# JAMA Cardiology | Review Potential Effects of Coronaviruses on the Cardiovascular System A Review

Mohammad Madjid, MD, MS; Payam Safavi-Naeini, MD; Scott D. Solomon, MD; Orly Vardeny, PharmD

**IMPORTANCE** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) has reached a pandemic level. Coronaviruses are known to affect the cardiovascular system. We review the basics of coronaviruses, with a focus on COVID-19, along with their effects on the cardiovascular system.

**OBSERVATIONS** Coronavirus disease 2019 can cause a viral pneumonia with additional extrapulmonary manifestations and complications. A large proportion of patients have underlying cardiovascular disease and/or cardiac risk factors. Factors associated with mortality include male sex, advanced age, and presence of comorbidities including hypertension, diabetes mellitus, cardiovascular diseases, and cerebrovascular diseases. Acute cardiac injury determined by elevated high-sensitivity troponin levels is commonly observed in severe cases and is strongly associated with mortality.

**CONCLUSIONS AND RELEVANCE** Coronavirus disease 2019 is associated with a high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias. Extensive efforts are underway to find specific vaccines and antivirals against SARS-CoV-2. Meanwhile, cardiovascular risk factors and conditions should be judiciously controlled per evidence-based guidelines.

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Author Affiliations: McGovern Medical School, Department of Medicine, University of Texas Health Science Center at Houston, Houston (Madjid); Texas Heart Institute, Houston (Safavi-Naeini); Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Solomon); University of Minnesota, Minneapolis (Vardeny).

Corresponding Author: Mohammad Madjid, MD, MS, McGovern Medical School, Department of Medicine, University of Texas Health Science Center at Houston, 6431 Fannin, MSB 1.246, Houston, TX 77030 (mmadjid@gmail.com).

oronaviruses (CoVs) are single-stranded positive-sense RNA viruses, with the capacity for rapid mutation and recombination. Coronaviruses are known to cause respiratory or intestinal infections in humans and animals.<sup>1</sup> Acute respiratory infections, including influenza, respiratory syncytial virus, and bacterial pneumonias, are well-recognized triggers for cardiovascular diseases (CVD),<sup>2,3</sup> and the underlying CVD is usually associated with comorbidities, which may increase the incidence and severity of infectious diseases.<sup>4</sup> The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which causes coronavirus disease 2019 (COVID-19), has rapidly grown into a pandemic, and a large proportion of affected patients have been reported to have underlying CVD.<sup>5,6</sup> In this report, we briefly review the basics of coronaviruses and their potential effects on the cardiovascular system. Our knowledge of COVID-19 is still evolving rapidly, and this review discusses previous learnings from outbreaks of SARS and Middle East respiratory syndrome (MERS), as well as seasonal influenza, to obtain further insight into effects of coronaviruses on the cardiovascular system. Understanding the effects of COVID-19 on the cardiovascular system is essential for providing comprehensive medical care for cardiac patients.

# Coronaviruses in Humans

Coronaviruses are named for crownlike spikes on their surface and belong to the *Coronavirinae* subfamily, which are further classified into 4 groups: the a,  $\beta$ ,  $\gamma$ , and  $\delta$  CoVs by phylogenetic clustering, of which a and  $\beta$  are known to cause infection in humans.<sup>7</sup> Coronaviruses contain 4 major structural proteins: the spike (S) protein (which mediates attachment to the host receptor and subsequent fusion of the virus and cell membrane), the nucleocapsid (N) protein, the membrane (M) protein, and the envelope (E) protein.<sup>8</sup>

The first human CoV (HCoV) was identified in the mid-1960s in human embryonic tracheal organ cultures, and until 2003, only 2 HCoV species, HCoV-229E and HCoV-OC43, were recognized. Currently, 7 different CoV strains are known to infect humans, including HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1, which generally cause self-resolving infection. There are also severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), and newly identified SARS-CoV-2, which can cause lethal respiratory infections in humans.<sup>9,10</sup>

Table 1. Coronaviruses Known to Cause Severe Viral Pneumonia									
		Incubation		%					
Coronavirus	Receptor	period, d	RO	Prevalence of underlying CVD	Average case fatality rate				
SARS CoV	ACE2	2-11	3	10	10				
MERS CoV	DPP4	2-13	2 to 5	30	30				
SARS-CoV-2	ACE2	2-14	2 to 3	4.2 Overall and up to 40 in hospitalized patients	0.7 to 8 (Varies per location and time)				

Abbreviations: CVD, cardiovascular disease; MERS CoV, Middle East respiratory syndrome coronavirus; RO, the basic reproduction number; SARS CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

# **Endemic Coronaviruses**

Four HCoV types, including HCoV-229E (a-CoV), HCoV-NL63 (a-CoV), HCoV-OC43 ( $\beta$ -CoV), and HCoV-HKU1 ( $\beta$ -CoV) are endemic in humans and usually cause mild, self-limiting respiratory infections, which account for 15% to 30% of common colds.<sup>11</sup> Infection with these HCoVs typically cause mild upper respiratory infections in young adults but may lead to hospitalization in elderly patients with underlying cardiac and lung disease.<sup>12</sup> Typically, coronaviruses account for a small percentage of patients hospitalized for acute respiratory illness.<sup>13</sup>

# Severe Acute Respiratory Syndrome Coronavirus

The SARS-CoV outbreak began in the Guangdong Province in southern China in November 2002, and was most likely linked to a zoonotic event in the wild-animal markets in China. Soon after the isolation of SARS-CoV, SARS-CoV-like viruses were found in Himalayan palm civets and raccoon dogs, with 99.8% nucleotide homology to human SARS-CoV.<sup>14</sup>

The SARS-CoV belongs to the  $\beta$ -CoVs group and binds to the zinc peptidase angiotensin-converting enzyme 2 (ACE2), a surface molecule that is localized on the endothelial cells of arteries and veins, arterial smooth muscle, respiratory tract epithelium, epithelia of the small intestine, respiratory tract epithelium, and immune cells, to enter the host cell.<sup>15-17</sup> Suppression of ACE2 expression during SARS-CoV infection has been proposed to play a role in the pathologic changes in the lung and contribute to the severe pneumonia and acute lung failure observed with this virus.<sup>18</sup>

Further studies of wild animals proved robust evidence that SARS-CoV might have originated in bats, when a SARS-like CoV was identified in Chinese horseshoe bats with a sequence similarity of 87% to 92% with human SARS-CoV, and it is believed that palm civets and raccoon dogs provided the intermediate amplification host for SARS-CoV before transmitting it to animal handlers in the animal market.<sup>14</sup> Transmission of SARS-CoV is primarily from personto-person close contact, via respiratory droplets, with an incubation period of 2 to 11 days after exposure.<sup>11</sup> The SARS-CoV may be shed into the environment and transferred from environmental surfaces to the hands of patients and health care clinicians. Transmission of infection could be facilitated through contact with the nose, eyes, or mouth.<sup>19,20</sup> The ability of an infected patient to transmit the virus to other individuals is assessed by RO (ie, R naught: basic reproduction number).<sup>21</sup> The estimated RO for SARS-CoV is about 3, which means that each person with SARS-CoV is expected to infect 3 other persons in a susceptible population (Table 1).<sup>22</sup>

In 2003, a total of 8096 people in 29 countries were reported ill with SARS and 774 of them died (around 10%). In the United States, there were 8 laboratory-confirmed and an additional 19 probable SARS cases, with no causal fatalities. The global SARS outbreak cost the world around \$40 billion over a period of 6 months.<sup>23,24</sup> Currently, there is no vaccine or specific antiviral effective against SARS-CoV. Therefore, treatment of SARS entailed supportive care and use of broad-spectrum antimicrobial coverage to treat secondary bacterial infection. Advanced age (especially older than 60 years), underlying comorbidities (such as diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease), and high-lactate dehydrogenase (LDH) at presentation were independent predictive factors of mortality in SARS-CoV infection.<sup>25</sup> Of note, during the SARS outbreak, there was not a significant increase in morbidity or mortality in infants and children.<sup>14</sup>

#### **Cardiovascular Complications of SARS**

The SARS-CoV also may have also resulted in cardiovascular complications, although most of the data have been anecdotal in the absence of systematic studies. Acute coronary syndrome and myocardial infarction were noted to occur after SARS.<sup>26,27</sup> In a limited study of 75 patients hospitalized with SARS, acute myocardial infarction (AMI) was the cause of death in 2 of 5 fatal cases.<sup>26</sup> Findings from this limited study have not been confirmed in other reports. A small prospective study among 46 patients with established clinical diagnosis of SARS and without preexisting cardiac disease collected information at the acute stage of infection (baseline) and 30 days later and showed no significant change in systolic function.<sup>28</sup> However, transient diastolic function was detected during SARS infection which was resolved on follow up.<sup>28</sup>

In another study of 121 patients (mean [SD] age of 37.5 [13.2] years; 36% men) with a diagnosis of SARS, in whom 12 patients had underlying cardiovascular disease, tachycardia was the most common finding (72%), and other complications were hypotension (50%), bradycardia (15%), transient cardiomegaly (11%), and transient paroxysmal atrial fibrillation in only 1 patient.<sup>29</sup> Most of these patients were asymptomatic, and these conditions were mostly self-limiting.

A study from Singapore<sup>27</sup> reported postmortem examinations in 8 patients who died from SARS in which 4 patients had pulmonary thromboemboli and 3 patients had deep vein thrombosis. One patient had subendocardial infarction with occlusive coronary disease (who had AMI on presentation with SARS). One patient had marantic 5- to 12-mm valvular vegetations involving the mitral, tricuspid, and aortic valves, along with infarction in heart, kidneys, spleen, and brain.<sup>27</sup> The presence of pulmonary embolism (PE) and deep vein thrombosis and AMI are of great clinical interest, but the generalizability of this limited study is not established.

# Middle East Respiratory Syndrome

The MERS-CoV epidemic emerged in Saudi Arabia in June 2012.<sup>30</sup> The virus transmitted from infected dromedary camels, as the intermediate host, to humans through close contact. It is believed that in the distant past, the MERS-CoV may have originated in bats and transmitted to dromedary camels.<sup>30,31</sup> Middle East respiratory syndrome CoV belongs to the  $\beta$ -CoVs group and use a serine peptidase, dipeptidyl peptidase 4, as the receptor to enter the host cell.<sup>15</sup> Middle East respiratory syndrome CoV spreads from an infected person's respiratory secretions to others through close contact, with an incubation period of 2 to 13 days.<sup>11,32</sup> Middle East respiratory syndrome CoV is likely shed into the environment and transferred from environmental surfaces to hands, which then could cause infection through contact with the nose, eyes, or mouth in patients similar to SARS-CoV.<sup>19</sup>

As of November 30, 2019, a total of 2494 laboratoryconfirmed infections of MERS-CoV have been reported, with 858 associated deaths (case-fatality rate: 34.4%) in 26 countries, with most cases from Saudi Arabia, with 2102 cases with a case-fatality rate of 37.1%.<sup>33</sup> The estimated RO of MERS-CoV outbreaks in Saudi Arabia and South Korea were between 2 to 5, which means that each person with MERS-CoV is expected to infect 2 to 5 other people in a totally susceptible population.<sup>34</sup> The clinical risk factors for mortality in MERS were older age, male sex, and underlying medical conditions including diabetes mellitus, cardiac diseases, chronic kidney disease, respiratory disease, hypertension, and cancer.<sup>35,36</sup> A systematic analysis of 637 MERS-CoV patients showed that 30% of cases had underlying cardiac diseases, 50% had hypertension, 50% had diabetes, and 16% had obesity.<sup>37</sup>

# Severe Acute Respiratory Syndrome Coronavirus 2, Causing COVID-19

On December 31, 2019, several local health facilities reported clusters of pneumonia of unknown etiology that were epidemiologically linked to a large seafood and live-animal market in Wuhan, Hubei Province, China. On January 9, 2020, a novel coronavirus, SARS-CoV-2, initially named as 2019-nCoV, was officially identified as the cause of an outbreak of viral pneumonia. This viral pneumonia disease was named COVID-19.<sup>38</sup> Severe acute respiratory syndrome CoV-2 belongs to the β-CoVs group that has 89% nucleotide identity with bat SARS-like CoVZXC21 and 82% with that human SARS-CoV, and similar to SARS-CoV, uses ACE2 as the receptor to enter the host cell.<sup>39,40</sup> The SARS-CoV-2 is less genetically similar to MERS-CoV (around 50% nucleotide identity).<sup>41</sup> The SARS-CoV-2 infection causes a severe respiratory illness with many epidemiologic, clinical, radiologic, and laboratory findings similar to SARS-CoV infection in 2003.<sup>42</sup> Transmission of SARS-CoV-2 seems to be primarily from person to person via close contact, through respiratory droplets, with a mean incubation period of 5.2 days (95% CI, 4.1-7.0 days), with the 95th percentile of the distribution at 12.5 days.<sup>42,43</sup> Another study estimated the incubation period to be up to 14 days (ranges from 2-14 days).<sup>44</sup>

There is some concern about a possible fecal-oral route of transmission for SARS-CoV-2 because patients with SARS and MERS frequently had diarrhea, and SARS-CoV RNA was detected in stools of patients with SARS.<sup>45</sup> Gastrointestinal symptoms, such as diarrhea, abdominal pain, and vomiting, have been reported in 2% to 10% of patients with COVID-19,<sup>45</sup> and a March 2020 report<sup>46</sup> from a US patient showed positive stool test for SARS-CoV-2.

As of March 19, 2020, there have been 213 254 confirmed cases of COVID-19 reported worldwide, with 8843 fatalities.<sup>47</sup> The estimated RO of SARS-CoV-2 is between 2 and 3, which means that each person with SARS-CoV-2 infection is expected to infect 2 to 3 other people in a susceptible population.<sup>43,48</sup> For comparison purposes, the average RO for seasonal influenza is around 1.3.<sup>49</sup>

The SARS-CoV-2 infection primarily affects adults, with fewer cases reported in children of 15 years or younger. 43,50,51 As of March 3, 2020, per World Health Organization Director-General's opening remarks, the global mortality rate has been about 3.4%. The overall crude fatality rate varies by location, intensity of transmission, and variations of care. The nationwide mortality rate in China has been around 3.8% (5.8% in Wuhan; 0.7% other areas in China).<sup>52</sup> In 1099 laboratory-confirmed cases, the overall mortality rate was 1.4%.<sup>53</sup> In China, the overall crude fatality rate was higher in the early stages of the outbreak and has decreased over time (to 0.7% for patients with symptom onset after February 1, 2020), which could possibly be owing to evolution in patients' standard of care.<sup>52</sup> A different method of mortality estimation using the number of death divided by the number of cases diagnosed 14 days prior (ie, the incubation period) yields a global mortality rate of 5.7%.<sup>54</sup> Of note, owing to presence of undiagnosed asymptomatic or mildly symptomatic cases, the full denominator remains unknown. However, the mortality rate is higher in Italy (about 8%), while it is much lower in South Korea (about 0.6%). It is not known whether these difference are due to higher percentage of older patients in Italy, widespread testing in South Korea that increases the denominator by including more asymptomatic or mildly symptomatic low-risk patients, or other undetermined factors. The overall symptomatic secondary attack rate (the rate of transmitting the disease to close contacts) in patients with COVID-19 is 0.45% for close contacts and 10.5% for household members.55

The 3 primary symptoms of COVID-19 are fever, cough, and shortness of breath. Less common symptoms are muscle pain, anorexia, malaise, sore throat, nasal congestion, dyspnea, and headache. Symptoms may appear in as few as 2 days or as long as 14 days after exposure.<sup>56</sup> The detected viral load is similar in the asymptomatic and symptomatic patients with COVID-19, which suggests potential transmission of the virus from asymptomatic or minimally symptomatic patients to other persons.<sup>57</sup> Higher viral loads were detected early after symptom onset, and viral loads were higher in the nose compared with the throat.<sup>57</sup> In the United States, diagnosis is currently through SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction diagnostic panel using upper and lower respiratory specimens.<sup>56</sup> New serologic tests, at-home test kits, and point-of-care tests are likely to become available in the near future. Simultaneous coinfection with other respiratory viruses has been reported.58

Chest computed tomography scan has been widely used to further assess patients with COVID-19. Early evidence suggests that initial chest computed tomography shows an abnormality in at least 85% of patients, with 75% of patients having a bilateral lung in-

volvement that most often manifests as subpleural and peripheral areas of ground-glass opacity and consolidation.<sup>59</sup>

# **Presentation Features of COVID-19**

In a large study<sup>53</sup> of 1099 hospitalized and outpatient laboratoryconfirmed patients with COVID-19, the median age was 47 years, 41.9% were women, and the most common symptoms were fever (43.8% on admission and 88.7% during admission) and cough (67.8%). Diarrhea was present in 3.8%. The median incubation period was 4 days, with interquartile range of 2 to 7 days. Pulmonary ground-glass opacity was seen in 56.4% on computed tomography scan.<sup>53</sup> Computed tomography did not show any significant abnormality in 17.9% of nonsevere and 2.9% of severe cases. Lymphocytopenia (83.2%), thrombocytopenia (36.2%), and leukopenia (33.7%) were frequently observed in patients on admission. The most common comorbidities among these patients include hypertension (14.9%), diabetes (7.4%), and coronary heart disease (2.5%).<sup>53</sup> Median length of hospital stay was 12 days (interquartile range, 10-14). Severe illness happened in 15.7% of patients after admission to a hospital, 5% were admitted to an intensive care unit (ICU), 2.3% were intubated, and 1.4% died. The most common significant complications were acute respiratory distress syndrome (ARDS) in 3.4% (1.1% in nonsevere cases and 15.6% in severe cases) and septic shock in 1.1% (0.1% in nonsevere cases and 6.4% in severe cases).<sup>53</sup>

Preliminary reports from 4226 patients with COVID-19 in the United States indicate that the highest fatality is seen in persons 85 years and older (10% to 27%), followed by persons aged 65 to 84 years (3% to 11%), persons aged 55 to 64 years (1% to 3%), and persons aged 20 to 54 years (<1%), with no fatalities among persons 19 years and younger.<sup>60</sup> However, hospitalization and ICU admission rates do not follow this pattern and are fairly common in younger age strata, and (in contrast to the earlier reports from China) 20% of deaths occurred among adults aged 20 to 64 years, and 20% of those hospitalized were aged 20 to 44 years.<sup>60</sup>

#### Comorbidities in Patients With COVID-19

In a series of 44 672 confirmed patients with COVID-19 from China (which included mild cases),<sup>61</sup>4.2% were reported to have CVD and 12.8% had hypertension (while 53% of cases had missing data on comorbid conditions). In this population, 80.9% were reported to have mild disease with no mortality, 13.8% had severe disease with no mortality, and 4.7% had critical disease with a case fatality rate of 49%.<sup>61</sup> The prevalence of CVD in different disease severity categories was not reported. The COVID-19 mortality rose with advanced age, with case-fatality rate of 1.3% in patients aged 50 to 59 years, 3.6% in patients aged 60 to 69 years, 8% in patients aged 70 to 79 years, and 14.8% in patients 80 years or older.<sup>61</sup> Patients with CVD composed 4.2% of confirmed cases yet made up 22.7% of all fatal cases, with a case fatality rate of 10.5%.<sup>61</sup> The case fatality rate for patients with hypertension was 6%, diabetes was 7.3%, and in chronic respiratory disease was 6.3%.<sup>61</sup> Coronavirus disease 2019 almost equally infects both sexes; however, men showed a higher case fatality rate than women (3.6% vs 1.6%, respectively). The overall case fatality rate in this study was 2.3%.<sup>61</sup> The high percentage of missing data (53%) in this study can affect the described prevalence and case fatality ratios.

In a single-center study<sup>10</sup> among 99 patients (mean age of 55.5 years; 67% men) with COVID-19, 40% of patients had underlying

cardiovascular or cerebrovascular disease. In another study<sup>50</sup> of 41 admitted hospital patients (median age of 49 years; 73% men) with COVID-19, 32% of patients had underlying diseases, including cardiovascular disease (15%), hypertension (15%), and diabetes (20%). The most common COVID-19-related complications were ARDS (29%), viremia (15%), acute cardiac injury determined by elevated high-sensitivity troponin (12%), and secondary infection (10%).<sup>50</sup> In this study.<sup>50</sup> a wide array of plasma inflammatory biomarkers were elevated in both ICU patients and non-ICU patients compared with healthy adults, which provides further evidence for presence of cytokine storm that can further contribute to complications.<sup>50</sup>

In another study<sup>62</sup> in 138 hospitalized patients with COVID-19, 36 (26.1%) were transferred to the ICU owing to complications, including ARDS (61%), arrhythmias (44%), and shock (31%). Sixtyfour patients (46.4%) had 1 or more comorbidities including hypertension (31%), diabetes (10%), cardiovascular disease (14.5%), and malignant neoplasms (7.2%).<sup>62</sup>

#### Factors Associated With Mortality in COVID-19

In 52 critically ill patients with COVID-19 who were admitted to the ICU, mean age was 59.7 years, and the mortality rate was 61.5% by 28 days.<sup>51</sup> Three patients from primary population had a fatal cardiac arrest before getting included in this study. The overall rate of comorbidities among the 2 groups of survivors (n = 20) vs nonsurvivors (n = 32) was 40% (20% vs 53%), with CVD (20% vs 53%), chronic cardiac disease (10% vs 9%) and cerebrovascular disease (0% vs 22%) accordingly.<sup>51</sup> Most critical patients showed signs of organ function damage, including ARDS in 67%, acute kidney injury in 29%, cardiac injury in 23%, liver dysfunction in 29%, and pneumothorax in 2%. Cardiac injury was defined as an elevated serum level of high-sensitivity cardiac troponin I (hs-TnI) greater than the upper limit of the reference range (>28 pg/mL), which was increased in 15% of survivors and 28% of nonsurvivors. Older age (>65 years), comorbidities, and ARDS were factors associated with death.51

In a series of 191 patients with laboratory-confirmed COVID-19, 54 died and 137 survived.<sup>63</sup> The odds of death increased with age, Sequential Organ Failure Assessment, and high D-dimer levels on admission. The median duration of viral shedding was 20 days in survivors (interquartile range, 17-24 days). Fatal cases showed a higher rate of comorbidities including hypertension (48% vs 23%), diabetes (31% vs 14%), and coronary heart disease (24% vs 1%) when compared with survivors, respectively.<sup>63</sup> The high-sensitivity troponin and inflammatory biomarkers (ie, interleukin-6 and serum ferritin) were higher in nonsurvivors. Nonsurvivors showed higher rates of heart failure (52% vs 12%) and acute cardiac injury (59% vs 1%) than survivors.<sup>63</sup>

Another small retrospective study<sup>64</sup> of 150 patients with laboratory-confirmed COVID-19 evaluated the factors associated with mortality. Cardiovascular disease was more prevalent in patients who died (13 of 68) than patients who survived (0 of 82). Among the 68 fatal cases, 36 died of respiratory failure, 5 died of myocardial damage and circulatory failure, 22 died of both causes, and 5 died from undetermined causes.<sup>64</sup> Patients who died had higher levels of troponin, myoglobin, C-reactive protein, serum ferritin, and interleukin-6. This study is further suggestive of a high inflammatory burden in COVID-19 and a possible rise in myocarditis-related cardiac events.<sup>64</sup>

#### Importance of Myocarditis in COVID-19

Severe acute respiratory syndrome CoV-2 appears to affect the myocardium and cause myocarditis.<sup>65</sup> Sporadic autopsy cases suggest infiltration of myocardium by interstitial mononuclear inflammatory cells.<sup>65</sup> In parallel, cases of severe myocarditis with reduced systolic function have been reported after COVID-19.<sup>66,67</sup> Cardiac biomarker studies suggest a high prevalence of cardiac injury in hospitalized patients.<sup>65,68,69</sup> Myocardial injury is likely associated with infection-related myocarditis and/or ischemia and is an important prognostic factor in COVID-19.

Shi et al<sup>68</sup> reported the importance of cardiac injury in COVID-19 mortality in 416 patients hospitalized with COVID-19, of whom 57 died. In these patients, 10.6% had coronary heart disease, 4.1% had heart failure, and 5.3% had cerebrovascular disease. Approximately 20% of patients had cardiac injury defined as hs-TNI greater than the 99% percentile upper reference limit. Patients with elevated hs-TNI were older, had more comorbidities, and had higher levels of leukocytes, N-terminal pro-brain natriuretic peptides, Creactive protein, and procalcitonin, but lower lymphocyte counts.<sup>68</sup> Patients with cardiac injury had a higher incidence of ARDS (58.5% vs 14.7%; *P* < .001) and a higher mortality rate (51.2% vs 4.5%; *P* < .001) than those without cardiac injury. In multivariable adjusted models, cardiac injury and ARDS were significantly and independently associated with mortality, with hazard ratios of 4.26 and 7.89, respectively.<sup>68</sup>

Similarly, Guo et al<sup>69</sup> reported factors associated with outcomes in 187 patients hospitalized with COVID-19 (43 died; 144 discharged) in Wuhan, China. In this study, 35% had underlying CVD (hypertension, coronary heart disease, or cardiomyopathy), and 28% showed evidence of acute myocardial injury (defined as elevated troponin T [TnT] greater than the 99th percentile upper limit).<sup>69</sup> Mortality was significantly higher in individuals with high TnT vs those with normal TnT levels (59.6% vs 8.9%, respectively; P < .001). Patients with high TnT levels were older, more likely to be men, and had higher comorbidities including hypertension, coronary heart disease, cardiomyopathy, and chronic kidney disease. Patients with high TNT levels also had higher leukocyte counts, lower lymphocyte counts, and higher levels of D-dimer, C-reactive protein, procalcitonin, and N-terminal pro-brain natriuretic peptides.<sup>69</sup> As for outcomes, patients with a high TNT level showed higher incidence of complications such as ARDS, malignant arrhythmias, acute renal injury, and acute coagulopathy. Copresence of CVD and elevated TnT was associated with the highest mortality rate in this group while patients without an elevated TnT, even in presence of CVD, had a lower mortality risk. Although more patients were using ACE inhibitor and angiotensin II receptor blocker (ARB) medications (owing to their baseline CVD) in the high TnT group, their use was not associated with patients' mortality rate.69

### Implications

Currently, COVID-19 has reached a pandemic level and is a threat to global health. Its course is still evolving, and it is too early to predict its trajectory over the next few months or years.

Lessons from the previous coronavirus and influenza epidemics suggest that viral infections can trigger acute coronary syndromes,<sup>3,70</sup> arrhythmias,<sup>71</sup> and development of exacerbation of heart failure, <sup>72</sup> primarily owing to a combination of a significant systemic inflammatory response plus localized vascular inflammation at the arterial plaque level along with other effects (**Figure**).<sup>3,73-75</sup> Coronavirus disease 2019 may either induce new cardiac pathologies and/or exacerbate underlying cardiovascular diseases. The severity, extent, and short-term vs long-term cardiovascular effects of COVID-19, along with the effect of specific treatments are not yet known, and are subject to close scrutiny and investigation.

Importantly, during most influenza epidemics, more patients die of cardiovascular causes than pneumonia-influenza causes.<sup>76</sup> Given the high inflammatory burden of COVID-19,<sup>50</sup> and based on early clinical reports, significant cardiovascular complications with COVID-19 infection are expected. The prevalence of CVVID-19 is likely lower.

Unlike influenza, COVID-19 shows a low incidence of severe cases in young children.<sup>5</sup> This is either owing to possible resistance to infection in the young (with very important clinical and epide-miologic implications) or owing to very mild symptoms in them (with implications for estimating the size of the denominator of the whole population).<sup>5</sup> To date, advanced age (>60 years), male sex, and presence of comorbidities are known to be the major risk factors for COVID-19 mortality.<sup>5</sup> Presence of cardiac injury (defined by elevated troponin levels), myocarditis, and ARDS are other strong and independent factors associated with mortality.<sup>64,68,69</sup>

Most available reports are primarily from China, where the smoking rate in the adult male population is very high (more than 50% in men and less than 3% in women), and it is not known whether the observed sex differences are primarily owing to disproportionate rate of smoking between genders or is associated with different immune responses or other factors.

The exact clinical course, severity, and complications of COVID-19 are not yet completely determined. In the latest report from China, 81% of infections were classified as mild, 14% as severe, and only 5% as critical.<sup>77</sup> Critical cases are defined as having respiratory failure, septic shock, and/or multiple organ dysfunction or failure (with fatal cases reported only in the last group).<sup>77</sup> It is reasonable to expect that severe and critical cases have more severe effects on the cardiovascular system owing to more robust inflammatory response. At this early stage, our knowledge is mainly based on available numerators data, and the exact population-level denominators are not known. Also, it is likely that the asymptomatic and mildly symptomatic cases are missing from most reports, which further skews our understanding of the disease.

At a population level, large-scale public health interventions with preparedness plans and mitigation interventions are being developed and implemented. Public health measures, such as selfisolation and quarantining the infected patients as well as early detection of the disease, are critical for containing and treating the disease. Aggressive compliance with basic hygiene skills along with minimizing the exposure to SARS-CoV-2 is key to preventing COVID-19 and should be strongly implemented. Strict adherence to universal precaution measures is crucial in health care settings. The US Centers for Disease Control and Prevention recommends using standard precautions, contact precautions, and eye protection when caring for patients with confirmed or possible COVID-19. Airborne precautions are particularly recommended for procedures in which aerosolized particles might be induced.



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		Estimated			
Drug	Status	No. of enrollment	Study start date	Primary completion date	ClinicalTrials.gov identifier
Remdesivir	Recruiting	394	February 21,	April 1,	NCT04280705
Recombinant human angiotensin-converting enzyme 2	Not yet recruiting	24	February 2020	April 2020	NCT04287686
Remdesivir	Not yet recruiting	400	March 2020	May 2020	NCT04292899
Injection and infusion of LV-SMENP-DC vaccine and antigen-specific CTLs	Recruiting	100	February 24, 2020	December 31, 2024	NCT04276896
Thalidomide	Not yet recruiting	100	February 20, 2020	June 30, 2020	NCT04273529
Fingolimod	Recruiting	30	February 22, 2020	July 1, 2020	NCT04280588
Human umbilical cord mesenchymal stem cells	Recruiting	48	February 24, 2020	February 1, 2021	NCT04293692
Carrimycin	Not yet	520	February 23, 2020	February 28, 2021	NCT04286503
Methylprednisolone	Recruiting	400	February 14, 2020	May 30, 2020	NCT04273321
PD-1 and thymosin	Not yet	120	February 10, 2020	October 31, 2020	NCT04268537
Bromhexine hydrochloride	Enrolling by invitation	60	February 16, 2020	April 30, 2020	NCT04273763
Washed microbiota transplantation	Enrolling by	40	February 2, 2020	April 16, 2020	NCT04251767
Intravenous immunoglobulin	Not yet recruiting	80	February 10, 2020	June 30, 2020	NCT04261426
Abidol hydrochloride	Not yet recruiting	400	February 1, 2020	February 1, 2020	NCT04255017
ASC09F+oseltamivir or ritonavir+oseltamivir	Not yet recruiting	60	February 1, 2020	July 1, 2020	NCT04261270
N-acetylcysteine+ Fuzheng Huayu tablet	Recruiting	136	February 15, 2020	December 2022	NCT04279197
Immunoglobulin from cured patients with 2019-nCoV pneumonia	Not yet recruiting	10	February 17, 2020	May 31, 2020	NCT04264858
Lopinavir/ritonavir tablets combined with Xiyanping injection	Not yet recruiting	80	March 14, 2020	April 14, 2021	NCT04295551
Bevacizumab injection	Recruiting	20	February 2020	May 2020	NCT04275414
Ganovo + ritonavir+/ -Interferon atomization or long-acting interferon or recombinant cytokine gene-derived protein or lopinavir plus ritonavir drug: Chinese medicines + interferon atomization	Recruiting	50	February 17, 2020	April 30, 2020	NCT04291729
Recombinant human interferon α1β	Not yet recruiting	328	March 1, 2020	June 30, 2020	NCT04293887
Vitamin C (24 g infusion)	Not yet recruiting	140	February 10, 2020	September 30, 2020	NCT04264533
Xiyanping injection or lopinavir/ritonavir, α-interferon nebulization	Not yet recruiting	348	February 14, 2020	December 14, 2021	NCT04275388
Darunavir and Cobicistat	Recruiting	30	January 30, 2020	December 31, 2020	NCT04252274
Hydroxychloroquine	Recruiting	30	February 6, 2020	December 31, 2020	NCT04261517
Meplazumab injection	Recruiting	20	February 3, 2020	December 31, 2020	NCT04275245
Sildenafil	Recruiting	10	February 9, 2020	November 9, 2020	NCT04275947
2019-nCoV vaccine (mRNA-1273)	Recruiting	45	March 3, 2020	June 1, 2021	NCT04283461
Losartan	Not yet recruiting	200	March 16, 2020	April 1, 2021	NCT04312009
Losartan	Not yet recruiting	478	March 16, 2020	April 1, 2021	NCT04311177

# Table 2. List of Selected Registered Clinical Trials for Treating COVID-19 (as of March 16, 2020)

Abbreviations: COVID-19, coronavirus disease 2019; CTLs, Cytotoxic T lymphocytes; mRNA, messenger ribonucleic acid; PD-1, programmed cell death-1; 2019-nCoV, the initial temporary name for severe acute respiratory syndrome coronavirus 2.

Until specific and effective antiviral therapies against SARS-CoV-2 become available, the treatment of COVID-19 will be primarily based on supportive care and treatment of complications. Treatment of cardiovascular complications should be based on optimal and judicious use of guideline-based therapies. As with other triggers for acute CVD events, the use of antiplatelet agents,  $\beta$ -blockers, ACE inhibitors, and statins are recommended per practice guidelines. Hypothetically, statins can curb systemic inflammation, help further stabilize the plaques, and prevent a viral-induced plaque destabilization, which can lead to acute coronary syndromes. The cytokine storm associated with COVID-19 likely plays a role in the development of ARDS and fulminant myocarditis and using immunomodulators to curtail this hyperinflammatory response might be beneficial in reducing mortality.

Extensive research is underway to develop vaccines and antivirals to control COVID-19. Remdesivir is a promising investigational nucleotide analog with broad-spectrum antiviral activity, which along with chloroquine, has been effective in inhibiting SARS-CoV-2 in vitro.<sup>78</sup> Originally developed to treat Ebola, for which it was not particularly effective, remdesivir is currently being tested in both mild to moderate (NCT04252664) and severe COVID-19 (NCT04257656). The Adaptive COVID-19 Treatment Trial sponsored by the National Institute of Allergy and Infectious Diseases has started enrolling patients, with remdesivir (vs placebo) as the first drug in the trial (NCTO4280705). This adaptive trial conducts series of 2-arm comparisons between different therapeutic agents vs a placebo. Interim analyses will introduce new arms and permit early stopping for futility, efficacy, or safety. Once a therapy is found to be efficacious, that treatment will then become the control arm for comparison(s) with additional experimental treatment(s).

A small, limited, single-arm French study<sup>79</sup> has tested the effect of hydroxychloroquine and azithromycin on the respiratory viral loads in patients with COVID-19. Twenty patients received hydroxychloroquine and 16 untreated patients from another center or cases refusing the protocol were included as controls. Six patients in the hydroxychloroquine arm also received azithromycin for superimposed infection. Patients treated with hydroxychloroguine showed a significant reduction in viral carriage by day 6 compared with control individuals.<sup>79</sup> In the 6 patients who received both hydroxychloroquine and azithromycin, virus elimination was faster and more effective.<sup>79</sup> This small study had multiple methodologic shortcomings, and further trials are testing this promising medication (NCT04261517).<sup>80</sup> A randomized, controlled, open-label trial<sup>81</sup> in 199 hospitalized patients with COVID-19 with low oxygen saturation indices tested a 14-day course of lopinavir-ritonavir vs standard care. The lopinavir-ritonavir treatment did not significantly accelerate clinical improvement, reduce 28-day mortality, or diminish throat viral RNA detectability vs standard care.<sup>81</sup> However, in a modified intention-to-treat analysis, lopinavir-ritonavir accelerated clinical improvement by 1 day.<sup>81</sup>

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Both SARS-CoV and SARS-CoV-2 use the ACE2 receptor to enter the host cells, and ACE2 negatively regulates the reninangiotensin system by inactivating angiotensin II and likely plays a protective role against the development and progression of acute lung failure.<sup>15,16</sup> The clinical role of this pathway in COVID-19 complications and any effect from possible modulation of this receptor is not yet fully known and going to be tested in upcoming clinical trials (NCTO4287686). At present, to our knowledge, there are no peerreviewed experimental or clinical data demonstrating a specific benefit or risk from using ACE inhibitors, ARBs, or renin-angiotensinaldosterone system antagonists in COVID-19.<sup>82</sup> A joint statement by the Heart Failure Society of America, American College of Cardiology, and American Heart Association recommends that these medications can be continued in patients with COVID-19 without interruption in compliance with available clinical guidelines.<sup>82</sup>

The ACE2-dependent entry of SARS-CoV-2 into host cells can be blocked by camostat mesylate, an inhibitor of the cellular serine protease TMPRSS2, which is used by SARS-CoV-2 for S protein priming.<sup>83</sup> Camostat mesylate is clinically available in Japan and is a promising agent to be tested further.<sup>83</sup> Among anti-influenza medications, oseltamivir does not affect SARS-CoV-2, while preliminary studies have suggested some benefit from using favipiravir. A few health officials have suggested avoiding the use of nonsteroidal antiinflammatory drugs in patients with COVID-19, but peer-reviewed data in support of this claim are not yet available. **Table 2** lists a number of medications that are either being tested or in planning stages for testing in patients with COVID-19.

Meanwhile, vaccinations against influenza and pneumonia should be optimized to prevent febrile diseases that can masquerade or mask the diagnosis of COVID-19. This is particularly important because a high seasonal influenza activity is still observed in the United States. Vaccination against pneumococcal pneumonia should also be increased to reduce the risk of superimposed bacterial pneumonia.

# Conclusions

Our understanding of COVID-19, its diagnosis, prevention, and treatment is rapidly evolving. Physicians are urged to check the website of the US Centers for Disease Control and Prevention and professional societies for the latest guidances.<sup>84</sup> As the disease spreads and new evidence emerges, it would be prudent to identify the risk factors for the development of cardiac complications in patients with COVID-19. A prospective registry of patients with COVID-19 with a systematic recording of clinical variables and cardiovascular complications, to develop a risk model for cardiac complications, and to identify and/or predict response to various treatment modalities.

consulted for Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GSK, Ironwood, Merck, Myokardia, Novartis, Roche, Sanofi-Pasteur, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Tenaya, Dinaqor, and Tremeau. No other disclosures were reported.

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