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Author's reply to: Arterial stiffness improvement after adding on PCSK9 inhibitors in patients with familial hypercholesterolemia, a letter from Papaioannou and colleagues

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We are very grateful to Papaioannou and his team for opening the interesting question about the potential link between lipid factors control, vascular and endothelial damage, pulse wave velocity (PWV), and cardiovascular (CV) risk.[1] Low-density lipoprotein cholesterol (LDL-C) and blood pressure are indeed two of the most important CV risk factors, and low variability of LDL-C and systolic blood pressure are associated with a significant reduction of CV events.[2] As they already underlined, we found that by reducing LDL-C with optimal lipid-lowering therapy, adding on ezetimibe and eventually PCSK9 inhibitors to highly effective statin, PWV profile may significantly improve in subjects with familial hypercholesterolemia.[3]

We also found that changes in LDL-C levels predicted PWV improvement; moreover, this effect seemed more evident in primary prevention subjects than in secondary prevention ones, at least in a limited observation period.

We are currently unable to provide explanations on the underlying mechanisms of our results. However, we believe that these data may suggest a new aspect of the protective role of lipid-lowering therapy on CV system.

We agree with Papaioannou and colleagues about the number of variables potentially able to play a role in improving PWV because many variables could change in individual cases, and thus, the individual changes could interfere with the final results. Interestingly, previous authors showed that rosuvastatin treatment significantly reduced arterial stiffness by lowering both blood pressure and LDL-C in hypercholesterolemic subjects.[4] These findings may suggest a previously unexplored pathophysiological link between LDL-C and blood pressure.

LDL-C reduction in fact is a well-acknowledged causal factor of CV disease, and its reduction is needed to significantly reduce the global CV disease burden.

The decrease of PWV during CV therapy has already been shown to predict a significant lowering of CV risk and all-cause mortality risk. We are not able to state if risk reduction is additive, complementary, or partially included in the one due to LDL-C lowering. Also, we don't know if these findings represent just a part of the well-acknowledged CV and global risk reduction due to lipid-lowering therapy, rather than an unexpected result.

This observational finding was beyond the aim of the present study, but a specifically designed prospective study on a larger scale cohort could verify the predictive role of PCSK9 inhibitors on cardiovascular disease burden in FH patients.

References

1. Papaioannou TG, Alexandraki KI, Tousoulis D. Arterial stiffness improvement after adding on PCSK9 inhibitors in patients with familial hypercholesterolemia. *J Clin Lipidol*. 2020;14. https://doi.org/10.1016/j.jacl.2020.03.007 [Epub ahead of print].
2. Bangalore S, Fayyad R, Messerli FH, et al. Relation of variability of low-density lipoprotein cholesterol and blood pressure to events in patients with previous myocardial infarction from the IDEAL trial. *Am J Cardiol*. 2017;119:379–387.
3. Mandraffino G, Scicali R, Rodriguez-Carrio J, et al. Arterial stiffness improvement after adding on PCSK9 inhibitors or ezetimibe to high-intensity statins in patients with familial hypercholesterolemia: a two-lipid center real-world experience. *J Clin Lipidol*. 2020;14:231–240.
4. Oh PC, Han SH, Koh KK, et al. Rosuvastatin treatment improves arterial stiffness with lowering blood pressure in healthy hypercholesterolemic patients. *Int J Cardiol*. 2014;176:1284–1287.

Misinterpreting data in lipidology in the era of COVID-19

To the Editor,

We read with interest the report by Wei et al. recently accepted for publication in the Journal.[1] After retrospectively evaluating cholesterol serum levels of 597 patients affected by coronavirus disease 2019 (COVID-19) and 50 age- and sex-matched healthy subjects, authors conclude that patients with COVID-19 develop hypolipidemia when symptoms are mild and that hypolipidemia worsens with disease severity. In an attempt to support their interpretation of the research, authors also report some statistically significant correlations among serum lipid levels and inflammatory parameters.

Authors state that "the hypolipidemia in COVID-19 patients shall raise an urgent awareness to physicians who are now in frontline fighting against this pandemic," but their

misinterpretation of the data runs the risk of misdirecting clinical practice.

First of all, although authors refer to "disease progression" throughout the article, their study is not suitable for evaluating the evolution of a clinical condition over time because it has a cross-over design (ie, patients were blood sampled only on admission).

Second, authors use "hypolipidemia" to refer to patients with total cholesterol <174 mg/dL. This definition of hypolipidemia is improper and substantially wrong in the absence of a genetic diagnosis. Furthermore, authors do not consider patients' pharmacological treatment (eg, Were patients treated with lipid-lowering drugs? It is likely, judging by the prevalence of type 2 diabetes and cardiovascular disease in the study cohort!). Actually, the prevalence of subjects at high or very high cardiovascular risk—that was significantly higher in the "critical" group—could explain the observed findings on low-density lipoprotein cholesterol (LDL-C). Indeed, low levels of LDL-C in this group were likely due to a more intensive lipid-lowering treatment, as recommended by the latest international guidelines.[2,3] Finally, it is not even surprising that the course of disease was more severe for patients with these characteristics.

In conclusion, a deeper analysis of data and more investigations are needed before concluding for a connection between low LDL-C levels and COVID-19 infection severity.

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References

1. Wei X, Zeng W, Su J, et al. Hypolipidemia is associated with the severity of COVID-19. *J Clin Lipidol*. 2020;14(3):297–304.
2. Mach F, Baigent C, Catapano AL, et al, ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111–188.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082–e1143 Erratum in: Circulation. 2019 Jun 18;139(25):e1182-e1186.

Authors' response to letter by Fogacci, Borghi, and Cicero, "Misinterpreting data in lipidology in the era of COVID-19"

Although we appreciate the comments from Drs Fogacci, Borghi, and Cicero on our publication "Hypolipidemia is associated with the severity of COVID-19",[1] we disagree on their opinions. Our data have been properly interpreted and our conclusions are supported by much emerging evidence from other studies.[2–5]

Those in our cohort of 597 COVID-19 inpatients were diagnosed and had lipid profiles taken at the time of admission. Patients were categorized according to the stage of disease course based on symptomatic severity. Therefore, the lipid profiles taken at the same time represented the corresponding disease courses. Furthermore, in a longitudinal study at another hospital in Wuhan, we examined lipid profiles from inpatients (n = 21) before viral infection, on admission, and during the course of their illness.[2] Levels of LDL-c, HDL-c, and TC decreased at the time the patients were hospitalized, remained low during the disease progression, and returned to the baseline in patients who were discharged, but decreased continuously in patients who did not survive.[2] In addition, a parallel study (n = 71) carried out in Wenzhou, China, found similar patterns with LDL-c, HDL-c, and TC levels in patients.[5] They also monitored lipid profiles daily for one ICU patient for 16 days[5] and obtained data consistent with our study.[2] Collectively, this evidence demonstrates that decreases in LDL-c levels are associated with severity of COVID-19 and reflect the disease course.

Either genetic or acquired factors (eg, viral infections) can cause hypolipidemia. Currently, there is no consensus of clear threshold to define hypolipidemia. Therefore, we followed the guidelines in the literature and set the median value of TC (174 mg/dL) of normal control subjects in Wuhan to define hypolipidemia for this cohort; this was a reasonable assessment. The concept of "hypolipidemia" was appropriately expanded and adapted in our report to describe the decreased cholesterol levels in COVID-19 patients.

We are well aware of the concerns raised by Drs Fogacci, Borghi, and Cicero about the potential effects of lipid-lowing medications being given routinely to those patients with cardiovascular disorders (CVD) or diabetes on their LDL-c levels on admission. In the United States, Italy, and other nations, as many as half or more of patients with