Arteriosclerosis, Thrombosis, and Vascular Biology

BRIEF REVIEW

COVID-19 and the Heart and Vasculature

Novel Approaches to Reduce Virus-Induced Inflammation in Patients With Cardiovascular Disease

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ABSTRACT: The coronavirus disease 2019 (COVID-19) pandemic presents an unprecedented challenge and opportunity for translational investigators to rapidly develop safe and effective therapeutic interventions. Greater risk of severe disease in COVID-19 patients with comorbid diabetes mellitus, obesity, and heart disease may be attributable to synergistic activation of vascular inflammation pathways associated with both COVID-19 and cardiometabolic disease. This mechanistic link provides a scientific framework for translational studies of drugs developed for treatment of cardiometabolic disease as novel therapeutic interventions to mitigate inflammation and improve outcomes in patients with COVID-19.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: inflammation ■ morbidity ■ mortality ■ pandemics ■ viruses

An outbreak of the novel severe acute respiratory syndrome (SARS) coronavirus-2 causing coronavirus disease 2019 (COVID-19) originally emerged from Wuhan, Hubei province in China, in December 2019.[1] On March 11, 2020, COVID-19 was declared a pandemic by the World Health Organization, and by July 30, 2020, the virus had infected over 17 million people worldwide across 216 countries with over 668 000 fatalities.[2]

SARS coronavirus-2 is a single-stranded enveloped RNA virus similar in structure and pathogenicity to SARS coronavirus from the 2002 SARS and the 2012 Middle East respiratory syndrome coronavirus outbreaks.[3] SARS-coronavirus-2 binds its S protein to ACE2 (angiotensin-converting enzyme 2) on the surface of cells and relies on the cellular serine protease TMPRSS2 to prime the S protein for host cell entry.[4] ACE2 is expressed in type II alveolar cells of the lung and is highly expressed in cardiac myocytes, cardiac pericytes, and vascular endothelium.[5,6] ACE2 converts angiotensin II to Ang (1–7; angiotensin 1–7) and exerts vasodilatory, natriuretic, anti-inflammatory, and antioxidant effects.[7,8]

CARDIOVASCULAR COMORBIDITIES OF COVID-19

In the original SARS outbreak, the presence of preexisting cardiovascular disease was independently associated with an increased risk of death.[9,10] Reports from China noted similar risks for a more severe clinical course in COVID-19 patients with hypertension, diabetes mellitus, or cardiovascular disease at baseline.[11–13] Data from 2 cohorts derived from academic medical centers in New York City identified age, obesity, and the presence of preexisting heart disease as strong predictors for hospitalization among COVID-19 patients.[14,15] National data from the Centers for Disease Control reported diabetes mellitus and cardiovascular disease as the most common comorbid conditions in hospitalized or intensive care unit patients.[16] Registry data from United Kingdom healthcare systems also identified advanced age, obesity, diabetes mellitus, and hypertension as risk factors for more severe COVID-19 morbidity and mortality.[17,18] In contrast, higher body mass index was not associated with increased mortality risk in hospitalized COVID-19 patients in a single center in New York City.[19] In this prepublication report,

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For Sources of Funding and Disclosures, see page 2050.

Arterioscler Thromb Vasc Biol is available at www.ahajournals.org/journal/atvb

Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
Ang 1–7	angiotensin 1–7
COVID-19	coronavirus disease 2019
DPP4	dipeptidyl peptidase-4
GLP-1	glucagon-like peptide-1
GLP-1-RA	glucagon-like peptide-1 receptor antagonists
IL	interleukin
IL-1R1	interleukin-1 receptor, type 1
IL-1Ra	interleukin-1 receptor antagonist
IRF	inferon regulator factor
LDL	low-density lipoprotein
NF-κB	nuclear factor-kappa B
NLRP3	nucleotide-binding oligomerization domain, leucine-rich repeat–containing receptor family pyrin domain-containing 3
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SARS	severe acute respiratory syndrome
SGLT2	sodium-glucose cotransporter 2

age and increased blood levels of proinflammatory cytokines were independently associated with decreased survival.

CARDIOVASCULAR MANIFESTATIONS OF COVID-19 INFECTION

Three distinct phases of COVID-19 are described beginning with mild upper respiratory syndrome, a parenchymal pulmonary phase characterized by marked hypoxemia, and progression to a hyperinflammatory prothrombotic phase with multiorgan dysfunction and thromboembolism in a subset of patients.[13,20,21] Elevation in serum cardiac biomarkers (troponin, brain natriuretic peptide) is common in hospitalized patients. Patients may present with COVID-19 and electrocardiographic findings consistent with ST-segment–elevation myocardial infarction with or without obstructive coronary lesions.[11,22] Isolated cases of suspected acute myocarditis have been reported in COVID-19 patients based on clinical findings of typical electrocardiographic changes, elevated biomarkers, echocardiographic wall motion abnormalities, cardiac magnetic resonance imaging, and hemodynamic instability.[23–25] However, histological changes consistent with myocarditis have not been identified in autopsy specimens.[26–28] A New York City autopsy series reported platelet-fibrin thrombi in the cardiac microvasculature and venules and cases of venous thrombosis associated with regional myocardial infarction.[29]

Highlights

- Patients with diabetes mellitus, obesity, and heart disease are at a greater risk for severe complications of coronavirus disease 2019 (COVID-19).
- Vascular inflammation and trained immunity associated with cardiometabolic diseases may increase risk of hyperinflammatory response to COVID-19 infection.
- Drugs with anti-inflammatory properties developed for the treatment of cardiometabolic disease are being evaluated in clinical trials of COVID-19 patients.

Vascular complications of COVID-19 have also been reported including stroke, cutaneous chilblains-like lesions on the toes, and case reports of systemic vasculitis resembling Kawasaki disease in children with severe COVID-19 (pediatric multisystem inflammatory syndrome).[30–36] Other autopsy series of COVID-19 patients report evidence of viral particles within vascular endothelial cells and diffuse vascular endothelial cell injury in lung, heart, kidney, and intestinal tissues.[37,38] The inflammatory response to viral infections upregulates expression of tissue factor, markers of thrombin generation and platelet activation, complement activation, and risk of intravascular thrombosis.[22,39,40] Whether, and to what degree, the clinically recognized cardiovascular manifestations of COVID-19 are a result of direct viral injury, prolonged hypoxemia, vascular endothelial cell infection or inflammation, cardiac pericyte infection, or intravascular thrombosis remains unknown.

POTENTIAL PATHOPHYSIOLOGIC AND PHARMACOLOGICAL LINKS BETWEEN CARDIOMETABOLIC DISEASE AND COVID-19 INFECTION

Innate immunity is increasingly recognized to mediate vascular inflammation and atherosclerosis progression, in part, via upregulation of the NLRP3 (nucleotide-binding oligomerization domain, leucine-rich repeat–containing receptor family pyrin domain-containing 3) inflammasome pathway in settings of hypercholesterolemia, diabetes mellitus, obesity, and atherosclerosis development.[41–46] This pathway regulates maturation and secretion of the proinflammatory cytokine IL (interleukin)-1β. In the LDL (low-density lipoprotein)-receptor knockout hypercholesterolemic mouse, activation of the NLRP3 inflammasome by exposure to the Western diet modulates long-term immune function by a transcriptomic and epigenetic reprogramming of myeloid precursors, so-called trained innate immunity.[47–49] As a result, the myeloid precursors, and their derived cells, exhibit an

enhanced inflammatory response upon secondary challenge with microbial ligands. Accordingly, NLRP3 inflammasome activation and trained immunity in association with cardiovascular risk factors and disease might confer increased risk of a hyperinflammatory response that augments the effects of COVID-19–induced inflammation or COVID-19–induced immune modulation of ACE2/Ang (1–7) signaling (Figure).[50–53] This double-hit hypothesis is concordant with epidemiological observations linking cardiometabolic conditions to increased risk of severe complications of COVID-19 and provides a scientific framework for translational studies of drugs developed for treatment of cardiometabolic disease as novel therapeutic interventions in patients with COVID-19.

ALDOSE REDUCTASE INHIBITION

Aldose reductase—the first and rate-limiting step of the polyol pathway—channels excess glucose away from energy metabolism in cardiomyocytes and vascular cells during hyperglycemia and ischemia.[54,55] Increased metabolic flux through the polyol pathway may mediate progression of diabetes mellitus–related end-organ complications due to increased osmotic stress, altered redox homeostasis, and augmented NF-κB (nuclear factor-kappa B) signaling and NLRP3 inflammasome activation.[54–58] Transgenic mice expressing human aldose reductase exhibit increased expression of the transcription factor early growth response 1 and increased vascular proinflammatory and prothrombotic signaling.[59] Aldose reductase inhibition protects both diabetic and nondiabetic hearts in experimental ischemia/reperfusion injury models, protects against lipopolysaccharide-induced cardiac dysfunction, reduces lung injury in experimental sepsis-induced inflammation, and reduces hyperglycemia-induced inflammasome activation in THP-1 monocytic cells and in the streptozotocin-induced diabetes mellitus mouse model.[56,60–63] A double-blind, randomized placebo-controlled clinical trial of an aldose reductase inhibitor (zopolrestat) in diabetic patients demonstrated

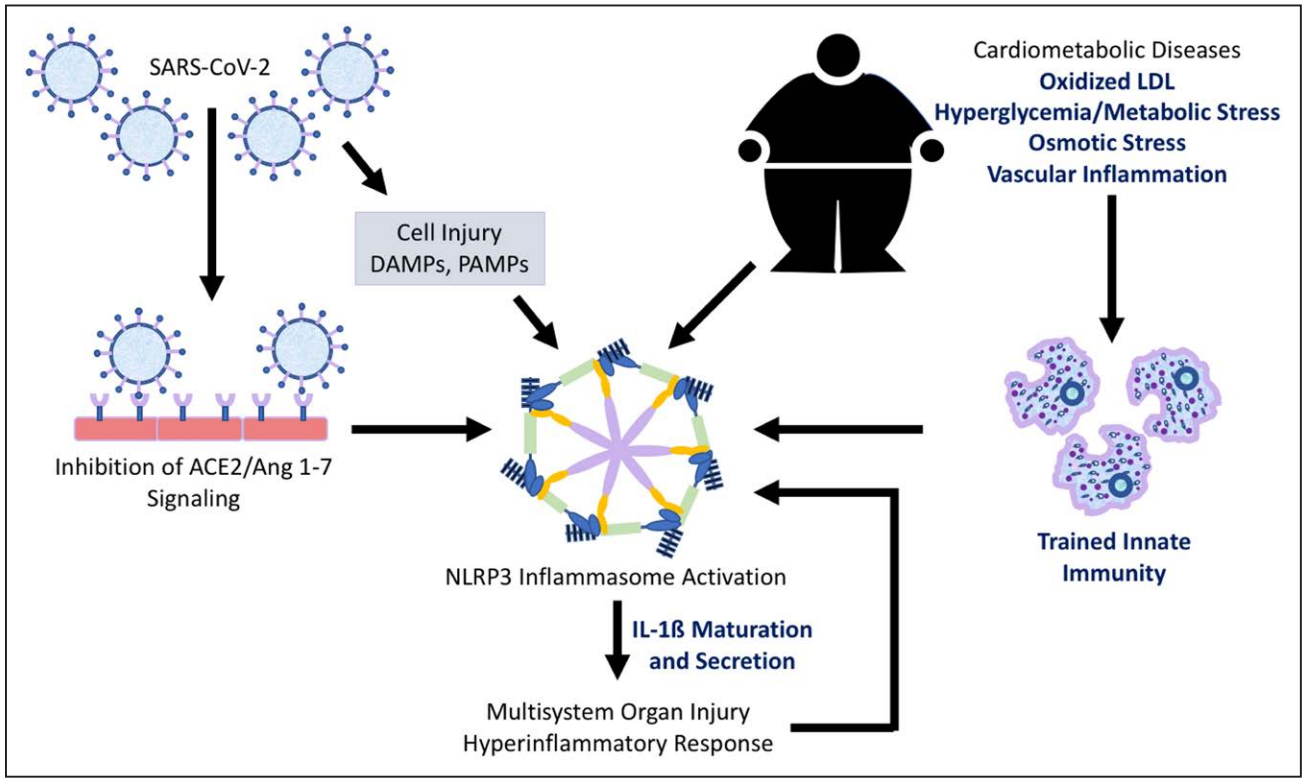

Figure. Possible mechanisms contributing to increased risk of severe complications in coronavirus disease 2019 (COVID-19) patients with comorbid cardiometabolic disease.
NLRP3 (nucleotide-binding oligomerization domain, leucine-rich repeat–containing receptor family, pyrin domain-containing 3) inflammasome activation and trained immunity in association with cardiovascular disease and risk-enhancing conditions such as hypercholesterolemia, diabetes mellitus, and obesity might confer increased risk of a hyperinflammatory response that augments the effects of COVID-19–induced inflammation or COVID-19–induced immune modulation of ACE2 (angiotensin-converting enzyme 2)/Ang (1–7; angiotensin 1–7) signaling. This double-hit hypothesis is concordant with epidemiological observations linking cardiometabolic conditions to increased risk of severe complications of COVID-19 infection and provides a scientific framework for translational studies of drugs developed for the treatment of cardiometabolic disease as novel therapeutic interventions in patients with COVID-19 infection. Potential targets to reduce excessive COVID-19–induced inflammation in patients with cardiometabolic disease are listed in bolded text. DAMP indicates damage-associated molecular pattern; IL, interleukin; LDL, low-density lipoprotein; PAMP, pathogen-associated molecular pattern; and SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

a significant increase in left ventricular ejection fraction during exercise when compared with placebo.[64]

AT-001 is a novel aldose reductase inhibitor in development to assess its safety and efficacy on functional capacity, biomarkers, and echocardiographic measures of cardiac structure and function in diabetic patients (NCT04083339). In a randomized proof-of-concept study conducted in diabetic patients, AT-001 therapy for 28 days reduced blood levels of sorbitol and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels when compared with placebo.[65] A phase 2 open-label trial of 14 days of AT-001 therapy in COVID-19 diabetic patients with heart disease is ongoing to assess the safety and serial biomarkers of inflammation and cardiac injury (NCT04365699).

SGLT2 INHIBITORS

SGLT2 (sodium-glucose cotransporter 2) inhibitors inhibit glucose reabsorption in the proximal convoluted tubule of the kidney.[66] This class of agents reduces risk of cardiovascular morbidity and mortality and progression of nephropathy in diabetic patients.[67–71] SGLT2 inhibitors induce transcriptomic reprogramming mimicking a fasting state with increased fatty acid utilization and ketogenesis.[72] This metabolic shift in response to SGLT2 inhibition is hypothesized to be associated with activation of SIRT-1 (Sirtuin 1) and HIF-1α (hypoxia-inducible factor-1 alpha) signaling, enhanced autophagy, decreased oxidative stress, and decreased NLRP3 inflammasome activation.[73,74]

The observed improvement in cardiorenal outcomes with SGLT2 inhibition is greater than that expected from the modest improvement in glycemic control reported in clinical trials.[73] Dapagliflozin reduces hospitalizations and death in heart failure patients with or without diabetes mellitus.[75] In light of these putative cytoprotective mechanisms not related directly to glycemic control, and its association with reduced cardiovascular risk in both diabetic and nondiabetic populations, dapagliflozin might reduce the inflammatory response in viral infections and sepsis and, therefore, decrease the risk of morbidity and mortality in COVID-19. This hypothesis will be tested in the DARE-19 trial (Dapagliflozin in Respiratory Failure in Patients With COVID-19; NCT04350593)—an international double-blind, placebo-controlled study of 900 COVID-19 patients.

INCRETINS

The DPP4 (dipeptidyl peptidase-4) inhibitors and GLP-1-RAs (GLP-1 [glucagon-like peptide-1] receptor antagonists) are pharmacological agents used to modulate the incretin pathway of gut hormones. DPP4 inhibitors improve glycemic control by inhibiting the degradation of GLP-1—a gut hormone secreted by intestinal neuroendocrine cells that stimulates postprandial insulin secretion.[76] The GLP-1-RAs are either endogenous or exogenous analogues of GLP-1. Prospective randomized placebo-controlled cardiovascular outcome trials of several GLP-1-RAs have demonstrated reduction in risk of major adverse cardiac events and reduction of cardiovascular death with liraglutide.[71,77,78] Pharmacological augmentation of incretin pathway signaling may improve cardiac outcomes, in part, by immunomodulatory pathways. DPP4 is a transmembrane glycoprotein expressed in cardiac and vascular tissues, kidneys, adipocytes, and inflammatory cells.[79] DPP4 upregulates T-cell CD86 (cluster of differentiation 86) expression and nuclear signaling via the NF-κB pathway and increases inflammasome expression and activity.[80] Inhibition of DPP4 increases incretin signaling, which in turn reduces proinflammatory and prothrombotic signaling in response to endotoxin in experimental models of sepsis.[81,82] Linagliptin was shown to attenuate cardiac dysfunction in diabetic mice with sepsis,[83] but there are no available data demonstrating a protective effect for DPP4 inhibitors in patients with sepsis. A meta-analysis of 74 studies showed no increased risk for respiratory infections associated with DPP4 inhibitors when compared with placebo or other antidiabetic agents.[84]

Immunomodulation by incretin signaling might provide therapeutic benefit for diabetic patients with COVID-19 illness. Two open-label randomized studies in diabetic patients with COVID-19 are planned to determine the effects of linagliptin and insulin versus insulin alone on glycemic control, COVID-19 disease progression, and hospital outcomes (NCT04341935 and NCT04371978).

COLCHICINE

Colchicine is an anti-inflammatory medication to treat gout, familial Mediterranean fever, and pericarditis. Colchicine decreases neutrophil-endothelial adhesion, neutrophil-platelet interaction, and neutrophil and NLRP3 inflammasome activation.[85,86] In observational studies of gout patients, colchicine treatment is associated with reduced high-sensitivity C-reactive protein and reduced risk of cardiovascular events.[87–89] In a double-blind randomized study, a short-term course of colchicine 1.8 mg administered at the time of percutaneous coronary intervention did not reduce postprocedure biomarkers of myocardial injury when compared with placebo but reduced postprocedure rises in IL-6 and C-reactive protein 24 hours after dosing.[90] In patients with coronary artery disease and stable symptoms or recent myocardial infarction, colchicine 0.5 mg daily decreased the risk of adverse cardiovascular outcomes end point when compared with placebo.[91,92]

Given this profile of putative anti-inflammatory mechanisms and cardiovascular risk reduction, the

COLCORONA trial (Colchicine Coronavirus SARS-CoV2 Trial) is currently recruiting ≈6000 subjects in a multinational, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of colchicine in outpatients diagnosed with COVID-19 (NCT04322682). There are 9 additional international trials of colchicine in COVID-19 listed on https://www.clinicaltrials.gov.

IL-1 INHIBITORS

The Toll-like receptor family plays a critical role in inducing innate immune signaling in response to microbial components (pathogen-associated molecular patterns), or damage-associated molecular patterns that occur with sterile inflammation and cell injury, including atherosclerosis and ischemic myocardial injury.[93–95] Activation of these transmembrane receptors initiates signaling that ultimately leads to activation of the transcription factors NF-κB, IRF (inferon regulator factor)-3, and IRF7 and induction of antibacterial and antiviral gene expression. Among the genes upregulated are pro–IL-1β and components of the NLRP3 inflammasome, which upon assembly activates caspase-1–mediated IL-1β and IL-18 secretion, and a form of cell death called pyroptosis. IL-1β is a potent proinflammatory cytokine that acts via the IL-1R1 (IL-1 receptor, type 1) to induce fever, activation of innate and adaptive immune cell responses, the acute-phase response, and leukocyte-endothelial cell interactions.[96] This proinflammatory signaling cascade is counterbalanced by IL-1Ra (IL-1 receptor antagonist), which binds to IL-1R1 without causing the conformational change required for IL-1R3 to bind, thereby abrogating transmembrane signaling. Anakinra is a recombinant form of IL-1Ra that was first approved for rheumatoid arthritis and is used to treat a variety of rheumatic and cardiovascular conditions. It is commonly used as a second-line agent for refractory pericarditis and has shown promising results in phase 2 studies of acute myocardial infarction and chronic heart failure.[97–99] There are 2 ongoing trials of anakinra to prevent disease progression and cytokine storm severity in COVID-19 (NCT04362111 and NCT04341584).

Canakinumab is a human monoclonal antibody that targets IL-1β and neutralizes its downstream inflammatory effects (including generation of IL-6) implicated in the pathogenesis of atherothrombosis.[100] The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study trial randomized over 10 000 patients with prior myocardial infarction and demonstrated a reduction in major adverse cardiovascular events (and cancer-related mortality) with canakinumab versus placebo.[101] However, this benefit was offset by increased risk of fatal infection and sepsis. A phase 2 single-center study of canakinumab is currently recruiting COVID-19 patients with evidence of myocardial injury (NCT04365153). Patients will be randomized to the intervention drug or placebo with a primary outcome of time to clinical improvement or hospital discharge.

HMG-COA REDUCTASE INHIBITORS (STATINS)

Immunomodulatory effects of statins contribute to their reduction of cardiovascular disease risk beyond LDL cholesterol-lowering effects and thereby might also attenuate the inflammatory response in COVID-19. Inhibition of HMG-coenzyme A reductase exerts downstream effects on the mevalonic acid pathway leading to a reduction in geranylgeranylation and farnesylation of GTPases responsible for immune cell migration, cytokine production, and T-cell signaling.[102,103] Statins reduce IL-6–induced expression of C-reactive protein at the transcriptional level and repress major histocompatibility complex class II molecule expression on antigen-presenting cells thereby decreasing the activation of T lymphocytes.[104,105] The effects of various statins on NLRP3 inflammasome activation differ according to dose and pharmacokinetic properties.[106,107] Simvastatin and mevastatin have been reported to inhibit oxidized LDL–mediated inflammasome activation in human endothelial cells by activation of nuclear pregnane X receptors.[108,109] Statin use is associated with reduced risk of influenza-related hospitalization and death in observational studies.[110–112] Conversely, a prospective randomized clinical trial of rosuvastatin for treatment of sepsis-associated adult respiratory distress syndrome was stopped early due to futility.[113] In light of these data derived from non–COVID-19 populations, a randomized trial of preemptive administration of standard medications used in acute coronary syndrome (including atorvastatin, antiplatelets, and anticoagulants) in patients hospitalized with COVID-19 illness is currently recruiting participants (NCT04333407). A smaller randomized study in statin-naive patients with COVID-19 aims to assess the efficacy of atorvastatin to mitigate disease progression (NCT04380402).

CONCLUSIONS

The COVID-19 pandemic presents an unprecedented challenge and opportunity for translational investigators to rapidly develop safe and effective therapeutic interventions based on limited preclinical data. As of May 10, 2020, >1000 clinical trials in COVID-19 patients are registered on the World Health Organization database (https://clinicaltrials.gov/ct2/who_table). This brief review describes a small representative sample of clinical trials targeting cardiometabolic inflammatory pathways as a novel strategy to improve outcomes in COVID-19 patients. Numerous trials testing other classes of drugs that target angiotensin II signaling, IL-6

signaling, or other vascular inflammation signaling pathways are omitted due to limited space. The results of these clinical trials and ongoing observational biospecimen studies may provide clues to elucidate potential mechanistic links between cardiometabolic disease and host response to COVID-19 and identify novel targets for intervention in COVID-19 patients with comorbid cardiometabolic disease.

ARTICLE INFORMATION

Received May 19, 2020; accepted July 9, 2020.

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Sources of Funding

B. Shah is supported, in part, by the Biomedical Laboratory Research and Development Service of the VA Office of Research and Development (iK2CX001074) and National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI; R01HL146206). S.D. Katz and M. Pillinger are supported, in part, by grant number NIH/NCATS (National Center for Advancing Translational Sciences) UL1 TR000038 from the National Center for Research Resources, National Institutes of Health. M.S. Garshick is supported by the American Heart Association Career Development Grant (Dallas, TX) 18CDA34080540. R. Ramasamy is supported, in part, by grants from NIH/NHLBI (P01HL143697-01 and R01 HL132516-01). J.D. Newman is supported, in part, by the NIH/NHLBI HL125991. K.J. Moore is supported by grants from the NIH/NHLBI P01HL131481 and R35HL135799.

Disclosures

S.D. Katz has received an investigator-initiated research grant from Applied Therapeutics, Inc. R. Ramasamy is a consultant for Applied Therapeutics, Inc, and has received a research grant from them. The other authors report no conflicts.

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