Coronavirus disease and the cardiovascular system: a narrative review of the mechanisms of injury and management implications

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Abstract: Coronavirus disease (COVID-19), first identified in Wuhan, China, in December 2019, is now a pandemic, having already spread to 188 countries, with more than 28,280,000 infections worldwide. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the responsible infectious agent, and similar to other human coronaviruses, uses membrane-bound angiotensin-converting enzyme 2 (membrane-bound ACE2) for entry into the host cells. COVID-19 has important cardiovascular implications, especially for patients with pre-existing cardiovascular co-morbidities, potentially mediated through several mechanisms, including direct myocardial injury, worsening of those pre-existing cardiovascular co-morbidities, and adverse cardiovascular effects of potential therapies for COVID-19. The disease is causing a significant burden on health systems worldwide. Elective surgeries and procedures were postponed for a considerable period of time, and many patients with known cardiovascular disease (CVD) risk factors presented late to hospitals, for fear of contracting COVID-19, with serious adverse consequences. Significant negative impact on a population level is highlighted by prolonged isolation, decreased exercise and physical activity, and higher levels of depression and anxiety, all predisposing to elevated cardiovascular risk. This article provides a timely overview of COVID-19 and its impact on the cardiovascular system, focusing on the pathogenesis, potential adverse cardiovascular events, the potential treatment options, protection for health care providers and patients, and what the cardiovascular community could do to mitigate the impact of COVID-19.

Keywords: Coronavirus disease; COVID-19; cardiovascular system; cardiovascular disease (CVD); membrane-bound ACE2

Introduction

The novel coronavirus disease (COVID-19), was declared a global pandemic on March 11, 2020 (1). First identified in Wuhan, China, in December 2019 (2), is now present in 188 countries (3). As of October 10, 37,278,000 cases were confirmed, with 1,075,000 deaths globally (3). The disease has spread across the United States (US), which tops the global tally with >7.3 million confirmed cases and 215,000 deaths, followed by India and Brazil, with 7,730,000 and
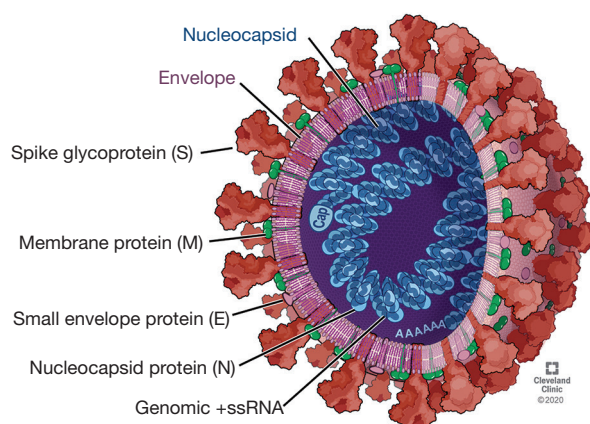
Figure 1 Structure of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. RNA, ribonucleic acid.

7,054,000 confirmed cases respectively (3).

The agent responsible is the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the third virus of the Coronaviridae family causing outbreaks in humans over the past two decades (4). The infection route is not well understood. The dominant hypothesis is a zoonotic infection transmitted from bats to an intermediate host (presumably the Malayan pangolin) and postulated contamination of food consumed by humans in a Wuhan market (5). After the exposure, infected patients presented with pneumonia-like syndromes to local hospitals, and subsequently, person-to-person spread via droplets contributed to the dissemination to other areas (2). Droplet spread occurs when fluids in the mucosa containing the virus travel short distances through the air by sneezing/coughing (6). Inanimate objects and surfaces are also reservoirs of contaminated droplets that can infect after hand contact, followed by touching the mouth, nose, or eyes (6). Airborne dissemination and fecal-oral transmission are also described (6). Fecal samples have been found to contain the virus, and 15% of patients debut with gastrointestinal symptoms (7). We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/cdt-20-779).

Pathogenesis

SARS-CoV-2 is a betacoronavirus with a positive single-stranded Ribonucleic Acid (RNA) envelope in the same genera as the Middle East Respiratory Syndrome (MERS-CoV) and the Severe Acute Respiratory Syndrome (SARS-CoV) viruses (8). SARS-CoV-2 shares 96% of its sequence

with two bat-derived SARS-like coronaviruses (BatCoV and RaTG13), 80% of its sequence with SARS-CoV, and 50% of its sequence with MERS-CoV (4,9). Like SARS-CoV, its components include the spike glycoprotein (S-protein), envelope (E), nucleocapsid (N) and membrane (M) proteins (*Figure 1*) (4). S-protein binds to membrane-bound angiotensin-converting enzyme 2 (membrane-bound ACE2), and along with a transmembrane protease serine 2 receptor (TMPRSS2) in host cells, are essential for viral fusion to the cellular membrane (9,10). An alternate entry pathway is clathrin-dependent and independent endocytosis (9). Upon cytoplasm entry, viral RNA is released to start replication. Translation of structural polypeptide chains initiates, and proteolysis occurs to create a replication-transcription complex with the catalytic enzyme RNA-dependent RNA polymerase. The synthesis and assembly of viral RNA into enveloped glycoproteins begins in the endoplasmic reticulum. Finally, after packing the vesicles containing the virus, the virion is released (4).

ACE2 is present in the lungs, heart, kidneys, intestine, and vascular endothelium, with higher expression in the lungs and heart (9). The vast majority of pulmonary membrane-bound ACE2 is expressed in Type II alveolar cells (approximately 83%), serving as a reservoir for the infection (10). The characteristics and the presence of high levels of regulatory genes in the type II alveolar cells constitute an ideal media for the virus to complete its life cycle, assembly, and replication (10). With the binding of the virus to membrane-bound ACE2 and other systemic factors, such as the cytokine storm, patients are highly predisposed to injury, sepsis, and acute respiratory distress syndrome (ARDS) (4,9).

The cardiovascular effects of COVID-19 are mediated through multiple mechanisms. Direct cardiotoxicity, as exemplified in prior influenza outbreaks and other coronavirus strains (MERS-CoV and SARS-CoV), can occur (11). ACE2 is an essential regulator of cardiac function. Its primary role is catalyzing the reaction that converts angiotensin I into angiotensin, and subsequently controlling blood pressure via vasoconstriction (9,12). Also, it counteracts the consequences of excessive activity of the renin-angiotensin system (RAS) by mitigating the effects of angiotensin II (*Figure 2*) (12). In conditions such as hypertension (HTN) and heart failure (HF), the RAS is hyperactive, with low expression/availability of cardiovascular membrane-bound ACE2. There is a hypothesis of worsening cardiovascular disease (CVD) due to the further binding of SARS-CoV2 (9). Furthermore,
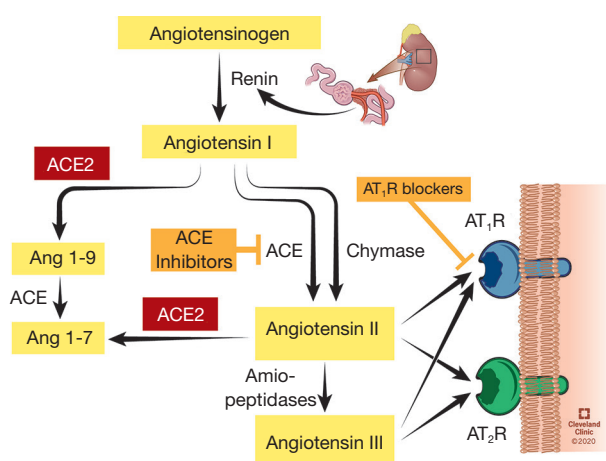
Figure 2 Diagram illustrating the angiotensin-converting enzyme 2 (ACE2) pathway, which is important for the pathogenesis of COVID-19. ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang 1-9, angiotensin 1-9; AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor.

the viral-induced systemic inflammatory response may exacerbate underlying CVD, predisposing to premature atherosclerotic plaque activation, and rupture (13). Another relevant effect to consider is the experimental therapies that are known to be, or potentially associated with cardiovascular adverse effects (discussed below).

COVID-19 is causing a significant burden on health systems worldwide. Elective surgeries and procedures are being postponed. In this context, some patients with known CVD may not be treated promptly (14). Finally, serious consequences impacting populations include prolonged isolation, decreased exercise, deficient diets, and higher levels of depression and anxiety, all predisposing to elevated cardiovascular risk (*Figure 3*).

COVID-19 and cardiovascular system

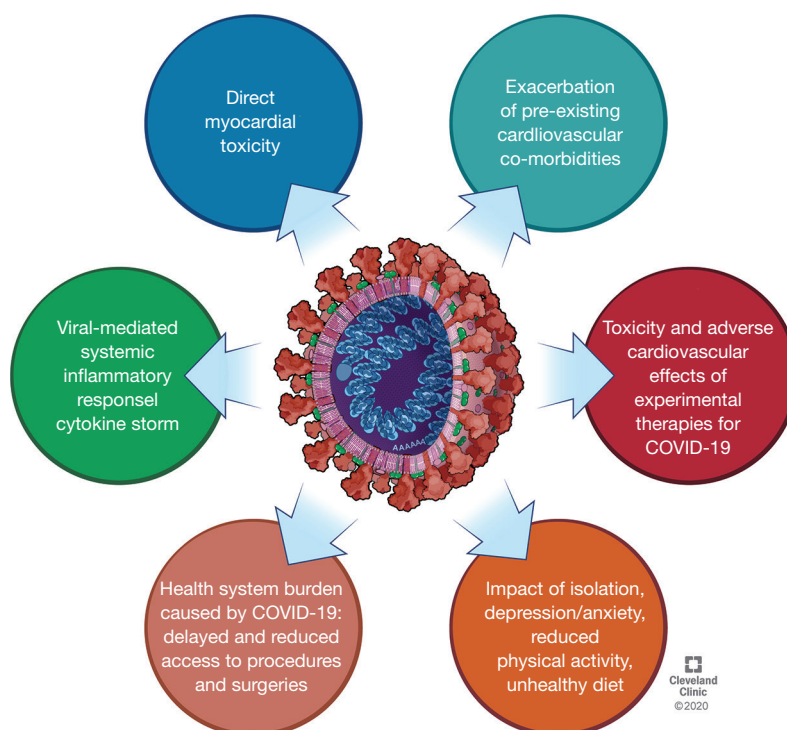China and Italy reported high prevalence rates of CVD and death in the current COVID-19 pandemic (5). A

Figure 3 he cardiovascular effects of COVID-19 are mediated through multiple mechanisms.

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recent single-center study of 416 hospitalized COVID-19 patients noted that cardiac injury occurred in 19.7% of patients (commonly the elderly and those with pre-existing cardiovascular comorbidities) (15). It was associated with higher levels of troponin and inflammatory markers with a 3 to a 4-fold elevated risk of all-cause mortality, both from the time of symptom onset and admission (15). In a retrospective cohort of 191 COVID-19 patients, the prevalence of HTN, diabetes mellitus (DM), and CVD were reported to be 30%, 19%, and 8%, respectively, with even higher rates observed in those requiring intensive care unit (ICU), and those who died (13). In comparison, Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) were reported having an associated prevalence of DM, ranging between 11% to 50%, which was associated with increased mortality (16,17).

While these reports aid in understanding the CVD burden of COVID-19, the lack of external validity needs to be considered. Epidemiologically, the Asian population generally has a lower prevalence of cardiovascular risk factors compared to the Western population (18). Early US and European data have recently become available. In a single center case series of 21 critically ill COVID-19 patients in Washington state, 86% of the cohort had comorbidities (19). Chronic kidney disease and congestive HF were the most common (47.6%, and 42.9%, respectively) (19). Cardiomyopathy developed in 33% of the patients, and the overall mortality was 67% (19). A prospective observational cohort study in the United Kingdom (UK), enrolling 16,749 hospitalized patients from 166 centers, is the largest study in Europe to date, characterizing the clinical features of critically ill COVID-19 patients (20). Similarly, comorbidities were commonly present (53% of the cohort) (20). CVD was the most common comorbidity (29%), followed by DM and non-asthmatic pulmonary diseases (19% each) (20). The presence of comorbidities were associated with higher mortality rates (33% in the comorbidity group) (20) (*Figure 4*).

Myocarditis and myocardial injury

COVID-19 has been associated with myocardial injury, as evidenced by elevated cardiac biomarkers (15). In a cohort of 416 confirmed cases from China, patients with confirmed cardiac injury had higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) {median [interquartile range (IQR)], 1,689 [698–3,327] *vs.* 139 [51–335] pg/mL}, high sensitivity Troponin I (hs-TNI) [median (IQR), 0.19 (0.08–1.12) *vs.* <0.006 (<0.006–0.009) μg/L], creatine

kinase-MB (CK-MB) [median (IQR), 3.2 (1.8–6.2) *vs.* 0.9 (0.6–1.3) ng/mL], and other acute-phase proteins such as C-reactive protein (CRP), and procalcitonin (15). Similarly, in 138 hospitalized patients from China, 7.2% of the patients had elevated cardiac biomarkers, electrocardiographic changes, or echocardiographic abnormalities. 22% of the cohort required ICU admission (21). Another retrospective study from China reported that hs-TNI levels were elevated >99th percentile of reference range more frequently in fatal cases (13). The summative findings from several Chinese studies reported that the severity of myocardial injury was significantly greater in patients needing ICU admission and in those who died (2,13,22).

Prior experiences from the MERS outbreak, showed that direct viral-mediated acute myocarditis could manifest as myocardial edema, and localized wall motion abnormalities (23). However, early pathological reports from COVID-19 cases, reported scarce mononuclear tissue infiltrates and a lack of substantial viral-induced myocardial damage, arguing against this being a dominant mechanism (23). The other suggested mechanism for myocardial injury is immune dysregulation and cytokine storm in the setting of systemic viremia (15). Huang *et al.* and Shi *et al.* reported higher levels of CRP, leucocytes, methemoglobinemia, elevated interleukin (IL)-2, IL-7, IL-10, and granulocyte-colony stimulating factor in hospitalized COVID-19 patients (8,15). The argument for cytokine storm is also supported by reports of patients with fulminant myocarditis and severely depressed left ventricular ejection fraction, who were treated successfully with high-dose immunoglobulins, steroids, antiviral therapy, and supportive care (24).

Acute coronary syndrome

There are no extensive published studies reporting Type I acute myocardial infarction (AMI) directly caused by COVID-19 as of May 13, 2020. It should be noted that prior reports have shown that the systemic inflammatory response in the context of acute viral illnesses can trigger plaque destabilization and subsequently increased risk of acute coronary syndrome (25). Kwon *et al.* showed a 6-fold increased risk of AMI within 7 days of an influenza-related illness compared to control cases and a 2.8-fold increased risk associated with non-influenza viral diseases (25). Also, it is interesting to note that these are a few reported cases of COVID-19 presenting with symptoms mimicking AMI without significant obstructive coronary lesions (24,26). These cases may result from an underlying cytokine storm or reflect a sympathetic overdrive mediated
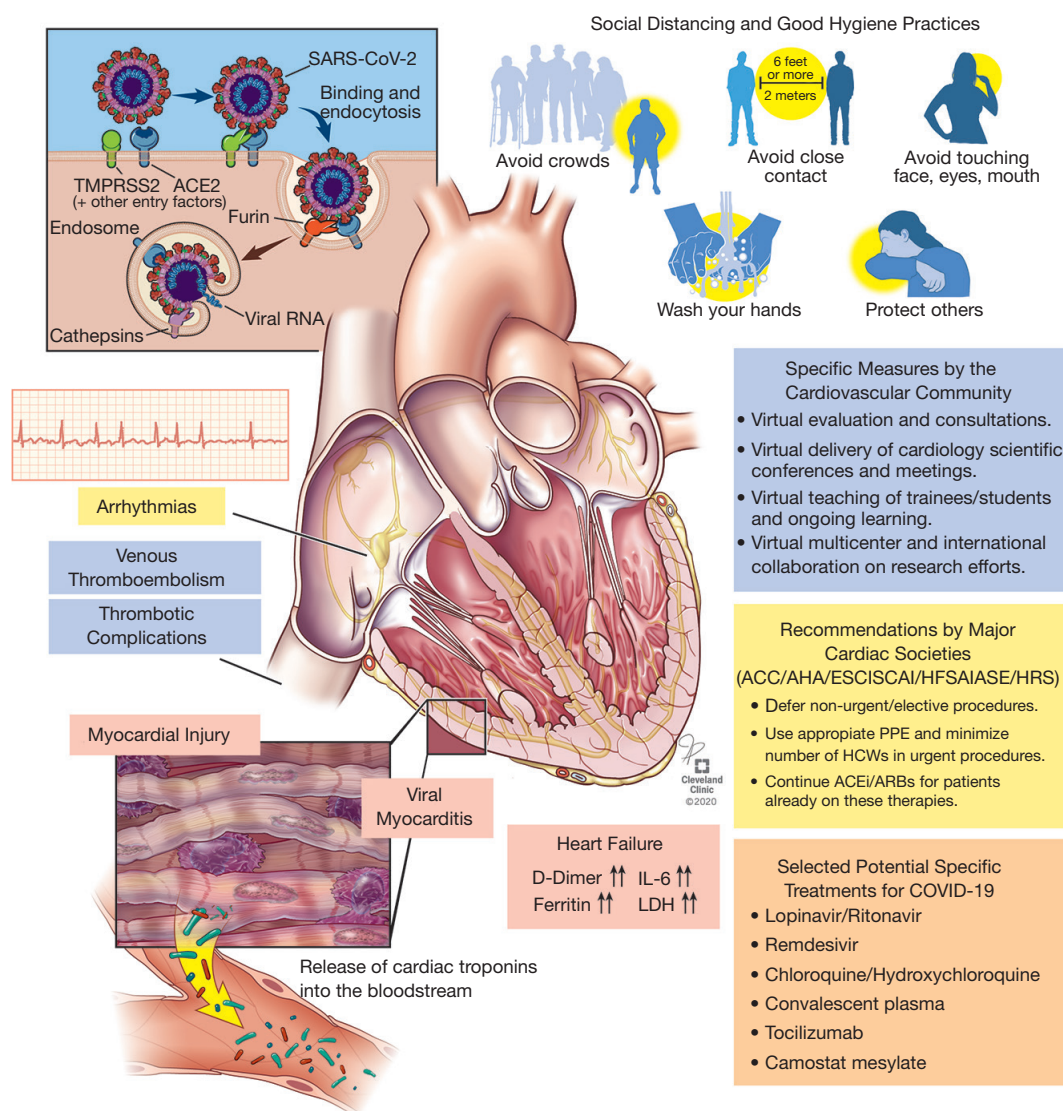
Figure 4 Central figure illustrating the impact of COVID-19 on the cardiovascular system, as well as the general and specific measures to combat COVID-19. SARS-CoV2, Severe Acute Respiratory Syndrome Coronavirus 2; TMPRSS2, transmembrane protease serine 2 Receptor; ACE2, angiotensin-converting enzyme 2; RNA, ribonucleic acid; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; SCAI, Society for Cardiovascular Angiography and Interventions; ASE, American Society of Echocardiography; HRS, Heart and Rhythm Society; PPE, personal protective equipment; HCWs, healthcare workers; COVID-19, coronavirus disease; ACEi/ARBs, angiotensin receptor inhibitors/angiotensin receptor blockers; IL, interleukin.

stress cardiomyopathy/Takotsubo-like pattern, and deserves further investigation.

Arrhythmia

The data surrounding the prevalence of electrophysiological abnormalities in COVID-19 patients are not robust. In two Chinese cohorts (138 and 137 patients), tachyarrhythmias were reported in 7% to 16% of hospitalized patients and were more common in patients needing ICU admission (21,27). Prevalence and description of the specific subtypes of arrhythmias are under-reported at this stage. Current data support that electrocardiographic changes consistent with ischemia in the setting of elevated biomarkers may be

indicative of cardiac injury and/or myocarditis (15).

Heart failure, shock and heart transplantation

A study of 191 hospitalized patients from two large tertiary hospitals in China, reported HF in 52% of the fatal cases, and 12% in the discharged patients. A significant proportion of these patients were complicated by cardiogenic shock (13). A substantial number of patients with underlying compromised cardiac function may also be at risk of developing acute right-sided HF (13). The same study also reported that 38 of 191 patients (20%) developed septic shock, a universally fatal outcome (13). The clinician should therefore maintain a high degree of suspicion for multifactorial shock.

Consideration of heart transplant in the setting of severe COVID-19 cardiomyopathy needs to be further studied. While it is known to be a viable treatment option in cases of acute myocarditis, early reports of two heart transplant patients presenting with COVID-19, raise concerns of potential allograft rejection in the setting of an infected donor (28). Both cases were treated with high-dose immunoglobulins and corticosteroids, and were eventually discharged (28). Strict protocols regarding donor exposure and pre-transplant evaluation may conceivably render heart transplantation a viable management option for select patients.

Extracorporeal membrane oxygenation (ECMO), may be offered as a therapeutic option in select cases, according to the World Health Organization (WHO) (29). Veno-venous (V-V) ECMO is indicated for refractory ARDS (29,30). In the context of cardiovascular complications causing cardiogenic shock, such as severe myocarditis, arrhythmias, significant pericardial effusions, and hemodynamically significant thrombotic complications, veno-arterial (V-A) ECMO may be considered (30,31). However, even with the most advanced supportive measures, the prognosis of certain severe cases remain poor (32). The decision to initiate ECMO therapy should take into account of factors, such as patient safety, and experience and expertise of the individual center (30,31).

Thrombotic disease

Emerging data suggest a higher risk of thrombotic and thromboembolic events associated with COVID-19 (33). A combination of prothrombotic factors (e.g., hyperinflammation, mechanical ventilation, the presence of central venous catheters, and prolonged immobilization), and hemostatic abnormalities (e.g., thrombocytopenia, increased D-dimer levels), likely

play important roles (34). Patients with COVID-19 infections, are prone to pulmonary embolism (PE) (34). In a French case series of 107 patients with a confirmed diagnosis of COVID-19 admitted to the ICU, 20.6% had PE. They found that compared to the hospitalized patients who tested negative for COVID-19, during a similar time interval, the frequency of PE in the COVID-19 series, was significantly higher [20.6% *vs.* 6.1%; absolute increased risk, 14.4% (95% CI, 6.1–22.8)] (35). In a Chinese study of 81 critically ill patients in the ICU, the incidence of lower extremity venous thromboembolism (VTE) was 25%, and 10% of the cohort with VTE, died (33). In a case series of 3 patients presenting with bilateral lower limb ischemia and cerebral infarcts, antiphospholipid antibodies were detected, implicating a possible role in the thrombotic events (36). These antibodies, as well as other coagulation markers, may become detectable, in response to severe infections and critical illness (34,36). In a cohort of 1,026 patients, Wang *et al.* reported that 40% had an elevated thrombotic risk, and without prophylaxis, 11% developed VTE (37). COVID-19 related thrombotic complications include arterial thromboembolism, deep vein thrombosis, intracardiac thrombus, PE, and stroke (37). The anticoagulation regimen of COVID-19 patients' needs to be tailored individually, and has to be balanced against potential bleeding complications associated with thrombotic prophylaxis (37).

Hyperinflammatory shock in children

The number of children affected by COVID-19 remains low around the world. In the US and the UK, only 1.7% and 2% of the positive cases, respectively, occurred in patients younger than 18 (38). However, there are emerging reports of an atypical hyperinflammatory syndrome in children (39). The symptoms include persistent fever, exanthema, lymphadenopathy, conjunctival injection, and other changes in the mucosae, raising the concern of COVID-19 as a trigger for Kawasaki disease (KW), or a Kawasaki-like syndrome (38,40). KW is a systemic vasculitis of childhood, with unknown etiology, which may seriously compromise the cardiovascular system (38,40), including long-term complications such as coronary artery aneurysms (38). Previous studies linked the disease with viral infections in the previous 30 days of presentation in 9–42% of the cases (40). The identification of different strains of the coronavirus family as a potential etiology has also been described following outbreaks (40,41). It is essential to highlight that these cases remain rare, and that children with COVID-19 usually present as asymptomatic cases or have

mild symptoms (38,40).

Antiviral drugs

Lopinavir/Ritonavir is an antiretroviral drug combination (42). It works by inhibiting the viral RNA replication, and has shown *in vitro* activity against SARS-CoV (43,44). However, Cao *et al*. reported showed no difference between those treated with lopinavir/ritonavir versus standard of care (SOC) in 199 COVID-19 patients [hazard ratio (HR) for clinical improvement: 1.24; 95% CI, 0.90 to 1.72] (42). In terms of 28-day mortality, lopinavir/ritonavir group was not statistically different from SOC (19.2% *vs.* 25.0%; difference, –5.8 percentage points; 95% CI, –17.3 to 5.7) (42). Cardiovascular adverse events are notable. Conduction disturbances, QT interval prolongation (especially combined with other QT-prolonging medications, and electrolyte disturbances), and PR prolongation (of particular risk in patients with structural heart disease, pre-existing conduction system abnormalities, and ischemic heart disease), have been reported, as has hyperlipidemia (42,45).

Remdesivir is a novel drug, which works by inhibiting the RNA-dependent RNA polymerase (46). Different research groups are studying its efficacy in COVID-19, because it demonstrated inhibition of SARS and MERS (46). A randomized controlled trial (RCT) involving 385 subjects from 10 centers in China demonstrated a numerical reduction in time to clinical improvement in those treated earlier, however this was not statistically significant [HR 1.23 (95% CI, 0.87–1.75)] (42). In contrast, Grein *et al*. studied the compassionate use of remdesivir in 53 patients, observing an improvement in oxygen support in 68% of the patients, extubation in 57% of the patients on mechanical ventilation, and the cessation of ECMO in 75% of the patients (47). Beigel *et al*. conducted a double-blind, randomized, placebo-controlled trial in 1,059 patients (538 assigned to remdesivir and 521 to placebo) (48). There was a shortening in the recovery time from 15 to 11 days for the remdesivir group (rate ratio for recovery: 1.32; 95% CI, 1.12–1.55; P<0.001). The National Institutes of Health released preliminary data from this clinical trial (#NCT04280705), and on May 1st, the Food and Drug Administration (FDA) approved the use of this drug in severe COVID-19 patients (49).

Regarding the optimal duration of the antiviral, a randomized, open-label, phase 3 trial was conducted in 397 patients (50). After adjusting for baseline clinical status, no significant difference between 5 *vs.* 10 days of treatment was reported (P=0.14) (50). There was no placebo control group, limiting the interpretation of the overall benefit of remdesivir (50). Specific cardiovascular toxicities of this therapy are not yet clear.

Chloroquine/hydroxychloroquine (CQ/HCQ)

These are antimalarial drugs (51). Theoretically, they could inhibit viral replication by increasing endosomal pH since the virus requires low pH to thrive, thus impairing the release of the genetic material, inhibiting replication (52). The available data are inconclusive. Two studies currently in pre-print reported conflicting results. A Chinese study involving 30 patients receiving HCQ reported high viral clearance (52). In comparison, an American study categorizing 368 hospitalized veterans into 3 groups [HCQ, HCQ + Azithromycin (AZ), and those unexposed to HCQ], demonstrated no significant benefit in mortality (27.8% in the HC group, 22.1% in the HC + AZ group, and 11.4% in the unexposed group) (53). In a multicenter Chinese RCT involving 150 patients, there were no statistically significant differences in the 28-day negative conversion rate of SARS-CoV-2 between the HCQ and SOC versus SOC groups (85.4% *vs.* 81.3%, P=0.341) (54). However, a possible beneficial effect on clinical symptoms (HR, 8.83; 95% CI, 1.09–71.3), and a significant reduction in CRP [6.986 (HCQ+SOC) *vs.* 2.723 (SOC) milligram/liter, P=0.045] were reported (54). The most common cardiovascular effects are QT prolongation and conduction disturbances (atrioventricular block and bundle branch block) (52). Other long-term adverse effects include cardiomyopathy (restrictive or dilated), and congestive HF (51).

Camostat mesylate

This is a serine protease inhibitor approved in Japan for chronic pancreatitis and reflux esophagitis (55). The interaction between membrane-bound ACE2 and S protein to enter the host cells is dependent on TMPRSS2 (10). A clinical trial is underway, investigating the potential of camostat mesylate for treating COVID-19 (56).

Monoclonal antibodies and convalescent plasma

In a preliminary uncontrolled study of five critically ill patients, the administration of convalescent plasma containing neutralizing antibody showed improvement (57). Any potential cardiovascular adverse effects are yet to be reported.

Vaccine

B cell and T cell epitopes derived from the S and N proteins in SARS-CoV-2 sequences, are being studied (58). Targeting these epitopes may potentially confer immunity against COVID-19 (58). The first clinical testing in humans of the COVID-19 vaccine was on March 16, 2020 (59). One hundred and fifteen vaccine candidates were available as of April 8, 2020 (59). As of September 3 2020, there was a 2.5-fold increase of vaccines candidates, and 33 of those 321 are currently in phase III clinical trials (60). Potential candidates include messenger RNA vaccine, mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute, and ChAdOx1 from Jenner Institute, University of Oxford. Adjuvant vaccine, which works by enhancing immunogenicity, is also being investigated (59).

Role of angiotensin receptor inhibitors/angiotensin receptor blockers (ACEi/ARBs)

Conflicting reports speculated a possible link between ACEi/ARBs and more severe COVID-19 cases (61). The concern arises from the theoretical overexpression of membrane-bound ACE2, predisposing to viral entry and propagation of SARS-CoV2 (12). On the contrary, several studies demonstrated a protective role of membrane-bound ACE2 and angiotensin in lung injury models (61). In viral pneumonia, it has shown a beneficial effect in reducing the pulmonary inflammatory response and cytokine release (61,62). To date, major international societies, including the American College of Cardiology (ACC), American Heart Association (AHA), Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC), recommend continuing treatment with ACEi /ARBs in patients already taking these therapies (62,63). Sudden cessation of ACEi/ARBs in high-risk patients could potentially lead to significant cardiac decompensation (61). Mehta *et al.* studied the association of ACEi/ARB use and COVID-19 test positivity. Out of 18,472 patients tested for COVID-19, 1735 (9.4%) had a positive test, and 12.4% were on either ACEi or ARB (64). No significant association was found between ACEi or ARB use and COVID-19 test positivity (overlap propensity score-weighted OR: 0.97; 95% CI, 0.81–1.15) (64). Selected experimental therapies being studied in clinical trials are shown in *Table 1*.

Healthcare workers (HCWs) are at increased risk of COVID-19, and infections continue to be on the rise worldwide. Zhou *et al.* reported hospital-associated transmission to HCWs in China, and as of February 11, 2020, there were 3019 reported cases of infections in Chinese HCWs and at least 22 deaths (66). To effectively battle the pandemic, specific measures need to be followed in the cardiovascular community.

Cardiac catheterization laboratory and COVID-19

The ACC, the ESC, and the Society for Cardiovascular Angiography and Interventions (SCAI), recommend deferring elective procedures in the pandemic, including diagnostic cardiac catheterization, percutaneous coronary intervention (PCI) for stable ischemic heart disease, and non-essential structural heart interventions (67,68). The purpose of this is to minimize patient and HCWs exposure to COVID-19 including asymptomatic carriers, and maximize the availability of inpatient beds and personal protective equipment (PPE). However, in all patients with suspected or confirmed COVID-19, it is paramount to wear appropriate PPE, including gown, gloves, goggles (face shields), and N95 masks (68). In patients with borderline respiratory status, consideration should be given to intubation prior to arrival to the catheterization laboratory, and non-invasive positive pressure ventilation [Continuous positive Airway Pressure (CPAP) and Bi-level Positive Airway Pressure (BiPAP)] should be avoided, given the risk of aerosolization and provider exposure. While fibrinolysis can be considered in patients with STEMI and confirmed COVID-19 infection, primary PCI should still be the treatment of choice if appropriate PPE can be utilized (68,69). In low-risk patients with type II non-ST-elevation myocardial infarction (NSTEMI) and confirmed COVID-19, medical management may be considered initially. Nevertheless, in clinically unstable patients with non ST-elevation acute coronary syndrome (NSTE-ACS), cardiac catheterization with PCI should be performed, aiming for rapid discharge (68,69). While waiting for confirmatory testing for COVID-19 is not recommended for patients with suspected STEMI, in medically stable patients with NSTE-ACS, it may be worthwhile to obtain confirmatory testing in patients with suspected COVID-19 (68,69). Patients with critical aortic stenosis or severe, symptomatic aortic stenosis (AS) should still proceed with transcatheter aortic valve replacement (TAVR) in a timely fashion. However, consideration should be given to deferring patients with severe AS who are not symptomatic or minimally symptomatic until the hospital can safely accommodate such patients.

Table 1 Potential treatment options being studied for COVID-19 and their cardiovascular adverse effects (65)

Drug	ClinicalTrial.gov identifier	Mechanism of action	CV side effects
Remdesivir	NCT04280705 NCT04292730 NCT04257656	Inhibition of RNA-dependent RNA polymerase	No CV effect described
Chloroquine/ Hydroxychloroquine	ISRCTN86534580; EUCTR2020-001254-22-BE; ChiCTR2000029559; NCT04316377; NCT04315896; NCT04308668; ACTRN12620000417987; ISRCTN83971151	Inhibition of viral replication (increases endosomal pH)	QT prolongation, conduction disturbances (AV block and BBB), cardiomyopathy (restrictive or dilated), and congestive HF
Tocilizumab	NCT04320615	IL-6 receptor antagonist. Modulates immune response	Hyperlipidemia
Camostat mesylate	NCT04321096	Inhibits viral entry	No CV effect described
Sarilumab	NCT04315298	IL-6 receptor antagonist. Modulates immune response	Hypertriglyceridemia
Convalescent plasma	NCT04323800 ChiCTR2000030010	Passive immunization	No CV effect described
Adalimumab	ChiCTR2000030089	TNF-alpha inhibitor. Modulates immune response	Hyperlipidemia, hypertension, HF, deep venous thrombosis
Fingolimod	NCT04280588	Sphingosine-1 phosphate modulator. Reduces lymphocyte migration. Modulates immune response	Bradyarrhythmia and AV block, hypertension, QT prolongation
Eculizumab	NCT04288713	Blocks complement protein C5 by inhibiting cleavage to C5a to C5b. Modulates immune response	Hypertension, peripheral edema
Bevacizumab	NCT04305106 NCT04275414	Inhibits VEGF, reducing vascular permeability and pulmonary edema. Modulates immune response	Direct myocardial toxicity *vs.* exacerbation of CV disease, hypertension, arterial thromboembolic events
Corticosteroids	NCT04273321 NCT04244591	Reduces inflammation by controlling protein synthesis, suppress migration of PMNs. Modulates immune response	Hypertension, hyperglycemia, Thromboembolic events
Interferon	EUCTR2020-001023-14-GB NCT04293887 ChiCTR2000030013	Activation of immunological response	Direct myocardial toxicity *vs.* exacerbation of CV disease, chest pain, edema, arrhythmia
Interferon	NCT04322682	Inhibits inflammasome NLP3 and microtubule formation, limiting the myocardial necrosis and pneumonia development	No CV effect described
Pirfenidone	NCT04282902 ChiCTR2000030333	Inhibits TGF-beta and TNF-alpha. Modulates immune response and reduces pulmonary fibrosis	No CV effect described
Favipiravir	NCT04310228ChiCTR2000030987	Inhibition viral RNA polymerase	No CV effect described

RNA, ribonucleic acid; CV, cardiovascular; AVB, atrioventricular block; BBB, bundle branch block; HF, heart failure; IL, interleukin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; PMNs, polymorphonuclear leukocytes; TGF, transforming growth factor.

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Echocardiography laboratory and COVID-19

The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) recommend that during the pandemic transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and stress echocardiography should be deferred if not urgent/emergent (70,71). Strict droplet precautions must occur in echocardiography laboratories/cardiac catheterization laboratories/ electrophysiology laboratory, wards, or emergency departments (EDs) while performing an imaging test in patients with suspected/confirmed COVID-19 (71). In ICUs, operating rooms (ORs), and with ventilated patients (invasive or non-invasive), airborne precautions are necessary (71). TEE warrants special attention because of the increased risk of spreading SARS-CoV2 via aerosolization that may be associated with coughing/ gagging during the procedure (71). Adjuvant imaging modalities such as computed tomography (CT) should be considered as an alternative to TEE when feasible (e.g., exclusion of left atrial appendage thrombus before cardioversion) (71). For TTE or stress echocardiography in patients without COVID-19, standard precautions should be implemented (71). With the need to provide rapid, bedside testing, cardiac point-of-care ultrasound (POCUS) has gained increasing attention, given its portability (71). ASE and EACVI have created a cardiac POCUS protocol for COVID-19 (70,71).

Additionally, the minimum number of HCWs should be involved in the acquisition of imaging data, with a review of previous study images where available, and performance of targeted examinations to answer the clinical questions, and where available, to use dedicated machines/laboratories for COVID-19 patients (71). If possible, procedures on the suspected/confirmed COVID-19 patients should be performed at the end of the day (to minimize delays in cleaning) and utilizing negative-pressure rooms or high-efficiency particulate (HEPA) filters if available (71). It is of utmost importance for the HCWs to practice correct PPE donning and doffing techniques (71). *Table 2* lists the effective use of PPE while performing various cardiovascular procedures.

Invasive and non-invasive electrophysiology procedures and COVID-19

The Heart Rhythm Society (HRS) recommends delaying non-urgent/elective electrophysiology (EP) procedures (72). For cases that would cause a threat to patient' lives, permanent dysfunction to an organ-extremity, or imminent deterioration to severe status, EP procedures should be done with appropriate PPE, adhering to the same recommendations as for other urgent procedures described above (67,72).

Cardiac arrest and cardiopulmonary resuscitation and COVID-19

During cardiac arrest of a suspected COVID-19 patient, according to the American Heart Association (AHA), cardiopulmonary resuscitation (CPR) must be performed with appropriate PPE (N95 mask, long-sleeve gown, gloves, and face shield) (72,73). Oxygenation/ventilation strategies should be prioritized to minimize aerosolization, and early endotracheal intubation should be performed when possible (73). Immediate defibrillation of a shockable rhythm provides less risk of aerosolization than compressions in a patient with an unsecured airway (73). If early resuscitation is unsuccessful, continuing with the maneuvers may be futile, and poses high-risk to the rescuer in the absence of adequate PPE (73). It is essential to consider the likelihood of success versus risks for the patients and the resuscitation team (73).

Management of critically ill patients and COVID-19

Other non-ICU HCWs may be called upon to assist critically ill patients on the front-line. Healthcare resources are of supreme importance in this pandemic. Cardiac ICUs and ORs may be transformed into medical ICUs due to the increasing demand for mechanical ventilation (74). A transition of inpatient wards and other facilities into dedicated COVID-19 units in anticipation of the surge in hospitalization has been observed (74). Likewise, staffing models in cardiac ICUs might need to be modified to allow for tiered oversight of non-critical care trained physicians (74). It is increasingly important to work as a team and utilize the available resources appropriately, while minimizing the exposure and spread of the infection.

COVID-19 and the rise of virtual cardiology

Telemedicine incorporating appropriate use of web portals, computers, and smartphones, is another valuable way to minimize the risk of infection. It allows the patients to be

Table 2 Personal protective equipment (PPE) recommendations for COVID-19, while performing various cardiovascular procedures

Catheterization laboratory procedures	Hand washing	Gloves/ double gloves	Isolation gown	Surgical mask	N-95 mask	Face shield	PAPR system	Surgical cap	Shoe cover
Primary PCI on proven non-COVID-19 cases	Y	Y	Y	Y		Y		Y	Y
Primary PCI on suspected/confirmed COVID-19 cases	Y	Y	Y		Y	Y	Y	Y	Y
Primary PCI on suspected/confirmed COVID-19 cases and patients intubated or vomiting	Y	Y	Y		Y	Y	Y	Y	Y
Imaging procedures									
TTE on non-COVID-19 cases	Y	Y		Y					
TTE on confirmed/suspected COVID-19 patients in ECHO/Cath/EP labs	Y	Y	Y	Y		Y		Y	Y
TTE on confirmed/suspected COVID-19 patients in ICUs, ORs or ventilated patients	Y	Y	Y		Y	Y		Y	Y
TEE on non-COVID cases	Y	Y		Y					
TEE on confirmed/suspected COVID-19 cases	Y	Y	Y		Y	Y	Y/N	Y	Y

PCI, percutaneous coronary intervention; TTE, transthoracic echocardiogram; ECHO, echocardiography; Cath, cardiac catheterization; EP, electrophysiology; Labs, laboratories; ICUs, intensive care units; ORs, operating rooms.

assessed while reducing the exposure of both the HCW and the patients (75). Virtual visits consultations during the pandemic are essential in containing the spread of COVID-19, while maintaining optimal cardiovascular care. Trainees should also be involved in telemedicine, with the transition of education to a virtual platform (75). Major societies should be applauded for transforming international conferences, including the ACC and ASE annual scientific meetings, to a virtual online platform (76). This unprecedented effort serves well to maintain ongoing research collaboration and education for cardiovascular professionals worldwide.

Conclusions

COVID-19 has important cardiovascular implications, potentially mediated through several mechanisms, including direct myocardial injury, worsening of pre-existing cardiovascular co-morbidities, and adverse cardiovascular effects of potential therapies for COVID-19. Multiple studies

of novel therapeutics are underway. A spotlight has been cast on virtual cardiology, as the cardiovascular community embraces international collaboration to combat COVID-19 and mitigate its impact on the cardiovascular system.

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