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 [4]. 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 threefold 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 temporally [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.
CRediT authorship contribution statement

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

References

[1] Myers KD, Wilkmon K, McGowan MP, Howard W, Staszak D, Rader DJ. COVID-19 associated risks of myocardial infarction in persons with familial hypercholesterolemia with or without ASCVD. Am J Prev Cardiol 2021;7:100197 Epub ahead of print. doi:10.1016/j.ajpcard.2021.100197.

[2] Lodigiani C, lapichino G, Careno L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9–14.

[3] Bilaloglu S, Aphinyanaphongs Y, Jones S, Itrarate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. JAMA 2020;324:799–801.

[4] Sorensen KE, Celermajar D, Georgakopoulos D, Hatcher G, Betteridge DJ, Deanfield JE. Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein(a) level. J Clin Invest 1994;93:50–5.

[5] Vuorio A, Watts GF, Schneider WJ, Tsimikas S, Kovonen PT. Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities. J Intern Med 2020;287:2–18.

[6] Vuorio A, Raal F, Kaste M, Kovonen PT. Familial hypercholesterolaemia and COVID-19: a two-hit scenario for endothelial dysfunction amenable to treatment. Atherosclerosis 2021;320:53–60.

[7] Vuorio A, Kovonen PT. Statins as adjuvant therapy for COVID-19 to calm the stormy immunothrombosis and beyond. Front Pharmacol 2021;11:95548.

[8] Pang J, Sullivan DR, Hare DL, et al. Gaps in the care of familial hypercholesterolaemia in Australia: first report from the national registry. Heart Lung Circ 2021;30:372–9.

[9] Vuorio A, Kovonen PT. Comment on: prior treatment with statins is associated with improved outcomes of patients with COVID-19: data from the SEMI-COVID-19 registry. Drugs 2021 Epub ahead of print. doi:10.1007/s40265-021-01537-7.

[10] Vuorio A, Kovonen PT, Strandberg TE. Older familial hypercholesterolemia patients with COVID-19. Gerontology 2021;1:81–3.

[11] Banach M, Pensom PE, Fras Z, et al. Brief recommendations on the management of adult patients with familial hypercholesterolemia during the COVID-19 pandemic. Pharmacol Res 2020;158:104891.

[12] Vuorio A, Kovonen PT. Prevention of endothelial dysfunction and thrombotic events in COVID-19 patients with familial hypercholesterolemia. J Clin Lipidol 2020;14:617–18.

[13] Vuorio A, Kovonen PT. PCSK9 inhibitors for COVID-19: an opportunity to enhance the antiviral action of interferon in patients with hypercholesterolaemia. J Intern Med 2021;289:749–51.

[14] Vuorio A, Watts GF, Kovonen PT. Familial hypercholesterolaemia and COVID-19: triggering of increased sustained cardiovascular risk. J Intern Med 2020;287:746–7.

[15] Myers KD, Knowles JW, Staszak D, et al. Precision screening for familial hypercholesterolaemia: a machine learning study applied to electronic health encounter data. Lancet Digit Health 2019;1(8):393–402.

[16] Vuorio A, Ramaswami U, Holven KB. Editorial: genetics of familial hypercholesterolemia: new insight. Front Genet 2021;12:669373.

Petri T. Kovonen
Wiñuri Research Institute, Biomedicum Helsinki 1, 00290 Helsinki, Finland

Frederick Raal
Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Alpo Vuorio*
University of Helsinki and Mehiäinen Airport Health Centre, 01530 Vantaa, Finland

*Corresponding author at: Mehiäinen Airport Health Centre, 01530 Vantaa, Finland.

E-mail address: alpo.vuorio@gmail.com (A. Vuorio)