

## Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic

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PII: S0735-1097(20)34637-4

DOI: <https://doi.org/10.1016/j.jacc.2020.03.031>

Reference: JAC 27204

To appear in: *Journal of the American College of Cardiology*

Received Date: 17 March 2020

Accepted Date: 17 March 2020

Please cite this article as: Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, Brown TS, Nigoghossian CD, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM, Parikh SA, Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic, *Journal of the American College of Cardiology* (2020), doi: <https://doi.org/10.1016/j.jacc.2020.03.031>.

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## Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic

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Running Title: CV considerations in COVID19

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**Disclosures:** Dr. Madhavan reports being supported by an institutional grant by the National Institutes of Health/ National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). Dr. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to a specific type of IVC filters. Dr. Brodie receives research support from ALung Technologies, he was previously on their medical advisory board. He has been on the medical advisory boards for Baxter, BREETHE, Xenios and Hemovent. Dr. Kirtane reports Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, Philips, ReCor Medical. Personal: conference honoraria and travel/meals only. The remaining authors report no relevant conflicts of interest. Dr. Stone has received speaker or other honoraria from Cook, Terumo, QOOL Therapeutics and Orchestra Biomed; serving as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme; and equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, Valfix. Dr. Krumholz works under contract with the Centers for Medicare & Medicaid Services to support quality measurement programs; was a recipient of a research grant, through Yale, from Medtronic and the U.S. Food and Drug

Administration to develop methods for post-market surveillance of medical devices; was a recipient of a research grant with Medtronic and is the recipient of a research grant from Johnson & Johnson, through Yale University, to support clinical trial data sharing; was a recipient of a research agreement, through Yale University, from the Shenzhen Center for Health Information for work to advance intelligent disease prevention and health promotion; collaborates with the National Center for Cardiovascular Diseases in Beijing; receives payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation, from the Ben C. Martin Law Firm for work related to the Cook Celect IVC filter litigation, and from the Siegfried and Jensen Law Firm for work related to Vioxx litigation; chairs a Cardiac Scientific Advisory Board for UnitedHealth; was a participant/participant representative of the IBM Watson Health Life Sciences Board; is a member of the Advisory Board for Element Science, the Advisory Board for Facebook, and the Physician Advisory Board for Aetna; and is the co-founder of HugoHealth, a personal health information platform, and co-founder of Refactor Health, an enterprise healthcare AI-augmented data enterprise. Dr Parikh reports institutional grants/research support from Abbott Vascular, Shockwave Medical, TriReme Medical, Sumodics, Silk Road, Medical, and the NIH; consulting fees from Terumo and Abiomed; and Advisory Board participation for Abbott, Medtronic, Boston Scientific, CSI, and Philips. The other others do not report any relevant conflicts of interest.

**Acknowledgments:** The authors would like to credit Julie Der Nigoghossian for assistance with graphic design.

**Abstract**

The coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 that has significant implications for the cardiovascular care of patients. First, those with COVID-19 and preexisting cardiovascular disease (CVD) have an increased risk of severe disease and death. Second, infection has been associated with multiple direct and indirect cardiovascular complications including acute myocardial injury, myocarditis, arrhythmias and venous thromboembolism. Third, therapies under investigation for COVID-19 may have cardiovascular side effects. Fourth, the response to COVID-19 can compromise the rapid triage of non-COVID-19 patients with cardiovascular conditions. Finally, the provision of cardiovascular care may place health care workers in a position of vulnerability as they become host or vectors of virus transmission. We hereby review the peer-reviewed and preprint literature pertaining to cardiovascular considerations related to COVID-19 and highlight gaps in knowledge that require further study pertinent to patients, health care workers, and health systems.

Key-words: coronavirus, cardiovascular therapy, health system

**Abbreviations**

ACE = angiotensin converting enzyme

ARDS = acute respiratory distress syndrome

COVID-19 = coronavirus disease 2019

CV = cardiovascular

CVD: cardiovascular disease

ECMO = extracorporeal membrane oxygenation

ICU = intensive care unit

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

**Introduction**

First appearing in Wuhan, China, the coronavirus disease of 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (1,2). Given the rapid spread of this virus with consequences on an international scale, COVID-19 was declared a pandemic by the World Health Organization on March 11<sup>th</sup> 2020 (2). It is imperative that health care workers and researchers across all disciplines be aware of the potential impact that this disease can have on their respective fields and the medical community at large (3).

Based on currently observed disease patterns, cardiovascular (CV) specialists will be actively engaged in the care of patients with COVID-19. The infection may directly impact cardiovascular disease (CVD). Preexisting cardiovascular disease (CVD) may predispose to COVID-19 infection. Those with CVD who are infected by the virus have an elevated risk of adverse outcomes; and infection, itself, is associated with cardiovascular complications (4-6). Moreover, COVID-19 infection may also have numerous indirect effects relevant to CV health. The large numbers of infected people requiring care may impact optimal treatment delivery to patients with acute CV conditions. Therapeutics for COVID-19 have the potential for adverse CV effects and clinicians delivering CV care are at risk of developing the illness or become vectors for the infection. The objective of this review is to characterize the CV impact of COVID-19, its potential consequences in patients with established CVD, as well as considerations for individual patients (with and without COVID-19), health care workers, and health systems, as understanding and addressing these issues will be crucial to optimize outcomes during the current critical period and beyond.

**Methodologic Considerations**

Given the time-sensitive nature of the challenges associated with this outbreak, we reviewed the published literature (including multiple search strategies in MEDLINE with PubMed interface) and critically assessed early reports on medRxiv, a pre-print server (<https://www.medrxiv.org/>) (date of last search: March 16, 2020). Since the initial epicenter for this outbreak was from China, the majority of data on patients with COVID-19 are from this region. Although a systematic attempt was made to include

reports and viewpoints from other heavily affected countries, data related to CV risk factors or presentation were limited. This is important, since the testing strategies, care seeking behavior, and hospitalization thresholds vary in different settings and can bias numerators and denominators, influencing estimates of the impact of the virus. This selection bias in testing, care and reporting can lead to differences in prevalence estimates of pre-existing risk factors and patient presentation across the reports from various countries. Further, the majority of the existing analyses, including those related to CV complications of COVID-19 are based on retrospective and often single-center series. Accordingly, data elements were usually reported via chart review, without external prospective ascertainment. No published or completed prospective cohort studies or randomized controlled trials were present in this literature search. These issues have important implications for research priority setting, and for interpretations of the results reported herein. There is an urgent need for high quality research in this area, but at this point it is useful to review the available data.

### **Pathophysiology, Epidemiology, and Clinical Features of COVID-19**

SARS-CoV2, like other members of the Coronaviridae family, is an enveloped virus with non-segmented, single stranded, positive-sense RNA genome (1,7). A number of SARS-related coronaviruses have been discovered in bats, and a working theory is that bats may have been the initial zoonotic host for SARS-CoV2 given that its genome is 96.2% identical to a bat coronavirus (8). Studies have demonstrated that SARS-CoV2 as well as other coronaviruses can use the angiotensin-converting enzyme 2 (ACE2) protein for cell entry. ACE2 is a type I integral membrane protein which serves many important physiologic functions. It is highly expressed in lung alveolar cells, providing the main entry site for the virus into human hosts (8,9). After ligand binding, SARS-CoV2 enters cells via receptor-mediated endocytosis in a manner akin to human immunodeficiency virus (HIV) (10). ACE2 also serves a role in lung protection and therefore viral binding to this receptor deregulates a lung protective pathway, contributing to viral pathogenicity (11). Figure 1 depicts the potential mechanisms for ACE2 with regard to viral pathogenicity and lung protection, as well as the potential effects on this from renin-angiotensin-aldosterone inhibition as noted in the section on Drug Therapy and COVID-19 below.

Since initial identification, the disease has spread to over 100 countries across the world (1). As of March 16, 2020 at 11:53AM, there have been a total of 174,961 COVID-19 cases reported globally (3,813 in the United States) associated with 6,705 deaths thus far (69 in the United States), resulting in a crude case-fatality rate of 3.8% (12,13). Johns Hopkins University is making current data available: <https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6> (12). The infectivity of COVID-19 is greater than that of influenza, with an estimated  $R_0$  value (the basic reproduction number, representing viral infectivity) of 2.28 (14). Notably, the death rate associated with COVID-19 is also considerably higher compared with the most recent WHO estimate of seasonal influenza mortality rate of less than 0.1%, and may reach much higher rates in elderly patients, those with comorbidities, and absent efficient intensive care support (13). While other zoonotic coronaviruses, including the 2002-2003 severe acute respiratory syndrome (SARS) epidemic and the Middle East respiratory syndrome (MERS-CoV), had higher associated case fatality rates of 9.6% and 34.4%, respectively (15), COVID-19 has resulted in many more deaths than both of these prior outbreaks combined, an issue that is in part related to the greater infectivity and higher attack rate of this virus, leading to a larger number of infected patients (15,16). Uncertain and inconsistent disease ascertainment have resulted in variability in reported case fatality rates for several reasons, including: 1) the disease may be asymptomatic or mildly symptomatic in a large proportion of patients (15), 2) inadequate testing capabilities in most geographies, leading to frequent underdiagnosis, especially in patients with less serious illness, and 3) complications and death often ensue much later than contagion (typically between 2 and 3 weeks after infection). Notably, the appraisal of SARS-CoV-2 infection may be further complicated by asymptomatic infection in a sizable portion of individuals (as many as 20%), which may significantly contribute to further spread of infection (17)

The clinical presentation for COVID-19 is quite variable. A large study from the Chinese Center for Disease Control and Prevention demonstrated that among 72,314 patients with COVID-19 (44,672 laboratory-confirmed, 16,186 suspected, and 10,567 clinically-diagnosed), the clinical severity was reported as mild in 81.4%, severe in 13.9% and critical in 4.7% (15). The clinical characteristics of mild

COVID-19 appear to include symptoms common to other viral infections (i.e. fever, cough, dyspnea, myalgias, fatigue, and diarrhea) as well as laboratory abnormalities such as lymphopenia (18), although knowledge of the clinical feature of the disease is evolving daily (1,19). In severe cases, COVID-19 may present as pneumonia, the acute respiratory distress syndrome (ARDS), with or without both distributive and cardiogenic shock, to which elderly populations with preexisting medical comorbidities are the most vulnerable (1,6,19,20). Notably while rates of concomitant infections with other viruses and bacterial superinfections in preliminary data appear low (15), patients with the most severe clinical presentations are likely still at risk for co-infections, and unsurprisingly, worse outcomes have been noted in such cases (20,21). Children account for the minority of laboratory-confirmed cases of COVID-19 in China and appear to be less susceptible to severe disease, possibly due to stronger innate immunity, fewer comorbidities, differences in maturation of viral receptors, and/or prior exposure to other coronavirus species (22). However, moderate-to-severe illness has been described in children as well (23). Moreover, it is not clear how often children were being tested.

Since an extremely large and increasing number of patients have been diagnosed with COVID-19, identification of prognostic factors associated with morbidity and mortality are crucial. To date, no approved preventative vaccines or approved therapies are available for COVID-19, although several are being actively studied (24).

### **Prevalence of CVD in Patients with COVID-19**

The lack of widespread testing, national surveillance and standardized data collection, as well as the potential sampling bias in sicker, hospitalized patients with more comorbidities such as CVD has complicated efforts to accurately estimate the prevalence of CVD in patients with COVID-19. Moreover, there is marked variation in testing by country. A number of studies in the available literature suggest an association between preexisting CVD and severe COVID-19, which are summarized in Tables 1 and 2. A meta-analysis of six studies inclusive of 1,527 patients with COVID-19 examined the prevalence of CVD and reported the prevalence of hypertension, cardiac and cerebrovascular disease, and diabetes to be 17.1%, 16.4%, and 9.7%, respectively (4). Patients who required intensive care unit (ICU) admission



were more likely to have these comorbidities compared to non-ICU patients. Increased case-fatality rates in the previously referenced analysis of 44,672 confirmed COVID-19 cases from Wuhan, China were noted in patients with CVD (10.5%), diabetes (7.3%), hypertension (6.0%), all notably higher than the overall case-fatality rate of 2.3% (15). Several smaller cohort studies have yielded similar results suggesting higher risk for adverse events in patients with CVD who contract COVID-19, although biases related to testing and standardized data apply here as well (1,19,25-28). Notably, while reports outside of China are limited, data from Italy suggest similar mortality rates and an elevated risk for death in patients with comorbidities (29). As emerging international data become available, analysis from multinational cohorts can help inform risk stratification for severe disease especially for patients with prior CVD.

#### ***COVID-19 Outcomes and CVD: Potential Mechanisms of Increased Risk***

Mechanisms that lead to CVD are increasingly recognized to overlap with pathways that regulate immune function. For instance, age is the strongest risk factor for CVD and the effect of aging on immune function may be equally important for COVID-19 susceptibility and severity. Exemplary of this, the effect of age on the immune system is exemplified by low protective titers among 50% of adults older than 65 who receive the influenza vaccine (30,31). Other traditional CVD risk factors such as diabetes and hyperlipidemia impact immune function, and conversely, dysregulated immunologic status corresponds with elevated risk of incident CVD (32-35). Thus, prevalent CVD may be a marker of accelerated immunologic aging/dysregulation and relate indirectly to COVID-19 prognosis. An increased frequency of adverse CVD events post COVID-19 infection might also play a role in prognosis, similar to other viral infections such as influenza with mechanistic underpinnings which are complex, multi-factorial, and bi-directional (36,37). In addition, COVID-19 infection may trigger pathways unique to this pathogen which contribute to outcomes in CVD patients. For instance, higher expression of ACE2 in patients with hypertension and CVD has been postulated to enhance susceptibility to SARS-CoV2, although the data are conflicting and without clear suggestion for treatment (Figure 1) (5). Additional study is needed to understand the potential mechanistic relationships between CVD and COVID-19 outcomes.

#### ***Heart transplantation***

In addition to the mechanisms by which COVID-19 can affect patients with CVD risk factors, it is also important to consider COVID-19 in the context of an especially vulnerable group of patients, such as individuals awaiting or post heart transplantation. There are now case reports of COVID-19 infection among heart transplant patients (38,39). Two heart transplant patients in China, one with mild and one with severe disease, presented with symptoms typical of COVID-19 disease. Both were managed by withholding baseline immunosuppressive regimens and treating aggressively with high dose steroids, intravenous immunoglobulin, and antibiotics, and both survived without evidence of allograft rejection. Previous viral outbreaks have noted particularly severe infection in immunosuppressed solid organ transplant recipients (40). Formal treatment guidelines in these patients do not exist at this time. Heart allocation teams need to consider the optimal screening strategies in order to prevent severe infection in recipients including whether all donor hearts should be screened, given the existence of asymptomatic COVID-19, versus limiting screening to patients with a history of symptoms or exposure of COVID-19. During the H1N1 influenza pandemic, potential donors were screened if symptomatic or if they had significant exposure history in order to prevent infection in the recipient or as an impetus to initiate prophylaxis if the donor was positive (41). Similarly, screening recipients for a history of symptoms or exposure of COVID-19 to avoid a post-transplant flare will be reasonable to be considered. Utmost precautions in infection control must be employed when interacting with these vulnerable immunosuppressed patients.

### **Cardiovascular Sequelae Associated with COVID-19**

Figure 2 summarizes some of the potential CV sequelae which may result from COVID-19 infection. Pending larger studies, several existing reports are suggestive of SARS-CoV2 infection leading to CV complications or exacerbation of preexisting CVD (6,15,21).

#### ***Myocardial injury, myocarditis, and acute coronary syndromes***

Myocardial injury, as defined by an increased troponin level, can occur due to myocardial ischemia or non-ischemic myocardial processes including myocarditis (6,42,43). With severe respiratory infection and hypoxia, especially in the setting of severe infection and ARDS due to COVID-19, it is

likely that a number of patients will develop such injury. Elevated serum troponin levels have been described in many patients infected with COVID-19, with significant differences noted between patients who died and those who survived to discharge (21,44). In a meta-analysis of 4 studies including a total of 341 patients, standardized mean difference of cardiac troponin I levels were significantly higher in those with severe COVID-19 related illness compared to those with non-severe disease (25.6, 95% CI 6.8-44.5) (45). Reports have also suggested that acute cardiac injury – which includes not only elevation of cardiac biomarkers to  $> 99^{\text{th}}$  percentile of the upper reference limit, but also electrocardiographic and echocardiographic abnormalities – is highly prevalent in patients with COVID-19 and is associated with more severe disease and worse prognosis. Cohort studies from hospitalized patients in China estimate that such injury occurs in 7-17% of hospitalized patients with the disease (1,6,19) and is significantly more common in patients admitted to the ICU (22.2% vs. 2.0%,  $p<0.001$ ) and among those who died (59% vs. 1%,  $p<0.0001$ ) (6,8). However, troponin levels can be exacerbated in patients with renal insufficiency due to delayed excretion, which is common in patients with advanced disease. Given limited high-quality data, and the heterogeneity of definitions across the studies, standardized data collection methods are recommended using the most recent Universal Definition of Myocardial Infarction (MI) (43).

Prior studies in other coronavirus species (MERS-CoV) have demonstrated evidence of acute myocarditis using cardiac magnetic resonance imaging (46), and myocardial inflammation and damage have been reported with COVID-19 infection. Among 68 deaths in a case series of 150 patients with COVID-19, 7% were attributed to myocarditis with circulatory failure and in 33% of cases which myocarditis may have played a contributing role to the patient's demise (21). Other reports have described fulminant myocarditis in the setting of high viral load with autopsy findings of inflammatory mononuclear infiltrate in myocardial tissue (26,47,48). Pericardial involvement has not yet been reported but further study is needed. In addition, the extent to which supply and demand mismatch (Type 2 MI) in patients with underlying CVD have contributed to the CV manifestations of the syndrome is uncertain.

Case reports of acute coronary syndromes (ACS) (Type 1 MI) in the setting of COVID-19 have yet to be published. Nonetheless, the profound inflammatory response and hemodynamic changes

associated with severe disease may confer risk for atherosclerotic plaque rupture in susceptible patients (6). In this regard, analysis by Kwong and colleagues demonstrated that patients with acute respiratory infections are at elevated risk for subsequently developing acute myocardial infarction after influenza (incidence ratio [IR] 6.1, 95% CI 3.9-9.5) and after non-influenza viral illnesses including other coronavirus species (IR 2.8, 95% CI 1.2–6.2) (36). The development of care pathways and protocols for COVID-19 patients with STEMI suggest that both within and outside of China such a clinical scenario is highly probable (49).

Additionally, it is important to note potential overlapping symptomatology between ACS and COVID-19. While the predominant presenting symptoms of COVID-19 are respiratory, a case report described a patient in Italy with chest pain and electrocardiographic changes for which the cardiac catheterization lab was activated. Notably, the patient was found to be free of obstructive coronary artery disease but ultimately tested positive for COVID-19 (50). Moving forward as the virus continues to infect patients with significant CV risk factors, or established CVD, cases of ACS in the setting of COVID-19 are likely to develop. The true prevalence in this setting may be underreported given the logistical challenges associated with limited testing and cardiac catheterization laboratory availability in the setting of this outbreak. For further recommendations for the care and management of COVID-19 patients in the cardiac catheterization laboratory, please see the joint American College of Cardiology (ACC) and Society of Cardiovascular Angiography and Intervention (SCAI) guidance statement (51).

***Cardiac Arrhythmia and Cardiac Arrest.*** Cardiac arrhythmias are another common CV manifestation described in patients with COVID-19 infection. While nonspecific, heart palpitations were part of the presenting symptomatology in 7.3% of patients in a cohort of 137 patients admitted for COVID-19 disease (26). In hospitalized COVID-19 patients, cardiac arrhythmia was noted in 16.7% of 138 patients in a Chinese cohort and was more common in ICU patients compared to non-ICU patients (44.4% vs. 6.9%) (19). Unfortunately, specifics about the types of arrhythmias that occur in these patients are yet to be published or presented. High prevalence of arrhythmia might be, in part, attributable to metabolic disarray, hypoxia, neurohormonal or inflammatory stress in the setting of viral infection in

patients with or without prior CVD. However, new onset of malignant tachyarrhythmias in the setting of troponin elevation should raise suspicion for underlying myocarditis (44,52).

**Cardiomyopathy and heart failure.** Zhou and colleagues reported that heart failure was observed in 23.0% of patients with COVID-19 presentations (6). Notably, heart failure was more commonly observed than acute kidney injury in this cohort and was more common in patients who did not survive the hospitalization compared to those who did survive (51.9% vs. 11.7%). Whether heart failure is most commonly due to exacerbation of pre-existing left ventricular dysfunction versus new cardiomyopathy (either due to myocarditis or stress cardiomyopathy) remains unclear (53). Right heart failure and associated pulmonary hypertension should be also considered, in particular in the context of severe parenchymal lung disease and ARDS.

**Cardiogenic and mixed shock.** The predominant clinical presentation of COVID-19 is acute respiratory illness, which may lead to ARDS manifested as ground-glass opacities on chest imaging (54) and hypoxemia. However, similar features may be seen in the case of *de novo* or coexisting cardiogenic pulmonary edema. As such, it is important consider cardiogenic or mixed cardiac plus primary pulmonary causes of respiratory manifestations in COVID-19. Historically, right heart catheterization was used to determine pulmonary capillary wedge pressure in order to aid in this distinction, although this has been removed from the Berlin criteria used for the diagnosis of ARDS. Rather, the Berlin criteria utilize timing of symptom onset, imaging with bilateral pulmonary opacities, and lack of volume overload to identify patients with ARDS (55). In many cases, serum brain natriuretic peptide (BNP) and echocardiography can help clarify the diagnosis (56,57). However, if these tests are unclear and there remains concern for mixed presentation, pulmonary artery catheterization should be considered in select cases to assess filling pressures, cardiac output, and to guide clinical decision-making, given the different management approaches for ARDS and cardiogenic shock. Finally, it is crucial to determine whether or not a concomitant cardiogenic component is present when considering mechanical respiratory and circulatory support with extracorporeal membranous oxygenation (ECMO) or other techniques, as this may lend to changes in device selection (e.g. venovenous vs. venoarterial ECMO cannulation). Regardless, in the

most severe of infections with ARDS and necrotizing pneumonias, patient prognosis may be poor even with ECMO support. In a case series of 52 critically ill patients with COVID-19, 83.3% (5/6) of patients who were treated with ECMO did not survive. Further studies regarding the utility of ECMO support in advanced COVID-19, including which patients may (or may not) benefit and whether concomitant left ventricular venting should be done, are warranted (58).

***Venous thromboembolic disease.*** COVID-19 infected patients are likely at increased risk venous of thromboembolism (VTE). Though there are no published case series thus far, there are reports of abnormal coagulation parameters in hospitalized patients with severe COVID-19 disease (59,60). In a multicenter retrospective cohort study from China, elevated D-dimer levels ( $>1\text{g/L}$ ) were strongly associated with in-hospital death, even after multivariable adjustment (OR 18.4 95% CI 2.6-128.6,  $p=0.003$ ) (6). In another study comparing COVID-19 survivors to non-survivors, non-survivors had significantly higher D-dimer and fibrin degradation products (FDP) levels and 71.4% of non-survivors met clinical criteria for disseminated intravascular coagulation (DIC) during the course of their disease (59). In addition to DIC, critically ill patients with prolonged immobilization are inherently at high risk for VTE. Vascular inflammation may also contribute to the hypercoagulable state and endothelial dysfunction in such patients. In the setting of critically ill COVID-19 patients who demonstrate clinical deterioration as evidenced by hypoxia or hemodynamic instability, thromboembolic disease should be considered. The optimal thromboprophylactic regimen for patients hospitalized with COVID-19 related illness is not known. As such, contemporary guideline endorsed strategies should be observed (61). Given the drug-drug interactions between some antiviral treatments and direct oral anticoagulants, low molecular weight heparins, or unfractionated heparin with or without mechanical prophylaxis are likely to be preferred in acutely ill hospitalized patients.

### **Drug Therapy and COVID-19: Interactions and Cardiovascular Implications**

Data regarding antiviral therapies and other treatment strategies, as well as their potential interaction with CV medications and CV toxicities are summarized in Tables 3-5. Although currently there are no specific effective therapies for COVID-19, various pharmacologic agents are under active

investigation. As these drugs are being studied, it is important to review the potential CV side effects and interactions with other CV medications.

**Antiviral Therapy.** Antivirals are at the forefront of medications under study for the treatment of COVID-19 and the clinical trial identifiers for each are listed in Table 3. Ribavirin and remdesivir are two such agents that bind to the active site on the RNA-dependent RNA polymerase on SARS-CoV2 (62), while lopinavir/ritonavir inhibits replication of RNA virus and has evidence of a synergistic effect *in vitro* with ribavirin (63). Ribavirin and lopinavir/ritonavir are under investigation in clinical trials for COVID-19 and have been used for years as components of treatment for hepatitis C and HIV, respectively (64,65). While ribavirin has no characterized direct CV toxicity, 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 (65). Both ribavirin and lopinavir/ritonavir have the potential to affect anticoagulant dosing: ribavirin has variable effects on warfarin dosing (66) and lopinavir/ritonavir may require dose reductions or avoidance of CYP3A-mediated drugs such as rivaroxaban and apixaban (67,68).

Lopinavir/ritonavir can also influence the activity of P2Y<sub>12</sub> inhibitors through CYP3A4 inhibition, which results in decreased serum concentrations of the active metabolites of clopidogrel and prasugrel and increased serum concentrations of ticagrelor. Given the increase in serum ticagrelor levels with such medications (69,70), concomitant use with ticagrelor is discouraged in the United States and Canada due to excess in bleeding risk. Conversely, there is evidence that clopidogrel may not always provide sufficient platelet inhibition in the setting of concomitant administration of lopinavir/ritonavir, whereas this was not the case with prasugrel as assessed by the VerifyNow P2Y<sub>12</sub> assay (71,72). If P2Y<sub>12</sub> inhibition is needed during treatment with lopinavir/ritonavir, prasugrel can be used; however, if contraindicated (i.e. history of stroke or TIA, low body mass index, or active pathological bleeding), a testing-guided approach (e.g. with P2Y<sub>12</sub> platelet function assays) may be considered with alternate antiplatelet agents. Details about switching between P2Y<sub>12</sub> inhibitors have been described elsewhere (73).

Finally, metabolism of the intravenous P2Y<sub>12</sub> inhibitor, cangrelor, is independent of hepatic function, therefore a drug interaction is not expected (74).

HMG-CoA reductase inhibitors (statins) also have the potential to interact with the combination of lopinavir/ritonavir and can result in myopathy due to elevated statin levels when administered together. Lovastatin and simvastatin, in particular, are contraindicated for co-administration with lopinavir/ritonavir due to risk of rhabdomyolysis. Other statins, including atorvastatin and rosuvastatin, should be administered at the lowest possible dose but not to exceed the maximum dose stated in the package insert while on lopinavir/ritonavir (65).

Remdesivir is an investigational drug previously evaluated in the Ebola epidemic and is now being studied in patients with COVID-19. The drug is currently available in clinical trials and through compassionate use from Gilead Sciences, Inc (Foster City, California). While extensive CV toxicities and medication interactions have yet to be reported, prior evaluation of this drug during the Ebola outbreak did note the development of hypotension and subsequent cardiac arrest after loading dose in one patient (among 175 total) (75).

**Other treatments.** Table 4 presents information on other treatments being studied for COVID-19 (including ClinicalTrials.gov identifiers). In addition to antiviral medications, numerous immune-modulating and secondary medications to prevent complications that could arise from COVID-19 are currently being investigated. Chloroquine, which has been used as an antimalarial agent, blocks virus infection by increasing the endosomal pH required for virus/cell fusion, and has been demonstrated *in vitro* to have inhibitory activity in SARS-CoV2 (76,77). Chloroquine and the closely related hydroxychloroquine have the potential for intermediate-to-delayed myocardial toxicity. Risk factors include long-term exposure (>3 months), higher weight-based dose, pre-existing cardiac disease, and renal insufficiency (78). Chloroquine cardiac toxicity presents as restrictive or dilated cardiomyopathy or conduction abnormalities thought to be due to intracellular inhibition of lysosomal enzymes in the myocyte (78,79). In addition, due to effects of chloroquine on CYP2D6 inhibition, beta-blockers metabolized via CYP2D6 (such as metoprolol, carvedilol, propranolol, or labetalol) can have increased



concentration of drug requiring careful monitoring for heart rate and blood pressure shifts. Lastly, both agents are associated with a conditional risk of torsade des pointes in patients with electrolyte abnormalities or with concomitant use of QT prolonging agents. Short-term exposure to these agents, as would be expected in treatment of COVID-19, confers lower risk of these dose-duration dependent side effects.

Methylprednisolone is another drug under investigation that is currently being used to treat severe cases of COVID-19 that are complicated by ARDS (48). This steroid is known to cause fluid retention, electrolyte derangement, and hypertension as direct CV effects, and also may interact with warfarin via an undescribed mechanism. Clinicians are advised to observe for these drug interactions.

Finally, patient debilitation from severe COVID-19 may pose challenges in administering routine CV medications, ranging from antiplatelet therapy to beta-blockers, thus putting patients with or at risk of ischemic heart disease or heart failure at risk of further deterioration of their clinical condition.

***ACE2 and potential therapeutic implications:*** As the ACE2 receptor is the mechanism of entry for SARS-CoV2, some data suggest that ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) may upregulate ACE2, thereby increasing susceptibility to the virus (Figure 1) (5). In contrast other studies show that ACEi/ARB may potentiate the lung protective function of ACE2, which is an angiotensin II inhibitor (80-82). Thus, the therapeutic implications for ACEi/ARB therapy during COVID-19 infection is unclear. Overall, there is insufficient data to suggest any mechanistic connections between ACEi/ARB therapy with contracting COVID-19 or with severity illness once infected.

### **Considerations for Health Care Workers**

***Protective equipment for CV health care workers.*** The Central Illustration demonstrates key considerations for treating patients in the current era of the COVID-19 pandemic. Early reports from the outbreak have suggested that transmission occurs most commonly via respiratory droplets that are produced when an infected individual coughs or sneezes. These droplets can land on exposed mucous membranes or be inhaled into the lungs of those within close proximity and the virus may remain active on surfaces for several days (83). While the CDC had previously recommended airborne precautions for

the care of patients with COVID-19, this recommendation was recently changed such that only patients undergoing aerosol-generating procedures require airborne isolation. Recommendations made by the WHO and CDC for personal protective equipment (PPE) are in agreement that standard, contact precautions with face mask, eye protection, gown, and gloves are necessary (51).

In addition, when performing certain procedures that are aerosol-generating, such as transesophageal echocardiography, endotracheal intubation, cardiopulmonary resuscitation and bag mask ventilation, additional PPE may be required including controlled or powered air purifying respirators (CAPR/PAPR). Thorough infection prevention and control measures specific to the procedural cardiology specialties must be considered in light of the COVID-19 outbreak. Such procedures are associated with the small but quantifiable risk of complications and patient deterioration. In the event of a cardiac arrest, efforts at cardiopulmonary resuscitation causing aerosolized pathogens could result in the wide dissemination of virus particles to clinicians, health care workers, and other patients. One measure which may help protect health care workers in the setting of cardiac arrest and chest compressions is the use of external mechanical compression devices to minimize direct contact with infected patients. Another important consideration for the catheterization laboratory is appropriate post-intervention cleaning of all equipment potentially contaminated with SARS-CoV2. The necessary downtime required for cleaning may seriously impact the availability of catheterization laboratory-based treatments for other patients. As such, many hospitals are minimizing or cancelling elective procedures during the growth phase of the outbreak. Another consideration is the fact that catheterization laboratories and operating rooms are typically configured with positive pressure ventilation, and there have been reports of centers in China converting such facilities to negative pressure isolation in the setting of COVID-19 (84). Guidance and recommendations in this space will be forthcoming from interventional communities, including the ACC and SCAI (51).

**Figure 3** depicts key information summarizing considerations to prevent infection among cardiovascular providers as summarized in an infographic. Overall, as CV healthcare workers are on the front-lines treating COVID-19 infected patients, all possible measures should be implemented to reduce

the risk of exposure (85). Health care workers are at elevated risk for contracting this virus, as demonstrated by Wu and colleagues, noting 1716 of the 44,672 (3.8%) of infected individuals were healthcare workers (15). This fact emphasizes the need for self-protection with PPE before caring for potentially exposed COVID-19 patients, and provides further rationale for delaying elective procedures. In teaching hospitals, it is imperative to minimize exposure among trainees and non-essential staff (e.g. medical students) not only for their own safety and that of their patients, but also for conservation of PPE, and for avoiding the unnecessary increase in the number of asymptomatic vectors. Finally, provider-to-provider transmission is also a major concern, especially in the setting of emergency or suboptimal logistics, or when devices for PPE have become scarce.

***Triaging CV patients and visits.*** There are numerous considerations specific to the care of CV patients that should be taken into account in order to minimize risk for COVID-19 transmission to patients and healthcare workers, which are outlined in Table 7. One important mechanism to help prevent transmission is the use of telemedicine. This technology, already utilized by numerous large health care systems around the world, is ideal in public health crises as it allows for patients to be triaged while minimizing exposure of patients and health care workers to potential infection. Additionally, telemedicine provides an opportunity for specialists that might not otherwise be available to evaluate patients. While there are currently barriers to the widespread implementation of telemedicine such as coordination of testing in patients triaged as high risk, this is a technology that will likely prove important to promote viral containment (86). Other essential principles are to minimize non-essential/non-urgent in-person provider-patient interactions as much as possible (i.e. social distancing), and limiting elective cardiac catheterization, operating room and echocardiographic procedures. If such procedures are necessary, the number of required personnel should be kept to a minimum.

#### **Considerations for Health Systems and Management of Non-Infected Cardiovascular Patients**

***CV societal leadership.*** Recently, due to potential health concerns for the cardiovascular health care workers and investigators, and in order to avert deterioration of the COVID-19 outbreak, the American College of Cardiology made the unprecedented but appropriate decision to cancel the 2020

Scientific Sessions meeting. Similarly, a number of medical conferences around the world are either being cancelled or postponed (87). Additionally, given the clear implications of this pandemic on CV care, numerous societies have already weighed in with guidance statements, which are summarized in Table 6. The ACC Clinical Bulletin provides a practical clinical summary about key implications and recommendations for CV care of COVID-19 patients (88). The ESC Council on Hypertension and European Society of Hypertension statements acknowledge the questions regarding ACEi and ARB therapy in the setting of COVID-19 patients (38,89). These societies as well as a number of others agree that further data would be vital to inform decisions on adjusting regimens of these agents in the setting of this outbreak (38,89-92). Moving forward, these important CV societies among other large physician groups and health systems will be critical allies to advance the knowledge generation and CV care in patients infected with this virus.

***Preparing for hospital surges and prioritizing care for the critically ill.*** A comprehensive package of measures is required for hospital systems to fully prepare for COVID-19 (Table 5). A significant increase in COVID-19 patients should be anticipated. At the same time, provisions for general health services for acute and severe chronic illnesses must be maintained. Specifically, regarding CV care, as the pandemic surges, hospitals may prioritize the treatment of severe and high-risk patients and enact policy to prevent overwhelming of the healthcare system by the "worried well." Given concerns of hospitals exceeding capacity, specific protocols will need to be developed for the care of CV patients while preserving limited in-patient resources and minimizing provider and patient exposures. There are reports of individual centers developing alternate ST-segment-elevation myocardial infarction (STEMI) pathways in the setting of the COVID-19 crisis, such as utilizing fibrinolytic therapy if delays to primary PCI are anticipated when hospitals are at capacity or staffing for the catheterization lab is inadequate (49). Additionally, repurposing cardiac ICUs as medical ICUs for the care of patients with COVID-19 will likely become necessary, but may limit the quality of specialty care for CV patients. Given the need for ICU beds after cardiac surgery, medical management or percutaneous interventional approaches may need to be preferentially considered for urgent scenarios that cannot wait (e.g. percutaneous coronary

intervention rather than coronary artery bypass graft surgery or transcatheter valve solutions rather than surgery) to minimize ICU bed utilization. Furthermore, as aforementioned, appropriate use and careful selection of ECMO-appropriate patients as well as having established ECMO protocols for COVID-19 patients are important strategies to consider (58).

***Need for education.*** Information on the most up to date evidence surrounding management and treatment of patients with COVID-19 should be widely disseminated and freely available, and should be provided in illustrative formats (e.g. infographics) that improve public knowledge and understanding. The free flow of communication between healthcare workers and hospitals is paramount to effectively combat the pandemic. The care of patients with COVID-19 will require the expertise of many specialty services including pulmonology/critical care, infectious diseases, cardiology, surgery, pharmacy, and hospital administration among others. Optimal infection control and treatment strategies for COVID-19 should be shared with the entire healthcare community. Accordingly, every effort must be made to provide clear and unambiguous information to patients and decision-makers, countering myths and false news which may generate panic or false optimism. As the evidence base surrounding COVID-19 and its management is evolving on a daily basis, the dissemination of accurate information must occur real-time.

***Ethical challenges.*** The unprecedented challenge represented by COVID-19 has brought novel and dramatic ethical dilemmas, ranging from policy issues (e.g. focusing on containment and mitigation vs. herd immunity), as well as clinical dilemmas (e.g. considering all patients alike vs triaging patients according to age, comorbidities and expected prognosis, similar to other catastrophic circumstances). Close interaction between patient advocates, government officials and regulators, as well as physician groups, hospital administrators and other societal leaders will be essential to navigate these ethical challenges.

## **Conclusions and Future Directions**

The COVID-19 pandemic has affected hundreds of thousands of patients and poses a major health threat on an international scale. The CV community will play a key role in the management and treatment of patients affected by this disease, and in addition in providing continuity of care to non-

infected patients with underlying CVD. In the coming months, efforts towards evaluating new therapies will be crucial to the treatment of this virus, and as this process develops, further appreciation of the intricate interplay between COVID-19, CVD, and the various stakeholders involved including patients, health care workers, and health care systems will be crucial to improving outcomes in at-risk and infected patients. Prospective randomized clinical trials and cohort studies are ongoing and will be important to helping treat patients affected by this virus.

A number of theories exist regarding the elevated risk for adverse events for patients with CVD who develop COVID-19. In particular, better understanding of the relationship between the ACE2 protein, antihypertensive agent use and COVID-19 prognosis will have important implications for patients with both COVID-19 and CVD. In this regard an ongoing randomized trial evaluating recombinant ACE2 in the setting of COVID-19 may help provide mechanistic information in patients infected with this virus (ClinicalTrials.gov Identifier: NCT04287686). Outside of the scope of individual trials, concerted efforts by all health care workers and providers and incisive leadership are required to help mitigate the health risk to population at large, as well as to CV health care workers, as demonstrated by the difficult decision to cancel the 2020 American College of Cardiology Scientific Sessions. Efficient use of resources, including leveraging of the tele-health capabilities, and optimal adherence to preventative population-wide and provider-level measures will enable the transition from this critical period until the disease outbreak is contained.

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**Figure Legend**

**Figure 1.** Postulated relationship between SARS-CoV2 and ACE2 receptor. SARS-CoV2 binds to ACE2 receptor via spike protein, which facilitates entry into the cell. Renin-angiotensin-aldosterone system (RAAS) blockers upregulate ACE2 expression thereby increasing viral entry and replication (top panel). ACE2 inhibits production of angiotensin II, which is a potent pro-inflammatory agent in the lung and leads to lung injury. RAAS blockers both directly inhibit production of angiotensin II and may also increase levels of ACE2, thereby indirectly inhibiting angiotensin II (bottom panel).

**Figure 2.** Risk factors for complications and cardiovascular sequelae of COVID-19. Risk factors for complications in patients afflicted with COVID-19 and potential cardiovascular issues that may result of this disease process.

**Figure 3.** Infographic with important considerations regarding COVID-19 for cardiovascular providers by specialty.

Central Illustration: Key considerations for patients with established cardiovascular disease (CVD), patients without CVD, and for health care workers and health care systems in the setting of the COVID-19 outbreak.



**Table 1. Relative Frequency of Cardiovascular Risk Factors or Underlying Cardiovascular Conditions in Available COVID-19 Cohorts, and Representative Parent Populations**

|                                                 | Cardiovascular disease    | Diabetes     | Hypertension | Smoking      | Coronary Artery Disease | Cerebrovascular Disease |
|-------------------------------------------------|---------------------------|--------------|--------------|--------------|-------------------------|-------------------------|
| Guan et al 2020 (28)<br>(N=1099)                | --                        | 81 (7.3%)    | 165 (15.0%)  | 158 (14.4%)  | 27 (2.5%)               | 15 (1.4%)               |
| Zhou et al 2020 (93)<br>(N=191)                 | --                        | 36 (18.8%)   | 58 (30.4%)   | 11 (5.8%)    | 15 (7.9%)               | --                      |
| Wang et al 2020 (19)<br>(N=138)                 | 20 (14.5%)                | 14 (10.1%)   | 43 (31.2%)   | --           | --                      | 7 (5.1%)                |
| Huang et al 2020 (1)<br>(N=41)                  | 6 (14.6%)                 | 8 (19.5%)    | 6 (14.6%)    | 3 (7.3%)     | --                      | --                      |
| Ruan et al 2020 (21)<br>(N=150)                 | 13 (8.7%)                 | 25 (16.7%)   | 52 (34.7%)   | --           | --                      | 12 (8.0%)               |
| Wu et al 2020 (27)<br>(N=201)                   | 8 (4.0%)                  | 22 (10.9%)   | 39 (19.4%)   | --           | --                      | --                      |
| Wu et al 2020 (15) <sup>C</sup><br>(N=44,672)   | 4690 (10.5%) <sup>B</sup> | 3261 (7.3%)  | 2903 (6.5%)  | --           | --                      | --                      |
| Fang et al 2020 <sup>C, D</sup><br>(N=2818)     | 233 (8.3%) <sup>A</sup>   | 206 (7.3%)   | 376 (13.3%)  | --           | --                      | --                      |
| Lu et. al. 2018 (94) <sup>E</sup><br>(N=12,654) | 1455 (11.5%)              | 2125 (16.8%) | 4884 (38.6%) | 4985 (39.4%) |                         | 278 (2.2%)              |

<sup>A</sup> To date, no publications have described these statistics for COVID-19 patients from other areas including South Korea, Iran, Italy, Spain, and others. Therefore, the comparator parent population was chosen from China.

<sup>B</sup> Composite cardiovascular + cerebrovascular disease

<sup>C</sup> These studies by Wu et al and Fang et al include a large, population-based dataset and a meta-analysis, respectively, from China that are inclusive of the other displayed cohort studies

<sup>D</sup> Reference: Fang et al 2020. Clinical Characteristics of Coronavirus Pneumonia 2019 (COVID-19): An Updated Systematic Review. medRxiv doi: <https://doi.org/10.1101/2020.03.07.20032573>

<sup>E</sup> Chinese population prior to COVID-19 included for comparison. Please note that disease ascertainment has been different in this study compared with studies of patients with COVID-19.

**Table 2. Association Between Underlying Cardiovascular Risk Factors (A), Known Cardiovascular Disease (B) and Outcomes in COVID-19<sup>A</sup>**

|                                |                           | Outcome Variable        | Guan et al 2020 (28)*<br>N=1090 | Zhou et al 2020 (93)<br>N=191 | Wang et al 2020 (19)<br>N=138 | Huang et al 2020 (1)<br>N=41 | Ruan et al 2020 (5)<br>N=150 | Wu et al 2020 (27) <sup>B</sup><br>N=201 |
|--------------------------------|---------------------------|-------------------------|---------------------------------|-------------------------------|-------------------------------|------------------------------|------------------------------|------------------------------------------|
| A. Cardiovascular Risk Factors | Diabetes                  | ICU vs. non-ICU         | --                              | --                            | 8 (22.2%) vs. 6 (5.9%)        | 1 (7.7%) vs. 7 (25.0%)       | --                           | --                                       |
|                                |                           | Severe vs. non-severe   | 28 (16.2%) vs. 53 (5.7%)        | --                            | --                            | --                           | --                           | --                                       |
|                                |                           | Dead vs. alive          | --                              | 17 (31.4%) vs. 19 (13.9%)     | --                            | --                           | 12 (17.6%) vs. 13 (15.9%)    | 11 (25.0%) vs. 5 (12.5%)                 |
|                                | Hypertension              | ICU vs. non-ICU         | --                              | --                            | 21 (58.3%) vs. 22 (21.6%)     | 2 (15.4%) vs. 4 (14.3%)      | --                           | --                                       |
|                                |                           | Severe vs. non-severe   | 41 (23.7%) vs. 124 (13.4%)      | --                            | --                            | --                           | --                           | --                                       |
|                                |                           | Dead vs. alive          | --                              | 26 (48.1%) vs. 32 (23.4%)     | --                            | --                           | 29 (42.6%) vs. 23 (28.0%)    | 16 (36.4%) vs. 7 (17.5%)                 |
|                                | Smoking                   | ICU vs. non-ICU         | --                              | --                            | --                            | 0 vs. 3 (10.7%)              | --                           | --                                       |
|                                |                           | Severe vs. non-severe   | 38 (22.0%) vs. 130 (14.0%)      | --                            | --                            | --                           | --                           | --                                       |
|                                |                           | Dead vs. alive          | --                              | 5 (9.3%) vs. 6 (4.4%)         | --                            | --                           | --                           | --                                       |
|                                | B. Cardiovascular Disease | Coronary artery disease | ICU vs. non-ICU                 | --                            | --                            | 9 (25.0%) vs. 11 (10.8%)     | --                           | --                                       |
| Severe vs. non-severe          |                           |                         | 10 (5.8%) vs. 17 (1.8%)         | --                            | --                            | --                           | --                           | --                                       |
| Dead vs. alive                 |                           |                         | --                              | 4 (7.4%) vs. 2 (1.5%)         | --                            | --                           | --                           | --                                       |
| Cerebrovascular disease        |                           | ICU vs. non-ICU         | --                              | --                            | 6 (16.7%) vs. 1 (1.0%)        | --                           | --                           | --                                       |
|                                |                           | Severe vs. non-severe   | 4 (2.3%) vs. 11 (1.2%)          | --                            | --                            | --                           | --                           | --                                       |
|                                |                           | Dead vs. alive          | --                              | --                            | --                            | --                           | 7 (10.3%) vs. 5 (6.1%)       | --                                       |
| Cardiovascular disease         |                           | ICU vs. non-ICU         | --                              | --                            | --                            | 3 (23.0%) vs. 3 (10.7%)      | --                           | --                                       |
|                                |                           | Severe vs. non-severe   | --                              | --                            | --                            | --                           | --                           | --                                       |
|                                |                           | Dead vs. alive          | --                              | --                            | --                            | --                           | 13 (19.1%) vs. 0 (10.0%)     | 4 (9.1%) vs. 4 (10.0%)                   |

<sup>A</sup>Only a few studies, with single center experience have presented data to date, which limits the generalizability of the findings, and the confidence in the point estimates.<sup>B</sup>This study used multivariable modeling for outcome of death for each CV risk factor for CVD

**Table 3. Antiviral Therapies Currently being Studied for COVID-19: Potential Cardiovascular Interactions and Toxicities**

| <b>Antiviral Therapy</b>        | <b>ClinicalTrials.gov Identifiers</b>                                                                                               | <b>Mechanism of Action</b>                                                                            | <b>CV Drug Class Interactions</b>                                | <b>CV Adverse Effects</b>                                                               |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| <b>Ribavirin</b>                | NCT04276688<br>NCT00578825                                                                                                          | Inhibits replication of RNA and DNA viruses                                                           | Anticoagulants*                                                  | Unknown                                                                                 |
| <b>Lopinavir/<br/>Ritonavir</b> | NCT04252885<br>NCT04275388<br>NCT04276688<br>NCT04286503<br>NCT02845843<br>NCT04307693<br>NCT04261907<br>NCT04295551<br>NCT00578825 | Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A metabolism increasing levels of lopinavir | Antiplatelets*<br>Anticoagulants*<br>Statin*<br>Antiarrhythmics* | -Altered cardiac conduction: QTc prolongation, high degree AV block, torsade de pointes |
| <b>Remdesevir</b>               | NCT04302766<br>NCT04280705<br>NCT04292899<br>NCT04292730                                                                            | Nucleotide-analog inhibitor of RNA-dependent RNA polymerases                                          | Unknown                                                          | Unknown                                                                                 |

\*Indicates drug class interactions. Table 5 summarizes specific recommendations in the setting of medication interactions.

**Table 4. Other Therapies Being Studied for COVID-19: Potential Cardiovascular Interactions and Toxicities**

| <b>Therapy</b>                             | <b>ClinicalTrials.gov Identifiers</b>                                                                 | <b>Mechanism of Action</b>                                                                                                                 | <b>CV Drug Interactions</b> | <b>CV Adverse Effects</b>                                                                                                                                                                                                                                |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Bevacizumab</b>                         | NCT04275414                                                                                           | Evidence has revealed higher VEGF levels in COVID-19 patients. By inhibiting VEGF, can decrease vascular permeability and pulmonary edema. | Unknown                     | -Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy<br>-Severe hypertension<br>-Thromboembolic events                                                                                                                              |
| <b>Chloroquine/<br/>Hydroxychloroquine</b> | NCT04286503<br>NCT04303507<br>NCT04307693<br>NCT04261517<br>NCT04303299                               | Alters endosomal pH required for virus/cell fusion                                                                                         | Antiarrhythmics*            | -Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy<br>-Altered cardiac conduction: AV block, bundle branch block, torsade de pointes, ventricular tachycardia/fibrillation                                                        |
| <b>Eculizumab</b>                          | NCT04288713                                                                                           | Inhibits complement activation                                                                                                             | Unknown                     | - Hypertension, tachycardia, peripheral edema                                                                                                                                                                                                            |
| <b>Fingolimod</b>                          | NCT04280588                                                                                           | Inhibits lymphocytes through sphingosine-1 phosphate regulation                                                                            | Antiarrhythmics             | - Hypertension, first and second degree AV block, bradycardia, QTc prolongation<br>-Contraindicated after myocardial infarction, unstable angina, CVA/TIA, ADHF<br>- Contraindication with: high degree AV block, sick sinus syndrome, QTc $\geq$ 500 ms |
| <b>Interferon</b>                          | NCT04275388<br>NCT04273763<br>NCT04276688<br>NCT02845843<br>NCT04293887<br>NCT04251871<br>NCT04291729 | Immune activation                                                                                                                          | Unknown                     | - Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy<br>- Reports of: hypotension, arrhythmia, cardiomyopathy, myocardial infarction                                                                                               |
| <b>Pirfenidone</b>                         | NCT04282902                                                                                           | Antifibrotic ability, possible IL-1 $\beta$ and IL-4 inhibition to reduce cytokine storm and resultant pulmonary                           | Unknown                     | Unknown                                                                                                                                                                                                                                                  |

|                           |                            |                                                  |                                                                            |                                                                                      |
|---------------------------|----------------------------|--------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
|                           |                            | fibrosis                                         |                                                                            |                                                                                      |
| <b>Methylprednisolone</b> | NCT04273321<br>NCT04244591 | Alters gene expression<br>to reduce inflammation | Anticoagulants*                                                            | - Fluid retention,<br>- Electrolyte disturbances<br>- Hypertension                   |
| <b>Tocilizumab</b>        | NCT04306705                | Inhibits IL-6 receptor                           | Possibility of increasing<br>metabolism of medications:<br>Unknown effects | -Hypertension, increased serum<br>cholesterol<br>-No known effect on QTc<br>interval |

\*Indicates drug class interactions. Table 5 summarizes specific recommendations in the setting of medication interactions. ADHF = acute decompensated heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack.

**Table 5. Recommendations Regarding Dosing and Adjustment in the Setting of Medication Interactions**

| Therapy                    | Specific Interaction                                                                      | MOA of Drug Interaction and Specific Dose Adjustments                                                                                                                                                                                          | Other Notes                                                                                                                                            |
|----------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ribavirin</b>           | <u><b>Anticoagulants</b></u><br>Warfarin                                                  | Unknown mechanism of action:<br>No dosage adjustment recommended.                                                                                                                                                                              | Monitor INR                                                                                                                                            |
| <b>Lopinavir/Ritonavir</b> | <u><b>Anticoagulants</b></u><br>• Apixaban<br>• Rivaroxaban                               | CYP3A4 inhibition:<br>Apixaban should be administered at 50% of dose (do not administer if requirement 2.5 mg per day).<br>Rivaroxaban should not be co-administered.                                                                          | Dabigatran and warfarin can be administered with caution                                                                                               |
|                            | <u><b>Antiplatelet</b></u><br>• Clopidogrel<br>• Ticagrelor                               | CYP3A4 inhibition:<br>Diminished effect of clopidogrel.<br>Do not co-administer. Increased effect of ticagrelor. Do not co-administer.                                                                                                         | Consider prasugrel if no contraindications. If other agents used, consider a testing-guided approach (e.g. P2Y <sub>12</sub> platelet function assay). |
|                            | <u><b>Statin</b></u><br>• Atorvastatin<br>• Rosuvastatin<br>• Lovastatin<br>• Simvastatin | OATP1B1 and BCRP inhibition:<br>Rosuvastatin should be adjusted to maximum dose 10 mg/day.<br><br>CYP3A4 inhibition:<br>Atorvastatin should be adjusted to maximum dose 20 mg/day<br>Lovastatin and simvastatin should not be co-administered. | Start at lowest possible dose of rosuvastatin and atorvastatin and titrate up. Pravastatin and pitavastatin can also be considered.                    |
|                            | <u><b>Antiarrhythmics</b></u><br>• QT-prolonging medication<br><br>• Digoxin              | P-glycoprotein inhibition:<br>Monitor digoxin level for possible dose reduction.                                                                                                                                                               | Use cautiously with antiarrhythmics                                                                                                                    |

|                                         |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                           |                                               |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>Chloroquine / Hydroxychloroquine</b> | <p><b><u>Beta Blockers</u></b></p> <ul style="list-style-type: none"> <li>metoprolol, carvedilol, propranolol, labetalol</li> </ul> <p><b><u>Antiarrhythmics</u></b></p> <ul style="list-style-type: none"> <li>QT-prolonging agents</li> <li>Digoxin</li> </ul>                                                                          | <p>CYP 2D6 inhibition:<br/>Dose reduction for beta blockers may be required.</p> <p>P-glycoprotein inhibition:<br/>Monitor digoxin level for possible dose reduction.</p> | Use cautiously with antiarrhythmics           |
| <b>Fingolimod</b>                       | <p><b><u>Bradycardia-Causing Agents:</u></b></p> <ul style="list-style-type: none"> <li>Beta blockers, Calcium channel blockers, Ivabradine</li> </ul> <p><b><u>Antiarrhythmics</u></b><br/>QT-Prolonging Medications:</p> <ul style="list-style-type: none"> <li>Class 1A Antiarrhythmics</li> <li>Class III Antiarrhythmics)</li> </ul> | Sphingosine-1-phosphate receptor inhibition (on atrial myocytes): do not co-administer with class IA and III antiarrhythmics.                                             | Use cautiously with other QT-prolonging drugs |
| <b>Methylprednisolone</b>               | <p><b><u>Anticoagulants</u></b></p> <ul style="list-style-type: none"> <li>Warfarin</li> </ul>                                                                                                                                                                                                                                            | Unknown mechanism: Dose adjust based on INR.                                                                                                                              | Monitor INR                                   |

INR = international normalized ratio; MOA = mechanism of action

**Table 6. Cardiovascular Society Guideline Key Considerations with regard to CVD and COVID-19**

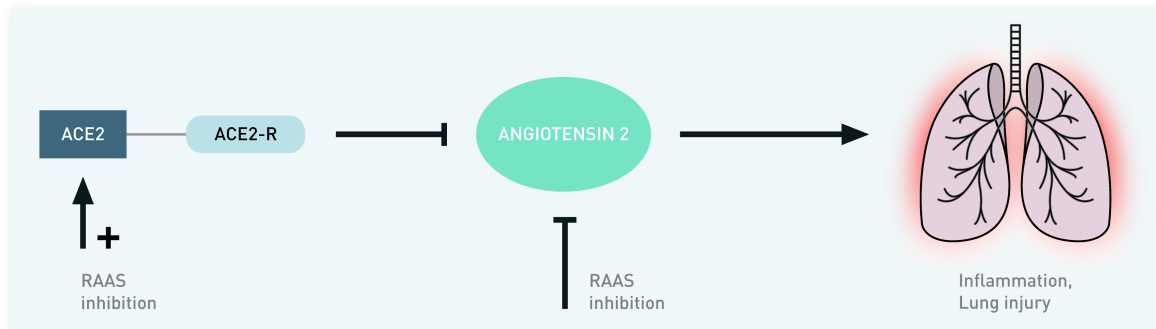
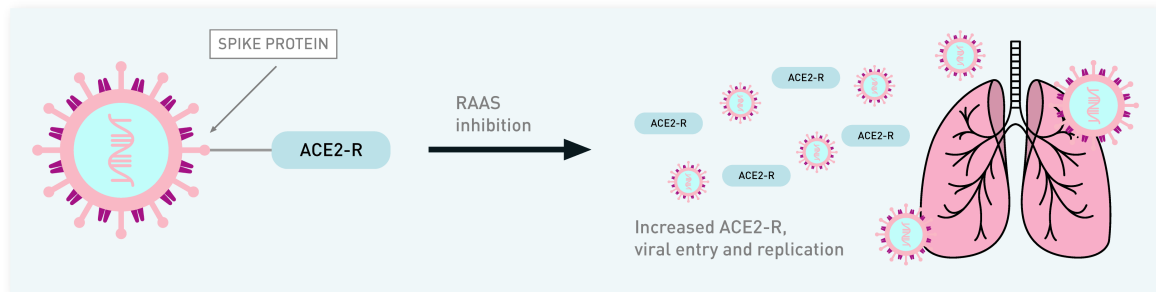
| <b>Society/Guideline</b>                                      | <b>Key Recommendations</b>                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ACC Clinical Guidance (88)</b>                             | <ul style="list-style-type: none"> <li>• Establish protocols for diagnosis, triage, isolation of COVID-19 patients with CVD or CV complications</li> <li>• Develop acute myocardial infarction-specific protocols (i.e. PCI and CABG) for COVID-19 outbreak</li> </ul>                                                                |
| <b>ESC Council on Hypertension Statement on COVID-19 (89)</b> | <ul style="list-style-type: none"> <li>• Patients with hypertension should receive treatment with ACEi and ARB according to 2018 ESC/ESH guidelines despite COVID-19 infection status (95)</li> <li>• In, the case of shock, health care workers should continue or discontinue ACEi and ARB therapy on case-by-case basis</li> </ul> |
| <b>European Society of Hypertension (38)</b>                  | <ul style="list-style-type: none"> <li>• As above</li> </ul>                                                                                                                                                                                                                                                                          |
| <b>Hypertension Canada (90)</b>                               | <ul style="list-style-type: none"> <li>• Patients with hypertension should continue their home blood pressure medical regimen</li> </ul>                                                                                                                                                                                              |
| <b>Canadian Cardiovascular Society (91)</b>                   | <ul style="list-style-type: none"> <li>• Continuation of ACEi, ARB, and ARNI therapy is strongly recommended in COVID-19 patients</li> </ul>                                                                                                                                                                                          |
| <b>Internal Society of Hypertension (92)</b>                  | <ul style="list-style-type: none"> <li>• Endorse the ESC Hypertension Statement (as above)</li> </ul>                                                                                                                                                                                                                                 |

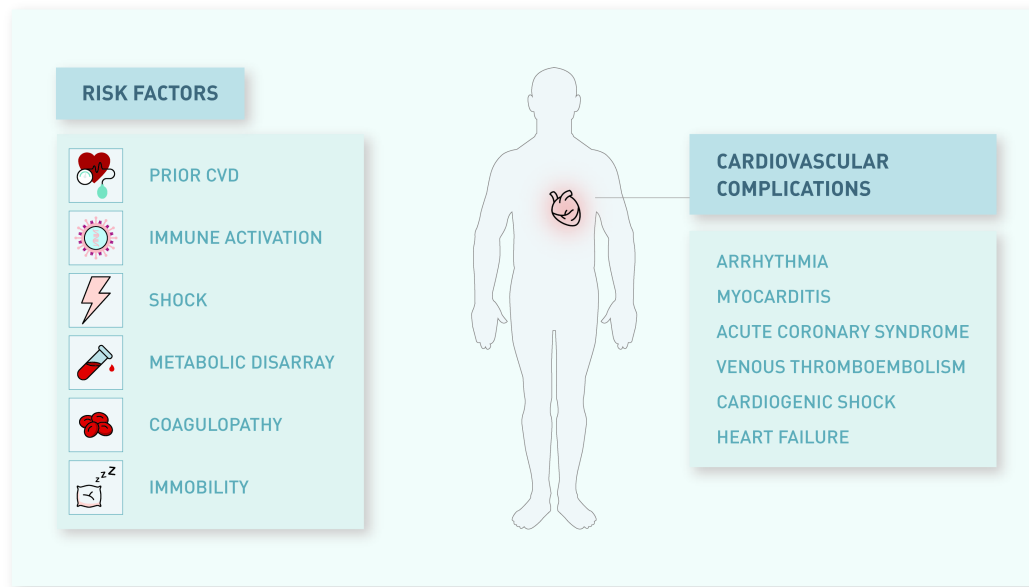
ACC = American College of Cardiology; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; COVID-19 = coronavirus disease 2019; CV = cardiovascular; CVD = cardiovascular disease; ESC = European Society of Cardiology; ESH = European Society of Hypertension



**Table 7. Considerations for Cardiovascular Health Care Workers and Health Systems Regarding COVID-19 and CVD**

| <b>Providers</b>                                                                                                                                                                                                                                          | <b>Health Systems</b>                                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>E-visits/telehealth for triage and patient management, when feasible</li> <li>Adherence to guidelines for optimal use of PPE</li> </ul>                                                                            | <ul style="list-style-type: none"> <li>Providing and expanding the knowledge and infrastructure for e-visits/telehealth</li> <li>Preparing sufficient PPE for patient families and healthcare personnel</li> </ul>                          |
| <ul style="list-style-type: none"> <li>Self-reporting symptoms, if present, and halting the role as provider in case symptoms arise</li> <li>Limit elective procedures (i.e. echocardiography, cardiac catheterization) if not urgent/emergent</li> </ul> | <ul style="list-style-type: none"> <li>Improving patient and public education regarding indications for quarantine versus hospital presentation</li> <li>Improve testing availability so appropriate containment can be achieved</li> </ul> |





**MINIMIZING COVID-19 EXPOSURE:**

Key Considerations for Cardiovascular Disease Providers

**PROCEDURAL CARDIOLOGY**

Interventional / electrophysiology / cardiac surgery

- Cancel elective procedures
- Minimize staffing in urgent / emergent cases
- Use negative pressure catheterization labs / operating rooms for urgent procedures
- Consider fibrinolysis in case PCI is not feasible

**CARDIAC CRITICAL CARE**

- Wear appropriate PPE according to institutional / national / international guidelines
- Use airborne PPE with intubation and ACLS
- Favor external compression devices for CPR

**ECHOCARDIOGRAPHY**

- Cancel elective procedures
- Use bedside studies
- Clean the machines and probes appropriately before and after each use
- Shorten exam length (e.g. fewer views)
- Use airborne PPE with TEE

**OVERALL GOAL**

Provide high quality care for patients with cardiovascular disease while minimizing infection risk to healthcare providers.

**OUTPATIENT CARDIOLOGY**

- Cancel in-person visits
- Utilize telemedicine

**INPATIENT CARDIOLOGY**

- Limit in-person consultation
- Utilize telehealth

**CARDIOLOGY TEACHING SERVICES**

- Minimize non-essential staff (e.g. medical students)
- Avoid large group rounds
- Develop over-the-phone rounds

