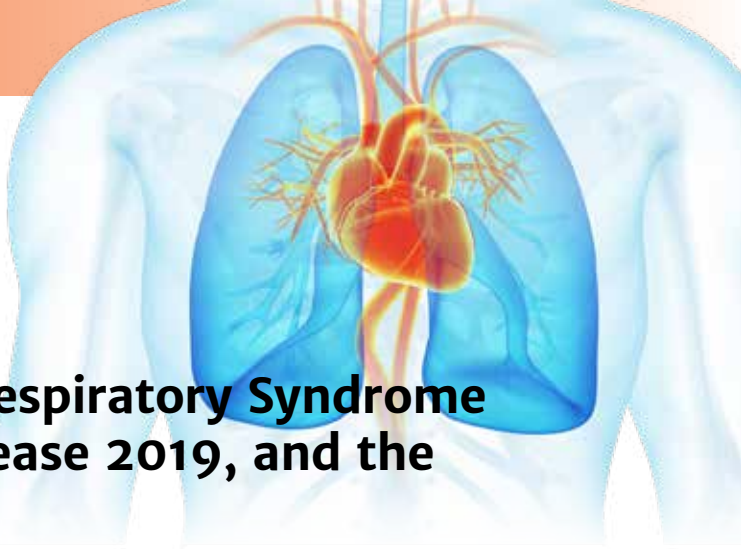

Intersections of Severe Acute Respiratory Syndrome Coronavirus 2, Coronavirus Disease 2019, and the Cardiovascular System

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has far-reaching impacts on human health. First identified as a disease of the respiratory system, COVID-19 also causes gastrointestinal, renal, neurological, and/or cardiovascular symptoms. This article elucidates biological relationships between COVID-19 and the cardiovascular system. It postulates molecular and physiological mechanisms behind COVID-19–related cardiovascular ailments and examines intersections among the cardiovascular system, SARS-CoV-2, COVID-19, and certain medications. New scientific information on COVID-19 and the cardiovascular system accumulates weekly. In recognition of such rapidity, this paper offers a framework in which the reader will be able to place the growing and evolving field of knowledge.

EFFECTS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION ON THE CARDIOVASCULAR SYSTEM

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells through an interaction between the virus's spike (S) protein and angiotensin-converting enzyme (ACE) 2 in host cells.[1-5] Within the cardiovascular system, ACE2 is reportedly located on heart muscle cells,[6-11] endothelial cells (ECs) that line the interior of blood vessels and regulate blood clotting and blood pressure,[12,13] pericytes that surround and aid ECs,[6-8] and arterial smooth muscle cells (SMCs) that control vascular diameter and thereby blood pressure and flow.[7,12,13] SARS-CoV-2 infection of these cells hinders their health-promoting work.

Cardiovascular health is also threatened when SARS-CoV-2 invades noncardiac areas and triggers immune responses. To fight the "intruder," local white blood cells activate, recruit other white blood cells, and produce pro-inflammatory chemicals, which increases inflammation. Interestingly, a source of these chemicals may be direct SARS-CoV-2 infection of macrophages—a type of white blood cell that expresses ACE2.[14] As the immune system battles the virus, the affected body organ may (temporarily) malfunction. These malfunctions and the pro-inflammatory chemicals released into the blood may elicit negative effects on blood vessels and the heart.[15]

Cardiovascular conditions induced by these direct and indirect effects of SARS-CoV-2 infection include myocarditis (inflamed heart tissue), blood pressure irregularities, abnormal blood clot (thrombus) formation, hypoxia, arteriosclerotic heart disease (ASHD), myocardial infarctions (MIs; heart attacks), arrhythmias, and heart failure (Figure 1).[16-29] If left unchecked or if severe enough, these ailments could be fatal.

Myocarditis

Myocarditis compromises contractility of the heart muscle. As a result, the heart compensates in order to insure proper delivery of blood (and O_2) to the body. Compensation occurs by one of at least 2 methods: (1) thickening of the heart muscle layer (hypertrophy), and (2) heart rate elevation (tachycardia). Both choices could progressively worsen the heart's already precarious condition.

Blood Pressure Irregularities

Some patients with coronavirus disease 2019 (COVID-19) present with hypertension.[19] The causal link between this elevated blood pressure and SARS-CoV-2 may be ACE2. Besides being the binding target of SARS-CoV-2's S protein, ACE2 is part of the renin–angiotensin system (RAS) pathway (Figure 2). The RAS pathway controls SMC contraction and relaxation and thereby influences blood pressure. SMC contraction narrows vessels' diameter (vasoconstriction) and raises blood pressure. SMC relaxation widens vessels' diameter (vasodilation) and lowers blood pressure. SMC contraction and relaxation are controlled by the RAS pathway's angiotensin II and angiotensin (1-7), respectively. ACE1 converts relatively inactive angiotensin I into angiotensin II, a highly active vasoconstrictor. ACE2 converts angiotensin II into angiotensin (1-7), a vasodilator (Figure 2).[30] ACE2 levels likely decline in SARS-CoV-2–infected

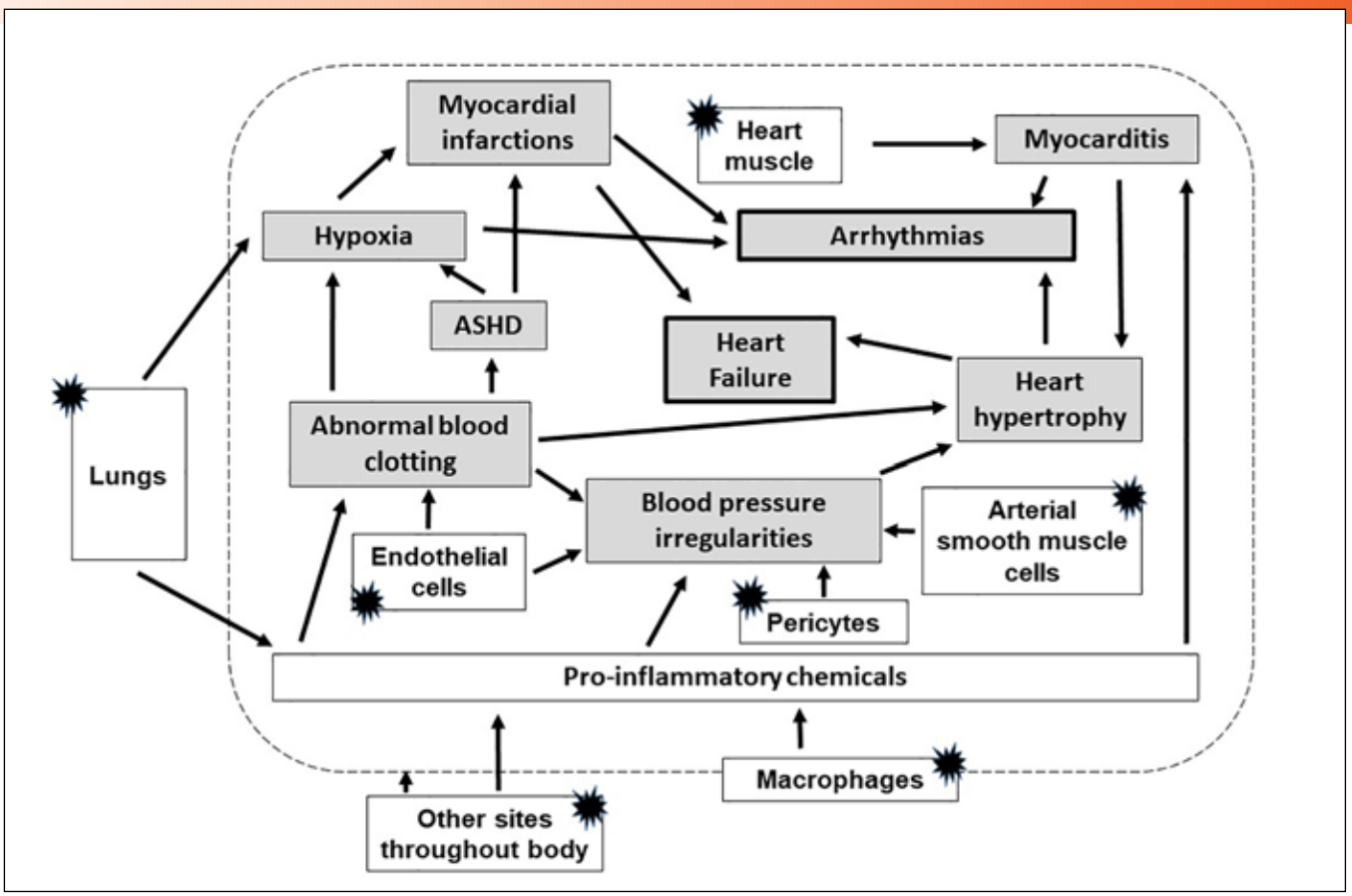

Figure 1. Confirmed and plausible mechanisms by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes cardiovascular symptoms. Several cell types and organs (indicated by the spiked star symbol) are reported targets for SARS-CoV-2 infection. Some of these host cells are part of the cardiovascular system, macrophages may lie within or outside of the cardiovascular system, and other sites lie outside of the cardiovascular system. (The cardiovascular system is defined by the thin-dashed enclosure.) Infections initiate a variety of cardiovascular symptoms (shaded boxes) that, if prolonged and severe enough, cause arrhythmias and heart failure (shaded boxes with thick outline). Viral infection of other organs may also affect the cardiovascular system in ways not specified here. Related schematics can be found in Guzik et al[17] and Atri et al.[16] ASHD, arteriosclerotic heart disease.

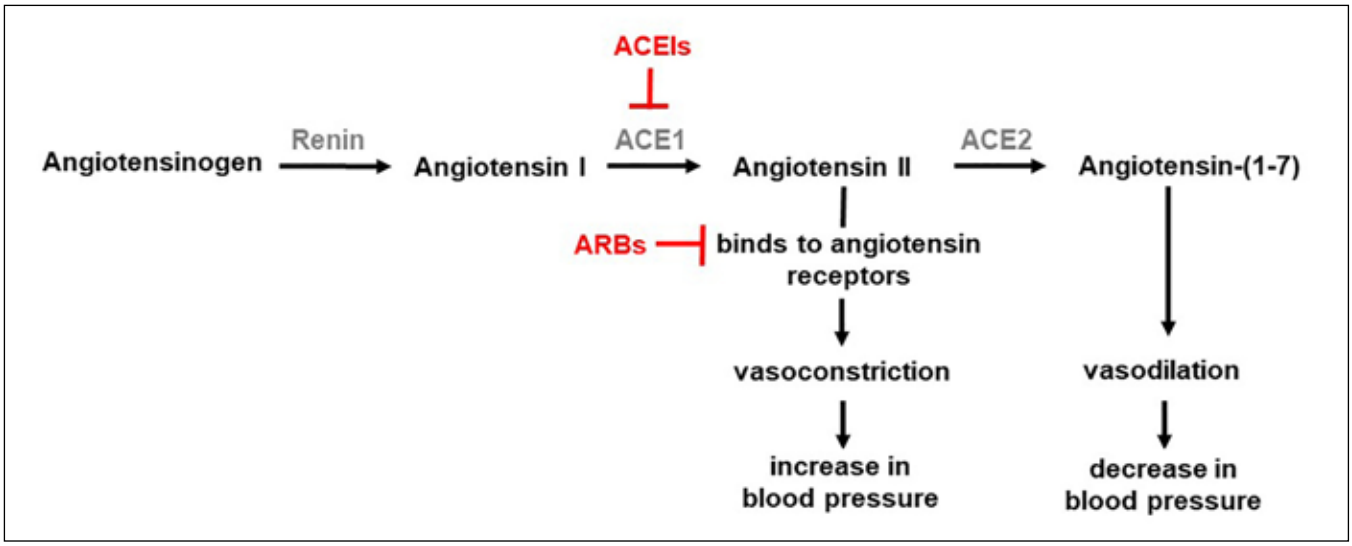

Figure 2. The renin–angiotensin system (RAS) pathway and sites of angiotensin-converting enzyme (ACE) inhibitor (ACEI) and angiotensin receptor blocker (ARB) inhibition. In the RAS pathway, renin (produced by the kidneys) converts angiotensinogen (produced by the liver) into angiotensin I. Angiotensin I is modified into angiotensin II, an active vasoconstrictor, by ACE1. ACE2 (the target for SARS-CoV-2 infection) produces the vasodilator angiotensin (1-7) from angiotensin II. The ACEI and ARB high-blood-pressure medications work by preventing vasoconstriction. They inhibit ACE1 and binding of angiotensin II to its receptors, respectively.

cells.[31-33] Without ACE2, levels of angiotensin (1-7) would decrease, and angiotensin II levels would likely increase. These events would tip the scales toward vasoconstriction and elevated blood pressure. This mechanistic explanation for hypertension, although plausible, needs to be strengthened with additional research.

Another explanation for hypertension development in patients with COVID-19 lies in direct viral infection of ECs and perhaps pericytes. Both of these cell types impact blood vessel diameter (Figure 1).[34-36] A deficit of vasodilation or a prevalence of vasoconstriction likely causes hypertension.

Some patients with COVID-19 develop low blood pressure (hypotension) rather than high blood pressure.[22] Hypotension is a symptom of acute respiratory distress syndrome (ARDS),[37] so it is likely the result of SARS-CoV-2 infection of lung cells.

Thrombi Formation and Hypoxia

Another blood-related condition found in some patients with COVID-19 is the presence of thrombi.[23-25] These abnormal blood clots form in arteries or veins. Interference of arterial blood flow jeopardizes delivery of O_2 and nutrients to areas downstream of the blockage, whereas impedance of blood flow through a vein may cause swelling in the body upstream of the clot.

Besides blood-flow alteration, thrombi pose an additional risk to patients: pieces may break off the clot, travel through the bloodstream, and lodge in another blood vessel. These traveling clots (emboli) endanger other organs. When an embolus in a large systemic artery flows to a narrower artery within an organ, it may get stuck, hinder blood flow, and deprive downstream organs—or areas within an organ—of O_2.

Emboli in veins pose a significant risk to the lungs. Such emboli could migrate through the right heart chambers, lodge in the lungs' narrow arterial branches, and impede blood flow to the pulmonary capillaries. Complications of pulmonary emboli include right ventricular hypertrophy, swelling (edema), and low O_2 levels in the blood (hypoxia) (Figure 1).

Right ventricular hypertrophy and edema are indirect effects of a pulmonary embolism. To force blood past the pulmonary embolism, the heart's right ventricle hypertrophies in an attempt to strengthen its pumping power. At best, this adjustment is a temporary fix. Persistence of the embolism increases blood pressure in the right side of heart, and by extension, in the body's veins. This elevated vascular pressure induces edema. Gravity causes the swelling to be most prominent in the lower limbs.

Such edema also occurs in the lungs. This fluid buildup impedes the diffusion of O_2 from the lungs' alveoli to the blood in the pulmonary capillaries. It also reduces alveolar ventilation (O_2 entry into the alveoli), as fluid-filled sacs fail to remain open. Diminished blood flow to alveoli on account of pulmonary emboli may also prevent the blood from picking up adequate O_2. Collectively, these emboli-initiated events cause hypoxia.

Two culprits induce thrombi formation: injured ECs and pro-inflammatory chemicals (Figure 1). ECs may be damaged by direct SARS-CoV-2 infection.[38] Such damaged cells activate platelets and make them more "sticky"; thus, they adhere to the vessel wall and to each other. Clotting factors in the blood set off a chain reaction that culminates in the modification of fibrinogen to fibrin. Fibrin threads attach to the mass of platelets to form the clot. If ECs are undamaged, a clot may still form: pro-inflammatory chemicals may activate platelets and clotting factors (Figure 1).[39]

Preexisting hypertension, ASHD, arrhythmias, MIs, and heart failure seem to increase the severity of COVID-19 symptoms in patients.

ASHD, MIs, and Arrhythmias

Thrombi may form in the coronary arteries of some patients with COVID-19, a condition known as ASHD.[26-28] Coronary arteries carry O_2-rich blood to the heart tissue. Such O_2 helps fuel the heart's vital blood-pumping actions. Partial or complete blockage of these coronary vessels is life-threatening. Whether through blocked delivery or through hypoxia, insufficient O_2 causes heart muscle cells to malfunction and die. The likelihood of MIs increases (Figure 1). MIs in a small number of patients with COVID-19 have been reported.[26-28]

Arrhythmias have also been reported in some patients with COVID-19.[16,18,29] In the general population, these altered heart rhythms are caused by ASHD, MIs, myocarditis, and heart hypertrophy. Therefore, these cardiovascular conditions are the current "suspects" for reported arrhythmias in COVID-19–related cases.[16,18,29]

Heart Failure

Persistence of these aforementioned cardiovascular problems gradually weakens the heart, compromises its pumping ability and effectiveness, and can lead to heart failure (Figure 1). The heart becomes progressively more incapable of delivering O_2- and nutrient-rich blood to the body. Preexisting heart failure appears to increase the likelihood of death from the disease in patients with COVID-19.[40]

MEDICATIONS AND HEALTH (COVID-19 AND CARDIOVASCULAR) RISKS

COVID-19 impacts the cardiovascular system, but the inverse may also be true. Percentages of patients with COVID-19 and cardiovascular conditions are not higher than the prevalence of these conditions in the general population.[18-20,40-46] Therefore, these cardiovascular illnesses do not appear to increase one's risk of developing COVID-19. However, preexisting hypertension,[18-20,40,41] ASHD,[18,19,40,41] arrhythmias,[19,20,41] MIs,[20] and heart failure[19,20,41] seem to increase the severity of COVID-19 symptoms in patients. This observation led scientists to examine whether certain cardiovascularly related medications alter patients' risk of SARS-CoV-2 infection and/or COVID-19 severity. (It is worth noting that classifications of "severity" vary among studies. Distinctions include normal vs high protein [troponin] concentrations in the blood, nonsevere vs severe disease, nonhospitalized patients vs hospitalized patients, non–intensive care unit [ICU] patients vs ICU patients, and survivors vs nonsurvivors.[17,29])

ACE Inhibitors and Angiotensin Receptor Blockers

Some antihypertensive medications are the focus of such research. Many Americans (13% to nearly 50%, depending on definitions and the data source) have hypertension.[42,45,46] This percentage increases as one ages.[45] To lower high blood pressure, physicians may prescribe ACE inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs). These medications minimize production of angiotensin II and block angiotensin II's interaction with receptors, respectively (Figure 2), thereby preventing the vasoconstriction that elevates blood pressure (Figure 2).

However, certain ACEIs and ARBs likely increase levels and activity of ACE2 throughout the body.[47-49] Because ACE2 is the receptor for SARS-CoV-2 binding, it is important to ascertain whether ACEIs and ARBs alter patients' risk of contracting SARS-CoV-2 and/or developing COVID-19. Mackey et al[50] provide regular updates on newly published research articles pertaining to this topic. Articles sampled from this compilation show wide variability in the study design.[44,50-54] Differences include variations in comparison groups, ethnic groups, statistical analyses, sample sizes, dates of studies (before or after widespread COVID-19 testing), lengths of time on ACEIs or ARBs, attention levels paid to confounding health issues, and definitions of "severe COVID-19." Some articles are retrospective observational studies. Such studies are subjective to selection bias; for example, a cohort of hypertensive patients tested for COVID-19 leaves out hypertensive patients who did not get tested because they were asymptomatic. Identification of patients prescribed ACEIs or ARBs also assumes that the patients take these medications as prescribed, which may not be the case.

Nevertheless, most studies come to the same conclusion: use of ACEIs or ARBs *does not* increase one's risk of SARS-CoV-2 infection or development of severe COVID-19.[55,56] Currently, the Centers for Disease Control and Prevention (CDC) and other cardiovascular health organizations advise patients to continue their ACEI or ARB prescriptions, unless advised otherwise by a physician.[57,58] Clinical trials concerning ACEIs, ARBs, and COVID-19 are ongoing.[59]

Interestingly, the ACEI- and ARB-induced increase in ACE2 expression levels may be advantageous to patients.[52,54] It may counteract virally induced reduction of ACE2 levels and thereby preserve the production of angiotensin (1-7), which lowers elevated blood pressure, promotes structural health of blood vessels and ECs, protects against cardiac hypertrophy, and may enhance blood cell production.[60,61]

COVID-19 Treatments and Cardiac Health Risks

Some medications—lopinavir/ritonavir, hydroxychloroquine (HCQ), favipiravir, remdesivir, and tocilizumab—were originally developed for other uses but demonstrate various levels of efficacy in treating patients with COVID-19. Lopinavir/ritonavir and HCQ reportedly disrupt SARS-CoV-2's entry into host cells.[62] Favipiravir and remdesivir likely prevent the replication of the virus's genome.[62] Tocilizumab reduces inflammation by limiting the effectiveness of pro-inflammatory chemicals.[62] Last year, a multinational study of more than 10,000 patients examined the effects of some of these drugs on the mortality of patients with COVID-19.[63] The tests using HCQ (low doses) and lopinavir/ritonavir were halted prematurely, as no improvements were seen.[64] Currently, the National Institutes of Health (NIH) recommends against their use as a treatment for COVID-19.[65,66]

These drugs have been linked to cardiovascular side effects. Lopinavir/ritonavir, HCQ, favipiravir and remdesivir may cause arrhythmias.[29,67-69] Lopinavir/ritonavir may trigger MIs.[70] Furthermore, lopinavir/ritonavir and tocilizumab may compromise the effectiveness of cardiovascular medications.[29,71] These cardiovascular risks are inferred primarily from a small number of studies with a small number of subjects without COVID-19. A more robust examination of these drugs' cardiovascular effects in patients with COVID-19 has begun in several clinical trials funded by the NIH.[29]

CONCLUSION

Approximately 1.5 years have passed since SARS-CoV-2 and COVID-19 were identified.[1,72,73] In this time, much scientific understanding of SARS-CoV-2 infection patterns and COVID-19 comorbidities has been acquired. Improved treatment procedures enhance patients' prognoses, and awareness of drug side effects likely reduces health complications. This article

illuminates the landscape of SARS-CoV-2 and COVID-19 in relationship with the cardiovascular system and provides a biological foundation to support readers as they engage with the burgeoning quantity of scientific studies on this topic. Indeed, the necessity of continued research remains. Some current information is conjecture, drawn from studies on the first severe acute respiratory syndrome coronavirus or in patients without COVID-19. Other knowledge is based on only a few small studies and needs stronger support. Longitudinal studies are necessary to determine the long-term effects of SARS-CoV-2 and COVID-19 on human health. Regardless, the approval of effective SARS-CoV-2 vaccines,[74,75] enhancements to patient care, and funded clinical trials provide hope for a future in which SARS-CoV-2 infection rates decline, patient mortality decreases, and life without social-distancing restrictions resumes.

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References

1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270-273. doi:10.1038/s41586-020-2012-7
2. Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature*. 2020;581(7807):221-224. doi:10.1038/s41586-020-2179-y
3. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science*. 2020;367(6485):1444-1448. doi:10.1126/science.abb2762
4. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271-280, e8. doi:10.1016/j.cell.2020.02.052
5. Wang Q, Zhang Y, Wu L, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell*. 2020;181(4):894-904, e9. doi:10.1016/j.cell.2020.03.045
6. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020;116(6):1097-1100. doi:10.1093/cvr/cvaa078
7. Nicin L, Abplanalp WT, Mellentin H, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *Eur Heart J*. 2020;41(19):1804-1806. doi:10.1093/eurheartj/ehaa311
8. Litvinuková M, Talavera-López C, Maatz H, et al. Cells of the adult human heart. *Nature*. 2020;588(7838):466-472. doi:10.1038/s41586-020-2797-4
9. Gallagher PE, Ferrario CM, Tallant EA. Regulation of ACE2 in cardiac myocytes and fibroblasts. *Am J Physiol-Heart Circ Physiol*. 2008;295(6):H2373-H2379. doi:10.1152/ajpheart.00426.2008
10. Pérez-Bermejo JA, Kang S, Rockwood SJ, et al. SARS-CoV-2 infection of human iPSC-derived cardiac cells predicts novel cytopathic features in hearts of COVID-19 patients. *Sci Transl Med*. Published online March 15, 2021. doi:10.1126/scitranslmed.abf7872
11. Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol*. 2020;16(7):e9610. doi:10.15252/msb.20209610
12. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203(2):631-637. doi:10.1002/path.1570
13. Bertram S, Heurich A, Lavender H, et al. Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. *PLoS One*. 2012;7(4):e35876. doi:10.1371/journal.pone.0035876
14. Zheng J, Wang Y, Li K, Meyerholz DK, Allamargot C, Perlman S. Severe acute respiratory syndrome coronavirus 2–induced immune activation and death of monocyte-derived human macrophages and dendritic cells. *J Infect Dis*. 2021;223:785-795. doi:10.1093/infdis/jiaa753
15. Akhmerov A, Marbán E. COVID-19 and the heart. *Circ Res*. 2020;126(10):1443-1455. doi:10.1161/CIRCRESAHA.120.317055
16. Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the cardiologist: basic virology, epidemiology, cardiac manifestations, and potential therapeutic strategies. *JACC Basic Transl Sci*. 2020;5(5):518-536. doi:10.1016/j.jacbts.2020.04.002
17. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res*. 2020;116(10):1666-1687. doi:10.1093/cvr/cvaa106
18. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585
19. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol*. 2020;76(5):533-546. doi:10.1016/j.jacc.2020.06.007
20. Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 registry. *Rev Clínica Esp Engl Ed*. 2020;220(8):480-494. doi:10.1016/j.rceng.2020.07.003
21. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):819-824. doi:10.1001/jamacardio.2020.1096
22. Robinson FA, Mihealsick RyanP, Wagener BM, et al. Role of angiotensin-converting enzyme 2 and pericytes in cardiac complications of COVID-19 infection. *Am J Physiol-Heart Circ Physiol*. 2020;319(5):H1059-H1068. doi:10.1152/ajpheart.00681.2020
23. Long H, Nie L, Xiang X, et al. D-dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis. *BioMed Res Int*. 2020;2020:1-10. doi:10.1155/2020/6159720
24. Chan NC, Weitz JI. COVID-19 coagulopathy, thrombosis, and bleeding. *Blood*. 2020;136(4):381-383. doi:10.1182/blood.2020007335
25. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;136(4):489-500. doi:10.1182/blood.2020006520
26. Tedeschi D, Rizzi A, Biscaglia S, Tumscitz C. Acute myocardial infarction and large coronary thrombosis in a patient with COVID-19. *Catheter Cardiovasc Interv*. 2021;97(2):272-277. doi:10.1002/ccd.29179
27. Guagliumi G, Sonzogni A, Pescetelli I, Pellegrini D, Finn AV. Microthrombi and ST-segment–elevation myocardial infarction in COVID-19. *Circulation*. 2020;142(8):804-809. doi:10.1161/CIRCULATIONAHA.120.049294
28. Stafanini GG, Montorfano M, Trabattoni D, et al. ST-elevation myocardial infarction in patients with COVID-19. *Circulation*. 2020;141(25):2113-2116. doi:10.1161/CIRCULATIONAHA.120.047525
29. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol*. 2020;75(18):2352-2371. doi:10.1016/j. jacc.2020.03.031
30. Crackower MA, Sarao R, Oudit GY, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature*. 2002;417(6891):822-828. doi:10.1038/nature00786

31. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nat Med*. 2005;11(8):875-879. doi:10.1038/nm1267
32. Wang H, Yang P, Liu K, et al. SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. *Cell Res*. 2008;18(2):290-301. doi:10.1038/cr.2008.15
33. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system. *Circ Res*. 2020;126(10):1456-1474. doi:10.1161/CIRCRESAHA.120.317015
34. Armulik A, Genové G, Betsholtz C. Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. *Dev Cell*. 2011;21(2):193-215. doi:10.1016/j.devcel.2011.07.001
35. Lee LL, Chintalgattu V. Pericytes in the heart. In: Birbrair A, ed. *Pericyte Biology in Different Organs. Adv Exp Med Biol*. Springer; 2019:187-210. doi:10.1007/978-3-030-11093-2_11
36. Hashitani H, Mitsui R. Role of pericytes in the initiation and propagation of spontaneous activity in the microvasculature. In: Hashitani H, Lang RJ, eds. *Smooth Muscle Spontaneous Activity: Physiological and Pathological Modulation. Adv Exp Med Biol.* Springer; 2019:329-356. doi:10.1007/978-981-13-5895-1_14
37. ARDS - symptoms and causes. Mayo Clinic. Accessed January 10, 2021. https://www.mayoclinic.org/diseases-conditions/ards/symptoms-causes/syc-20355576
38. Zhang J, Tecson KM, McCullough PA. Endothelial dysfunction contributes to COVID-19-associated vascular inflammation and coagulopathy. *Rev Cardiovasc Med*. 2020;21(3):315-319. doi:10.31083/j.rcm.2020.03.126
39. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med*. 2020;8(6):e46-e47. doi:10.1016/S2213-2600(20)30216-2
40. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3
41. Gold JAW, Wong KK, Szablewski CM, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19—Georgia, March 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69. doi:10.15585/mmwr.mm6918e1
42. Raised blood pressure (SBP>=140 OR DBP>=90) (age-standardized estimate). The Global Health Observatory. Published 2021. Accessed January 9, 2021. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/raised-blood-pressure-(sbp-=140-or-dbp-=90)-(age-standardized-estimate)
43. Centers for Disease Control and Prevention. Heart disease facts. Centers for Disease Control and Prevention. Published September 8, 2020. Accessed January 9, 2021. https://www.cdc.gov/heartdisease/facts.htm
44. Bean DM, Kraljevic Z, Searle T, et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. *Eur J Heart Fail*. 2020;22(6):967-974. doi:10.1002/ejhf.1924
45. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension prevalence and control among adults: United States, 2015–2016. cdc.gov. Published October 2017. Accessed April 8, 2021. https://www.cdc.gov/nchs/products/databriefs/db289.htm
46. American Heart Association News. Is high blood pressure inevitable? Here's how to keep it in check. www.heart.org. Published May 18, 2020. Accessed January 9, 2021. https://www.heart.org/en/news/2020/05/18/is-high-blood-pressure-inevitable-heres-how-to-keep-it-in-check
47. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. 2020;382:1653-1659. doi:10.1056/NEJMsr2005760
48. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 2005;111(20):2605-2610. doi:10.1161/CIRCULATIONAHA.104.510461
49. Igase M, Strawn WB, Gallagher PE, Geary RL, Ferrario CM. Angiotensin II AT1 receptors regulate ACE2 and angiotensin-(1–7) expression in the aorta of spontaneously hypertensive rats. *Am J Physiol-Heart Circ Physiol*. 2005;289(3):H1013-H1019. doi:10.1152/ajpheart.00068.2005
50. Mackey K, King VJ, Gurley S, et al. Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults. *Ann Intern Med*. 2020;173(3):195-203. doi:10.7326/M20-1515
51. Dublin S, Walker R, Floyd JS, et al. Renin-angiotensin-aldosterone system inhibitors and COVID-19 infection or hospitalization: a cohort study. *Am J Hypertens*. Published online October 13, 2020. doi:10.1093/ajh/hpaa168
52. Palazzuoli A, Mancone M, Ferrari GM, et al. Antecedent administration of angiotensin-converting-enzyme inhibitors or angiotensin II receptor antagonists and survival after hospitalization for COVID-19 syndrome. *J Am Heart Assoc*. 2020;9(22):e017364. doi:10.1161/JAHA.120.017364
53. Xu J, Huang C, Fan G, et al. Use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in context of COVID-19 outbreak: a retrospective analysis. *Front Med*. 2020;14(5):601-612. doi:10.1007/s11684-020-0800-y
54. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126(12):1671-1681. doi:10.1161/CIRCRESAHA.120.317134
55. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–angiotensin–aldosterone system inhibitors and risk of COVID-19. *N Engl J Med*. 2020;382(25):2441-2448. doi:10.1056/NEJMoa2008975
56. Fernández-Ruiz I. RAAS inhibitors do not increase the risk of COVID-19. *Nat Rev Cardiol*. 2020;17(7):383-383. doi:10.1038/s41569-020-0401-0
57. Centers for Disease Control and Prevention. COVID-19 and your health: people with certain medical conditions. Centers for Disease Control and Prevention. Published February 11, 2020. Accessed January 2, 2021. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
58. Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician. American Heart Association. Published March 17, 2020. Accessed January 2, 2021. https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician
59. Search of: COVID-19, ACE, ARB. ClinicalTrials.gov. Published 2021. Accessed January 11, 2021. https://clinicaltrials.gov/ct2/results?cond=Covid19&term=ACE%2C+ARB&type=&rslt=&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=
60. Santos RA. Angiotensin-(1-7). *Hypertension*. 2014;63(6):1138-1147. doi:10.1161/HYPERTENSIONAHA.113.01274
61. Iusuf D, Henning RH, van Gilst WH, Roks AJM. Angiotensin-(1–7): pharmacological properties and pharmacotherapeutic perspectives. *Eur J Pharmacol*. 2008;585(2-3):303-312. doi:10.1016/j.ejphar.2008.02.090
62. Vijayvargiya P, Garrigos ZE, Almeida NEC, Gurram PR, Stevens RW, Razonable RR. Treatment considerations for COVID-19. *MAYO Clin Proc*. 2020; 95(7):1454-1466.
63. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity trial results. *N Engl J Med*. 2021; 384(6):497-511. doi:10.1056/NEJMoa2023184
64. WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. World Health Organization. Published July 4, 2020. Accessed April 7, 2021. https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19

65. Chloroquine or hydroxychloroquine with or without azithromycin. COVID-19 Treatment Guidelines. Published October 9, 2020. Accessed October 31, 2020. https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/chloroquine-or-hydroxychloroquine-with-or-without-azithromycin/
66. Lopinavir/ritonavir and other HIV protease inhibitors. COVID-19 treatment guidelines. National Institutes of Health. Published February 11, 2021. Accessed April 7, 2021. https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/lopinavir-ritonavir-and-other-hiv-protease-inhibitors/
67. Naksuk N, Lazar S, Peeraphatdit TB. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. *Eur Heart J Acute Cardiovasc Care*. 2020;9(3):215-221. doi:10.1177/2048872620922784
68. Hooks M, Bart B, Vardeny O, Westanmo A, Adabag S. Effects of hydroxychloroquine treatment on QT interval. *Heart Rhythm*. 2020;17(11):1930-1935. doi:10.1016/j.hrthm.2020.06.029
69. Costedoat-Chalumeau N, Hulot JS, Amoura Z, et al. Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases. *Rheumatology*. 2007;46(5):808-810. doi:10.1093/rheumatology/kel402
70. Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. Landay A, ed. *PLoS One*. 2013;8(3):e59551. doi:10.1371/journal.pone.0059551
71. Kaletra tablets and oral solution. AbbVie. Accessed January 9, 2021. https://www.rxabbvie.com/pdf/kaletratabpi.pdf
72. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017
73. Naming the coronavirus disease (COVID-19) and the virus that causes it. World Health Organization. Accessed September 10, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
74. Office of the Commissioner. Pfizer-BioNTech COVID-19 vaccine. US Food and Drug Administration. Published online January 5, 2021. Accessed January 11, 2021. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine
75. Office of the Commissioner. Moderna COVID-19 vaccine. US Food and Drug Administration. Published online January 6, 2021. Accessed January 11, 2021. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine