> The overall case-fatality rate of COVID-19 remains in flux but was initially reported to be 2.3% in mainland China, while Italy has reported a case-fatality rate of 7.2%.<sup>2,3</sup> Of note, case-fatality rates have been reportedly higher in patients with pre-existing cardiovascular disease.<sup>2</sup>

The transmission of SARS-CoV-2 occurs by person-to-person spread through respiratory droplets and self-inoculation after contact with virus on contaminated surfaces. The disease has an incubation period of approximately 5 days.<sup>4</sup> The most common signs and symptoms of COVID-19 include fever, dry cough, shortness of breath, and myalgia; however, some patients present with gastrointestinal (eg, diarrhea, nausea, and vomiting) or neurological (eg, headache, hypogeusia, and hyposmia) symptoms.<sup>5,6</sup> Cardiovascular complications, such as myocarditis, acute myocardial infarction, and heart failure have been reported, as has been previously observed with other acute upper respiratory infections (eg, influenza).<sup>7</sup> An extensive discussion of these complications and their relationship to COVID-19 has been described elsewhere.<sup>8</sup>

Currently, there is no established treatment or vaccine against SARS-CoV-2. Several antiviral and immunomodulating therapies have been used and are under clinical investigation. SARS-CoV-2 infection seems to lead to a more severe disease in patients who are elderly or have comorbidities.<sup>9</sup> In this review, we provide an overview of the pharmacology and cardiovascular considerations with the most promising therapies being investigated for use in patients with COVID-19 with a particular consideration on how the treatment of SARS-CoV-2 infection may be particularly challenging in patients with, or at risk for, cardiovascular diseases (Fig. 1).

## PHARMACOLOGICAL MANAGEMENT OF COVID-19

While a complete understanding of COVID-19 is lacking, reports from China and Italy describe 2 phases of the disease.<sup>10,11</sup> The initial phase is primarily an infection characterized by predominantly lower respiratory symptoms,

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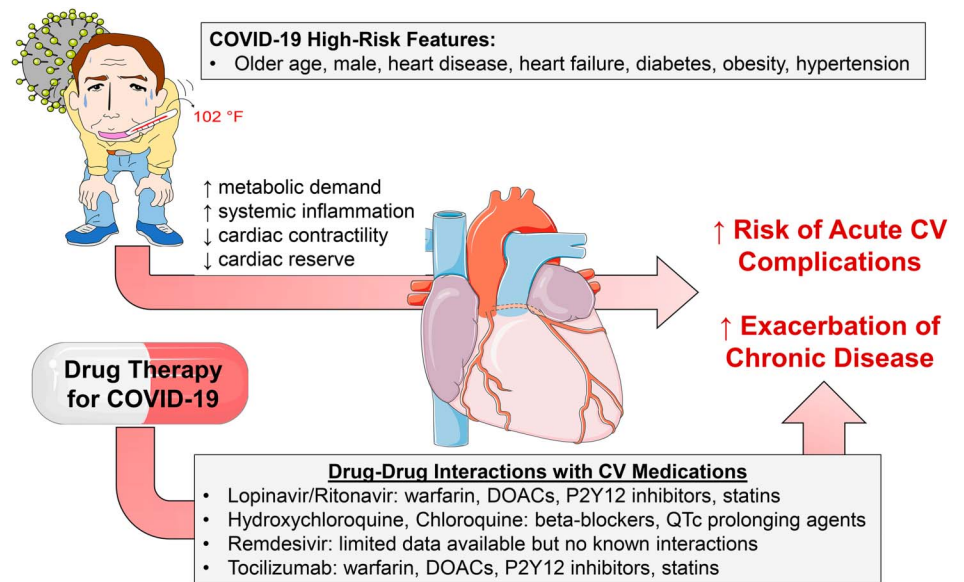
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**FIGURE 1.** Cardiovascular considerations in patients with COVID-19. In patients with COVID-19, an increase in metabolic demand occurs along with a progressive decrease in cardiac contractility and cardiac reserve, which are responsible for the acute cardiovascular complications, or decompensation, of chronic cardiovascular disorders. As well, COVID-19 is characterized by a severe systemic inflammation, which has a procoagulant effect and may pave the way to thrombotic events or impair the immune response leading to myocardial injury. Interestingly, individuals with a history of cardiovascular disease, hypertension, or diabetes are at higher risk to develop a more aggressive, potentially life-threatening disease. Currently, available drugs that are under evaluation may have important implications for cardiovascular health care providers as many of these agents have significant drug–drug interactions and cardiovascular-related side effects, both acute and chronic. This figure has been partially created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported license; <https://smart.servier.com>. CV, cardiovascular; DOAC, direct oral anticoagulants.



of which most patients recover. However, some patients progress to an immune-mediated respiratory failure leading to acute respiratory distress syndrome (ARDS) and multiple organ failure, which is associated with a very high mortality rate.<sup>9</sup>

Early approaches to treatment have involved antiviral therapies aimed at reducing viral replication, representing the main pathogenetic mechanism, at least in the early phase. Immunomodulatory therapies targeting the inflammatory response that leads to ARDS are also being explored. It is important to recognize that, at this time, there are only low-quality data to support the use of any therapy for COVID-19, and the field is evolving rapidly. Therefore, this review should not be considered to be comprehensive. A summary of

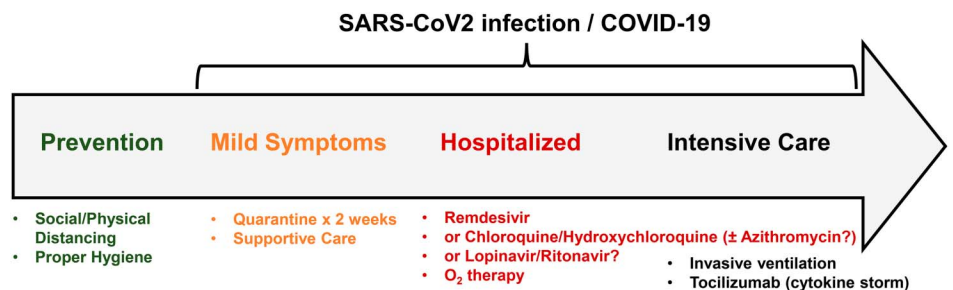
the current approaches to prevention and treatment is described in Figure 2.

It is important to consider that the patients at greatest risk for COVID-19–related mortality, and in whom aggressive treatment should be considered, are also receiving concomitant cardiovascular therapies. Therefore, drug–drug interactions must be considered and accounted for when managing cardiovascular patients with COVID-19 (Table 1).

### ANTIVIRAL THERAPIES

SARS-CoV-2 is an RNA betacoronavirus that uses a glycosylated spike protein to gain host cell entry.<sup>12</sup> A single region of spiked protein, the receptor-binding domain, binds

**FIGURE 2.** Investigational approach to COVID-19 management. It is important to recognize that, at this time, there are no approved therapies for COVID-19. Preventative approaches are critical to prevent person-to-person spread and include social and physical distancing and proper hygiene. Patients who are COVID-19 positive but are either asymptomatic or have mild symptoms should self-quarantine for 2 weeks and receive supportive care at home so as not to overburden the health care system. Patients with more severe illness (eg, worsening shortness of breath) may receive one of several investigational therapies and oxygen therapy. A minority of patients will require intensive care and ventilation and may be appropriate candidates for therapies aimed at preventing cytokine storm to blunt the inflammatory response.



**TABLE 1. Drug–Drug Interactions Between Cardiovascular and COVID-19 Therapies**

Cardiovascular Medication/Class	Lopinavir/Ritonavir	Chloroquine/Hydroxychloroquine	Remdesivir	Tocilizumab
<b>Antiarrhythmics</b>				
Amiodarone	↑	↑	↔	↔
Dofetilide	↑	↔*	↔	↔
Flecainide	↑	↑	↔	↔
Mexiletine	↑	↑	↔	↔
Propafenone	↑	↔*	↔	↔
<b>Anticoagulants</b>				
Apixaban	↑	↑	↔	↓
Dabigatran	↔ or ↓	↑	↔	↔
Edoxaban	↑	↑	↔	↔
Enoxaparin	↔	↔	↔	↔
Heparin	↔	↔	↔	↔
Rivaroxaban	↑	↑	↔	↓
Warfarin	↓ or ↑	↑	↔	↓
<b>Antihypertensives</b>				
Beta-blockers	↑	↓	↔	↔
Diltiazem/Verapamil	↑	↑	↔	↔
Amlodipine	↑	↑	↔	↔
Eplerenone	↑	↔	↔	↔
Fosinopril	↑	↔	↔	↔
Irbesartan/Losartan	↓	↔	↔	↔
Spirolactone	↔	↔	↔	↔
Sacubitril/Valsartan	↑	↔	↔	↔
Valsartan	↑	↔	↔	↔
<b>Antiplatelets</b>				
Aspirin	↔	↔	↔	↔
Clopidogrel	↓	↔	↔	↓
Prasugrel	↔	↔	↔	↓
Ticagrelor	↑	↔	↔	↓
<b>Lipid-lowering therapies</b>				
Atorvastatin	↑ max: 20 mg	↔	↔	↓
Ezetimibe	↔	↔	↔	↔
Fenofibrate	↔	↔	↔	↔
Fluvastatin	↔	↔	↔	↓
Gemfibrozil	↓	↔	↔	↔
Lovastatin	↑	↔	↔	↓
Pitavastatin	↔	↔	↔	↔
Pravastatin	↔	↔	↔	↔
Rosuvastatin	↑ max: 10 mg	↔	↔	↓
Simvastatin	↔	↔	↔	↓
<b>Other</b>				
Digoxin	↑	↑	↔	↔
Ivabradine	↑	↔*	↔	↔
Ranolazine	↑	↔*	↔	↔

█, avoid use; █, consider alternative/adjust dose; █, monitor; █, safe to coadminister; ↔, no significant effect; ↑, increased exposure; ↓, decreased exposure.

\*No change in drug exposure, but coadministration increases QTc prolongation risk.

References: (1) Liverpool Drug Interaction Group. Available at: <http://www.covid19-druginteractions.org/>. Accessed March 22, 2020. (2) Medscape Online, Drug Interaction Checker, New York, NY: Medscape, LLC; Accessed March 22, 2020. (3) Kaletra (lopinavir/ritonavir) [package insert]. North Chicago, IL: AbbVie Inc. 2019. (4) Aralen (chloroquine) [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2017. (5) Plaquenil (hydroxychloroquine) [package insert]. St. Michael, Barbados; 2017. (6) Actemras (tocilizumab) [package insert]. Genentech, Inc. 2013.

the host-cell receptor. A host protease cleaves the spike, which allows virus entry into the host cell. In humans, SARS-CoV-2 uses the angiotensin-converting enzyme II (ACE2) as its entry receptor.<sup>13</sup> Thus, antiviral therapies that either interrupt the replication of SARS-CoV-2<sup>14</sup> (eg, remdesivir) or prevent virus/cell fusion and glycosylation of cellular receptors of SARS-CoV-2 necessary for binding to ACE2<sup>15</sup> (eg, chloroquine) are being investigated as potential treatments.

## Hydroxychloroquine and Chloroquine

The antimalarial agents, hydroxychloroquine and chloroquine, are commonly used to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, and disrupt immune activation at the cellular level by inhibiting both innate and adaptive immune responses. In addition, by impairing endosomal and lysosomal acidification, which is required for virus/cell binding, these therapies may exert antiviral activity.<sup>16</sup> *In vitro* studies suggest that chloroquine may be more potent at inhibiting SARS-CoV-2 than hydroxychloroquine, but hydroxychloroquine seems to be less toxic.<sup>16</sup>

Hydroxychloroquine is administered orally in a loading dose of 400 mg twice daily, followed by a maintenance dose of 200 mg twice daily for 4 days.<sup>17</sup> Electrocardiogram (ECG) monitoring is recommended to watch for cardiac arrhythmias, including QT prolongation, Torsade de Pointe, and atrioventricular block.<sup>8</sup> A reduction in the dose or discontinuation should be considered with QTc >500 ms or an increase in QTc >60 ms, and caution is advised if used together with other therapies that prolong QTc, especially antiarrhythmics. An antimalarial-induced hypertrophic, restrictive cardiomyopathy can also occur, but this is exceedingly rare and occurs with prolonged use, which is not a concern given the short duration (5 days) of treatment required for COVID-19.<sup>18</sup> Chloroquine and hydroxychloroquine also inhibit CYP2D6, which may increase beta-blocker exposure and risk of bradycardia, PR interval prolongation, and atrioventricular block. Other potential adverse effects include severe hypoglycemia, erythroderma, hematological, and psychiatric disturbances. Thus, routine monitoring should include a complete blood count and comprehensive metabolic panel.

A small pilot study<sup>19</sup> randomized 30 patients to either the intervention (hydroxychloroquine 400 mg daily for 5 days) or conventional therapy only. On day 7, patients were tested through respiratory pharyngeal swab for evidence of COVID-19 nucleic acid. There was no difference in the number of negative swabs between the hydroxychloroquine (n = 13) and control (n = 14) groups ( $P > 0.05$ ). No favorable trends were observed in other secondary measures, including duration of hospitalization, body temperature regulation, or radiological progression.

In another small, single-arm study, the effects of hydroxychloroquine 600 mg daily in hospitalized patients on the presence or absence of virus at day 6 were studied.<sup>20</sup> Twenty-six French subjects received the protocol and 16 served as controls. Six stopped hydroxychloroquine therapy early due to either being transferred to the intensive care unit (n = 3), leaving the hospital (n = 1), death (n = 1), or nausea

(n = 1). On day 6 of treatment, 70% of hydroxychloroquine-treated patients were virologically cured compared with only 12.5% in the control group ( $P = 0.001$ ). The addition of the macrolide antibiotic, azithromycin, to hydroxychloroquine was significantly more effective for virus elimination with a 100% cure rate, suggesting this combination may be superior to hydroxychloroquine alone. The same authors have published a preprint<sup>21</sup> of a larger sample (n = 80) of patients who received the combination of hydroxychloroquine and azithromycin showing clinical improvement in all but 2 patients. The authors report that only 15% of subjects required oxygen therapy, 93% had a negative nasopharyngeal viral load on day 8, and the length of stay was limited to an average of 5 days. Despite the favorable outcomes reported in these observational studies, a proper randomized controlled trial is warranted before any definitive decisions can be made regarding the role of these therapies in treating COVID-19.

Although the mechanism of how azithromycin would be effective in patients with COVID-19, azithromycin has been found to have antiviral and anti-inflammatory effects in both *in vivo* and *in vitro* studies.<sup>20,22,23</sup> Azithromycin also has activity against proinflammatory cytokines (interleukin [IL]-6 and IL-8), which may reduce the development of cytokine storm, but this warrants further study.<sup>22</sup> One potential concern, however, with concomitant antimalarial therapy with azithromycin is the potential for QTc prolongation warranting daily ECG monitoring.<sup>24</sup> Although other macrolides have demonstrated similar effects, azithromycin minimally inhibits CYP3A4, while others (eg, erythromycin and clarithromycin) are strong inhibitors of CYP3A4 and not as well tolerated as azithromycin. At this time, the data supporting the combination of hydroxychloroquine and azithromycin for COVID-19 are very limited; given the potential for significant toxicity, use of this regimen should be considered with caution.

Some have also suggested there may be a role for hydroxychloroquine or chloroquine to be used for prophylaxis in high-risk individuals, such as health care workers. Therefore, chloroquine is being studied as a potential preventative measure against COVID-19 in health care workers and other individuals in high-risk environments (NCT04303507). Participants will be randomized to placebo or chloroquine (loading dose of 10 mg/kg followed by 150 mg daily) for 3 months. The primary outcome will be the number of COVID-19 cases at 100 days. At this time, however, there is little evidence for pharmacological measures to reduce the transmission of SARS-CoV-2 in health care workers or other high-risk individuals.

## Remdesivir

Remdesivir (Gilead Sciences, Inc., Foster City, CA) is a nucleotide analog prodrug with broad antiviral activity initially used against Ebola.<sup>25</sup> *In vivo* and *in vitro* testing has shown to inhibit human coronavirus replication, including SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV).<sup>15,26,27</sup> Remdesivir was initially only available for compassionate use but received orphan drug status from the U.S. Food and Drug Administration (FDA) on March 23, 2020. The recommended dosing is an initial single dose of 200 mg intravenously

followed by 100 mg every 24 hours for the duration of the hospitalization up to 10 days.<sup>25</sup>

Several phase 3 clinical trials are underway in the United States, South Korea, China, and Europe (NCT04302766, NCT04280705, NCT04292899, NCT04292730, 2020-000936-23). Two of the larger ongoing multicenter clinical trials (NCT04292899, NCT04292730) are evaluating remdesivir in hospitalized patients with moderate (n = 600) or severe (n = 400) symptoms not yet requiring mechanical ventilation. Patients in these studies are randomized to 5 or 10 days of remdesivir (or to an additional standard of care arm in the moderate disease trial) with a focus on discharge, fever, and oxygen saturation at 14 days. Patients with more severe symptoms requiring mechanical ventilation must pursue individual compassionate use protocols in to receive access to remdesivir. Importantly, these trials have no cardiovascular-specific reasons for exclusion.

Overall, remdesivir is generally well tolerated, but self-limiting hepatotoxicity has been observed. Nephrotoxicity is also possible; thus, its use is not recommended in patients with an estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup> or those on dialysis. Monitoring recommendations include a complete blood count with differential and a comprehensive metabolic panel. There is limited information available at this time regarding the potential for drug–drug interactions with remdesivir. Information from a clinical trial protocol (NCT04280705) suggests that “remdesivir is a prodrug that is metabolized to its active form as a substrate of CYP3A4” and “remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4 in vitro,” yet it also states that coadministration with drugs that affect these CYP isoforms is unlikely to significantly affect the metabolism of remdesivir.

### Lopinavir/Ritonavir

Lopinavir is a protease inhibitor primarily used for the treatment of HIV that is combined with ritonavir, and another protease inhibitor that also inhibits CYP3A4 and is combined with lopinavir to enhance its potency.<sup>28</sup> From a cardiovascular perspective, lopinavir/ritonavir does not induce endothelial dysfunction or insulin resistance; however, it can cause hypertriglyceridemia.<sup>29,30</sup> A retrospective, single-center study suggests that ritonavir-boosted regimens may worsen cardiovascular outcomes in patients with HIV and heart failure.<sup>31</sup> Importantly, these data are not sufficient to restrict the use of lopinavir/ritonavir in patients with cardiovascular disease or heart failure given the life-threatening potential of COVID-19 and short-term (2 weeks) duration of treatment.

There are notable drug–drug interactions with lopinavir/ritonavir and select cardiovascular therapies because ritonavir is a potent inhibitor of CYP3A4 and P-glycoprotein (MDR1).<sup>32</sup> This may result in increased concentrations of cardiovascular therapies metabolized through CYP3A4, such as rivaroxaban, apixaban, simvastatin, and lovastatin, all of which should not be used in combination with ritonavir.<sup>33,34</sup> Likewise, ritonavir inhibits the bioactivation of clopidogrel and prasugrel, which may decrease antiplatelet activity; however, this may not affect the antiplatelet activity of prasugrel making it still a reasonable option.<sup>35,36</sup> Ticagrelor should not be used with strong inhibitors of CYP3A4, such as ritonavir,

due to an increased risk of bleeding.<sup>35,36</sup> The use of P2Y<sub>12</sub> platelet function assays may be appropriate to ensure adequate antiplatelet activity. Gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea) and elevations in hepatic transaminases can also occur. Routine monitoring includes complete blood count, comprehensive metabolic panel, and a baseline ECG is recommended when used with concomitant agents (eg, antiarrhythmics) that prolong the QT interval.

Recently, 199 hospitalized patients with severe COVID-19 disease were randomized to either a fixed dose of lopinavir/ritonavir (400 and 100 mg, respectively) twice daily for 14 days or standard of care.<sup>28</sup> The intervention did not improve time to clinical improvement or mortality, although the study was underpowered to detect a mortality benefit. Gastrointestinal complaints (nausea, vomiting, and diarrhea) were also common, and 13.8% of patients discontinued therapy due to adverse events. Additional clinical trials are ongoing, including one clinical trial comparing lopinavir/ritonavir with hydroxychloroquine (NCT04307693) and another clinical trial comparing lopinavir/ritonavir with remdesivir (2020-000936-23) in patients with COVID-19. Of note, interferon-beta may also be used in combination with lopinavir/ritonavir, which has been shown to improve pulmonary function and reduce viral loads in marmosets and mice with Middle East respiratory syndrome coronavirus, but this has not yet been evaluated in humans.<sup>26,37</sup>

## IMMUNE MODULATORS

### Interleukin-6 (IL-6) Inhibitors

Patients with severe infection may progress to severe respiratory failure due to ARDS mediated by a catastrophic inflammatory cascade.<sup>38,39</sup> Early observations in China and Italy led to widespread use of tocilizumab, a fully humanized monoclonal antibody against the interleukin-6 receptor (IL-6R).<sup>40,41</sup> Although originally FDA approved for use in rheumatoid arthritis, tocilizumab is routinely used in the treatment of cytokine release syndrome secondary to chimeric antigen receptor T-cell therapy in hematologic malignancies.<sup>42</sup> An observational series of patients with severe respiratory symptoms in China showed recovery in 19/21 (91%) after treatment with tocilizumab 4 mg/kg IV (maximum dose of 400 mg).<sup>43</sup> Other emerging treatment protocols recommend more aggressive doses (8 mg/kg up to 800 mg) and repeated doses at 12 and 24 hours for patients showing inadequate responses. The primary risks of tocilizumab relate to immunosuppression through neutropenia and interruption of T-cell-mediated immunity. Infusion reactions and transient transaminase elevations may also occur frequently. Although tocilizumab significantly increases cholesterol levels and blood pressure, a recent network meta-analysis found the cardiovascular risk with tocilizumab was comparable with other disease-modifying antirheumatic drugs.<sup>44</sup> Regardless, given the high mortality rate among patients with COVID-19–mediated ARDS (>50%), the potential benefits of short-term tocilizumab use seem to outweigh risks of treatment for most patients.

The parallels in inflammatory pathophysiology between chimeric antigen receptor T-cell therapy–mediated cytokine release syndrome and COVID-19–mediated ARDS suggest that IL-6 suppression is a key advancement in treatment of severe COVID-19 infection. Sarilumab (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) is the only other IL-6 blocker currently on the market if tocilizumab is unavailable; however, there is limited evidence to guide the selection and dosing of these agents at this time.

## VACCINE

An urgent public health priority to combat COVID-19 in the future is to develop a safe and effective vaccine. Widespread vaccination could also play a role in modulating the cardiovascular risk similar to what has been observed with influenza, thus, the importance of identifying a safe and effective vaccine.<sup>45</sup> The first Phase 1 clinical trial (NCT04283461) evaluating a vaccine for COVID-19, mRNA-1273, began on March 19, 2020, and is being sponsored by the National Institutes of Health. The open-label study will enroll 45 healthy adults between 18 and 55 years over 6 weeks. Although 40 vaccine candidates are in the pipeline, it is unlikely a vaccine will be available until at least 2021.

## CONTROVERSIAL USE OF RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM INHIBITORS

There has been increased concern regarding the use of ACE inhibitors and angiotensin receptor blockers (ARBs) in patients with COVID-19.<sup>46</sup> This is due to the potential of ACE inhibitors and ARBs to upregulate ACE2 receptors, which are found in vascular endothelial cells of the heart, kidneys, and lungs, and have been shown to be the host cell entry point for SARS-CoV-2.<sup>47</sup> Thus, there is a theoretical increased risk for COVID-19 in patients taking these medications. It also seems that SARS-CoV-2 consumes ACE2 and increases angiotensin2 (AT2) activity, which activates an inflammatory response resulting in microvascular constriction and ischemic injury.<sup>48</sup> Moreover, the SARS-CoV led to downregulation of ACE2 and more severe lung injury in mice, which could theoretically be attenuated by administration of an ARB.<sup>49</sup> Mice lacking ACE2 have also been shown to have worse outcomes with influenza H7N9 infection.<sup>50</sup> Observational evidence suggests that ACE inhibitors, but not ARBs, may reduce the risk of pneumonia.<sup>51</sup> Given the limited data available supporting either harm or benefit, multiple professional organizations have released statements to provide guidance. A Joint Statement from the Heart Failure Society of America, American Heart Association, and American College of Cardiology recommends, “not to add or remove any RAAS-related treatments, beyond actions based on standard clinical practice,” and calls for further research in this area.<sup>52</sup> Likewise, the Council on Hypertension of the European Society of Cardiology also released a Position Statement recommending, “physicians and patients should continue treatment with their usual

antihypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the COVID-19 infection.”<sup>53</sup>

To help determine the potential role, or harm, of ACE inhibitors and ARBs, 2 randomized, multicenter, clinical trials are underway. Patients with a presumptive positive test for COVID-19, who require hospitalization and are not already taking an ACE inhibitor or ARB, will be randomized to either losartan 25 mg daily or placebo (NCT04312009). The primary outcome of this study is the Sequential Organ Failure Assessment Respiratory Score, which is used to determine the risk of mortality from respiratory failure. A similarly designed study (NCT04311177) will compare losartan 25 mg daily to placebo in patients who test positive for COVID-19 but do not require hospitalization. The primary outcome of this study will be hospitalization rates at 28 days.

## CONTROVERSIAL USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

In addition to ACE inhibitors and ARBs, ibuprofen was purported in a recent correspondence to also increase ACE2 and, potentially, the risk of worsening COVID-19.<sup>46</sup> Despite no definitive evidence supporting this claim, it was promoted by the French Health Minister on social media.<sup>54</sup> Although the World Health Organization originally backed the claim, they later retracted that advice and now do not recommend against nonsteroidal anti-inflammatory drug (NSAID) use.<sup>55</sup> The European Medicines Agency<sup>56</sup> and FDA<sup>57</sup> have also confirmed the lack of evidence to support a link between NSAIDs and worsening COVID-19. Regardless, NSAIDs should still be avoided in patients with cardiovascular disease, especially those with heart failure, and renal disease, because they can increase BP and cause fluid retention.

## POTENTIAL ROLE OF STATINS

It is well established that statins have vascular and myocardial anti-inflammatory effects, which may exert some potential benefit in patients with acute viral respiratory infections.<sup>58</sup> Observational studies have reported an improvement in cardiovascular outcomes, and even mortality, in statin-treated patients with influenza or pneumonia; however, a healthy user bias could be a contributing factor to these findings.<sup>59,60</sup> The randomized controlled trial data are very limited and has found conflicted results.<sup>61,62</sup> Importantly, there has been no reported harm associated with statin use in these patients, which supports the continued use of statins in patients with an indication for statin therapy, such as those with established cardiovascular disease, diabetes, or other high-risk features. This is particularly true given the higher mortality rates observed in COVID-19 patients with cardiovascular and cardiometabolic comorbidities. As previously discussed, however, dose reductions or therapy substitutions may be warranted if patients receive lopinavir/ritonavir treatment while on statin therapy (Table 1). In rare instances, patients with COVID-19 may develop rhabdomyolysis or

acute liver injury, which would require prompt statin discontinuation.

### SUPPORTIVE CARDIOVASCULAR MANAGEMENT IN PATIENTS WITH COVID-19

The spectrum of COVID-19 disease ranges from mild to severe, and it has been well described elsewhere.<sup>8</sup> Patients with, or at risk for, cardiovascular disease are at particular high risk of severe illness and mortality.<sup>9</sup> Myocardial injury, as witnessed by elevation in troponin levels, is common in patients with COVID-19,<sup>38,63</sup> and is likely to reflect demand/supply mismatch (type II) myocardial infarction or septic cardiomyopathy for which no specific therapy is recommended, other than attempting to optimize oxygen supply, delivery, and demand as much as possible by intervening on the pulmonary, hematologic, cardiac, and vascular systems. Increased troponin I identifies patients with severe COVID-19 and is associated with very high mortality, but whether myocardial injury reflects a specific pathologic mechanism of disease or a subgroup of patients with more severe disease is unclear.<sup>64</sup> Anecdotal cases of myocarditis have been reported,<sup>65,66</sup> but they seem to be rare.

An elevation in D-dimer levels<sup>38</sup> suggests an activation of the coagulation cascade in patients with COVID-19; however, an increase in thrombosis or disseminated intravascular coagulation has not been widely reported. Regardless, anticoagulation with unfractionated heparin or enoxaparin in patients with markedly elevated D-dimer levels should be considered, although precise recommendations are challenging given the lack of evidence. Recently, the International Society on Thrombosis and Haemostasis released a pragmatic statement recommending clinician's measure D-dimers, prothrombin time, and platelet count in all patients with COVID-19.<sup>67</sup> Furthermore, they also recommend a prophylactic dose of low molecular weight heparin in all patients, including those who are not critically ill, barring any contraindications. Additional study is warranted to understand the anticoagulation needs of patients with COVID-19.

For patients with COVID-19 who experience an acute coronary syndrome, access to emergency coronary angiography can become restricted in some instances, and fibrinolysis can become first-line therapy for lower risk ST-segment elevation patients to preserve personal protective equipment and prevent spread of the infection across different areas of the hospital. Hospitals should also develop protocols for ST-segment elevation management for patients with COVID-19 in collaboration with their Infection Prevention departments to optimize patient management while reducing the risk for patient and health care worker transmission.

In patients with heart failure and reduced ejection fraction, a careful review of medical treatments should be considered in case of the initiation of the aforementioned investigational drugs to treat COVID-19. When possible, guideline-directed medical therapy should be continued, but additional monitoring is warranted. Lopinavir/ritonavir may only modestly affect ACE inhibitors and ARBs, while sacubitril/valsartan levels can increase, warranting close

monitoring of BP. Lopinavir/ritonavir can increase levels of beta-blockers warranting ECG monitoring and, potentially, dose downtitration, while hydroxychloroquine and chloroquine may reduce levels of beta-blocker and require a dose uptitration.<sup>68</sup> Among mineralocorticoid receptor antagonists, spironolactone can be safely used with lopinavir/ritonavir, whereas eplerenone, which is mainly metabolized by CYP3A4, should not be coadministered. For the same reason, coadministration of ivabradine and lopinavir/ritonavir should be avoided. Digoxin levels should be followed closely in patients on lopinavir/ritonavir, hydroxychloroquine, or chloroquine.

### IMPACT OF COVID-19 ON ROUTINE CARDIOVASCULAR CARE

Limited contact with others to minimize the spread of SARS-CoV-2 during the epidemic phase of the disease is advised. This usually implies rescheduling routine follow-up visits. Options include the use of telehealth to conduct brief, focused remote visits, or postponement of visits for more stable patients. Regardless, there are some additional considerations for managing these patients. Home blood pressure monitoring devices, weight scales, heart failure telemonitoring, and other remote equipment should be offered, when possible, to augment telehealth visits. Such equipment may require training of the patients and health care providers but also may reveal unequal access to such resources. Reinforcing heart healthy lifestyle and stress management are also important given the inherent impact of social distancing and quarantine during a pandemic on daily routines and mental health. Additional medication-related considerations include ensuring patients have sufficient refills and prescribing a longer supply for maintenance medications. These represent some of the potential challenges of social isolation during the pandemic.

### CONCLUSION

In closing, SARS-CoV-2 is a novel virus that has spread rapidly throughout the world causing a potentially life-threatening disease, COVID-19, causing disproportionately high mortality among elder patients with concomitant pulmonary and cardiovascular diseases. Although no approved therapies currently exist, multiple collaborative efforts are underway to identify effective therapies and a vaccine to prevent future infection. Cardiovascular clinicians, however, may not be accustomed to the concomitant use of antivirals and immunomodulators in their patients; thus, the need to understand how these therapies might impact underlying cardiovascular conditions and medications. Despite the significant morbidity and mortality associated with COVID-19, there is an immense opportunity to enhance our understanding of how to prevent and treat such emerging infections as well as improve our understanding of the relationship between infection, immune response, and cardiovascular disease.

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