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Letter to the Editor

# Familial hypercholesterolemia and statins in the COVID-19 era: Mitigating the risk of ischemic stroke

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ABSTRACT

There is a continuing need for research about the underlying mechanisms behind ischemic strokes in COVID-19 patients. Pre-existing endothelial dysfunction, especially if it is accompanied by a viral infection of the endothelial cells may present an important mechanism behind the immunothrombotic/thromboembolic complications of the COVID-19 illness. Here we emphasize that pharmacotherapy with statins could partly counteract such pathophysiological scenarios. Accordingly, using familial hypercholesterolemia (FH) as a pertinent example of a lifelong endothelial dysfunction, we aim to make the clinicians and consulting neurologists aware of statins as a possible adjuvant therapy in the context of an increased risk of ischemic stroke in patients with COVID-19. Based on recent clinical evidence, there is a need to encourage clinicians and consulting neurologists to continue or initiate effective statin treatment to prevent an ischemic stroke, particularly when they encounter a hypercholesterolemic COVID-19 patient with FH.

## 1. Introduction

Usually, when a clinician or a consulting neurologist encounters in clinical work a patient with the inherited form of hypercholesterolemia, i.e., the familial hypercholesterolemia (FH), they associate this disease with atherosclerotic vascular diseases (ASCVD), and their concern is mainly about the risk of premature acute myocardial infarction (AMI). Nevertheless, the clinicians and consulting neurologists need to associate FH patients also with an increased risk of ischemic stroke, particularly regarding FH patients with COVID-19. Currently (April 16, 2021), we still lack data on COVID-19 patients with FH. Accordingly, any treatment suggestion or expert opinion must be based on data obtained from COVID-19 patients in whom the cause of hypercholesterolemia – whether inherited or not – has not been reported [1,2]. In this Letter, we discuss this challenge.

In a very recent analysis, 174 hospitalized patients with COVID-19 and an acute ischemic stroke were pooled from 16 countries, and the disease outcomes were compared with those in patients with an ischemic stroke but without COVID-19 [3]. The comparison revealed that the functional outcomes and mortality rates in the patients with COVID-19 were worse than in those without COVID-19. In another new study, Merkler and co-workers presented data implying that patients with COVID-19 have a greater risk of acute ischemic stroke than patients with influenza [4]. Although the baseline stroke risk factors were more common in the COVID-19 cohort, this difference did not explain the higher risk of ischemic stroke associated with COVID-19, thus highlighting the need to identify COVID-19–specific factors.

## 2. COVID-19 and endothelial dysfunction

The authors of the latter comparative study [4] emphasized that inflammation, prothrombotic coagulopathy, and endothelial injury could have explained the increase in ischemic stroke in the COVID-19 patients. Indeed, in severe COVID-19, the virus also infects endothelial cells, and the high levels of circulating proinflammatory cytokines cause inflammatory damage to the vascular endothelium of the entire vascular tree, i.e., both at the macrovascular and microvascular level in various organs [5]. The damaged endothelial cells lose their anticoagulant surface properties, or they may die and expose the procoagulant subendothelial tissue, and in both cases, a local thrombus quickly develops. Stroke-causing thrombi in patients with COVID-19 have been observed both in the carotid and intracerebral arteries, emphasizing the pathogenic role of endothelial injury in atherosclerosis-susceptible large vessels as a causative mechanism of ischemic stroke in SARS-CoV-2 infected patients [6,7]. Importantly, recent radiologic and histopathologic findings have also revealed cerebral microvascular injuries in patients with severe COVID-19 [8].

## 3. COVID-19 patients with familial hypercholesterolemia and the risk of ischemic stroke

We wish to introduce here that a long-term pre-existing endothelial dysfunction may predispose to the development of vascular injury in COVID-19 patients. A notable subgroup of patients with a permanent pre-existing systemic endothelial dysfunction consists of those with untreated FH. Patients with FH (estimated prevalence 1 in 250, corresponding to approximately 30 million patients worldwide) have highly elevated serum low-density lipoprotein cholesterol (LDL-C) levels since birth, and correspondingly, endothelial dysfunction that develops already in childhood. Such endothelial dysfunction can be restored by statin treatment, and if left untreated, it increases cardiovascular risk later in life [9]. The FH-dependent endothelial dysfunction is present at the arterial and microcirculatory levels [11,12]. Notably, untreated adult patients with FH are known to have an increased risk of premature

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myocardial infarction and ischemic brain infarction. Thus, before the statin era, the FH patients were found to have approximately a 20-fold increased risk for ischemic stroke, whereas later in the statin era, no increased risk for ischemic brain lesions was observed in statin-treated FH patients [13,14]. Since effective statin treatment normalizes endothelial function, we propose that the ability of statins to stabilize the vulnerable endothelial surfaces of unstable atherosclerotic plaques in cerebrovascular arteries is one of the mechanisms underlying the observed risk reduction in the statin-treated FH-patients.

## 4. Concluding remarks

In the study by Merkler et al. [4], the COVID-19 patients suffering from an acute ischemic stroke had significantly elevated levels of serum D-dimer revealing an activated coagulation system. In other studies, statin use has been found to associate with a modest decrease in the D-dimer levels, thereby revealing that statins may also act as mild anticoagulants [15]. It is then quite conceivable that statins have improved the prognosis among the hospitalized COVID-19 patients due to their endothelium-stabilizing and anticoagulant effects [16]. Accordingly, we are proposing that, based on individual considerations, clinicians treating COVID-19 patients initiate/continue or even intensify statin treatment in the context of stroke prevention in FH patients and also in other patients with severe hypercholesterolemia. This recommendation is highly relevant against the background that a significant fraction of FH patients uses statins either irregularly, at too low a dose, or not at all [17–19]. So, clinicians need to take care that hospitalized FH patients with COVID-19 reach the treatment goals for LDL-C, which usually requires a high-efficiency combined lipid-lowering therapy that includes a high dose of a high-intensity statin. The urgent call for continuing statin treatment in the hospital extends to all COVID-19 patients on statin therapy when hospitalized. Thus, as shown in the large observational, retrospective multicenter SEMI-COVID-19 Network study in Spain, more than half (1791/2921) of hospitalized COVID-19 patients receiving statin treatment had been discontinued from statin therapy during the hospitalization [20]. Of note, the authors found that the COVID-19 patients maintained on chronic statin therapy during the hospitalization had a lower mortality rate than those in whom statin therapy was withdrawn.

In addition to an elevated LDL-C level, FH patients have, on average, also higher levels of the highly proinflammatory and prothrombotic LDL-like lipoprotein particles, the lipoprotein(a) [Lp(a)] since birth [21]. Quite alarmingly, an elevated Lp(a) level likely increases the risk of ischemic stroke risk especially in COVID-19 patients [22]. Unfortunately, the statins do not usually lower the level of plasma Lp(a); instead, they may even slightly increase it [23]. Since our treatment goal is to reduce endothelial dysfunction in an FH patient with COVID-19, besides maintaining a low level of serum LDL-C, a markedly increased Lp(a) level should also be lowered [24]. In an FH patient, this may be achieved by adding to the combined high-efficiency lipid-lowering therapy (statin and ezetimibe) a PCSK9 inhibitor, which will further lower LDL-C by about 60%, and also lower Lp(a) by approximately 30% [21,24]. Additionally, the potential benefits of adding a PCSK9 inhibitor to the lipid-lowering regimen may also improve the cellular antiviral defense in a COVID-19 patient [25].

Currently, the data and expert opinions regarding any amenable effect of statins in hospitalized COVID-19 patients are based on observational retrospective studies and meta-analyses, and the consensus is that lipid-lowering drugs are generally safe in patients with coronavirus infections and should be continued [20,26–28]. In observational studies, reductions in the risk of severe illness and mortality due to COVID-19 among statin users have been studied. However, no comparable information exists regarding the effect of statin use on the risk of stroke. To test the hypothesis that statins, either alone or as a component of a lipid-lowering regimen, will mitigate the risk of ischemic stroke in hospitalized FH-patients with COVID-19, a large multinational and multi-ethnic registry study needs to be performed.

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AV, PTH: writing the first draft and editing to produce the final draft; MK reviewing the final draft.

## Declaration of competing interest

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Alpo Vuorio[a,b,*], Markku Kaste[c,d], Petri T. Kovanen[e]
[a] *University of Helsinki, Department of Forensic Medicine, 00014 Helsinki, Finland*
[b] *Mehiläinen Airport Health Centre, 01530 Vantaa, Finland*
[c] *Department of Neurosciences, University of Helsinki, Helsinki, Finland*
[d] *Department of Neurology, Helsinki University Hospital, Helsinki, Finland*
[e] *Wihuri Research Institute, Biomedicum Helsinki 1, 00290 Helsinki, Finland*

[*] Corresponding author: Lentäjäntie 1 E, 01530 Vantaa, Finland.
*E-mail address:* alpo.vuorio@gmail.com (A. Vuorio).