



# Long-Term Cardiovascular and Cerebrovascular Challenges Posed by COVID-19 in Patients With Familial Hypercholesterolemia

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## INTRODUCTION

Follow-up studies have revealed that during the severe acute respiratory syndrome (SARS) caused by coronavirus SARS-CoV epidemic between 2002 and 2003, a significant proportion of those infected had a deterioration in the general health and exercise capacity, especially during the 24 months post-infection (Ngai et al., 2010; Zhang et al., 2020a). Although the emphasis of the follow-up by Ngai and coworkers (2010) was on monitoring alterations in the lung function, a significant impairment in quality of life, as assessed by the SF-36 quality-of-life measures, was reported (Ngai et al., 2010). The long-term effects of SARS-CoV infection have been found to also affect lipid and glucose metabolism in recovered SARS patients (Wu et al., 2017). Thus, the impaired metabolic pathologies were observed 12 years after the infection, and they were considered to be long-term effects of the initial lung damages, and to be potentially also related to the one-month-long high-dose prednisolone treatment given during the acute phase of the disease. Long-term symptoms, usually lasting for about 24 months, have also been reported in survivors of the epidemic influenza A (H7N9) (Chen et al., 2017) and Dengue (Garcia et al., 2011). As could have been envisaged, numerous COVID-19 patients also suffer from long-term impairment of health after an acute SARS-CoV-2 infection, particularly if the symptoms of the disease have been severe and the patients had to be hospitalized (Nalbandian et al., 2021).

In an earlier commentary, we have discussed the acute phase of COVID-19 in patients with familial hypercholesterolemia (FH) (Vuorio et al., 2021a). We now wish to highlight concerns related to the long-term effects of SARS-CoV-2 infections and the increases in the risk for complications and potentially a poor outcome in this group of patients.

## FAMILIAL HYPERCHOLESTEROLEMIA AND COVID-19

FH is the most common monogenic inherited metabolic disease worldwide, and it affects an estimated one in every 330 individuals (Beheshti et al., 2020). Accordingly, we can estimate that among the currently reported over 500 million total cases of COVID-19 worldwide, more than one million are likely FH patients. FH patients have a markedly elevated serum low-density lipoprotein cholesterol (LDL-C) already *in utero* which is often accompanied by an elevated level of serum lipoprotein(a) [Lp(a)], and if left untreated, a lifelong dysfunction of the arterial endothelium ensues in these patients (Sorensen et al., 1994; Vuorio et al., 2020; Nurmohamed et al., 2022). In FH patients with COVID-19, the pre-existing endothelial dysfunction is likely to increase the risk of

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macrovascular and microvascular thrombosis caused by a direct viral attack of the endothelial cells (endothelitis) and by the cytokine storm typically seen during severe COVID-19 illness (Vuorio et al., 2021b). In FH patients, such compounded endothelial injuries with ensuing thrombosis/thromboembolism pose a danger to cardiovascular health, particularly when they affect the coronary vessels supplying the heart and/or the extracranial and intracranial vessels supplying the brain (Quick et al., 2021). Thus, severe COVID-19 illness has been found to increase the risk of myocardial infarction in FH patients whether they have or have not been diagnosed with atherosclerotic cardiovascular disease (ASCVD) (Myers et al., 2021). Additionally, the elevated risk of ischemic stroke associated with COVID-19 potentially also applies to FH patients with COVID-19 (Vuorio et al., 2021c).

## LONG COVID OR POST-COVID SYNDROME

Long COVID or the post-COVID-19 syndrome has been defined as a condition characterized by persistent symptoms lasting more than 2 months after the onset of SARS-CoV-2 infection (Soriano et al., 2021). The severity of the post-COVID syndrome is highly variable, and research suggests that even persons with mild COVID-19, i.e., nearly asymptomatic SARS-CoV-2 infection, may experience long-term symptoms ranging from neuropsychiatric symptoms, such as chronic fatigue, to arterial, venous, and microvascular thrombotic complications in various organs (Di Toro et al., 2021; Nalbandian et al., 2021). In fact, because the long COVID symptoms are frequent among COVID-19 patients (about 30% or more) who have been hospitalized, the American Heart Foundation has initiated an extensive program in order to determine if those individuals who have ASCVD or have survived stroke are more prone to develop long COVID (<https://newsroom.heart.org/news/10-million-invested-to-study-long-term-impact-of-covid-19-on-heart-and-brain-health>).

## POTENTIAL THREATS TO CARDIAC FUNCTION AFTER SARS-COV-2 INFECTION

Although research into the etiological factors of long COVID needs further study, some causal mechanisms potentially relevant also for FH patients with long COVID have already been identified, as discussed below. However, it is important to remember that the data refer to a very wide variety of patients with SARS-CoV-2 infection, and, accordingly, the clinicians need to be careful when trying to generalize the results so far available. Moreover, no long-term cardiovascular or cerebrovascular clinical data on FH patients after COVID-19 have yet been published; so, we have to utilize indirect measures when assessing the significance of the results already obtained in non-FH patients.

One potentially interesting cause of dyspnea due to COVID-19 was found in patients without a known pre-existing

cardiopulmonary disease (mean age  $51 \pm 11$  years), and who underwent a 1-year intensive clinical follow-up (Luchian et al., 2022). All of the patients had persistent dyspnea, and in more than a third, the echocardiographic evaluation revealed significant changes in cardiac global constructive work and global work index, suggesting that these patients had decreased myocardial performance and a subclinical cardiac dysfunction. Earlier studies have suggested that dyspnea in the recovered patients who suffered SARS-CoV-2 infection could be related to myocarditis or ischemic injury of the heart (Kotecha et al., 2021; Özer et al., 2021). Regarding FH patients, COVID-19-associated impairment in myocardial performance is highly relevant, particularly among those patients with pre-existing ASCVD, a condition which is often present in untreated FH patients already in early adulthood, even if left undiagnosed (Representatives of the Global Familial Hypercholesterolemia Community, 2020). It is possible that decreased myocardial performance continuing after COVID-19 potentially affects a much wider range of FH patients, including those without clinically evident ASCVD. A very recent study among 46 male FH patients without known ASCVD (and without COVID-19) demonstrated a mildly reduced global longitudinal left ventricular strain when compared with controls (Vartela et al., 2021). This finding suggests that, particularly in FH males, the presence of subclinical vasculopathy adversely affecting the cardiac function might predispose the patients to even greater deleterious post-COVID-19 sequelae.

## CONVALESCENT PERIOD OF COVID-19 AND THE POTENTIAL RISK OF ISCHEMIC STROKE AND INTRACRANIAL HEMORRHAGE

In an early study on neurological and psychiatric sequelae of COVID-19, the risk of cerebrovascular events, notably acute ischemic stroke and intracranial hemorrhage, was found to be significantly increased within the first 6 months after COVID-19, particularly in patients who had suffered from severe acute COVID-19 and associated encephalopathy (Taquet et al., 2021). In a study of South Asian males aged 50 years or younger, the estimated annual incidence rate of acute ischemic stroke was significantly higher (82.6 cases per 100,000 persons) in those with COVID-19 infection when compared with historical data (38.2 cases per 100,000 persons) (Tu et al., 2021). Importantly, in this study, acute ischemic stroke was reported to occur during the convalescent phase after an asymptomatic COVID-19 infection, the median time from a positive serological test result to stroke being 55 days (range 0–130 days).

Bikdeli and coworkers (2020) have reported acute ischemic stroke as a secondary wave of complications of COVID-19 and postulated that the prothrombotic state associated with acute COVID-19 may persist long-term (Bikdeli et al., 2020). A recent study utilizing healthcare databases from the US Department of Veterans Affairs indicated that the period of increased risk and burden for cerebrovascular disorders (stroke and transient

ischemic attack) may persist at least for 1 year after the infection (Xie et al., 2022). Thus, the authors reported that persons who survived the first 30 days of COVID-19 exhibited an increased risk of stroke and transient ischemic attack for 12 months after the acute infection. In this register study, the exact mechanisms underlying cerebrovascular events remained undetermined, but the high incidence of high-risk cardioembolic conditions (atrial fibrillation, heart failure, acute coronary syndrome, myocarditis) suggests that strokes may be secondary to cardiac disease, while other COVID-19-related mechanisms (hypercoagulopathy, endotheliitis) likely contribute to the final events.

Regarding hypercoagulability, elevated levels of plasma factor VII and plasminogen activator inhibitor-1 have been shown to persist after SARS-CoV-2 infection (von Meijenfeldt et al., 2021). There is also a concern about coagulopathy and the appearance of antiphospholipid antibodies, which can arise transiently in patients with various infections including COVID-19 (Zhang et al., 2020b). Such antibodies, particularly the anticardiolipin antibodies, may have an acute ischemic stroke risk-impacting effect jointly with other well-recognized risk factors for stroke, such as hypertension, hyperlipidemia, and obesity (Rothstein et al., 2020). What could such scenarios potentially mean in the context of FH? An early study found that untreated FH patients, i.e., those not receiving lipid-lowering therapy, have a markedly increased risk for acute ischemic stroke (Kaste and Koivisto, 1988). More recently, i.e., during the statin era, such increased risk appears to have largely disappeared, most likely reflecting an effective treatment of the hypercholesterolemia (Huxley et al., 2003; Soljanlahti et al., 2005; Hovland et al., 2018; Beheshti et al., 2018). Unfortunately, however, the great majority of FH patients have not been diagnosed, and, accordingly, they remain untreated or, even if correctly diagnosed, remain undertreated (Representatives of the Global Familial Hypercholesterolemia Community, 2020). Therefore, the concern regarding the risk of an acute ischemic stroke in most FH patients with COVID-19 continues.

## A PERSISTENT HYPERCOAGULABLE STATE AFTER SARS-COV-2 INFECTION

A recently reported South African study was searching for a common explanator of the large variety of long COVID symptoms (Pretorius et al., 2021). The study included patients who had suffered from long COVID for at least 2 months, and as control groups healthy persons and patients with type 2 diabetes mellitus without known previous SARS-CoV-2 infection. Although the study was small in size, it revealed that the plasma derived from the long COVID patients contained large anomalous deposits of microclots. After trypsinization of the plasma, increased concentrations of several pro-inflammatory molecules such as alpha (2)-antiplasmin, various fibrinogen chains, and serum amyloid A (SAA) were detected in the samples derived from the long COVID patients, but not in those from the healthy or diabetic control subjects. The authors concluded that the clotting proteins were dysfunctional and that an imbalance between the supply and

demand of lytic enzymes existed. Three mechanisms were postulated as an explanation of the clotting pathology in the long COVID-19 patients: first, the increased levels of pro-inflammatory molecules in the plasma caused a hypercoagulable state; second, platelets were hyperactivated and led to microclot formation in the circulation, and third, an aberrant fibrinolytic system prevailed. Based on their findings, the authors recommended considering prolonged anticoagulation for COVID-19 patients after discharge from the hospital. Regarding the FH patients, an elevated serum Lp(a) is also a matter of major concern because the unique apolipoprotein(a) component present in the Lp(a) particles prevents fibrinolysis and so tends to promote thrombus growth wherever the thrombus is forming in the vasculature (Vuorio et al., 2020).

## CONCLUDING REMARKS

When compared with non-FH patients who have suffered an acute SARS-CoV-2 infection, in FH patients a hypercoagulable state may persist for even longer periods after the infection. This assumption is relevant because the endothelial cells have been exposed to a lifelong high LDL-C concentration, and often also to an elevated Lp(a) level, which jointly cause endothelial dysfunction even in childhood (Vuorio et al., 2021b). This can be particularly harmful in the FH patients whose LDL-C-lowering therapy is lacking or sub-optimal, and among those FH patients who also have a highly elevated serum Lp(a) level. Thrombus formation in an arterial, venous, or microvascular vascular segment, is likely to occur with greater frequency among FH patients not only because of a pre-existing endothelial dysfunction but also as a result of the acute direct viral endothelial damage and the hypercoagulability state during the post-COVID period.

The COVID-19 pandemic will increase health inequalities, and particularly in low-income countries, there is a need to increase vaccination coverage in the most vulnerable patient groups (Vuorio et al., 2022). Significant health inequalities between high-to-low-income countries are demonstrated by the fact that by April 2022, only about 15% of people in low-income countries had received at least one dose of a COVID-19 vaccine (<https://www.ourworldindata.org/covid-vaccinations>). The COVID-19 vaccination program is important not only to prevent acute SARS-CoV-2 infections but also to potentially decrease long-term COVID-19 complications.

Although reliable epidemiological data are not yet available, it is obvious that the entire FH population, i.e., about 30 million FH patients worldwide, are at an increased risk of serious vascular complications which can occur after COVID-19. Consequently, when a clinician encounters an FH patient with symptoms that match with those typical of the post-COVID syndrome, it is of importance that the clinician ascertains that lipid-lowering pharmacotherapy is being taken regularly, is adequate, and follows the current guidelines. In this context, it is relevant to remember that statins also act as mild antithrombotic

medications (Vuorio et al., 2021d). When appropriate, PCSK9 inhibition may be included in the lipid-lowering therapy even among younger FH patients with COVID-19 and thereafter, as, unlike statins, the PCSK9 inhibitors can also reduce the level of serum Lp(a) (Vuorio et al., 2020).

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