

## Letter to the Editor

**Prevention of endothelial dysfunction  
and thrombotic events in COVID-19  
patients with familial  
hypercholesterolemia**


The importance of dyslipidemia medications in patients with coronavirus disease 2019 (COVID-19) is currently not sufficiently recognized in the prevention of thrombotic events.<sup>1</sup> This is especially true for COVID-19 patients with familial hypercholesterolemia (FH), a genetically determined form of hypercholesterolemia.

FH is the most common genetic cause of cardiovascular disease, with an estimated worldwide prevalence of 1 in 250. The lifelong highly elevated serum LDL cholesterol (LDL-C) concentration leads to a strongly increased risk of a premature atherosclerotic cardiovascular disease (ASCVD) event.<sup>2</sup> The persistent high level of LDL-C also causes endothelial dysfunction already in young children, and there is a positive correlation between serum LDL-C and severity of endothelial dysfunction in children with FH.<sup>3,4</sup> Moreover, Charakida et al.<sup>4</sup> found that plasminogen activator inhibitor 1 levels were higher in children with FH and were associated with the concentrations of both total cholesterol and lipoprotein(a) [Lp(a)], the latter of which, besides carrying cholesterol into atherosclerotic lesions, also possesses direct proinflammatory and atherothrombotic features.<sup>5</sup> Thus, in patients with FH, throughout their lives, the vascular endothelium is exposed to metabolic abnormalities, notably high plasma LDL-C and Lp(a) levels, which are associated with endothelial dysfunction.<sup>3</sup>

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects humans via angiotensin-converting enzyme 2 receptors, which are expressed primarily in endothelial cells. Analysis of in-hospital deaths among COVID-19 patients has confirmed that previous ASCVD associates with increased mortality.<sup>6</sup> Of note, SARS-CoV-2 causes endotheliitis (ie, inflammation particularly of the microvascular endothelium), which may be related to systemic impairment of microcirculatory function and lead to activation of the coagulation cascade.<sup>7</sup> Indeed, COVID-19 patients suffer from the formation of microthrombi, which is potentially even more prevalent in FH patients with pre-existing endothelial dysfunction caused by the lifelong elevated serum LDL-C and Lp(a) levels.

FH patients with diagnosed ASCVD usually need a combination of a statin and a PCSK9 inhibitor to achieve very low LDL-C target levels. Regarding FH patients with COVID-19, it is noteworthy that statins decrease serum D-dimer levels by about 15%,<sup>8</sup> and PCSK9 inhibitors decrease the level of the atherothrombogenic Lp(a) by about 30%.<sup>9,10</sup> Accordingly, statin-PCSK9 inhibitor dual therapy has the potential to decrease two factors underlying the increased risk of thrombotic complications in COVID-19, and FH patients suffering from COVID-19 should receive maximal cholesterol-lowering therapy also for this reason. In particular, the unique feature of statins as mild anticoagulants<sup>11</sup> and the demonstrated favorable prognosis in hospitalized COVID-19 patients on statin therapy<sup>6</sup> favor such conclusion.

**Conflict of interest**

AV has no conflict of interest. PTK has received lecture honoraria and/or travel fees from Amgen, Novartis, Raisio Group, and Sanofi.

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**References**

1. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol.* 2020;75: 2352–2371.
2. Tada H, Kawashiri M, Okada H, et al. Assessment of coronary atherosclerosis in patients with familial hypercholesterolemia by coronary computed tomography angiography. *Am J Cardiol.* 2015;115: 724–729.

3. Sorensen KE, Celermajer DS, 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;93:50–55.
4. Charakida M, Tousoulis D, Skoumas I, et al. Inflammatory and thrombotic processes are associated with vascular dysfunction in children with familial hypercholesterolemia. *Atherosclerosis.* 2009;204:532–537.
5. 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;287:2–18.
6. Mehra MR, Desai SS, Kuy SR, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Med.* 2020.
7. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* 2020;395:1417–1418.
8. Schol-Gelok S, Hulle T, Biedermann JS, et al. Clinical effects of antiplatelet drugs and statins on D-dimer levels. *Eur J Clin Invest.* 2018;48:e12944.
9. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;385:331–340.
10. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolemia. *Eur Heart J.* 2015;36:2996–3003.
11. Undas A, Brummel-Ziedins KE, Mann KG. Statins and Blood Coagulation. *Arterioscler Thromb Vasc Biol.* 2005;25:287–294.