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LETTER TO THE EDITOR

Comment on: "Prior Treatment with Statins is Associated with Improved Outcomes of Patients with COVID-19: Data from the SEMI-COVID-19 Registry"

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Dear Editors,

We found the multicenter registry study by Torres-Peña et al. [1] very interesting and well organized. The authors were able to show that hospitalized COVID-19 patients who maintained long-term statin treatment that had been initiated before hospitalization had better prognoses when measured by all-cause mortality, acute respiratory distress syndrome, and acute kidney injury. For example, all-cause mortality was 20.6% for those continuing on statins and 27.6% for those who withdrew from statins ($P < 0.001$). The patient data showed that there were altogether 1130 patients in the study who continued in-hospital statin use and 1791 patients who withdrew statin use in the hospital. It can be calculated that over 60% of hospitalized patients with COVID-19 had for unknown reasons stopped their statin consumption during the hospitalization period. This is an astonishingly large number of patients; however, the authors did not comment on this aspect.

Who then are these patients who were on chronic statin treatment before hospitalization for COVID-19? According to lipid treatment guidelines, the initiation of statin treatment is targeted to those who have a significantly elevated risk for atherosclerotic cardiovascular disease (ASCVD) [2]. The real-world example of 541,221 non-COVID-19 patients who were on statins included those in the diabetes cohort (61.1%), followed by those who had a recent acute coronary syndrome (ACS) event (15.8%), recent non-ACS cardiovascular (CV) event (9.9%), peripheral artery disease (4.7%), coronary heart disease (4.4%), or history of ischemic stroke (4.1%) [3]. In another recent study of hospitalized COVID-19 patients ($N = 951$) who were antecedent statin users, 74% had hypertension, 55.8% had diabetes, 22.5% had coronary artery disease, and 13.9% had a history of stroke/transient ischemic attack [4]. The respective significantly smaller percentages for non-statin users were 43.3%, 26.1%, 6,9%, and 5.6%.

Based on the data presented above, any discontinuation of statin therapy, even temporarily, is potentially detrimental to a patient with a cardiovascular risk profile that, according to the current guidelines, is an indication for statin treatment. It has been shown in a recent population-based cohort study in France among 75-year-old non-COVID-19 patients treated for primary prevention that the adjusted ratios for statin discontinuation were 1.33 (95% confidence interval (CI) 1.1.8–1.50) for any cardiovascular event, 1.46 (95% CI 1.21–1.75) for a coronary event, and 1.26 (95% CI 1.05–1.51) for a cerebrovascular event [5]. It should be noticed that these risks were seen in this older population who did not have clinical signs of ASCVD.

Among the statin-treated patients, some individuals have an inherited cholesterol disease such as heterozygous familial hypercholesterolemia (HeFH), in which the serum low-density cholesterol (LDL-C) is elevated two- to threefold since birth [6]. The prevalence of HeFH is about one out of 250 individuals in the general population [7]. If left untreated with a statin, HeFH patients develop premature atherosclerosis and results in an approximate tenfold increase in the risk of early ASCVD [8]. Accordingly, among the HeFH population, the risk of discontinuation of statin treatment is potentially detrimental.

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In the study by Torres-Peña et al. [1], in the group of COVID-19 patients who stopped statin treatment, we can estimate that some patients, despite being symptomless and having a normal LDL-cholesterol level, had subclinical ASCVD, and accordingly had lost the plaque-stabilizing effect of statins on vulnerable coronary plaques [9, 10]. Moreover, discontinuation of statin treatment resulted in a loss of the potential adjunct benefit of statin therapy in the treatment of COVID-19 infection, i.e., a mild anticoagulant, anti-inflammatory, and endothelium-stabilizing effect [11]. On the other hand, the group of COVID-19 patients who continued their statin use potentially benefited from the effects of statins expected to improve the prognosis of pre-existing ASCVD and additionally the outcome of COVID-19.

It can be assumed that both the detrimental effect of stopping statin treatment and the favorable effect of continuation of statin treatment is largest among those who are at the highest risk of ASCVD, i.e., HeFH patients [12]. This applies especially to older HeFH patients with COVID-19 [13]. The clinical challenge is how to make physicians treating COVID-19 patients aware of the prognostic effect of statin therapy and the importance of continuing statin therapy during hospitalization. Current data suggest that statin therapy could be a cost-effective treatment for improving the prognosis of COVID-19 in patients even before admission to hospital.

A practical challenge may be to continue statin therapy in the intensive care unit because statins are most commonly administered orally as tablets. In this situation, clinicians need to consider the possibility to continue LDL-C lowering using injectable lipid-lowering medications like a PCSK9 inhibitor. This applies especially to those patients having very high ASCVD risk, i.e., HeFH patients with COVID-19. An additional potential advantage of PCSK9 inhibitors is that they lower the serum lipoprotein(a) [Lp(a)] concentration by about 30%. This additional benefit is of particular importance to the many HeFH patients who have, in addition to elevated serum LDL-C, an elevated Lp(a) level [14]. Elevated Lp(a) potentially increases ASCVD risk in patients with COVID-19 [15]. As a further note, statins fail to lower Lp(a) levels [16], while a PCSK9 inhibitor lowers LDL-C by about 60%, and additionally Lp(a) by approximately 30% [14]. Additionally, PCSK9 inhibitors may improve the antiviral defense in patients with COVID-19 [17]. Since hypercholesterolemia may increase the mortality of severely ill COVID-19 patients by even 25% [18], in future studies it would be important to test the potential effect of PCSK9 inhibitors on the outcomes of severely hypercholesterolemic hospitalized COVID-19 patients, including those with HeFH.

Declarations

Declaration of competing interest PTK has received lecture honoraria and/or travel fees from Amgen, Novartis, Raisio Group, and Sanofi.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials Not applicable.

Code availability Not applicable.

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References

1. Torres-Peña JD, Pérez-Belmonte LM, Fuentes-Jiménez F, et al. Prior treatment with statins is associated with improved outcomes of patients with COVID-19: data from the SEMI-COVID-19 Registry. Drugs. 2021;81(6):685–95.
2. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.
3. Lin I, Sung J, Sanchez RJ, et al. Patterns of statin use in a real-world population of patients at high cardiovascular risk. J Manag Care Spec Pharm. 2016;22(6):685–98.
4. Gupta A, Madhavan MV, Poterucha TJ, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Preprint. Res Sq. 2020;rs.3.rs-56210.
5. Giral P, Neumann A, Weill A, Coste J. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. Eur Heart J. 2019;40(43):3516–25.
6. Brown MS, Kovanen PT, Goldstein JL. Regulation of plasma cholesterol by lipoprotein receptors. Science. 1981;212(4495):628–35.
7. Representatives of the Global Familial Hypercholesterolemia Community, Wilemon KA, Patel J, et al. Reducing the clinical and public health burden of familial hypercholesterolemia: a global call to action. JAMA Cardiol. 2020;5(2):217–29.
8. Tada H, Kawashiri MA, Okada H, et al. Assessment of coronary atherosclerosis in patients with familial hypercholesterolemia by coronary computed tomography angiography. Am J Cardiol. 2015;115(6):724–9.
9. Fernández-Friera L, Fuster V, López-Melgar B, et al. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. J Am Coll Cardiol. 2017;70(24):2979–91.
10. Vähätalo J, Holmström L, Pakanen L, Kaikkonen K, Perkiömäki J, Huikuri H, Junttila J. Coronary artery disease as the cause of sudden cardiac death among victims < 50 years of age. Am J Cardiol. 2021;147:33–8.
11. Vuorio A, Kovanen PT. Prevention of endothelial dysfunction and thrombotic events in COVID-19 patients with familial hypercholesterolemia. J Clin Lipidol. 2020;14(5):617–8.

12. Vuorio A, Raal F, Kaste M, Kovanen PT. Familial hypercholesterolaemia and COVID-19: a two-hit scenario for endothelial dysfunction amenable to treatment. Atherosclerosis. 2021;320:53–60.
13. Vuorio A, Kovanen PT, Strandberg TE. Older familial hypercholesterolemia patients with COVID-19. Gerontology. 2021;1–3.
14. Vuorio A, Watts GF, Schneider WJ, Tsimikas S, Kovanen PT. Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities. J Intern Med. 2020;287(1):2–18.
15. Moriarty PM, Gorby LK, Stroes ES, Kastelein JP, Davidson M, Tsimikas S. Lipoprotein(a) and its potential association with thrombosis and inflammation in COVID-19: a testable hypothesis. Curr Atheroscler Rep. 2020;22(9):48.
16. Tsimikas S, Gordts Philip LSM, Nora C, Yeang C, Witztum JL. Statins and increases in Lp(a): an inconvenient truth that needs attention. Eur Heart J. 2020;41(1):192–3.
17. Vuorio A, Kovanen PT. PCSK9 inhibitors for COVID-19: an opportunity to enhance the antiviral action of interferon in patients with hypercholesterolaemia. J Int Med. 2012;289(5):749–51.
18. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1345–55.