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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic

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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 pre-existing cardiovascular disease 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 hosts or vectors of virus transmission. We hereby review the peer-reviewed and pre-print reports 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. (J Am Coll Cardiol 2020;75:2352–71)
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First appearing in Wuhan, China, coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (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, 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 affect cardiovascular disease (CVD). Pre-existing 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 CV 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 affect 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 becoming 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 reports (including multiple search strategies in MEDLINE with PubMed interface) and critically assessed early reports on medRxiv, a pre-print server (date of last search: March 16, 2020). Because 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, because 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. Furthermore, 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 publications 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-CoV-2, like other members of the Coronaviridae family, is an enveloped virus with nonsegmented,

ABBREVIATIONS AND ACRONYMS

ACE2 = angiotensin-converting enzyme 2

ARB = angiotensin receptor blocker

ARDS = acute respiratory distress syndrome

CI = confidence interval

COVID-19 = coronavirus disease 2019

CV = cardiovascular

CVD = cardiovascular disease

ECMO = extracorporeal membrane oxygenation

ICU = intensive care unit

MI = myocardial infarction

PPE = personal protective equipment

RNA = ribonucleic acid

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

Diseases in Beijing; has received payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation; has received payment from the Ben C. Martin Law Firm for work related to the Cook CELECT inferior vena cava filter litigation; has received payment from the Siegfried and Jensen Law Firm for work related to Vioxx litigation; has chaired the Cardiac Scientific Advisory Board for UnitedHealth; was a participant/participant representative of the IBM Watson Health Life Sciences Board; has served on the Advisory Boards of Element Science and Facebook; has served on the Physician Advisory Board for Aetna; and cofounded HugoHealth, a personal health information platform, and Refactor Health, an enterprise health care artificial intelligence-augmented data enterprise. Dr. Parikh has received institutional grants/research support from Abbott Vascular, Shockwave Medical, TriReme Medical, Sumodics, Silk Road Medical, and the National Institutes of Health; has received consulting fees from Terumo and Abiomed; and has served on the Advisory Boards of Abbott, Medtronic, Boston Scientific, CSI, and Philips. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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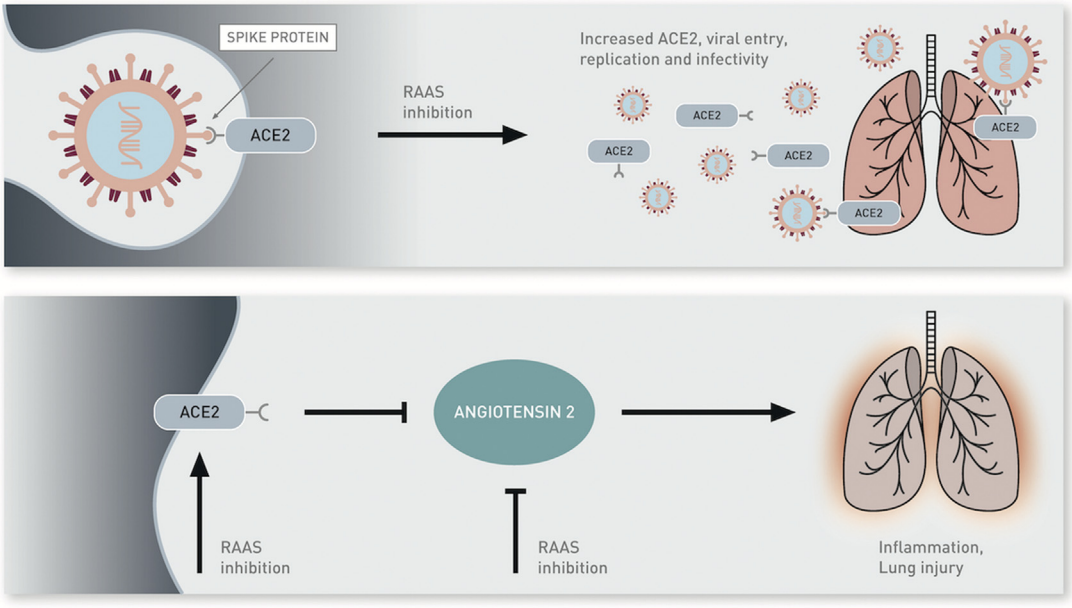
single-stranded, positive-sense ribonucleic acid (RNA) genome (1,7). A number of SARS-related coronaviruses have been discovered in bats, and a working theory is that bats may have been the initial zoonotic host for SARS-CoV-2 given that its genome is 96.2% identical to a bat coronavirus (8). Studies have demonstrated that SARS-CoV-2 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 that 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-CoV-2 enters cells via receptor-mediated endocytosis in a manner akin to human immunodeficiency virus (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.

HIGHLIGHTS

- Patients with pre-existing CVD appear to have worse outcomes with COVID-19.
- CV complications include biomarker elevations, myocarditis, heart failure, and venous thromboembolism, which may be exacerbated by delays in care.
- Therapies under investigation for COVID-19 may have significant drug-drug interactions with CV medications.
- Health care workers and health systems should take measures to ensure safety while providing high-quality care for COVID-19 patients.

Since initial identification, the disease has spread to over 100 countries across the world (1). As of March 16, 2020, at 11:53 AM, 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

FIGURE 1 Postulated Relationship Between SARS-CoV-2 and ACE2



Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to angiotensin-converting enzyme 2 (ACE2) via spike protein, which facilitates entry into the cell. It is hypothesized that renin-angiotensin-aldosterone system (RAAS) inhibition may up-regulate ACE2 expression, thereby increasing viral entry and replication **(top)**. ACE2 reduces levels of angiotensin II, which is a potent proinflammatory agent in the lungs and can contribute to lung injury. RAAS inhibitors may block the production or function of angiotensin II and potentially also increase levels of ACE2, thereby indirectly inhibiting angiotensin II **(bottom)**.

TABLE 1 Relative Frequency of CV Risk Factors or Underlying CV Conditions in Available COVID-19 Cohorts and Representative Parent Populations

First Author, Year (Ref. #)	CVD	Diabetes	Hypertension	Smoking	Coronary Artery Disease	Cerebrovascular Disease
Guan et al. 2020 (29) (N = 1,099)	–	81 (7.3)	165 (15.0)	158 (14.4)	27 (2.5)	15 (1.4)
Zhou et al. 2020 (6) (N = 191)	–	36 (18.8)	58 (30.4)	11 (5.8)	15 (7.9)	–
Wang et al. 2020 (20) (N = 138)	20 (14.5)	14 (10.1)	43 (31.2)	–	–	7 (5.1)
Huang et al. 2020 (1) (N = 41)	6 (14.6)	8 (19.5)	6 (14.6)	3 (7.3)	–	–
Ruan et al. 2020 (22) (N = 150)	13 (8.7)	25 (16.7)	52 (34.7)	–	–	12 (8.0)
Wu et al. 2020 (28) (N = 201)	8 (4.0)	22 (10.9)	39 (19.4)	–	–	–
Wu et al. 2020 (16)* (N = 44,672)	4,690 (10.5)†	3,261 (7.3)	2,903 (6.5)	–	–	–
Fang et al. 2020 (100)* (N = 2,818)	233 (8.3)†	206 (7.3)	376 (13.3)	–	–	–
Lu et al. 2018 (101)§ (N = 12,654)	1,455 (11.5)	2,125 (16.8)	4,884 (38.6)	4,985 (39.4)	–	278 (2.2)

Values are n (%). 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. *These studies by Wu et al. (16) and Fang et al. (98) include a large, population-based dataset and a systematic review, respectively, from China that are inclusive of the other displayed cohort studies. †Composite of CVD and cerebrovascular disease. §Chinese population prior to COVID-19 included for comparison. Please note that disease ascertainment was different in this study compared with studies of patients with COVID-19.

COVID-19 = coronavirus disease 2019; CV = cardiovascular; CVD = cardiovascular disease.

rate of 3.8% (12,13). Johns Hopkins University is making current data available (12,14). 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 (15). Notably, the death rate associated with COVID-19 is also considerably higher compared with the most recent World Health Organization estimate of seasonal influenza mortality rate of <0.1%, and may reach much higher rates in elderly patients, those with comorbidities, and in those for whom efficient intensive care support is absent (13). While other zoonotic coronaviruses, including the 2002 to 2003 SARS-CoV epidemic and the Middle East respiratory syndrome (MERS-CoV), had higher associated case fatality rates of 9.6% and 34.4%, respectively (16), 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 (16,17). 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 (16); 2) there are 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, which may significantly contribute to further spread of infection (18).

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% (16). 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 (19), although knowledge of the clinical feature of the disease is evolving daily (1,20). 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 pre-existing medical comorbidities are the most vulnerable (1,6,20,21). Notably whereas rates of concomitant infections with other viruses and bacterial superinfections in preliminary data appear low (16), patients with the most severe clinical presentations are likely still at risk for coinfections, and unsurprisingly, worse outcomes have been noted in such cases (21,22). 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 (23). However, moderate-to-severe illness has been described in children as well (24). Moreover, it is not clear how often children were being tested.

Because 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

TABLE 2 Association Among Underlying CV Risk Factors, Known CVD, and Outcomes in COVID-19

	Outcome Variable	Guan et al. 2020 (29) (N = 1,090)	Zhou et al. 2020 (6) (N = 191)	Wang et al. 2020 (20) (N = 138)	Huang et al. 2020 (1) (N = 41)	Ruan et al. 2020 (5) (N = 150)	Wu et al. 2020 (28)* (N = 201)
CV Risk Factors							
Diabetes	ICU vs. non-ICU	–	–	8 (22.2) vs. 6 (5.9)	1 (7.7) vs. 7 (25.0)	–	–
	Severe vs. nonsevere	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. nonsevere	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)	–	–	–	–
Known CVD							
Coronary artery disease	ICU vs. non-ICU	–	–	9 (25.0) vs. 11 (10.8)	–	–	–
	Severe vs. nonsevere	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. nonsevere	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. nonsevere	–	–	–	–	–	–
	Dead vs. alive	–	–	–	–	13 (19.1) vs. 0	4 (9.1) vs. 4 (10.0)

Values are n (%). 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. *This study used multivariable modeling for outcome of death for each CV risk factor for CVD.

ICU = intensive care unit; other abbreviations as in Table 1.

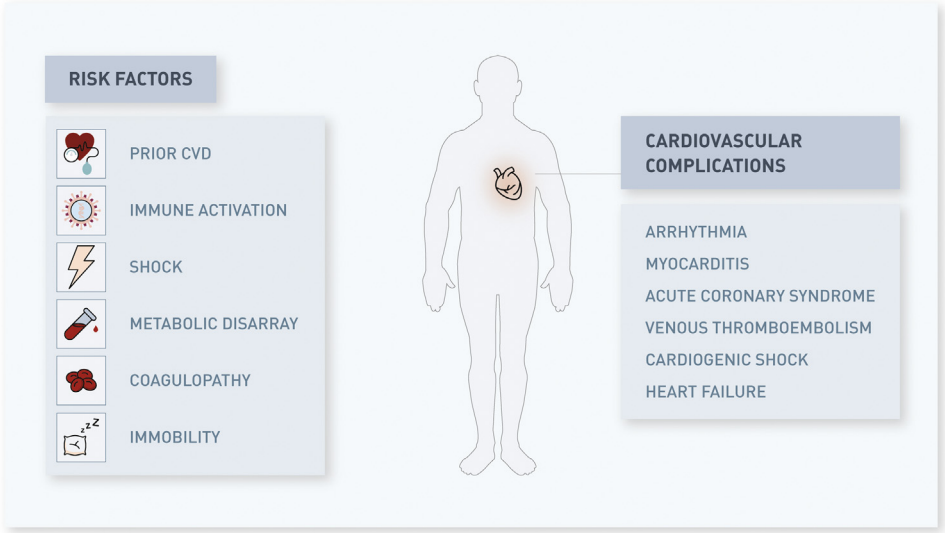
therapies are available for COVID-19, although several are being actively studied (25).

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 reports suggest an association between pre-existing CVD and severe COVID-19, which are summarized in Tables 1 and 2. A meta-analysis of 6 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 than were 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%), and hypertension (6.0%), all notably higher than the overall case-fatality rate of 2.3% (16). 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 (1,20,26–29). Notably, whereas reports outside of China are limited, data from Italy suggest similar mortality rates and an elevated risk for death in patients with comorbidities (30). 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

FIGURE 2 **Risk Factors for Complications and Cardiovascular Sequelae of COVID-19**



Risk factors for complications in patients afflicted with coronavirus disease 2019 (COVID-19) and potential cardiovascular issues that may result from this disease process. CVD = cardiovascular disease.

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 years who receive the influenza vaccine (31,32). Other traditional CVD risk factors such as diabetes and hyperlipidemia affect immune function, and conversely, dysregulated immunologic status corresponds with elevated risk of incident CVD (33–36). 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 that are complex, multifactorial, and bidirectional (37,38). In addition, COVID-19 infection may trigger pathways unique to this pathogen that 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-CoV-2, 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 who have undergone heart transplantation. There are now case reports of COVID-19 infection among heart transplant patients (39,40). Two heart transplant patients in China, 1 with mild and 1 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 (41). Formal treatment guidelines in these patients do not exist at this time. Heart allocation teams need to consider the optimal screening strategies 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 influenza A subtype H1N1 pandemic, to prevent infection in the recipient or as an impetus to initiate prophylaxis if the donor was positive, potential donors were screened if they were

symptomatic or had significant exposure history (42). 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 that may result from COVID-19 infection. Pending larger studies, several existing reports are suggestive of SARS-CoV-2 infection leading to CV complications or exacerbation of pre-existing CVD (6,16,22).

MYOCARDIAL INJURY, MYOCARDITIS, AND ACUTE CORONARY SYNDROMES. Myocardial injury, as defined by an increased troponin level, can occur due to myocardial ischemia or nonischemic myocardial processes including myocarditis (6,43,44). 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 (22,45). 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 with in those with nonsevere disease (25.6; 95% confidence interval [CI]: 6.8 to 44.5) (46). Reports have also suggested that acute cardiac injury—which includes not only elevation of cardiac biomarkers to >99th 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% to 17% of hospitalized patients with the disease (1,6,20) 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) (44).

Prior studies in other coronavirus species (MERS-CoV) have demonstrated evidence of acute myocarditis using cardiac magnetic resonance imaging (47), 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 33% to cases in which myocarditis may have played a contributing role to the patient's demise (22). Other reports have described fulminant myocarditis in the setting of high viral load with autopsy findings of inflammatory mononuclear infiltrate in myocardial tissue (27,48,49). While glucocorticoid therapy and other agents have been administered (50), the most effective treatment strategy for such patients is yet to be defined. Pericardial involvement has not yet been reported, but further study is needed. 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 (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 et al. (37) demonstrated that patients with acute respiratory infections are at elevated risk for subsequently developing acute MI after influenza (incidence ratio: 6.1; 95% CI: 3.9 to 9.5) and after noninfluenza viral illnesses including other coronavirus species (incidence ratio: 2.8; 95% CI: 1.2 to 6.2). The development of care pathways and protocols for COVID-19 patients with ST-segment elevation MI suggest that both within and outside of China such a clinical scenario is highly probable (51).

Additionally, it is important to note potential overlapping symptomatology between acute coronary syndromes and COVID-19. Even though 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 (52). Moving forward as the virus continues to infect patients with significant CV

TABLE 3 Antiviral Therapies Currently Being Studied for COVID-19: Potential Cardiovascular Interactions and Toxicities

Antiviral Therapy	ClinicalTrials.gov Identifiers	Mechanism of Action	CV Drug Class Interactions	CV Adverse Effects
Remdesevir	NCT04302766 NCT04280705 NCT04292899 NCT04292730 NCT04315948 NCT04321616	Nucleotide-analog inhibitor of RNA-dependent RNA polymerases	N/A	Unknown
Ribavirin	NCT04276688 NCT00578825	Inhibits replication of RNA and DNA viruses	Anticoagulants*	Drug-induced hemolytic anemia Avoid in patients with significant/ unstable cardiac disease
Lopinavir/ritonavir	NCT04252885 NCT04275388 NCT04276688 NCT04286503 NCT04307693 NCT04261907 NCT02845843 NCT04321174 NCT04295551 NCT04315948 NCT04251871 NCT00578825 NCT04328012 NCT04321993	Lopinavir is a protease inhibitor; ritonavir inhibits CYP3A metabolism increasing levels of lopinavir	Antiplatelets* Anticoagulants* Statin* Antiarrhythmics*	Altered cardiac conduction: QTc prolongation, high-degree AV block, torsade de pointes; increased serum cholesterol

Table 5 summarizes specific recommendations in the setting of medication interactions. *Indicates drug class interactions.
AV = atrioventricular; DNA = deoxyribonucleic acid; RNA =ribonucleic acid; other abbreviations as in Table 1.

risk factors or established CVD, cases of acute coronary syndromes in the setting of COVID-19 are likely to develop. The true prevalence in this setting may be under-reported 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 and Society of Cardiovascular Angiography and Intervention guidance statement (53).

CARDIAC ARRHYTHMIA AND CARDIAC ARREST. Cardiac arrhythmias are another common CV manifestation described in patients with COVID-19 infection. Though nonspecific, heart palpitations were part of the presenting symptomology in 7.3% of patients in a cohort of 137 patients admitted for COVID-19 disease (27). 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 than in non-ICU patients (44.4% vs. 6.9%) (20). 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, or 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 (45,54).

CARDIOMYOPATHY AND HEART FAILURE. Zhou et al. (6) reported that heart failure was observed in 23.0% of patients with COVID-19 presentations. 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 than in 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 (55). 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 (56) and hypoxemia. However, similar features may be seen in the case of de novo or coexisting cardiogenic pulmonary edema. As such, it is important to 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 to aid in this distinction, although this has been removed

TABLE 4 Other Therapies Being Studied for COVID-19: Potential Cardiovascular Interactions and Toxicities

Therapy	ClinicalTrials.gov Identifiers	Mechanism of Action	CV Drug Interactions	CV Adverse Effects
Anakinra	NCT04341584 NCT04339712 NCT04330638	Recombinant human decoy IL-1Ra. Blocks IL-1α and IL-1β. IL-1β overproduction is associated with the pathogenesis of macrophage activation syndrome.	None	None
Bevacizumab	NCT04275414	COVID-19 patients may have elevated VEGF levels. Inhibits VEGF and decreases vascular permeability and pulmonary edema.	None	Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy Severe hypertension Thromboembolic events
Chloroquine/ hydroxychloroquine	NCT04303507 NCT04307693 NCT04318444 NCT04341493 NCT04316377 NCT04333654 NCT04322123 NCT04307693 NCT04261517 NCT04341727 NCT04328961 NCT04321278 NCT04342169 NCT04332835 NCT04332991 NCT04315948 NCT04334967 NCT04321993 NCT04342221 NCT04321616 NCT04338698 NCT04315896 NCT04328012 NCT04330586	Alters endosomal pH required for virus/cell fusion and interferes with glycosylation of SARS-CoV-2 cellular receptors.	Antiarrhythmics*	Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy Altered cardiac conduction: AV block, bundle-branch block, QT prolongation, torsades de pointes, ventricular tachycardia/fibrillation
Colchicine	NCT04322682 NCT04326790 NCT04322565	Anti-inflammatory properties to potentially inhibit the pathogenetic cycle of SARS-COV-2 by counteracting the assembly of the NLRP3 inflammasome and (less likely) to inhibit viral endocytosis in myocardial and respiratory cells.	Non-DHP CCB* Statins* Antiarrhythmics*	None
Eculizumab	NCT04288713	Inhibits complement activation and prevents the formation of the membrane attack complex.	None	Hypertension or hypotension, tachycardia, peripheral edema
Fingolimod	NCT04280588	Inhibits lymphocytes through sphingosine-1 phosphate regulation.	Antiarrhythmics*	Hypertension, first and second degree AV block (contraindicated with high degree AV block and sick sinus syndrome), bradycardia, QTc prolongation (contraindicated if QTc ≥500 ms) Contraindicated after myocardial infarction, unstable angina, CVA/TIA, ADHF in previous 6 months
Interferon-alpha, beta	NCT04275388 NCT04273763 NCT04276688 NCT04293887 NCT04251871 NCT04320238 NCT02845843 NCT04291729 NCT04315948	Immune activation.	Warfarin	Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy Reports of: hypotension, arrhythmia, cardiomyopathy, myocardial infarction
Pirfenidone	NCT04282902	Antifibrotic ability, possible IL-1β and IL-4 inhibition to reduce cytokine storm and resultant pulmonary fibrosis.	None	None
Methylprednisolone	NCT04273321 NCT04244591 NCT04323592	Alters gene expression to reduce inflammation.	Warfarin	Fluid retention Electrolyte disturbances Hypertension
Sarilumab	NCT04324073 NCT04327388 NCT04322773	Binds to both soluble and membrane-bound IL-6Rs and inhibit signaling that could help mitigate cytokine storm.	Antiplatelets* Anticoagulants* Statins* Antiarrhythmics*	Unknown

Continued on the next page

TABLE 4 Continued

Therapy	ClinicalTrials.gov Identifiers	Mechanism of Action	CV Drug Interactions	CV Adverse Effects
Tocilizumab	NCT04306705 NCT04335071 NCT04331808 NCT04310228 NCT04339712 NCT04330638	Inhibits IL-6 receptor.	Antiplatelets* Anticoagulants* Statins* Evolocumab Beta blockers* Antiarrhythmics*	Hypertension Increased serum cholesterol
Tranexamic acid	NCT04338126 NCT04338074	Reduced conversion of plasminogen to plasmin could potentially reduce the infectivity and virulence of the virus.	None	Venous and arterial thrombosis and thromboembolism, including retinal artery/vein obstruction, has been reported Use caution in patients with uncorrected cardiovascular or cerebrovascular disease due to complications of thrombosis

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

ADHF = acute decompensated heart failure; CVA = cerebrovascular accident; IL = interleukin; NLRP3 = nucleoside-binding domain-like receptor protein 3; non-DHP CCB = non-dihydropyridine calcium-channel blocker; TIA = transient ischemic attack; VEGF = vascular endothelial growth factor.

from the Berlin criteria used for the diagnosis of ARDS. Rather, the Berlin criteria use timing of symptom onset, imaging with bilateral pulmonary opacities, and lack of volume overload to identify patients with ARDS (57). In many cases, serum brain natriuretic peptide and echocardiography can help clarify the diagnosis (58,59). 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 a concomitant cardiogenic component is present when considering mechanical respiratory and circulatory support with extracorporeal membranous oxygenation (ECMO) or other techniques, as this may lead 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 of 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 (60).

VENOUS THROMBOEMBOLIC DISEASE. COVID-19 infected patients are likely at increased risk of venous thromboembolism, and data from Klok et al. (61) suggests that rates of thrombotic complications may be as high as 31% in critically ill patients with COVID-19. Reports suggest abnormal coagulation parameters in hospitalized patients with severe COVID-19 disease (62,63). In a multicenter retrospective cohort study from China, elevated D-dimer levels (>1 g/l) were strongly associated with in-hospital death, even after multivariable adjustment (odds ratio: 18.4; 95% CI: 2.6 to 128.6; p = 0.003) (6). In another study comparing COVID-19 survivors to nonsurvivors, nonsurvivors had significantly higher D-dimer and fibrin degradation products levels, and 71.4% of nonsurvivors met clinical criteria for disseminated intravascular coagulation during the course of their disease (62). In addition to disseminated intravascular coagulation, critically ill patients with prolonged immobilization are inherently at high risk for venous thromboembolism. 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. Retrospective data from 97 patients with severe COVID-19, the majority of whom received prophylactic dose low-molecular-weight heparin in the setting of sepsis-induced coagulopathy, suggests that anticoagulation in such patients may be associated with lower mortality rates (64). The optimal thromboprophylactic regimen for patients hospitalized with COVID-19-related illness is not known, however. As such, contemporary guideline-endorsed strategies should be observed (65). 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.

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
Chloroquine / hydroxychloroquine	Beta-blockers Metoprolol, carvedilol, propranolol, labetalol	CYP2D6 inhibition: Dose reduction for beta-blockers may be required	
	Antiarrhythmics QT-prolonging	Intensified QTc prolongation	Monitor ECG
	Digoxin	P-glycoprotein inhibition: Dose reduction for digoxin may be needed	Monitor digoxin levels
Colchicine	Non-DHP CCB Verapamil Diltiazem	CCB-Induced CYP3A4 and P-glycoprotein inhibition: See package insert for dose reduction recommendations based on dosing scheme.	Monitor for signs of colchicine toxicity.
	Statins Simvastatin Atorvastatin Fluvastatin Lovastatin Pravastatin	Potential CYP3A4 inhibition or impaired excretion: No specific dose reductions in statins recommended	Monitor for signs of muscle pain and/or weakness with concomitant therapy
	Antiarrhythmics Digoxin	P-glycoprotein inhibition: Dose reduction for digoxin may be needed	Monitor digoxin levels
Fingolimod	Bradycardia-causing medications Beta blockers, calcium-channel blockers, ivabradine	Inhibition of sphingosine-1-phosphate on atrial myocytes can decrease AV conduction; if co-administration is necessary, overnight continuous ECG monitoring recommended after first dose	Stop AV nodal blocking medications if possible.
	QT-prolonging antiarrhythmics Class Ia antiarrhythmics Class III antiarrhythmics	Do not co-administer	Monitor ECG
Interferon-alpha, beta	Warfarin	Unknown mechanism of action: Decreased dose may be needed	Monitor INR
Lopinavir/ritonavir	Anticoagulants Apixaban Edoxaban Rivaroxaban Warfarin	CYP3A4 and P-glycoprotein inhibition: Apixaban: administered at 50% of dose (do not administer if requirement 2.5 mg twice daily) Rivaroxaban: do not co-administer P-glycoprotein inhibition: Edoxaban: do not co-administer CYP2C9 induction (99): May decrease serum concentration of warfarin	Dabigatran and warfarin can be administered with caution Monitor INR with warfarin
	Antiplatelets Clopidogrel Ticagrelor	CYP3A4 inhibition: Reduction in clopidogrel active metabolite. Do not co-administer Increased effect of ticagrelor; do not co-administer	Based on limited evidence, recommend prasugrel if no contraindications
	Statins Atorvastatin Rosuvastatin Lovastatin Simvastatin	OATTP1B1 and BCRP inhibition: Rosuvastatin: dose adjust to maximum dose of 10 mg/day CYP3A4 inhibition or transporter- related inhibition: Atorvastatin: adjust to maximum dose of 20 mg/day Lovastatin and simvastatin: do not co-administer	Start at lowest possible dose of rosuvastatin and atorvastatin and titrate up Can consider pitavastatin and pravastatin
	Antiarrhythmics QT-prolonging medication Digoxin Ranolazine	Intensified QTc prolongation P-glycoprotein inhibition: Consider reducing digoxin dosing by 30%-50% CYP3A4 inhibition Ranolazine: do not co-administer	Monitor ECG Monitor digoxin level
	Ivabradine	CYP3A4 inhibition: Do not co-administer	
Methylprednisolone	Anticoagulants Warfarin	Unknown mechanism: Decreased dose may be needed	Monitor INR

Continued on the next page

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 to 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 COVID-19 and the clinical trial identifiers for each are listed in Table 3. Ribavirin and remdesivir are 2 such agents that bind to the active site on the RNA-dependent RNA polymerase on SARS-CoV-2 (66), whereas lopinavir/ritonavir inhibits replication of

TABLE 5 Continued

Therapy	Specific Interaction	MOA of Drug Interaction and Specific Dose Adjustments	Other Notes
Remdesivir	N/A	Potential inducer of CYP1A2, CYP2B6 and CYP3A4 No dose adjustment recommended	N/A
Ribavirin	Anticoagulants Warfarin	Unknown mechanism of action: Increased dose may be needed	Monitor INR
Sarilumab	Anticoagulants Apixaban Rivaroxaban Warfarin Antiplatelets Ticagrelor Clopidogrel Statins Simvastatin Atorvastatin Lovastatin Antiarrhythmics Amiodarone	Increased CYP3A4 expression: No dose adjustment recommended	Monitor INR Monitor ECG
Tocilizumab	Anticoagulants Apixaban Rivaroxaban Warfarin Antiplatelets Ticagrelor Clopidogrel Statins Simvastatin Atorvastatin Lovastatin Beta-blockers Metoprolol, carvedilol, propranolol, labetalol Antiarrhythmics Amiodarone	Can increase expression of CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A4 leading to increased metabolism. No dose adjustment recommendation	Monitor INR Monitor ECG

AV = atrioventricular; BCRP = breast cancer resistance protein; ECG = electrocardiogram; INR = international normalized ratio; MOA = mechanism of action; non-DHP CCB = non-dihydropyridine calcium-channel blocker; OATP1B1 = organic anion transporting polypeptide 1B1.

RNA virus and has evidence of a synergistic effect in vitro with ribavirin (67). 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 human immunodeficiency virus, respectively (68,69). Whereas 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 (69). Both ribavirin and lopinavir/ritonavir have the potential to affect anticoagulant dosing: ribavirin has variable effects on warfarin dosing (70) and lopinavir/ritonavir may require dose reductions or avoidance of CYP3A-mediated drugs such as rivaroxaban and apixaban (71,72).

Lopinavir/ritonavir can also influence the activity of $P2Y_{12}$ inhibitors through CYP3A4 inhibition, which results in decreased serum concentrations of the active metabolites of clopidogrel and prasugrel and increased serum concentrations of ticagrelor. The active metabolite for clopidogrel is mostly formed by CYP2C19, but several other CYP enzymes contribute, including CYP1A2, 2B6, and 3A (73,74). Given the increase in serum ticagrelor levels with such medications (75,76), 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 ritonavir, whereas this was not the case with prasugrel as assessed by the VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, California) (73,74). If $P2Y_{12}$ inhibition is needed during treatment with lopinavir/ritonavir, prasugrel can be used; however, if contraindicated (i.e., history of stroke or transient ischemic attack, low body mass index, or active pathological bleeding), a testing-guided approach (e.g., with $P2Y_{12}$ platelet function assays) may be considered with alternate antiplatelet agents. Details about switching between $P2Y_{12}$ inhibitors

have been described elsewhere (77). Finally, metabolism of the intravenous $P2Y_{12}$ inhibitor, cangrelor, is independent of hepatic function, therefore a drug interaction is not expected (78).

β-Hydroxy-β-methylglutaryl-coenzyme A (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 coadministration 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 (69).

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). Whereas 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 1 patient (among 175 total) (79).

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-CoV-2 (80,81). 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 (82). 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 (82,83). 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-interval-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 (49). A retrospective analysis in patients with COVID-19 who develop ARDS demonstrated that methylprednisolone use was associated with decreased mortality (28). This steroid is known to cause fluid retention, electrolyte derangement, and hypertension as direct CV effects, and it also may interact with warfarin via an undescribed mechanism. Clinicians are advised to observe for these drug interactions.

Ibuprofen, a nonsteroidal anti-inflammatory agent, is often used as part of treatment of patients with viral illnesses. However, recent anecdotal evidence has raised wider concerns that the use of ibuprofen can potentially contribute to severe disease in patients with COVID-19 (84). While data is limited, one of the working theories is that ibuprofen may interfere with the host's immune response to infection. Therefore, at least preliminarily, this mechanism for worse outcomes in patients taking ibuprofen does not appear to involve the CV system.

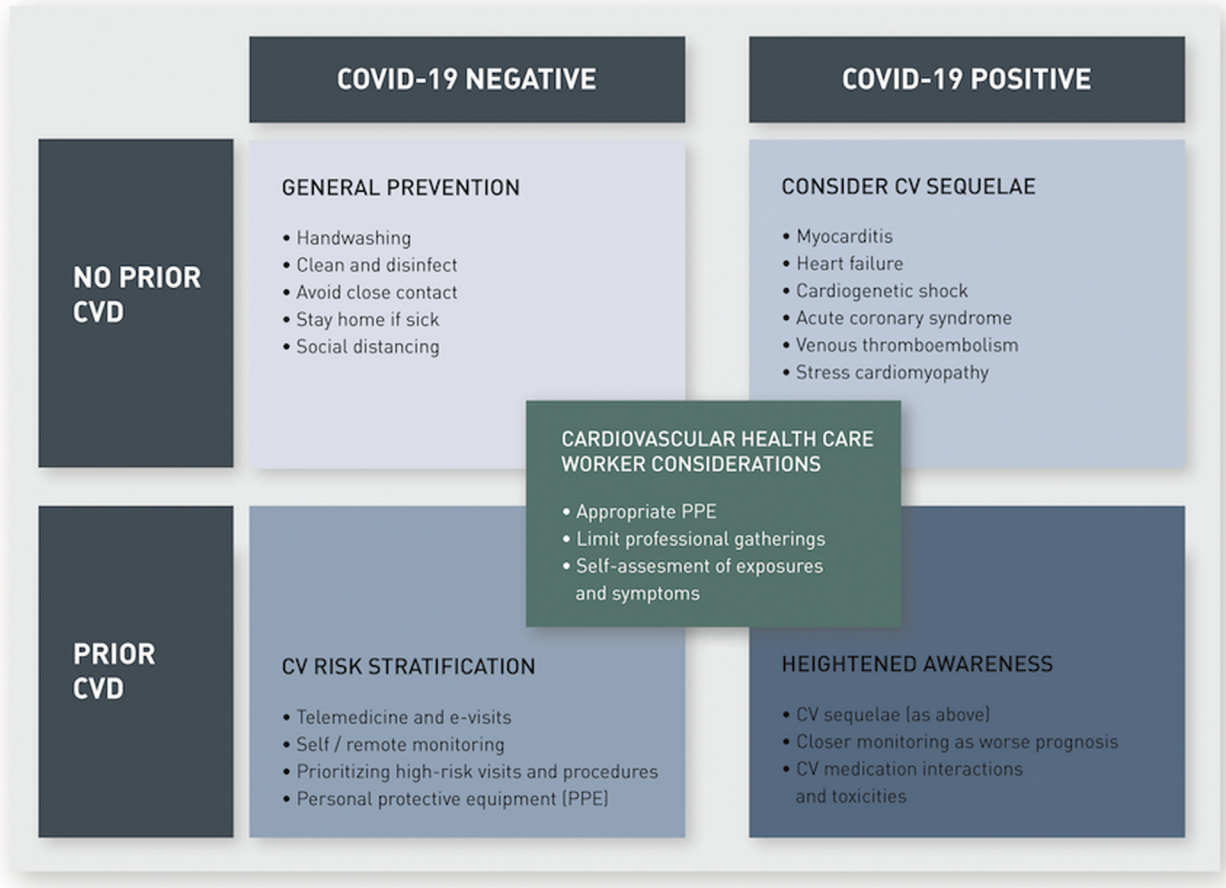
Finally, patient debilitation from severe COVID-19 may pose challenges in administering routine CV medications, ranging from antiplatelet therapy to beta-blockers, thus putting patients with or at risk of ischemic heart disease or heart failure at risk of further deterioration of their clinical condition.

ACE2 AND POTENTIAL THERAPEUTIC IMPLICATIONS. As the ACE2 receptor is the mechanism of entry for SARS-CoV-2, some data suggest that ACE inhibitors and angiotensin receptor blockers (ARBs) may up-regulate ACE2, thereby increasing susceptibility to the virus (**Figure 1**) (5). In contrast, other studies show that ACE inhibitors/ARBs may potentiate the lung protective function of ACE2, by reducing angiotensin II levels through its conversion to angiotensin (1-7,85-87). Thus, the therapeutic implications for ACE inhibitor/ARB therapy during COVID-19 infection is unclear. Overall, there are insufficient data to suggest any mechanistic connections involving ACE inhibitor/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

CENTRAL ILLUSTRATION **Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic**



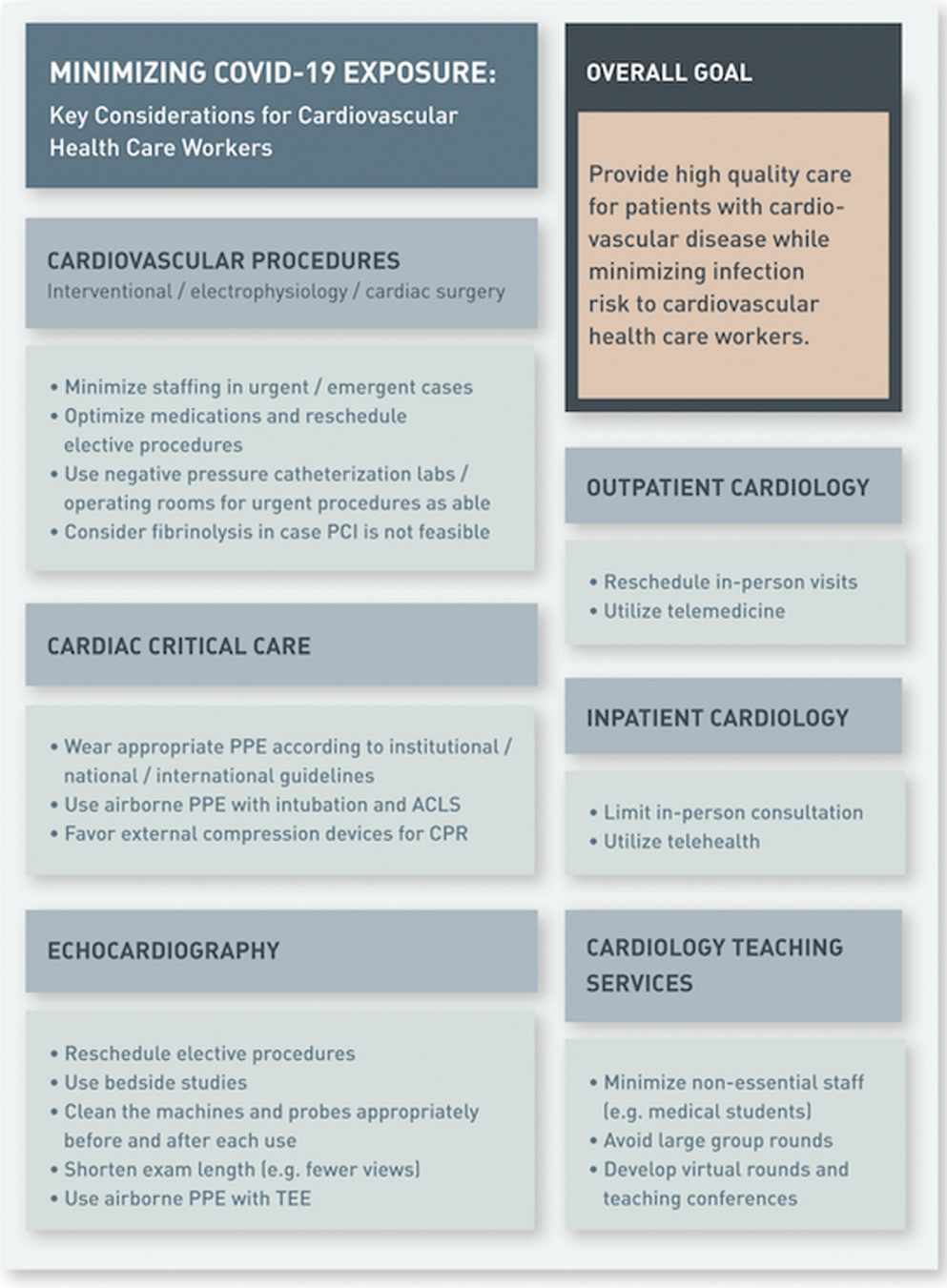
Driggin, E. et al. J Am Coll Cardiol. 2020;75(18):2352–71.

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 coronavirus disease 2019 (COVID-19) outbreak. CV = cardiovascular; PPE = personal protective equipment.

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 (88). Whereas the Centers for Disease Control and Prevention 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 World Health Organization and Centers for Disease Control and Prevention for personal protective equipment (PPE) are in agreement that standard, contact precautions with face mask, eye protection, gown, and gloves are necessary (53). When available, respirators are preferred.

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. 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

FIGURE 3 **Considerations Regarding COVID-19 for Cardiovascular Health Care Workers by Specialty**



Infographic with important considerations regarding coronavirus disease 2019 (COVID-19) for cardiovascular disease health care workers by specialty. ACLS = advanced cardiac life support; CPR = cardiopulmonary resuscitation; PCI = percutaneous coronary intervention; PPE = personal protective equipment; TEE = transesophageal echocardiography.

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 that 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-CoV-2. The necessary downtime required for cleaning may seriously affect 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 (89). Guidance and recommendations in this space will be forthcoming from interventional communities, including the American College of Cardiology and Society of Cardiovascular Angiography and Intervention (53).

Figure 3 depicts key information summarizing considerations to prevent infection among CV health care workers as summarized in an infographic. Overall, as CV health care workers are on the front lines treating COVID-19-infected patients, all possible measures should be implemented to reduce the risk of exposure (90). Health care workers are at elevated risk for contracting this virus, as demonstrated by Wu et al. (16), noting 1,716 of the 44,672 infected individuals (3.8%) were health care workers. 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 nonessential 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, transmission between health care workers 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 to minimize risk for COVID-19 transmission to patients and health care workers; these considerations are outlined in **Table 6**. One important mechanism to help prevent transmission is the use of telemedicine. This technology, already used 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. Although there are currently barriers to the widespread implementation of telemedicine, such as coordination of testing in patients triaged as high

TABLE 6 Considerations for Cardiovascular Health Care Workers and Health Systems Regarding COVID-19 and CVD

Health Care Worker	Health Systems
E-visits/telehealth for triage and patient management, when feasible	Providing and expanding the knowledge and infrastructure for e-visits/telehealth
Adherence to guidelines for optimal use of PPE	Preparing sufficient PPE for patient families and healthcare personnel
Self-reporting symptoms, if present, and halting the role as health care worker in case symptoms arise	Improving patient and public education regarding indications for quarantine versus hospital presentation
Limit elective procedures (i.e. echocardiography, cardiac catheterization) if not urgent/ emergent	Improve testing availability so appropriate containment can be achieved

PPE = personal protective equipment; other abbreviations as in Table 1.

TABLE 7 CV Society Guideline Key Considerations With Regard to CVD and COVID-19

Society/Guideline (Ref. #)	Key Recommendations
ACC Clinical Guidance (93)	Establish protocols for diagnosis, triage, isolation of COVID-19 patients with CVD or CV complications Develop acute myocardial infarction–specific protocols (i.e., PCI and CABG) for COVID-19 outbreak
ESC Council on Hypertension Statement on COVID-19 (94)	There is insufficient evidence regarding the concerns surrounding safety of ACE inhibitor or ARB treatment in patients with COVID-19 Current recommendations are to continue ACE inhibitor or ARB therapy given no sufficient evidence to discontinue therapy because of this infection
European Society of Hypertension (95)	Patients with hypertension should receive treatment with ACE inhibitors and ARBs according to 2018 ESC/ESH guidelines despite COVID-19 infection status (102) In, the case of shock, health care workers should continue or discontinue ACE inhibitor and ARB therapy on case-by-case basis
Hypertension Canada (96)	Patients with hypertension should continue their home blood pressure medical regimen
Canadian Cardiovascular Society (97)	Continuation of ACE inhibitor, ARB, and ARNI therapy is strongly recommended in COVID-19 patients
Internal Society of Hypertension (98)	Endorse the ESC Hypertension Statement

ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CABG = coronary artery bypass graft; ESC = European Society of Cardiology; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

risk, this is a technology that will likely prove important to promote viral containment (91). Other essential principles are to minimize nonessential/nonurgent in-person health care worker-patient interactions as much as possible (i.e., social distancing) and limit 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 NONINFECTED CV PATIENTS

CV SOCIETAL LEADERSHIP. Recently, due to potential health concerns for the CV health care workers and investigators, and 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 canceled or postponed (92). 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 7**. The American College of Cardiology Clinical Bulletin provides a practical clinical summary about key implications and recommendations for CV care of COVID-19 patients (93). The European Society of Cardiology Council on Hypertension and European Society of Hypertension statements acknowledge the questions regarding ACE inhibitor and ARB therapy in the setting of COVID-19 patients (94,95). 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 (96–98). 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 health care 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 health care worker and patient exposures. There are reports of individual centers developing alternate ST-segment elevation MI pathways in the setting of the COVID-19 crisis, such as using fibrinolytic therapy if delays to primary percutaneous coronary intervention are anticipated when hospitals are at capacity or staffing for the catheterization lab is inadequate (51). A recent report from China also suggests substantial delays in door-to-device time in patients presenting with STEMI during the COVID-19 outbreak (99). Additionally, repurposing cardiac ICUs as medical ICUs for the care of patients with COVID-19 will likely become necessary, but this 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 mentioned, 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 (60).

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 health care 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 health care community. Accordingly, every effort must be made to provide clear and unambiguous information to patients and decision makers, countering myths and false news that 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 in 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 among 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 in addition to providing continuity of care to noninfected patients with underlying CVD. In the coming months, efforts toward evaluating new therapies will be crucial to the treatment of this virus, and as this process develops, further appreciation of the intricate interplay among 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 relationships involving the ACE2 protein, antihypertensive agent use, and COVID-19 prognosis will have important implications for patients with both COVID-19 and CVD. Outside of the scope of individual trials, concerted efforts by all health care workers and incisive leadership are required to help mitigate the health risk to the 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 telehealth capabilities, and optimal adherence to preventative population-wide and health care worker-level measures will enable the transition from this critical period until the disease outbreak is contained.

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