# Endothelial dysfunction and COVID-19 (Review)

JALIL DAHER

Department of Biology, Faculty of Arts and Sciences, University of Balamand, Tripoli PO Box 100, Lebanon

Received August 15, 2021; Accepted September 16, 2021

DOI: 10.3892/br.2021.1478

**Abstract.** It is hypothesized that several comorbidities increase the severity of COVID-19 symptoms. Cardiovascular disease including hypertension was shown to play a critical role in the severity of COVID-19 infection by affecting the survival of patients with COVID-19. Hypertension and the renin-angiotensin-aldosterone system are involved in increasing vascular inflammation and endothelial dysfunction (ED), and both processes are instrumental in COVID-19. Angiotensin-converting enzyme 2 is an essential component of the renin-angiotensin-aldosterone system and the target receptor that mediates SARS-CoV-2 entry to the cell. This led to speculations that major renin-angiotensin-aldosterone system inhibitors, such as angiotensin receptor blockers and angiotensin-converting enzyme inhibitors might affect the course of the disease, since their administration enhances angiotensin-converting enzyme (ACE)2 expression. An increase in ACE2 activity could reduce angiotensin II concentration in the lungs and mitigate virus-driven lung injury. This could also be associated with a reduction in blood coagulation, which plays a critical role in the pathogenesis of SARS-CoV-2; of note, COVID-19 is now regarded as a disorder of blood clotting. Therefore, there is an urgent need to better understand the effect of targeting ACE2 as a potential treatment for SARS-CoV-2 driven injury, and in alleviating COVID-19 symptoms by reversing SARS-CoV-2-induced excessive coagulation and fatalities. Ongoing therapeutic strategies that include recombinant human ACE2 and anti-spike monoclonal antibodies are essential for future clinical practice in order to better understand the effect of targeting ED in COVID-19.

*Correspondence to:* Dr Jalil Daher, Department of Biology, Faculty of Arts and Sciences, University of Balamand, 108 Murr, UOB road, El Koura, Tripoli PO Box 100, Lebanon
E-mail: jalil.daher@balamand.edu.lb

*Key words:* cardiovascular disease, COVID-19, endothelial dysfunction, SARS-COV-2, spike protein, inflammation, renin-angiotensin-aldosterone system, coagulation, fibrinolysis, reactive oxygen species, angiotensin converting enzyme 2, angiotensin II, angiotensin receptor blocker, angiotensin converting enzyme inhibitor, von Willebrand factor, plasminogen activator inhibitor-1

**Contents**



## 1. Introduction

Cardiovascular disease (CVD) and hypertension have emerged as critical comorbid risk factors affecting the survival of patients with COVID-19 (1). Inflammation is a major player in the progression of CVD, and the renin-angiotensin-aldosterone system (RAAS) plays an important role in producing and maintaining vascular inflammation (2). While RAAS serves a key role in regulating blood pressure and hypertension, it also mediates pro-inflammatory functions. Most importantly, blocking RAAS has beneficial and protective outcomes in CVD treatment. Indeed, the use of major RAAS inhibitors, such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) improves CVD by effectively treating hypertension-induced injury (3). Angiotensin-converting enzyme 2 (ACE2) is a major component of RAAS, and the receptor to which SARS-CoV2 binds to enter the cells. Endothelial cell dysfunction (ED) driven-ACE2 depletion is associated with an increase in inflammation and blood coagulation; both are considered critical factors in the progression of COVID-19. To date, this association remains unclear and thus, there should be an increased effort to better understand the relationship between ACE2, blood hemostasis and inflammation in the pathogenesis of COVID-19 disease.

## 2. CVD, ED and RAAS

In CVD, chronic inflammation leads to ED and the initiation and progression of atherosclerosis by enhancing the migration of inflammatory cells into the vessel wall, foam cell formation and the stimulation of smooth muscle cell hyperplasia, which ultimately leads to tissue injury (4). Strong associations between Angiotensin II (AngII), a major actor in RAAS, and inflammation have been demonstrated, implicating AngII in enhancing pro-inflammatory responses through the upregulation of pro-inflammatory cytokines and chemokines, including IL-6, MCP-1, VCAM-1 and TNF-α (5-8). In addition, AngII

is a strong pro-oxidant and it mediates its effects through the activation of NADH/NADPH signaling, production of superoxide anions and reduction in nitric oxide (NO) bioavailability, which is a key marker for a healthy endothelium (9-12).

Inhibiting RAAS signaling pathways reduces CVD mortality (13). Blocking RAAS involves either ACEIs, which inhibit AngII formation or ARBs, which block angiotensin receptors (Fig. 1). Targeting RAAS decreases inflammation, vascular remodeling and oxidative stress, and improves endothelial cell function by increasing NO production (14).

## 3. ACE2 and COVID-19

ACE2 is the target receptor to which SARS-CoV-2 binds with to gain entry into cells (1). Since ACE2 is an essential component of RAAS, concerns arise regarding the plausible relationships between hypertension, the use of ACEIs and ARBs, and the role of cardiovascular disease in aggravating COVID-19 symptoms, restoring the balance in the RAAS system may be a critical factor in attenuating organ injuries. Indeed, this was addressed early during the COVID-19 pandemic; drugs that block RAAS could affect the severity of the disease (15). Results from the initial outbreak in China showed that a majority of patients with COVID-19 with severe symptoms had hypertension; this led to speculations that ACEIs and ARBs may increase the risk of viral infection since their administration enhances ACE2 expression (16,17). However, studies in humans and animal models did not provide any convincing proof of this association, and thus remains unclear and contested (18-20). Adding to this controversy is the fact that the virus-binding target, ACE2, converts AngII to Ang(1-7), which decreases inflammation and lowers blood pressure. ACE2 therefore plays an important role in balancing the two RAAS arms, the pro-inflammatory and hypertensive arm mediated by ACE, AngII and Angiotensin Type 1 Receptor (AT1R), and the cardioprotective, anti-inflammatory arm mediated by MAS1 oncogene (MasR) and AT2R. Disruption of this balance is a crucial player in the pathophysiology of CVD and COVID-19 (21). Indeed, while the ACE/AngII pathway is important in vasoconstriction, hypertension and oxidative stress, which leads to inflammation, the ACE2/Ang(1-7) pathway counteracts the above effects, and both pathways coexist in various tissues including in the lungs, heart, blood vessels and kidneys where they regulate blood pressure and contribute to CVD pathophysiology (22,23).

The SARS-CoV-2 spike protein recognizes, with high affinity, ACE2 present on the surface of host cells mediating the entry of the virus. Endocytosis of the virus-ACE2 complex can potentially lead to ACE2 downregulation and shedding from the surface of the cell (24). This loss of ACE2 function in infected cells could be a critical factor in the progression and course of the disease (25). Even though there is no compelling evidence that links ACEI and ARB treatment with an increase in SARS-CoV-2 infection, it is becoming evident that these drugs may attenuate AngII-driven lung injury (26). Since AngII promotes inflammation and acute lung injury (27), any increase in ACE2 activity could reduce AngII concentration in the lungs and mitigate virus-driven lung injury. Indeed, a recent study revealed correlations between biochemical and clinical markers of lung injury, viral load and AngII concentrations in patients with COVID-19 (28). Similarly, results link SARS-CoV-2 with a decrease in ACE2 expression and acute heart injury (29). However, it was reported that the use of ACEIs or ARBs in hospitalized patients with COVID-19 had no effect on their survival rate; actually, there was no significant difference in the mean number of days alive for patients who were hospitalized with mild to moderate symptoms of COVID-19 and who were assigned to continue vs. discontinue these medications (30). Conversely, another cohort study that assessed ACEIs and ARBs and included more than 8 million individuals, has shown that these drugs are associated with significantly reduced severe risks of the disease, such as requiring intensive care. This study also hinted to the role of ethnicity in modulating ACEIs/ARBs effects in relation to the severity of the disease; it was shown that the risk of the disease in association with the use of these drugs was higher in Black African and Caribbean groups when compared with the Caucasian group (31). Overall, the use of ACEIs/ARBs is still a paradoxical issue that requires extended investigation to resolve; it is also an area of research where the benefit/risk analysis and potential efficacy of those drugs should be addressed in connection with other comorbidities that are related to COVID-19 (22).

## 4. COVID-19, the exposure of a masquerading illness

There is growing evidence for COVID-19 being a disorder of blood clotting where the virus uses the respiratory route to gain entry to blood circulation (32). It has been initially reported that COVID-19 is strongly associated with ischemic strokes in patients that required vacuum and clot retrieval devices as well as blood thinning medications (33,34). It was shown that when the virus enters the blood stream, it triggers a cascade of events resulting in blood clotting and strokes. This all starts with the attachment of the virus to the ACE2 receptor on endothelial cells, making use of transmembrane protease, serine-2 (TMPRSS-2) which initiates the process of ED (35). Thus, SARS-CoV-2 mediated ACE2 downregulation on the surface of the cell results in AngII accumulation and NADPH activation fueling the generation of reactive oxygen species (ROS) and thus increasing oxidative stress (36,37). ROS assists in the conversion of β2-glycoprotein 1 into its oxidized form, which can no longer bind competitively to the von Willebrand factor (vWF) that is secreted by dysfunctional endothelial cells; subsequently, this will promote the coagulation cascade, as vWF binds to the sub-endothelial layer, crosslinking collagen and platelets together and accentuating coagulation mechanisms that lead to strokes of the large vessels (38,39).

During viral infection, the dysfunctional endothelium plays a detrimental role by worsening inflammation which is associated with a poor prognosis in patients with COVID-19 (Fig. 2) (35). As the coagulation mechanism is a highly organized process that involves endothelial cells, endotheliitis plays a critical role in the pathogenesis of SARS-CoV-2 by increasing the risk of excessive and disseminated intravascular coagulation and the rates of fatality (40). During infection, pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α are amplified and lead to a simultaneous increase in the vWF and tissue factor release from endothelial

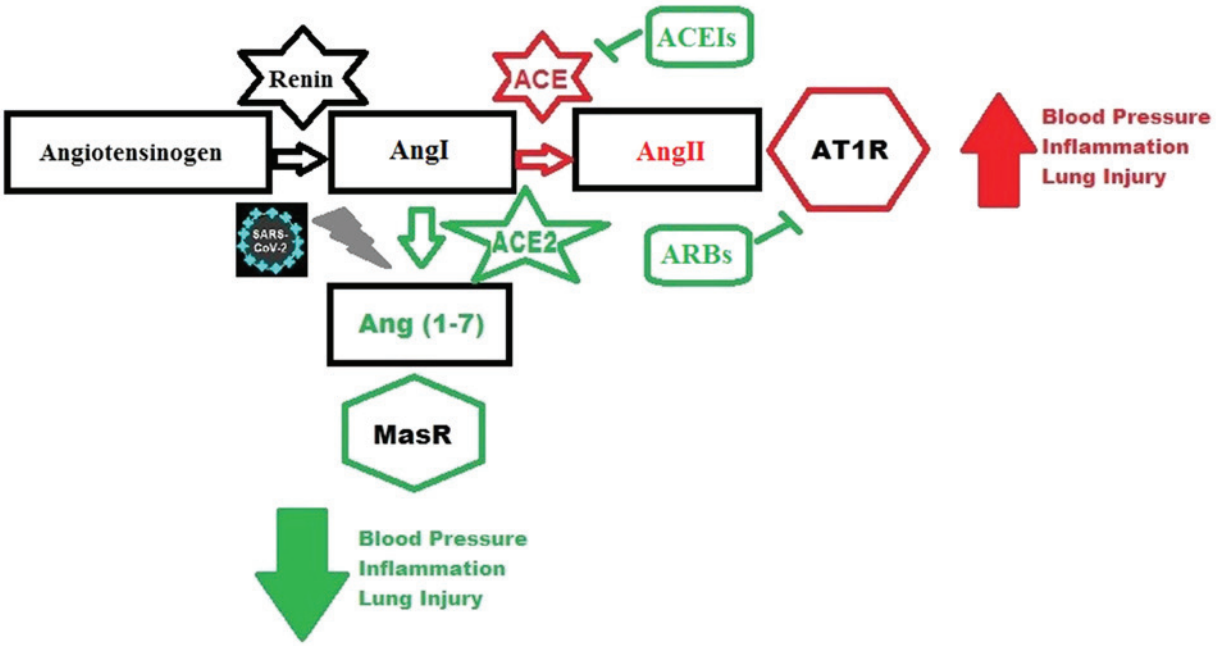


Figure 1. RAAS is essential for regulating blood pressure and inflammation in the body. While the ACE/AngII/AT1R pathway is responsible for the increase in blood pressure and inflammation, the other ACE2/Ang(1-7)/MasR arm of RAAS is involved in the opposing effects, and in lowering blood pressure and inflammation. ACE2 mediates SARS-CoV-2 entry to the cell and is a key player in abrogating the detrimental effects of the ACE/AngII/AT1R arm of RAAS and mitigating virus-driven lung injury. ACEIs and ARBs block ACE (and therefore the conversion of AngI to AngII) and AT1R respectively, which affect the progression of COVID-19 symptoms. RAAS, renin-angiotensin-aldosterone system; ACE, angiotensin converting enzyme; AngII, angiotensin II; AT1R, Angiotensin Type 1 Receptor; MasR, MAS1 oncogene; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

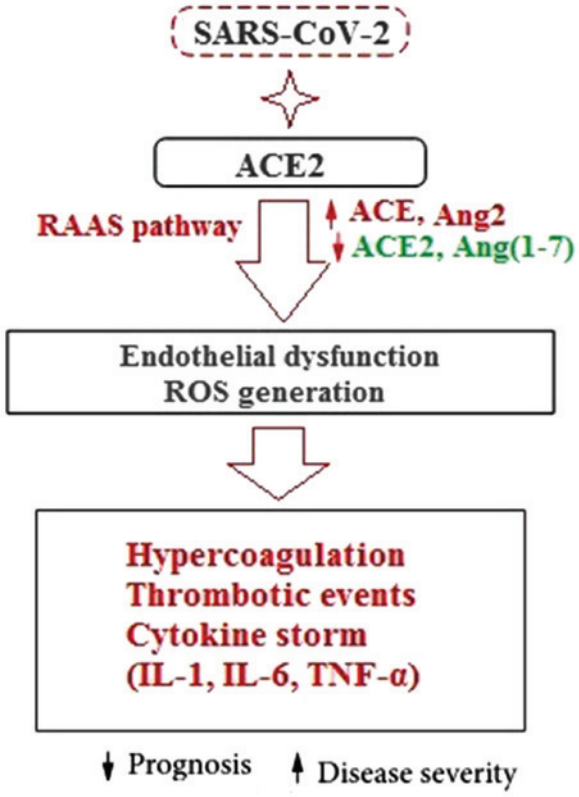


Figure 2. SARS-Cov-2 binds to ACE2 in order to enter the cell. Subsequent activation of the RAAS pathway induces endothelial dysfunction, which will lead to the generation of ROS and the secretion of pro-inflammatory cytokines (IL-1, IL-6, TNF-α), resulting in a cytokine storm as well as hypercoagulation and a rise in thrombotic events culminating in an increase in the severity of the disease. ACE, angiotensin converting enzyme; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; IL, interleukin; TNF-α, tumor necrosis factor-α; Ang, angiotensin.

cells, which will promote blood clotting through the increase in platelet aggregation and the initiation of the clotting cascade (41). Similarly, those cytokines enhance blood clotting by downregulating pro-fibrinolytic and anticoagulant factors, including endothelial protein C receptor and thrombomodulin and by upregulating anti-fibrinolytic factors, namely plasminogen activator inhibitor-1 (PAI-1) (42,43). There is cumulative proof that ACE2 downregulation may contribute to an increase in the thrombotic risk in patients with COVID-19 (44). It has been speculated that the decrease in ACE2 activity seen in patients with COVID-19 may lead to a series of mechanisms that are promoted by the dysfunctional endothelium and that affect blood hemostasis. This comprises an increase in vascular permeability, as well as an upregulation of tissue factor and PAI-1 culminating in the activation of the extrinsic coagulation pathway and the reduction in fibrinolysis (45). On this same note, it has been reported that, in animal models of thrombosis, there is a clear association between coagulation and ACE2 pathways. In rats with an induced thrombosis, ACE2 inhibition is significantly correlated with the increase in blood clot weight; conversely, ACE2 administration induced a decrease in thrombus size as well as a reduction in platelet adhesion to the endothelium (46). Similarly, it has been shown that a decrease in ACE2 activity is associated with an increase in blood coagulation in spontaneous hypertensive rats, and that the activation of ACE2 attenuates thrombosis by reducing the attachment of platelets to the vessel wall (47).

Interestingly, it was reported that SARS-CoV-2 can directly bind to platelets through its spike protein, which will enhance platelet activation. It was shown that platelets are hyperactive in patients with COVID-19 and that they express ACE2 and TMPRSS2. ACE2-mediated viral binding to platelets

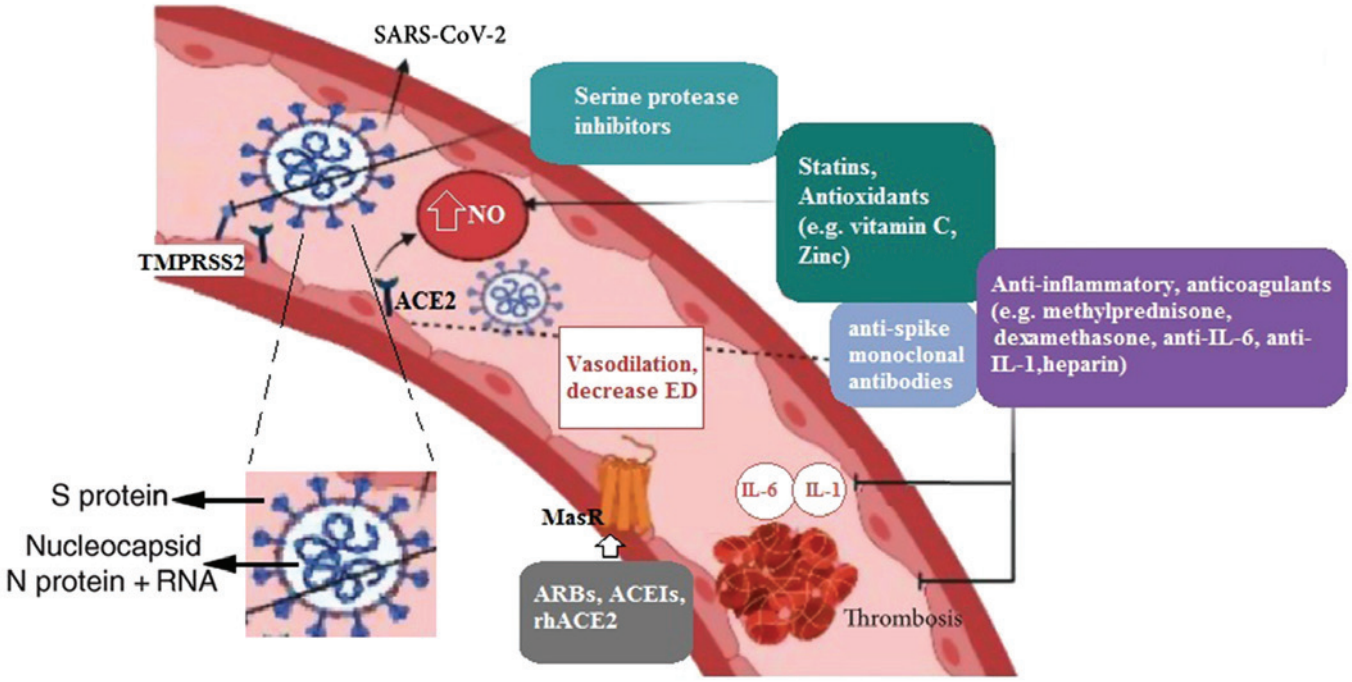


Figure 3. Therapeutic processes that address inflammation, oxidative stress and blood coagulation, which are considered hallmarks of ED during SARS-CoV-2 infection. The proposed mechanisms include targeting the interaction between the virus and endothelial cells through the use of rhACE2, serine protease inhibitors and SARS-CoV-2 anti-spike monoclonal antibodies in order to decrease ED, viral infection and tissue injury. The therapeutic procedures described here also target ED-induced hyperinflammation and hypercoagulability syndromes by using ACEIs, ARBs and antioxidants, as well as anticoagulant and anti-inflammatory drugs and antibodies, such as dexamethasone, methylprednisone, heparin, anti-IL1 and anti-IL-6. TMPRSS-2, transmembrane protease, serine-2; ED, endothelial dysfunction; ACE, angiotensin converting enzyme; rhACE2, recombinant human ACE2; ARB, angiotensin receptor blocker; IL, interleukin; NO, nitric oxide.

stimulated them to release inflammatory and coagulation factors, which lead to an enhancement in leukocyte-platelet aggregation (48).

## 5. Ongoing therapeutic strategies and disease management

At present, the treatment of COVID-19 is limited to alleviating the symptoms of the disease, with no specific antiviral drugs that are effective in targeting the virus (49). Accordingly, there exist numerous ongoing clinical trials and treatments that aim to target COVID-19-associated ED in order to mitigate disease progression and the high mortality rate associated with it. Such treatments include the use of RAAS inhibitors, serine protease inhibitors, recombinant human ACE2, monoclonal anti-spike antibodies, heparin, corticosteroids as well as other agents directed towards specific cytokines and inflammatory signaling pathways (Fig. 3) (50-54). Serine protease inhibitors may affect SARS-CoV-2 entry to the cell by inhibiting TMPRSS-2, which plays an instrumental role in mediating S protein fusion to the endothelial cell membrane (49). One study showed that targeting TMPRSS2 using a clinically proven protease inhibitor can effectively prevent SARS-CoV-2 infection *in vitro* (25). Additionally, numerous studies and ongoing clinical trials point to the vital role that the RAAS inhibitors may contribute to improving ED and the pathogenesis of COVID-19 (55-59). On this same note, statins were also reported to improve endothelial cell function in a manner distinct from their major lipid-lowering activities. These drugs can increase the expression of NO synthase, whilst inhibiting NADPH oxidase, which leads to the suppression of pro-inflammatory pathways in endothelial cells (60). Meanwhile, there is a growing evidence showing that statins can improve the prognosis of COVID-19 through the decrease in the production of inflammatory biomarkers (61). In addition, heparin is known to have anti-inflammatory and protective effects in endothelial cells, and recent studies confirmed its role in improving the prognosis of severely infected patients and reducing mortality rates through its well-known anticoagulation properties (62). Furthermore, given the importance of inflammation in the pathophysiology of COVID-19, clinical evaluation of the anti-inflammatory effects of corticosteroids has gained high priority recently. One study has shown the efficacy of methylprednisone in treating severely ill patients with acute respiratory distress syndrome (63). Another study also confirmed the significant role of dexamethasone in decreasing mortality rates in patients who are severely affected with COVID-19 (64). Lastly, other promising therapeutic approaches include targeting cytokines, such as interferon-γ, IL-1 and IL-6 and, as well as the VEGFA/VEGFR2 signaling pathways in order to alleviate virus-driven injury and inflammation (54).

## 6. Conclusion and future perspectives

Overall, ACE2 is a key player in SARS-CoV-2 infection and in abrogating the detrimental effects of the ACE/AngII/AT1R arm of RAAS; namely, the ACE2/Ang(1-7) pathway instigates a shift away from ACE/AngII/AT1R, which affects the progression of COVID-19 symptoms. Moreover, there is a clear association linking ACE2 and blood coagulation

pathways, which could play an important role in COVID-19. This relationship suggests that ACE2 may be a novel target for the treatment of thrombogenic diseases, including COVID-19. Future investigations into the role of ACEIs and ARBs in this disease shall expose their potential value for managing COVID-19 symptoms. In addition, there is an urgent need to better understand the effect of recombinant human ACE2 as a potential treatment for SARS-CoV-2 driven injury. Equally important is the need to define the promising role of anti-Spike monoclonal antibodies in alleviating COVID-19 symptoms by reversing SARS-CoV-2 spike protein-induced platelet activation, excessive coagulation and the rates of strokes and fatalities. Future research shall hopefully address these issues as there remain significant gaps in our knowledge pertaining to these related subjects. Accordingly, it is extremely essential that future clinical practice deals with the precise therapeutic processes pertaining to the action of anti-spike monoclonal antibodies and recombinant human ACE2 as fully integrated subjects of high priority. This should help scientists in confirming and verifying the efficacy of those recommended therapeutic strategies in well-designed clinical trials since, as to date, the pathogenesis of COVID-19 is still a vaguely understood subject. Shedding more light onto ED in clinical practice may be more significant than we expect; in this context, a collaborative effort of biomedical and clinical science is urgently required, as this will assist in completing our understanding of the paradigm of the pathogenesis of COVID-19, and in translating our current understanding of the disease to successful treatment strategies.

**Acknowledgements**

The author would sincerely like to thank the University of Balamand for their unbounded support.

**Funding**

No funding was received.

**Availability of data and materials**

Not applicable.

**Authors' contributions**

JD wrote and revised the manuscript, and has read and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The author declares that he has no competing interests.

**References**

1. South AM, Brady TM and Flynn JT: ACE2 (angiotensin-converting enzyme 2), COVID-19, and ACE inhibitor and Ang II (angiotensin II) receptor blocker use during the pandemic: The pediatric perspective. Hypertension 76: 16-22, 2020.
2. Pacurari M, Kafoury R, Tchounwou PB and Ndebele K: The Renin-Angiotensin-aldosterone system in vascular inflammation and remodeling. Int J Inflamm 2014: 689360, 2014.
3. Ferrario CM and Strawn WB: Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. Am J Cardiol 98: 121-128, 2006.
4. Daher J: Other forms of oxidized LDL: Emerging functions. World Acad Sci J 2: 1-1, 2020.
5. Álvarez A, Cerdá-Nicolás M, Naim Abu Nabah Y, Mata M, Issekutz AC, Panés J, Lobb RR and Sanz MJ: Direct evidence of leukocyte adhesion in arterioles by angiotensin II. Blood 104: 402-408, 2004.
6. Kranzhöfer R, Schmidt J, Pfeiffer CA, Hagl S, Libby P and Kübler W: Angiotensin induces inflammatory activation of human vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 19: 1623-1629, 1999.
7. Hahn AW, Jonas U, Bühler FR and Resink TJ: Activation of human peripheral monocytes by angiotensin II. FEBS Lett 347: 178-180, 1994.
8. Tummala PE, Chen X-L, Sundell CL, Laursen JB, Hammes CP, Alexander RW, Harrison DG and Medford RM: Angiotensin II induces vascular cell adhesion molecule-1 expression in rat vasculature: A potential link between the renin-angiotensin system and atherosclerosis. Circulation 100: 1223-1229, 1999.
9. Rajagopalan S, Kurz S, Münzel T, Tarpey M, Freeman BA, Griendling KK and Harrison DG: Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest 97: 1916-1923, 1996.
10. Wassmann S and Nickenig G: Pathophysiological regulation of the AT1-receptor and implications for vascular disease. J Hypertens Suppl 24 (Suppl 1): S15-S21, 2006.
11. Judkins CP, Diep H, Broughton BRS, Mast AE, Hooker EU, Miller AA, Selemidis S, Dusting GJ, Sobey CG and Drummond GR: Direct evidence of a role for Nox2 in superoxide production, reduced nitric oxide bioavailability, and early atherosclerotic plaque formation in ApoE$^{-/-}$ mice. Am J Physiol Heart Circ Physiol 298: H24-H32, 2010.
12. Förstermann U and Münzel T: Endothelial nitric oxide synthase in vascular disease: From marvel to menace. Circulation 113: 1708-1714, 2006.
13. Ferrari R: RAAS inhibition and mortality in hypertension. Glob Cardiol Sci Pract 2013: 269-278, 2013.
14. Mansur SJ, Hage FG and Oparil S: Have the renin-angiotensin-aldosterone system perturbations in cardiovascular disease been exhausted? Curr Cardiol Rep 12: 450-463, 2010.
15. South AM, Tomlinson L, Edmonston D, Hiremath S and Sparks MA: Controversies of renin-angiotensin system inhibition during the COVID-19 pandemic. Nat Rev Nephrol 16: 305-307, 2020.
16. Fang L, Karakiulakis G and Roth M: Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 8: e21, 2020.
17. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI and Gallagher PE: Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 111: 2605-2610, 2005.
18. Bean D, Kraljevic Z, Searle T, Bendayan R, Pickles A, Folarin A, Roguski L, Noor K, Shek A, O'Gallagher K, *et al*: Treatment with ACE-inhibitors is associated with less severe disease with SARS-Covid-19 infection in a multi-site UK acute Hospital Trust. medRxiv: Apr 11, 2020 (Epub ahead of print). doi: https://doi.org/10.1101/2020.04.07.20056788.
19. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA and Solomon SD: Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 382: 1653-1659, 2020.
20. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, Widmer AF and Osswald S: SARS-CoV2: Should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 41: 1801-1803, 2020.
21. Simões E Silva AC and Flynn JT: The renin-angiotensin-aldosterone system in 2011: Role in hypertension and chronic kidney disease. Pediatr Nephrol 27: 1835-1845, 2012.

22. South AM, Shaltout HA, Washburn LK, Hendricks AS, Diz DI and Chappell MC: Fetal programming and the angiotensin-(1-7) axis: A review of the experimental and clinical data. Clin Sci (Lond) 133: 55-74, 2019.
23. Masi S, Uliana M and Virdis A: Angiotensin II and vascular damage in hypertension: Role of oxidative stress and sympathetic activation. Vascul Pharmacol 115: 13-17, 2019.
24. Wan Y, Shang J, Graham R, Baric RS and Li F: Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol 94: e00127-e20, 2020.
25. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, *et al*: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181: 271-280.e8, 2020.
26. Gu H, Xie Z, Li T, Zhang S, Lai C, Zhu P, Wang K, Han L, Duan Y, Zhao Z, *et al*: Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep 6: 19840, 2016.
27. Li X, Molina-Molina M, Abdul-Hafez A, Uhal V, Xaubet A and Uhal BD: Angiotensin converting enzyme-2 is protective but downregulated in human and experimental lung fibrosis. Am J Physiol Lung Cell Mol Physiol 295: L178-L185, 2008.
28. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, *et al*: Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 63: 364-374, 2020.
29. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM and Butany J: SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 39: 618-625, 2009.
30. Lopes RD, Macedo AVS, de Barros E Silva PG, Moll-Bernardes RJ, Dos Santos TM, Mazza L, Feldman A, D'Andréa Saba Arruda G, de Albuquerque DC, Camiletti AS, *et al*; BRACE CORONA investigators: Effect of discontinuing vs. continuing angiotensin-converting enzyme inhibitors and angiotensin ii receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: A Randomized Clinical Trial. JAMA 325: 254-264, 2021.
31. Hippisley-Cox J, Young D, Coupland C, Channon KM, Tan PS, Harrison DA, Rowan K, Aveyard P, Pavord ID and Watkinson PJ: Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: Cohort study including 8.3 million people. Heart 106: 1503-1511, 2020.
32. Simko F and Baka T: Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers: Potential allies in the COVID-19 pandemic instead of a threat? Clin Sci (Lond) 135: 1009-1014, 2021.
33. Janardhan V, Janardhan V and Kalousek V: COVID-19 as a blood clotting disorder masquerading as a respiratory illness: a cerebrovascular perspective and therapeutic implications for stroke thrombectomy. J Neuroimaging 30: 555-561, 2020.
34. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, *et al*: Coagulopathy and antiphospholipid antibodies in patients with COVID-19. N Engl J Med 382: e38, 2020.
35. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, *et al*: Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 382: e60, 2020.
36. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F and Moch H: Endothelial cell infection and endotheliitis in COVID-19. Lancet 395: 1417-1418, 2020.
37. Hess DC, Eldahshan W and Rutkowski E: COVID-19-related stroke. Transl Stroke Res. 11: 322-325, 2020.
38. Garrido AM and Griendling KK: NADPH oxidases and angiotensin II receptor signaling. Mol Cell Endocrinol 302: 148-158, 2009.
39. El-Assaad F, Krilis SA and Giannakopoulos B: Posttranslational forms of beta 2-glycoprotein I in the pathogenesis of the antiphospholipid syndrome. Thromb J 14 (Suppl 1): 20, 2016.
40. Ho YC, Ahuja KDK, Körner H and Adams MJ: β2GP1, anti-β2GP1 antibodies and platelets: Key players in the antiphospholipid syndrome. Antibodies (Basel) 5: E12, 2016.
41. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH and Zhu CL: Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 58: 1116-1120, 2020.
42. Wang J, Saguner AM, An J, Ning Y, Yan Y and Li G: Dysfunctional coagulation in COVID-19: From cell to bedside. Adv Ther 37: 3033-3039, 2020.
43. Gong J, Dong H, Xia SQ, Huang ZY, Wang DK, Zhao Y, Liu WH, Tu SH, Zhang MM, Wang Q, *et al*: Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19: a retrospective study. BMC Infect Dis 20: 963, 2020.
44. Lipinski S, Bremer L, Lammers T, Thieme F, Schreiber S and Rosenstiel P: Coagulation and inflammation. Molecular insights and diagnostic implications. Hamostaseologie 31: 94-102, 104, 2011.
45. Lupi L, Adamo M, Inciardi RM and Metra M: ACE2 down-regulation may contribute to the increased thrombotic risk in COVID-19. Eur Heart J 41: 3200, 2020.
46. Mehrabadi ME, Hemmati R, Tashakor A, Homaei A, Yousefzadeh M, Hemati K and Hosseinkhani S: Induced dysregulation of ACE2 by SARS-CoV-2 plays a key role in COVID-19 severity. Biomed Pharmacother 137: 111363, 2021.
47. Fraga-Silva RA, Sorg BS, Wankhede M, Dedeugd C, Jun JY, Baker MB, Li Y, Castellano RK, Katovich MJ, Raizada MK, *et al*: ACE2 activation promotes antithrombotic activity. Mol Med 16: 210-215, 2010.
48. Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y, Liu M, Zhao X, Xie Y, Yang Y, *et al*: SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol 13: 120, 2020.
49. Deng H, Tang TX, Chen D, Tang LS, Yang XP and Tang ZH: Endothelial dysfunction and SARS-CoV-2 infection: Association and therapeutic strategies. Pathogens 10: 582, 2021.
50. Libby P and Lüscher T: COVID-19 is, in the end, an endothelial disease. Eur Heart J 41: 3038-3044, 2020.
51. Batlle D, Wysocki J and Satchell K: Soluble angiotensin-converting enzyme 2: A potential approach for coronavirus infection therapy? Clin Sci (Lond) 134: 543-545, 2020.
52. Jahanshahlu L and Rezaei N: Monoclonal antibody as a potential anti-COVID-19. Biomed Pharmacother 129: 110337, 2020.
53. Fodor A, Tiperciuc B, Login C, Orasan OH, Lazar AL, Buchman C, Hanghicel P, Sitar-Taut A, Suharoschi R, Vulturar R, *et al*: Endothelial dysfunction, inflammation, and oxidative stress in COVID-19-mechanisms and therapeutic targets. Oxid Med Cell Longev 2021: 8671713, 2021.
54. Jin Y, Ji W, Yang H, Chen S, Zhang W and Duan G: Endothelial activation and dysfunction in COVID-19: From basic mechanisms to potential therapeutic approaches. Signal Transduct Target Ther 5: 293, 2020.
55. Shahin Y, Khan JA, Samuel N and Chetter I: Angiotensin converting enzyme inhibitors effect on endothelial dysfunction: A meta-analysis of randomised controlled trials. Atherosclerosis 216: 7-16, 2011.
56. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, *et al*: Renin-angiotensin-Aldosterone system inhibitors and risk of covid-19. N Engl J Med 382: 2441-2448, 2020.
57. Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, Schou M, Phelps M, Gislason GH, Gerds TA, *et al*: Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA 324: 168-177, 2020.
58. Flacco ME, Acuti Martellucci C, Bravi F, Parruti G, Cappadona R, Mascitelli A, Manfredini R, Mantovani LG and Manzoli L: Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: A meta-analysis. Heart 106: 1519-1524, 2020.
59. De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G, De Tré G, Belmans L, Dobson R, Wynendaele E, Van De Wiele C, Vandaele F, *et al*: The effects of ARBs, ACEis, and statins on clinical outcomes of COVID-19 infection among nursing home residents. J Am Med Dir Assoc 21: 909-914.e2, 2020.
60. Reriani MK, Dunlay SM, Gupta B, West CP, Rihal CS, Lerman LO and Lerman A: Effects of statins on coronary and peripheral endothelial function in humans: A systematic review and meta-analysis of randomized controlled trials. Eur J Cardiovasc Prev Rehabil 18: 704-716, 2011.
61. Nägele MP, Haubner B, Tanner FC, Ruschitzka F and Flammer AJ: Endothelial dysfunction in COVID-19: Current findings and therapeutic implications. Atherosclerosis 314: 58-62, 2020.
62. Ayerbe L, Risco C and Ayis S: The association between treatment with heparin and survival in patients with Covid-19. J Thromb Thrombolysis 50: 298-301, 2020.
63. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, *et al*: Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180: 934-943, 2020.
64. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, *et al*; RECOVERY Collaborative Group: Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 384: 693-704, 2021.