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### Permalink

<https://escholarship.org/uc/item/5j7320tx>

### Journal

Current Atherosclerosis Reports, 22(9)

### ISSN

1523-3804

### Authors

Moriarty, Patrick M  
Gorby, Lauryn K  
Stroes, Erik S  
[et al.](#)

### Publication Date

2020-09-01

### DOI

10.1007/s11883-020-00867-3

Peer reviewed



# Lipoprotein(a) and Its Potential Association with Thrombosis and Inflammation in COVID-19: a Testable Hypothesis

Patrick M. Moriarty<sup>1</sup> · Lauryn K. Gorby<sup>1</sup> · Erik S. Stroes<sup>2</sup> · John P. Kastelein<sup>2</sup> · Michael Davidson<sup>3</sup> · Sotirios Tsimikas<sup>4,5</sup>

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## Abstract

**Purpose of Review** The COVID-19 pandemic has infected over > 11 million as of today people worldwide and is associated with significant cardiovascular manifestations, particularly in subjects with preexisting comorbidities and cardiovascular risk factors. Recently, a predisposition for arterial and venous thromboses has been reported in COVID-19 infection. We hypothesize that besides conventional risk factors, subjects with elevated lipoprotein(a) (Lp(a)) may have a particularly high risk of developing cardiovascular complications.

**Recent Findings** The Lp(a) molecule has the propensity for inhibiting endogenous fibrinolysis through its apolipoprotein(a) component and for enhancing proinflammatory effects such as through its content of oxidized phospholipids. The *LPA* gene contains an interleukin-6 (IL-6) response element that may induce an acute phase-type increase in Lp(a) levels following a cytokine storm from COVID-19.

**Summary** Thus, subjects with either baseline elevated Lp(a) or those who have an increase following COVID-19 infection, or both, may be at very high risk of developing thromboses. Elevated Lp(a) may also lead to acute destabilization of preexisting but quiescent atherosclerotic plaques, which might induce acute myocardial infarction and stroke. Ongoing studies with IL-6 antagonists may be informative in understanding this relationship, and registries are being initiated to measure Lp(a) in subjects infected with COVID-19. If indeed an association is suggestive of being causal, consideration can be given to systematic testing of Lp(a) and prophylactic systemic anticoagulation in infected inpatients. Therapeutic lipid apheresis and pharmacotherapy for the reduction of Lp(a) levels may minimize thrombogenic potential and proinflammatory effects. We propose studies to test the hypothesis that Lp(a) may contribute to cardiovascular complications of COVID-19.

**Keywords** Lipoprotein(a) · COVID-19 · Fibrinolysis · Thrombosis · Inflammation

## Introduction

The COVID-19 pandemic has infected millions of people around the world. Severity of respiratory distress and cardiovascular disease (CVD) in response to infection ranges from asymptomatic individuals to death. Respiratory failure is most often the cause of death in COVID-19 patients [1]. Patients

develop acute respiratory distress syndrome (ARDS) characterized by a rapid onset of bilateral inflammation in the lungs. The inflammation involves an acute increase in several proinflammatory cytokines, a process termed “cytokine storm.” This severe inflammatory response causes increased leakiness of the blood vessels and an induction of a procoagulant state, eventually increasing the risk of multiorgan damage.

This article is part of the Topical Collection on *Hot Topics in Atherosclerosis*

✉ Patrick M. Moriarty  
pmoriart@kumc.edu

✉ Sotirios Tsimikas  
stsimikas@ucsd.edu

<sup>1</sup> Division of Clinical Pharmacology, University of Kansas Medical Center, Kansas City, KS, USA

<sup>2</sup> Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

<sup>3</sup> Lipid Clinic, The University of Chicago Pritzker School of Medicine, Chicago, IL, USA

<sup>4</sup> Division of Cardiovascular Medicine, University of California San Diego, La Jolla, CA, USA

<sup>5</sup> Vascular Medicine Program, Sulpizio Cardiovascular Center, University of California San Diego, 9500 Gilman Drive, BSB 1080, La Jolla, CA 92093-0682, USA

Persistent elevation of cytokines, predominantly IL-1b and interleukin-6 (IL-6), predicts a higher likelihood of an unfavorable outcome, including death [2, 3]. In addition to respiratory failure, data from China suggests that 20–30% COVID-19 patients report cardiovascular injury, which contributes to 40% of deaths [4]. Most commonly, up to 30% of hospitalized subjects develop microangiopathy characterized by either microthrombi or clinically apparent deep venous thromboses and pulmonary emboli. In addition, myocardial injury, defined by elevated cardiac biomarkers such as high-sensitivity troponin I (hs-cTnI), was commonly found in non-survivors. The rise of hs-cTnI follows the increase of inflammatory markers such as IL-6 and may be a consequence of the cytokine storm [5, 6]. Finally, stroke in otherwise young individuals has been reported with no identified etiology to date. In view of the high rates of cardiovascular complications in patients infected with COVID-19, we propose that elevated Lp(a) levels should be studied as an etiological agent that links thrombosis and inflammation. We outline the rationale behind this hypothesis and propose avenues of research to address it [7].

## COVID-19 and Risk of Thrombosis

A predisposition for arterial and venous thromboembolic complications has been recently discovered as a result of COVID-19 infection. This might be due to the prolonged inflammatory response, decreased physical activity during infection, and reduced oxygen levels in the circulation. In a Dutch cohort study, 13% of hospitalized COVID-19 patients had symptomatic venous thromboembolism despite routine thrombosis prophylaxis, as compared with 0.85–2.89% in high-risk non-COVID-19 patients using thrombosis prophylaxis [8]. In COVID-19 patients admitted to the ICU, the rate of thrombotic complications increased to 31% [9]. Mechanistically, Harzallah et al. reported a positive lupus anticoagulant test in 45% of COVID-19 patients [10]. In addition, although antiphospholipid antibodies are directed to many antigens, a proportion have been shown to bind to oxidized phospholipids, which are also carried by Lp(a) [11, 12]. Additionally, researchers at Mount Sinai Hospital have reported, over a 2-week period, a sevenfold increase in large vessel stroke for COVID-19 patients under 50 years old. Among these patients, all experienced either no or mild COVID-19 symptoms [7]. Finally, Zhang and colleagues found that COVID-19-infected patients presenting with thrombocytopenia, coagulopathy, and the presence of anticardiolipin antibodies had developed cerebral infarcts [9, 13, 14–16].

## Lp(a) and Antifibrinolytic Effects

Lp(a) is composed of an LDL particle bound to apolipoprotein(a) (apo(a)). Lp(a) is an independent risk factor

for CVD, and levels are primarily genetically determined, with a small influence of environmental factors. Approximately, 20–30% of the world's population have an elevated Lp(a), defined as > 50 mg/dL or > 125 nmol/L [17]. There are exceptions to generally stable levels, including a stressful environment such as sepsis, in which Lp(a) levels are acutely elevated [18, 19]. Normal lifestyle activities such as diet, exercise, and weight loss have limited effect on Lp(a), and lipid medications, such as statins, may modestly raise Lp(a) levels [20, 21]. Lp(a) may act as an acute phase reactant and has been noted to be increased in acute cardiovascular events [22–26]. There is currently no available pharmacotherapy approved by regulatory agencies which is targeted at the reduction of Lp(a), which limits therapeutic options solely to lipid apheresis.

Apo(a) is highly homologous to plasminogen but has no fibrinolytic activity. Data suggests that the apo(a) component of Lp(a) inhibits activation of plasminogen to plasmin by endogenous tissue plasminogen activators as well as competing for binding of plasminogen and plasmin to established fibrin clots, thus compromising clot lysis. Other potential prothrombotic actions by Lp(a) include an increase in the expression of PAI-1 to inhibit fibrinolysis and the inactivation of tissue factor pathway inhibitor (TFPI), which augments factor VII activation and promotes blood coagulation [27, 28].

In regard to venous thromboembolism (VTE), von Depka and colleagues analyzed the role of elevated Lp(a) levels (> 30 mg/dL) in a population of 685 patients with at least one episode of VTE, compared with a control group, and discovered elevated Lp(a) levels were found in 20% of all patients, compared with 7% in the control group ( $P < .001$ , odds ratio [OR] 3.2, 95% confidence interval [CI] 1.9–5.3) [29]. A recent meta-analysis of 90,904 individuals and 5029 stroke events found an association with Lp(a) when comparing high and low Lp(a) levels and revealed an estimated OR of 1.41 (95% CI, 1.26–1.57) for case-control studies and an estimated RR of 1.29 (95% CI, 1.06–1.58) for prospective trials [30]. However, other data and in particular genome-wide association studies have not supported a role of Lp(a) in VTE [31]. These data suggest that Lp(a) may be more relevant in clot propagation initiated by another primary etiologic agent, rather than clot initiation, and may tip the balance of endogenous coagulation and fibrinolysis to clot enlargement and clinical awareness. Interestingly, elevated Lp(a) levels have also been linked with childhood arterial ischemic strokes [32, 33].

## The Role of IL-6 in Plasma Lp(a) Levels

Due to the strong association of inflammatory factors and poor clinical outcome, the FDA has provided emergency use

authorizations and expedited initiation of clinical trials to evaluate various therapies targeted at cytokine reduction as treatment options for COVID-19 [34, 35]. Anticytokine drugs which block IL-6 function using a monoclonal antibody against its receptor (e.g., tocilizumab) as well as apheresis therapy (Spectra Optia Apheresis System) for the removal of cytokines from blood have initiated clinical trials for COVID-19, NCT04372186 and NCT04358003, respectively [36, 37]. In conjunction with the ongoing clinical trial, the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge received an emergency use authorization from the FDA to treat patients 18 years of age or older with confirmed COVID-19 admitted to the intensive care unit with confirmed or imminent respiratory failure. We hypothesize that in addition to the aforementioned risk factors, an elevated Lp(a) may indicate that an individual is at a higher risk of developing a severe reaction to COVID-19 infection, due to the extensive relationship between Lp(a) and multiple proinflammatory pathways, as well as proatherogenic and prothrombotic properties.

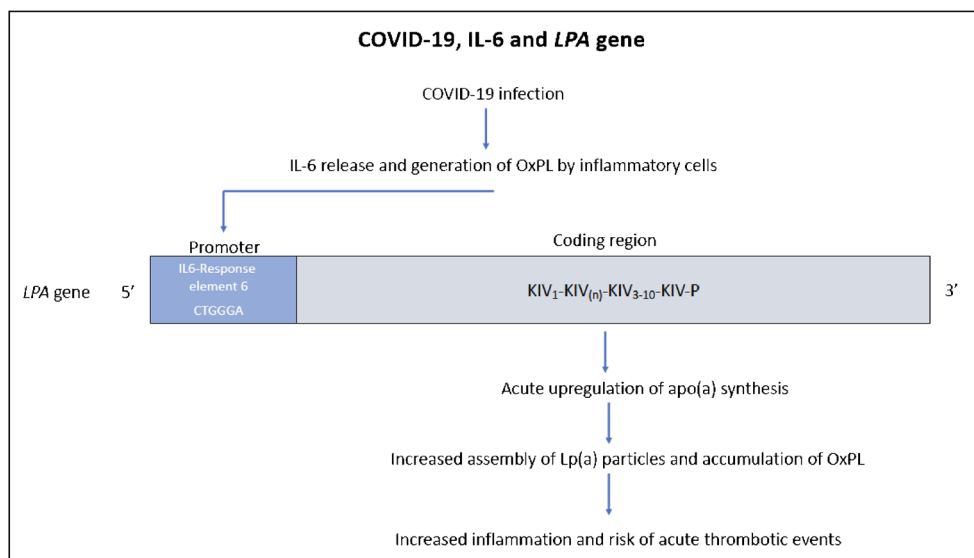
IL-6 is a 27KD cytokine involved in a variety of immune and inflammatory responses. Plasma levels are generally very low, but in the context of acute infection, plasma levels rise substantially due to increased production by a variety of cell types, including macrophages and T and B lymphocytes. IL-6 then participates in host defense functions, including potentiating the production of immunoglobulins and stimulating the production of acute phase proteins by the liver [38]. It has been shown that the genes of several such proteins contain an IL-6 response element (RE) CTGGGA, including the *LPA* gene [39]. In fact, the promoter of the *LPA* gene contains 5 IL-6 REs, but it appears that only IL-6 RE6 participates in upregulation of apo(a) production [40]. In view of these properties, one could postulate that during COVID-19 infection,

the increases in plasma IL-6 levels, which can be more than 20-fold compared with baseline levels, could also upregulate hepatic apo(a) synthesis, leading to increased assembly and secretion into plasma of Lp(a) particles into the circulation (Fig. 1). In addition, although it has not been studied in COVID-19, it has been shown that OxPL are produced in the lungs of humans and animals infected with SARS, anthrax, or H5N1 [41]. Lp(a) is the preferential lipoprotein accumulator of OxPL [12] and has been shown to be responsible for many of its proinflammatory effects [42–44, 45, 46, 47].

Lp(a) has been documented to be an acute phase reactant in a variety of settings, including in myocardial infarction and acute coronary syndromes [22–24], post percutaneous coronary intervention [25, 26], major non-cardiac [22, 48] and cardiac surgery [22, 48, 49], Crohn’s disease [50], and rheumatological disorders [51, 52], with an increase in Lp(a) levels more than 100% of baseline in some studies. In contrast, the effect of acute bacterial and viral infections on the plasma Lp(a) level has not been reported in the literature to the best of our knowledge, outside of one small study showing an approximate doubling of Lp(a) levels 4 months after infectious mononucleosis with Epstein-Barr virus [53].

In addition to preclinical studies in genetic, molecular biology and cell culture models, the relationship of IL-6 plasma levels to Lp(a) has been evaluated in several clinical studies. Horvath et al. [54] reported a strong relationship between Lp(a) and plasma IL-6, which seemed to be stronger in subjects with a higher number of KIV repeats on apo(a), which are also associated with lower Lp(a) levels. Additional clinical evidence has been provided with the approval of the IL-6 receptor (IL-6R) monoclonal antibody (mAb) tocilizumab [40, 55, 56]. These studies have shown a 30–40% decrease in Lp(a) levels in response to tocilizumab that occurs within 1 month of therapy. In contrast, in an elegant study by Muller

**Fig. 1** Relationship of IL-6 to LPA gene responses. In response to any proinflammatory stimulus, an increase in IL-6 may lead to IKL-6 binding to a response element in the *LPA* gene promoter, which then leads to higher production of apo(a) and Lp(a). The acute inflammatory state may also lead to generation of oxidized phospholipids that can bind to and be trafficked by Lp(a) particles. An acute increase in Lp(a)-OxPL may then predispose to acute thrombotic events by tilting the balance of coagulation to a prothrombotic state by inhibiting natural fibrinolysis



et al. [40], the anti-TNF $\alpha$  antibody (adalimumab) did not affect Lp(a) levels, showing a specific effect to IL-6 on Lp(a) biology as opposed to a generalized proinflammatory effect [40]. In addition, sarilumab another anti-IL-6R mAb has been shown to lower Lp(a) by 41% compared with 2.8% for adalimumab [57]. Both tocilizumab and sarilumab have completed phase 2 trials in severe COVID-19 patients, and phase 3 trials are currently underway.

The specificity of IL-6 in regulating Lp(a) was further demonstrated in 1153 subjects showing that subjects with elevated serum IL-6 also were more likely to have elevated Lp(a). In transcriptomic analysis of human liver biopsies, IL-6 response genes correlated with *LPA* gene expression in vivo. Furthermore, tocilizumab inhibited IL-6-induced *LPA* mRNA and protein expression in human hepatocytes and the Lp(a)-lowering effect was mediated by the responsive element CTGGGA at promoter positions -46 to -40 [40].

## Prevalence of Lp(a) and Population Differences in Ethnic/Racial Groups

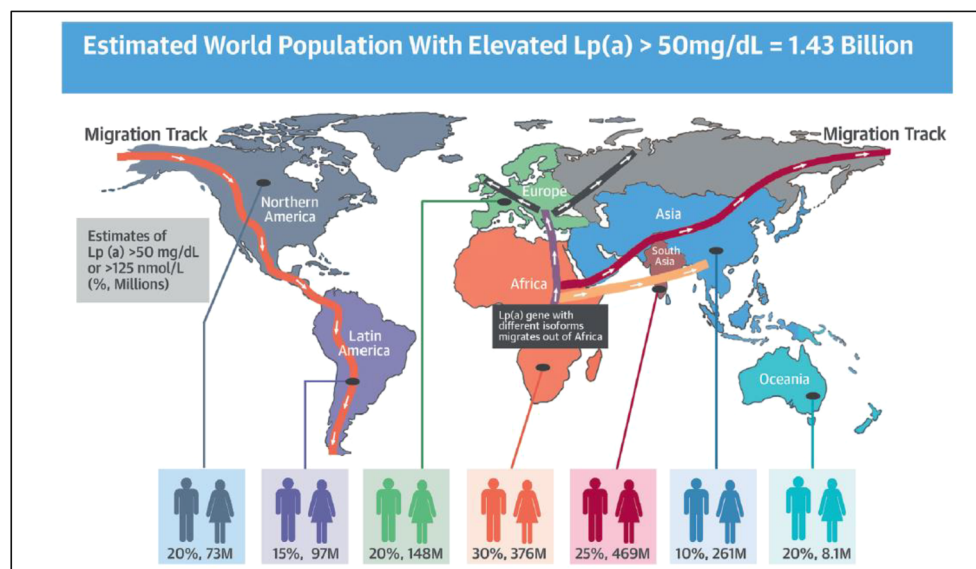
While data is still being collected, the CDC has reported that racial and ethnic minority groups represent a greater proportion of COVID-19 patients relative to the percentage of the surrounding population. The preeminent driving force that determines disease severity in each individual is unclear, but a combination of socioeconomic status, age, and multiple comorbidities including weight, diabetes, hypertension, and CVD history likely plays a partial role [58]. Furthermore, living conditions including multigenerational households and densely populated neighborhoods are more common in minority groups. Working environment and types of employment can increase an individual's risk of exposure for those

who have to continue working due to financial obligations. Hispanic workers are less likely to have access to paid sick leave compared with white non-Hispanic workers [59]. In the USA, African Americans appear to have an increased risk of morbidity and mortality in response to contracting COVID-19 infection and the disproportional response between races is currently not elucidated.

Estimates vary between individual states, but higher mortality has been documented in African Americans across the USA. For example, in Louisiana where African Americans make up 32% of the population, they account for 70% of the people who have died from COVID-19 and similar projections are being seen across the country [60]. Compared with other races, individuals of African descent have a higher rate of elevated Lp(a), as well as larger sized lipoproteins, which is associated with an additional inflammatory risk, including IL-6 elevations [54, 61]. Global estimates of Lp(a) levels are noted in Fig. 2.

Apolipoprotein E (APOE) may also be implicated in racial disparities in COVID-19. The *APOE* gene is composed of 3 alleles (E2, E3, and E4) with six genotypes (E2/2, E2/3, E2/4, E3/3, E3/4, and E4/4). The presence of *APOE4* indicates a higher risk for developing CVD and dementia relative to the other isoforms [62, 63]. Subjects with African descent have a higher frequency of *APOE4* genotypes, in addition to a higher mean Lp(a) level by 2–4-fold compared with Caucasians [64]. Relative to those of European and Asian descent, individuals of African descent may have up to twice the frequency of the E4 allele [65, 66]. *APOE4* is also associated with a higher level of proinflammatory cytokines and promotes prothrombotic properties [67]. Furthermore, in an analysis of >400,000 individuals, *apoE4* isoforms strongly influenced mass levels of Lp(a) with 65% higher Lp(a) levels in *APOE4/4*

**Fig. 2** Global prevalence of elevated Lp(a) levels. Estimated prevalence of elevated Lp(a) (> 50 mg/dL or > 125 nmol/L) is > 1 billion people. Due to population differences in the presence of the number of KIV<sub>2</sub> isoform repeats and other unknown factors, the population Lp(a) means are variable, with the highest mean levels present in subjects from Africa or with African descent. The lowest population Lp(a) means are present in subjects from South America and East Asia. Reprinted with permission from reference [61]

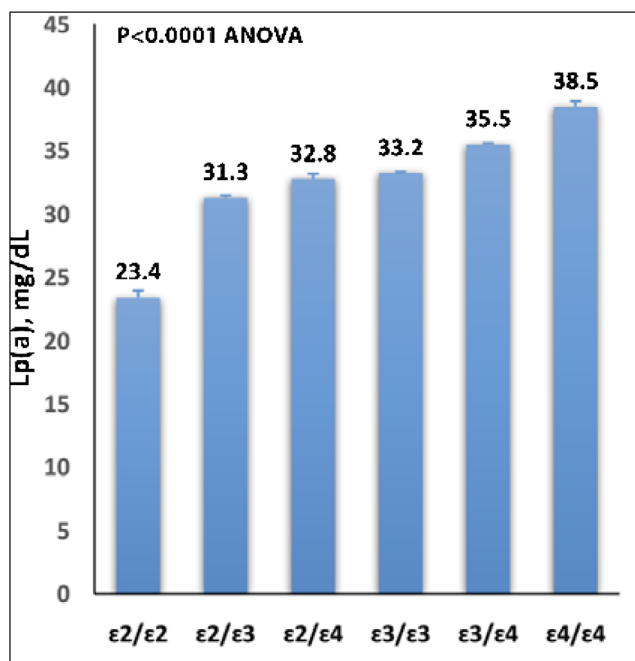


subjects (Fig. 3) [68••], linking the presence of apoE and Lp(a) in subjects with elevated levels of both. It has been suggested that, possibly due to an increase innate immune response, individuals with an *APOE4* polymorphism may be at a higher risk for a severe response to COVID-19 [66••]. Whether *APOE* genotypes influence the prognosis of COVID-19 has not been explored to date.

## Proposals for Research in COVID-19 to Define a Potential Role in Lp(a) in COVID-19 Infection

The observation that COVID-19 is associated with a very high rate of thromboses, its relationship to the cytokine storm and specifically with high levels of IL-6, coupled with IL-6's ability to strongly upregulate Lp(a) levels, and the high homology of Lp(a) to plasminogen, suggests the hypothesis that some of the prothrombotic and inflammatory effects of COVID-19 may be emanating from either baseline elevated Lp(a) or acute increases in Lp(a). We propose the following studies to evaluate this hypothesis:

1. Measure Lp(a) serially in hospitalized subjects and analyze according to the incidence of thrombotic phenotypes. Consider measurement of OxPL-apoB levels to identify Lp(a) particles with particularly high OxPL content that may reflect high oxidative stress and potential for inflammation and procoagulant effects. This could be enhanced



**Fig. 3** Relationship of *APOE* genotypes to Lp(a) mass. Corresponding mean (SD) Lp(a) levels increased significantly according to *APOE* genotype ranging from 23.4 for  $\epsilon 2/\epsilon 2$  to 38.5 (44.1) mg/dL for  $\epsilon 4/\epsilon 4$  ( $P < 0.0001$ ; ANOVA). Median Lp(a) levels also increased by genotype, from 11 for  $\epsilon 2/\epsilon 2$  to 20 mg/dL for  $\epsilon 4/\epsilon 4$

by organizing consortia and pooling data for additional power (Dutch COVID-19 biobank, Columbia University COVID-19 biobank, UK biobank coronavirus research, etc.). This will define the prevalence of baseline elevated Lp(a) in subjects hospitalized with COVID-19 and also assess temporal changes in levels. The population prevalence of Lp(a) is well known, and any deviation for this would suggest a potential link [69].

2. Measure Lp(a) in subjects presenting with COVID-19 and VTE, pulmonary emboli, acute ST-elevation MI, and acute stroke; those who are troponin positive; and those presenting with other manifestations of CVD, such as heart failure and myocarditis. In particular, the transition of a stable plaque to an inflamed, prothrombotic one may be highly relevant to Lp(a)-OxPL as an etiologic entity [70].
3. Measure Lp(a) at serial time points in ongoing clinical trials of IL-6 inhibitors and other cytokine-directed therapies and assess whether levels change in response to IL-6 inhibition. We hypothesize that Lp(a) levels would increase significantly in subjects treated with the control and this rise would be blunted in subjects treated with IL-6-directed therapy. In prior studies with IL-6 antagonists in patients with rheumatoid arthritis, this effect entailed a 30% reduction [51, 52].
4. Correlate baseline levels and the change in Lp(a) levels with prothrombotic and inflammatory biomarkers measured.
5. Assess if an association is present with Lp(a) levels and ICU/ventilation parameters and in-hospital and long-term outcomes.

With the association of high rates of thrombotic complications in COVID-19 patients, efforts are already underway to assess for clinically silent DVT/PE and to treat with systemic anticoagulation. Such a process can be considered for study as a prophylactic measure in subjects with elevated Lp(a).

If indeed an association is shown and is suggestive of being causal, consideration can also be given to lipid apheresis which was recently approved by the FDA as a therapeutic option for elevated Lp(a) (> 60 mg/dL) in conjunction with CVD and persistently elevated LDL-C > 100 mg/dL. Lipid apheresis has been shown to rapidly reduce Lp(a) levels substantially and also to improve blood rheology as well as reduce apoE4 isoforms and inflammatory markers, including IL-6 and oxidized phospholipids [71, 72]. In fact, lipid apheresis has been shown to reduce the frequency of refractory angina and improved magnetic resonance imaging measured coronary blood flow in subjects with elevated Lp(a) [73]. Consideration should be given to initiating pharmacotherapy trials using RNA therapeutics [74•, 75] which can lower Lp(a) > 80% and which are currently in phase 2 and 3 outcome studies, respectively, to assess whether this may improve prognosis.

In conclusion, the confluence of a large variety of cardiovascular complications in COVID-19 patients, which have the commonality of both thromboses and inflammation, may support the hypothesis that one potential etiological agent in the clinical course is elevated Lp(a). Testing this hypothesis is straightforward and would simply require the measurement of Lp(a) levels in several clinical scenarios of the COVID-19 presentation and assessing relationships to clinical phenotypes that may be linked pathophysiologically. We urge interested parties to participate in such clinical research to further understand if a potential role exists and if so to consider Lp(a)-lowering approaches to minimize cardiovascular complications.

## Compliance with Ethical Standards

**Conflict of Interest** Erik Stroes reports personal fees from Amgen, Akcea, Sanofi-Regeneron, Esperion, and Novartis outside the submitted work. John Kastelein reports personal fees from AstraZeneca, CIVI Biotechnology, CSL Behring, Draupnir, Esperion, Gemphire, Madrigal Pharmaceuticals, Matinas BioPharma, NorthSea Therapeutics, Novo Nordisk, Novartis, Regeneron, RegenXBio, Staten Biotech, 89Bio, Omeicos, and Serometrix outside the submitted work. Michael Davidson reports he is the Chief Medical Officer of Corvidia Therapeutics. Sotirios Tsimikas reports personal fees from Ionis Pharmaceuticals, being co-founder of Oxitope, Inc., and Kleanthi Diagnostics, LLC, outside the submitted work. In addition, Dr. Tsimikas has a patent for methods of identifying a subject having or at risk of having or developing coronary artery disease with royalties paid to Kleanthi Diagnostics; two patents for methods for assessing atherogenesis by determining oxidized phospholipid to apolipoprotein B ratios with royalties paid to Kleanthi Diagnostics; and a patent for oxidative biomarkers in predicting risk of stroke, transient ischemic attack (TIA), and peripheral arterial disease (PAD) with royalties paid to Kleanthi Diagnostics. Patrick M. Moriarty and Lauryn K. Gorby declare no conflicts of interest relevant to this manuscript.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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