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Letter to the Editor in response to "Response to Kovanen PT, et al. Letter to the Editor" for original article COVID-19 increases risk of myocardial infarction in persons with familial hypercholesterolemia with or without ASCVD

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The primary objective of our analysis was to test the hypothesis that individuals with high-risk cardiovascular conditions, including those with diagnosed atherosclerotic cardiovascular disease (ASCVD) and/or familial hypercholesterolemia (FH), suffered worse clinical outcomes (specifically, increased rates of Acute Myocardial Infarction – AMI) after contracting COVID-19 than those individuals without high-risk conditions. Our data demonstrated this effect with high statistical significance across all the main study groups.

The FH Foundation believes strongly in the efficacy of lipid lowering therapies (LLTs) in the treatment of elevated blood cholesterol. As pointed out by Kovanen PT, et al. in this Letter to the Editor, prior data have shown the strong protective effect of statins against AMIs among high-risk patients. However, a lack of randomized clinical trial data exist to definitely quantify the increased protection of statins for those who contract COVID-19. Several observational studies utilizing hospital data have documented reduced mortality and/or hospitalizations in individuals on statin therapy [1–3]. Conversely, other observational studies have shown limited or no additional protective effect of statins [4,5]. We hoped our robust dataset could add to our understanding of the potential role of statin and other LLT use in SARS-CoV2-infected high risk patients such as those with FH (diagnosed and undiagnosed) and ASCVD.

To perform this sensitivity analysis, we subdivided each of the main study groups into those with a history of LLT and those without. We then propensity-score matched these groups across all covariates except those explicitly related to LLT. While the annual incidence density rates (AIHD) for the matched populations with LLT were directionally lower than those without LLT, indicating possible therapeutic protection for those with LLT, none of the comparisons reached statistical significance. Unfortunately, this meant that we were unable to make a definitive statement with our dataset. We think several factors led to the lack of statistical significance, including that the exposure window was only 4 months (the first four months of COVID) limiting follow-up as well as the relatively small sample sizes during this time period.

Finally, as pointed out by Kovanen PT, et al., The FH Foundation has strongly advocated for continuation of statin and all LLT therapy during the COVID-19 pandemic arguing that statins are known to protect against vascular events and that statins, in particular, have many protective effects that might theoretically be protective should a person with FH contract COVID-19. Perhaps the sentence in our paper should have read "*Finally, we were unable to answer a practical question, namely, did LLT have a protective effect on the outcomes for those with FH in COVID-19 and No-Covid Groups?*" rather than "*Finally, we were unable to answer a*

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practical question, namely, did LLT have a protective or deleterious effect on the outcomes for those with FH in COVID and No-Covid Groups?" Clearly, based on the fact that we saw a directionally favorable (although not statistically significant) effect of LLT we do not have any evidence from our data of a deleterious effect of statins in the setting of COVID-19 infection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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