SARS-CoV-2 and ACE2: The biology and clinical data settling the ARB and ACEI controversy


a Heart, Vascular and Thoracic Institute, United States
b Lerner Research Institute, Cleveland Clinic, United States
c Cleveland Clinic Lerner College of Medicine, United States
d Case Western Reserve University, United States
e University Hospitals Cleveland Medical Center, Cleveland, OH, United States

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ABSTRACT

Background: SARS-CoV-2 enters cells by binding of its spike protein to angiotensin-converting enzyme 2 (ACE2). Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) have been reported to increase ACE2 expression in animal models, and worse outcomes are reported in patients with comorbidities commonly treated with these agents, leading to controversy during the COVID-19 pandemic over whether these drugs might be helpful or harmful.

Methods: Animal, in vitro and clinical data relevant to the biology of the renin-angiotensin system (RAS), its interaction with the kallikrein-kinin system (KKS) and SARS-CoV-2, and clinical studies were reviewed.

Findings and Interpretation: SARS-CoV-2 hijacks ACE2 to invade and damage cells, downregulating ACE2, reducing its protective effects and exacerbating injurious Ang II effects. However, retrospective observational studies do not show higher risk of infection with ACEI or ARB use. Nevertheless, study of the RAS and KKS in the setting of coronaviral infection may yield therapeutic targets.

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1. Introduction

In the unprecedented crisis of the COVID-19 pandemic, we must define the epidemiology, predictors of complications and mortality, and potential modifiable risk factors that might prevent or decrease the severity of the disease. Recently there has been controversy over whether use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) might be harmful in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with cardiovascular disease, hypertension, or diabetes mellitus under treatment with these agents. In contrast, it has been suggested that ARBs could be protective in the setting of SARS-CoV-2 infection.

SARS-CoV-2, the coronavirus causing COVID-19, enters host cells via binding of the virus spike protein to angiotensin-converting enzyme 2 (ACE2). ACEIs or ARBs have been reported to increase expression of ACE2 in animal models [1]. This has led to speculation that use of ACEIs or ARBs might contribute to a higher risk of contracting the infection and worse outcomes of COVID-19 in patients with cardiovascular diseases, hypertension and diabetes [2], as these drugs are commonly used in these conditions. Moreover, these comorbid conditions are increased with age, which is itself also associated with worse outcomes. As we await evidence from and plan clinical studies, it is essential to understand the biology of the renin-angiotensin system (RAS) and its modulation by the SARS-CoV-2 virus.

2. Brief primer on ACE, ACE2 and the renin-angiotensin system (Fig. 1)

Angiotensin converting enzyme (ACE) catalyzes the removal of two residues from the decapeptide angiotensin I (Ang I) to form the
octapeptide angiotensin II (Ang II). Secreted proteases, including mast cell chymase (human heart chymase), play a minor role in forming Ang II, but are more active when patients are on long-term ACE inhibitor therapy. Ang II binding to the type 1 angiotensin II receptor (AT1R) activates pro-inflammatory, vasoconstrictor, pro-oxidant, pro-thrombotic, anti-fibrotic, and pro-fibrotic signaling pathways. ACEIs inhibit conversion of Ang I to Ang II, thereby reducing Ang II production, while ARBs block the downstream effects of Ang II by blocking its receptor, AT1R. The functions of ACE are balanced by its homologue ACE2, which catalyzes the removal of one residue from Ang II to form Ang 1–7 and one residue from Ang I to form Ang 1–9. In doing so, ACE2 reduces Ang II and its effects, while enabling the Ang 1–7 and Ang 1–9 pathways that protect against Ang II effects by promoting vasodilation, as well as anti-inflammatory, anti-oxidant, anti-thrombotic, and anti-fibrotic activity via the receptors Mas1 (a G-protein-coupled receptor [GPCR]) and AT2R, respectively [3]. Ang 1–7-activated Mas1 receptors trigger downstream signaling pathways, including arachidonic acid release and activation of phospholipase A1, NOS, PI3K/Akt, MAP kinases, RhoA, and cAMP/PKA [4].

The Mas1 receptor also acts as an antagonist of the AT1R, and Ang 1–7/Mas1 signaling suppresses Ang II effects, including Ang II-induced reactive oxygen species (ROS) overproduction, apoptosis, phosphorylation of MAPKs and c-Src, leading to TGF-β1 and collagen production, ICAM-1, VCAM-1, and MCP-1 expression [4]. Additionally, if expressed in molar excess to the AT1R, AT2R will directly bind Ang II, leading to its protective activity.

Supporting a complex balance of the ACE/AEC2 pathways in vivo, downregulation of ACE2 is associated with an increase in Ang II and activation of the Ang II / AT1R pathway. However, ACE2 upregulation increases Ang I degradation limiting the substrate for ACE, increases Ang II degradation limiting its adverse effects, and increases the production of Ang 1–7 and Ang 1–9, leading to their protective effects (Fig. 1) [5]. The mechanism of the reported increase of ACE2 expression by ACEIs and ARBs is not well understood, but may be mediated by increased Ang II metabolism by ACE2 and Ang1–7-mediated mitogen-activated (MAP) kinase activity [1]. [6] [7] ACE2 is shed from the cell surface by the action of a disintegrin and metalloproteinase (ADAM) 17, also called tumor necrosis factor-alpha converting enzyme, and ADAM10, which leads to release of a soluble active form of ACE2 and reduced membrane-bound ACE2 [3]–[8]; elevated plasma ACE2 activity in heart failure is associated with worse prognosis [9].

3. ACE, ACE2, and Bradykinin (Fig. 2)

ACE and ACE2 also have intimate roles with the plasma kallikrein-kinin system (KKS), a hormonal pathway that modulates the intrinsic blood coagulation system, endothelial cell growth and angiogenesis, the complement pathway and RAS. The KKS consists of plasma and tissue kallikreins, plasma high (HK) and low (LK) molecular weight kininogens, their derivative kinin peptides, including bradykinin (BK) and des-Arg9-BK, and two G-protein-coupled bradykinin receptors (B2R and B1R) [10]. Plasma prekallikrein (PK) is activated by blood coagulation factor XII or an endothelial cell serine protease, prolylcarboxypeptidase, to preferentially cleave high molecular HK to liberate BK; the residual cleaved kininogen (cHK) is stable in plasma and may be used as a biomarker of KKS activation [11]. BK binds to its receptor B2R, which is constitutively expressed in the intravascular compartment, and des-Arg9-BK binds to the B1R, which arises in inflammatory states. Separately, tissue kallikreins have preference to cleave LK, releasing Lys-BK, which when acted on by several carboxypeptidases, generates des-Arg8-Lys-BK, which also activates B1R receptor.

The vasodilatory effects of BK are predominantly mediated through B2R, which is abundant in vascular endothelium and constitutively expressed in most tissues. B2R activation causes a cascade involving nitric oxide synthase (NOS), leading to synthesis of nitric oxide (NO) and cGMP [12]. BK and its active metabolite des-Arg9-b Bradykinin also agonize B1R, which is minimally expressed in healthy tissue, but induced by tissue injury and inflammatory stimuli, playing a role in chronic pain and inflammation [13,14]. Activation of both the B1 and B2 receptors mediates massive vascular permeability and inflammation, causing marked increases in the levels of inflammatory cytokines, such as IL-1, IL-2, IL-6, IL-8, and TNF-alpha that have been...
implicated in the cytokine storm observed with SARS-CoV-2 ARDS [15,16].

The crosstalk between the RAS and the KKS is profound [17]. Plasma kallikrein converts prorenin to renin. ACE is the major intra-vascular peptidase of BK, producing des-Arg^9-BK and several inactive intermediates, including BK1-5. ACE2 inactivates des-Arg^8-BK by cleaving its C-terminal residue, but has no effect on BK [18]. BK receptors are also known to heterodimerise with angiotensin receptors AT1R, AT2R, and Mas that may augment or diminish their activity [19–21]. Benefits of ACE inhibition can also be attributed to an intra-cellular signaling cascade that prevents B2R desensitisation. ACEIs inhibit BK and des-Arg^9-BK degradation, potentiating their effects [22]. Prolylcarboxypeptidase, an enzyme that also produces Ang 1-7, is known to stimulate Type II pneumocytes to release neutrophil and monocyte chemotactic molecules [32]. A decrease in ACE2 in lung injury would reduce metabolism of des-Arg^9-BK, potentially increasing its effect via the B1R to increase vascular permeability and fluid extravasation. B1R antagonism attenuates lipopolysaccharide-induced neutrophil influx in murine models of acute lung injury [33].

5. Lessons from SARS-CoV

SARS-CoV was the coronavirus causing the SARS outbreak in 2003. The highly glycosylated viral spike proteins form club-shaped projections extending from the surface of the virions, giving the defining appearance of the “corona” around all CoVs, including SARS-CoV and SARS-CoV-2, the causative agent of COVID-19. The spike protein is a key determinant for virus attachment and entry into target cells. Animal studies confirm ACE2 as the important receptor for the SARS-CoV spike protein. In Ace2 knockout mice, only a very small amount of virus could be recovered from lung tissue, supporting the importance of ACE2 as the SARS-CoV receptor [34]. Infection of wild type mice with SARS-CoV reduces ACE2 expression [34]. SARS spike protein bound to ACE2 induces shedding of ACE2 with downregulation of ACE2 [Fig. 3] [35]. Intrapulmonary injection of a SARS-CoV Spike-Fc fusion protein into mice with acute acid-induced lung injury worsens acute lung failure that is attenuated by the AT1 receptor blocker losartan [34]. Combining the infection and lung injury studies, the data suggest that both cell surface and released ACE2 catalytic activity producing Ang 1–7 is protective against lung injury. As SARS-CoV binding to ACE2 is associated with shedding and downregulation of ACE2 that may worsen injury, loss of Ang 1–7 protective effects and increased Ang II and des-Arg^8-BK as a result of diminished ACE2 activity may also lead to deleterious effects. Injury in these models was attenuated with AT1 receptor blockade. Ace2 expression is lower in rat lung tissues with age [36], kidney tissues in type 2 diabetes
with renal disease [37] and post-mortem brain tissue in Alzheimer's disease [38].

6. The SARS-CoV-2 spike protein and ACE2

Given the novel emergence of SARS-CoV-2, studies on cellular and animal models are just emerging. Similar to SARS-CoV, the receptor for SARS-CoV-2 is ACE2. The early availability of sequence information of virus isolates facilitated structural studies confirming the binding of SARS-CoV-2 spike protein to ACE2. The SARS-CoV-2 spike protein has significant structural homology to the spike protein of SARS-CoV. Both spike proteins bind to ACE2, but SARS-CoV-2 spike protein has been reported to bind with tighter affinity than SARS-CoV [39], so the lessons from SARS-CoV are expected to apply to SARS-CoV-2, perhaps to an even higher degree. The contribution of the enhanced binding to ACE2 to the infectivity of SARS-CoV-2 is not well understood, and binding affinity may reflect genetic variation in ACE2, but the distribution of ACE2 in lung alveolar cells, mouth, intestines, heart, endothelium, kidneys, testes, and brain may explain effects on lung injury, gastrointestinal symptoms, cardiac damage, acute kidney injury, and reports of late potentially neurally mediated cardiorespiratory depression (Fig. 4). Like SARS-CoV, SARS-CoV-2 spike protein requires priming by the serine protease TMPRSS2 for optimal cell entry [40]. Lung and intestines show ACE2 and TMPRSS2 expression and are primary sites of viral entry. The heart shows high levels of ACE2, but low levels of TMPRSS2 expression, which calls into question the mechanism of injury and myocarditis observed in severe cases of COVID-19. However, a polybasic furin cleavage site has been recently identified in the SARS-CoV-2 spike protein [41]: furin-like proteases that may contribute to SARS-CoV-2 spike protein processing are more ubiquitously expressed and may explain an expanded cell and tissue tropism of SARS-CoV-2 compared to SARS-CoV, which lacks this site [41–43].

We now know that SARS-CoV-2 cell entry involves two spike protein subunits, which mediate distinct functions. The S1 subunit mediates ACE2 attachment through the receptor binding domain, whereas the S2 subunit, containing the fusion peptide and transmembrane domains, drives fusion of viral and host cell membranes. In addition to attachment, viral entry is determined by spike protein cleavage at two proteolytic cleavage sites, termed S1/S2 and S2′ subunits. Unlike SARS-CoV, the S1/S2 site of the SARS-CoV-2 spike protein is processed by the cellular protease furin [44]. Subsequently, processing of the S2′ site by the cellular serine protease TMPRSS2 (transmembrane protein serine protease 2) occurs, and both furin and TMPRSS2 are required for entry into human lung cells [45]. Spike protein priming by TMPRSS2 was also shown to be essential for spread of SARS-CoV in infected mouse models [46–48]. Although SARS-CoV-2 fusion is thought to occur in the endosomes of target cells, the requirement of cathepsins B and L for optimal membrane fusion efficiency in vivo remains unclear. Chloroquine increases the pH of lysosomes and is thought to inhibit the activity of proteases that promote membrane fusion and viral release into the cell. Ang I - angiotensin I. Ang II - angiotensin II. Ang 1-7 - angiotensin 1–7. ACE - angiotensin converting enzyme. ACE 2 - angiotensin converting enzyme 2. AT1 R - angiotensin 1 receptor. Mas1 R - mitochondrial assembly receptor. ACEI - angiotensin converting enzyme inhibitor. ARB - angiotensin 1 receptor blocker. TMPRSS2 - transmembrane protein serine protease 2.

7. ACE2, platelets and thrombosis

Thrombotic disorders, including MI and stroke, are common features in patients with SARS-CoV-2 infection [49]. SARS-CoV-2 virus has been found in endothelium and leads to vessel apoptosis, a risk factor for thrombosis [50]. The coagulopathy associated with COVID-19 is like disseminated intravascular coagulation (DIC) with elevated d-dimer, but high fibrinogens and, in the majority of the patients in the USA, lacking strict criteria for DIC. The cross-talk between the KKS and coagulation system via the activation of Factor XII by kallikrein may contribute to the pro-coagulant state. Kallikrein has also been shown to stimulate activation of the complement system through C3 activation, which likely contributes to the associated coagulopathy [51]. In experimental models of thrombosis, ACE2 expression was detected in thrombus extract raising the possibility that ACE2 may play a role in the regulation of both thrombotic and homostatic functions of circulating platelets [52]. Activation of the ACE2/Ang1–7/Mas pathway and/or reduction of Ang II by use of an ACE2 activator (XNT) demonstrated antithrombotic activity in an animal
model [52]. SARS-CoV-2 replicates in lung tissue, and the lung is a major site for extra-medullary thrombopoiesis [53]. Single-stranded RNA (SSRNA) viruses, including influenza, were recently demonstrated to augment platelet activation and platelet-to-leukocyte recruitment through the platelet toll-like receptor 7 (TLR7) [54]. Since SARS-CoV-2, like influenza, is also a SSRNA virus, the possibility exists that SARS-CoV-2 may promote dysregulated platelet activity directly through surface receptor-mediated pathways or indirectly by secreting platelet-derived molecules that regulate the coagulation cascade. Lastly, angiotensin receptors are expressed on the surface of platelets, and medications inhibiting the RAS attenuate platelet activation [55,56]. Therefore, the impact of anti-platelet medications and ACEIs/ARBs on platelet function and thrombotic events in patients with SARS-CoV-2 needs further investigation.

8. ACEIs and ARBs

Helpful or harmful? Though ARBs and ACEIs may be associated with an increase in ACE2 expression, which theoretically may enhance viral infection, their inhibition of the RAS with increase in ACE2 expression, reduction of Ang II or Ang II effects, and increase in Ang1–7 and Ang 1–9 may have protective effects. ARBs may increase Ang II by competing with binding to AT1R, but this may create more available substrate for ACE2 and formation of Ang1–7 with its downstream protective effects. Binding of substrates to ACE2 may induce conformational changes in ACE2; it is unknown whether these interactions would enable or reduce SARS-CoV-2 spike protein binding. Specific effects of ACEIs and ARBs on this process are not known. Genetic factors, including genetic variability in ACE2 polymorphisms, may also determine functional roles of ACE2 for ACEIs and ARBs, as well as in its interaction with the CoV-2 spike protein, and will be important to dissect in the future [57]. Finally, ACEI could reduce metabolism of BK, leading to B1R- and B2R-mediated inflammatory, vasodilatory, vascular permeability and fluid extravasation effects.

9. Clinical studies

Initial clinical data showing conflicting outcomes in COVID-19 associated with ARB or ACEI use were confounded by lack of adjustment for co-morbidities (Table). In a study of 187 COVID-19 patients from Wuhan, China, ACEI or ARB use was higher in patients with myocardial injury and elevated troponin T (TnT) levels (21 ±1%) compared to patients with normal TnT (5 ±9%), p = 0.002 [58]. In 41 patients with COVID-19 on antihypertensive therapy, severe disease was observed in 23±5% on and 48% not on an ACEI or ARB, but this was not significant due to the small sample size [59]. A pre-publication report of 78 COVID-19 + patients with hypertension reported ARB use (n = 10) was associated with lower occurrence of severe disease (OR 0.343, 95% CI 0.128–0.916, p = 0.025). In a study of 362 hospitalized COVID-19 patients with hypertension, ACEI and/or ARB use (n = 115) was not significantly different between patients with severe vs. non-severe illness or in non-survivors vs survivors [60].

In a report of 399 acute inpatients from the UK Acute Hospital Trust, 53 died or were transferred to a critical care unit within 21
Studies of ACEIs and/or ARBs in COVID-19 patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Design</th>
<th>Outcome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo, et al. [58]</td>
<td>COVID-19+ (Wuhan, China)</td>
<td>187</td>
<td>Retrospective; unadjusted</td>
<td>Retrospective; unadjusted</td>
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<tr>
<td>Meng, et al. [59]</td>
<td>COVID-19+ on antihypertensive therapy (Shenzhen, China)</td>
<td>42</td>
<td>Retrospective; unadjusted</td>
<td>Severe disease</td>
<td></td>
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<tr>
<td>Liu, et al. [60]</td>
<td>COVID-19 hypertension (Shenzhen, Wuhan, Beijing, China)</td>
<td>78 HTN</td>
<td>Meta-analysis</td>
<td>Severe disease (Whole cohort NS)</td>
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<tr>
<td>Li, et al. [61]</td>
<td>COVID-19+ hypertension Hospitalized (Wuhan, China)</td>
<td>115 ACEI/ARB</td>
<td>Retrospective, unadjusted</td>
<td>Graftfailure</td>
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<tr>
<td>Bean, et al. [62]</td>
<td>UK Acute Hospital Trust acute inpatients (London, UK)</td>
<td>399</td>
<td>Retrospective; adjusted</td>
<td>Graftfailure</td>
<td></td>
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<tr>
<td>Rentsch, et al. [63]</td>
<td>Veterans Administration Birth Cohort; veterans (USA)</td>
<td>3789 tested</td>
<td>Retrospective cohort study; adjusted</td>
<td>Graftfailure</td>
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<tr>
<td>Zhang, et al. [64]</td>
<td>COVID-19+ hypertension (Hubei, China)</td>
<td>1128 HTN</td>
<td>Retrospective, adjusted and propensity score</td>
<td>Propensity score matched (1:2)</td>
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<td>Mehta, et al. [65]</td>
<td>Patients undergoing testing for COVID-19 (Ohio, Florida)</td>
<td>18,472 tested</td>
<td>Retrospective cohort study; overlap propensity score</td>
<td>SARS-CoV-2 test positivity</td>
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<td>Mancia, et al. [66]</td>
<td>Patients tested for SARS-CoV-2 vs Regional Health Service controls (Italy)</td>
<td>6,722 SARS-CoV-2+ 30,759 controls</td>
<td>Population-based case-control, conditional logistic regression multivariate analysis</td>
<td>Adjusted OR, 95% CI cases vs. matched controls</td>
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### Propensity score matched, All Matched patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study Population</th>
<th>Design</th>
<th>Outcome</th>
<th>P value</th>
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| ACEI | [Reynolds, et al.][65] Patients tested for Covid-19 | 12,594 tested patients, including 5894 who tested positive, ACEI, or ARB use was not associated with degree of disease [64]. Another study of 12,594 tested patients, including 5894 who tested positive, ACEI, ARB, or either were not associated with test positivity or severe COVID-19 disease [65]. In a study of 287 patients with COVID-19, 850 had hypertension of which 183 were treated with renin-angiotensin-aldosterone system inhibitors (RAASI) and 527 were not; RAASI use was not associated with severity of disease or mortality [66]. Lastly, in a study of 4480 patients with COVID-19 in Danish national administrative registries, prior ACEI or ARB use was not associated with death or severe COVID-19 in a nested case-control study of patients with hypertension. ACEI/ARB use was not significantly associated with COVID-19 diagnosis [67]. Taken together, it is now consistent clinical evidence that ACEI or ARB use does not appear to predispose to SARS-CoV-2 infection, which was the main concern raised due to postulated effects of ACEIs or ARBs in raising ACE2 expression. Recent studies have shown no association of ACEI or ARB use with SARS-CoV-2 test positivity. Studies do not indicate harm from ACEI or ARB use in terms of severity of disease but with some conflicting results regarding the benefit vs. risk of ACEIs. However, the overall balance appears to be in favor of no significant harm from ACEI or ARB use in COVID-19, though larger studies are needed to assess the relative effects of ACEIs versus ARBs, whether continuation or withdrawal of these agents impact outcomes, or if ACEI/ARB use may actually be beneficial in alleviating lung or other organ injury in patients with COVID-19.

**10. Recommendations regarding ACEIs and ARBs**

Given the current reassuring data showing no significant association of ACEI or ARB use with test positivity, lack of consistent or convincing evidence as to the risk or benefit of an ACEI or ARB, as well as the potential harm that may occur with withdrawing of ACEIs or ARBs in patients with cardiovascular and other diseases [68], findings support the European Society of Cardiology, American Heart Association, American College of Cardiology, and the Heart Failure Society of America recommendations that patients on these therapies should be continued as clinically indicated. The recent data show consistent lack of an association with SARS-CoV-2 positivity. However, there remains a need to further assess impact of ACEIs and ARBs on severity of disease, potentially through larger or randomized studies.
11. Implications for novel and repurposable therapeutics

The spike protein is a target for drug discovery and vaccine development. Blocking the spike protein-ACE2 interaction sites may be targetable with antibodies or small molecules, and use of soluble ACE2 may competitively bind to the spike protein [69]. Strategies to increase ACE2 shedding from cells may be protective against viral infection [70]. Furin inhibitors or other serine protease inhibitors may inhibit SARS-CoV-2 replication via the S1/S2 cleavage site [45]. TMPRSS2 is dispensable for homeostatic function and blocked by the serine protease inhibitor camostat mesilate, a drug approved in Japan for unrelated conditions [40]. Our recent systems biology study suggested several repurposable drugs for potential treatment of COVID-19, including melatonin and ARBs (i.e., irbesartan) [71]. Melatonin regulates expression of several cellular targets of human CoV, including ACE2, Ang II and AT1R [72]. Hydroxychloroquine and chloroquine have been commonly tried for treatment of COVID-19. Besides inhibiting viral-endosome fusion and release of viral particles to the cell by reducing endosomal acidification, chloroquine impairs terminal glycosylation of ACE2, which may have effects on binding affinity between ACE2 and Co-V spike protein [73]. However, efficacy remains to be established, and randomized trials are ongoing. Therapeutic application of Ang1–7 and Ang1–9 is limited because of the short half-life of these peptides and unavailability of FDA-approved drugs that can substitute for the potential benefits attributed to these peptides. Interventions directed at blocking BK and the pathways leading to its formation may also be of benefit. Hereditary angioedema, a rare genetic disorder causing predisposition to attacks of angioedema, is treated with medications to suppress activity in the KKS. These medications largely consist of direct kallikrein inhibitors, B2R antagonists, and replacement with C1 inhibitor. BK’s role in COVID-19 is under investigation, and use of these suppressive medications is being explored. Until such time when there is a highly effective antiviral or a vaccine, these adjunctive approaches need to be developed.

12. Summary

In clinical practice the protective effects of ARBs and ACEIs are thought to be associated with an increase in ACE2 expression and their inhibition of the overactive renin-angiotensin system through reduction of Ang II effects. Coronavirus infection hijacks ACE2 expression to invade cells and spread infection-associated damage, downregulating ACE2 expression, reducing its protective effects and exacerbating the injurious Ang II effects. Retrospective observational studies do not show associations with higher risk of infection for persons receiving ACEIs or ARBs. However, controlled clinical trials would be needed to determine the risks or benefits of these agents in treating COVID-19. Studies in SARS-CoV-2 models and clinical retrospective and prospective studies in patients might further clarify these important questions. Such studies may also identify plausible therapeutic agents for targets within the RAS and KKS in the setting of coronaviral infection.

13. Outstanding Questions

Important questions remaining for future research include whether drugs targeting components of the RAS or the KKS might be helpful in the treatment of patients with COVID-19. Prospective controlled clinical trials are needed. Basic research on mechanisms to determine if ACE2 expression affects viral infectivity in vitro and expression of components of the RAS and KKS in infected tissues are needed to help clarify the role of cell-bound or shed ACE2 in COVID-19 pathophysiology. Investigations into specific cell types vulnerable to SARS-CoV-2 infection may help focus targeting of therapies.

Search Strategy and Selection Criteria. Data for this Review were identified by searches of PubMed with search terms including combinations of ACE inhibitors, ARBs, COVID-19, SARS-CoV-2, renin-angiotensin system, kallikrein-kinin system.

Authors’ contributions

Mina K. Chung, MD - writing, revisions, literature search, figures, responsibility for the manuscript
Sadashiva Karnik, PhD - RAS expertise, critical writing and revisions, figures
Joshua Saef, MD - KKS expertise, critical writing and revisions, figure
Cornelia Bergmann, PhD - coronavirus expertise, critical writing and revisions
John Barnard, PhD - GTeX query/data, figure
Michael M. Lederman, MD - virology, infectious disease expertise, critical writing and revisions
John Tilton, MD - virology expertise, critical writing and revisions
Feixiong Cheng, PhD - expertise in COVID-19 drug repurposing, writing/revisions
Clifford, V. Harding, III, MD, PhD - cell biology and immunology expertise, critical revisions
James B. Young, MD - ACEI/ARB, heart failure/cardiology expertise, critical comments/revisions
Neil Mehta, MD - ACEI/ARB expertise, contributed data/studies on ACE/ARBs
Scott J. Cameron MD, PhD - expertise in platelets and thrombosis in COVID-19, critical writing, revisions
Keith R. McCrave, MD - expertise in thrombosis, critical revisions
Alvin H. Schmaier, MD - expertise in thrombosis, KKS, critical revisions
Jonathan D. Smith, PhD - revisions, insights in ACE2 shedding
Ankur Kalra, MD - ACEI/ARB expertise in COVID-19, review and suggestions for manuscript
Surafel K. Gebreselassie, MD - RAS revisions/suggestions for manuscript
George Thomas, MD - RAS revisions/suggestions for manuscript
Edward S. Hawkins, MD - RAS revisions/suggestions for manuscript
Lars G. Svensson, MD, PhD - critical comments, revisions

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