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Angiotensin-converting enzyme 2, coronavirus disease 2019, and abdominal aortic aneurysms

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ABSTRACT

Objective: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the etiologic agent of the current, worldwide coronavirus disease 2019 (COVID-19) pandemic. Angiotensin-converting enzyme 2 (ACE2) is the SARS-CoV-2 host entry receptor for cellular inoculation and target organ injury. We reviewed ACE2 expression and the role of ACE2-angiotensin 1-7-Mas receptor axis activity in abdominal aortic aneurysm (AAA) pathogenesis to identify potential COVID-19 influences on AAA disease pathogenesis.

Methods: A comprehensive literature search was performed on PubMed, National Library of Medicine. Key words included COVID-19, SARS-CoV-2, AAA, ACE2, ACE or angiotensin II type 1 (AT1) receptor inhibitor, angiotensin 1-7, Mas receptor, age, gender, respiratory diseases, diabetes, and autoimmune diseases. Key publications on the epidemiology and pathogenesis of COVID-19 and AAAs were identified and reviewed.

Results: All vascular structural cells, including endothelial and smooth muscle cells, fibroblasts, and pericytes express ACE2. Cigarette smoking, diabetes, chronic obstructive pulmonary disease, lupus, certain types of malignancies, and viral infection promote ACE2 expression and activity, with the magnitude of response varying by sex and age. Genetic deficiency of AT1 receptor, or pharmacologic ACE or AT1 inhibition also increases ACE2 and its catalytic product angiotensin 1-7. Genetic ablation or pharmacologic inhibition of ACE2 or Mas receptor augments, whereas ACE2 activation or angiotensin 1-7 treatment attenuates, progression of experimental AAAs. The potential influences of SARS-CoV-2 on AAA pathogenesis include augmented ACE-angiotensin II-AT1 receptor activity resulting from decreased reciprocal ACE2-angiotensin 1-7-Mas activation; increased production of proaneurysmal mediators stimulated by viral spike proteins in ACE2-negative myeloid cells or by ACE2-expressing vascular structural cells; augmented local or systemic cross-talk between viral targeted nonvascular, nonleukocytic ACE2-expressing cells via ligand recognition of their cognate leukocyte receptors; and hypoxemia and increased systemic inflammatory tone experienced during severe COVID-19 illness.

Conclusions: COVID-19 may theoretically influence AAA disease through multiple SARS-CoV-2-induced mechanisms. Further investigation and clinical follow-up will be necessary to determine whether and to what extent the COVID-19 pandemic will influence the prevalence, progression, and lethality of AAA disease in the coming decade. (J Vasc Surg 2021;74:1740-51.)

Keywords: Angiotensin-converting enzyme 2; Severe acute respiratory syndrome (SARS); Coronavirus disease 2019 (COVID-19); Abdominal aortic aneurysm (AAA)

Abdominal aortic aneurysm (AAA) is a common and lethal disease of mature adults worldwide. The prevalence and progression of the disease is influenced by the age, sex, race, tobacco consumption, exercise habits, comorbidities, and medication regimens of affected individuals.[1-5] Although the implementation of targeted screening programs for at-risk individuals and decreased surgical risk associated with endovascular repair has substantially reduced aneurysm-specific mortality,[6] nearly 10,000 Americans died owing to rupture or other AAA-related complications in 2017 (https:/www.cdc.org).

Multiple pathogenic mechanisms promote AAA disease initiation and progression, including the hemodynamic consequences of sedentary existence or asymmetric iliac arterial flow; imbalances between proteinase and antiproteinase activity; renin-angiotensin (Ang) system (RAS) activation; accelerated innate and adaptive effector immunity; impaired immunoregulatory and tissue reparative mechanisms; increased oxidative stress; disturbed fibrinolytic pathways; and destabilized extracellular matrix architecture (Table I).[68-71]

Of these, substantial experimental evidence supporting RAS modulation of AAA risk and progression has been developed in murine modeling systems incorporating genetic deficiencies of angiotensin-converting enzyme (ACE) or Ang II type 1 (AT1) receptors, or wild-type mice treated with either ACE inhibitor (ACEi) or AT1 receptor blockers (ARB).[16-23] Retrospective clinical evidence has

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Table I. Evidence summarizing potential mechanistic links between severe acute respiratory syndrome coronavirus-2 (*SARS-CoV-2*) and abdominal aortic aneurysms (*AAAs*)

Evidence category	Evidence	References
Common risk factors	Male sex, advanced age, cigarette smoking Chronic obstructive pulmonary disease and obesity	7-15
Effects on/consequences of RAS dysregulation.	ACE-Ang II-AT1 receptor activity promotes, whereas ACE2-Ang 1-7-Mas receptor activity inhibits, experimental AAAs Reduced clinical AAA expansion associated with ARB use ACE2 expression is reduced in aneurysmal aorta. Apelin and resveratrol, protective against experimental AAA, increases ACE2 expression. Circulating ACE2 inversely associated with AAA risk and operative mortality following repair. Cell surface ACE2 internalization and shedding following SARS-CoV-2 entry impairs Ang II degradation and Ang 1-7 formation. Increased Ang II and reduced Ang 1-7 serum levels in patients with COVID-19.	1,16-44
Influences on/effects of inflammatory mediator expression	SARS-CoV-2-infected cells (respiratory epithelial cells, vascular endothelial cells, smooth muscle cells and fibroblasts) secrete chemokines and cytokines such as CCL2, CXCL12, MIF, IL-1β, TNF-α, IL-6, IL-8, type 1 interferons Recognition of chemokines and cytokines by their myeloid cell receptors mediates myeloid cell migration and inflammatory activity	45-48
Biologic response to viral spike protein exposure.	Spike protein exposure increases IL-1β, IL-6, IL-8, IL-12, TNF-α, MHC II, and costimulatory molecule (CD80 and CD86) expression by ACE2-neagtive macrophages and dendritic cells, augmenting their inflammatory and T cell-stimulatory activity	49-55
SARS-CoV-2 RNA recognized by TLR7 and TLR8	TLR signaling triggers proinflammatory type 1 interferon production by infected ACE2-expressing cells and impact leukocyte activity by interacting with their leukocyte type 1 receptor Directly or indirectly influence interferon regulatory factor expression on T cells and macrophages promoting the differentiation or activation of proinflammatory Th1 cells, Th17 cells and M1 macrophages	49,56
Viral pulmonary injury	Pulmonary injury creates hypoxemia stabilizing and increasing proaneurysmal HIF-1 levels Increases LPS owing to secondary pulmonary bacterial infection	13,56-63
Other	Intracranial and coronary arterial aneurysms have been reported in adults and children, respectively, with COVID-19	64-67

ACE, Angiotensin-converting enzyme; *Ang*, angiotensin; *COVID-19*, coronavirus disease-2019; *HIF*, hypoxia-inducible factor; *LPS*, lipopolysaccharide; *MHC*, major histocompatibility complex; *RAS*, renin-angiotensin system; *Th*, T helper cell; *TLR*, Toll-like receptor; *TNF*, tumor necrosis factor.

linked the presence of ARB therapy with decreased enlargement rate of small AAAs,[1,24] although recently completed, prospective, randomized clinical trials failed to confirm their efficacy.[72,73] Despite lingering uncertainty as to the effect size and specific mechanism(s) of action, the preponderance of clinical and experimental evidence clearly links RAS activity with AAA pathogenesis.

The ACE2 receptor serves three major recognized biological functions.[74] As a surface carboxypeptidase enzymatic agent, ACE2 converts Ang I and Ang II to Ang 1-9 and Ang 1-7, respectively. Ang 1-7 binds to its surface receptor Mas on target cells, initiating anti-inflammatory and antiproliferative responses in target cells, decreasing oxidative stress and vasoconstriction, and generally offsetting reciprocal responses engendered via AT-1

receptor activation by Ang II. In this regard ACE2 activity is felt to be critical for maintaining cardiovascular health.[75]

In conjunction with the amino acid transporter SLC6A19, ACE2 activity is required for amino acid uptake in the renal and intestinal epithelia.[76,77] Coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and human coronavirus NL63 (HCoV-NL63), also use ACE2 as their entry portal for infecting host cells.[78-82] Subsequent endocytosis of viruses through, and proteinase-mediated shedding of, surface ACE2 have been shown to downregulate surface ACE2 (Table I; Fig 1). Although the involvement of ACE2 in promoting COVID19-related cardiovascular complications is the focus of intense investigation currently,[75,83-85] the potential impacts on AAA pathogenesis and progression have yet to undergo comprehensive review.

With this monograph, we review the influence of COVID-19-and AAA-shared risk factors on ACE2 expression, the significance of the ACE2-Ang 1-7-Mas axis in AAA pathogenesis, and the theoretical potential for SARS-CoV-2/COVID-19 to influence AAA disease prevalence and progression in the years after the COVID-19 pandemic.

ACE2 EXPRESSION AND ACTIVITY IN HEALTH AND DISEASE

Tissue expression patterns and cellular sources. ACE2 expression was originally recognized in heart, kidney, and testis tissues in the setting of advanced congestive heart failure.[86] Subsequent studies identified constitutive ACE2 expression in healthy human lung, intestine, blood vessels, nasal and oral mucosa, nasopharynx, and adipose tissues, with low or rare expression in immune organs such as bone marrow, spleen, and lymph nodes.[87,88] By cell type, expression is present in cardiomyocytes and endothelial and smooth muscle cells, as well as in intestinal, renal, respiratory, and testicular epithelial cells.[87] With the identification of ACE2 as the entry receptor for SARS and SARS-CoV-2,[26-30] studies using bulk tissue and single cell transcriptomic analysis have extended known tissue and cellular expression patterns to include pericytes, fibroblasts, and certain immune cells.[45,89-95]

Age and sex. Advanced age and male sex are nonmodifiable risk factors for COVID-19 infection and AAA disease (Table I). Although differences exist, it remains uncertain the degree to which age or sex differences influence ACE2 expression, and the degree to which observed changes, when present, are tissue or organ specific. Increased ACE2 mRNA expression is present in adult nasal mucosae compared with that of children.[96] ACE2 protein levels, but not ACE2 mRNA expression, were noted to decrease in rodent lung and thoracic aorta with increasing age in both genders but more rapidly in males,[7,89,97,98] Additionally, increased ACE2 expression and activity were present in renal but not lung or heart tissue of male rats.[8,89] No similar data exist regarding vascular cell ACE2 expression as a function of age or sex.

Cigarette smoking. Cigarette smoking increases ACE2 mRNA expression in the respiratory system, more significantly in current as opposed to former smokers[7,9-12] and increasing with smoking intensity (packs per year).[7] Expression is similarly increased in mice exposed to cigarette smoke.[7] In addition to increased ACE2 expression per cell, smoking also stimulates respiratory secretory cell proliferation, both accounting for most of the increased ACE2 expression in smokers.[7]

Increased ACE2 expression and activity may serve to counteract pulmonary inflammation in response to cigarette smoke. In this scenario, ACE2 either converts Ang I to Ang 1-10 or degrades Ang II formed by ACE to Ang 1-7. At the same time, however, smoking-induced ACE2 upregulation also accelerates the entry of SARS-CoV-2 into host respiratory cells, exacerbating existing pulmonary pathologies and impairing gas exchange, even in convalescent patients with COVID-19.[13] Cigarette smoking has long been recognized as the single most important modifiable risk factor for the prevalence and progression of AAA disease. Smoking-related respiratory diseases such as chronic obstructive pulmonary disease and asthma also promote AAA disease risk[14,15,99]; thus, the potential influence of smoking on COVID-19 susceptibility and related pulmonary pathologies may further enhance AAA disease risk.

Comorbidities. Some preexisting conditions relevant for COVID-19 and AAA disease risk also influence ACE2 expression.[3,100,101] For instance, chronic obstructive pulmonary disease, lupus, inflammatory bowel disease, and certain malignancies are associated with augmented ACE2 expression (Table I).[7,102-105] Diabetes has also been associated with increased ACE2 expression in the proximal tubular epithelial cells in diabetes-induced chronic kidney disease as well as aortic endothelial cells.[106-108] This latter finding potentially provides additional insight into the known inhibitory influence of diabetes on AAA disease while simultaneously explaining increased morbidity and mortality in COVID-19 illness. ACE2 expression has also been negatively associated with the degree of type 2 immunity or IgE levels in patients with allergic asthma, an association also potentially relevant to a decreased AAA disease risk in diabetics.[109-111]

Medications. Because ACE2 activation counteracts ACE activity in many pathophysiologic processes, the influence of ACEis or ARBs on ACE2, and its catalytic product Ang 1-7, have been extensively investigated in rodent models. A large body of experimental evidence,

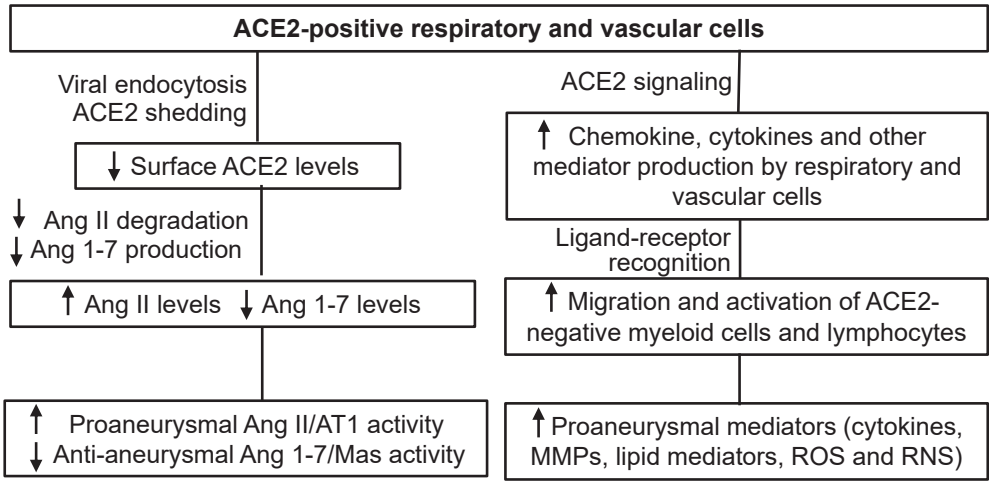

Fig 1. Angiotensin-converting enzyme 2 (*ACE-2*)-dependent potential influences of COVID-19 on abdominal aortic aneurysm (AAA) disease. *AT1*, Angiotensin II type receptor; *EC*, endothelial cells; *HIF*, hypoxia inducible factor; *Mas*, receptor for Ang 1-7; *MMPs*, matrix metalloproteinases; *RNS*, reactive nitrogen species; *ROS*, reactive oxygen species; *SMCs*, smooth muscle cells

summarized recently by Kreutz and colleagues,[112] suggests that ACE-Ang II-AT1 axis inhibition augments the expression and/or activity of ACE2 and Ang 1-7. For example, either genetic deficiency or pharmacologic inhibition of AT1 reversed the downregulation of arterial ACE2 mRNA and protein levels in mice following surgical manipulation.[113] ACEi or ARB administration produced increased rat myocardial ACE2 mRNA levels, with or without surgical myocardial infarction, in conjunction with elevated Ang 1-7.[114,115] In the mouse model of high fat diet-induced metabolic syndrome, treatment with the ARB telmisartan effectively reversed the downregulation of ACE2 in adipose tissue.[116] Additionally, well-controlled hyperglycemia was associated with less mortality in patients with COVID-19 and type II diabetes.[117] Metformin, the world's most commonly prescribed oral hypoglycemic agent for type II diabetes, may promote conformational changes in ACE2 via AMPK-mediated phosphorylation without influencing ACE2 expression.[118]

Clinical data on the influence of ACEi and ARBs on ACE2 expression and activity are somewhat more limited. In patients with either chronic congestive heart failure or atrial fibrillation, ACEi treatment increased circulating Ang 1-7 levels and ACE2 mRNA expression, respectively.[119,120] Neither ACEi nor ARB treatment increased plasma ACE2 levels in patients with congestive heart failure, however.[120,121] Similarly, no upregulation of ACE2 mRNA expression was noted in the lungs of patients treated with either ACEis or ARBs.[122] Despite great interest regarding the influence of ARBs or ACEis on clinical outcomes in COVID-19, no data exist regarding plasma levels of ACE2 or Ang 1-7 in affected patients with or without either medication.[101,123-128]

Other influences. IL-13, apelin, Ang II, hypoxia, resveratrol, and type 1 interferons have all been reported to upregulate ACE2 expression and/or activity.[7,25-27,43] Conversely, IFN-γ, IL-4, and estrogen are all associated with downregulated ACE2 expression.[28] Infection with pathogenic viruses, such as seasonal influenza, respiratory syncytial virus, SARS-CoV, and Middle East respiratory syndrome, also upregulate ACE2 mRNA expression in airway cells.[7]

SIGNIFICANCE OF THE ACE2-ANG 1-7-MAS AXIS IN AAA PATHOGENESIS

ACE2 in AAA disease. Transmural aortic ACE2 expression, although present in human AAAs,[29] is diminished compared with that present in control aorta obtained at the time of organ donation (Table I).[25] Serum ACE2 activity is negatively associated with AAA diagnosis, and circulating ACE2 is an independent risk factor for postoperative mortality after open surgical repair of ruptured AAA (Table I).[25,30] ACE2 mRNA expression is increased in human and mouse vascular smooth muscle cells after exposure to Ang II.[43]

Influence on exogenous Ang II-dependent experimental AAAs. In functional studies of Ang II-induced experimental AAAs (aneurysmal degeneration preceded and precipitated by focal, segmental aortic dissection), genetic deficiency of ACE2 accelerated, whereas pharmacologic activation of or adenovirus-mediated overexpression of ACE2 inhibited, AAA formation in hyperlipidemic mice (Table I and Fig 1).[25,29,31] ACE2 expression was profoundly localized to the adventitia of aneurysmal, as compared with non-aneurysmal aortic segments.[25] Furthermore, treatment

with the Mas receptor ligand Ang 1-7 or its analogue ameliorated, whereas genetic deficiency or pharmacologic inhibition of the Mas receptor augmented, AAAs in this same modeling system (Table I; Fig 1).[32,33,129] Apelin and resveratrol, agents known to be effective in inhibiting experimental AAA formation and progression in multiple modeling systems, mediate aneurysm suppression in part by increasing ACE2 expression (Table I),[25,43,130,131] additionally underscoring the potential antianeurysmal effects of ACE2 activity in experimental modeling systems.

Influence on experimental AAAs in alternative modeling systems. Published results are inconsistent regarding the importance of ACE2 in the pathogenesis of experimental AAAs not initiated with exogenous Ang II supplementation (nondissection-related AAAs). One study unexpectedly reported no apparent influence of ACE2 deficiency on AAA formation in the porcine pancreatic elastase intra-aortic infusion model.[29] This model demonstrates greater pathologic fidelity to the human condition than aneurysms that develop after focal aortic dissection in the Ang II infusion models. In a third modeling system, one dependent on abluminal application of calcium chloride to initiate aneurysm formation, ACE2 deficiency was again found to augment experimental AAA formation, a similar response noted to that demonstrated in the Ang II models (Table I; Fig 1).[25]

In the report describing the absence of AAA augmentation in ACE2-deficient mice after porcine pancreatic elastase infusion, the magnitude of aneurysmal enlargement varied substantially in ACE2-deficient mice; thus, the relatively small numbers of mice in each group may have increased the risk for a type II error. In our own studies, conducted in an elastase fusion model,[132] pretreatment with Ang 1-7 suppressed, whereas pretreatment with a Mas receptor antagonist promoted, the formation and progression of AAA-related pathologic changes (Table I; Fig 1). The initiation of Ang 1-7 supplementation in mice after AAA initiation halted further enlargement, suggesting a therapeutic application for Ang 1-7 or its analogues for clinical disease. Additionally, treatment with a Mas receptor antagonist promoted further AAA expansion and "rescuing" the AAA phenotype in mice treated with the AT1 blocker telmisartan, implying that the demonstrated ability of telmisartan to suppress experimental AAA progression may be dependent on Ang 1-7/Mas activity.[16,17]

Altogether, although inconsistencies exist, the balance of experimental evidence suggests that the ACE2-Ang 1-7-Mas axis exerts a regulatory role in AAA pathogenesis.

Potential impact of COVID-19 on clinical AAA disease. The natural history of AAA disease is progressive aortic diameter enlargement over the course of months to years to the point of symptomatic evolution or rupture. Although intracranial and coronary arterial aneurysms have developed in adults and children with COVID-19, respectively (Table I),[64-67,133-135] no similar relationship is yet recognized between SARS-CoV-2, COVID-19, and AAA disease. However, several COVID-19-related mechanisms, either ACE2 dependent or independent, could impact AAA disease risk and progression currently and in the years to come (Table I; Figs 1 and 2).

Influence on ACE2-Ang 1-7-Mas axis expression and activity. As noted elsewhere in this article, coronaviruses, including SARS, SARS-CoV-2, and HCoV-NL63, infect host cells via the binding of viral spike proteins to constitutively expressed ACE2 receptors. Viral spike protein endocytosis results in downregulation of cell surface ACE2 in infected cells (Table I; Fig 1).[34,35] Cleavage of the ACE2 ectodomain by ADAM17/TACE releases soluble extracellular ACE2 (Table I; Fig 1).[36,44] Both processes together decrease cell surface expression of ACE2, critical for optimal catalytic activity (although soluble ACE2 also remains active).

During the SARS pandemic, SARS-CoV infection was associated with decreased cardiac ACE2 protein levels in patients who succumbed to the disease.[37] The administration of human SARS-CoV, or its surface spike protein, attenuates mRNA and protein levels of ACE2 in mouse lung and heart tissue, with an increase in Ang II levels in the lung.[37,38] Exposure of human lung and kidney epithelial cells to SARS-CoV or its spike proteins also remarkably decrease ACE2 mRNA and protein expression.[38,39] The SARS-CoV spike protein alone was sufficient for increasing pulmonary Ang II levels and promoting lung injury, although this effect could be blocked by ARB treatment.[38]

In patients with COVID-19, plasma Ang II is elevated, whereas Ang 1-7 was decreased, compared with healthy controls (Table I; Fig 1).[40-42] Thus, it is reasonable to speculate that SARS-CoV-2 also downregulates systemic ACE2, potentially impairing Ang II degradation and Ang 1-7 formation. ACE2 is highly expressed in the lung, where epithelial ACE activity is the predominant source for systemic Ang II. Attenuation of ACE2 by SARS-CoV-2 increases systemic Ang II levels by reducing conversion of Ang II to Ang 1-7 or Ang 1 to Ang 1-9.

Alternatively, all vascular endothelial cells, smooth muscle cells, pericytes, fibroblasts, and certain immune cells also express ACE2. Downregulation of ACE2 by SARS-CoV-2 on these cells will increase vascular Ang II and AT1 activity. Shifting the Ang II/Ang 1-7 balance as a consequence of SARS-CoV-2 infection may increase AAA risk or accelerate the progression of early disease. To better assess this risk, Ang II or Ang 1-7 production should be investigated in a large cohort of active and convalescent patients with COVID-19.

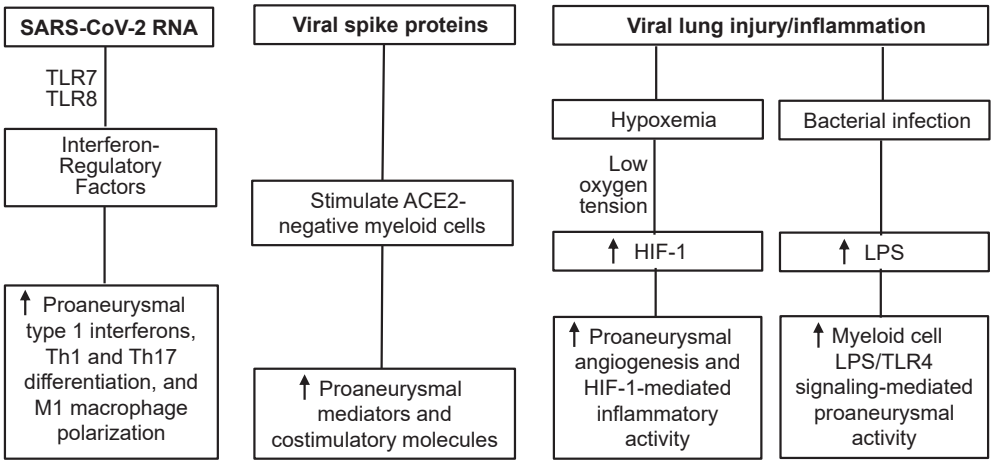

Fig 2. angiotensin-converting enzyme 2 (*ACE-2*)-independent potential influence of COVID-19 on clinical adbominal aortic aneurysm (AAA) disease. *HIF*, Hypoxia inducible factor; *LPS*, lipopolysaccharide; *M1*, classically activated; *Th*, helper T cells; *TLR*, Toll-like receptor.

Inflammatory mediator expression by ACE2-positive nonimmune cells. The binding of viral spike protein to ACE2 initiates the intracellular signaling cascade promoting inflammatory mediator production. SARS-CoV proteins (including spike proteins) augmented proaneurysmal chemokine CCL2 expression in human type II pneumocytes.[136] In various tissues of patients with SARS-CoV-2, the expression of multiple mediators thought to promote (CCL2, IL-1β, IL-6, tumor necrosis factor [TNF]-α) and inhibit (transforming growth factor-β1) AAA disease progression were enhanced in ACE2-positive cells.[137] In a recent single cell RNA analysis, CCL2 and CXCL12 were highly enriched in ACE2-positive type II alveolar epithelial cells and arterial vascular cells from healthy and diseased heart and lung as compared with ACE2-negative cells.[90] Because essentially all constitutive vascular cells express ACE2,[137] COVID-19 may promote AAA pathogenesis by increasing aortic recruitment of inflammatory leukocytes and/or enhancing aortic wall inflammation (Table I; Fig 1).

Inflammatory mediator expression by ACE2-negative immune cells. Immune cells, particularly macrophages and dendritic cells, modulate immune-mediated aneurysmal degradation despite a lack of surface ACE2 receptor expression. The SARS-CoV spike proteins induced IL-1β, IL-6, IL-8, and TNF-α mRNA and protein expression in human peripheral mononuclear cells via the nuclear factor-κB pathway without additional stimulus.[50] Similarly, increased IL-6, IL-8, and TNF-α mRNA and protein expression were reported in mouse macrophages in the presence of the SARS-CoV spike protein.[51] In the absence of intracellular replication, SARS-CoV upregulated the expression levels of costimulatory molecules (CD40 and CD86) and major histocompatibility complex II on the surface of macrophages and dendritic cells, augmented spontaneous and lipopolysaccharide-induced secretion of IL-6 and IL-12 by macrophages and dendritic cells, and enhanced the ability of dendritic cells to stimulate naive helper T cells to proliferate in vitro.[52] Inflammasome NLRP3, critical for experimental AAAs, was activated and correlated with disease severity in COVID-19 patients.[49,53-55] These findings suggest that SARS-CoV-2 infection may also enhance AAA pathogenesis by altering the production of proaneurysmal mediators by ACE2-negative myeloid cells present in aneurysmal tissue (Table I; Fig 2).

Cross-talk between ACE2-positive and -negative cells. ACE2-positive lung and vascular cells may promote AAA pathogenesis by cross-talk with ACE2-negative immune cells via ligand-receptor interaction (Table I; Fig 1). ACE2-positive cells produce ligands recognized by cognate receptors on immune cells across various tissues.[45] The production of IL-6 and IL-8 by SARS-CoV-infected lung epithelial cells was effective in promoting the production of IL-1β, IL-6, IL-8, G-CSF, MIP-1α, MIP-1β, and TNF-α by macrophages, and IL-6, IL-8, and CCL2 by dendritic cells.[47] Additional ligand-receptor pairs include macrophage migration inhibition factor, VEGF-A, GALS9, GRN, and SCGB31A on ACE2-positive cells and corresponding receptors CD74, NRP1/2, CD44, TNFSRF1B, and MARCO on macrophages, which enable SARS-CoV-2-targeted host cells to alter macrophage activity remotely or locally by secreting ligands. In bronchoalveolar lavage cells from patients with COVID-19, several proaneurysmal mediators, including CCL2, CCL7, HIF-1α, and type 1 interferons, were upregulated in myeloid cells, including macrophages and neutrophils, correlating with disease severity.[48]

ACE2 expression levels have been shown to correlate with type 1 interferon gene expression, which mediates

Table II. Prioritized research on the impact of coronavirus disease-2019 (*COVID-19*) on abdominal aortic aneurysm (*AAA*) disease

Research question	Approaches
Does COVID-19 alter systemic levels of angiotensin II and Ang1-7?	Participants: COVID-19 convalescent patients with or without AAAs 3, 6, and 12 months after hospital discharge as well as matched non-COVID-19 controls with or without AAAs Approaches: Analyze plasma/serum; Ang II and Ang 1-7 via ELISA assays
Are systemic levels of selected proaneurysmal mediators modified following COVID-19?	Participants: COVID-19 convalescent patients with or without AAAs 3, 6, and 12 months after hospital discharge as well as matched non-COVID-19 controls with or without AAAs Approaches: Proteomic or specific protein arrays to determine plasma/serum key proaneurysmal mediators such as IL-1β, IL-6, IL-17, TNF-α, CCL2, CCL5, MMP2, MMP9 and VEGF-A
Is AAA enlargement rate, risk for rupture, or surgical repair at any given baseline aortic diameter increased following COVID-19?	Participants: All AAA patients (regardless of COVID-19), or convalescent COVID-19 AAA patients and non-COVID-19 AAA patients. Approaches: Compare AAA enlargement rate, rupture, or the need for surgical repair (primary end points) using retrospective case-control study, perform multi-variable analysis to determine whether COVID-19 is an independent factor for the development of a primary end point.
Is aneurysm prevalence increased following COVID-19?	Data source: Hospital electronic health record or Medicare database Compare AAA prevalence before, during and after the COVID-19 pandemic period
Does vaccination against SARS-CoV-2 modulate enlargement rate, risk for rupture or surgical repair of clinical AAAs?	Data source: Hospital electronic health record or Medicare database Approaches: Compare enlargement rate, rupture, or the need for AAA surgical repair in COVID-19 convalescent patients with non-COVID-19 convalescent patients or those who have received a vaccination

Ang, angiotensin; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus-2; *TNF*, tumor necrosis factor; *VEGF*, vascular endothelial growth factor.

AAA pathogenesis via its receptor activity and interferon regulatory factors (Table I; Figs 1 and 2).[57,89,138,139] Additionally, dysregulated lipid and amino acid metabolism, acute-phase amyloid A components, kynurenine pathway mediators, and complement system activation in patients with COVID-19 may also promote AAA disease risk,[56] as well as attenuation of antianeurysmal mediators including HIF-1α-degrading enzyme inhibitors succinate and fumarate, serotonin-derived ant-aneurysmal melatonin and sphingosine-1-phosphate.[58-63,140]

Additional influences. Enhanced IL-6, IL-8, IFN-γ, and CCL-2 expression in patients with COVID-19 may promote aneurysm pathogenesis by promoting aortic accumulation and activation of macrophages and neutrophils (Table I; Figs 1 and 2).[46] Serum levels of lipopolysaccharide, the ligand for Toll-like receptor 1 and important for AAA pathogenesis, were also elevated in patients with severe COVID-19 or hospitalized at intensive care units as compared with healthy controls (Table I; Fig 2).[141,142] Hypoxemia, a common consequence of COVID-19 pulmonary involvement, may reduce aortic mural oxygen tension (Table I; Fig 2).[13,100,143-149] To the extent to which hypoxia reduces aortic mural HIF-1α ubiquination, the balance between ACE-Ang II and ACE2-Ang 1-7 may be tipped toward enhanced inflammation.[150] Given the importance of HIF-1 in AAA pathogenesis,[151-155] SARS-CoV-2 may influence AAA progression through its effects on the HIF-1 pathway.[143,156]

To combat the COVID-19 pandemic, several clinical trials for SARS-CoV-2 vaccines have completed or are ongoing worldwide.[157,158] Immunity is achieved by injection of inactivated SARS-CoV-2, nonreplicating adenovirus expressing SARS-CoV-2 proteins (particularly spike protein 1), or stabilized spike protein 1 mRNA. Although potentially protective against SARS-CoV-2 infection, it remains to be seen whether vaccination per se, or the resultant humoral and cellular immunity after vaccination, may increase AAA disease risk via immunologic bystander effects.

CONCLUSIONS

Current concepts of SARS-CoV-2 infection and aneurysm pathogenicity suggest that COVID-19 may

theoretically augment AAA disease progression. Table II prioritizes research questions on, and corresponding approaches for, the potential influence of COVID-19 on AAA disease. Time will tell whether this is indeed the case, and if so, how screening or surveillance protocols or intervention thresholds should be modified in AAA patients who have recovered from COVID-19.

AUTHOR CONTRIBUTIONS

Conception and design: BX, KK, RD
Analysis and interpretation: BX, KK, RD
Data collection: BX, GL, JG, TI, SZ
Writing the article: BX, RD
Critical revision of the article: BX, GL, JG, TI, KK, SZ, RD
Final approval of the article: BX, GL, JG, TI, KK, SZ, RD
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Overall responsibility: BX

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