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LETTER TO THE EDITOR

Patients with familial hypercholesterolemia and COVID-19: Efficient and ongoing cholesterol lowering is paramount for the prevention of acute myocardial infarction

We respectfully submit this letter in response to the May 2021 article "COVID-19 associated risks of myocardial infarction in persons with familial hypercholesterolemia with or without ASCVD [1]. This interesting study, which is based on a large US national database showed that both diagnosed and probable familial hypercholesterolemia (FH) significantly increased the risk of acute myocardial infarction (AMI). Thus, during the period from March 1 to June 30, 2020, the AMI incidence in the diagnosed FH patients with ASCVD and COVID-19 was significantly higher (1.57%; n = 1 399) than in those without COVID-19 (0.56%; n = 89 396). Two recent studies, one in Milan Italy [2], and the other in New York City USA [3], involved hospitalized patients from the general population. The patients were treated in intensive care units and the prevalences of AMI were 3.7% and 2.1%, respectively. Since the study by Myers et al. [1] included all available healthcare encounter data on individuals being evaluated or treated for cardiovascular diseases, it also included non-hospitalized patients.

The logical follow-up question is whether lipid-lowering as a preventive measure could reduce the increased risk of AMI among FH patients with COVID-19? Regarding the effect of lipid-lowering therapies, the authors state that their data are unable to provide information on whether lipid-lowering therapies have protective or deleterious effects on outcomes for those with FH in the COVID-19 and No-COVID-19 groups. Addressing potentially deleterious effects of pharmacological lipid-lowering is quite unexpected, as the information on the FH Foundation's website advises continuing statin therapy unless there is a contraindication. More specifically, the following instructions are available on the website: Statins, first-line therapy for individuals with FH, have many positive attributes that could be useful in treating COVID-19 including anti-inflammatory effects, positive immunomodulatory effects, antioxidant effects, improvement in endothelial function, and antithrombotic effects (https://thefhfoundation.org/fh-treatments-and-covid-19; https://thefhfoundation.org/cardiovascular-complications-of-covid-19). Furthermore, the FH Foundation Guidance recommends that "it is recommended that patients continue with their prescribed statin therapy".

Albeit no published clinical data are available regarding the efficiency of adjunctive lipid-lowering therapy in FH patients with COVID-19, we wish to provide diverse circumferential inference strongly favoring the concept of a potentially protective effect of lipid-lowering therapy in this patient group. In FH patients the level of low-density lipoprotein cholesterol (LDL-C) is elevated from birth by two to three-fold compared to the general population. The markedly elevated LDL-C correlates with the severity of vascular endothelial dysfunction already from childhood in FH patients [4]. Moreover, many FH patients are exposed to elevated lipoprotein(a) [Lp(a)] which causes further endothelial dysfunction [4,5]. Endothelial dysfunction pre-exposes FH patients to the surplus endothelial damage caused by the SARS-CoV-2 viral attack [6].

Evidence based on meta-analysis and cohort studies has shown the benefit of statins among hospitalized patients, reducing not only the severity of SARS-CoV-2 infection but also decreasing mortality [7]. We argue that effective statin therapy is of utmost importance among FH patients to effectively lower serum LDL-C and to improve endothelial function. Unfortunately, even diagnosed FH patients are often treated with ineffective statin dosages [8]. Additionally, it has been reported that among hospitalized patients with COVID-19 statin treatment is in very many cases discontinued. Such abrupt discontinuation increases the risk of cardiovascular events especially among those FH patients with pre-existing subclinical or clinical ASCVD, which itself increases the risk of COVID-19 -associated cardiovascular events [9]. Such an additional increase in risk is particularly harmful to older FH patients who, because of their high age, have a very high cholesterol burden [10].

To mitigate the risk of AMI in FH patients with COVID-19, continuing ongoing efficient statin medication, whether at home or in hospital, is of utmost importance [6,11]. Indeed, strict adherence to the current evidence-based guidelines regarding serum LDL-C target levels should be aimed for. Furthermore, in very high-risk FH patients with severe COVID-19, a triple regimen including a statin, ezetimibe, and a PCSK9 inhibitor should be strongly considered - at least temporarily [6,10]. PCSK9 inhibitors offer the possibility to continue lipid-lowering medication in ventilated ICU-treated FH patients with COVID-19 who are unable to take oral medication. Besides LDL-cholesterol, PCSK9 therapy also effectively lowers the thrombogenic high serum Lp(a) concentrations and may potentially enhance the antiviral action of interferon [12,13].

It is also important to remember that an FH patient who is a COVID-19 survivor has a prolonged heightened post-infectious risk of suffering an AMI, which adds to the increased risk caused by FH itself [14]. One, therefore, needs to ensure that after COVID-19 effective cholesterol-lowering therapy is continued in FH patients, and that it needs to be continued lifelong. In the study by Myers et al. [1], FH patient identification was carried out by using a machine learning model [15]. The next logical step would be to collect comprehensive epidemiologic data of clinically diagnosed FH patients who have had COVID-19 [16], and to demonstrate the likely beneficial effects of effective lipid-lowering therapies in FH patients with current or past COVID-19. This can only be successfully achieved through validated international cooperation.

Declaration of Competing Interest

Author PTK has received consultancy fees, lecture honoraria and/or travel fees from Amgen, Novartis, Raisio Group and Sanofi. FJR has received consultancy fees, lecture honoraria and/or travel fees from Amgen, Sanofi, Regeneron and Novartis

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Petri T. Kovanen: Writing – original draft, Writing – review & editing. **Frederick Raal:** Writing – review & editing. **Alpo Vuorio:** Writing – original draft, Writing – review & editing.

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